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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE TRADEMARK TRIAL AND APPEAL BOARD

Proceeding	91186641
Party	Defendant TechWorld Corporation, Inc.
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Submission	Motion for Summary Judgment
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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE TRADEMARK TRIAL AND APPEAL BOARD

U.S. Application Serial No.: 77/073,950
For the Mark: SINUPRO
Published in the OG dated: July 29, 2008
Opposition No.: 91186641

APPLICANT'S RESPONSE TO OPPOSER'S MOTION FILED ON APRIL 2, 2010 AND A COUNTER MOTION OF SUMMARY JUDGEMENT AGAINST OPPOSER

TechWorld Corporation, Inc. Applicant V. Bionorica AG, Opposer

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Applicant, TechWorld Corporation, Inc., requests that Opposer's motion filed on April 2, 2010 be considered as untrue and be denied; and a summary judgment against Opposer be granted. Below is the factual evidence and legal basis:

A. Applicant's Mark Application Was Correctly Filed

1. US PTO Trademark law and common sense. As it is understood, the date of first use of the mark was traditionally determined by the date on which goods were first shipped in commerce with the mark affixed to the goods, not by on any later day on which the goods were sold for how many dollars. In the modern society, online marketing is a well established interstate commerce. Placing the product in the nationally and internationally searchable website for sale is a common commerce. Even if it was not sold any dollar on that day for the product bearing the Mark, the starting use of the Mark on a commercial product became a fact. For example, if a new car bearing "BMW" mark were placed in a showroom on December 27, 2006, but it was not sold for any dollar within a week, the Applicant's application for the "BMW" mark, based on the first use on December 27, 2006, should be granted according to the trademark law without consideration of the goods being sold for how much.

2. First Use in Commerce of Applicant's Mark. Nasal Care Kit bearing SinuPro™ was placed in the nationally and internationally searchable website of www.sinupro.com on December 27, 2006, and it was available for worldwide consumers to purchase started on that day. On that day, $0.00 of goods was sold. However, SinuPro™ was fixed on the commercial product "Nasal Care Kit", and it was available for consumers to review and purchase started on December 27, 2006. According to the trademark law, it was the correct date of "First Use in Commerce."

3. Common Knowledge in Medicine. Nasal irrigation and nasal drug delivery have been recognized by the major medical societies in the US and abroad for preventing and treating a variety of diseases. Exhibits 1 to 19 provided a small portion of these

medical publications before December 27, 2006. Those medical experts have clearly demonstrated the usefulness of nasal irrigation and nasal drug delivery. If Opposer conducted a preliminary search by typing “nasal irrigation” in GOOGLE site, Opposer might be surprised that so many beneficial effects have been reported by medical professionals and experienced by so many users before 2007. The 5 national medical societies: The American Academy of Allergy, Asthma, and Immunology; the American Academy of Otolaryngic Allergy; the American Academy of Otolaryngology–Head and Neck Surgery; the American College of Allergy, Asthma, and Immunology; and the American Rhinologic Society—convened a group of 30 physicians in 2003 and, in a consensus document, “Rhinosinusitis: Establishing definitions for clinical research and patient care,” proposed definitions and drafted initial clinical trial designs for several classifications of rhinosinusitis. (Exhibit 1). Nasal irrigation was listed as one of the standard therapy in this important guideline. The European Academy of Allergology and Clinical Immunology (EAACI) issued apposition paper in 2005. Nasal irrigation was listed a few places as a well accepted therapy for nasal sinus disorders (Exhibit 2).

4. During the recently held US-Canada conference of Cough, Cold and Allergy, Applicant’s product, NasalCare® Nasal Rinse Starter Kit, developed based on Applicant’s proprietary technologies (two patents granted by PTO in 2001 and 2004, Exhibits 19 and 20), which is very similar to the product of SinuPro™ Nasal Care Kit, was elected by those conference participants as the “Best New Product” in this category. Applicant’s nasal irrigator and solution were well designed to meet a variety of un-met medical needs.

5. Nasal Care Kit bearing SinuPro Mark had a variety of usages, as nasal irrigation was a portion of what could be used with SinuPro™ Nasal Care Kit. The kit contained a number of items for meeting the different needs. Below is specifically but briefly clarify one by one of all filed uses in a hope to benefit Opposer for not prematurely making his judgment without reading medical literature, or without consulting any physician:

1) All purpose disinfecting and deodorizing preparations – was part of the usefulness of SinuPro™ Nasal Care kit as nasal irrigation can remove any kind of

infectious agents, such as viruses, bacteria, fungi, from nasal and sinus cavities, and can remove those substance in the sinonasal cavities to cause bad smell. This is well accepted by medical societies and consumers. From the motion filed on April 2, 2010, Opposer is lack of knowledge in this.

2) Allergy medications - was part of the usefulness of SinuPro™ Nasal Care kit since nasal irrigation has been well recognized to relieve nasal allergy symptoms. From the motion filed on April 2, 2010, Opposer is lack of knowledge in this.

3) Allergy relief medication – same as above.

4) Analgesic preparations - was part of the usefulness of SinuPro™ Nasal Care kit as nasal irrigation can relieve sinus pain very effectively. From the motion filed on April 2, 2010, Opposer seems lack of knowledge in this.

5) Anti-arthritic compositions and preparations - was part of the usefulness of SinuPro™ Nasal Care kit as therapeutic agents delivered through nasal route is one of the best ways of treating arthritis on a daily basis without frequent injection of the drug.

6) Anti-cancer preparations - was part of the usefulness of SinuPro™ Nasal Care kit as these detached cancer cells/tissues in nasal cavities should be removed to ease breathing, and anticancer agents delivered through nasal route is one of the new ways of helping cancer patient on a daily basis.

7) Anti-diabetic pharmaceuticals - was part of the usefulness of SinuPro™ Nasal Care kit as improved breathing helps these patients to have a better energy metabolism as oxygen will be more readily available. Also, anti-diabetic agents delivered through nasal route is one of the ways of treating diabetes on a daily basis.

8) Anti-inflammatory and antipyretic preparations - was part of the usefulness of SinuPro™ Nasal Care kit as nasal irrigation alone can help to achieve these anti-inflammatory therapeutic effects since these mediators were removed.

9) Antibacterial pharmaceuticals - was part of the usefulness of SinuPro™ Nasal Care kit as nasal irrigation alone or with anti-infective agents can help to achieve the antibacterial effects. This was included in our patent granted by US PTO in 2001 (Exhibit 19).

10) Antibacterial substances for medical purposes – same as above.

11) Antibiotic preparations – was part of the usefulness of SinuPro™ Nasal Care kit, same as above and included in our patent granted by US PTO in 2001.

12) Antifungal creams for medical use - was part of the usefulness of SinuPro™ Nasal Care kit. Nasal application of antifungal creams can help patients with a fungal infection.

13) Biological and chemical preparations and reagents for medical or veterinary use - was part of the usefulness of SinuPro™ Nasal Care kit. Nasal delivery was indeed used by a veterinary medical doctor for treating her horses.

14) Biological preparations for medical purposes – same as above.

15) Cardiovascular treatment preparations - was part of the usefulness of SinuPro™ Nasal Care kit as improved breathing with a SinuPro™ Nasal Care Kit can help the patients to reduce the cardiac burden since lung has a better oxygen supply. In addition, nasal delivery of anti-cardiovascular disorder agent can help patients with cardiovascular disorders.

16) Cleansing solutions for medical use – obviously, it was part of the usefulness of SinuPro™ Nasal Care kit. How could Opposer ignore this such obvious part in his filed motion on April 2, 2010?

17) Cold sore treatment preparations - obviously, it was part of the usefulness of SinuPro™ Nasal Care kit, as nasal irrigation has a long history in this use.

18) Cotton swabs for medical purposes - it was part of the usefulness of SinuPro™ Nasal Care kit. Before and after using nasal irrigation, a swab in the kit can be used by a medical professional for any purpose she/he decides.

19) Diagnostic agents, preparations and substances for medical purposes - it was part of the usefulness of SinuPro™ Nasal Care kit. Collection of nasal wash specimen and nasal delivery of any agents have long been used by medical professionals for diagnosing or treating a patient.

20) Diagnostic preparations for clinical or medical laboratory use – same as above.

21) Diagnostic preparations for medical or veterinary purposes - it was part of the usefulness of SinuPro™ Nasal Care kit, as collection of nasal wash specimen and nasal

delivery of any agents have long been used by medical professionals for diagnosing or treating a patient or an animal.

22) Drug delivery agents consisting of compounds that facilitate delivery of a wide range of pharmaceuticals - it was part of the usefulness of SinuPro™ Nasal Care kit, since nasal drug delivery is a very hot research area.

23) Fungal medications - it was part of the usefulness of SinuPro™ Nasal Care kit. Medical community clearly knows that nasal irrigation can help patients with chronic sinusitis infected by fungi to have an improved life quality.

24) Fungicides for medical use – same as above.

25) Headache treatment preparations - it was part of the usefulness of SinuPro™ Nasal Care kit. Nasal irrigation has a significant effect in relieve headache caused by sinus infection or sinus blockage.

26) Herbal products, namely, aromatherapy packs containing herbs used for relief from headaches, insomnia and sinus discomfort - it was part of the usefulness of SinuPro™ Nasal Care kit as Aloe extract was part of the mix to make irrigation solution.

27) Hydrogen peroxide for medical use - it was part of the usefulness of SinuPro™ Nasal Care kit. Like a swab packed in the kit, medical professional or regular consumer can use it for a good purpose.

28) Inhaled pharmaceutical preparations for the treatment of respiratory diseases and disorders; Inhalers filled with antimicrobial and anti-inflammation agents - it was part of the usefulness of SinuPro™ Nasal Care kit. Those agents were included in our patent granted by US PTO in 2001 (Exhibit 19).

29) Medical diagnostic reagents - it was part of the usefulness of SinuPro™ Nasal Care kit for collecting and analyzing nasal wash specimens.

30) Medical diagnostic reagents and assays for testing of body fluids - it was part of the usefulness of SinuPro™ Nasal Care kit for collecting and analyzing nasal secretion specimens.

31) Medicated mouth care and treatment preparations; Medicated mouthwash - it was part of the usefulness of SinuPro™ Nasal Care kit, as the liquid administered from

nostril can irrigate nasopharyngeal and oral pharyngeal area, an upper part of oral/nasal cavity, to which a regular mouth wash is hard to reach.

32) Medicinal herbal extracts for medical purposes – it was part of the usefulness of SinuPro™ Nasal Care kit as Aloe extract was used in our kit.

33) Medicinal preparations for the mouth and as sprays - it was part of the usefulness of SinuPro™ Nasal Care kit, as the liquid administered from nostril can irrigate nasopharyngeal and oral pharyngeal area, an upper part of oral/nasal cavity, to which a regular mouth wash is hard to reach.

34) Migraine treatment preparations – it was part of the usefulness of SinuPro™ Nasal Care kit. Performing nasal irrigation helped a number of patients to reduce headache with or without an actual diagnosis of migraine.

35) Mixed antibiotic preparations – it was part of the usefulness of SinuPro™ Nasal Care kit. We claimed those in our patent granted by the PTO in 2001.

36) Nasal spray preparations - it was part of the usefulness of SinuPro™ Nasal Care kit.

37) Oxygen for medical use - it was part of the usefulness of SinuPro™ Nasal Care kit. Cleaning upper airway can help patients to breathe better, so oxygen can reach lungs more easily.

38) Pain relief medication – it was part of the usefulness of SinuPro™ Nasal Care kit. Performing nasal irrigation helped a number of patients to reduce headache, or sinus pain.

39) Pharmaceutical anti-allergic preparations and substances – it was part of the usefulness of SinuPro™ Nasal Care kit. Performing nasal irrigation with scientifically formulated solution is well recognized as an effective treatment for allergy.

40) Pharmaceutical antitussive-cold preparations – it was part of the usefulness of SinuPro™ Nasal Care kit. Performing nasal irrigation has a long history of treating cold/flu.

41) Pharmaceutical for the treatment of erectile dysfunction - it was part of the usefulness of SinuPro™ Nasal Care kit. Performing nasal irrigation and/or with a

stimulation substance can help the patient breath better to gain energy, reduce snore, and improve sexual opportunity and function.

42) Pharmaceutical preparations for inhalation for the treatment of pulmonary hypertension – it was part of the usefulness of SinuPro™ Nasal Care kit. Performing nasal irrigation and/or with an active substance helped the patient to reduce airway resistance, improve lung function, and help the patient with a pulmonary hypertension.

43) Pharmaceutical preparations for the treatment of infectious diseases - it was part of the usefulness of SinuPro™ Nasal Care kit. This was included in our patent granted by PTO in 2001.

44) Pharmaceutical preparations for treating allergic rhinitis and asthma - it was part of the usefulness of SinuPro™ Nasal Care kit. This was partially included in our patent granted by PTO in 2001.

45) Pharmaceutical preparations for treating diabetes - it was part of the usefulness of SinuPro™ Nasal Care kit. Same as stated in the earlier part.

46) Pharmaceutical preparations for treating skin disorders - it was part of the usefulness of SinuPro™ Nasal Care kit as a number of skin disorders can be treated though nasal-route delivered therapy.

47) Pharmaceutical preparations for use in chemotherapy - it was part of the usefulness of SinuPro™ Nasal Care kit. Chemotherapy resulted in more death of nasal epithelial cells. Those dead cells should be removed from the narrow airway. Nasal administration of a useful substance is also helpful for some cancer patients.

48) Pharmaceutical preparations for use in urology – it was part of the usefulness of SinuPro™ Nasal Care kit. Nasal administration of a useful substance is helpful for treating urinary tract diseases.

49) Pharmaceutical preparations for wounds – it was part of the usefulness of SinuPro™ Nasal Care kit, as wounds after nasal surgery can be recovered fast if nasal irrigation is performed. Numerous ENT surgeons recommend nasal irrigation after nasal surgery. If Opposer asked a few ENT doctors in recommending this practice, he would appreciate that Applicant was doing a great thing for these patients.

50) Pharmaceutical preparations, namely, anticoagulants - it was part of the usefulness of SinuPro™ Nasal Care kit, as substance administered nasally can improve blood flow.

51) Pharmaceutical preparations, namely, antidepressants – it was part of the usefulness of SinuPro™ Nasal Care kit, as nasal irrigation improved the patient's life quality, hence these patients became much happier. In addition, the substance administered nasally can help improve depression.

52) Pharmaceutical preparations, namely, appetite suppressants – it was part of the usefulness of SinuPro™ Nasal Care kit, as improved smell after performing nasal irrigation can help to increase appetite.

53) Pharmaceutical preparations, namely, a blood clotting aid and delivery system for use in human and veterinary medicine - it was part of the usefulness of SinuPro™ Nasal Care kit, as substance administered nasally can help stop bleeding.

54) Pharmaceutical preparations, namely, a drug delivery system comprising polymer-based oral tablets for the continuous release of a wide variety of therapeutic agents - it was part of the usefulness of SinuPro™ Nasal Care kit, as nasal delivery of a drug in a slowly released motion is a well recognized system for treating a variety of diseases.

55) Pharmaceutical products for the treatment of bone diseases – it was part of the usefulness of SinuPro™ Nasal Care kit, as nasal irrigation helped lung function – then the blood charged with high oxygen is more beneficial for the bone. Also, delivery of an active substance is a well recognized method for preventing or treating osteoporosis.

56) Pharmaceutical products for the treatment of viral and infectious diseases, for the treatment of cancer – it was part of the usefulness of SinuPro™ Nasal Care kit, as nasal irrigation and nasal drug delivery are well recognized in treating a variety of diseases. Part of these was included in our patent granted by US PTO in 2001.

57) Pharmaceutical products for treating respiratory diseases and asthma – it was part of the usefulness of SinuPro™ Nasal Care kit, as nasal irrigation helps to reduce asthma attack, and to help patients recover fast after having cold/flu, the most common respiratory tract diseases.

58) Pharmaceuticals, namely, anti-infectives – it was part of the usefulness of SinuPro™ Nasal Care kit, as nasal irrigation largely removes infectious agents away from the upper respiratory tract, and helps patients recover fast after having cold/flu.

59) Plant extracts for medical, veterinary and pharmaceutical purposes - it was part of the usefulness of SinuPro™ Nasal Care kit, as Aloe extract was used in the product.

60) Preparations for detecting genetic predispositions for medical purposes – it was part of the usefulness of SinuPro™ Nasal Care kit, as nasal mucosal and secretion specimen can provide detached cells for detecting genetic predispositions for medical purposes. This is a much better way than traditional biopsy in obtaining biological specimen for this purpose.

61) Preparations for the treatment of asthma - it was part of the usefulness of SinuPro™ Nasal Care kit, as nasal irrigation removing these triggering agents so asthma occurrence can be reduced.

62) Preparations for treating colds - it was part of the usefulness of SinuPro™ Nasal Care kit, as nasal irrigation has been used to treat cold for a long history. Again, it is advised that Opposer log on to any web site to become familiar in this common practice.

63) Radioactive pharmaceutical preparations for use in vivo diagnostic or therapeutic use – it was part of the usefulness of SinuPro™ Nasal Care kit, as nasally administered tracing substance can be used for in vivo diagnostic or therapy.

64) Reagents and media for medical and veterinary diagnostic purposes – it was part of the usefulness of SinuPro™ Nasal Care kit, as nasally administered media to collect nasal secretion can be used for diagnosis or personalized therapy, or for treating animals, like dog or horse.

65) Sanitary preparations for medical use – it was part of the usefulness of SinuPro™ Nasal Care kit, as nasal cleansing pre-surgery could help to reduce the chance of in-process and post-nasal surgery infection. Seems Opposer never read this far to realize that nasal irrigation is a way of medical sanitation.

66) Sinus pillows containing aromatic substances for relief from headaches, insomnia and sinus discomfort - it was part of the usefulness of SinuPro™ Nasal Care kit, as it is a very useful tool to supply these aromatic substances for relief from headaches.

67) Smoking cessation preparations – it was part of the usefulness of SinuPro™ Nasal Care kit, as smoker can see how much dirty materials could be washed out from his nasal cavities, and help him to quit smoking. Also, nasally administrating these smoking-cessation substances is a good way to stop smoking.

68) Stimulatory medications for use in weight reduction programs - it was part of the usefulness of SinuPro™ Nasal Care kit, as improved breathing after performing nasal irrigation encourages these overweighed people to exercise more. In addition, a number of active ingredients administered through nasal cavity can help patients to lose weight. Applicant recently filed a new international patent application of using nasal administered formulation to reduce body weight (Confidential Information – will not further elaborate).

All those items of usefulness were included in the filed Mark application. The FIRST USE IN COMMERCE on 2006-12-27 was a fact, and it was based on the sound medical judgment. How can Opposer ignore so many common practices by medical professionals and by so many common consumers?

Applicant filed the Mark application based on the (1) Internet marketing of Nasal Care Kit bearing SinuPro™ started on 2006-12-27; (2) All claimed uses were from the medical needs to treat or prevent a variety of disorders; (3) PTO Examiner conducted a thorough search – no same or similar trademark was found. Therefore, the application of the SinuPro mark was filed correctly following the trademark law. The publication of the mark was based on the sound judgment by the PTO's examiner. Opposer is too naïve in medical needs of nasal care kit. His direct attack against Applicant and indirectly attack against the PTO examiner was from his very wrong judgment. Therefore, his motion filed on April 2, 2010 is worth nothing for consideration.

B. Applicant's Application Was Correctly Allowed for Publication

Trademark examiner at US PTO did an exhausting search and did not find any same or similar Mark. Those many beneficial effects of nasal irrigation were realized by the Examiner. The conclusion made by the PTO examiner is correct. There was no perjury involved in any of the filing and examining process.

C. Opposer Misinterpreted the Trademark Law of Current Commercialization of a Product

1. The motion filed by Opposer on April 2, 2010 failed to recognize that internet marketing is a way of commercialization. Opposer's motion could be granted if the motion were filed before 1960, at that time selling product through internet or worldwide web was not commonly or legally accepted as a way of commercialization. If selling the product through internet were judged by Opposer as a non-commercial mean at the end of 2006, then Opposer would have numerous opportunities to win his cases. The internet marketing community and US economy would suffer severely. Applicant is glad that there is a law to recognize and regulate internet marketing. Applicant sincerely believes that the Board will not agree with Opposer's conclusion that internet selling is not a right commercial activity. Applicant started internet commercialization of Nasal Care Kit bearing the filed mark on December 27, 2006. Opposer's motion of claiming the "non-use" of the Mark was against the fact, was against PTO Examiner's sound judgment, and was against US Trademark law. Therefore, his attack-claim was false and his motion of filing another opposition is baseless. Therefore, his motion filed on April 2, 2010 must be dismissed.
2. Opposer was lack of basic medical knowledge in nasal care and his conclusion in the filed motion on April 2, 2010 has no quality. For all items of these filed uses of the Nasal Care Kit bearing SinuPro Mark, Opposer failed to recognize any of them. It is to share with Opposer that nasal irrigation has been well accepted by medical communities for preventing and treating those common diseases. Nasal delivery of a

therapy is a new trend in pharmaceutical and medical research. The attached medical publications (only a small fraction collected by Applicant) are the supporting evidence for our claimed uses. Applicant respectively requests that the Board consider these medical conclusions/decisions/recommendations as the experts' opinions in this regard. Those medical publications are also strong basis for the decision made by the PTO examiner for publishing Applicant's mark. Opposer's motion of claiming the "non-use" of the Mark in these uses was against the commonly accepted medical practices, against fact, against PTO Examiner's sound judgment, and against US Trademark law. Therefore, his judgment made on a very poor medical knowledge was false and his motion of filing another opposition is baseless. Therefore, his motion must be dismissed.

D. Opposer Wrongly Attacked Applicant

It is a fact that Applicant, by no mean, is fully knowledgeable in trademark laws and procedures. However, Applicant tried very hard to following the Board's direction, and showed the "good faith" in providing each of Opposer's requests for documents, and answering each of these interrogatories, which was recognized by the Board in the previously issued notifications. On the other hand, during this civil procedure, Opposer used these terms of "perjury" and "fraud" solely based on his poor medical knowledge in how nasal care kit could be used, and how many beneficial effects by using a well designed and tested nasal irrigation system. Opposer finally concluded that "Applicant fraudulently claimed use of the mark on a vast number of goods knowing that the mark had not been used on the goods for the purpose of obtaining a trademark registration covering those goods." After reading through one by one of those clarifications for each of the use, Opposer should regret what he said. Most people are not experts in more than two areas. Practicing well in a law firm does not mean he can practice medicine in a hospital without a formal medical training. Opposer, in this case, is basically no knowledge in medical uses of Nasal Care Kit – a FDA reviewed and registered medical device. Therefore, his attack against Applicant, no matter how many strong words were used, was wrong. For this, Applicant reserves the right to answer these attacks when

the time is right. Applicant respectively requests that the Board teach Opposer to refrain from use of his unjustified terms in any further communication with Applicant.

E. Opposer Contradicted to Himself in Agreeing of Using Email

In the filed Motion on April 2, 2010, Opposer used the ending "was served upon Applicant on the date set forth below by email, as agreed to by Applicant, to the following email address: info@techworldcorp.com." Any agreement must be reached by at least two parties. There is no such case the agreement does only apply to one party, not the other party. As the Board can recall, Opposer previously claimed that he did not consent to use email service. This time, he stated above. When this agreement was reached? It was agreed by the two parties during the teleconference conducted on January 27, 2009. Since then, Applicant and Opposer delivered virtually all communications via emails to the other party during the procedure after January 27, 2009. In the previously filed opposition to Applicant's motion to compel discovery, Opposer stated that "In this regard, despite Opposer's numerous reminders that it did not consent to email service, Applicant only served Opposer electronically, without a paper copy, failing to make proper service." Since Opposer made such a strong allegation, which is contradictory to what both parties have been doing for so long, and finally, contradictory to what he wrote. So far, Opposer failed to provide these evidences showing "numerous reminders." Opposer in fact admits that he contradicted to himself, and lied to the Board in the past. Opposer's statement is hard to trust.

Opposer has been continually misspelling Applicant's email address. From the Exhibits provided by Opposer on April 2, 2010, it is evidenced that Opposer has been misspelling Applicant's email many times, and is particularly unforgivable since Applicant directly told Opposer on April 1, 2009 that his document had a misspelling of Applicant's email address. We already submitted the evidence of these errors to the Board in the past. It is clear that Opposer made so many mistakes in spelling

Applicant's email address, therefore he is not entitled to complain that his email was not delivered. Any word from Opposer in complaining of using emails cannot be trusted.

F. Opposer Never Provides the Key Evidence from US Consumers

Opposer never can provide evidence whether the two marks are different or similar. During the entire opposition procedure, Opposer failed to produce any evidence to support his biased and subjective claims that the two marks are similar. Applicant, on the other hand, asked the independent third party to have conducted the survey among US consumers.

The US consumers overwhelmingly support Applicant's conclusion that the two marks are very different in visual, sound and commercial impression. The survey conducted by the University of Pennsylvania Wharton Business School is attached here as Exhibit 22. Although Opposer tried hard to devalue this survey conducted by a third party, Applicant respectively requests that the Board use this only available evidence to dismiss Opposer filed opposition, as Opposer never provides any such survey result. Since Opposer requests a summary judgment, it is the time for the Board to use the available evidence to issue the summary judgment against Opposer.

G. Summary Judgment against Opposer is Warranted

During this long and exhausting opposition process – to which Applicant spent so much invaluable time and resource to defend this opposition, Applicant is very pleased to agree with Opposer that the Board move to issue the summary judgment without further procedures.

To aid the Board in issuing the summary judgment, below is a list of what had been done mistakenly by Opposer:

1. Opposer is knowingly and willingly to not follow Board's role in utilizing the Board's standard Protective Order, and delayed the entire process for so long as possible to withholding the final approval of Applicant's mark. Even signing a single document took Opposer months, not days. And by implementing this designed delay-to-

maximum malpractice, he created so much hardship and problems for Applicant. Finally, based on his poor medical knowledge in nasal care and nasal irrigation, he submitted a motion to start another opposition to extend the process to many more months.

2. Opposer is knowingly and willingly to departure from the Board's standard to request Applicant to hire an attorney, and acted like a legal bull and created much unnecessary hardship to Applicant because Applicant did not honor his request.

3. Opposer has been misspelling Applicant's email address many times in the written documents, but complained and misled the Board that Applicant's email system had problem.

4. Opposer is knowingly and willingly to mislead the Board that he never provided any consent in using email to serve the other party, which is contradictory to what he has been doing for so long and so many times. This is evidenced again in the motion filed on April 2, 2010.

5. Opposer is against internet marketing, and mis-claims that Applicant's internet selling activity was not counted as a way of commercialization of the Nasal Care Kit bearing the applied mark.

6. Opposer is against trademark law to use the number of selling dollars of the goods as evidence, instead of using the date on which the actual product was presented to consumers as a "first use in commerce."

7. Opposer is lack of basic medical knowledge in nasal care and nasal irrigation, and misjudged that Applicant's application did not cover these uses.

8. Opposer is knowingly and willingly to mislead the process by focusing only on the procedures, not focusing on the key evidence from the US consumers whether the two marks are different or similar.

The above wrong doings by Opposer should logically and legally result in a summary judgment of dismissing his opposition.

H. Summary

In light of the above eight areas, Applicant respectively requests that:

1. Opposer's motion of leave to file another Notice of Opposition be denied;
2. Opposer's request for Summary Judgment against Applicant without a basic medical support be denied.

Conclusion:

Due to the facts that:

1. Opposer failed to provide any feedback from the US consumer whether the two marks are different or similar.
2. Opposer blindly ignores the fact of internet marketing as an actual commercialization of the product bearing the applied mark.
3. Opposer is in a big hurry to file a motion for a summary judgment against Applicant without a basic understanding of Applicant's product and its uses.
4. The US consumers overwhelmingly support Applicant's conclusion that the two marks are very different in visual, sound and commercial impression.

Applicant, therefore, respectively requests that the Board issue the summary judgment against Opposer. His opposition is lack quality, lack of credibility, lack of basic medical knowledge. Opposer's opposition, therefore, be entirely dismissed. The US PTO published Mark be fully granted.

Respectively submitted by
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Exhibits:

Exhibit1. 5 National Medical Societies Guideline – Nasal Irrigation was a standard 2006

Exhibit 2. EU Medical Society Position Paper on Sinonasal Diseases 2005

Exhibit 3. Nasal Irrigation benefits-Children 2005

Exhibit 4. Nasal Irrigation is highly effective 2002

Exhibit 5. Fungi Infection – Sinusitis 1997

Exhibit 6. Saline Nasal Irrigation 2006

Exhibit 7. Nasal irrigation for Chronic sinusistis 2004

Exhibit 8. Nose and Lung – one system 2006

Exhibit 9. Mayo Clinic – Fungi infection-specimen2005

Exhibit 10. Nasal Wash removes Bacteria 2005

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Exhibit 13. Nasal and Lung Talk to each other 1999

Exhibit 14. Nasal drug Delivery News 20006

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Exhibit 16. Nasal-Lung-Lavage 2002

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Exhibit. 20. Applicant's patent granted in 2001

Exhibit 21. Applicant's patent granted in 2004

Exhibit 22. Survey results from US Consumers conducted by University of Pennsylvania Wharton Business School in 2009

Exhibit 23. Applicant's NasalCare Product won "Best New Product" award on March 4, 2010 during Cough, Cold and Allergy Conference.

CERTIFICATE OF SERVICE

I hereby certify that a true and correct copy of the foregoing Applicant's response to Opposer filed Motion on April 2, 2010 was served upon Opposer on the date set forth below by email, as agreed by Opposer's attorney on January 27, 2009, and written expressed agreement on April 2, 2010, to the following email address:

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Dated: April 3, 2010

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Rhinosinusitis: Developing guidance for clinical trials

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The Rhinosinusitis Initiative was developed by 5 national societies. The current guidance document is an expansion of the 2004 publication "Rhinosinusitis: Establishing definitions for clinical research and patient care" and provides templates for clinical trials in antimicrobial, anti-inflammatory, and symptom-relieving therapies for the following: (1) acute

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presumed bacterial rhinosinusitis, (2) chronic rhinosinusitis (CRS) without nasal polyps, (3) CRS with nasal polyps, and (4) classic allergic fungal rhinosinusitis. In addition to the templates for clinical trials and proposed study designs, the Rhinosinusitis Initiative has developed 6 appendices, which address (1) health outcomes, (2) nasal endoscopy and staging of CRS, (3) radiologic imaging, (4) microbiology, (5) laboratory measures, and (6) biostatistical methods. (J Allergy Clin Immunol 2006;118:S17-61.)

Key words: *Acute bacterial rhinosinusitis, chronic rhinosinusitis with or without polyps, allergic fungal rhinosinusitis, clinical trials*

The development of sound clinical research trials that target the various causes of rhinosinusitis is necessary to gain a better understanding of how to effectively prevent and treat the detrimental health consequences associated with this condition. Recognizing this need, 5 national societies—the American Academy of Allergy, Asthma, and Immunology; the American Academy of Otolaryngic Allergy; the American Academy of Otolaryngology–Head and Neck Surgery; the American College of Allergy, Asthma, and Immunology; and the American Rhinologic Society—convened a group of 30 physicians in 2003 and, in a consensus document, ''Rhinosinusitis: Establishing definitions for clinical research and patient care,'' proposed definitions and drafted initial clinical trial designs for several classifications of rhinosinusitis.[1]

The 5-society collaboration is now referred to as the Rhinosinusitis Initiative. This document is the latest product of this initiative, expanding on the previous work of the group by developing a template for clinical trials for antimicrobial, anti-inflammatory, and symptom-relieving therapies for acute presumed bacterial rhinosinusitis (ABRS), chronic rhinosinusitis (CRS) without nasal polyps (CRSsNP), CRS with nasal polyps (CRSwNP), and classic allergic fungal rhinosinusitis (AFRS).[1]

Abbreviations used

ABRS:	Acute presumed bacterial rhinosinusitis
AE:	Adverse event
AE-CRS:	Acute exacerbation of chronic rhinosinusitis
AFRS:	Classic allergic fungal rhinosinusitis
AR:	Allergic rhinitis
CRS:	Chronic rhinosinusitis
CRSsNP:	Chronic rhinosinusitis without nasal polyps
CRSwNP:	Chronic rhinosinusitis with nasal polyps
CT:	Computed tomography
ECG:	Electrocardiogram
FDA:	US Food and Drug Administration
iNOS:	Inducible nitric oxide synthase
INS:	Intranasal steroid
LT:	Leukotriene
MRI:	Magnetic resonance imaging
NO:	Nitric oxide
NP:	Nasal polyp
PK:	Pharmacokinetics
QOL:	Quality of life
SNOT-20:	Sinonasal Outcome Test–20 items
TSS:	Total symptoms score
URI:	Upper respiratory tract infection

METHODS

The guidelines set forth in this article were developed by using consensus discussions and rigorous literature review. Twenty-seven individuals were selected to serve on this Rhinosinusitis Initiative Committee. They were chosen by the Editorial Committee, whose members represented the 5 national societies, because each one was a research scientist deemed to be an expert in clinical trials. These specialists were from the disciplines of allergy/immunology, otolaryngology, infectious disease, radiology, and biostatistics. The Rhinosinusitis Initiative Committee met in Bethesda, Maryland, from February 25, 2005, to February 27, 2005, to consider various trial components and designs and to produce the following recommendations. The attendees were initially divided into 3 working groups. Each group provided rationales and recommendations for the inclusion of specific trial components pertaining to the 4 target rhinosinusitis disease states: (1) ABRS; (2) CRSsNP; (3) CRSwNP; and (4) AFRS. These were then reviewed and revised in the full committee discussions. If consensus was difficult to reach because of dissenting opinions, a majority vote was taken and recorded. A systematic literature review was conducted based on key words determined during the 2005 conference, and the Editorial Committee selected appropriate source documents. In drafting this guidance, the existing grade of evidence for each issue was considered, but no further elaboration of them occurred. Many have been recently reviewed in the excellent European Academy of Allergology and Clinical Immunology position paper.[2] An unrestricted educational grant was provided by Schering-Plough Corporation to the American Academy of Allergy, Asthma and Immunology and the journals to help pay the costs of the conference and the supplements. The grant agreement prohibited Schering-Plough from having any role in the selection of the attendees, in the design of the content and conduct of the meeting, and/or in the preparation of the manuscript. Reflective of their experience, many of the participants had extensive industry relationships. During the initial part of the meeting, the requirement for each participant to be objective and set aside bias was reviewed. A great deal of self-policing was manifest in group discussions. During the conference, broad categories of therapeutic agents were discussed rather than specific generic or brand-name products.

This guidance should be reviewed as a work in progress. Although they have been endorsed by each of the participating societies, they should not be considered authoritative by medical organizations, commercial companies, or regulatory agencies. Some elements of trial designs remain controversial and will require further discussion. However, it is the sincere hope of this task force that this initiative will promote better clinical research and improved patient care for individuals with rhinosinusitis.

US FOOD AND DRUG ADMINISTRATION: DRUG DEVELOPMENT AND CLINICAL TRIAL DESIGN GUIDANCE

The role of the US Food and Drug Administration (FDA) is to ensure a drug is proved safe and effective for clinical use. As a result, this agency adheres to strict standards, and clinical trials must be designed appropriately to document that an investigational drug or an

approved drug under examination for a new indication is evaluated for drug safety and efficacy.

The FDA requires investigations be ''adequate and well-controlled,'' defined by the Code of Federal Regulations (21 CFR 314.126)[3] as ''evidence consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could fairly and responsibly be concluded by such experts that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling or proposed labeling thereof.''

Drugs are approved based on both clinically and statistically significant results of well-designed clinical trials, and in general, the FDA requires confirmatory evidence from 2 independent trials to demonstrate the efficacy of new drug products. Many factors must be taken into consideration to demonstrate a statistically significant result, and any benefits recorded from drug effectiveness must be well supported while minimizing the possibility of fraud, bias, or chance.

There are 3 components of trial design the FDA considers necessary for an adequate and well-controlled investigation[4]: (1) the objective of the study must be clearly stated, coupled with a summary of the methods used for analysis of the trial results; (2) the design must permit quantitative assessment of drug effectiveness by a valid comparison with a control group; and (3) the study protocol should accurately define the design and duration of the study, sample size issues, and whether treatments are parallel or sequential. Furthermore, the FDA requires clinical trials to provide a clear description of the method of patient selection and treatment assignment, depict methods for bias minimization (eg, blinding), and describe appropriate measures for assessing patient response.

Evidentiary requirements for drug approval focus on proving statistical significance and avoiding the type I error (incorrectly assuming a drug is effective). Detailed statistical plans and analytic methodologies are required. Before data analysis, the null hypothesis is in place. If the research objective is to assess treatment effectiveness, the null hypothesis states there is no difference between the control group and the treatment group. The *P* value is calculated under the assumption that the null hypothesis is true and represents the probability of achieving the observed data result or something more extreme. If the *P* value is less than .05, the finding is considered statistically significant because the probability of the type I error is small. In such a case, the null hypothesis is rejected, and researchers often conclude the observed result might not be due to a type I error but represents a real treatment effect.

The FDA prefers that trials designed to show drug effectiveness designate a single primary outcome, although 2 outcomes might be appropriate. A single primary outcome is preferred because multiple outcome measures increase the overall probability of a type I error.

It is also important to note that acceptance of surrogate end points for determination of drug effectiveness is growing. A surrogate end point is defined as ''a laboratory measure or other test that has no direct or obvious relationship to how a patient feels or to any clinical symptom, but on which a beneficial effect of a drug is presumed to predict a desired beneficial effect on such a clinical outcome.''[5] There are 2 types of surrogate end points: validated and unvalidated. Validated surrogate end points are tests for which there is adequate evidence that a drug effect on the measure predicts the clinical benefit desired (eg, decrease in blood pressure to measure antihypertensive drugs). Unvalidated surrogate end points are measures for which evidence does not exist that a drug effect on the measure predicts the desired clinical outcome. The FDA prefers the use of validated surrogate end points; however, in 1992, a regulation was established that allowed approval of a treatment based on its effects on an unvalidated surrogate end point. This regulation applies to serious or life-threatening illnesses.

The FDA has issued specific ''guidance documents'' for the purposes of designing clinical trials of certain diseases, including a draft guidance for studying acute bacterial sinusitis. No guidance document currently exists for chronic (rhino)sinusitis, and this condition has not been officially defined by the FDA; however, the FDA has reviewed several industry-sponsored trials for forms of chronic sinusitis, and recently, 2 of these trials lead to drug approval for the indication of nasal polyposis.[6,7] Existing barriers to clinical trials in these conditions include the following: current controversy regarding the terms *rhinosinusitis* versus *sinusitis*, the lack of consensus regarding the classification and definitions of these conditions, and the lack of consensus regarding end points that should be applied to clinical trials of these conditions. As a result, the trial designs outlined in this document should be viewed as guidance based on expert opinion. Before any trial for rhinosinusitis is initiated, the investigator/sponsor should plan a prestudy meeting with the FDA or other appropriate regulatory agency to review the protocol and address controversial areas.

CLINICAL TRIAL COMPONENTS GUIDE

This document provides guidance for research trials in 4 disease categories of rhinosinusitis (Table I). It is formatted in an outline fashion to address 3 therapeutic modalities, namely antimicrobial agents, anti-inflammatory medications, and symptom-relieving treatments, for each of the 4 disease categories (Table II). The Rhinosinusitis Initiative conference attendees discussed different types of trials, and rather than presenting duplicate anti-inflammatory trial designs for ''intranasal corticosteroids'' under CRSsNP and CRSwNP, intranasal corticosteroids are covered under CRSsNP, and oral corticosteroids are addressed under CRSwNP. Similarly, under the category of ''symptom reliever,'' intranasal decongestants are covered under

TABLE I. Rhinosinusitis consensus research definitions[1] and clinical trial guidelines

	Type of rhinosinusitis			
Criteria for diagnosis	**ABRS**	**CRSsNP**	**CRSwNP**	**AFRS**
Pattern of symptoms	• Symptoms present for a minimum of 10 d up until a maximum of 28 d OR • Severe disease* (presence of purulence for 3-4 d with high fever) OR • Worsening disease (symptoms that initially regress but worsen within the first 10 d)	Symptoms present for ≥12 wk	Symptoms present for ≥12 wk	Symptoms present for ≥12 wk
Symptoms for diagnosis	Requires: • Anterior and/or posterior mucopurulent drainage PLUS • Nasal obstruction OR • Facial pain/pressure/fullness	Requires ≥2 of the following symptoms: • Anterior and/or posterior mucopurulent drainage • Nasal obstruction • Facial pain/pressure/fullness	Requires ≥2 of the following symptoms: • Anterior and/or posterior mucopurulent drainage • Nasal obstruction • Decreased sense of smell	Requires ≥1 of the following symptoms: • Anterior and/or posterior drainage • Nasal obstruction • Decreased sense of smell • Facial pain/pressure/fullness
Objective documentation	Requires either: • Nasal airway examination for mucopurulent drainage: (1) beyond vestibule by either anterior rhinoscopy or endoscopy OR (2) posterior pharyngeal drainage, OR • Radiographic evidence of acute rhinosinusitis	Requires both: • Endoscopy to exclude the presence of polyps in middle meatus and document presence of inflammation, such as discolored mucus or edema of middle meatus or ethmoid area AND • Evidence of rhinosinusitis on imaging by CT	Requires both: • Endoscopy to confirm presence of bilateral polyps in middle meatus AND • Imaging by CT with confirmation of bilateral mucosal disease	Requires: • Endoscopy to document presence of allergic mucin (pathology showing sparse fungal hyphae with degranulating eosinophils) and inflammation, such as edema of middle meatus or ethmoid area or NPs • Evidence of rhinosinusitis by CT or MRI • Evidence of fungal specific IgE (skin test or *in vitro* blood test) • No histologic evidence of fungal invasion when risk factors for invasive fungal disease are present. Other possible documentation (not required): • Fungal culture • Total serum IgE level • Imaging by more than one technique (CT or MRI) highly suggestive of AFRS

*Patients who have intracranial extension, have orbital cellulitis, or require hospitalization are considered to have severe disease and should be excluded from clinical trials of uncomplicated ABRS.

TABLE II. Master list of clinical trial guidance presented based on disease category

	I. ABRS	II. CRSsNP	III. CRSwNP	IV. AFRS
A. Antimicrobial	Fig 1 Example: Oral antibiotic	Figs 2-4 Example: Systemic or topical antimicrobial	Figs 3 and 4 Example: Long-term antimicrobial	Figs 3 and 4 Example: Topical or oral antifungal
B. Anti-inflammatory	Fig 1 Example: Intranasal corticosteroid	Figs 2-4 Example: Intranasal corticosteroid	Figs 2-4 Example: Oral corticosteroid	Figs 2-4 Example: Systemic immunomodulator
C. Symptom reliever or mediator blocker	Fig 1 Example: Intranasal decongestant	Figs 2-4 Example: Intranasal hypertonic saline	Figs 3 and 4 Example: Aspirin desensitization, LT modifier	Figs 3 and 4 Example: LT modifier

ABRS, and leukotriene (LT) modifiers are discussed under CRSwNP and AFRS. This minimized the duplication of protocols for different conditions and expanded the scope of trial designs that were covered. Sufficient detail is provided in each protocol, such that information not covered can be culled from the other protocols.

A key issue in designing trials for rhinosinusitis is the selection of outcome measures. There are multiple options (eg, symptoms, quality of life [QOL], imaging, and laboratory tests) discussed throughout the document. Although this document is the work of a collaborative task force, it should be noted there was no attempt to develop a standard or recommended outcome or level of improvement. In each section recommended outcome measures were taken directly from the discussion in each subgroup meeting. In general, subgroups concluded that symptom severity is an important outcome and proposed different variations on a similar theme (eg, reduction in symptom score of 50%, clinically significant reduction, and full resolution of symptoms). Therefore the issue of outcome quantification should be considered carefully in trial design.

TIPS FOR NAVIGATING THIS DOCUMENT EFFECTIVELY

Table III is the master list of clinical trial components and is essential for navigation of each of the 12 clinical trial guidance documents. Because of space limitations and because not all items were discussed, it is not possible to outline every number listed in Table III for each disease condition and intervention; therefore if a guidance number is missing (eg, IB7), refer to the guidance document for IA7 because much of the guidance is interchangeable, and in general, the ''A'' sections (eg, IA, IIA, IIIA, and IVA) hold the majority of information (REF PREV = reference prior guidance). It is important to note that at the end of this clinical trial components guide, there are 6 detailed appendices (Appendices 1-6[8-99]) filled with detailed recommendations on the following subjects: (1) health outcomes and QOL; (2) nasal endoscopy and CRS staging; (3) radiologic imaging; (4) microbiology; (5) laboratory measures; and (6) biostatistical methods.

CLINICAL TRIAL GUIDANCE IA. ACUTE PRESUMED BACTERIAL RHINOSINUSITIS: ANTIMICROBIAL TRIAL

IA1. Title

Treatment of ABRS with an oral antibiotic (see Table III).

IA2. DEFINITION/BACKGROUND/RATIONALE

IA2a. Definition. See Table I for consensus definition of ABRS.

IA2e. Rationale. The rationale was to demonstrate the clinical benefit associated with eradication of bacterial pathogens in ABRS.[100] Previous antimicrobial trials have demonstrated improvement in symptoms, reduction in objective evidence of infection, and improvement in radiographic findings associated with acute infection.[100] Several antimicrobials have been approved by the FDA for treatment of ABRS in adults or children. Reasons for studying a new drug for ABRS could be to demonstrate one of the following: superiority over existing therapies (clinical cure rate or improved time to clearance of symptoms), equivalence with existing therapies, or superiority with respect to safety profile. An additional rationale could be to demonstrate efficacy against a new or drug-resistant pathogen. A clinical equivalence trial is regarded as acceptable to the FDA but is generally discouraged.[4]

Because most antimicrobial trials have demonstrated clinical cure rates of 80% to 90% at 14 days,[101] the Rhinosinusitis Initiative committee believed that it was important to demonstrate superiority to existing therapies. Furthermore, the recent trend has been to develop antimicrobials with greater potency or bactericidal activity that will shorten the duration of active antimicrobial treatment. The hope is that this will lessen the chances for emergence of antimicrobial-resistant bacterial pathogens.[102-104]

IA3. STUDY OBJECTIVES

IA3a. Primary efficacy objective. The recommended primary outcome variable is time to symptom resolution or significant improvement based on total symptom score

TABLE III. Master list of clinical trial components

1. Title of trial	IA=ABRS: Antimicrobial treatment; IB=ABRS: Anti-inflammatory treatment; IC=ABRS: Symptomatic treatment; IIA=CRSsNP: Antimicrobial treatment; IIB=CRSsNP: Anti-inflammatory treatment; IIC=CRSsNP: Symptomatic treatment; IIIA=CRSwNP: Antimicrobial treatment; IIIB=CRSwNP: Anti-inflammatory treatment; IIIC=CRSwNP: Asymptomatic treatment; IVA=AFRS: Antimicrobial treatment; IVB=AFRS: Anti-inflammatory treatment; IVC=AFRS: Symptomatic treatment
2. Background/definitions/rationale	a. Introduction about the disease b. Chemistry of the agent, including pharmacology and PK c. Animal studies d. Prior clinical information in human subjects e. Rationale for the study f. Rationale for the dose
3. Study objectives	a. Primary efficacy objective (on which subjects, over what period of time, using what end point, using what scale, as reported by whom [subject, parent, specific objective test]; eg, time to symptom resolution, improvement in sinus CT score) b. Secondary efficacy objective (can include PK end points, instantaneous vs reflective scores, subjective or objective; eg, microbial cure) c. Safety objective (can be subjective or objective; eg, absence of AEs) d. Exploratory objective (eg, weight of secretions on day 3) There can be more than 1 primary and more than 1 secondary objective. Study should be powered to meet objectives for efficacy and/or safety.
4. Study design	a. Overview: (1) For what phase (1-4) of drug development is the study? (This guidance especially focuses on phase 3 and 4 studies). Is this a parallel, crossover, cohort study? Is this a single or multicenter study? (2) Should include screening period, run-in period, randomization period, run-out period, extension period, follow-up period (see study design figures). (3) Should include timing of each visit. (4) Should include procedures to be performed at each study visit. (5) Should include placebo control (single blind, double blind). b. Treatment (1) Treatment plan for study medication (formulation, dose, concentration of dose, frequency of administration, timing of dosing, relationship to meals, duration of treatment, delivery system, method of delivering dose, extent of exposure) (2) Treatment plan for control subjects (Is there a placebo control, what is the placebo, is there an active control, what is the active control?) (3) Criteria and treatment plan for clinical worsening and/or discontinuation visit. The study design should include methods to monitor subject's progress, document worsening, and provide rescue medications, if deemed appropriate, for disease exacerbations. (4) Allowed prior medications/treatments (prior medications, allowed asthma therapy, allowed rhinitis medication, allowed immunotherapy, allowed medications for other diseases) (5) Prohibited therapy (include for how long before screen period and if also during the study periods) (6) Concomitant medication (include related to disease [ie, rescue medication] and unrelated to disease [eg, for hypertension], dysmenorrhea). Allowed medications permitted for use during the study are best summarized in a convenient table that is provided to each subject. Use of concomitant medications should be monitored during the clinical trial. (7) Restrictions re: diet, exercise, alcohol, caffeine, tobacco smoking (8) Allowable contraception (drugs, doses, devices)
5. Study population	a. A consent form should be read, understood, and signed by each participant. b. Lower and upper ages, sex, ethnicity issues c. Sample size, number of sites, itemize countries d. Inclusion criteria (need to be defined by each protocol in context of study objectives) (1) Previous history requirement of symptoms and signs (2) Current symptom/sign defined requirement based on the disease state definition and any additional qualifiers (eg, severity categorization as mild, moderate, or severe disease and how these are defined, whether subject has previously had sinus surgery, whether subject is aspirin sensitive)

TABLE III. *Continued*

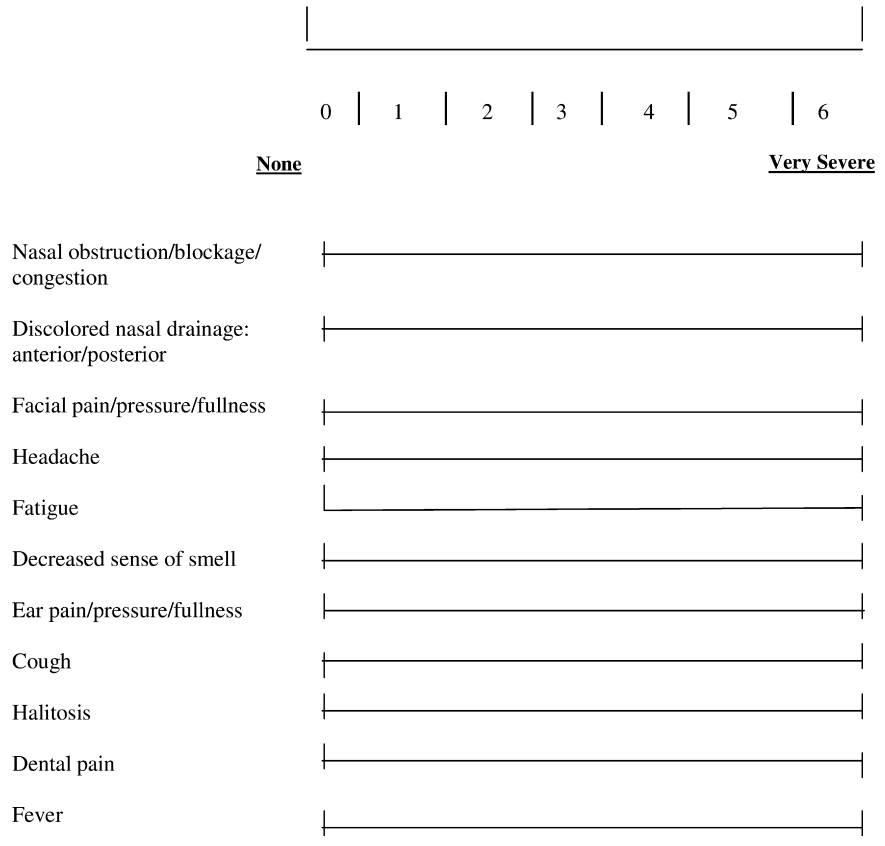
	(3) Good general health (4) Able to adhere to dosing and visit schedules (5) Acceptable screening skin/clinical laboratory/imaging tests (6) Medically accepted birth control issues (7) Subject/guardian willing/able to comprehend study/comply with study/record study data e. Exclusion criteria (need to be defined by each protocol in context of study objectives) (1) Birth control issues (not using birth control, pregnant, nursing) (2) Subjects who are not adequately symptomatic or whose symptoms are too severe (3) Subjects with local pathology or pathology that might compromise the ability to either administer the agent or assess the benefits/risks (eg, immotile cilia syndrome, atrophic rhinitis, concomitant seasonal allergic rhinitis, allergic or intolerant to study antibiotic) (4) Subjects with abnormal screening laboratory/imaging test results that compromise the ability to assess the benefits/risks (eg, abnormal ECG) (5) Affiliation with investigational site or participation too recently in a clinical trial (6) Subjects with known allergy or intolerance to the study medication f. Randomization criteria (need to be defined by each protocol in context of study objectives)
6. Efficacy assessments	a. Subjective (1) Symptom score (what symptoms, what scoring system, how many points in the visual analogue scale/categoric scale?; what constitutes mild, moderate, severe disease?; does the duration of symptoms indicate a specific category of rhinosinusitis, for example, viral/bacterial?; does the pattern of symptoms indicate a specific category of rhinosinusitis, for example, worsening symptoms implies bacterial?; how to differentiate between rhinitis and rhinosinusitis?) (2) Daytime symptoms (what symptoms, how often to score, how to score [0-3, 0-6, 0-100], reflective scores, instantaneous scores, how long is the interval to be considered in the ''instantaneous'' score?) (3) Nighttime symptoms (what symptoms, how to score?) (4) Global symptoms assessment by patient (is this an important/valuable outcome variable?) (5) Patient-assessed other upper, lower respiratory tract symptoms (what is included, how this is scored, how frequently assessed, how does this differ from individual symptoms/global score?) (6) Physician assessment of overall signs/symptoms (parameters used for scoring must be specified) (7) Therapeutic response (who generates this score, what does it mean, how is it scored?) (8) Onset of action (how is this defined-subjective/objective parameters, what intervals are used for scoring, is this relative to baseline, relative to placebo?) (9) Health outcomes-QOL questionnaire (which rhinosinusitis instrument, generic, specific, or both, is the questionnaire validated, does it measure what is needed for this category of rhinosinusitis and for this intervention, how often measured?) (10) Product characteristics questionnaire (11) Device characteristics questionnaire b. Objective (1) Physical examination (what elements to include in the physical examination, how often to examine, what is being assessed, how is it rated, what is required for entry into the study, what constitutes change?; what is the quality/color/consistency of the mucus?) (2) Endoscopy (when to be done, how is it done, what is being assessed, what is required for entry into the study, what constitutes change, how it is it scored/rated?) (3) Nasal patency measures (peak nasal inspiratory flow rate, peak nasal expiratory flow rate, acoustic rhinometry, rhinomanometry, what technique, how to score, when to do, is the technique validated, what is the evidence to support this validation, what are the advantages/limitations of the technique?) Should pulmonary function be measured? (4) Imaging (what technique, when to do, how to score, for which studies is this necessary?) (5) Skin testing and/or *in vitro* testing for specific IgE (what is being tested, how is it scored, what is the time of scoring, what constitutes a positive/negative result, what controls should be used?) (6) Pollen count (how often, how would this information be useful?) (7) Identifying organisms: viral, bacterial, fungal (what methods to use [how to obtain specimens, what stains should be used, how to quantify], what are the normal values, what is a significant change, what constitutes colonization vs infection?)

TABLE III. *Continued*

	(8) Laboratory measures (which hematology, chemistry, immunochemistry, pathology tests [eg, CBC, peripheral eosinophil count, sedimentation rate, glucose, mediators, cytokines, chemokines, nasal cytology, biopsy, exhaled NO] to do, when to test, how to test, what is significant?) (9) PK/pharmacodynamic outcomes (10) Tests of olfaction (qualitative tests, quantitative tests?) (11) Health economic assessments (a) Medical care (regular office visit, urgent office visit) (b) Hospital visit (emergency department, inpatient care) (c) Medications (d) Surgery (e) Indirect costs because of missed time from work/school (absenteeism) (f) Indirect costs because of decreased productivity at work/school (presenteeism)
7. Safety assessments	a. Subjective (1) Evaluating and recording AEs and serious AEs (how should this be scored, who should rate, how frequent, what type, how severe, what relationship to intervention, what action should be taken, over what period should they be assessed, should they be elicited or spontaneously reported, what follow-up is required?) (2) Treatment failures, discontinuations, exacerbation rates b. Objective (1) Vital signs, height, weight (how often?) (2) Routine general physical examinations (what is important to focus on for this rhinosinusitis category and for this intervention [eg, mucosal changes from intranasal corticosteroids]?) (3) Ear, nose, and throat examinations (is this different from the physical examination, is this about efficacy or safety or both?) Are special eye examinations needed (eg, with intranasal or oral corticosteroids ophthalmologic examinations for lens opacification/increased intraocular pressure)? (4) Routine laboratory investigations (what are the specific concerns for this class of rhinosinusitis medications, what to measure, when to measure, what is the normal range, what is acceptable outside the normal range, when should patient be discontinued?) (5) Special clinical laboratory parameters (eg, with intranasal or oral corticosteroids measures of hypothalamic-pituitary-adrenal axis, markers of bone metabolism and bone mineral density, hemoglobin A1C, tuberculin reactivity) (6) Pregnancy/serum, β-human chorionic gonadotropin (which women, what age?) (7) PK/pharmacodynamic outcomes (8) ECGs (should these be manually read at the site, what should exclude a subject, what aspects of the ECG should be evaluated, should the QTc be measured, what correction method should be used, when should the ECG be performed relative to dosing, how often should they be done?) (9) 24-h Holter ECG monitoring (is this necessary, for which class of drugs?)
8. Biostatistical methods	(What are the hypotheses, what comparisons are of interest, what sample size, what statistics to do/how to analyze the data, how to deal with multiple primary and secondary objectives, what is statistically significant, what are clinically relevant end points, what change is clinically relevant, what to do with missing data, how should discontinuation be handled, how to evaluate compliance?). Objectives should be stated with appropriate statistical considerations for power and sample size.

(TSS). Use of this variable requires that the patients record symptoms daily or more often (eg, every 12 hours) during active treatment. The TSS should capture critical rhinosinusitis symptoms (Table IV). A validated symptom-scoring instrument is preferred, if available. The baseline TSS should be documented, and the treatment arms should be balanced with respect to this variable at baseline. Improvement could be defined by the protocol as achievement of at least a certain percentage reduction in TSS or achievement of a minimally important (clinically relevant) difference in TSS. The primary outcome measure could be defined by the protocol as the time point at which at least a certain percentage reduction in TSS or a minimally important (clinically relevant) difference in TSS is achieved. Other potential primary outcome variables include the following: clinical cure rate (generally defined as resolution of signs and symptoms and at least no worsening in radiographic appearance) at a predefined ''test-of-cure'' time point (eg, 3, 7, 14, or 21 days) or radiographic resolution (percentage achieving radiographic resolution at a

TABLE IV. Symptom scoring



Key to Symptom Scoring
0 = None – to an occasional limited episode
1
2 = Mild – Steady symptoms but easily tolerable
3
4 = Moderately bothersome – Symptoms hard to tolerate, might interfere with activities of daily living, sleep, or both
5
6 = Very severe – Symptoms are so bad that person cannot function virtually all the time

Note: Global assessment of rhinosinusitis symptom severity uses the same 7-point Likert scale and definitions.

predefined time point). Traditionally, the primary efficacy variable has been the clinical cure rate, and the new drug has been compared with a standard therapy, such as amoxicillin-clavulanic acid, for 14 days. Criteria for radiographic resolution are not well established (see Appendix 3).

IA3b. Secondary efficacy objectives. These might include the following: rate of relapse after treatment (expressed as percentage relapse at a predefined time point); bacterial eradication (test of cure) requiring demonstration of the presence of a bacterial pathogen before initiation of treatment and absence of the pathogen after treatment has been completed (collection of microbial data at baseline and end point is strongly recommended as a coprimary or secondary outcome measure); end-of-treatment evaluation; end-of-study evaluation; and change in QOL measure.

The shorter the duration of treatment, the more important it becomes to include an assessment of relapses on treatment versus placebo. For treatment studies of 5 days or less, this is essential. Likewise, the incidence of dropouts for worsening of symptoms should be compared in the active treatment and placebo arms. Dropouts for worsening of symptoms can be considered to have shown no improvement if this is prespecified. Other outcome measures might include per-patient clinical cure or physician-assessed clinical cure (ie, whether the patient or the physician believes that the infection has resolved, even though there might be residual symptoms). These are recorded as ''yes'' or ''no'' at the test-of-cure time point, which could be at the end of treatment or end of study.

IA3c. Safety objectives. These can be subjective or objective and might include adverse events (AEs).

IA3d. Exploratory objectives. These might include the following: bacterial eradication in cases shown to

involve drug-resistant organisms; improvement in biomarker for ABRS, and weight of secretions on designated day or days of treatment.

IA4. STUDY DESIGN

IA4a. Overview. The recommended trial design, as shown in Fig 1, is that of a short-term therapeutic intervention for acute disease.

IA4a1. The typical ABRS antimicrobial trial is a parallel-arm, randomized, placebo-controlled clinical trial. (The same is true for all other trial designs presented.)

IA4a2. The trial should include a screening period, run-in period, randomization period, run-out period, and follow-up period. As outlined in the Rhinosinusitis definitions document,[1] study subjects should have acute symptoms for a minimum of 7 to 10 days. It is acknowledged that patients frequently seek antibiotic treatment much earlier, and some past studies have enrolled patients after only 2 to 5 days of acute symptoms. One strategy is to enroll subjects early and have a run-in period. Only subjects with symptoms persisting through the run-in period are then randomized to drug treatment.

IA4a4. Study visit procedures. Obtaining twice-daily TSSs might be helpful for the first 4 to 5 days, with once-daily TSS scoring at approximately the same time of the day each day thereafter. This scoring should be performed before dosing. A bacterial culture is recommended at entry, although a positive culture need not be an absolute requirement for randomization. The culture subsets can then be analyzed in the context of treatment response.

IA4a5. Study groups. Study groups should include an arm for active treatment, a comparator drug, and a placebo. An additional treatment arm can be added to study 2 doses of active treatment, but this has implications for sample size determination. Because patients might experience worsening of disease whether on the active or placebo treatment arms, the study design should include specific methods to monitor progress, document worsening, and specify times for intervention of worsening and measures to do so.

IA4b1. Treatment plan for study medication (see Table III). The study medication should be described in detail, including the formulation, dose, concentration of dose, frequency of administration, timing of doses, relationship to meals, duration of treatment, delivery system, method of delivering dose, and extent of exposure. The recommended duration of prescription therapy should be based on drug pharmacokinetic (PK) considerations but will generally be between 5 and 14 days.

IA4b2. Treatment plan for control subjects. The placebo should also be described in detail, with consideration given to matching the formulation, color, taste, and smell as closely as possible to that of the active treatment. The active treatment control (comparator drug) should be similarly described. The administration of the treatment or treatments should be given in a described blinded fashion.

IA4b3. Criteria and treatment plan for clinical worsening, discontinuation visit, or both. As a safety net, subjects who experience a worsening of symptoms during the trial should be deemed clinical failures and promptly scheduled for a treatment failure visit. Detailed criteria defining a treatment failure should be included, such as worsening of TSS by 50%, temperature of greater than 102.5°F, and symptoms or signs of extrasinus complications. Depending on the protocol, treatment failures might also be considered as serious AEs.

IA4b4. Prior medications/treatment. Topical antimicrobial agents should be excluded for 30 days before the study, and oral antibiotics should not be used for a minimum of 15 days before study admission. Baseline medications, such as oral antihistamines, intranasal antihistamines, guaifenesin, LT modifiers, and antitussives, which the patient has been taking for at least 2 month, need not be stopped.

IA4b5. Prohibited therapy. Oral or intranasal decongestants should be excluded at the start of the study. Medications excluded during the study should be listed and reviewed with each subject at each study visit.

IA4b6. Concomitant medications. Concomitant medications allowed during the clinical trial should be monitored, and the use of potential agents, such as saline nasal spray and acetaminophen, should be documented. Medications permitted for use during the study are best summarized in a convenient table that should be provided to each subject at the start of active treatment.

IA4b7. Restrictions regarding diet, exercise, alcohol, caffeine, and tobacco smoking. These should be discussed as deemed appropriate.

IA4b8. Contraception issues (see Table III). This should be discussed with each subject.

IA5. STUDY POPULATION

The size of the subject population and allowable demographics should be specified in the protocol, and each subject should understand the purposes of the trial and their risks and benefits for participating. A consent form should be read and signed by each participant.

IA5d. Inclusion criteria

IA5d2. See Table I. Symptoms of ABRS include anterior/posterior discolored drainage, facial pain/pressure/fullness, and nasal obstruction/congestion (see Table IV). Subjects must meet eligibility criteria for minimal level of symptoms (defined on the basis of TSS).

IA5d5. Subjects must have radiographic evidence of an air-fluid level or opacification in 1 or more of the following sinuses: right or left maxillary or ethmoid sinuses or, depending on the study, frontal or sphenoid sinuses.

IA5e. Exclusion criteria

IA5e1. Subjects who are pregnant, nursing or unwilling to adhere to contraception requirements are generally excluded from this type of trial.

IA5e2. Subjects who are not adequately symptomatic or subjects whose symptoms are too severe should be excluded (eg, temperature >102.5°F or signs of systemic

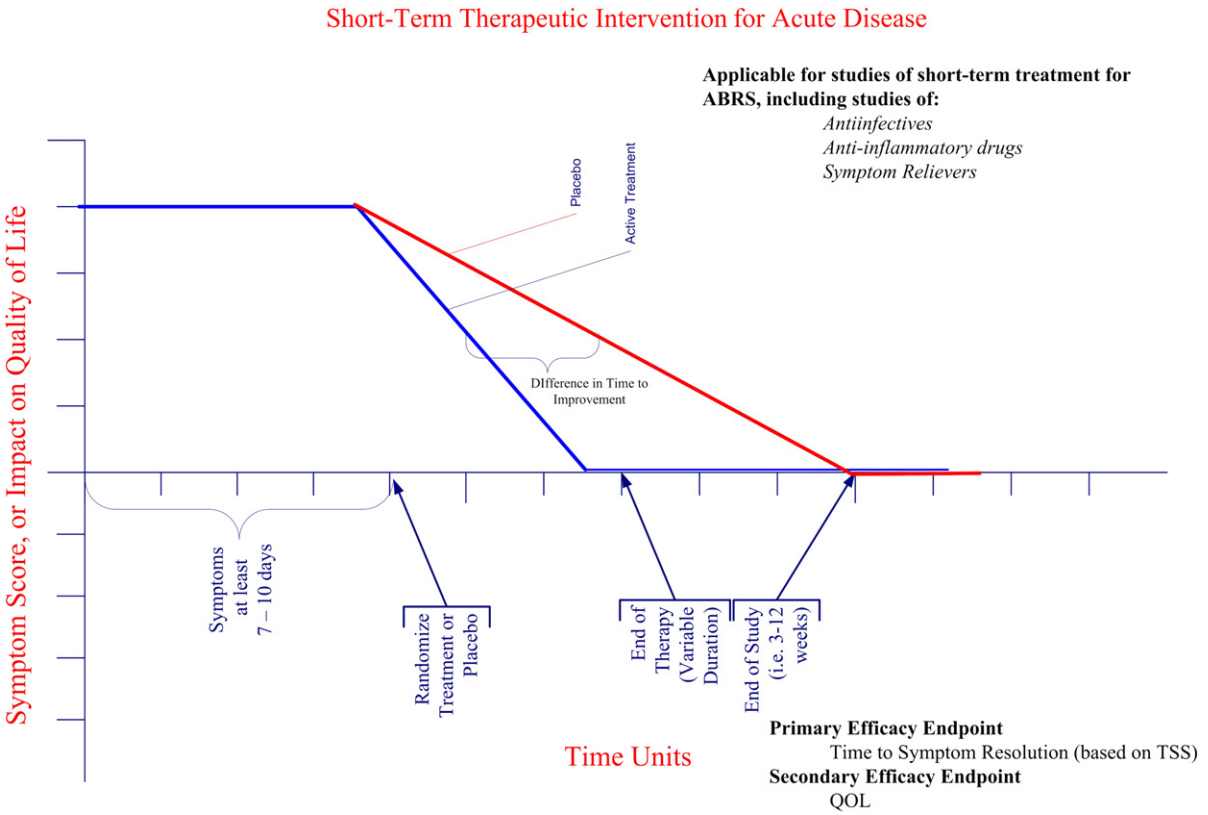


FIG 1. The rationale for the illustrated study design is to determine the effect of a treatment intervention on the clinical course of ABRS, as measured by time to resolution of symptoms. Patient symptoms, QOL, or both are measured on the y-axis, and time is measured on the x-axis. The therapeutic intervention that is to be tested can be compared with either placebo or a comparator intervention. Success of the treatment intervention is based on a statistically significant difference in rate of symptom (or QOL) resolution between the comparator interventions. This graph is intended to convey the conceptual aspects of the type of study design. Therefore variables, such as timing of intervention, duration of treatment, type of intervention, and end of study, can be modified based on the specifics of the proposed study.

toxicity; extrasinus manifestations, such as orbital cellulitis; dental or facial abscess; cavernous vein thrombosis; or altered mental status).

IA5e3. The following conditions should be excluded. Subjects with local pathology that would compromise the ability to either administer the agent or assess the benefits/risks (eg, mucocele, cyst, antrochoanal polyp, facial trauma, or birth defect); subjects with expansile mass with bony erosion on sinus radiography; subjects with CRS, nasal polyposis, or both; subjects with a known history of hypogammaglobulinemia, immotile cilia syndrome, atrophic rhinitis, rhinitis medicamentosa, cystic fibrosis, or allergy to the study medication or a related drug; or subjects with a serious underlying medical condition (eg, malignancy other than squamous or basal cell carcinoma of the skin or severe renal or hepatic disease).

IA5e4. Subjects with abnormal screening laboratory/imaging test results that compromise the ability to assess the benefits/risks should be excluded.

IA5e5. Use of another experimental medication within the past 1 month.

IA5f. Allergic rhinitis (AR) is an important comorbidity. It might be worthwhile to consider limiting enrollment of patients to a certain percentage in each season of the year or not to enroll during a pollen season.

IA6. EFFICACY ASSESSMENTS

IA6a. Subjective. See Tables I, III, and IV.

IA6a1-4. Symptom scores. The scoring of symptoms should capture critical rhinosinusitis symptoms. A validated instrument is preferred. There are 11 individual symptoms on the scoring assessment for ABRS, the first 3 of which are the most critical symptoms in ABRS and might be collectively considered as the main symptoms score. The sum of all 11 can be considered as the total symptoms score (TSS). These 11 symptoms are nasal obstruction/blockage/congestion; anterior/posterior nasal discolored drainage (not clear), facial pain/pressure/fullness, headache, fatigue/tiredness, decreased sense of smell, ear pain/pain/pressure/fullness, cough, halitosis/bad breath, dental pain/toothache, and fever/chills.

Patients should score these symptoms on a scoring sheet using a 7-point Likert scale (Table IV). The scale begins with 0, defined as none, and ranges to 6, defined as very severe. The subject should fill out individual symptoms scores in the evening and the morning, identifying how he or she is at that time (instantaneous score) and also how he or she has been over the last approximately 12 hours (reflective score). These represent the daytime and nighttime scores. In addition, he or she should also provide a global symptom assessment of rhinosinusitis symptoms at baseline and at other designated points of the study (see Table IV).

IA6a7. Therapeutic response. Another subjective measure is an end-of-study evaluation of therapeutic response completed within a reasonable time after treatment is terminated (eg, 2 weeks). The Global Rating of Response to Treatment is graded on a 13-point scale as follows: −6, severely worse; −4, moderately worse; −2, mildly worse; 0, no change; 2, mild relief; 4, moderate relief; and 6, complete relief.

IA6a8. Assessment of the onset of efficacy is optional, depending on the goals of the study.

IA6a9. Health outcomes. QOL can be measured by using such tools as Short Form 36 or 12, Work Productivity Activity Index–Sinus, and the Rhinosinusitis Quality of Life Survey, although these have not been validated in acute rhinosinusitis (see Appendix 1).[105-109]

IA6a5, 10, and 11. Other subjective measures that might be useful include patient assessment of other than nasal/sinus symptoms, physician assessment of overall signs/symptoms, a product characteristics questionnaire, and/or a device characteristics questionnaire.

IA6b. Objective. See Table III.

IA6b1. Physical examination. See Table V.

IA6b2. Endoscopy. Endoscopy is not required but might be useful to document the presence of purulence in the middle meatus, to obtain endoscopic bacterial cultures, and to assess the mucosal response to antibiotic treatment (see Appendix 2).[1]

IA6b3. Nasal patency measures. Nasal spirometry can measure air flow and demonstrate patient variability abnormalities and changes with time, interventions, or both.[1] Nasal patency studies are useful.[1,110-112]

IA6b4. Imaging. As discussed in Appendix 3, conventional radiography is adequate for the diagnosis of clinically uncomplicated ABRS. Coronal sinus computed tomographic (CT) imaging, however, provides greater precision for assessing the presence of air-fluid levels, mucosal thickening, or partial or complete opacification of 1 or more of the anterior ethmoid sinuses or maxillary sinuses (right/left).

IA6b5-11. Other studies might or might not be done, depending on the study objectives and expected effects of treatment. These include skin testing, PK and pharmacodynamic outcomes, and health economic assessments (see Table III).

IA6b7. Identifying organisms. A microbiologic end point is recommended. Baseline evaluation in cases of acute maxillary sinusitis should include sinus aspiration in children and adults. Cultures of the middle meatus might be acceptable in adults but not in children. Bacteria in a density of 10^3 to 10^4 colony-forming units per milliliter or a positive Gram stain are considered evidence of infection. Lower colony counts or cultures associated with a negative Gram stain might represent colonization. At the end of treatment, either a repeat sinus aspiration or middle meatal culture (in adults) should be obtained, clinical outcome should be assessed, or both. An objective measure of efficacy is bacteriologic eradication based on culture. See Appendix 4 for further details.

IA6b8. Laboratory measures. It might be desirable to know the predominant cellular inflammatory type and determine any change with an intervention. See Appendix 5 for additional considerations.

IA7. SAFETY ASSESSMENTS

IA7a. Subjective. See Table III.

IA7a1. Adverse events. See Table VI.

IA7b. Objective. Specific evaluations should be conducted based on knowledge and history of disease/drug/intervention.

IA7b2. Routine general physical examination. This should be conducted to document, for example, skin rash and mouth thrush.

IA7b4. Routine laboratory investigations. CBC, blood chemistries, and urinalysis, for example, should be performed.

IA7b5. Special clinical laboratory parameters. Such as pulmonary function testing.

IA7b8. ECG. This should be performed based on knowledge of disease/drug.

IA8. BIOSTATISTICAL METHODS

Objectives should be predefined, with appropriate statistical considerations of power and sample size. Critical rhinosinusitis symptoms should be captured with the TSS, and significant improvement could be defined by the protocol of achievement of at least a certain percentage reduction in TSS or achievement of a minimally important difference in TSS. A clinically meaningful level of improvement in TSS can be estimated by ''anchoring'' the improvement in TSS to the Global Assessment of Symptom Severity measurement (ie, determining what level of change in TSS is associated with ''slight improvement'' on the Global Assessment of Symptom Severity measurement or Global Rating of Response to Treatment, see Table IV and IA6a7). The primary outcome variable is time to improvement in TSS. This requires a log-rank test, which compares the treatment and control survival curves. For the power and sample calculation, typically 1.5 to 2.0 is used as the effect size for the hazard ratio or relative risk. This relative risk represents the ratio of the probabilities of improvement for the treatment versus control groups. The incidence of dropouts because of worsening of symptoms should be compared in the active treatment and placebo

TABLE V. Physical examination

NOSE			
Septum			
–	Normal	☐No	☐Yes
–	Deviated	☐No	☐Yes ☐ to right ☐to left
–	Bleeding, crusting, ulceration, perforated	☐No	☐Yes
Mucosa			
–	Color	☐Normal	☐Pale ☐Erythematous
–	Swelling/edema	LEFT ☐Mild ☐Moderate ☐Severe	RIGHT ☐Mild (inferior turbinate prominent but visualization of middle turbinate) ☐Moderate (middle turbinate obscured but inferior turbinate not touching septum) ☐Severe (inferior turbinate touching septum)
Secretions			
–	Color	☐Clear ☐Discolored, white, yellow, green	
–	Consistency	☐Thin ☐Thick ☐Crusty	
–	Blood	☐None ☐Streaked ☐Marked	
–	Amount	☐None/minimal ☐Moderate ☐Profuse	
Obstruction		☐Absent ☐Present	☐ right ☐ left
Polyps		☐Absent ☐Present	
EYES			
Extraoccular movements		☐Normal	☐Impaired
Swelling		☐No	☐Yes
–	Proptosis	☐No	☐Yes
EARS			
–	Middle ear effusion	☐No	☐Yes
–	Erythema	☐No	☐Yes
FACE			
–	Swelling	☐No	☐Yes
–	Tenderness	☐No	☐Yes
MOUTH/THROAT			
–	Posterior discharge	☐No	☐Yes
–	Dental abnormalities	☐No	☐Yes
–	Halitosis	☐No	☐Yes
NECK			
–	Cervical adenopathy	☐No	☐Yes
CHEST			
–	Wheezing	☐No	☐Yes
–	Rales	☐No	☐Yes
–	Rhonchi	☐No	☐Yes
OTHER ABNORMALITY/COMMENTS:			

TABLE VI. AEs

AE definition: Any physical or clinical change or diseases experienced by the subject at any time after signing the informed consent form, irrespective of whether considered related to the use of the study drug	● Onset of new illness ● Exacerbation of preexisting conditions
AEs are documented by recording the following	● Change in medication regimen ● Change in frequency ● Change in duration ● Change in severity
AE reporting only when there is a real change in the event	● If not considered an AE, place a clear note in the source document that this is a preexisting condition (medical history) and that the condition remained stable during the course of the study. ● To elicit AEs, the investigator/designee must ask open-ended questions and/or conduct an examination for evidence of AEs. ● The presence or absence of AEs should not be solicited from subjects. ● Examples of subjective AEs: sleepiness, dry mouth, dizziness. Should be scored on the Likert scale or visual analogue scale.
AE information	● Event description ● Onset date, end date ● Severity ● Relationship to study drug ● Action/outcome ● Concomitant medication
AE severity grading	● Mild: Awareness of sign, symptom, or event but easily tolerated ● Moderate: Discomfort enough to cause interference with usual activity and might warrant intervention ● Severe: incapacitation with inability to do usual activities or significantly affects clinical status and warrants intervention ● Life-threatening: Immediate risk of death
AE relationship to study drug	● Unlikely: No temporal association, the cause of the event has been identified, or the drug cannot be implicated. ● Possible: Temporal association, but other causes are likely to be the cause; however, involvement of the drug cannot be excluded. ● Probable: Temporal association; other causes are possible but unlikely.

arms. Alternatively, dropouts because of worsening of symptoms can be incorporated into the overall rate of no improvement or failure rate.

CLINICAL TRIAL GUIDANCE IB. ABRS: ANTI-INFLAMMATORY TRIAL

IB1. Title

Treatment of ABRS with an intranasal corticosteroid: only design modifications from the treatment of ABRS with an oral antibiotic are included (see Table III).

IB2. DEFINITION/BACKGROUND/RATIONALE

IB2e. Rationale for the study. ABRS is an infection characterized by an inflammatory response to the presence of bacteria. The rationale for the study is to determine whether treatment with an anti-inflammatory agent, either alone or as an adjuvant, results in more rapid resolution of symptoms and improves objective measures of disease compared with placebo. Recent studies suggest that anti-inflammatory therapy (specifically intranasal corticosteroids) might reduce the severity and possibly shorten the duration of symptoms when used either in combination with antibiotics or as a monotherapy for ABRS.[113-118]

IB3. STUDY OBJECTIVES

The recommended primary efficacy variable is time to resolution (improvement) of symptoms. A significant change in the extent of sinus mucosal disease measured by using one of the established CT scoring systems can also be considered.

Preferred secondary outcome measures include end-of-treatment or end-of-study evaluation of change in TSS and change in QOL. An essential secondary measure should be the rate of relapse (ie, symptom recurrence) after treatment. It is important to ascertain whether the active

treatment is associated with a higher rate of treatment failure or other complications from bacterial infection.

IB4. STUDY DESIGN

IB4a. Overview. The recommended trial design is analogous to that for an ABRS–antimicrobial trial, namely a short-term therapeutic intervention for acute disease (see Fig 1).

IB4a4. Study visit procedures. The baseline TSS should be documented, and the comparison groups should be balanced. Obtaining twice-daily TSSs is recommended for the first 4 to 5 days, with consideration of once-daily TSS scoring at the same time each day thereafter. It is recommended that a bacterial culture be obtained at entry, although a positive culture need not be an absolute requirement for randomization. The culture information can then be analyzed in the context of treatment failures.

IB4a5. Study groups. The typical ABRS anti-inflammatory trial will be a randomized, parallel-group study of an anti-inflammatory treatment, possibly an antimicrobial drug and a placebo. An additional treatment arm can be added to study 2 doses of active treatment, but this has implications for sample size determination.

IB4b. Treatment

IB4b1. The optimum duration of an ABRS anti-inflammatory clinical trial is believed to be a minimum of 2 weeks, with a posttherapy observation of 3 weeks. A posttherapy period of at least 2 weeks is required.

IB4b3. Clinical worsening. It is important to include a safety net for patients who experience sufficient deterioration during the study. Such subjects are deemed treatment failures and must be dropped out of the study. It is further recommended that a standardized protocol be included for antibiotic treatment for treatment failures. In addition, these subjects should be monitored on antibiotic treatment to assess their outcomes.

IB4b4. Prior medications. There should be no use of intranasal corticosteroids, systemic corticosteroids, or immunosuppressive drugs for 30 days before the study.

IB4b5. Prohibited therapy. Systemic antibiotic treatment should be discontinued at least 15 days before study entry. Chronic use of an intranasal decongestant should be disallowed during the study period. Furthermore, topical antimicrobial agents should also be stopped for 30 days before the study.

IB4b6. Concomitant medication. Limits should be specified for any medications because of the potential for drug interactions. There should be limits on use of intranasal saline rinses.

IB5. Study population. Ref Prev IA

IB6. Efficacy assessments. Ref Prev IA

IB7. Safety assessments. Ref Prev IA. See Table III.

IB8. Biostatistical methods

An improvement could be defined by the protocol as achievement of at least a certain percentage reduction in TSS or achievement of a minimally important difference (considered clinically significant) in TSS. A clinically meaningful level of improvement in TSS can be estimated by anchoring the improvement in TSS to the Global Assessment of Symptom Severity measurement, as discussed under IA8.

CLINICAL TRIAL GUIDANCE IC. ABRS: SYMPTOM-RELIEVER TRIAL

IC1. Title

Treatment of ABRS with an intranasal decongestant (only design modifications from the treatment of ABRS with an oral antibiotic are included, see Table III).

IC2. DEFINITION/BACKGROUND/RATIONALE

IC2e. Rationale for study of intranasal decongestants. ABRS is an infectious disease process associated with nasal and sinus inflammation, including edema. The rationale for the study is to determine whether treatment with an intranasal decongestant results in relief of the symptoms of infection and of congestion and possibly improves objective measures of nasal patency.[119-123] Another rationale is to determine whether symptom-relieving medications reduce the health effect of illness, lessen the severity of illness, and/or shorten its duration.

IC2f. Rationale for the dose. The frequency and duration of dosing (eg, 3-7 days or longer for the intranasal decongestant) needs to be specified.

IC3. STUDY OBJECTIVES

IC3a. Primary efficacy objective. Time to symptom improvement is the recommended outcome variable. Another primary efficacy variable could be radiographic cure or significant change in the extent of sinus mucosal disease seen on CT.

IC3b. Additional secondary outcomes. Improvement in TSS, improvement in individual symptoms (eg, congestion), per-protocol clinical cure, improvement in validated QOL measure, time to resolution of symptoms, physician-assessed clinical cure, and bacteriologic eradication.

IC4. STUDY DESIGN

IC4a. Overview. As in the ABRS antibiotic trial (see Fig 1).

IC4a3. Consider additional end point evaluation within 3 days of cessation of treatment for evaluation of rebound because of a topical decongestant.

IC4b. Treatment

IC4b2. The placebo is the vehicle control.

IC4b4. There should be no prior use of the symptom-relieving medication for 30 days before the study.

IC4b5. Prohibited therapy. No antimicrobial treatment for at least 15 days before the study, no oral corticosteroids for 30 days before the study, and no intranasal corticosteroids for at least 15 days before the study.

IC4b6. Concomitant medication. There should be no concomitant use of other symptom-relieving medication during the study. Limits should be specified for use of topical decongestants, oral decongestants, antihistamines, LT modifiers, antitussives, and antiseptics, and limits should be specified for use of intranasal saline rinses. Certain medications for other medical conditions might confound evaluation of drug effect.

IC5. Study population. See Trial IA.

IC6. Efficacy assessments. See Trial IA.

IC6b7. See Trial IA, see Tables I, III, and IV. Bacterial culture is strongly suggested but need not necessarily be positive for study entry.

IC7. Safety assessments. Ref Prev IA

IC8. Biostatistical methods. Ref Prev IA

CLINICAL TRIAL GUIDANCE IIA. CRSsNP: ANTIMICROBIAL TRIAL

IIA1. Title

Treatment of CRSsNP with an oral antibiotic (see Table III).

IIA2. DEFINITION/BACKGROUND/ RATIONALE

IIA2a. Definition. See Table I for consensus definition of CRSsNP.

IIA2a. Background. The separation of CRS into distinct subcategories of CRSsNP and CRSwNP was proposed by members of the Rhinosinusitis Initiative based primarily on pathologic studies showing distinct histologic patterns of disease in these 2 groups.[1] CRSsNP refers to persistent chronic disease rather than acute exacerbations in the setting of chronic disease. Persistent bacteria-induced inflammation is one of several potential mechanisms of disease in CRSsNP.[1] It can occur because of a persistent infection in the narrow clefts of the ethmoid sinuses,[102,104] an infection caused by the presence of antibiotic-resistant organisms or a persistent nidus of infection involving bone (osteitis) or because of the development of a bacterial biofilm.[105] (Analogously, a rationale could be given for the study of an antifungal drug for CRSsNP, as discussed in section IIIA2a.)

IIA2e. Rationale for this study. Persistent bacterial infection or bacterial biofilm might account for the presence of sinus mucosal inflammatory changes and symptoms of CRSsNP. The rationale for this study is to determine whether antibiotic treatment reduces the symptom burden and health effect of illness, lessens the severity of the disease, shortens the duration of illness, and/or reduces sinus mucosal inflammation.[124-126]

IIA3. STUDY OBJECTIVES

IIA3a. Primary efficacy objective. The recommended primary efficacy objective should be improvement in the TSS area under the curve over approximately 4 months of treatment with daily scoring and monthly evaluation intervals. Another primary outcome variable could be change in the sinus CT score from the beginning of the study to the end of treatment.

IIA3b. Secondary efficacy objectives. An essential secondary outcome variable is the TSS at the end of the study (recommended to be 6 months) or at end point if many subjects drop out. The shorter-term improvement effects can also be monitored as a secondary outcome measure. Other subjective potential secondary outcome measures include validated QOL measures or change in individual symptoms. Objective clinical and laboratory outcome measures include change in rhinoscopic grading from before to after therapy and microbial eradication or reduction in inflammatory markers (eg, IL-8 or neutrophil elastase) at the end of the study.

IIA4. STUDY DESIGN

IIA4a. Overview. The trial design, as shown in Fig 2, is that of a short-term (maximum of 4 months) therapeutic intervention for chronic disease. (A protocol for long-term treatment with an antimicrobial is outlined under CRSwNP. Either protocol could be applied to either condition.)

IIA4a2. In the short-term therapeutic intervention trial a treatment period of 3 to 4 months was arbitrarily selected. One argument for extending treatment beyond a few weeks is that the underlying condition might transiently improve on antibiotic treatment, only to relapse within weeks or months.[127] For this reason, active treatment for 3 to 4 months is recommended, with a minimum of 2 additional months for monitoring after treatment. This recommendation is subject to modification based on drug PK/pharmacodynamic considerations. The entire study duration should be at least 6 months.

IIA4a4. Study visit procedures. Daily TSSs should be recorded throughout the study. A baseline and end-of-treatment sinus CT scan should be performed. A bacterial culture is recommended at entry, and it might be advisable to require a positive culture for randomization.

IIA4a5. Study groups. Ref Prev IA

IIA4b. Treatment

IIA4b1. Treatment plan for study medication. A run-in period is desirable to enroll only those subjects who remain symptomatic at the end of this period. However, because patients with CRSsNP are required to have symptoms for at least 12 weeks before enrollment in the study despite previous treatment, there was no consensus as to whether a run-in period should be required. Furthermore, a run-in period might make it difficult to enroll subjects who are highly symptomatic.

IIA4b2. Placebo control. See Fig 2 for details.

IIA4b3. Criteria and treatment plan for clinical worsening, discontinuation visit, or both. The longer the duration of active treatment, the greater the likelihood that the patient will experience an intercurrent upper

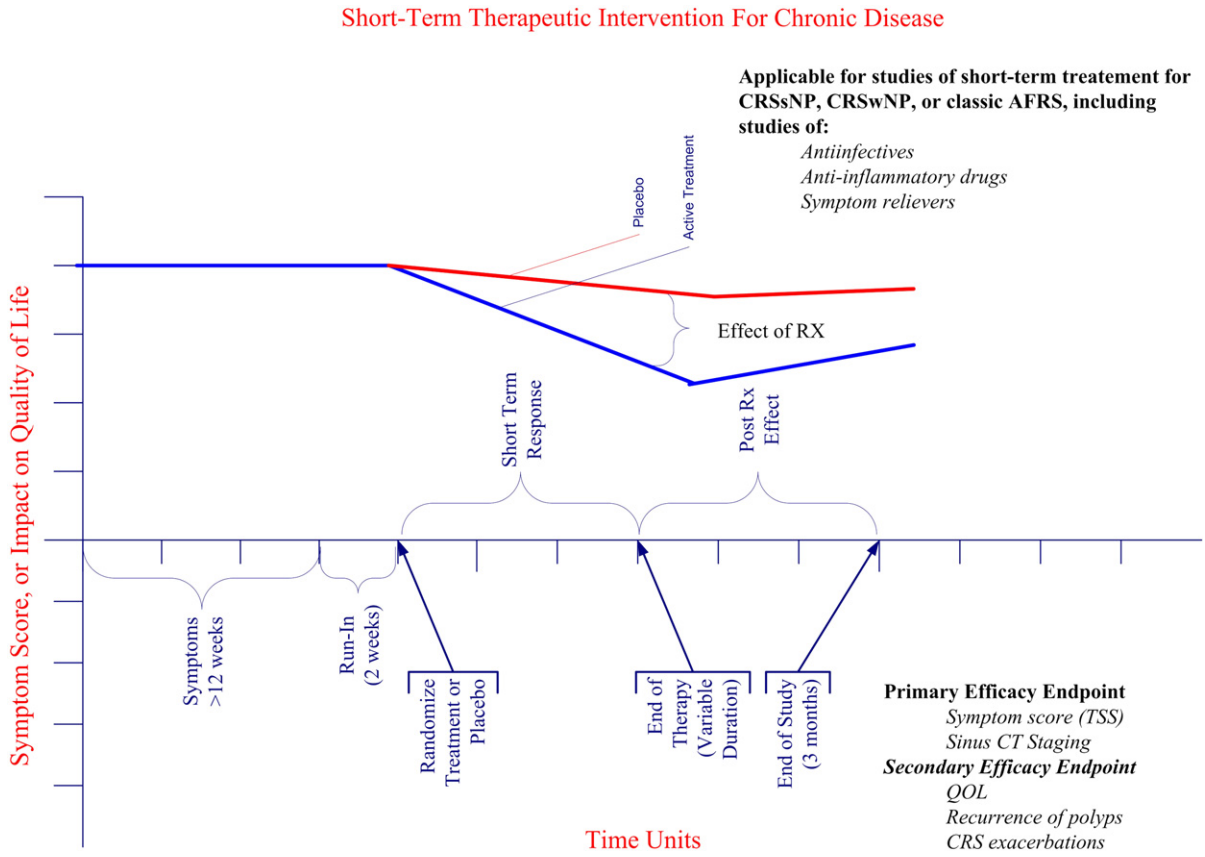


FIG 2. The rationale for the illustrated study design is to determine the effect of a short-term treatment intervention on the clinical course of CRS (CRSwNP, CRSsNP, or AFRS), as measured by improvement and duration of symptoms experienced by the patient. Patient symptoms, QOL, or both are measured on the y-axis, and time is measured on the x-axis. The therapeutic intervention that is to be tested can be compared with either placebo or a comparator intervention. Success of the treatment intervention is based on a statistically significant difference in rate of symptom (or QOL) resolution or change from baseline symptom scores. This graph is intended to convey the conceptual aspects of the type of study design (as in Fig 1).

respiratory tract infection (URI) or an acute exacerbation of CRS (AE-CRS). With respect to a typical viral URI, the committee believed that these could be managed during the clinical trial, provided that guidelines were provided for the use of symptomatic treatment for a period of 5 to 7 days.

There is no consensus definition for an AE-CRS, and in the setting of an antimicrobial trial for CRSsNP, it would be difficult to determine whether an acute exacerbation of symptoms represented a new bacterial infection or a worsening of chronic infection. Therefore the committee did not advocate defining an AE-CRS in the context of this trial. However, a possible definition would be that an AE-CRS usually follows an acute viral URI and is defined as an increase in symptoms for a minimum of 10 days up to a maximum of 28 days. The symptoms are those that define ABRS. Alternatively, an AE-CRS might be defined as a severe exacerbation defined as the presence of purulence for 3 to 4 days with fever or worsening of disease or defined as URI symptoms that initially regress but worsen within the first 10 days. Objective criteria include anterior, posterior, or both purulent drainage plus nasal obstruction or facial pain/pressure/fullness. This requires either nasal airway examination for purulent drainage (1) beyond the vestibule by means of either anterior rhinoscopy or endoscopy, (2) posterior pharyngeal drainage, or (3) radiographic evidence of acute rhinosinusitis. These definitions would be applicable to AE-CRS in CRSsNP, CRSwNP, and AFRS.

IIA4b5. Prohibited therapy. The protocol should specify the duration of prohibition of specific therapies, both before the screening period and during the study periods. Specific limitations on the use of drugs or biologic agents that would interfere with the study (eg, anti-TNF antibodies) or nebulized antimicrobials must also be clarified in the protocol.

IIA4b6. Concomitant medications. These can be allowed if used for a minimum of 2 weeks before study entry, including but not limited to oral decongestants, antihistamines, LT modifiers, and guaifenesin, based on the assumption there is a bacterial basis of the disease. Intranasal corticosteroids are an important consideration because roughly 50% of patients with CRS have coexisting AR, and they are commonly used in patients with CRS. Withdrawal of intranasal corticosteroids might

complicate the analysis of treatment effect. Continuation of intranasal corticosteroids might be problematic if the treatment arms are imbalanced with respect to their use. Introduction of intranasal corticosteroids might have a significant therapeutic effect that complicates the analysis of treatment effect. Therefore the protocol should indicate whether intranasal corticosteroids are prohibited, allowed, or introduced (ie, required) during the trial. If prohibited, adequate time for elimination of drug effect should be incorporated into the study design. If optional, their use should be recorded and held constant during the trial, and the treatment effect should be analyzed before and after stratifying the data analysis with respect to their use. If introduced, the effect of intranasal corticosteroids on treatment effect should be estimated and incorporated into the study design.

IIA5. STUDY POPULATION

IIA5d. Inclusion criteria. The following inclusion criteria are recommended (see Table I).

IIA5d1. Symptoms compatible with CRS for at least 12 weeks before enrollment despite treatment with medications (this might include antibiotics, intranasal saline irrigations, decongestants, and intranasal or oral corticosteroids); the use of intranasal saline irrigation during the run-in period is optional.

IIA5d2. A minimal level of symptoms defined on the basis of the primary outcome variable should be required at entry to ensure that patients are adequately symptomatic at entry into the study.

IIA5d5. Radiographic evidence of CRSsNP as outlined in Table I and Appendix 3. Minimal criteria for a positive sinus CT scan should be specified (see Table VII). Comorbid AR is present in 50% or more of patients with CRSsNP and might affect the patient's CRS symptoms. Therefore the presence or absence of AR should be determined at enrollment and considered in the randomization process. Alternatively, the data analysis can incorporate an analysis based on stratification by AR status. Patients with prior sinus operations should also be identified because this is an important covariable and might affect treatment response. Under some circumstances, it might be appropriate to exclude or restrict enrollment of these subjects. Alternatively, the data analysis can incorporate a stratification based on prior surgery. However, powering for subgroups would be difficult.

IIA5e. Exclusion criteria

IIA5e2. Subjects who are not adequately symptomatic or whose symptoms are too severe, as defined in the protocol, should be excluded.

IIA5e3. The following conditions should be excluded: subjects who have nasal polyps (NPs; endoscopy is required to exclude their presence, see Appendix 2), subjects with local pathology that would compromise the ability to either administer the agent or assess the benefits/risks (eg, mucocele, cyst, antrochoanal polyp, facial trauma, radiation injury, or birth defect), subjects with serious underlying medical condition (eg, severe renal or hepatic disease), subjects with a history of viral URI in the past 4 weeks, and subjects with a history of malignancy other than skin squamous or basal cell carcinoma, hypogammaglobulinemia, ciliary dysmotility, atrophic rhinitis, rhinitis medicamentosa, cystic fibrosis or allergy to the study medication or a related drug.

IIA5e4. Subjects with laboratory or imaging test results inconsistent with diagnosis, including expansile mass or bony erosion on the sinus radiograph or CT scan should be excluded.

IIA5f. Randomization criteria. Randomization will require subjects who are symptomatic at the end of the run-in period.

IIA6. Efficacy assessments. Ref Prev. See Tables I, III, and IV

IIA6a1. See Table IV for symptoms and scoring. A validated symptom-scoring instrument is strongly preferred, although one does not currently exist. The symptoms should be scored reflectively once daily. Symptoms most important to the patient can be determined on the basis of the highest scores of the original 11 symptoms.

IIA6a4. Obtain global symptoms assessments at baseline and at other designated points of the study (see Table IV).

IIA6a9. Obtain weekly QOL measurements (see Appendix 1).

IIA6b. Objective

IIA6b1. Perform physical examinations for monitoring patient during trial (see Table V).

IIA6b2. Endoscopy. See Appendix 2.

IIA6b4. Imaging. A sinus CT scan is recommended with a standardized method of imaging and with similar cuts repeated at specific time intervals to allow for consistent CT scoring (see Appendix 3).

IIA6b5 through IIA6b11f. Others studies might or might not be done, depending on the study objectives and expected effects of treatment.

IIA6b7. Microbiologic cultures. Cultures should be performed at entry, but it is not mandatory that their results are positive. However, for a trial of prolonged antibiotic treatment, a positive culture is strongly recommended or a justification as to why this is not required should be presented (eg, for immunomodulation). Baseline evaluation should include sinus aspiration in children and adults. Cultures of the middle meatus might be acceptable in adults but not in children. Bacteria in a density of 10^3 to 10^4 colony-forming units per milliliter or a positive Gram stain are considered evidence of infection. Lower colony counts or cultures associated with a negative Gram stain might represent colonization. At the end of treatment, either a repeat sinus aspiration or middle meatal culture (in adults) should be obtained, clinical outcome should be assessed, or both. An objective measure of efficacy is bacteriologic eradication based on culture. Because this is an antimicrobial trial, investigators might want to include patients with at least maxillary sinus disease. See Appendix 4 for further details.

TABLE VII. CT scoring system for paranasal sinuses

Based on degree of obstruction				
Nasal passages (1 unit)	0-3 points			
Ostiomeatal complex (2 units)	0-3 points			
Based on amount of mucosal thickening	0 points	1 point	2 points	3 points
Frontal (2 units)	0-1 mm	2-5 mm	6-9 mm	≥10 mm
Maxillary (2 units)	0-1 mm	2-5 mm	6-9 mm	≥10 mm
Sphenoid (1 unit)	0-1 mm	2-5 mm	6-9 mm	≥10 mm
Ethmoid (2 units)	0 mm	1 mm	2-3 mm	≥4 mm

Reproduced with permission from Hoover et al.[40] The nasal passages and ostiomeatal complexes are scored on a scale of 0 to 3 points based on the degree of soft tissue obstruction. The paranasal sinuses were also scored on a scale of 0 to 3 points but, based on the amount of mucosal thickening present, as measured in millimeters. The nasal passages and sphenoid sinuses are each considered as being single units, whereas the ostiomeatal complexes and other sinuses are considered as having 2 units, a right and a left. The ethmoid sinuses, because of their smaller size, are given higher scores for lesser amounts of mucosal thickening. A CT scan has a maximum of 30 points possible.

IIA8. BIOSTATISTICAL METHODS

Test of cure should be performed at the end of the treatment or shortly thereafter.

Rationale comments: Clinical success regarding cure and improvement are determined by resolution or significant improvement of signs and symptoms at the test-of-cure visit and at least no worsening in radiographic appearance. Success incorporates categories of cure (resolution of all signs and symptoms) and improvement (all signs and symptoms at least improved or partially resolved compared to baseline). Clinical failure is defined as the persistence of 1 or more signs and symptoms of rhinosinusitis or patients who have received additional (or new) antibiotics. Categoric data analysis, such as a χ^2 test or Fisher exact test, can be performed. Prior surgery and the presence of AR are important covariables in the analysis of treatment response. Under some circumstances, it might be appropriate to exclude or restrict enrollment to subjects who either have or have not undergone prior operations. Alternatively, the data analysis can incorporate a stratification based on prior surgery and the presence of AR.

CLINICAL TRIAL GUIDANCE IIB. CRSsNP: ANTI-INFLAMMATORY TRIAL

IIB1. Title

Treatment of CRSsNP with an intranasal corticosteroid (only design modifications from the treatment of CRSsNP with an oral antibiotic are included, see Table III).

IIB2. DEFINITION/BACKGROUND/ RATIONALE

IIB2e. CRSsNP is associated with inflammation of the nasal and sinus mucosa. The rationale for the study is to determine whether treatment with an anti-inflammatory agent improves the symptoms of CRSsNP, reduces the health care effect of the disease, and/or results in improvement in objective measures of sinus mucosal inflammation.[128,129]

IIB3. STUDY OBJECTIVES

IIB3a. The recommended primary efficacy objective is improvement in the TSS area under the curve during 4 months of treatment with daily scoring and at monthly evaluation intervals. Another primary outcome variable should be change in the sinus CT score at the beginning of the study to the end of treatment.

IIB3c. Safety measures could include the number of AE-CRSs during the study period (see IIA4b3).

IIB4. STUDY DESIGN

IIB4a. Overview. The recommended trial design could be either a short-term therapeutic intervention for chronic disease (see Fig 2), a long-term therapeutic intervention for chronic disease (see Fig 3), or prevention of disease recurrence for chronic disease (see Fig 4). For purposes of illustration, the long-term therapeutic intervention is presented here.

IIB4a4. Study visit procedures are the same as in IIA4a4, except that a bacterial culture is not recommended at entry.

IIB4b1. Treatment plan for study medication. A run-in period is desirable during which subjects should be started on a single-blind intranasal placebo spray.

IIB4b5. Prohibited therapy. There should be no antibiotic treatment for 2 to 4 weeks before the study run-in period, as dictated by PK considerations. In addition, there should be no oral corticosteroids, topical decongestants, or intranasal antimicrobials for 4 weeks before the study. There should be no oral decongestants, antihistamines, topical antihistamines, topical anticholinergics, LT modifiers, or antitussives for 2 weeks before the study and no surgery for 6 months before the study. There should be no use of intranasal corticosteroids for 2 to 4 weeks before the study run-in period.

IIB4b6. Concomitant medications can be allowed, provided they are not allowed to change during the trial. Specific limits should be placed on the use of intranasal saline rinses.

IIB5. Study population. Ref Prev IIA.

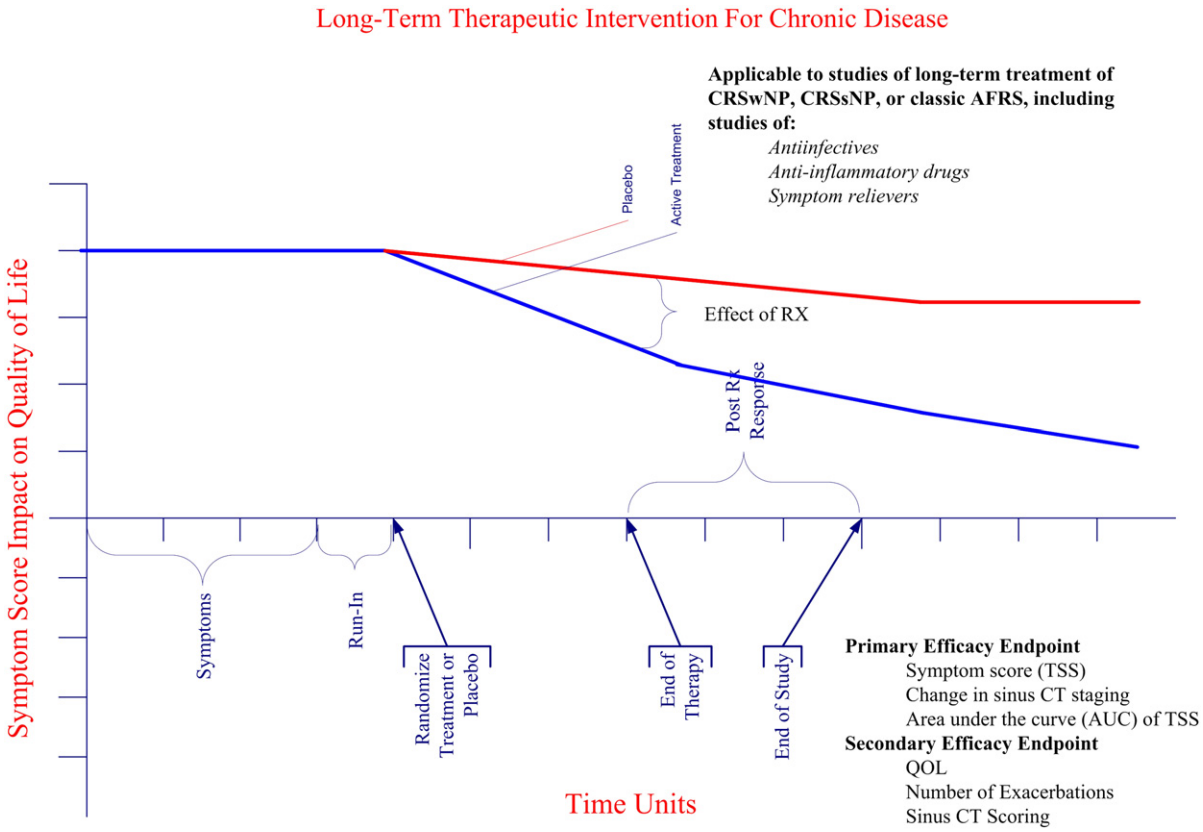


FIG 3. The rationale for the illustrated study design is to determine the effect of a long-term treatment intervention on the clinical course of CRS (CRSwNP, CRSsNP, or AFRS), as measured by improvement and duration of symptoms experienced by the patient. Patient symptoms, QOL, or both are measured on the y-axis, and time is measured on the x-axis. The therapeutic intervention that is to be tested can be compared with either placebo or a comparator intervention. Success of the treatment intervention is based on a statistically significant difference in rate of symptom (or QOL) resolution or change from baseline symptom scores. This graph is intended to convey the conceptual aspects of the type of study design (as in Fig 1).

IIB6. Efficacy assessments. Ref Prev IIA. See Tables I, III, and IV.

IIB7. Safety assessments. Ref Prev IIA. See Table III.

IIB8. Biostatistical methods. Ref Prev IIA.

CLINICAL TRIAL GUIDANCE IIC CRSsNP: SYMPTOM-RELIEVER TRIAL

IIC1. Title

Treatment of CRSsNP with intranasal hypertonic saline (only design modifications from the treatment of CRSsNP with an oral antibiotic are included, See Table III).

IIC2. DEFINITION/BACKGROUND/ RATIONALE

IIC2e. CRSsNP is a chronic inflammatory condition. Patients experience bothersome symptoms and reduced QOL and productivity. The rationale for the study is to determine whether symptom-relieving medications reduce the symptom burden and health effect of illness, lessen the severity of illness, and/or shorten its duration. One example of a possible symptom reliever is intranasal hypertonic saline.[130-133]

IIC3. STUDY OBJECTIVES

IIC3a. The primary efficacy objective could be improvement in TSS or improvement in validated QOL measure. An improvement in sinus CT score is also an appropriate primary efficacy variable, although it should not be the sole primary end point in a symptomatic disease.

IIC3b. Secondary efficacy objectives might include an improvement in rhinoscopic grading measure or a reduction in an inflammatory marker.

IIC4. STUDY DESIGN

IIC4a. Overview. For purposes of illustration, the trial design selected is that of a long-term therapeutic intervention for chronic disease (see Fig 3).

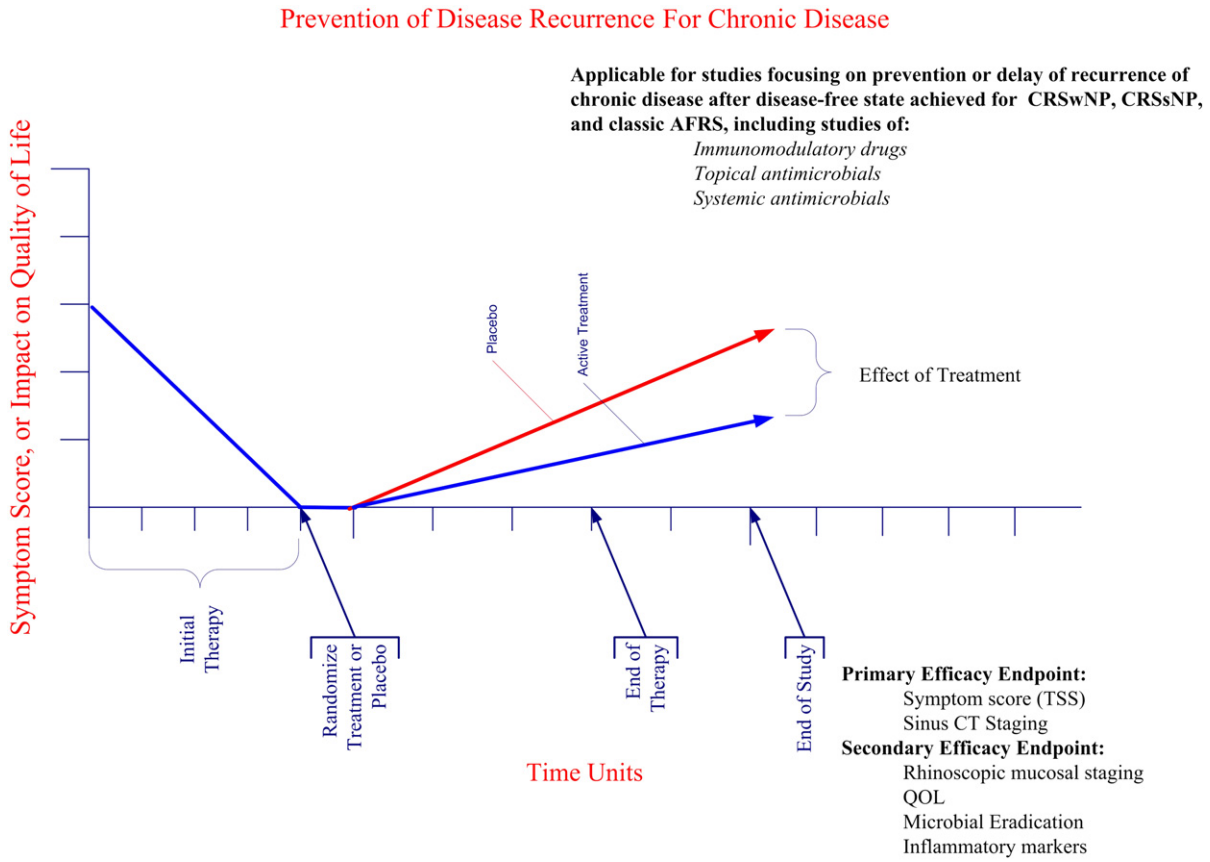


FIG 4. The rationale for the illustrated study design is to determine the ability of a treatment intervention to attenuate recurrence of CRS (CRSwNP, CRSsNP, or AFRS) after a preceding intervention (eg, surgery and long-term systemic corticosteroids). Patient symptoms, QOL, or both are measured on the y-axis, and time is measured on the x-axis. The therapeutic intervention that is to be tested can be compared with either placebo or a comparator intervention. Success of the treatment intervention is based on a statistically significant difference in the rate of symptom recurrence, as measured by worsening symptom score or diminishing QOL. This graph is intended to convey the conceptual aspects of the type of study design (as in Fig 1).

IIC4a2. For the long-term therapeutic intervention design, a run-in period, end-of-treatment time point, and end-of-therapy time point need to be defined (see Fig 3). These time points also need to be defined with respect to when efficacy assessments are made. The run-in period is recommended to ensure that subjects randomized to treatment are sufficiently symptomatic. Double blinding is maintained throughout the 1 year of the study.

IIC4a4. Study visit procedures are the same as in IIA4a4, except that a bacterial culture is not strongly recommended at entry.

IIC4b5. Prohibited therapy. The protocol should specify no antibiotic treatment for 15 days before the study, no oral corticosteroids for 30 days before the study, and no topical corticosteroids for at least 15 days before the study.

IIC4b6. Concomitant medications. Limits should be specified for use of topical decongestants, oral decongestants, antihistamines, LT modifiers, antitussives, and antiseptics. Limits should also be specified for intranasal saline rinses. Certain medications for other conditions might confound evaluation of drug effect. (See IIA4b6 regarding use of intranasal corticosteroids.)

IIC5. Study population. Ref Prev IIA.

IIC6. Efficacy assessments. See Tables I, III, and IV. Ref Prev IIA.

IIC6b. Objective. Ref Prev IIA. Obtaining a bacterial culture is not strongly recommended.

CLINICAL TRIAL GUIDANCE IIIA. CRSwNP: ANTIMICROBIAL TRIAL

IIIA1. Title

Treatment of CRSwNP with a chronic therapy (eg, long-term antimicrobial; see Table III).

IIIA2. DEFINITION/BACKGROUND/ RATIONALE

IIIA2a. Definition. See Table I.

IIIA2a. Background. Microbial mechanisms of disease pathogenesis in CRSwNP are important considerations.[1] Immune hyperresponsiveness to colonizing bacteria in sinus mucus, particularly *Staphylococcus aureus*, has been proposed as a factor in NP pathogenesis. Prior studies have focused on immune responses to locally produced staphylococcal exotoxins, which function as superantigens. Local production of staphylococcal superantigen-specific IgE production has been found in NP tissue but not in sinus tissue from patients with CRSsNP.[134] Immune hyperresponsiveness to colonizing fungi has also been proposed as a mechanism of disease broadly applicable to CRS, including CRSsNP, CRSwNP, and AFRS. Systemic T-cell hypersensitivity to certain fungal species and local eosinophil-mediated attack of fungal hyphae in mucus has been demonstrated in patients with CRS,[135] and this provides a rationale for antifungal trials in CRSwNP.[136] To date, there are no clinical trials fully testing whether bacterial or fungal eradication will improve NPs or prevent their recurrence. There have been long-term trials of macrolide antibiotics, but these studies were not focused on *S aureus*.[128,129] Conflicting reports exist regarding the efficacy of topical antifungal agents for nasal polyposis.[136-138]

IIIA2e. Rationale for this study. The rationale is to determine whether long-term antimicrobial treatment aimed at reducing or eradicating mucosal colonization with either bacteria or fungi will reduce the symptom burden and health effect of illness, reduce NP size and sinus inflammatory changes, or slow the rate of recurrence of NPs after surgical removal.[136-138]

IIIA3. STUDY OBJECTIVES

IIIA3a. Primary efficacy objective. The recommended end point should be change in TSS, as determined by means of measurement of area under the curve. Analysis of scores at monthly intervals is also recommended, as is change in the extent of sinus mucosal disease, as measured by sinus CT scoring or photoendoscopy. CT scanning will be preferred in certain studies, but cost and radiation exposure are valid concerns that might be circumvented with careful use of nasal photoendoscopy.

IIIA3b. Secondary efficacy objective. End points should include improvements in QOL measures, frequency of AE-CRS, and frequency of polyp recurrence. Again, polyp recurrence can be measured with either CT or photoendoscopy (see Figs 5-7).

IIIA4. STUDY DESIGN

IIIA4a. Overview. For purposes of illustration, the trial design selected is that of a long-term therapeutic intervention for chronic disease (see Fig 3).

IIIA4a2. Determination of the presence or absence of microbial infection or colonization should be incorporated in the study design to justify a long-term antimicrobial intervention. For an antibiotic trial, sinus cultures have traditionally been used for this purpose, but the site of culture and the technique to be used have not been established in CRS. This is particularly an issue in CRS because the primary site of disease might be in the ethmoid, frontal, or sphenoid sinuses. One strategy would be to require that cultures be performed at the time of sinus surgery and then require a positive culture as an entry criterion. Other possible markers of the presence of bacteria could be considered in lieu of culture, but these cannot be advocated in the absence of culture (which should be considered the gold standard for the presence of bacteria). Examples include the presence of bacterial specific IgE antibodies directed against staphylococcal enterotoxins (also known as exotoxins), molecular probe studies for the detection of bacterial specific ribosomal RNA, histologic evidence of osteitis in bone fragments removed at the time of sinus surgery or scanning electron microscopic studies, or other investigations that are able to demonstrate the presence of specific glycocalyx components of bacterial biofilm. It might be difficult to obtain bacterial cultures at the end of the trial because this might necessitate a surgical procedure. Before initiating such a trial, a prestudy meeting with officers from a regulatory agency is highly advisable to review some of these controversial and difficult areas.

Similar issues pertain to the quantification of fungal bioburden in an antifungal trial. At a minimum, it is recommended that the study design include some attempt to speciate and quantify the fungal bioburden before and after treatment (See Appendix 4).

IIIA4a4. Study visit procedures. Daily TSSs should be recorded throughout the study. A baseline and end-of-treatment sinus CT scan or photoendoscopy should be performed. A bacterial culture or alternative indirect measure of the presence of bacteria is recommended at entry (see above and Appendix 4), and it is advisable to require a positive test result for randomization.

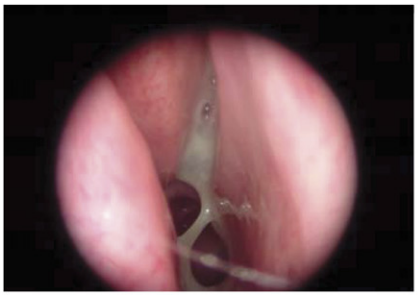
IIIA4a5. Ref Prev IA

IIIA4b2. Placebo controlled

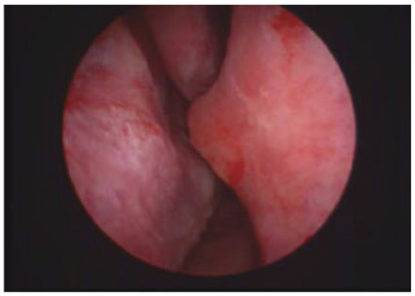
IIIA4b4. Allowed prior medications/treatment. Specific criteria for use of medications before the study must be included. It is recommended that no antibiotic treatment be allowed for 2 to 4 weeks before the study run-in period or as determined by PK considerations; no oral corticosteroids, topical decongestants, or topical antimicrobials should be allowed for 4 weeks before the study.

IIIA4b5. Prohibited therapy. This includes chronic use of an intranasal decongestant. In addition, the patient can have no oral decongestants, antihistamines, topical antihistamines, topical anticholinergics, LT modifiers, or antitussives for 4 weeks before the study.

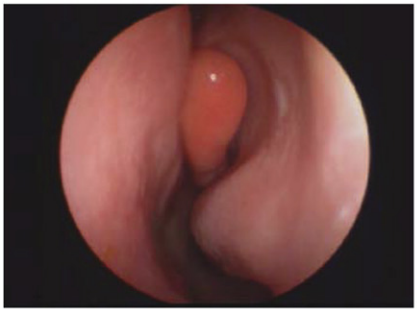
IIIA4b6. Concomitant therapy. Limits should be placed on the use of intranasal steroids (INSs) during the study, and INSs should neither be started nor stopped during the study. The use of INSs should be monitored throughout the study. Topical antimicrobials (other than the study drug) should be disallowed during the trial. (See IIA4b6 regarding use of intranasal corticosteroids.)



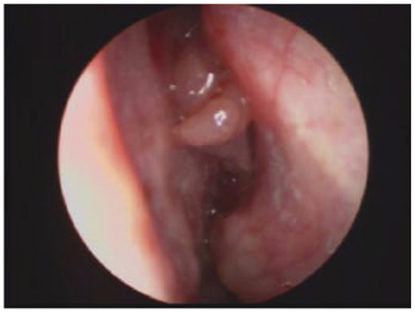
Example of nasal endoscopic diagnosis of acute rhinosinusitis



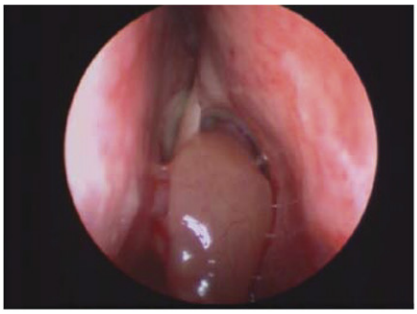
Example of nasal endoscopic diagnosis deviation of nasal septum



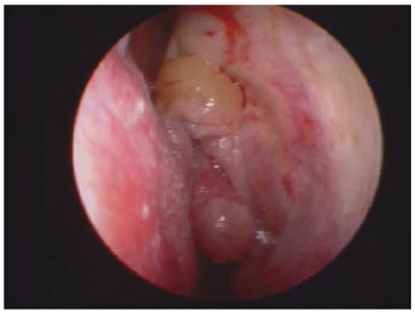
Stage 0 Endoscopy: No polyps visualized and open middle meatus



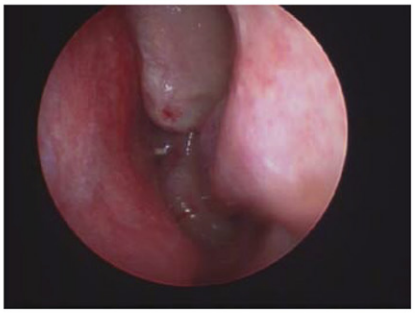
Stage 1 Endoscopy: Small polyps noted in middle meatus



Stage 2 Endoscopy: Middle meatus completely filled with polypoid disease



Stage 3 Endoscopy: Polyps extending out of middle meatus but above the inferior turbinate



Stage 4 Endoscopy: Massive nasal polyposis completely filling the entire nasal cavity and spheno-ethmoid regions.

FIG 5. Examples of endoscopic images.

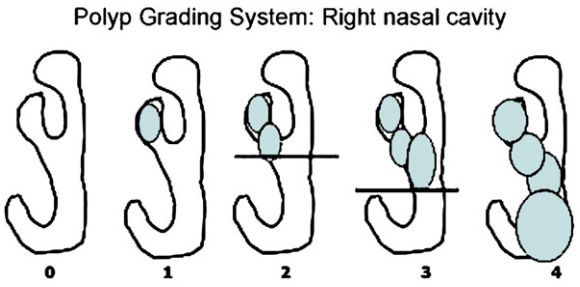


FIG 6. Polyp grading system: 0, no visible NPs; 1, small amount of polypoid disease confined within the middle meatus; 2, multiple polyps occupying the middle meatus; 3, polyps extending beyond the middle meatus, within the sphenoethmoid recess but not totally obstructing, or both; 4, polyps completely obstructing the nasal cavity.

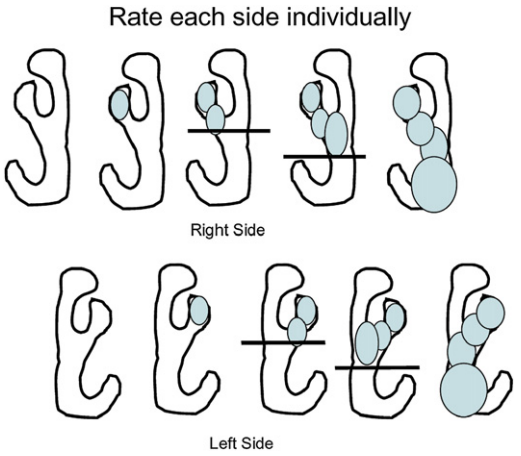


FIG 7. Polyp side rating.

IIIA5. STUDY POPULATION

IIIA5d. Inclusion criteria. Ref Prev IIA. See Table I. (Endoscopy is required to confirm the presence of NPs.)

IIIA5d2. Ref Prev IIA.

IIIA5d5. Acceptable screening skin/clinical laboratory tests and radiographic evidence of CRSwNP are as outlined in Table I and Appendix 3. See IIA5d5 regarding comorbid AR and prior sinus operations.

IIIA5e. Exclusion criteria

IIIA5e3. No polyps identified and otherwise same as CRSsNP. Subjects with local pathology that would compromise the ability to either administer the agent or assess the benefits/risks.

IIIA5e4. Ref Prev IIA.

IIIA6. EFFICACY ASSESSMENTS

IIIA6a. Subjective. See section IA6a. See Tables I, III, and IV.

IIIA6b. Objective. See section IA6b.

IIIA6b2. Polyps should be graded by means of endoscopy (see Appendix 2). Size should be determined through anterior rhinoscopy with a standardized scale with measures. Nasal endoscopy should be used to measure the size and location of polyps on the right and left.

IIIA6b4. A baseline and end-of-treatment CT scan should be performed and serve as a primary outcome measure. Volumetric CT scoring is highly desirable, but such a technique is not yet in general use.

IIIA6b7. See IIIA4a2 and Appendix 4.

IIIA6b8. Ref Prev IA. See Appendix 5. Markers for eosinophilic inflammation could include complete blood count, total eosinophils in the peripheral count, IL-5, IL-13, eosinophil cationic protein, and major basic protein in the tissue homogenate or secretions (see Table VIII). Studies suggest the value of blood eosinophilia because a marginal increase can represent a pathologic process related to polyps. Therefore a peripheral eosinophil count is recommended to point to an eosinophilic condition. Changes of tissue eicosanoid metabolism occur in CRSsNP and CRSwNP, and these changes appear to be related to the severity of eosinophilic inflammation. These include increases in LTC_4 synthase, 5-lipoxygenase mRNA, LTC_4, LTD_4, and LTE_4 values.[139] Therefore these markers should also be considered. Neutrophils and their markers, such as myeloperoxidase, are increased in the tissue of patients with CRSsNP and CRSwNP without differences between these groups.

IIIA6b10. Tests of olfaction could provide a valuable objective measure of disease.

IIIA7. Safety assessments. Ref Prev IA.

IIIA8. Biostatistical methods. Ref Prev IA.

The patient must experience a sustained effect from the intervention for at least 3 months for therapy to be considered effective. The magnitude of anti-inflammatory change was not discussed by the committee.

CLINICAL TRIAL GUIDANCE IIIB. CRSwNP: ANTI-INFLAMMATORY TRIAL

IIIB1. Title

Treatment of CRSwNP with an oral corticosteroid (only design modifications from the treatment of CRSwNP with an oral antibiotic are included, see Table III).

IIIB2. DEFINITION/BACKGROUND/ RATIONALE

IIIB2a. Background. Short-term treatment with oral corticosteroids has been a mainstay of treatment to reduce NP size and prevent their regrowth over weeks to months.[139] This treatment might also delay the need for sinus surgery; however, there are no controlled clinical trials using systemic corticosteroids alone without concomitant intranasal corticosteroids. The clinical trials involving systemic corticosteroids have been reviewed, and the clinical evidence supporting their use was graded at level III.[140] Likewise, there are no studies for depot injection of corticosteroids or local injection into NPs or the inferior turbinate.

IIIB2e. Rationale for the study. The rationale for treatment of CRSwNP with systemic corticosteroids is

TABLE VIII. List of possible direct and indirect biomarkers of disease activity rhinosinusitis clinical trials*

	ABRS	CRSsNP	CRSwNP	AFRS
Blood	Leukocytes, CRP	Unknown	Eosinophils, ECP	Eosinophils, ECP
Mucosal biopsy specimen or mucus	MPO, IL-1, IL-6, TNF-α, soluble ICAM-1, IL-8, neutrophil elastase	MPO, IL-1, IL-8, TGF-β, soluble IL-2R, neutrophil elastase, ECP, MBP, IL-5, IL-13, CysLTs, eotaxin, RANTES	ECP, MBP, IL-5, IL-13, CysLTs, eotaxin, RANTES, staphylococcal-specific IgE	ECP, MBP, IL-5, IL-13, CysLTs, eotaxin, RANTES, staphylococcal-specific IgE
Exhaled/tissue levels	eNO, iNOS	eNO, iNOS	eNO, iNOS	eNO, iNOS

CRP, C-reactive protein; *ECP*, eosinophil cationic protein; *MPO*, myeloperoxidase; *ICAM-1*, intercellular adhesion molecule 1; *IL-2R*, IL-2 receptor; *MBP*, major basic protein; *CysLTs*, cysteinyl LTs; *eNO*, exhaled nitric oxide.
*Markers listed are based on currently available literature. This table serves as an initial guidance and is intended to be neither all inclusive nor restrictive.

to attenuate the inflammation responsible for the clinical expression of CRSwNP, thereby reducing NP size and the associated sinus mucosal hyperplasia/edema to improve symptoms and QOL and possibly prevent the need for sinus surgery. Similarly, the rationale for corticosteroid treatment after surgical removal of NPs would be to reduce sinus mucosal hyperplasia and any residual NP tissue, improve symptoms and QOL, possibly accelerate the recovery time from sinus surgery, reduce postoperative complications, or prevent recurrence of NP disease.

IIIB3. STUDY OBJECTIVES

IIIB3b. Secondary efficacy objective. Measures should include improvement in rhinoscopic grading with photoendoscopy and reduction in study-specific inflammatory markers.

IIIB3c. Safety objective. This should include measuring the number of AE-CRSs during the study (see IIA4b3).

IIIB4. STUDY DESIGN

IIIB4a. Overview. The recommended trial design is either a short-term therapeutic intervention for chronic disease (see Fig 2), a long-term therapeutic intervention for chronic disease (see Fig 3), or prevention of disease recurrence for chronic disease (see Fig 4). For purposes of illustration, the latter is described.

IIIB4a2. In the prevention of disease recurrence trial design, subjects might be enrolled after they have received treatment to stabilize their disease. The classic example would be subjects with NPs who have recently undergone surgery to remove the polyps. Alternatively, subjects with active disease could first receive open-label treatment to stabilize their disease. In this case the nature of the open-label treatment must be specified (eg, a course of systemic corticosteroids), and only those subjects who achieve disease stabilization would be eligible for the trial.

IIIB4a4. Study visit procedures are the same as in IIIA4a4, except that a bacterial culture is not recommended at entry.

IIIB4b6. See IIA4b6 regarding use of intranasal corticosteroids.

IIIB5. Study population. Ref Prev IIIA5.

IIIB5d. Inclusion criteria. Criteria to define ''stable'' disease must be specified. See IIA5d5 regarding comorbid AR and prior sinus surgery.

IIIB6. Efficacy assessments. See Tables I, III, and IV. Ref Prev.

IIIB6b. Objective. Ref Prev IA, IIIA.

IIIB6b8. Ref Prev IIIA. See Appendix 5. Laboratory testing is recommended as a measure of pathologic processes to better characterize the patient population under study and evaluate treatment effectiveness.

IIIB7. Safety assessments (see Table III)

IIIB7b4. Safety studies are encouraged for evaluation of the potential adverse effects of the dosing of corticosteroids sufficient for the clinical management of rhinosinusitis. Laboratory testing is important for safety, specifically with protracted corticosteroid use. The particular safety assessments and inclusion and exclusion criteria related to them should be defined by the protocol.

IIIB7b5. Pretreatment tuberculosis screening should be considered. Pretreatment and posttreatment ophthalmologic evaluations and bone mineral density determination should be considered if corticosteroid treatment course is protracted.

IIIB8. Biostatistical methods. Ref Prev IIA.

CLINICAL TRIAL GUIDANCE IIIC. CRSwNP: SYMPTOM-RELIEVER OR MEDIATOR-BLOCKER TRIAL

IIIC1. Title

Treatment of CRSwNP with a mediator blocker (eg, aspirin desensitization or LT modifier; only design modifications from the treatment of CRSwNP with an oral antibiotic are included, see Table III).

IIIC2. DEFINITION/BACKGROUND/ RATIONALE

IIIC2e. Rationale. CRSwNP is a chronic inflammatory condition. Patients experience bothersome symptoms and reduced QOL and productivity. The rationale for the study is to determine whether a mediator-blocker therapy reduces the symptom burden and health effect of illness,

lessens the severity of illness, and/or shortens its duration.[139,141] The selection of aspirin desensitization and LT modifier treatments are appropriate clinical trials because of data demonstrating upregulation of CysLTs and CysLT receptors in some patients with CRSwNP.[142] Therefore novel approaches to modulate mediator activity would be an important strategy.

IIIC3. STUDY OBJECTIVES

IIIC3a. Primary efficacy objective. The recommended primary efficacy variable should be improvement in TSS. Another could be change in the sinus CT or photoendoscopy score from the beginning of the study to the end of treatment.

IIIC3b. Secondary efficacy objective. Improvement in QOL measure, improvement in rhinoscopic grading with photoendoscopy, organism eradication, and reduction in inflammatory markers.

IIIC4. STUDY DESIGN

IIIC4a. Overview. There are 2 potential study designs: (1) long-term therapeutic intervention for chronic disease (see Fig 3) or (2) prevention of disease recurrence for chronic disease (see Fig 4).

IIIC4a4. Study visit procedures are the same as in IIIA4a4, except that a bacterial culture is not recommended at entry.

IIIC4b6. See IIA4b6 regarding use of intranasal corticosteroids.

IIIC5. Study population. Ref Prev.

IIIC6. Efficacy assessments. See Tables I, III, and IV. Ref Prev IIIA.

IIIC6b7. Because antimicrobial intervention is not being assessed, sinus aspiration or precise microbiologic ascertainment is less important.

IIIC6b10. Tests of olfaction might be especially valuable.

IIIC7. Safety assessments. Ref Prev.

IIIC8. Biostatistical methods. Ref Prev.

CLINICAL TRIAL GUIDANCE IVA. AFRS: ANTIMICROBIAL TRIAL

IVA1. Title

Treatment of AFRS with a topical antifungal agent (see Table III).

IVA2. DEFINITION/BACKGROUND/ RATIONALE

IVA2a. Definition. See Table I.

IVA2a. Background. The characteristics of AFRS that are important to its definition include the presence of eosinophilic mucin containing noninvasive fungal hyphae, objective evidence of IgE-mediated sensitivity to fungi, and gross clinical manifestations of the inflammatory disease. The defining characteristics serve as the basis for potential forms of therapeutic intervention.

IVA2e. Rationale. By definition, fungi represent the primary microorganisms associated with AFRS.[143,144] The rationale for this type of study is to demonstrate the clinical benefit associated with eradication or reduction of fungal burden in patients with AFRS. Antimicrobial treatment in the form of topical or systemic antimycotic medications possesses the potential to attenuate fungal colonization within the nose, thereby theoretically decreasing the local, systemic, or both immunologic mechanisms responsible for AFRS. There is further evidence to suggest that the use of azole antifungal agents might lead to attenuation of CD4 lymphocyte–driven inflammation.[1,145-147] Antimycotic agents might also change Na/K ion pump dynamics and represent another mechanism of improvement in disease, irrespective of the effect on fungi.[148] Reasonable approaches to address these questions could assess either the effect of long-term intervention on disease or of intervention on the recurrence of disease after eradication by other means.

IVA3. STUDY OBJECTIVES

IVA3a. The primary efficacy objective can be improvement in sinus CT score at the end of therapy or in changes documented by means of photoendoscopy.

IVA3b. Secondary efficacy objectives can include change in photoendoscopy assessment, change in QOL measurement, laboratory measures to assess eradication or reduction of fungal bioburden, and/or reduction in study-specific inflammatory markers.

IVA3c. Safety objectives. These can include AEs.

IVA4. STUDY DESIGN

IVA4a. Overview. Two trial designs are recommended, namely either (1) long-term therapeutic intervention for chronic disease (see Fig 3) or (2) prevention of disease recurrence for chronic disease (see Fig 4). For the purposes of illustration, the former is presented here.

IVA4a4. Study visit procedures. A baseline and end-of-treatment sinus CT scan should be performed. Volumetric CT scoring is highly desirable, but such a technique is not yet in general use. Additional quantifiable measures, such as differentiation of mucosal thickening from retained allergic mucin can be derived from magnetic resonance imaging (MRI) by using postgadolinium magnetic resonance images (see Appendix 3). Daily TSSs should be recorded throughout the study. A fungal culture or alternative indirect measure of the presence of fungi is recommended at entry (see Appendix 4), and it might be advisable to require a positive test result for randomization.

IVA4a5. Study groups. Ref Prev IA.

IVA4b. Treatment plan

IVA4b1. Treatment plan for study medication (eg, topically applied antifungal agent).

IVA4b4. Prior medications/treatment. Systemic steroids and antibiotics (and systemic antifungal agents) should not be used for a minimum of 15 days before study admission.

IVA4b5. Prohibited therapy. Oral or intranasal decongestants should be excluded at the start of the study.

IVA4b6. See IIA4b6 regarding use of intranasal corticosteroids.

IVA5. STUDY POPULATION

IVA5d. Inclusion criteria. This study should include those patients given diagnoses of AFRS, as defined in Table I. For certain studies, the patient must have had prior sinus surgery because this could be either a newly diagnosed case or a recurrence of AFRS. Subjects must have acceptable skin/clinical laboratory/imaging tests.

IVA5e. Exclusion criteria

IVA5e2. Subjects who are not adequately symptomatic or whose symptoms are not too severe, as defined in the protocol.

IVA5e3. History of viral URI in prior 4 weeks, signs of local complications, and subjects possessing risk factors associated with the development of invasive fungal disease (eg, poorly controlled diabetes mellitus, lymphoreticular malignancies, aplastic anemia, significant immunodeficiency, recent use of immunosuppressive medications, and transplant recipients). Additional exclusions are similar to those outlined above in section IIA5e3.

IVA5e4. Subjects with abnormal screening laboratory/imaging test results that compromise the ability to assess the benefits/risks.

IVA5e5. Randomization criteria. AR is an important comorbidity. It might be advisable to stratify subjects, limit enrollment to a certain percentage in each season of the year, or both.

IVA6. Efficacy assessments. See Tables I, III, and IV. Ref Prev IA.

IVA6a. Subjective. Ref Prev IA. Most critical symptoms in AFRS can be calculated on the basis of highest score of original 11 symptoms (see Tables I and IV).

IVA6b. Objective. Ref Prev IA6, IIIA6.

IVA6b1. Physical examination. Mucin characteristics and presence of nasal polyposis are findings commonly noted in AFRS.

IVA6b2. Endoscopy should be performed on patients after treatment with a decongestant. If allergic mucin is present on endoscopy (see Appendix 4), a sample should be collected and sent to pathology for an objective measure (see Appendix 2).

IVA6b3. Nasal patency measures might be useful (see Table III).

IVA6b4. Imaging. A sinus CT scan is recommended as the radiographic study of choice and whenever possible should be performed with volumetric measures (see Appendix 3).

IVA6b5. Skin testing, *in vitro* testing, or both for IgE specific to fungal antigens and appropriate controls should be performed.

IVA6b7. Identifying organisms. It is recommended that the study include quantification of fungal bioburden before and after treatment using one of the methods discussed in Appendix 4. Histopathologic definition of allergic mucin with silver methenamine staining (polysaccharides) and calcofluor white are recommended. A standard fungal culture should also be attempted (see Appendix 4).

IVA6b8. Ref Prev IIIA6. See Appendix 5.

IVA6b10. Tests of olfaction could be used as an outcome measure.

IVA6b11. Health economic assessments could be used as outcome measures.

IVA7. Safety assessments

IVA7a. Ref Prev IA7. See Table III.

IVA7a1. See Table I (eg, nasal burning).

IVA7a2. Treatment failures, discontinuations, and exacerbation rates should be documented.

IVA7b. Objective

IVA7b5. Special clinical laboratory parameters:

- Systemic effects of antifungals
- Liver function tests and renal function studies
- Drug-drug interactions
- ECG (P450), for example.
- Cytochrome P 450 tests, for example.

IVA7b8. Electrocardiograms (eg, QTc changes).

IVA8. Biostatistical methods

Assessments could include changes in CT scores during the course of treatment.

CLINICAL TRIAL GUIDANCE IVB AFRS: ANTI-INFLAMMATORY TRIAL

IVB1. Title

Treatment of AFRS with a systemic immunodulator (eg, immunotherapy, omalizumab, cytokine antagonist, or systemic steroid [long or short course]; only design modifications from the treatment of AFRS with a topical antifungal agent are included, see Table III).

IVB2. DEFINITION/BACKGROUND/RATIONALE

IVB2e. Rationale. AFRS is characterized by an inflammatory response to the presence of fungi. The rationale for the study is to determine whether anti-inflammatory therapy results in more rapid resolution of symptoms and improves objective measures of disease compared with placebo or prevents recurrence of disease after control by other means. Although the exact cause and pathogenesis of AFRS remain unclear, eosinophilic inflammation plays an

important role in the propagation of the disease. Patients with AFRS, by definition, possess an IgE-mediated immunologic response to fungi recovered from affected sinuses. Further evidence[149,150] appears to implicate additional non-IgE–mediated immunologic mechanisms in the pathogenesis of the inflammatory component of the disease. As such, the control of the inflammatory component of AFRS, through the use of immunomodulatory therapies, has the potential to attenuate its severity.

IVB3. STUDY OBJECTIVES

IVB3a. Primary efficacy objectives can be assessments of changes in TSS and sinus CT score or alternatively in nasal photoendoscopy.

IVB3b. Secondary objectives can include an objective mucosal staging system with monthly scoring, changes in QOL measures, or changes in rhinoscopic grading through photoendoscopy.

IVB4. STUDY DESIGN

IVB4a. Overview. Two trial designs are recommended, namely either (1) long-term therapeutic intervention for chronic disease (see Fig 3) or (2) prevention of disease recurrence for chronic disease (see Fig 4). For the purposes of illustration, the latter is presented here.

IVB4a2. In the trial design for prevention of disease recurrence trial design, subjects are enrolled after they receive treatment to stabilize their disease. The classic example would be a patient with possible AFRS whose diagnosis is confirmed at the time of sinus surgery. Surgery, possibly combined with systemic corticosteroids, can be regarded as a treatment to stabilize their disease. Only subjects who achieve disease stabilization are eligible for the preventive treatment trial. Criteria for what constitutes stable disease must be specified under inclusion criteria.

IVB4a4. Ref Prev IVA.

IVB4a6. See IIA4b6 regarding use of intranasal corticosteroids.

IVB4b5. Prohibited therapy. Oral or intranasal decongestants should be excluded at the start of the study. No antifungal treatment should be used for 30 days before study initiation.

IVB5d5. See IIA5d5 regarding comorbid AR and prior sinus surgery.

IVB6. Efficacy assessments. See Tables I, III, and IV. Ref Prev.

IVB7. Safety assessments. See Table III.

IVB7b5. Special clinical laboratory parameters. The particular safety assessments and inclusion and exclusion criteria related to them should be defined by the protocol.

- Systemic effect of corticosteroids
  - Bone density evaluation
  - Hemoglobin A1C
- Systemic effects of immunomodulator
  - Immunologic, hematologic, chemistry tests
- Drug-drug interactions
  - Cytochrome P450 tests

IVB8. Biostatistical methods

Biostatistics will be based on changes in CT scores, TSSs, or both during the course of treatment.

CLINICAL TRIAL GUIDANCE IVC AFRS: SYMPTOM-RELIEVER OR MEDIATOR-BLOCKER TRIAL

IVC1. Title

Treatment of AFRS with an LT modifier (only design modifications from the treatment of AFRS with a topical antifungal agent are included, see Table III).

IVC2. DEFINITION/BACKGROUND/RATIONALE

IVC2e. Rationale. AFRS is a chronic inflammatory condition. The rationale for the study is to determine whether symptom-relieving medications or mediator-blocker drugs reduce the health effect of illness, lessen the severity of illness, and/or shorten its duration.

IVC3. STUDY OBJECTIVES

IVC3a. Primary efficacy objectives can be change in TSS and sinus CT score or alternatively in nasal photoendoscopy.

IVC3b. Secondary objectives can include an objective mucosal staging system with monthly scoring, improvement in QOL measures, improvement in rhinoscopic grading through nasal photoendoscopy, and reduction in inflammatory markers.

IVC4. STUDY DESIGN

IVC4a. Overview. There are 2 potential trial designs, as outlined in IVA4a. For the purposes of illustration, a long-term therapeutic intervention for chronic disease (see Fig 3) is presented here.

IVC4b. Treatment

IVC4b5. Prohibited therapy. Oral or intranasal decongestants should be excluded at the start of the study. No antifungal treatment should be used for 30 days before study initiation.

IVC4a6. See IIA4b6 regarding use of intranasal corticosteroids.

IVC5. Study population. Ref Prev.

IVC6. Efficacy assessments. See Tables I, III, and IV. Ref Prev.

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APPENDIX 1. HEALTH OUTCOMES: QOL QUESTIONNAIRES AND SYMPTOM SCALES

INTRODUCTION

The assessment of patient-reported outcomes is important in clinical trials, and in some cases symptomatic outcome should be the primary treatment outcome. Therefore a need exists for validated instruments to assess patient-based outcomes.

Several instruments have been validated to assess disease-specific QOL in upper respiratory disease. This appendix addresses instruments that were evaluated and reported to be valid, reliable, and responsive for rhinosinusitis and designed to be evaluative and assess or compare QOL in groups of patients rather than assess changes in a single patient over time. However, the content of many of these instruments might not be well suited for use in clinical trials of patients with acute rhinosinusitis because of instrument length, content, and validated period of data collection. The QOL instruments are developed to be disease-specific functional status measurement tools helpful in assessing baseline status and level of functional improvement (or lack thereof) in groups of patients with rhinosinusitis in clinical research trials.[8-12]

DISEASE-SPECIFIC VALIDATED INSTRUMENTS

- Rhinosinusitis Disability Index, Benninger and Senior[8]
  - 30 items
  - No defined time period of symptom recall
  - Graded into 3 subscales: emotional, physical, and functional
  - Designed for CRS
  - Sample items
    - Because of my problem I feel (eg, frustrated, confused, do not like to socialize).
    - My frequent sniffing is irritating to my family and friends.
- Sinonasal Outcome Test–20 items (SNOT-20), Piccirillo et al[9]
  - 20 items
  - No defined period of symptom recall
  - Single summary score
  - Designed for CRS
  - Sample items
    - Runny nose, cough, thick nasal discharge, wake up at night or wake up tired, reduced productivity, sad, embarrassed. Does not include nasal blockage, a symptom most patients and clinicians believe is important in a comprehensive subjective assessment of rhinosinusitis.

Of note, the SNOT-20 was developed from the Rhinosinusitis Outcome Measure–31 by the same authors. The Rhinosinusitis Outcome Measure–31 had ''magnitude'' and ''important'' scores, which were multiplied. The authors found after using the instrument that using 2 scores for each item greatly complicated completion and scoring and did not contribute to score differences. Thus the items with the greatest magnitude tended to be of greatest importance, and on the revised SNOT-20, only magnitude was assessed.

- Chronic Sinusitis Survey, Gliklich and Metson[10]
  - 6 items
  - Period of symptom recall: 8 weeks
  - 2 subscales: symptom, medication
  - Designed for CRS
  - Actual items: sinus headache, facial pain or pressure; nasal drainage or postnasal drip; nasal congestion or difficulty breathing through the nose; antibiotic use; nasal sprays prescribed by your doctor; sinus medications in pill form
- Rhinosinusitis Quality of Life Survey, Atlas et al[11]
  - 17 items
  - Period of symptom recall: 7 days
  - 3 subscales: symptom frequency, symptom bother, symptom effect
  - Designed for acute rhinosinusitis and CRS (no consensus among the Rhinosinusitis Initiative Committee that symptoms/item content for acute rhinosinusitis and CRS should be the same)
  - Sample items: sinus headaches, facial pain, or facial pressure; blocked or stuffy nose; postnasal drip; thick nasal discharge; runny nose; trouble sleeping; harder to do the things you normally do; embarrassed; and irritable

GLOBAL QOL INSTRUMENTS

In addition to disease-specific QOL, there is a role for the assessment of global QOL, with a multitude of validated global QOL instruments of different length, content, subscales, and scoring. Advantages to a global instrument include comparability with other disease states. Commonly used instruments include the following:

- Short Form 36[12]
- Short Form 12[13]
- Quality of Well-Being Scale[14]

NASAL OBSTRUCTION

There is significant controversy about the best method to assess the effect of nasal obstruction. A validated instrument for assessing patient symptoms of nasal obstruction is the Nasal Obstruction Symptom Evaluation instrument.[15] The instrument is valid, reliable, and responsive to changes in clinical status and has been used successfully in a multicenter prospective study of septoplasty effectiveness. Other tools, such as acoustic rhinometry and volumetric analysis, are controversial and not standardized or uniformly accepted.

DETERMINING THE BEST OUTCOME ASSESSMENT TOOL

1. Has the minimally significant difference been achieved with either or both groups?
2. Compare outcomes statistically.
3. Benchmark outcomes against standards for clinical significance.

Although disease-specific QOL measures are assessing important outcomes, perhaps none are ideal for assessment of symptom severity in clinical trials comparing different treatments, particularly if both treatments are at least partially beneficial or if the outcome instrument will be administered multiple times during a trial. When comparing differences between 2 different effective treatments (ie, 2 different classes of antibiotics), any treatment can result in improvement in QOL, and disease-specific instruments might not distinguish differences between groups. Furthermore, these QOL instruments are designed to assess more than symptom burden, and therefore a disease-specific symptom severity scale might be a preferred outcome measure for many clinical trials versus a QOL instrument.

RECOMMENDATIONS

Development of an accepted instrument

A standardized symptom score instrument should be developed for use in clinical trials in rhinosinusitis. This instrument should be brief, contain only symptom-based items, and be graded only on severity/magnitude (ie, not importance) on a 5- to 7-point Likert (categoric) scale. Distinct instruments should be developed for acute rhinosinusitis and CRS and validated for content by testing in patients with rhinosinusitis and assessing for reliability and responsiveness.

Clinical versus statistical significance

Clinically important score changes on the new instrument should be assessed by using prospective trials. Health status instruments should include a minimally significant difference in score, which is typically 0.2 to 0.5 on a 7-point scale or 3 to 7 points on a 100-point scale. This minimally significant difference is not necessarily the same as the clinically significant difference and should be defined for any given instrument and disease state. Techniques include statistical assessments, benchmarking (''anchoring'') techniques using global change rating scales, or both.

Understand baseline/disease-free scores

Patients in good health do not typically score 100 or 0 on global QOL or disability instruments. Similarly, patients given disease-specific rhinosinusitis QOL instruments who do not complain of nasal or sinus disease do not typically score 100 or 0. Thus the change in symptoms corresponding to resolution of a disease process should be carefully considered. For example, a study of the SNOT-16 (scored from 0 to 48, with higher scores meaning worse QOL) showed a mean score of 22.4 in patients with rhinosinusitis versus a mean score of 10.5 in patients with otologic disease.[16] A study of the SNOT-20 (scored as mean item score from 0 to 3) showed patients with rhinosinusitis had a mean score of 1.9 versus patients without rhinologic disease, who had a mean score of 0.6.[9] These findings indicate that it cannot be assumed that scores should approach 0 as rhinosinusitis is resolved. The presence of baseline problems, such as anatomic obstruction or allergy, can result in increased scores, even after resolution of an acute or chronic inflammatory process.

APPENDIX 2. NASAL ENDOSCOPY AND STAGING OF CRS

Diagnostic nasal endoscopy permits comprehensive evaluation of the nasal cavity drainage pathways of the paranasal sinuses. The technique uses either a rigid nasal endoscope (2.7 or 4 mm in diameter) or a flexible fiberoptic nasopharyngoscope, a fiberoptic light source, and a light cord.[17] Smaller-diameter telescopes and flexible scopes are recommended for use in children or patients with difficult nasal anatomy. Photographic nasal endoscopy (photoendoscopy) can be used as an alternative to CT as a primary objective outcome variable or as a secondary outcome variable when appropriate (eg, CRSwNP and AFRS). This might be especially valuable where radiation exposure or cost are concerns when repeated objective measures are required.

SYSTEMATIC NASAL ENDOSCOPY

Topical vasoconstrictive and anesthetic agents are typically used to facilitate nasal endoscopy unless contraindicated, with examination of the nose recommended before and after administration of these medications.

The systematic approach to the nasal endoscopic examination is divided into 3 passes, each of which permits

evaluation of the nasal valve and vestibule and nasal septum (these 3 passes are ideal and might not be possible in patients with significant anatomic abnormalities):

1. The inferior examination passes the endoscope along the floor of the nose to visualize the floor of the nasal cavity, the inferior turbinate/meatus, the eustachian tube orifice, and the posterior nasal pharynx. Occasionally, the lacrimal drainage at Hasner's valve can be observed within the inferior meatus.
2. The second passage evaluates the middle turbinate, the olfactory cleft, the sphenoethmoidal recess, the superior turbinate, and occasionally the sphenoidal ostium.
3. The third passage examines the superior aspect and nasal vault, the attachment of the middle turbinate to the lateral wall, the ostiomeatal complex, the uncinate process, and possibly the anterior ethmoidal bulla.

Endoscopic findings can be divided into inflammatory, neoplastic, and anatomic findings. Nonspecific allergic and inflammatory findings might include a bluish discoloration or boggy distention of the nasal mucosa, inflamed erythematous mucous membranes, and/or nasal polyposis. Inflammation associated with infection might include erythema of the mucosa and purulent discharge, which can drain from ostial sites. The endoscopist should document the quality of secretions, color, and site of origin. Additional findings might include observation of fungal hyphae, inspissated secretions, or the loss of nasal tissue from invasive bacterial and fungal pathogens. Other more insidious inflammatory findings can include granulation tissue in the context of a severe systemic process, such as Wegener's granulomatosis. Anatomic abnormalities can be observed and should be correlated with the patient's specific symptoms. These include a septal deviation, a spur formation, or the presence of concha bullosa with restriction of the outflow tract of a specific paranasal sinus.

ENDOSCOPIC DIAGNOSIS OF ABRS

Infection caused by bacteria often presents with thickened, discolored nasal secretions streaming into the middle meatus toward the posterior nasal cavity. The color of the secretions can vary from clear or milky-white to greenish-yellow. The nasal membranes will also show signs of swelling or minor erythema (see Fig 5).

STAGING OF NASAL POLYPOID DISEASE

A proposed system to grade or stage the obstruction of the nasal passage by NPs involves assessment of the nasal obstruction proceeding from anterior to posterior and from inferior to superior (see Figs 6 and 7).

Other scoring systems for staging of nasal polyposis have been developed,[18-21] but this proposed endoscopic scoring system is reproducible and easy to interpret for outcome management. The staging system can be used to follow the course of the disease, recognizing that certain disorders, such as antrochoanal polyp, might have 1 large polyp in the middle meatus, and a large polyp might obscure several smaller polyps. In the case of clinical trials, the staging system can be used to grade NPs at sequential visits to document intervention effect.

Patients who have already undergone surgery might present with a different clinical finding. Although the above scoring system might be valid, the investigator could note other findings, such as cobblestoning of the lateral nasal wall mucosa, compared with a true NP. The postoperative scoring system adapted by Fokkens et al[22] can also be considered.

APPENDIX 3. RADIOLOGIC IMAGING CONSIDERATIONS AND SCORING SYSTEMS FOR RHINOSINUSITIS

OVERVIEW OF RADIOLOGIC IMAGING FOR ACUTE RHINOSINUSITIS AND CRS AND AFRS

Conventional plain-film radiography can be used as a screening method for acute rhinosinusitis and CRS.[23] This provides orientation and direction to further examinations such as ultrasonography, CT, and MRI.[23-25] Although a plain-film sinus series can be of value, significant discrepancies are noted between a sinus series and a CT scan.[24] CRS associated with inspissated mucus has a characteristic CT appearance. This appearance might be hard to appreciate on plain film and could be missed or misinterpreted on MRI.[24,26,27]

Correct imaging strategies must be obtained to maximize information obtained from CT.[28-30] It is important to use thin sections (up to 3 mm) to avoid missing small polyps or abscess cavities. Scans in both the coronal and axial planes are useful, with axial sections taken parallel to the orbitomeatal line or parallel to the hard palate.[24,29] The coronal sections are obtained with the patient prone or supine, the head hyperextended, and the gantry tilted to a plane as close to 90° to the canthomeatal line as possible. Thinner sections (2.5-3.75 mm) are used to identify small lesions and evaluate the ostiomeatal complex.[23-25,26,30] Some authors recommend an intermediate window width/level technique with regard to filming or viewing on a picture archiving and communications system monitor.[26,31] CT images should be viewed or filmed for routine soft tissue setting and bone setting with extended window width–window level bone technique (4000/700-800 window width/level).[24,28-30]

In addition to infectious processes, inflammatory and immunologic (cellular and molecular) responses play a role in the pathophysiology of soft tissue and hard tissue of the sinonasal cavities (mucosal response and osteoblastic and osteoclastic response). Soft tissue changes are better evaluated on CT viewed with soft tissue setting. Osteolysis, demineralization or loss of bone density, and

pressure atrophy of the sinus walls, such as in long-standing sinonasal polyps and osteoblastic sclerosis changes, are best evaluated on CT scans viewed with the extended window width–window level bone technique. There might be air bubbles scattered within the fluid or thick mucus in the sinus with mucosal thickening and air-fluid level in the sinus cavity. These changes are better seen with a soft tissue setting technique. Subperiosteal edema/fluid is also best seen on CT scans viewed with a soft tissue technique. Although sinus CT scores do not correlate well with baseline CRS symptoms,[32-34] changes in CT scores are sensitive to therapeutic intervention.[127,134]

IMAGING OF ACUTE RHINOSINUSITIS

In a patient with viral rhinosinusitis, sinus CT scans might reveal mucosal thickening of nasal passages, along with mucosal thickening and air-fluid level in the paranasal sinuses. There might be air bubbles scattered within the fluid (transudate or exudates) in the sinuses. After resolution of this common cold, sinus CT scans demonstrate complete resolution of mucosal changes, as well as clearing of the fluid in the sinuses. Subperiosteal edema and bony changes (osteolysis and demineralization) are not seen unless there are associated superimposed bacterial or fungal infections.

An acutely infected sinus caused by bacterial or fungal infection shows thickening of the mucosa, (reflecting edematous tissue of the paranasal sinuses), an air-fluid level, or both, and 1 or more of the sinus cavities might be completely opacified. Conventional radiography is adequate for the diagnosis of clinically uncomplicated acute sinusitis.[23,24] Bacterial and invasive fungal infection of the paranasal sinuses can extend through the cortical bone, resulting in a collection of edema or purulence between the bone and the periorbita or intracranially.[35] Such complications of acute rhinosinusitis can be evaluated on enhanced CT scans or MRI, with an abscess depicted as a low-density region surrounded by an enhancing abscess wall.

Imaging of CRSsNP

Acute sinus infections cause demineralization (rarefaction) of the wall of the sinus and, when the process becomes chronic, result in reactive sclerosis of the sinus walls.[23,36] These changes in the wall of the sinus often indicate the presence of osteitis, which further raises the question of whether it is a focus of persistent infection.[36] CRS on CT scans appears as mucosal thickening, which can be associated with sclerosis of the wall of the sinus and bony septae. Complete opacification of 1 or more anterior ethmoid air cell is commonly seen and might represent the underlying cause of persistent symptoms. Although less common, other sinus cavities can be completely opacified.

Variable degrees of sinus ostial obstruction are common in CRS. Obstruction of the ostiomeatal unit has been given individual weighting in CRS staging systems, such as the Lund and Mackay system,[18] but not in more recently developed systems (see below).

Sinus opacification in CRSsNP raises the question of persistent bacterial infection, mucus inspissation, or possibly focal polypoid thickening or even a focus of allergic mucin caused by AFRS; however, the latter is rarely seen in patients without a history of nasal polyposis. In contrast, sinus opacification in CRSwNP is commonly seen in the absence of gross infection.

Imaging of CRSwNP

Mucosal thickening, sinus opacification, or both are typically more pronounced in CRSwNP than in CRSsNP. Polyps are seen on CT scans as mucosal protrusions into the nasal cavity. The CT density of polyps cannot be differentiated from nonpolypoid mucosal thickening. When the mucosal thickening appears polypoid in configuration, the CT appearance is used in favor of polyp or polyps. The combination of CT and MRI, including enhanced MRI, provides an imaging appearance that highly favors the presence of polyps.

A solitary polyp might not be distinguished from a retention cyst on unenhanced CT and MRI scans. Unlike cysts, polyps demonstrate moderate-to-marked contrast enhancement. When multiple polyps are present, sinus secretions become entrapped within the crevices between the polyps, as well as on their surfaces. On CT scans, polyps show soft tissue attenuation values; however, depending on the concentration of the entrapped secretions, the CT attenuation values increase, and the chronic sinonasal polyposis might show mixed CT attenuation values with areas of increased density, simulating focal or diffuse dystrophic calcifications. These findings suggest that CRSwNP is complicated further by the presence of AFRS. In aggressive long-standing polyposis, there might be significant expansion of the sinuses, as well as focal bone erosion, and these findings are again suggestive of AFRS. Polyps tend to have various signal intensities on magnetic resonance pulse sequences. The MRI characteristics of polyps reflect the various stages of polyps, as well as the various stages of desiccation of the entrapped secretions within crevices between the polyps and on the polyp surfaces.[23,24]

Imaging of AFRS

Most patients with AFRS have sinonasal polyposis, and therefore the imaging appearance might be indistinguishable from that of CRSwNP, although certain radiologic features are highly distinctive and suggestive of AFRS. The sinuses most often involved are the maxillary, ethmoid, and sphenoid sinuses. CT scan is the study of choice. The CT findings include foci of increased density within the opacified sinuses, and areas of focal hyperattenuation vary in size. At times they might form a cast of increased density within the sinus. As these materials accumulate, bony demineralization of the sinus wall ensues caused by the release of inflammatory mediators and pressure, resulting in expansion of the sinus and possibly mucocele formation.[37] True bone erosion is less common, occurring in 20% of cases.[38]

Both mucus accumulation and mucosal thickening contribute significantly to sinus opacification in AFRS and are difficult to differentiate with sinus CT imaging. Assuming that more precise estimates of mucus accumulation and mucosal thickening are desired, MRI will be necessary. T_1-weighted imaging might show peripheral enhancement of the involved paranasal sinus on postgadolinium magnetic resonance images indicative of thickened mucosal lining. In addition, the involved paranasal sinus and nasal cavity demonstrate variable but predominantly hypointense signal intensity. In contrast, T_2-weighted imaging is best for identification of allergic fungal mucin. The high protein and low water concentration of allergic fungal mucin, coupled with the high water content within surrounding edematous paranasal sinus mucosa, gives rise to a hypointense appearance of the sinus lumen. The reactive granulations or associated subacute or acute rhinosinusitis will demonstrate hyperintense signal on T_2-weighted magnetic resonance images. There is only enhancement of the mucosal rim on enhanced T_1-weighted magnetic resonance images.

Sinus CT scoring systems for rhinosinusitis

Scoring systems for ABRS. There are no published scoring systems for ABRS. The most commonly used criteria for ABRS include the presence of an air-fluid level, sinus opacification, or sinus mucosal thickening of 6 mm or greater in the affected sinus (most commonly the maxillary sinus)[39] or 10 mm.[40] In the latter study criteria found to be most predictive of the presence of bacteria in the sinus cavity included colored nasal discharge, facial pain, and radiologically determined maxillary sinusitis (complete opacity, air-fluid level, or mucosal thickening >10 mm). However, the best predictive model had a sensitivity of 69% and a specificity of 64% and was therefore not considered sufficient to establish a bacterial cause for the acute rhinosinusitis.

In the 1998 FDA guidance document and a later FDA report on past approvals for acute bacterial sinusitis, the following points were made. First, radiographic inclusion criteria are required for an ABRS trial. In trials reviewed by the FDA, these included criteria for sinus opacification and air-fluid level in all studies and criteria for mucosal thickening in most studies. ''Clinical cure'' was defined as resolution of all symptoms and signs, and no worsening in radiographic appearance. Although end-of-study or end-of-treatment radiography was done in most studies, the results were seldom used as the basis for assessing drug efficacy. There appears to be little information on how the time course of resolution of radiographic abnormalities correlates with clinical outcomes in ABRS. Nonetheless, a guidance document from 2003 recommended that radiologic entry criteria and outcome measures be incorporated in a preliminary noninferiority trial and a second noncomparative trial. This suggests radiographic criteria for drug efficacy might be mandated in future ABRS trials, and this issue will require clarification with the FDA.

Scoring systems for CRSsNP, CRSwNP, AFRS. LUND AND MACKAY STAGING SYSTEM. The Lund-Mackay staging system,[18] summarized in the first Rhinosinusitis Initiative document,[1] represents the most widely established method of sinus CT scoring in clinical trials.[41,42] It scores each sinus area as 0, 1, or 2 depending on the extent of mucosal opacification present and also includes a score for patency of the ostiomeatal unit. Anatomic variants, such as absent frontal sinus, concha bullosa deformity, paradoxical middle turbinate, everted uncinate process, Haller cells, and Agger nasi cells are also scored with this instrument but would not contribute to scoring of a nonsurgical therapeutic intervention. The major drawback of the Lund-Mackay system is its inability to subgrade the volume of inflammatory disease in grade I, which can represent any degree of sinus involvement from greater than 0% to less than 100%. When evaluating a specific medical therapeutic agent, if grade I disease with 10% sinus involvement is cured, it is reduced to grade 0. However, if grade I disease with 90% involvement is reduced to 30%, a substantial improvement, the classification is still grade I, suggesting there has been no change. The Zinreich method (discussed below) represents a modification of the Lund-Mackay staging system designed to overcome this limitation.

NEWMAN METHOD. Newman et al[43] studied 80 adult patients with chronic sinus symptoms and examined the extent of sinonasal disease depicted on CT scans quantified by the scoring system first introduced by Newman et al (Table VII).[40]

This scoring system differs from others in that it includes a score for nasal passages, it considers only 1 score for the right and left sphenoid sinus, and it uses absolute criteria for mucosal thickening to grade each sinus area. A minor concern in the Newman study[43] has to do with the fact that Fig 2 is reported to show ''severe mucosal thickening in the maxillary and ethmoid sinuses'' but in fact appears to show relatively clear maxillary sinuses, except for the presence of likely small- to medium-sized retention cysts. In our opinion retention cysts should not contribute to a score for ''mucosal thickening'' because they often appear unchanged on longitudinal CT or MRI studies.

ZINREICH METHOD. The Zinreich method[44] represents a modification of the Lund-Mackay scoring system, and like the Newman and Hoover System, is based on grading of coronal CT images. The extent of sinus opacification is computed based on the sum of the scores of the 5 major right and left sinuses (frontal, maxillary, anterior, and posterior ethmoid and sphenoid), each scored on a 5-point opacification scale as follows: 0, 0%; 1, 1% to 25%; 2, 26% to 50%; 3, 51% to 75%; 4, 76% to 99%; and 5, 100%.

Also distinct from the Lund-Mackay staging system, the Zinreich method independently grades sinus ostial obstruction, namely the percentage change from baseline in the total right and left obstruction score of the frontal recess, middle meatus, infundibulum, and sphenoethmoid recesses, each scored as 0 for ''patency'' or 1 for ''obstruction.'' As mentioned above, ostiomeatal unit obstruction might be difficult to assess precisely on sinus CT scans, and it is uncertain whether the ostial obstruction score provides additional information to that derived from

the opacification score. A recent CRS study used the Zinreich method to assess the response to treatment with a systemic antifungal drug.[45]

SEMIQUANTITATIVE VOLUMETRIC METHOD. Ponikau et al[137] used a semiquantitative ''volumetric'' scoring system to assess the response to intranasal amphotericin B over a period of 6 months for CRS. The primary outcome measure was reduction from baseline in the percentage of inflammatory mucosal thickening in the sinus cavities, as measured by CT scan.

Consistent head orientation and distinctive bony landmarks were used to select the coronal image plane showing the ostium of the maxillary sinus to standardize the comparison of the pretreatment and posttreatment scans. The CT scans were digitized and transferred to a graphics software program so the area of inflammatory mucosal thickening, as represented by a specific grayscale value on the CT scan, could be converted into a number of pixels and then quantified before and after treatment. Analogous to the other scoring techniques, this technique used only coronal CT images. Although it resulted in semiquantitative volumetric measurement of disease, it took into account disease only in the maxillary and anterior ethmoid cavities. Furthermore, the technique was limited to 2-dimensional sections through the sinuses and could not accurately determine the true volumetric extent of disease in these or the other sinuses.

The use of computerized software to quantify the extent of sinus mucosal thickening is the ultimate goal of sinus CT scoring. The technique of Ponikau et al[137] represents a step in this direction but is not truly ''volumetric.'' Use of multiple sections and multiple planes might allow the method to more closely approximate volumetric measurements.

Concerns regarding existing scoring systems for CRS

The scoring systems discussed above do not account for the undeveloped sinus or the patient who has had previous surgery. They could also be modified by other considerations, such as hyperplastic rhinosinusitis associated with or without periosteal reaction or pressure bone atrophy (often interpreted by radiologists as bone erosion). Polypoid mucosal thickening (polyps) and periosteal bone thickening are absolute imaging findings for chronic extensive or localized sinus disease. At times, the reactive periosteal bone formation is so extensive, the sinus appears contracted, particularly if viewed on soft tissue CT algorithm. This appears to represent a reactive inflammatory osteitis of the sinus wall and ethmoid trabeculae and should not be confused with osteomyelitis.

The scoring systems are based solely on coronal CT views. Until a technique for volumetric sinus CT study and scoring becomes available, coronal CT scanning is a reasonable procedure; however, it is inadequate for complete evaluation of sinonasal disease. New CT scanning with multiple detector and spiral (helical) capability provides outstanding reformatted images, particularly sagittal sections, with no additional radiation to the patient, and these techniques might be preferred for grading of anatomic variation/pathologic changes at strategically important locations, such as the ostiomeatal complexes. Disease processes in the frontal recess, sphenoethmoid recess, and onodi cells are best evaluated on sagittal views. The inclusion of a sagittal-reformatted image (routinely used for image-guided endoscopic sinus surgery) is recommended and can be used in combination with axial and coronal CT scans to improve any scoring system used to compare pretreatment and posttreatment CT scans.

Another concern pertains to the ethmoid air cells. Depending on the number of coronal sections imaged, a single completely opacified ethmoid air cell can be scored as extensive sinus disease; however, the combination of direct axial, reformatted coronal, and reformatted sagittal CT scans will provide a 3-dimensional approach for more accurate quantitative imaging.

Risk of radiation from sinus imaging

The risk of radiation from the sinus series or screening sinus CT is small.[46] Approximately 0.3 cGy is given per each film view obtained during plain radiographic sinus series.[47,48] The organs most likely to be affected by a cumulative radiation dose are the lens, thyroid gland, and gonads. The dose to the lens of the eye is small. If Waters and Caldwell views are obtained for posterior-inferior projection, the dose to the eye in a sinus series should be on the order of 0.0001 Gy (0.01 cGy) to 0.005 Gy (0.5 cGY).[46,47] The radiation dose to the lens of the eye from a CT examination of the head can range from 3 to 6 cGY.[47,49] The radiation from a CT scan of the sinuses to the lens, cornea, and other organs included in the CT sections can be significantly reduced by decreasing mAs (140 to 200 mAs), without significantly sacrificing details.[50] The imaging plane also can be chosen to avoid scanning directly through the lens of the eye.

SUMMARY RECOMMENDATIONS: INCLUSION CRITERIA, TECHNIQUES, AND OUTCOME SCORING SYSTEMS

ABRS

Inclusion criteria. (1) Must have an air-fluid level, mucosal thickening, partial or complete opacification of 1 or more anterior ethmoid or maxillary sinuses (right or left). (Similar criteria could be applied to the frontal or sphenoid sinus.)

Exclusion criteria. Depending on the study design, the following exclusions might or might not be appropriate: (1) NPs visible by means of rhinoscopic nasal examination of decongested and anesthetized nasal passages in the middle meatus or sphenoethmoid area on either side; (2) expansile mass or bony erosion on sinus radiograph; (3) history of a sinus mucocele or current evidence of a sinus mucocele; and (4) history of previous Caldwell-Luc surgery on either side.

Technique. Conventional radiography is adequate for the diagnosis of clinically uncomplicated acute sinusitis and has been used in most new drug FDA

submissions.[23,24] However, coronal sinus CT imaging limited to no more than 4 cuts through the anterior ethmoid and maxillary sinuses or affected sinuses provides more precise identification of mucosal thickening, air-fluid levels, and sinus opacification and is a much more accurate technique for assessing radiologic resolution of disease, which might be mandated in future studies. Local complications, such as subperiosteal edema and abscess formation, are also best evaluated by means of enhanced CT scan or MRI, including diffusion-weighted imaging.[51]

Outcome scoring system. There is no published radiographic scoring system for ABRS. The following criteria could be considered in assessing radiologic resolution of ABRS: (1) improvement or resolution of sinus opacification; (2) resolution of air-fluid level in the affected sinus; (3) resolution of mucosal thickening in the affected sinus (no more than 2-mm residual thickening); or (4) some combination of 1, 2, and 3. The option of 4 is preferred.

CRSsNP and CRSwNP

Inclusion criteria. (1) Must have mucosal thickening, partial or complete opacification of 1 or more of the following, or both: anterior ethmoid sinus (right or left) or maxillary sinus (right or left; for a trial of CRSwNP, add the requirement for bilateral mucosal disease). (2) Must satisfy criteria for minimum severity of disease based on a sinus CT score, which is prespecified by using one of the scoring systems described above.

Exclusion criteria. Depending on the study design, the following exclusions might or might not be appropriate: (1 [for a trial of CRSsNP]) Radiographic evidence of NPs; (2) expansile mass or bony erosion on sinus CT scan; (3) current evidence of a sinus mucocele; and (4) evidence of previous Caldwell-Luc surgery on either side.

Technique. (1) Use a sinus CT scan with multiple detector and spiral (helical) capability, allowing for coronal, axial and reformatted saggital images. (2) MRI, including postgadolinium magnetic resonance images, is recommended to differentiate mucosal thickening from retained mucus.

Outcome scoring system. (1) At present, the use of one of the semiquantitative sinus CT scoring methods described above is recommended. The newer methods offer some advantage over the traditional Lund and Mackay staging system; however, the latter remains the most extensively used in clinical trials. (2) When available, use of a true volumetric scoring method will be the preferred technique.

AFRS

Inclusion criteria. (1) Must have mucosal thickening, partial or complete opacification of one or more of the following, or both: anterior ethmoid sinus (right or left) or maxillary sinus (right or left). (2) Must satisfy criteria for minimum severity of disease based on a sinus CT score that is prespecified by using one of the scoring systems described above.

Exclusion criteria. Depending on the study design, the following exclusions might or might not be appropriate: (1) expansile mass or bony erosion on sinus CT scan; (2) current evidence of a sinus mucocele; and (3) evidence of previous Caldwell-Luc surgery on either side.

Technique. (1) Use a sinus CT scan with multiple detector and spiral (helical) capability, allowing for coronal, axial and reformatted saggital images. (2) MRI is highly desirable to help delineate allergic mucin. (3) MRI, including postgadolinium magnetic resonance images, is recommended to differentiate mucosal thickening from retained mucus.

Outcome scoring system. The comments about CRS apply equally to AFRS. In addition, the unique features of AFRS, including bony demineralization, bone expansion, bone erosion, and extent of mucus accumulation, should be considered for radiologic assessment. However, scoring criteria would need to be developed to consider them as outcome variables.

APPENDIX 4. MICROBIOLOGY

BACTERIAL PATHOGENS

The microbiology of acute rhinosinusitis and CRS was reviewed in the Rhinosinusitis definitions document.[1] The most common bacterial pathogens associated with acute rhinosinusitis are *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Moraxella catarrhalis*, and *Streptococcus pyogenes* (group A β-hemolytic streptococci). *Staphylococcus aureus* and the oropharyngeal anaerobes (eg, *Prevotella* species, peptostreptococci, and *Fusobacterium* species) are less commonly involved and are typically associated with less acute inflammation. In approximately 25% to 40% of cases, cultures are negative. The most common bacterial pathogens associated with CRS include coagulase-negative staphylococci, *S aureus*, viridians group streptococci, gram-negative enteric rods (especially *Pseudomonas aeruginosa*), and anaerobes.

Specimen collection for aerobic bacterial culture

1. Specimen collection should be performed by a clinician trained in this procedure.
2. Depending on the study group, outcome variable sought, and exclusion criteria, it might be desirable for the patient to be off antibiotics for some period before obtaining cultures.
3. Culture of draining secretions
   a. Instill an intranasal decongestant and a topical anesthetic.
   b. Collect drainage from the middle meatus or sinus ostium with a small swab on a wire (eg, Calgiswab; Hardwood Products Company, Guilford, Me) or with a sinus aspirator (eg, Xomed aspiration system with a Lukens collection trap; Medtronic Xomed Tami Sinus Secretion Collector; Medtronic Xomed, Inc, Minneapolis, Minn).

4. Maxillary sinus puncture and aspiration
   a. The area of puncture is typically beneath the inferior meatus. Clean the anterior nares and the area of puncture with an antiseptic solution, such as povidone-iodine.
   b. Apply a topical anesthetic.
   c. Puncture the maxillary antrum and aspirate secretions with a needle and syringe.
   d. If no material is aspirated, irrigate with 2 mL of nonbacteriostatic saline.
   e. Alternatively, the canine fossa can be accessed through puncture under the upper lip.
   f. Aspirated specimens should be placed in a transport medium (see below) to avoid desiccation and to support the growth of pathogens. Sinus swabs should not be sent when aspiration has been performed, although a study reported that endoscopically guided aspiration is no better than properly obtained swabs.[52]
   g. NOTE: Nasal swabs (not sinus swabs) are unacceptable for diagnosis of acute bacterial rhinosinusitis.
5. Generally, the most reliable cultures can be expected when the mucus collected is visibly purulent.[53,54]

Specimen collection for anaerobic bacterial culture

1. Collection of specimens for anaerobic culture requires special handling.[55,56]
2. If possible, the specimen should be collected by means of sinus puncture without introduction of air into the sinus cavity. Alternatively, purulent material draining from a sinus cavity can be collected.
3. The specimen should be aspirated into a syringe and then injected immediately into an anaerobic transport tube (Port-A-Cult; BBL, Cockeysville, Md). Once inoculated, the anaerobic transport medium should be immediately stripped of oxygen by use of a nitrogen bubbler. Alternatively, specimens can be transported to the laboratory in a syringe sealed with a rubber stopper after evacuation of the air in the syringe.
4. Transport to the laboratory should occur within 60 minutes for syringes and within 3 hours for transport tubes.

Specimen handling

1. All specimens should be transported to the laboratory within the time constraints set for the transport media selected; otherwise, the culture results might not be valid.
2. The time of specimen collection should be documented and sent along with each sample.
3. For quantitative cultures, the approximate volume of the specimen collected should be documented with each specimen. Specimens that are unusually small or large might invalidate the results of the quantitation.

Culture for aerobic bacteria

1. The microbiology laboratory should inoculate a 5% sheep blood agar plate and a chocolate agar plate.
2. Swabs should be firmly rolled over one sixth (no more) of the agar surfaces. Alternatively, 3 or 4 drops of fluid specimen should be placed onto the agar surfaces.
3. The plates should be carefully streaked by using a 4-quadrant method to optimize isolation of potential pathogens while minimizing overgrowth by usual commensal microbiota.
4. Plates should be incubated at 35°C to 37°C in 5% CO_2 for a minimum of 48 hours.
5. A Gram stain should be performed from the swab or fluid such that a preliminary sense of potential organisms might be appreciated. The presence of inflammatory cells, as well as the numbers and morphology of any visualized bacteria, should be reported.
6. Plates should be examined for the presence of growth after 24 and 48 hours of incubation.
7. Potential pathogens should be identified according to standard clinical microbiology procedures, as published in the *Clinical Microbiology Procedures Handbook*, Second edition (ASM Press, 2004).
8. Perform antimicrobial susceptibility testing following Clinical and Laboratory Standards Institute guidelines, testing antimicrobials as requested.
9. Perform β-lactamase testing on isolates of *H influenzae*.
10. Observe plates at 24 and 48 hours for growth of enteric gram-negative bacilli and *S aureus*. In the past, these organisms have generally been considered contaminants in sinus specimens; however, there is growing appreciation for their involvement in the pathogenesis of CRS. In general, only identify these species (with concomitant antimicrobial susceptibility testing) if they represent the predominant organism in the culture, the Gram stain suggests that they are involved in an inflammatory process, and no other typical pathogens are recovered.
11. Usual skin microbiota (coagulase-negative staphylococci and coryneform bacteria) should not be identified to the species level.
12. Any fungi that are recovered should be identified.
13. Yeasts need not be identified because they have not been implicated in acute rhinosinusitis.
14. All organisms predominant in culture that do not represent part of the usual skin or oropharyngeal microbiota should be identified.
15. Cultures are not typically performed for identification of viral agents in cases of acute rhinosinusitis.

Culture for anaerobic bacteria

1. Special care must be taken to inoculate sinus aspirates or tissue specimens directly into anaerobic transport vessels and to culture in appropriate media to maximize the yield of anaerobic cultures.[56,57] It is likely

that technical differences in handling of specimens account for the broad range of reported prevalence of anaerobes in chronic maxillary sinusitis aspirates, ranging from 80% to 100% to 0% to 25%.[57-60]
2. Specimens should be plated onto prereduced vitamin K1-enriched Brucella blood agar, an anaerobic blood agar plate containing kanamycin sulfate and vancomycin hydrochloride (KV agar), an anaerobic blood plate containing colistin sulfate and nalidixic acid (CNA agar), and an enriched thioglycolate broth (containing hemin and vitamin K1).[61] The anaerobic plates and thioglycolate broth should be incubated in jars and examined at 48 and 96 hours.

Reporting considerations

1. The Gram stain report should quantify and give the Gram morphology of all bacteria seen, as well as the relative number of inflammatory cells (few, moderate, or many). Bacteria present on Gram stains have typically been used to signify the presence of at least 10^3 to 10^4 colony-forming units. Bacteria in a density of 10^3 to 10^4 colony-forming units per milliliter or a positive Gram stain are considered evidence of infection.
2. Negative cultures should be reported as ''no growth.''
3. The number of days of culture incubation should be reported.
4. All pathogens with accompanying antimicrobial susceptibility testing results should be reported.
5. The presence of usual skin microbiota without species identification should be reported.
6. If a culture is mixed with no predominating pathogen, a general description of the findings should be reported (eg, ''Mixed microbiota present consisting of 3 types of gram-negative bacilli along with usual skin flora.''). NOTE: The presence of mixed microbiota without a predominating pathogen usually indicates a specimen was collected inappropriately. An exception should be made if the Gram stain revealed inflammation, as evidenced by the presence of polymorphonuclear leukocytes.
7. Anaerobes are identified by using techniques previously described.[61] Aerobic bacteria are identified with conventional methods.[62] β-Lactamase activity is determined for all isolates by using the chromogenic cephalosporin analogue 87/312 method.[62]

FUNGAL PATHOGENS

Fungi are ubiquitous. Detection of fungi by means of culture in nasal/sinus mucus is difficult to interpret because the organisms might be transient contaminants from inhalation. The causative significance of fungi in mucus is controversial. Identification of fungi in mucosal biopsy specimens provides proof that the fungus is invading tissue and not just a contaminant or saprophyte growing on debris/mucus crust. However, there is good evidence that colonizing fungal organisms can elicit local immune hyperresponsiveness relevant to the pathogenesis of CRS. Therefore there is a need for better means of quantifying the type and bioburden of colonizing fungi in mucus samples, particularly those collected from sinus cavities or sinus ostia. At a minimum, it is recommended that any study of topical or systemic antifungal therapy in CRSsNP, CRSwNP, or AFRS should include some attempt to speciate and quantify the fungal bioburden before and after treatment.

1. Fungal organisms can be stained by using conventional techniques, such as Gomori methenamine silver or calcofluor, a fluorochrome that appears brilliant white under fluorescence microscopy, or with a chitin-specific immunofluorescence technique for fungal hyphae. The latter has much greater sensitivity and has been used to demonstrate the presence of fungal hyphae in the mucus in subjects with CRS. Viable fungus can also be stained with periodic acid–Schiff reagent. DNA probes for hybridization to fungal RNA in tissue are commercially available for certain fungi. Classic fungal stains (potassium hydroxide or ''wet mount'') are not useful for diagnosis of fungal sinus disease. Fungal-specific antigen levels, such as levels of *Alternaria* protein, have been measured in sinus secretions before and after antifungal treatment.[63,64]
2. Fungal cultures can be obtained as described previously as an aspirate similar to that of a bacterial culture. Broth macrodilution antifungal susceptibility testing for fungi can be conducted to determine the minimal inhibitory concentration.
3. In AFRS, the histopathology from specimens provides the diagnosis.[65-74] It is a massive inspissate of peanut-buttery, tan to dark green mucin primarily composed of thousands (if not millions) of pyknotic eosinophils compressed into laminated dense masses surrounded by areas where Charcot-Leyden crystals can be seen. Within the allergic mucin, sparse fungal hyphae can be visualized by stains. Allergic mucin in the absence of fungal hyphae occurs in eosinophilic mucin rhinosinusitis.[74] Hematoxylin and eosin staining shows hypertrophic sinus mucosa that is edematous and contains a chronic inflammatory infiltrate of small lymphocytes, plasma cells, and eosinophils. The epithelium often shows desquamation, and the basement membrane is thickened. There should be no evidence for mucosal necrosis, granulomata, or giant cells.
4. An alternative technique has been described for measurement of viable fungi and spores in nasal/sinus secretions; however, the relevance of this as an indicator of fungal involvement in CRS is still debatable.[75] The nasal passages are first sprayed with a topical decongestant in each nostril. After approximately 2 minutes, each nostril is instilled

with 20 mL of sterile saline by using a sterile syringe with a sterile, curved, blunt needle. Patients are instructed to take a deep breath and hold it before the instillation. Then the patient forcefully exhales the solution through the nose. The mucus is collected in a sterile container and sent to the mycology laboratory.

RESPIRATORY VIRUS PATHOGENS

Rhinoviruses are the most common pathogens associated with acute rhinosinusitis and are thought to set the stage for ABRS. Rhinoviruses do not colonize the nose; rhinovirus inoculation of a nonimmune individual causes infection, with rhinovirus shedding from the nose for up to 3 weeks. Rhinoviruses are present year round and can be detected, on average, in half of all patients with acute rhinosinusitis. Other respiratory viruses that can cause acute rhinosinusitis include influenza types A and B; parainfluenza types I, II, and III; respiratory syncytial virus; coronaviruses; herpes simplex; adenovirus; human metapneumovirus; and enteroviruses. In approximately 40% of cases, cultures are negative for viruses. Viral identification can be accomplished by means of cultures or PCR testing, depending on local facilities. Screening for all respiratory viruses is not cost-effective; selection of viruses to be identified in clinical trials depends on the antiviral compound being tested. In studies of pathogenesis, selection of viruses other than rhinovirus can be decided on the basis of knowledge of virus surveillance in the community. For influenza, this is available on the Centers for Disease Control and Prevention Web site: http://www.cdc.gov/flu/professionals/surveillance. Immunokit assays for influenza and respiratory syncytial virus provide good guidance for patient selection for studies, but further viral identification is required in clinical trials.

Specimen collection

1. Secretions from the nasopharynx can be obtained by using different methods:
2. Transnasally
   - Using suction: The suction catheter (eg, sinus secretion collector, Xomed) is guided under direct vision by means of rigid endoscopy or anterior rhinoscopy along the floor of the nasal cavity to the nasopharynx. Secretions retained in the suction catheter can be collected into the trap by flushing the suction tip with a small amount of saline.
   - Using a Calgiswab: The swab can be guided by using rigid endoscopy or anterior rhinoscopy along the floor of the nasal cavity to the nasopharynx.
3. Per oral
   - A Calgiswab is bent 45° and positioned behind the uvula under visual guidance. The swab is swiped on the posterior wall of the nasopharynx.
4. Swabs are eluted in 1 mL of Virus Transport Media (eg, Minimum Essential Media with 1% BSA).
5. Secretion from suctioning procedures needs addition of 0.1 mL of Virus Transport Media (eg, Minimum Essential Media with 2.5% BSA) per 0.9 mL of sample (secretion and saline).
6. Samples are transported on ice immediately to the laboratory or frozen at −70°C and transported without thawing.

Cultures

1. Viral isolation
   - The virology laboratory will inoculate the specimen into cell culture lines, which support growth of the respiratory virus to be identified.
   - A monolayer of fibroblasts (eg, MRC-5, WI-38, or HeLa cells) is used for isolation of rhinovirus. Quantitation of rhinovirus in positive samples can be reported as tissue culture infective dose per milliliter or plaque-forming units per milliliter.
2. Detection of virus genome by using PCR technology
   - Although not FDA approved for clinical diagnosis, commercial kits are available for:
   - certain DNA viruses (adenovirus and herpes simplex virus)
   - some RNA viruses (influenza A and B; parainfluenza I, II, and III; and respiratory syncytial virus) by means of RT-PCR.
   - PT primer-polymerase chain reaction (PT-PCR) methods for rhinoviruses, enteroviruses, coronaviruses, and human metapneumovirus have also been published.
   - New and improved methods, which are more rapid and less expensive, continue to evolve.

APPENDIX 5. LABORATORY MEASURES

CIRCULATING BIOMARKERS

Indirect biomarkers in the peripheral blood might be useful for disease classification or as a surrogate marker of disease activity or drug effect.

Application to CRS disease classification

The definitions for CRSsNP and CRSwNP do not contain criteria for circulating biomarkers. The definition for AFRS requires confirmation of the presence of fungal-specific IgE, which can be accomplished by evidence of fungal-specific IgE in the serum.

Application to CRS disease activity or drug effect

The following is a list of potential surrogate markers of disease activity or drug effect. To date, these have not been widely used in clinical trials.

1. Circulating eosinophil or eosinophil/basophil progenitor ($CD34^+$IL-$5R\alpha^+$) cell count. A circulating eosinophil count or count of eosinophil/basophil progenitor cells might be useful to assess the presence of an eosinophilic versus a noneosinophilic condition. An increase might be reflective of a disease process, such as CRSwNP or AFRS, and might be especially useful in clinical trials if the therapeutic intervention targets eosinophils specifically; however, other concurrent diseases, most notably asthma, allergic bronchopulmonary aspergillosis, atopic dermatitis, and Churg-Strauss syndrome, also cause eosinophilia, which greatly limits the specificity of these measures for sinus mucosal inflammation. Therefore tests of eosinophils and their precursors should be interpreted with caution and might have limited significance in the presence of these coexistent conditions.
2. Products of eosinophil degranulation in the circulation. Similar to a peripheral eosinophil count, the presence of eosinophil-derived components in the circulation might be an indirect marker of CRS disease activity, most notably that of CRSwNP or AFRS. The same caveats apply to these as apply to a peripheral eosinophil count.
3. Eosinophilopoietic cytokines in the circulation. Increased levels of eosinophilopoietic cytokines might be present in the circulation in association with an eosinophilic CRS disease process, such as CRSwNP or AFRS. Their measurement might be useful in clinical trials that target specific cytokines. The same caveats apply to these as apply to a peripheral eosinophil count.
4. Circulating neutrophils, products of neutrophil degranulation, or neutrophil-associated cytokines: an increase in any of these might be a circulating biomarker of ABRS, CRSsNP, or both.

DIRECT BIOMARKERS OF CRS DISEASE ACTIVITY

There are likely multiple allergic and immunologic mechanisms associated with the development of rhinosinusitis. Perennial AR is a predisposing factor for acute bacterial rhinosinusitis and an important comorbidity in CRS. The presence of AR is likely to be seen in nasal mucosal biopsy specimens of patients with CRS, even though its role in the pathogenesis of sinus inflammation is less clear. Markers of eosinophil tissue infiltration have been found in sinus mucosal biopsy specimens of patients with CRSsNP, CRSwNP, and AFRS and in NPs and might help elucidate underlying mechanisms of disease. Tissue eosinophil numbers do not clearly distinguish allergic from nonallergic patients. Other more specific markers, such as measurement of local IgE production directed against staphylococcal-derived superantigens or local immune responses to colonizing fungi, offer exciting insights into the pathogenesis of these diseases and might ultimately turn out to be important biomarkers of drug effects in therapeutic trials.

Direct biomarkers of CRS disease activity can include tests done on sinus-derived pathology specimens, such as staining for cellularity (hematoxylin and eosin), activated eosinophils (EG2), eosinophil-derived components (eosinophil cationic protein, major basic protein), neutrophil-derived components (elastase and myeloperoxidase), and cytokines associated with eosinophilic (IL-5, IL-13, eotaxin, RANTES) or neutrophilic (IL-8) inflammation. Similar measures might be useful in sinus mucus (see below).

Numerous mediators are measurable from nasal or sinus secretions, and some have shown changes in disease versus nondisease status. They might help to differentiate diseases to a certain degree but have not proved to be useful for monitoring of disease. Theoretically, they could be used for both antimicrobial and anti-inflammatory treatment approaches. A number of additional mediators can be measured from tissue specimens by using immunohistochemistry, *in situ* hybridization, or PCR. The relevance of these to clinical trials remains to be studied.

Eosinophils are found in sinus mucosal biopsy specimens from patients with CRSsNP, CRSwNP, and AFRS and in NPs, including both allergic and nonallergic patients. Although there might be quantitative differences in eosinophil numbers in these conditions, nonetheless, their presence might be importantly involved in the pathogenesis of each. Reductions in tissue eosinophil numbers has been demonstrated in response to topical corticosteroids in NPs.[76] One study of patients with CRS not preselected by CRS category found that the density of eosinophils, major basic protein, and the extent of eosinophil degranulation was greater in extraluminal mucus than the adjacent mucosal tissues,[77] suggesting that quantification of eosinophils or products of eosinophil degranulation in mucus might also be worthwhile in therapeutic trials.

In CRSwNP assessments for measuring the effect of staphylococci could include the presence and number of colonies of staphylococci; assays to detect the presence or absence of enterotoxin protein or IgE antibody levels to *Aeromonas* enterotoxin, toxic shock syndrome toxin-1; or a mixture (in homogenates). These have been performed on nasal secretions, as well as tissue samples. Intraepithelial *S aureus* has also been demonstrated within sinus tissues by means of confocal laser microscopy and immunohistochemistry.[78] Evidence of epithelial surface biofilm with bacteria resembling *S aureus* has also been demonstrated with electron microscopy.[79] Of these measurements, only IgE to *S aureus* enterotoxins indicates an immune reaction within the tissue, and this has been reported to differentiate patients with CRSwNP from control subjects and patients with CRSsNP in a statistically significant and potentially clinically relevant fashion[80,133]; however, these antibodies might also be found in the sera of some patients, especially those with asthma. There are no studies yet assessing whether the level of

these antibodies in secretions, tissues, or peripheral blood are altered by drug treatment.

Less is known about the local specific immune responses to colonizing fungi in CRS, although measures of *Alternaria* species–specific responses might ultimately prove to be useful in trials of antifungal agents.[81]

EXHALED NITRIC OXIDE AND TISSUE LEVELS OF INDUCIBLE NITRIC OXIDE SYNTHASE

Nitric oxide (NO) has a range of physiologic functions. In the upper airway these might include vasodilation and participation in innate immune function. NO is produced constitutively and in an inducible manner. There is a high level of constitutive NO production by sinus epithelium, and this is reduced in certain forms of rhinosinusitis, including primary ciliary dyskinesia, cystic fibrosis, and maxillary sinusitis. One mechanism for this reduction is blockage of the sinus ostia that reduces NO levels in nasally exhaled air, but there is also evidence for a reduced expression of inducible NO synthase (iNOS).[82] Conversely, there is evidence for increased expression of iNOS in allergic inflammation and nasal polyposis.[83] The interplay of baseline high constitutive NO production with vacillations caused by sinus ostial obstruction, diseased epithelium, and increased iNOS levels makes for a complex pathologic picture. The value of measurement of exhaled NO or tissue iNOS in clinical trials remains to be shown but could be considered in both ABRS, as well as CRS, trials.

Please see Table VIII for a summary list of biomarkers.

APPENDIX 6. BIOSTATISTICAL METHODS

Clinical trials in rhinosinusitis are no different than clinical trials in other diseases in that there are many aspects to the statistical design issues. Some of the major design issues are described below.

ELIGIBILITY CRITERIA

Before selection of an appropriate experimental design, the researchers need to ascertain the population that will be studied and the treatment modalities that will be investigated in that population. The eligibility criteria listed in the protocol must coincide with the study population. If the eligibility criteria for study entry are not very restrictive, then any conclusions drawn from the trial are generalizable to a large population (external validity). The drawback to this is that if the members of the population are very heterogeneous, then estimated treatment effects can be imprecise and not yield definitive conclusions. An obvious solution is to impose restrictive eligibility criteria to reduce the heterogeneity and provide more precise comparisons of the randomized groups. Criteria that are too restrictive, however, can yield a very narrow window of eligibility, which compromises participant recruitment and reduces external validity. Therefore determining optimal participant eligibility criteria requires balancing minimally restrictive and highly restrictive selection criteria.[74]

OUTCOME VARIABLES

The primary outcome variables to be measured during the course of a clinical trial in rhinosinusitis should represent the severity and condition of disease and should reflect responses to the proposed interventions. Rhinosinusitis researchers have invoked numerous outcome variables in clinical trials, such as symptoms, therapeutic responses, health outcomes, time to resolution or improvement, and bacteriologic eradication.

For the sake of simplicity of analysis, usually 1 outcome variable is selected as primary. If 2 outcome variables are selected as coprimary, then the researchers need to decide *a priori* how the results of the trial should be interpreted. For example, is it necessary for both outcome variables to yield a statistically significant result to claim treatment effectiveness, or is it necessary for only one of the outcome variables to be statistically significant to claim treatment effectiveness? If it is the former, then the researchers do not need to impose any adjustment to the significance levels and each of the 2 primary outcome variables would be analyzed at the preselected significance level (usually .05). If it is the latter, then the researchers should impose a correction factor to the significance level for each outcome variable so that the overall significance level of the trial is not inflated (the Bonferroni correction factor, for example, would require that each primary outcome variable be analyzed at the $0.05/2 = 0.025$ significance level).

TRIAL DESIGN

Based on the chosen intervention or interventions for a rhinosinusitis trial, 1 or more control therapies need to be determined. If the control group in a trial is a placebo, then the research objective of the trial is straightforward, namely to demonstrate the superiority of the intervention or interventions over the control. This is called a superiority trial and is the most common type of design in rhinosinusitis trials. In some circumstances, however, the researchers might decide to invoke a noninferiority trial design, in which the research objective is to demonstrate that the intervention is not inferior to some standard therapy (active control). A noninferiority trial design is appealing if the intervention is not as invasive or has fewer adverse effects than the active control, yet might yield nearly the same level of efficacy.[84-86]

The first major issue in designing a noninferiority trial is the selection of the active control. In particular, the active control should have been demonstrated to be superior to placebo in a published superiority trial. The dosage

strength and route of administration for the active control in the noninferiority trial should mimic that of the superiority trial when it was compared with placebo. The second major issue in designing a noninferiority trial is that the researchers need to define ''noninferiority'' for the primary outcome variable during the protocol development phase. This choice of a cutoff value for the primary outcome is based on clinical judgment, and there will not be universal consensus. For example, suppose the primary outcome variable in a rhinosinusitis trial is a quality-of-life measurement on a 7-point scale, and the active control yielded a 1.0-unit improvement over placebo (effect size) in the superiority trial. What cutoff value should be used to claim that the intervention is not inferior to the active control? A standard approach is that the difference between the intervention and the active control should be no larger than one-half times the effect size from the superiority trial. In our example this translates into the difference between the intervention and the active control being smaller than 0.5 units. This ''one-half times the effect size'' approach is very arbitrary, and it is better for the cutoff value to be determined based on clinical judgment, if possible.

RANDOMIZATION

Randomization is a critical feature of a clinical trial because it prevents procedure-selection biases. Stratified randomization is useful in a multicenter clinical trial because participants are (1) grouped into blocks or strata according to selected criteria and (2) randomized to treatment arms within each stratum. The objective of stratified randomization is to balance the treatment arms with respect to the stratifying variables. A permuted blocks scheme within each stratum might be necessary to ensure that in a trial with K treatment groups, the treatment groups are balanced after each set of $P \times K$ randomized participants, where P is a positive integer. Variability across clinical centers typically is the largest source of variation in multicenter clinical trials, and therefore randomization always should be stratified according to clinical center.[87] Depending on the primary outcome variables and the trial design, there might be prognostic variables that could serve as stratifiers, such as disease severity, classification of disease, sex, age, and ethnicity. The construction of strata should be limited so that empty, sparsely filled, or both strata do not result. If there are too many strata, then adaptive stratified randomization schemes should be considered.[74] The adaptive schemes balance the treatment arms according to marginal totals of participants already in the trial within certain strata. A trial with a relatively large sample size might not require stratification to achieve balance with respect to prognostic factors. It is prudent in a multicenter trial, however, to invoke stratification with clinical center as the stratifier, regardless of the sample size.

From a logistic perspective, a randomization scheme should not be discoverable. In other words, researchers, the participant, or both should not be able to ''discover'' the identity of the treatment before its initiation in the participant. Modern procedures for implementing randomization schemes typically involve Web-based systems or interactive telephone systems.

MEASUREMENT

Corresponding to the selection of the primary outcome variable or variables for a trial is the determination of the frequency and timing of measurement. Most rhinosinusitis trials incorporate a longitudinal component (repeated measurements of the outcome variables over time). A longitudinal trial provides the advantage of examining changes within treatment arms over the course of time. Within the context of a longitudinal trial, parallel and crossover designs are possible. In a parallel design the participants are randomized to treatments and remain on those treatments throughout the course of the trial.

In a crossover design the participants are randomized to sequences of treatment administrations. The simplest crossover design is the 2×2 crossover design, which consists of randomizing participants to receive (1) treatment A followed by treatment B or (2) treatment B followed by treatment A. The advantage of a crossover design is that it typically provides better precision for estimating the treatment comparisons. Crossover designs are not appropriate for every clinical trial. The disease condition must be chronic and stable, whereby treatments alleviate symptoms or improve physiology. Thus under some circumstances, crossover designs might be well suited for rhinosinusitis trials. The disadvantage of a crossover design is that sometimes there is confounding of treatment effects with carryover effects, defined as the residual effect of the treatments administered in previous visits. This confounding yields biased estimates of the treatment differences. If the treatments are pharmaceutical products that do not affect underlying physiology, then carryover effects can be minimized through adequate washout periods interspersed between treatment administrations.[88] Another approach is to invoke a crossover design that is more complex than the 2×2 crossover design, such that treatment effects and carryover effects are not confounded.[89,90]

INTERIM ANALYSES AND STOPPING RULES

A clinical trial has a fixed design if no interim analyses of the data are planned. If a clinical trial is brief in terms of participant recruitment and involvement ($\leq$6 months), a fixed design is reasonable. In a clinical trial of longer duration, however, it is prudent to schedule interim analyses of the data, so that strong evidence of treatment superiority, treatment adverse effects, or both would be uncovered as early as possible.[74,87] When the data analyses are scheduled at regular intervals, the clinical trial is

said to have a group sequential design. The cost of multiple analyses of the data is incurred by the use of a smaller target significance level (ie, < .05) at each scheduled data analysis. The Pocock approach for the stopping rules from interim analyses uses a constant significance level across scheduled analyses, whereas the O'Brien and Fleming approach uses increasing significance levels across scheduled analyses, with the significance level at the final analysis approaching the overall significance level, usually .05.[91,92] A more flexible approach for interim data analyses is the α-spending function, which does not require data analyses at equally spaced intervals.[93-95] An additional tool for interim analyses is to calculate the conditional power of treatment efficacy or futility, given the observed results at the interim stage.[74] It is important that the plans for any interim analyses be described in the protocol before trial onset. For large multicenter clinical trials, it is typical for an independent monitoring board to assess the results of the interim analyses and to determine whether the trial should continue or be terminated.

Although treatment compliance and protocol adherence of participants will be monitored and encouraged, some data might be suspect because of noncompliance and protocol violations. If the research objective of the trial is to assess the overall effectiveness of a new therapy regimen, then the researchers should include all available data from all randomized participants in the primary data analyses. This is known as the ''intent-to-treat'' paradigm and is recommended for a trial designed to investigate treatment effectiveness because it maintains (1) the randomization-induced prognostic balance among the treatment arms, (2) the total sample size, and (3) the validity of the statistical tests.[96,97] Supplemental data analyses with subsets of the data will be performed as deemed necessary. These can corroborate the conclusions of the intent-to-treat analyses, generate new hypotheses for study in future trials, or both. Alternatively, if the trial objective is to assess the efficacy or feasibility of a new therapy, then a ''treatment-received'' analysis might be more appropriate than an intent-to-treat analysis.[74] Phase III trials tend to be large effectiveness studies, whereas Phase II trials tend to be smaller efficacy studies.

SAMPLE SIZE CALCULATIONS

Every randomized clinical trial should include a sample size calculation in the protocol. The estimated sample size provides a target for patient recruitment effort. If the researchers reach the target, then there should be sufficient statistical power to attain statistical significance of the treatment comparison, provided that the anticipated difference between the treatment groups is realized. There are numerous sample size algorithms in the literature, and each is based on the statistical test that is proposed for the analysis of the primary outcome variable. For example, suppose that the statistical test for the primary outcome variable in a rhinosinusitis trial is a 2-sample t test. Suppose that during the planning stages of the trial, the researchers decided that they wanted to be able to detect a difference of δ units between the treatment groups (effect size). In addition, suppose that the primary outcome variable for the trial is known to have an approximate normal distribution with SD in the population of interest denoted as σ. Usually, σ is ''guesstimated'' from some pilot data or a published report. If the researchers plan to apply a 2-sided, .05 significance level, 2-sample t test to the data that result from the trial and they want to have 90% statistical power for detecting the effect size, then the approximate number of randomized patients per treatment group needed in the trial is as follows[74]:

$$n = 21(\sigma/\delta)^2.$$

As a simple example, if $\delta = 2$ units and $\sigma = 4$ units, then the number of randomized patients needed per treatment group is $n = 84$, for a total of 168 randomized patients. If the trial is longitudinal and some randomized patients are expected to withdraw consent and not complete the trial, then the sample size should be adjusted accordingly. For example, if the researchers expect a 10% withdrawal rate, then the sample size should be inflated to $168/(1-0.1) = 168/0.9 = 186$ randomized patients.

Obviously, this sample size formula is not appropriate for all situations. Sample size formulas and algorithms for other types of analyses are more complex.[74,98,99]

EAACI

European

Position Paper on Rhinosinusitis

and Nasal Polyps

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European Position Paper on Rhinosinusitis and Nasal Polyps

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1. Introduction

Rhinosinusitis is a significant health problem which seems to mirror the increasing frequency of allergic rhinitis and which results in a large financial burden on society (1-3). The last decade has seen the development of a number of guidelines, consensus documents and position papers on the epidemiology, diagnosis and treatment of rhinosinusitis and nasal polyposis (4-6).

Data on (chronic) rhinosinusitis is limited and the disease entity is badly defined. Therefore, the available data is difficult to interpret and extrapolate. Although of considerable assistance, the available consensus documents on chronic rhinosinusitis and nasal polyps do not answer a number of relevant questions that would unify the information and current concepts that exist in epidemiology, diagnosis, treatment and research. To add to this, none of these documents are evidence based.

There is considerable interest in guidelines as tools for implementing health care based on proof of effectiveness. Guidelines should be informative, simple and easy to use and in a form that can be widely disseminated within the medical community in order to improve patient care.

Evidence-based medicine is an important method of preparing guidelines (7, 8). Moreover, the implementation of guidelines is equally important.

The European Academy of Allergology and Clinical Immunology (EAACI) has created a Taskforce to consider what is known about rhinosinusitis and nasal polyps, to offer evidence based recommendations on diagnosis and treatment, and to consider how we can make progress with research in this area. The EP3OS document is also approved by the European Rhinologic Society (ERS).

The present document is intended to be state-of-the art for the specialist as well as for the general practitioner:

- to update their knowledge of rhinosinusitis and nasal polyposis;
- to provide an evidence-based documented revision of the diagnostic methods;
- to provide an evidence-based revision of the available treatments;
- to propose a stepwise approach to the management of the disease;
- to propose guidance for definitions and outcome measurements in research in different settings.

Table 1-1. Category of evidence (8).

Ia	Evidence from meta-analysis of randomised controlled trials
Ib	Evidence from at least one randomised controlled trial
IIa	Evidence from at least one controlled study without randomisation
IIb	Evidence from at least one other type of quasi-experimental study
III	Evidence from non-experimental descriptive studies, such as comparative studies, correlation studies, and case-control studies
IV	Evidence from expert committee reports or opinions or clinical experience of respected authorities, or both

Table 1-2. Strength of recommendation.

A	Directly based on category I evidence
B	Directly based on category II evidence or extrapolated recommendation from category I evidence
C	Directly based on category III evidence or extrapolated recommendation from category I or II evidence
D	Directly based on category IV evidence or extrapolated recommendation from category I, II or III evidence

2. Definition of rhinosinusitis and nasal polyps

2-1 Introduction

Rhinitis and sinusitis usually coexist and are concurrent in most individuals; thus, the correct terminology is now rhinosinusitis. The diagnosis of rhinosinusitis is made by a wide variety of practitioners, including allergologists, otolaryngologists, pulmonologists, primary care physicians and many others. Therefore, an accurate, efficient, and accessible definition of rhinosinusitis is required. A number of groups have published reports on rhinosinusitis and its definition. In most of these reports definitions are based on symptomatology and duration of disease and one definition aims at all practitioners (4-6, 9).

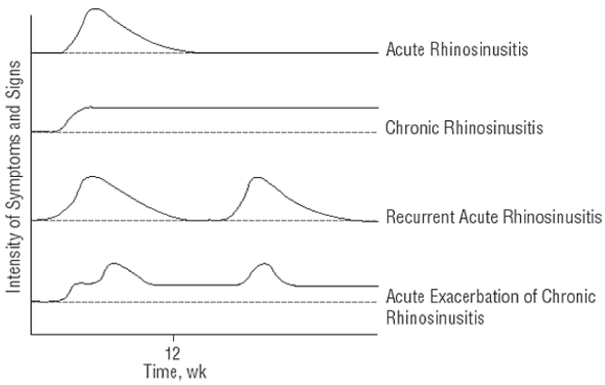
In 2001 the WHO put together a working group on rhinitis and its impact on asthma (ARIA)(10). In this group rhinitis was classified according to duration and severity.

Table 2-1. Classification of allergic rhinitis (10).

1-	"Intermittent" means that the symptoms are present: • Less than 4 days a week, • And for less than 4 weeks.
2-	"Persistent" means that the symptoms are present: • More than 4 days a week, • Or for more than 4 weeks. (should it be "and", not or?)
3-	"Mild" means that there are none of the following items: • No sleep disturbance, • No impairment of daily activities, leisure and/or sport, • No impairment of school or work, • Symptoms are not troublesome.
4-	"Moderate-severe" means that there are one or more of the following items: • Sleep disturbance, • Impairment of daily activities, leisure and/or sport, • Impairment of school or work, • Troublesome are symptoms.

Until recently rhinosinusitis was usually classified based on the duration into acute, subacute, chronic and acute on chronic (see figure 1). Yet this division does not correlate with the classification of rhinitis. Moreover it does not incorporate the severity of the disease. Also due to the long timeline of 12 weeks in chronic rhinosinusitis it can be difficult to discriminate between recurrent acute rhinosinusitis and chronic rhinosinusitis with or without exacerbations.

Figure 2-1. Former classification of Rhinosinusitis (11).



Due to the large differences in technical possibilities to diagnose and treat rhinosinusitis/nasal polyps by various professions, the need to differentiate between subgroups varies. On one hand the epidemiologist wants a workable definition that does not impose too many restrictions to study larger populations. On the other hand researchers in a clinical setting are in need of a set of clearly defined items that describes their patient population accurately and avoids the comparison of 'apples and oranges' in studies that relate to diagnosis and treatment. The taskforce tried to accommodate these different needs by giving definitions that can be applied in appropriate studies. In this way the taskforce hopes to improve the comparability of studies and thus enhance the evidence based diagnosis and treatment of patients with rhinosinusitis and nasal polyps.

2-2 Clinical definition

2-2-1 Clinical definition of rhinosinusitis/nasal polyps

Rhinosinusitis (including nasal polyps) is defined as:

- Inflammation of the nose and the paranasal sinuses characterised by two or more symptoms:
  - blockage/congestion;
  - discharge: anterior/post nasal drip;
  - facial pain/pressure,
  - reduction or loss of smell;

and either

- Endoscopic signs:
  - polyps;
  - mucopurulent discharge from middle meatus;
  - oedema/mucosal obstruction primarily in middle meatus,

and/or

- CT changes:
  - mucosal changes within ostiomeatal complex and/or sinuses.

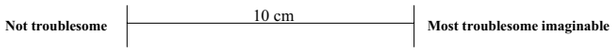
2-2-2 Severity of the disease

The disease can be divided into MILD and MODERATE/SEVERE based on total severity visual analogue scale (VAS) score (010 cm):

MILD = AS 0-4
MODERATE/SEVERE = VAS 5-10

To evaluate the total severity the patient is asked to indicate on a VAS the question:

How troublesome are your symptoms of rhinosinusitis?



2-2-3 Duration of the disease

Acute/Intermittent
< 12 weeks
Complete resolution of symptoms.

Chronic/Persistent
>12 weeks symptoms
No complete resolution of symptoms.

2-3 Definition for epidemiology/General Practice

For epidemiological studies the definition is based on symptomatology without ENT examination or radiology.

Acute/Intermittent Rhinosinusitis is defined as
sudden onset of two or more of the symptoms:
- blockage/congestion;
- discharge anterior/post nasal drip;
- facial pain/pressure;
- reduction/loss of smell;

for <12 weeks,
with symptom free intervals if the problem is intermittent,
with validation by telephone or interview.
Questions on allergic symptoms i.e. sneezing, watery rhino rhea, nasal itching and itchy watery eyes should be included.

Common cold/viral rhinosinusitis is defined as:
duration of symptoms for less than 10 days.

Acute/Intermittent non-viral rhinosinusitis is defined as:
increase of symptoms after 5 days or persistent symptoms after 10 days with less than 12 weeks duration.

Persistent/Chronic Rhinosinusitis/nasal polyps is defined as:
nasal congestion/obstruction/blockage with
- facial pain/pressure, or
- discoloured discharge(anterior / posterior nasal drip), or
- reduction/loss of smell

for >12 weeks,
with validation by telephone or interview.
Questions on allergic symptoms i.e. sneezing, watery rhino rhea, nasal itching and itchy watery eyes should be included.
Also include questions on intermittent disease (see definition above).

2-4 Definition for research

For research purposes Chronic Rhinosinusitis (CRS) is the major finding and Nasal Polyposis (NP) is considered a subgroup of this entity. For the purpose of a study, the differentiation between CRS and NP must be based on out-patient endoscopy.

The research definition is based on the presence of polyps and prior surgery.

2-4-1 Definitions when no earlier sinus surgery has been performed

Polyposis: bilateral, endoscopically visualised in middle meatus

Chronic rhinosinusitis: bilateral, no visible polyps in middle meatus, if necessary following decongestant

This definition accepts that there is a spectrum of disease in CRS which includes polypoid change in the sinuses and/or middle meatus but excludes those with polypoid disease presenting in the nasal cavity to avoid overlap.

2-4-2 Definitions when sinus surgery has been performed

Once surgery has altered the anatomy of the lateral wall, the presence of polyps is defined as pedunculated lesions as opposed to cobblestoned mucosa > 6 months after surgery on endoscopic examination. Any mucosal disease without overt polyps should be regarded as CRS .

2-4-3 Conditions for sub-analysis

The following conditions should be considered for sub-analysis:
- aspirin sensitivity based on positive oral, bronchial or nasal provocation or an obvious history;
- asthma/bronchial hyper-reactivity /COPD based on symptoms, respiratory function tests;
- allergy based on specific serum IgE or SPTs;
- finding of purulent discharge/pus.

2-4-4 Exclusion from general studies

Patients with the following diseases should be excluded from general studies on chronic rhinosinusitis and/or nasal polyposis:
- cystic fibrosis based on positive sweat test or DNA alleles;
- gross immunodeficiency (congenital or acquired);
- congenital mucociliary problems e.g. primary ciliary dyskinesia (PCD);
- non-invasive fungal balls and invasive fungal disease;
- systemic vasculitic and granulomatous diseases.

3. Chronic rhinosinusitis and nasal polyps

3-1 Anatomy and (patho)physiology

The nose and paranasal sinuses constitute a collection of air-filled spaces within the anterior skull. The paranasal sinuses communicate with the nasal cavity through small apertures. The nasal cavity and its adjacent paranasal sinuses are lined by pseudostratified columnar ciliated epithelium. This contains goblet cells and nasal glands, producers of nasal secretions that keep the nose moist and form a "tapis roulant" of mucus. Particles and bacteria can be caught in this mucus, rendered harmless by enzymes like lysozyme and lactoferrin, and be transported down towards the oesophagus. Cilia play an important role in mucus transport. All paranasal sinuses are normally cleared by this mucociliary transport, even though transport from large areas of sinuses passes through small openings towards the nasal cavity.

A fundamental role in the pathogenesis of rhinosinusitis is played by the ostiomeatal complex, a functional unit that comprises maxillary sinus ostia, anterior ethmoid cells and their ostia, ethmoid infundibulum, hiatus semilunaris and middle meatus. The key element is the maintenance of optimal sinus ventilation and clearance. Specifically, ostial patency significantly affects mucus composition and secretion; moreover, an open ostium allows mucociliary clearance to easily remove particulate matters and bacteria eventually come in contact with the sinusal mucosa.
Problems occur if the orifice is too small for the amount of mucus, if mucus production is increased, for instance during an upper respiratory tract infection (URI), or if ciliary function is impaired. Stasis of secretions follows and bacterial export ceases, causing or exacerbating inflammation of the mucosa whilst aeration of the mucosa is decreased, causing even more ciliary dysfunction. This vicious cycle can be difficult to break, and if the condition persists, it can result as chronic rhinosinusitis. In chronic rhinosinusitis the role of ostium occlusion seems to be less pronounced than in acute rhinosinusitis.

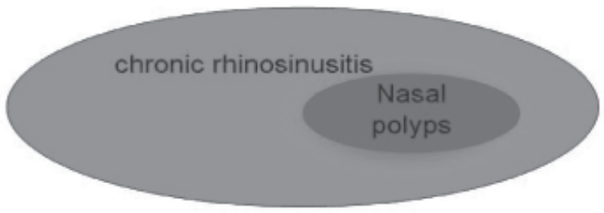
3-2 Rhinosinusitis

Rhinosinusitis is an inflammatory process involving the mucosa of the nose and one or more sinuses. The mucosa of the nose and sinuses form a continuum and thus more often than not the mucous membranes of the sinus are involved in diseases which are primarily caused by an inflammation of the nasal mucosa. Chronic rhinosinusitis is a multifactorial disease (12). Factors contributing can be mucociliary impairment (13, 14), (bacterial) infection (15), allergy (16), swelling of the mucosa for another reason, but only rarely physical obstructions caused by morphological/anatomical variations in the nasal cavity or paranasal sinuses (17, 18). A role in the pathogenesis of rhinosinusitis is certainly played by the ostiomeatal complex, a functional unit that comprises maxillary sinus ostia, anterior ethmoid cells and their ostia, ethmoid infundibulum, hiatus semilunaris and middle meatus. The key element is the maintenance of the ostial patency. An in depth discussion on factors contributing to chronic rhinosinusitis and nasal polyps can be found in chapter 4-4 and 4-6.

3-3 Nasal polyps and chronic rhinosinusitis

Nasal polyps and chronic rhinosinusitis are often taken together as one disease entity, because it seems impossible to clearly differentiate between them (19-21). Nasal Polyposis is therefore considered a subgroup of Chronic Rhinosinusitis (fig. 1).
The question remains as to why "ballooning" of mucosa develops in polyposis patients and not in all rhinosinusitis patients. Nasal polyps have a strong tendency to recur after surgery even when aeration is improved (22). This may reflect a distinct property of the mucosa of polyp patients which has yet to be identified. Some studies have tried to divide chronic rhinosinusitis and nasal polyps based on inflammatory markers (23-27). Although these studies point to a more pronounced eosinophilia and IL-5 expression in nasal polyps than that found in patients with chronic rhinosinusitis, these studies also point to a continuum in which differences might be found at the ends of the spectrum but at the moment no clear cut division can be made.

Figure 3-1. The spectrum of chronic rhinosinusitis and nasal polyps.



Nasal polyps appear as grape-like structures in the upper nasal cavity, originating from within the ostiomeatal complex. They consist of loose connective tissue, oedema, inflammatory cells and some glands and capillaries, and are covered with varying types of epithelium, mostly respiratory pseudostratified epithelium with ciliated cells and goblet cells. Eosinophils are the most common inflammatory cells in nasal polyps, but neutrophils, mast cells, plasma cells, lymphocytes and monocytes are also present, as well as fibroblasts. IL-5 is the predominant cytokine in nasal polyposis, reflecting activation and prolonged survival of eosinophils (28).

The reason why polyps develop in some patients and not in others remains unknown. There is a definite relationship in patients with 'Samter triad': asthma, NSAID sensitivity and nasal polyps. However, not all patients with NSAID sensitivity have nasal polyps, and vice-versa. In the general population, the prevalence of nasal polyps is 4% (29). In patients with asthma, a prevalence of 7 to 15% has been noted whereas, in NSAID sensitivity, nasal polyps are found in 36 to 60% of patients (30, 31). It had long been assumed that allergy predisposed to nasal polyps because the symptoms of watery rhinorrhoea and mucosal swelling are present in both diseases, and eosinophils are abundant. However, epidemiological data provide no evidence for this relationship: polyps are found in 0.5 to 1.5% of patients with positive skin prick tests for common allergens (31, 32).

4. Epidemiology and predisposing factors

4-1 Introduction

The incidence of acute viral rhinosinusitis (common cold) is very high. It has been estimated that adults suffer 2 to 5 colds per year, and school children may suffer 7 to 10 colds per year. The exact incidence is difficult to measure because most patients with common cold do not consult a doctor. More reliable data are available on acute rhinosinusitis. As mentioned earlier acute non-viral rhinosinusitis is defined as an increase of symptoms after 5 days or persistent symptoms after 10 days after a sudden onset of two or more of the symptoms: blockage/congestion, discharge, anterior/post nasal drip, facial pain/pressure and/or reduction/loss of smell. It is estimated that only 0.5% to 2% of viral URTIs are complicated by bacterial infection; however, the exact incidence is unknown given the difficulty distinguishing viral from bacterial infection without invasive sinus-puncture studies. Bacterial culture results in suspected cases of acute community-acquired sinusitis are positive in only 60% of cases (33). Signs and symptoms of bacterial infection may be mild and often resolve spontaneously (34, 35). In spite of the high prevalence and significant morbidity of chronic rhinosinusitis and nasal polyps, there is only limited accurate data on the epidemiology of these conditions. This observation mainly relates to the lack of a uniformly accepted definition for CRS. In addition, patient selection criteria greatly differ between epidemiologic studies complicating comparison of studies.

When interpreting epidemiologic data, one should be aware of a significant selection bias of the different studies presented below. The purpose of this section of the EPOS document is to give an overview of the currently available epidemiologic data on rhinosinusitis and nasal polyps, and illustrate the factors which are believed to predispose to the development.

4-2 Acute bacterial rhinosinusitis

When describing the incidence of acute bacterial rhinosinusitis there has been a lot of debate about the definition of acute bacterial rhinosinusitis. For example in the Cochrane Review on antibiotics for acute sinusitis, studies were included if sinusitis was proven by a consistent clinical history, and radiographic or aspiration evidence of acute sinusitis (36). However, most guidelines on the diagnosis of acute bacterial rhinosinusitis base the diagnosis on symptoms and clinical examination. However, if the diagnosis is based on clinical examination alone, the rate of false positive results is high. In patients with clinical diagnosis of acute rhinosinusitis less than half have significant abnormalities at X-ray examination (37). Based on sinus puncture/aspiration (considered diagnostically the most accurate), 49-83% of symptomatic patients had acute sinusitis (38). Compared with puncture/aspiration, radiography offered moderate ability to diagnose sinusitis Using sinus opacity or fluid as the criterion for sinusitis, radiography had sensitivity of 0.73 and specificity of 0.80 (38).

An average of 8.4% of the Dutch population reported at least one episode of acute rhinosinusitis per year in 1999 (39). The incidence of visits to the general practioner for of acute sinusitis in the Netherlands in 2000 was 20.0 per 1,000 men and 33.8 per 1,000 women (40). According to National Ambulatory Medical Care Survey (NAMCS) data in the USA rhinosinusitis is the fifth most common diagnosis for which an antibiotic is prescribed. Rhinosinusitis accounted for 9% and 21% of all paediatric and adult antibiotic prescriptions, respectively, written in 2002 (5).

4-3 Factors associated with acute rhinosinusitis

4-3-1 Pathogens

Superinfection of bacteria on mucosa damaged by viral infection (common cold) is the most important cause of acute rhinosinusitis. The most common bacterial species isolated from the maxillary sinuses of patients with acute rhinosinusitis are Streptococcus pneumoniae, Haemophilus influenzae, and Moraxella catarrhalis, the latter being more common in children (41, 42). Other streptococcal species, anaerobic bacteria and Staphylococcus aureus cause a small percentage of cases. Resistance patterns of the predominant pathogens vary considerably (43, 44). The prevalence and degree of antibacterial resistance in common respiratory pathogens are increasing worldwide. The association between antibiotic consumption and the prevalence of resistance is widely assumed (45).

4-3-2 Ciliary impairment

Normal mucociliary flow is a significant defence mechanism in the prevention of acute rhinosinusitis. Viral rhinosinusitis results in the loss of cilia and ciliated cells, with a maximum around one week after the infection. Three weeks after the beginning of the infection the number of cilia and ciliated cells increases to nearly normal. However, as a sign of regeneration, immature short cilia (0.7 to 2.5 microns in length) were often seen (46). The impaired mucociliary function during viral rhinosinusitis results in an increased sensitivity to bacterial infection.

Also in animal experimental work it was shown that early after exposure to pathogenic bacteria, like Streptococcus pneumoniae, Hemophilus influenzae, Pseudomonas aeruginosa, a significant loss of ciliated cells from sinus mucosa and a corresponding disruption of normal mucociliary flow was found (47).

4-3-3 Allergy

Review articles on sinusitis have suggested that atopy predisposes to rhinosinusitis (48). This theory is attractive given the popularity of the concept that disease in the ostiomeatal area contributes to sinus disease in that the mucosa in an individual with allergic rhinitis might be expected to be swollen and more liable to obstruct sinus ostia, reduce ventilation, lead to mucus retention that might be more prone to become infected. Furthermore there has been an increase in the body of opinion that regard the mucosa of the nasal airway as being in a continuum with the paranasal sinuses and hence the term rhinosinusitis (49). The number of studies determining the occurrence of acute rhinosinusitis in patients with and without allergy is very limited.

Savolainen studied the occurrence of allergy in 224 patients with verified acute rhinosinusitis by means of an allergy questionnaire, skin testing, and nasal smears. Allergy was found in 25% of the patients and considered probable in another 6.5%. The corresponding percentages in the control group were 16.5 and 3, respectively. There were no differences between allergic and non-allergic patients in the number of prior acute sinusitis episodes or of previously performed sinus irrigations. Bacteriological and radiological findings did not differ significantly between the groups (50). Alho showed that subjects with allergic IgE-mediated rhinitis had more severe paranasal sinus changes in CT scans than nonallergic subjects during viral colds. These changes indicate impaired sinus functioning and may increase the risk of bacterial sinusitis (51).

In conclusions: although an attractive hypothesis we can repeat the statement made a decade ago, there remain no published prospective reports on the incidence of infective rhinosinusitis in populations with and without clearly defined allergic rhinosinusitis (52).

4-4 Chronic rhinosinusitis (CRS)

CRS is one of the most common health care problems, with significant direct medical costs and severe impact on lower airway disease and general health outcomes (53, 54). The paucity of accurate epidemiologic data on CRS and nasal polyps contrasts with the more abundant information on microbiology, diagnosis and treatment options for these conditions. When reviewing the current literature on CRS, it becomes clear that giving an accurate estimate of the prevalence of CRS remains speculative, because of the heterogeneity of the disorder and the diagnostic imprecision often used in publications. In a survey on the prevalence of chronic conditions, it was estimated that CRS, defined as having 'sinus trouble' for more than 3 months in the year before the interview, affects 15.5% of the total population in the United States (55), ranking this condition second in prevalence among all chronic conditions. Later, the high prevalence of CRS was confirmed by another survey suggesting that 16% of the adult US population has CRS (56). However the prevalence of doctor diagnosed CRS is much lower; a prevalence of 2% was found using ICD-9 codes as an identifier(57).

Of note, the prevalence rate of CRS was substantially higher in females with a female/male ratio of 6/4 (55). In Canada, prevalence of CRS, defined as an affirmative answer to the question 'Has the patient had sinusitis diagnosed by a health professional lasting for more than 6 months?' ranged from 3.4% in male to 5.7% in female subjects (58). The prevalence increased with age, with a mean of 2.7% and 6.6% in the age groups of 20-29 and 50-59 years respectively. After the age of 60 years, prevalence levels of CRS levelled off to 4.7% (58). In a nationwide survey in Korea, the overall prevalence of chronic sinusitis, defined as the presence of at least 3 nasal symptoms lasting more than 3 months along with the endoscopic finding of a nasal polyp and/or mucopurulent discharge within the middle meatus, was 1.01% (59), without differences neither in age groups nor in sexes. By screening a non-ENT population, which may be considered representative of the general population in Belgium, Gordts et al. (60) reported that 6% of subjects suffered from chronic nasal discharge and 40% had signs of mucosal swelling of more than 3 mm on MRI . Notwithstanding the shortcomings of epidemiologic studies on CRS, it represents a common disorder of multifactorial origin. A list of factors will be discussed in the following chapter which are believed to be etiologically linked to CRS.

4-5 Factors associated with chronic rhinosinusitis (CRS)

4-5-1 Ciliary impairment

As may be concluded from the section on anatomy and pathophysiology, ciliary function plays an important role in the clearance of the sinuses and the prevention of chronic inflammation. Secondary ciliary dyskinesia is found in patients with chronic rhinosinusitis, and is probably reversible, although restoration takes some time (61) It will be clear that in patients with Kartagener's syndrome and primary ciliary dyskinesia, chronic rhinosinusitis is a common problem. These patients usually have a long history of respiratory infections. In patients with cystic fibrosis (CF), the inability of the cilia to transport the viscous mucus causes ciliary malfunction and consequently chronic rhinosinusitis. Nasal polyps are present in about 40% of patients with CF (62). These polyps are generally more neutrophilic than eosinophilic in nature but may respond to steroids as well, as inhaled steroids in patients with CF reduce neutrophilic inflammation (63-65).

4-5-2 Allergy

Review articles on rhinosinusitis have suggested that atopy predisposes to its development (48, 66). It is tempting to speculate that allergic inflammation in the nose predisposes the atopic individual to the development of CRS. Both conditions share the same trend of increasing prevalence (67, 68) and are frequently associated.

It has been postulated (69) that swelling of the nasal mucosa in allergic rhinitis at the site of the sinus ostia may compromise ventilation and even obstruct sinus ostia, leading to mucus retention and infection. Furthermore, there has been an increase in the body of opinion that regard the mucosa of the nasal airway as being in a continuum with the paranasal sinuses and hence the term 'rhinosinusitis' was introduced (49). However, critical analysis of the papers linking atopy as a risk factor to infective rhinosinusitis (chronic or acute) reveal that whilst many of the studies suggest a higher prevalence of allergy in patients presenting with symptoms consistent with sinusitis than would be expected in the general population, there may well have been a significant selection process, because the doctors involved often had an interest in allergy (27, 70-74). A number of studies report that markers of atopy are more prevalent in populations with chronic rhinosinusitis. Benninger reported that 54% of outpatients with chronic rhinosinusitis had positive skin prick tests (75). Among CRS patients undergoing sinus surgery, the prevalence of positive skin prick tests ranges from 50 to 84% (50, 76, 77), of which the majority (60%) have multiple sensitivities (77). As far back as 1975, Friedman reported an incidence of atopy in 94% of patients undergoing sphenoethmoidectomies (78).

However, the role of allergy in CRS is questioned by other epidemiologic studies showing no increase in the incidence of infectious rhinosinusitis during the pollen season in pollen-sensitized patients (52). In a small prospective study, no difference in prevalence of purulent rhinosinusitis was found between patients with and without allergic rhinitis (79). Furthermore, allergy was found in 31.5% of patients with verified acute maxillary sinusitis and there were no differences between allergic and non-allergic patients in the number of prior acute sinusitis episodes (50). Newman et al. reported that whilst 39% of patients with CRS had asthma, raised specific IgE or an eosinophilia, only 25% had true markers to show they were atopic (80). Finally, Emanuel et al. (77)found relatively lower percentages of allergic patients in the group of patients with the most severe sinus disease on CT scan and Iwens et al. (81) reported that the prevalence and extent of sinus mucosa involvement on CT was not determined by the atopic state.

Taken together, epidemiologic data show an increased prevalence of allergic rhinitis in patients with CRS, but the role of allergy in CRS remains unclear.

Radiological studies are unhelpful in unravelling the correlation between allergy and rhinosinusitis. High percentages of sinus mucosa abnormalities are found on radiological images of allergic patients, e.g. 60% incidence of abnormalities on CT scans among subjects with ragweed allergy during the season (82). However, one should interpret this data with caution in view of the fact that high percentages of incidental findings are found on radiological images of the sinus mucosa in individuals without nasal complaints, ranging from 24.7% to 49.2% (83-86), that the normal nasal cycle induces cyclical changes in the nasal mucosa volume (87), and that radiological abnormalities contribute minimally to the patient's symptoms (82).

Notwithstanding the lack of hard epidemiologic evidence for a clear causal relationship between allergy and CRS, it is clear that failure to address allergy as a contributing factor to CRS diminishes the probability of success of a surgical intervention (88). Among allergy patients undergoing immunotherapy, those who felt most helped by immunotherapy were the subjects with a history of recurrent rhinosinusitis, and about half of the patients, who had had sinus surgery before, believed that the surgery alone was not sufficient to completely resolve the recurrent episodes of infection (88).

4-5-3 Lower airway involvement

Recent evidence suggests that allergic inflammation in the upper and lower airways coexist and should be seen as a continuum of inflammation, with inflammation in one part of the airway influencing its counterpart at a distance. The arguments and consequences of this statement are summarized in the ARIA document (10). Rhinosinusitis and lower airway involvement are also frequently associated in the same patients, but their interrelationship is poorly understood. The evidence that treatment of rhinosinusitis improves asthma symptoms and hence reduces the need for medication to control asthma mainly results from research in children and will be discussed below (Chapter 7-6). In short, improvements in both asthma symptoms and medication have been obtained after surgery for rhinosinusitis in children with both conditions (89-91).

Studies on radiographic abnormalities of the sinuses in asthmatic patients have shown high prevalences of abnormal sinus mucosa (92, 93). All patients with steroid dependant asthma had abnormal mucosal changes on CT compared to 88% with mild to moderate asthma (94). Again caution should be exercised in the interpretation of these studies. Radiographically detected sinus abnormalities in sensitized patients may reflect inflammation related to the allergic state rather than to sinus infection.

4-5-4 Immunocompromised state

Among conditions associated with dysfunction of the immune system, congenital immunodeficiencies manifest themselves with symptoms early in life and will be dealt with in the paediatric CRS section (see Chapter 7-6). However, dysfunction of the immune system may occur later in life and present with CRS. In a retrospective review of refractory sinusitis patients, Chee et al. found an unexpectedly high incidence of immune dysfunction (95). Of the 60 patients with in vitro T-lymphocyte function testing, 55% showed abnormal proliferation in response to recall antigens. Low immunoglobulin G, A and M

titres were found in respectively 18, 17 and 5% of patients with refractory sinusitis. Common variable immunodeficiency was diagnosed in 10% and selective IgA deficiency in 6% of patients. Therefore, immunological testing should be an integral part of the diagnostic pathway of patients with CRS not responding to conservative treatment. In a cross-sectional study to assess the overall prevalence of otolaryngologic diseases in patients with HIV-infection, Porter et al. (96) reported that sinusitis was present in more than half of the HIV-positive population, ranking this condition one of the most prevalent diseases in HIV-positive persons. However, the relevance of these data is questioned as there was no difference in sinonasal symptom severity between HIV-positive and AIDS patients nor was there a correlation between CD4+ cell counts and symptom severity. In a more detailed study, Garcia-Rodrigues et al. (97) reported a lower incidences of rhinosinusitis (34%), but with a good correlation between low CD4+ cell count and the probability of rhinosinusitis. It should also be mentioned here that atypical organisms like Aspergillus spp, Pseudomonas aeruginosa and microsporidia are often isolated from affected sinuses and that neoplasms such as non-Hodgkin lymphoma and Kaposi's sarcoma, may account for sinonasal problems in patients with AIDS (98).

4-5-5 Genetic factors

Although chronic sinus disease has been observed in family members, no genetic abnormality has been identified linked to CRS. However, the role of genetic factors in CRS has been implicated in patients with cystic fibrosis (CF) and primary ciliary dyskinesia (Kartagener's syndrome). CF is one of the most frequent autosomal recessive disorders of the Caucasian population, caused by mutations of the CFTR gene on chromosome 7 (99). The most common mutation, DF508, is found in 70 to 80% of all CFTR genes in Northern Europe (100, 101). Upper airway manifestations of CF patients include chronic rhinosinusitis and nasal polyps, which are found in 25 to 40% of CF patients above the age of 5 (102-105). Interestingly, Jorissen et al. (106) reported that DF508 homozygosity represents a risk factor for paranasal sinus disease in CF.

4-5-6 Pregnancy and endocrine state

During pregnancy, nasal congestion occurs in approximately one-fifth of women (107). The pathogenesis of this disorder remains unexplained, but there have been a number of proposed theories. Besides direct hormonal effects of oestrogen, progesterone and placental growth hormone on the nasal mucosa, indirect hormonal effects like vascular changes may be involved. Whether pregnancy rhinitis predisposes to the development of sinusitis, is not clear. In a small prospective study, Sobol et al. (108) report that 61% of pregnant women had nasal congestion during the first trimester, whereas only 3% had sinusitis. In this study, a similar percentage of non-pregnant women in the control group developed sinusitis during the period of the study. Also in an earlier report, the incidence of sinusitis in pregnancy was shown to be quite low, i.e. 1.5% (109).

In addition, thyroid dysfunction has been implicated in CRS, but there is only limited data on the prevalence of CRS in patients with hypothyroidism.

4-5-7 Local host factors

Certain anatomic variations such as concha bullosa, nasal septal deviation and a displaced uncinate process, have been suggested as potential risk factors for developing CRS (110). However, Bolger et al. (111) found no correlation between CRS and bony anatomic variations in the nose. Also in the survey by Min et al. (112), no correlation was found between septal deviation and the prevalence of CRS. However, one should mention here that no study has so far investigated whether a particular anatomic variation can impair drainage of the ostiomeatal complex per se. Whilst some authors have postulated that anatomical variations of the paranasal sinuses can contribute to ostial obstruction (113) there are several studies that show the prevalence of anatomical variations is no more common in patients with rhinosinusitis or polyposis than in a control population (17, 18, 114, 115). One area where conjecture remains is the effect of a deviated septum. Whilst there is no recognised method of objectively defining the extent of a deviated septum, some studies have found a deviation of more than 3mm from the midline to be more prevalent in rhinosinusitis (116, 117)whilst others have not (18, 118). Taken together, there is no evidence for a causal correlation between nasal anatomic variations in general and the incidence of CRS. In spite of the observation that sinonasal complaints often resolve after surgery, this does not necessarily imply that anatomic variation is etiologically involved.

CRS of dental origin should not be overlooked when considering the aetiology of CRS. Obtaining accurate epidemiologic data on the incidence of CRS of dental origin is not possible as the literature is limited to anecdotal reports.

4-5-8 Micro-organisms

4-5-8-1 Bacteria

Although it is often hypothesized that CRS evolves from acute rhinosinusitis, the role of bacteria in CRS is far from clear. A number of authors have described the microbiology of the middle meatus and sinuses. However if and which of these pathogen are contributory to the disease remains a matter of debate.

Arouja isolated aerobes from 86% of the middle meatus samples CRS patients, anaerobes were isolated in 8%. The most frequent microorganisms were Staphylococcus aureus (36%), coagulase-negative Staphylococcus (20%), and Streptococcus pneumoniae (17%). Middle meatus and maxillary sinus cultures presented the same pathogens in 80% of cases. In healthy

individuals, coagulase-negative Staphylococcus (56%), S. aureus (39%), and S. pneumoniae (9%) were the most frequent isolates. (119).

Some authors suggest that as chronicity develops, the aerobic and facultative species are gradually replaced by anaerobes (120, 121). This change may result from the selective pressure of antimicrobial agents that enable resistant organisms to survive and from the development of conditions appropriate for anaerobic growth, which include the reduction in oxygen tension and an increase in acidity within the sinus. Often polymicrobial colonisation is found; the contribution to the disease of the different pathogens remains unclear.

4-5-8-2 Fungi

Fungi have been cultured from human sinuses with many different ramifications (122). Their presence may be relatively benign, colonizing normal sinuses or forming saprophytic crusts. They also may cause a range of pathology, ranging from non-invasive fungus balls to invasive, debilitating disease (123).

There is an increasing interest in the concept that the most common form of sinus disease induced by fungus may be caused by the inflammation stimulated by airborne fungal antigens. In 1999 it was proposed that most patients with CRS exhibit eosinophilic infiltration and the presence of fungi by histology or culture (124). This assertion was based on finding positive fungal culture by using a new culture technique in 202 of 210 (96%) patients with CRS who prospectively were evaluated in a cohort study. No increase in type I sensitivity was found in patients as compared with controls. The term "eosinophilic chronic rhinosinusitis" was proposed to replace previously used nomenclature. Using this new culture technique, the same percentage of positive fungi cultures was also found in normal controls (125).

A broad array of fungi has been identified in the sinus cavities of patients with sinusitis through varied staining and culture techniques (124, 125).

As with the isolation of bacteria in sinus cavities in these patients, the presence of fungi does not prove that these pathogens directly create or perpetuate disease.

4-5-9 "Osteitis"—the role of bone

Areas of increased bone density and irregular bony thickening are frequently seen on CT in areas of chronic inflammation and may be a marker of the chronic inflammatory process. However, the effect during the initial phases of a severe chronic rhinosinusitis frequently appears as rarefaction of the bony ethmoid partitions. Although to date bacterial organisms have not been identified in the bone in either humans or animal models of chronic rhinosinusitis, it has been suggested that that this irregular bony thickening is sign of inflammation of the bone. This inflamed bone might maintain mucosal inflammation (126).

In rabbit studies it was demonstrated that not only the bone adjacent to the involved maxillary sinus become involved, but that the inflammation typically spreads through the Haversian canals and may result in bone changes consistent with some degree of chronic osteomyelitis at a distance from the primary infection (127, 128). It is certainly possible that these changes, if further confirmed in patients, may at least in part, explain why chronic rhinosinusitis is relatively resistant to therapy.

4-5-10 Environmental factors

Cigarette smoking was associated with a higher prevalence of rhinosinusitis in Canada (58), whereas this observation was not confirmed in a nationwide survey in Korea (59). Other lifestyle-related factors are undoubtedly involved in the chronic inflammatory processes of rhinosinusitis. For instance, low income was associated with higher prevalence of CRS (58). In spite of in vitro data on the toxicity of pollutants on respiratory epithelium, there exists no convincing evidence for the etiologic role of pollutants and toxins such as ozone in CRS.

4-5-11 Iatrogenic factors

Among risk factors of CRS, iatrogenic factors should not be forgotten as they may be responsible for the failure of sinus surgery. The increasing number of sinus mucocoeles seems to correlate with the expansion of endoscopic sinus surgery procedures. Among a group of 42 patients with mucocoeles, 11 had prior surgery within 2 years before presentation (129). Another reason for failure after surgery can be the recirculation of nasal mucus out of the natural maxillary ostium and back through a separate surgically created antrostomy resulting in an increased risk of persistent sinus infection (130).

4-6 Nasal polyps

In the light of epidemiologic research, a distinction needs to be made between clinically silent NP, or preclinical cases, and symptomatic NP. Asymptomatic polyps may transiently be present or persist, and hence remain undiagnosed until they are discovered by routine examination. On the other hand, polyps that become symptomatic may remain undiagnosed, either because the patient is not investigated properly or because they are missed on anterior rhinoscopy. Endoscopy of the nasal cavity makes it possible to visualize NP and to give a reliable estimate of the prevalence of NP.

In a population-based study in Skövde, Sweden, Johansson et al. (131) reported a prevalence of nasal polyps of 2.7% of the total population. In this study, NP were diagnosed by nasal endoscopy and were more frequent in men (2.2 to 1), the elderly (5% at 60 years of age and older) and asthmatics. In a nationwide survey in Korea, the overall prevalence of polyps diagnosed by nasal endoscopy was 0.5% of the total population (112). Based on a postal questionnaire survey in Finland, Hedman et al. (29) found that 4.3% of the adult population

answered positively to the question as to whether polyps had been found in their nose. However, nasal endoscopy appears to be a prerequisite for an accurate estimate of the prevalence of NP, as 1.4% of the sample population studied by Johansson et al. (131) said to have NP, did not actually have any polyps on nasal endoscopy. From autopsy studies, a prevalence of 2% has been found using anterior rhinoscopy (132). After removing whole naso-ethmoidal blocks, nasal polyps were found in 5 of 19 cadavers (133), and in 42% of 31 autopsy samples combining endoscopy with endoscopic sinus surgery (134). The median age of the cases in the 3 autopsy studies by Larsen and Tos ranged from 70 to 79 years. From these cadaver studies, one may conclude that a significant number of patients with NP do not feel the need to seek medical attention or that the diagnosis of NP is often missed by doctors.

It has been stated that between 0.2 and 1% of people develop nasal polyps at some stage (135). In a prospective study on the incidence of symptomatic NP, Larsen and Tos (136) found an estimated incidence of 0.86 and 0.39 patients per thousand per year for males and females respectively. The incidence increased with age, reaching peaks of 1.68 and 0.82 patients per thousand per year for males and females respectively in the age group of 50-59 years. When reviewing data from patient records of nearly 5000 patients from hospitals and allergy clinics in the US in 1977, the prevalence of NP was found to be 4.2% (137), with a higher prevalence (6.7%) in the asthmatic patients.

In general, NP occur in all races (138-141) and becomes more common with age. The average age of onset is approximately 42 years, which is 7 years older than the average age of the onset of asthma (142-144). NP are uncommon under the age of 20 (145) and are more frequently found in men than in women (29, 136, 146), except in the population studied by Settipane (137).

4-7 Factors associated with NP

4-7-1 Allergy

0.5-4.5% of subjects with allergic rhinitis have NP (31, 32, 147), which compares with the normal population (135). In children the prevalence of NP has been reported to be 0.1% (31) and Kern found NP in 25.6% of patients with allergy compared to 3.9% in a control population (148). On the other hand, the prevalence of allergy in patients with nasal polyps has been reported as varying from 10% (149), to 54% (150) and 64% (151). Contrary to reports that have implicated atopy as being more prevalent in patients with NP, others have failed to show this (31, 147, 152-154). Recently, Bachert at al. (155) found an association between levels of both total and specific IgE and eosinophilic infiltration in nasal polyps. These findings were unrelated to skin prick test results. Positive intradermal tests to food allergies have been reported in 81% of polyp patients compared to 11% of controls (156). Food and drug sensitivities have been reported in 31% of patients with nasal polyposis and this was more common in men (43% vs. 24%) (140).

4-7-2 Asthma

In patients with asthma 7% have nasal polyps (31) with a prevalence of 13% in non-atopic asthma (skin prick test and total and specific IgE negative) and 5% in atopic asthma (145). Late onset asthma is associated with the development of nasal polyps in 10-15% (31). Asthma develops first in approximately 69% of patients with both asthma and NP and NP take between 9 and 13 years to develop. Ten percent develop both polyps and asthma simultaneously and the remainder develop polyps first and asthma later that (between 2 and 12 years) (138). However, not all patients with nasal polyps have lower respiratory tract symptoms (157).

Generally NP are twice as prevalent in men although the proportion of those with polyps and asthma is twice that in women than men. Women that have nasal polyps are 1.6 times more likely to be asthmatic and 2.7 times to have allergic rhinitis (141).

4-7-3 Aspirin sensitivity

In patients with aspirin sensitivity 36-96% have nasal polyps (32, 145, 158-163) and up to 96% have radiographic changes affecting their paranasal sinuses (164). Patients with aspirin sensitivity, asthma and nasal polyposis are usually non-atopic and the prevalence increases over the age of 40 years.

The children of probands with asthma, nasal polyps and aspirin sensitivity had nasal polyps and rhinosinusitis more often than the children of controls (165). Concerning hereditary factors, HLA A1/B8 has been reported as having a higher incidence in patients with asthma and aspirin sensitivity (166).

4-7-4 Genetics

An interesting observation is that NP are frequently found to run in families, suggestive of an hereditary or shared environmental factor. In the study by Rugina et al. (140), more than half of 224 NP patients (52%) had a positive family history of NP. The presence of NP was considered when NP had been diagnosed by an ENT practitioner or the patients had undergone sinus surgery for NP. A lower percentage (14%) of familial occurrence of NP was reported earlier by Greisner et al. in smaller group ($n = 50$) of adult patients with NP (59). Thus, these results strongly suggest the existence of a hereditary factor in the pathogenesis of NP. In this regard, recent genetic studies found a significant correlation between certain HLA alleles and NP. Luxenberger et al. (167) reported an association between HLA-A74 and nasal polyps, whereas Molnar-Gabor et al. (168) report that subjects carrying HLA-DR7-DQA1*0201 and HLA-DR7-DQB1*0202 haplotype had a 2 to 3 times odds ratio of developing NP.

Of note, studies of monozygotic twins have not shown both siblings always develop polyps, indicating that there are likely to be environmental factors influencing their development (169, 170). Nasal polyps have been described in identical twins but given the prevalence of nasal polyps it might be expected that there would be more than a rare report of this finding (171).

4-7-5 Environmental factors

The role of environmental factors in the development of NP is unclear. No difference in the prevalence of NP has been found in the patient's habitat or pollution at work (140). One study found that a significantly smaller proportion of the population with polyps were smokers compared to an unselected population (15% vs. 35%) (140) whilst another found an association between the use of a woodstove as a primary source of heating and the development of NP (172).

4-8 Epidemiology and predisposing factors for rhinosinusitis in children

4-8-1 Epidemiology

Since the introduction of CT scanning, it has become clear that a runny nose in a child is not only due to limited rhinitis or adenoid hypertrophy, but that in the majority of the cases the sinuses are involved as well. Van der Veken in a CT scan study showed that in children with a history of chronic purulent rhino rhea and a nasal obstruction 64% showed involvement of the sinuses (173). In a MRI study of a non-ENT paediatric population (60) it was shown that the overall prevalence of sinusitis signs in children is 45%. This prevalence increases in the presence of a history of nasal obstruction to 50%, to 80% when bilateral mucosal swelling is present on rhinoscopy, to 81% after a recent upper respiratory tract infection (URI), and to 100% in the presence of purulent secretions. Kristo et al. found a similar overall percentage (50%) of abnormalities on MRI in 24 school children (174). They included, however, a follow-up after 6 to 7 months, and found that about half of the abnormal sinuses on MRI findings had resolved or improved without any intervention.

Unfortunately, most studies in the paediatric ENT literature deal with patient populations (children with nasal complaints attending outpatient clinics) and few involve normal populations. Very few prospective studies are available and practically no documentation exists on the natural history of the disease.
The first prospective epidemiologic and long-term longitudinal study was performed by Maresh and Washburn (175) (see Table 4.1). It was started in 1925 and these authors followed on a regular basis 100 healthy children from birth to maturity, looking at the history, and performing a physical examination and routine postero-anterior radiograph of the paranasal sinuses 4 times a year (a total of 3,501 roentgenograms). The oldest children underwent over 50 radiographs. It was noted that there existed a relatively constant percentage (30%) of "pathologic" antra in the films taken between 1 and 6 years of age, the range being 23% to 35%. From 6 to 12 years, this percentage dropped steadily to approximately 15%. Interestingly, the authors noted that variations in size of the sinuses occur frequently, without any demonstrable relation to the amount or frequency of infections as seen on the radiographs and without following any definitive pattern. When there was a recent upper respiratory tract infection ("URI") (in the previous 2 weeks), less than 50% showed clear sinuses. Tonsillectomy had no demonstrable effect on the radiographic appearance of the sinuses.

Although this is one of the only long term follow-up studies one has to realize that a postero-anterior standard X-ray of the sinuses in a child gives only information about the maxillary sinuses and gives little information about the ethmoids so it may well be that the prevalence of sinusitis was under- or over-estimated.

In an MRI study of 60 children (mean age 5.7 years) with symptoms of uncomplicated URI for an average of 6 days, Kristo et al. found in 60% major abnormalities in maxillary and ethmoidal sinuses, 35% in sphenoidal sinuses, and 18% in the frontal sinuses (174). The MRI scores correlated significantly with the symptom scores, especially nasal obstruction, nasal discharge and fever. Of the 26 children with major abnormalities in the first MRI, these findings subsequently (after 2 weeks) improved significantly, showing that these abnormalities after an URI do not need antimicrobial therapy.

Therefore, it seems from all these studies that in younger chil-

Table 4-1. Results of epidemiologic studies in rhinosinusitis is children.

Author/year	*Included group*	*Examination method*	*Result*	*Conclusion*
Maresh, Washburn 1940 (175)	100 healthy children from birth to maturity	ENT-examination and pa-Xray of sinuses	30% pathologic antra overall >50% pathologic antra with previous upper airway infection (URI) in the last two weeks	high rate of pathology, can be under or over estimated because of the examination technique
Bagatsch 1980 (176)	24 000 children in the area of Rostock followed up for 1 year		one or more URI in the year: 0-2 years: 84% 4-6 years: 74% > 7years: 80%	

dren with chronic rhinosinusitis, there exists a spontaneous tendency towards recovery after the age of 6 to 8 years. This finding of a decrease in prevalence of rhinosinusitis in older children was also confirmed by other authors in patient populations (177).

4-8-2 Predisposing factors

In an extensive prospective study Bagatsch et al. (see Table 1) saw an influence of day-care (176). If children stay in day care centres, 72% in the group from 0 to 5 year develop one or more episodes of upper airway infection per year compared to 27% of the children staying at home.

Lind (178) and Bjuggren et al. (179) found a much higher prevalence of up to 100% of maxillary sinusitis in children staying in day care centres compared with the same age group staying at home or older children in schools.

The relationship between poor nasal patency and rhinosinusitis was confirmed by Van Cauwenberge (180) , who showed a significant relationship between the results of passive anterior rhinomanometry and pronounced oedema of the nasal mucosa ($p=0.09$ for the rights side, 0.03 for the left side) and the presence of purulent rhinitis ($p=0.006$ for the right side and <0.05 for the left side).

Breast feedings seems to have a beneficial influence on lower respiratory disease, but such an influence on sinusitis in infants and young children has not yet been demonstrated (181-183).

Passive smoking is a putative risk factor, especially in allergic children (183). There is a clearly increased risk for recurrent coryza (odds ratio 3.00) and sinus problems (odds ratio 4.73) in children with smoking mothers compared with children from non-smoking families (184).

4-9 Conclusion

The overview of the currently available literature illustrates the paucity of accurate information on the epidemiology of CRS and NP, especially in European countries, and highlights the need for large-scale epidemiologic research exploring their prevalence and incidence. Only by the use of standardized definitions for CRS and well-defined inclusion criteria for epidemiologic research, will it be possible to obtain accurate epidemiologic data on the natural evolution of CRS and NP, the influence of ethnic background and genetic factors on CRS and NP, and the factors associated with the disease manifestation. Such studies need to be performed in order to make significant progress in the development of diagnostic and therapeutic strategies for affected patients.

5. Inflammatory mechanisms in acute and chronic rhinosinusitis and nasal polyposis

5-1 Introduction

Rhinosinusitis is a heterogeneous group of diseases, with different underlying aetiologies and pathomechanisms, and may indeed represent an umbrella, covering different disease entities. It is currently not understood whether acute recurrent rhinosinusitis necessarily develops into chronic rhinosinusitis, which then possibly gives rise to polyp growth, or whether these entities develop independently from each other. All of these items may be referred to as "rhinosinusitis", meaning "inflammation of the nose and sinuses"; however, for didactic reasons and for future clinical and research purposes, a differentiation of these entities is preferred. For this purpose, we differentiate between acute rhinosinusitis (ARS), chronic rhinosinusitis (CRS) without polyps and chronic rhinosinusitis with nasal polyposis (NP), and omit an ill-defined group of "hyperplastic chronic rhinosinusitis", which might be included in CRS, or represent an overlap between CRS and NP.

5-2 Acute rhinosinusitis

Sinus mucosal tissue from subjects with acute bacterial rhinosinusitis (ARS) is difficult to sample, with the exception of acute complications of ARS, resulting in emergency sinus surgery. As a consequence, there is a relative lack of studies on cytokines and mediators in ARS. One of the first studies reported in 10 subjects undergoing surgery for complications, with mucosal tissue sampled from the maxillary sinus, which demonstrated significantly elevated protein concentrations of IL-8 compared to 7 controls (185) . Similar results, though not reaching significance, were obtained for IL-1ß and IL-6, whereas other cytokines such as GM-CSF, IL-5 and IL-4 were not upregulated. Recently, IL-8 and also TNF-alpha and total protein content were increased in nasal lavage from subjects with ARS compared to controls and allergic rhinitis subjects (186).

Proinflammatory cytokines such as IL-1ß, IL-6 and TNF play a prominent role in ongoing inflammatory reactions by activating endothelial cells, T-lymphocytes and others, inducing the expression of cell adhesion molecules and the release of other cytokines such as IL-8. IL-8 belongs to the CXC-chemokine group and is a potent neutrophil chemotactic protein, which is constantly synthesized in the nasal mucosa (187). The cytokine pattern found in ARS resembles that in naturally acquired viral rhinitis lavage (188).

5-3 Chronic rhinosinusitis

5-3-1 Histopathology

In the sinus fluid of patients with chronic rhinosinusitis undergoing surgery, the inflammatory cells are predominantly neutrophils, as observed in acute rhinosinusitis, but a small number of eosinophils, mast cells and basophils may also be found (189, 190). The mucosal lining in chronic rhinosinusitis is characterized by basement membrane thickening, goblet cell hyperplasia, subepithelial oedema, and mononuclear cell infiltration. In a recent study evaluating the percentage of eosinophils (out of 1000 inflammatory cells counted per vision field), 31 patients with untreated chronic rhinosinusitis without nasal polyps all had less than 10% eosinophils (overall mean 2%), whereas in 123 untreated nasal polyp specimen, 108 samples showed more than 10% eosinophils (overall mean 50%) (191). These observations suggest that tissue eosinophilia is not a hallmark of chronic rhinosinusitis without polyp formation, and that there are major differences in the pathophysiology of both sinus diseases.

5-3-2 Pathomechanism: cytokines, chemokines and adhesion molecules

A highly potent chemoattractant for neutrophils, IL-8 has been demonstrated in chronic rhinosinusitis tissue (192) and IL-8 protein concentrations in nasal discharge from chronic rhinosinusitis patients were significantly higher than in allergic rhinitis patients in a study also involving immunohistochemistry and in situ hybridization (193). In a study measuring cytokine protein concentrations including IL-3, IL-4, IL-5, IL-8 and GM-CSF in tissue homogenates, IL-8 was found to be significantly increased in acute rhinosinusitis, and IL-3 in chronic rhinosinusitis mucosa compared to inferior turbinate samples (194). IL-3 might be involved in the local defense and repair of chronically inflamed sinus mucosa by supporting various cell populations and indirectly contributing to fibrosis and thickening of the mucosa (195).

A range of mediators and cytokines has been described to be increased in CRS versus control tissue, mostly inferior turbinates, which comprises IL-1, IL-6, IL-8, TNF-a, IL-3, GM-CSF, ICAM-1, MPO and ECP (194, 196-198). Interestingly, VCAM-1, an adhesion molecule involved in selective eosinophil recruitment, and IL-5, a key cytokine for eosinophil survival and activity, have been shown not to be increased (194, 197). This cytokine and mediator profile resembles very much the profile found in viral rhinitis or acute rhinosinusitis, with the exception of a small though significant increase of

ECP. This profile is different from the pattern in nasal polyposis (see below).

The expression of transforming growth factor beta 1 (TGF-b1) at protein and RNA level is significantly higher in CRS versus NP and linked to a fibrotic cross anatomy (199). In CRS, MMP-9 and TIMP-1, a natural antagonist, but not MMP-7 are increased (200), probably resulting in a low MMP-9 activity.

5-4 Nasal polyps

5-4-1 Histopathology

Histomorphological characterisation of polyp tissue reveals frequent epithelial damage, a thickened basement membrane, and oedematous to sometimes fibrotic stromal tissue, with a reduced number of vessels and glands, but virtually no neural structure (201-203). The stroma of mature polyps is mainly characterised by its oedematous nature and consists of supporting fibroblasts and infiltrating inflammatory cells, localized around "empty" pseudocyst formations. Among the inflammatory cells, EG2+ (activated) eosinophils are a prominent and characteristic feature in about 80% of polyps (204), whereas lymphocytes and neutrophils are the predominant cells in cystic fibrosis and in CRS. Eosinophils are localised around the vessels, glands, and directly beneath the mucosal epithelium (202).

In small polyps, not larger than 5 mm, growing on normal looking mucosa of the middle turbinate in patients with bilateral polyposis, the early processes of polyp growth have been studied (205). Numerous subepithelial EG2+ eosinophils were present in the luminal compartment of the early stage polyp, forming a cap over the central pseudocyst area. In contrast, mast cells were scarce in the polyp tissue, but were normally distributed in the pedicle and the adjacent mucosa, which had a normal appearance. This contrasts to mature polyps, where degranulated mast cells and eosinophils are often diffusely distributed in the polyp tissue. Fibronectin deposition was noticed around the eosinophils in the luminal compartment of the early stage polyp, was accumulated subepithelially, and formed a network-like structure in the polyp centre and within the pseudocysts. The presence of myofibroblasts was limited to the central pseudocyst area. Interestingly, albumin and probably other plasma proteins were deposited within the pseudocysts, adjacent to the eosinophil infiltration. These observations suggest a central deposition of plasma proteins, regulated by the subepithelial eosinophilic inflammation, as a pathogenetic principle of polyp formation and growth.

5-4-2 Pathomechanism: cytokines, chemokines and adhesion molecules

5-4-2-1 Eosinophilic inflammation

A large body of studies has focussed on eosinophilic mediators in nasal polyp tissue, and demonstrated that different cell types generate these mediators. Early studies by Denburg et al. (206, 207) demonstrated that conditioned medium, derived from cultured nasal polyp epithelial cells, contained potent eosinophil colony-stimulating activities, as well as an interleukin-3-like activity. The authors suggested that accumulation of eosinophils in polyps may partly be a result of differentiation of progenitor cells stimulated by soluble haemopoietic factors derived from mucosal cell populations. An increased synthesis of GM-CSF by epithelial cells, fibroblasts, monocytes, and eosinophils was suggested later (71, 208, 209). According to Hamilos et al. (27), polyp tissue samples from patients with or without allergy contained different cytokine profiles.
They found by in situ hybridization studies that patients with "allergic" polyps had higher tissue densities of GM-CSF, IL-3, IL-4, and IL-5 transcripts than controls, whereas patients with non-allergic polyps had higher tissue densities of GM-CSF, IL-3, and IFN-gamma transcripts. From these results, distinct pathomechanisms for allergic versus non-allergic polyps were suggested. Other studies involving protein measurements in tissue homogenates could not support these findings (28, 194).

In contrast, IL-3 and GM-CSF protein were found in only a small number of polyp and control turbinate samples. However, IL-5 was found to be significantly increased in nasal polyps, compared to healthy controls, and the concentration of IL-5 was independent of the atopic status of the patient. Indeed, the highest concentrations of IL-5 were found in subjects with non-allergic asthma and aspirin sensitivity. Furthermore, eosinophils were positively stained for IL-5, suggesting a possible autocrine role for this cytokine in the activation of eosinophils, and a strong correlation between concentrations of IL-5 protein and eosinophilic cationic protein (ECP) was demonstrated later (155). The key role of IL-5 was supported by the finding that treatment of eosinophil-infiltrated polyp tissue with neutralizing anti-IL-5 monoclonal antibody (mAB), but not anti-IL-3 or anti-GM-CSF mAbs in vitro, resulted in eosinophil apoptosis and decreased tissue eosinophilia (210).

Collectively, these studies suggest that increased production of IL-5 is likely to influence the predominance and activation of eosinophils in nasal polyps independent of atopy. The lack of difference in the amounts of cytokines detected in polyps from allergic or non-allergic patients was meanwhile supported by several other studies (211, 212). Furthermore, Wagenmann et al. (213) demonstrated that both Th1 and Th2 type cytokines were upregulated in eosinophilic NP, irrespective of allergen skin test results.

Recently, the regulation of the IL-5 receptor, which exists in the soluble and transmembrane isoform, has been investigated (214). Whereas the probably antagonistic soluble isoform is upregulated, the signal transducing transmembrane isoform is down-regulated in nasal polyps, especially if associated with asthma.

Recent studies have also shown that nasal polyps also express high levels of RANTES and eotaxin, the predominant recognised eosinophil chemoattractants. Bartels and colleagues (215) demonstrated that expression of eotaxin- and RANTES mRNA, but not MCP-3 mRNA, was elevated in non-atopic and atopic nasal polyps, when compared to normal nasal mucosa. Similarly, Jahnsen and colleagues (216) demonstrated an increased mRNA expression for eotaxin, eotaxin-2, and MCP-4. The expression of eotaxin-2, another CCR3-specific chemokine, was found to be the most prominent of the three chemokines investigated. According to other data (28, 155, 205), it appears that eotaxin, rather than RANTES, in cooperation with IL-5, plays a key role in chemo-attraction and activation of eosinophils in NP tissue. This is in accordance with the findings of a recent extensive study of about 950 non-allergic and allergic polyp patients, which has also suggested that nasal polyp eosinophilic infiltration and activation may correlate mainly with increased eotaxin gene expression, rather than with RANTES expression (217).

Studies of cell adhesion molecules are relatively few. Early studies by Symon and colleagues (218) demonstrated that ICAM-1, E-selectin and P-selectin were well expressed by nasal polyp endothelium, whereas VCAM-1 expression was weak or absent. An elegant study by Jahnsen et al. (219), employing three-colour immunofluorescence staining, has however demonstrated that both the number of eosinophils and the proportion of vessels positive for VCAM-1 were significantly increased in nasal polyps compared with the turbinate mucosa of the same patients. Moreover, treatment with topical glucocorticosteroids decreases the density of eosinophils and the expression of VCAM-1 in polyps (220). The interaction between VLA-4 on eosinophils and VCAM-1 on endothelial cells may not only be of particular importance for transendothelial migration of eosinophils, but may also modify their activation and effector functions (221).

5-4-2-2 Extracellular matrix regulation

The expression of TGF-β_1 and TGF-β_2, predominantly by eosinophils, and their putative effects on fibroblast activity and pathogenesis of nasal polyps have been suggested in several studies (222-224). These studies again compared protein levels in tissue homogenates from patients with nasal polyps who were either untreated or treated with oral corticosteroid, and control subjects.

Patients with untreated polyp samples and controls showed significantly higher concentrations of IL-5, eotaxin, ECP and albumin, and significantly lower concentrations of TGF-β_1. In contrast, corticosteroid treatment significantly reduced IL-5, ECP and albumin concentrations, whereas TGF-β_1 was increased (205).

These observations suggest IL-5 and TGF-β_1 represent cytokines with counteracting activities, with a low TGF-β protein concentration in IL-5 driven nasal polyps. Furthermore, they supported the deposition of albumin and other plasma proteins as a possible pathogenic principle of polyp formation, regulated by the subepithelial eosinophilic inflammation.

TGF-β_1 is a potent fibrogenic cytokine that stimulates extracellular matrix formation, acts as a chemoattractant for fibroblasts, but inhibits the synthesis of IL-5 and abrogates the survival-prolonging effect of haematopoietins (IL-5 and GM-CSF) on eosinophils (225). Staining of nasal polyp tissue shows that TGF-β_1 is mainly bound to the extracellular matrix, where it is found in its latent, inactive form.

Oedema and pseudocyst formation characterize NP, with only a few areas of fibrosis. An imbalance of metallo-proteinases with an upregulation of MMP-7 and MMP-9 in nasal polyps has been recently demonstrated(200). This results in the enhancement of MMP-9 in NP, which may account for oedema formation with albumin retention.

5-4-2-3 Role of Staphylococcus aureus enterotoxins (SAEs)

Early studies have shown that tissue IgE concentrations and the number of IgE positive cells may be raised in nasal polyps, suggesting the possibility of local IgE production (226). The local production of IgE is a characteristic feature of nasal polyposis, with a more than tenfold increase of IgE producing plasma cells in NP versus controls. Analysis of specific IgE revealed a multiclonal IgE response in nasal polyp tissue and IgE antibodies to Staphylococcus aureus enterotoxins (SAEs) in about 30-50% of the patients and in about 60-80% of nasal polyp subjects with asthma (155, 205, 227). A recent prospective study revealed that colonization of the middle meatus with Staphylococcus aureus is significantly more frequent in NP (63.6%) compared to CRS (27.3%, $p < 0.05$), and is related to the prevalence of IgE antibodies to classical enterotoxins (27.8 vs 5.9%) (228). If aspirin sensitivity, including asthma, accompanied nasal polyp disease, the Staph. aureus colonization rate was as high as 87.5%, and IgE antibodies to enterotoxins were found in 80% of cases.

Total and specific IgE in polyp homogenates is only partially reflected in the serum of these patients. In contrast, staining of NP tissue revealed follicular structures characterised by B- and T-cells, and lymphoid agglomerates with diffuse plasma cell infiltration, demonstrating the organization of secondary lymphoid tissue with consecutive local IgE production in NP(229).

The classical SAEs, especially TSST-1 and Staphylococcus protein A (SPA), are excellent candidates to induce multiclonal IgE synthesis by increasing the release of IL-4 as well as the expression of CD40 ligand on T-cells and B7.2 on B-cells cells (230, 231).

SPA furthermore interacts with the VH3-family of immunoglobulin heavy chain variable gene products and thus preferentially selects plasma cells presenting such immunoglobulins on their surface, which leads to a VH3 bias (232). In fact, follicle-like aggregates can be found in nasal polyps, expressing CD20+ B-cells, CD3+ T-cells and IgE plasma cells, but largely lacking CD1a+ dendritic antigen presenting cells, supporting the concept of a superantigen stimulation(229). SAEs furthermore stimulate T-cells by binding to the variable beta-chain of the T-cell receptor, which induces cytokine production of IL-4 and IL-5, directly activate eosinophils and prolong their survival and also may directly activate epithelial cells to release chemokines (233). SAEs furthermore activate antigen presenting cells to increase antigen uptake. In fact, when comparing SAE-IgE positive nasal polyps to SAE-IgE negative, the number of IgE positive cells and eosinophils is significantly increased. The more severe inflammation is also reflected by significantly increased levels of IL-5, ECP and total IgE. In conclusion, SAEs are able to induce a more severe eosinophilic inflammation as well as the synthesis of a multiclonal IgE response with high total IgE concentrations in the tissue, which would suggest that SAEs are at least modifiers of disease in nasal polyposis (233). Interestingly, similar findings have recently been reported in asthma, which is known to be associated with NP (234). IgE antibody formation to SAE can be seen in nasal polyp tissue, but rarely in CRS.

5-5 Conclusion

Although far from being completely understood, pathomechanisms in ARS, CRS and NP are better understood today and begin to allow us to differentiate these diseases via their cytokine profile, their pattern of inflammation as well as remodelling processes. In NP, but not in CRS, staphylococcus-derived superantigens may at least modulate disease severity and expression. For these reasons, CRS and NP should probably be considered as distinct diseases.

6. Diagnosis

6-1 Assessment of rhinosinusitis symptoms

6-1-1 Symptoms of rhinosinusitis

Subjective assessment of rhinosinusitis is based on symptoms:

- nasal blockage, congestion or stuffiness;
- nasal discharge or postnasal drip, often mucopurulent;
- facial pain or pressure, headache, and
- reduction/loss of smell.

Besides these local symptoms, there are distant and general symptoms. Distant symptoms are pharyngeal, laryngeal and tracheal irritation causing sore throat, dysphonia and cough, whereas general symptoms include drowsiness, malaise and fever. Individual variations of these general symptom patterns are many (21, 235-239).

The symptoms are principally the same in intermittent and persistent rhinosinusitis as well as in nasal polyposis, but the symptom pattern and intensity may vary. Acute forms of infections, both acute intermittent and acute exacerbations in persistent, have usually more distinct and often more severe symptoms.

Simple nasal polyps may cause constant non-periodic nasal blockage , which can have a valve-like sensation allowing better airflow in only one direction. Nasal polyps may cause nasal congestion, which can be a feeling of pressure and fullness in the nose and paranasal cavities. This is typical for ethmoidal polyposis, which in severe cases can cause widening of the nasal and paranasal cavities demonstrated radiologically and in extreme cases, hyperteliorism. Disorders of smell are more prevalent in patients with nasal polyps than in other chronic rhinosinusitis patients (22).

6-1-2 Subjective assessment of the symptoms

Subjective assessment of the symptoms should consider the strength or degree of the symptoms, the duration of the symptom. During the last decade more attention has been paid not only to symptoms but also to their effect on the patient's quality of life (QoL) (240, 241).

The assessment of subjective symptoms is done using questionnaires or in clinical studies recorded in logbooks. Evaluation frequency depends on the aims of the study, usually once or twice daily. Continuous recording devices are also available.

The degree or strength of the symptoms can be estimated using many different grading tools:

- recorded as such: severe, moderate, slight and no symptom;
- recorded as numbers: from 4 to 0 or as many degrees as needed;
- recorded as VAS score on a line giving a measurable continuum (0 – 10 cm).

Terms such as mild, moderate or severe may include both symptom severity estimation, but also an estimate of duration i.e. "moderate symptom severity" can mean an intense symptom but only for a short time in the recorded period or less severe symptom but lasting for most of the recording period.

The duration of the symptoms is evaluated as symptomatic or symptom free moments in given time periods, i.e. as hours during the recording period or as day per week.

"No symptom" can be regarded as a consistent finding in most studies. It provides the possibility to record time periods (e.g. days) without symptoms, which can be reliably compared between testees (inter-patient) and from study to study.

These criteria are inconsistent and not always comparable when considering rhinosinusitis (239), where the symptoms may fluctuate from time to time. Nevertheless in many randomised, controlled and prospective rhinosinusitis intervention studies, both allergic and infective, these methods of recording symptoms have given statistically significant results.

6-1-3 Validation of subjective symptoms assessment

Validation of the rhinosinusitis symptoms to show the relevance in distinguishing disease modalities and repeatability between ratings of the same patient (intrapatient) and between different patients (interpatient) have been done. Lately, more specific and validated subjective symptom scoring tools have become available with the development of quality of life (QoL) evaluations. These are either assess general health evaluating (242, 243) or are disease specific (240, 241).

6-1-3-1 Nasal obstruction

Validation of subjective assessment of nasal obstruction or stuffiness has been done by studying the relationship between subjective and objective evaluation methods for functional nasal obstruction.

Generally the subjective sensation of nasal obstruction and rhinomanometric or nasal peak flow evaluations show a good intra-individual correlation in a number of studies considering normal controls, patients with structural abnormalities, hyperreactivity or infective rhinitis (244-248). However, there are also some studies where this correlation is not seen (249) or the correlation was poor (250, 251).

The interpatient variation in subjective scoring suggests that every nose is "individually calibrated", which makes interpatient comparisons less reliable but still significant (244, 246).

Subjective nasal obstruction correlates better with objective functional measurements of nasal airflow resistance (rhinomanometry, peak flow) than with measurements of nasal cavity width, such as acoustic rhinometry (248, 252).

Nasal obstruction can also be assessed objectively by tests using personal nasal peak flow instruments, inspiratory or expiratory, which patients can take home or to their work place and do measurements at any desired time intervals.

Subjective assessment of nasal obstruction is a well validated criterion.

6-1-3-2 Nasal discharge

Techniques for objective assessment of nasal discharge are not as good as for nasal obstruction: Counting the nose blowings in a diary card or using a new handkerchief from a counted reservoir for each blow and possibly collecting the used handkerchiefs in plastic bags for weighing have been used in acute infective rhinitis (253) and in "autonomic (previously termed vasomotor) rhinitis" (254).

Validating correlation studies between "objective" discharge measures (collecting and measuring amount or weight of nasal secretion as drops, by suction, or using hygroscopic paper strips etc) and subjective scoring of nasal discharge or postnasal drip has not been done.

6-1-3-3 Smell abnormalities

Fluctuations in the sense of smell are associated with chronic rhinosinusitis. This may be due to mucosal obstruction of the olfactory niche (conductive loss) or degenerative alterations in the olfactory mucosa due to the disease or its treatment e.g. repeated nasal surgery.

Subjective scoring of olfaction is a commonly used assessment method. In validating clinical settings subjective scores have been found to correlate significantly to objective olfactory threshold and qualitative tests in normal population, rhinosinusitis and other disease conditions (255-257) as well as numerous clinical studies concerning other diseases than rhinosinusitis (Evidence level Ib).

6-1-3-4 Facial pain and pressure

Facial or dental pain, especially unilateral, have been found to be predictors of acute maxillary sinusitis with fluid retention in patients with a suspicion of infection, when validated by maxillary antral aspiration (235) or paranasal sinus radiographs (258). In CRS symptoms are more diffuse and fluctuate rendering the clinical correlation of facial pain and pressure scorings against objective assessments unconvincing. Poor correlation between facial pain localisation and the affected paranasal sinus CT pathology in patients with supposed infection, both acute and chronic, has been reported (259). However, rhinosinusitis disease specific quality of life studies also include facial pain-related parameters, which have been validated (260).

6-4-3-5 Overall rating of rhinosinusitis severity

Overall rating of rhinosinusitis severity can be obtained as such or by total symptoms scores, which are summed scores of the individual symptoms scores. These are both commonly used, but according to an old validation study for measuring the severity of rhinitis, scores indicating the course of individual symptoms should not be combined into a summed score, rather the patient's overall rating of the condition should be used (261). QoL methods have produced validated questionnaires which measure the impact of overall rhinosinusitis symptoms on everyday life (240).

Objective experiments to differentiate patient groups according to rhinosinusitis severity or aetiology have been done using nasal provocation with histamine or metacholine (262, 263) which test mucosal hyper-reactivity. The tests can differentiate subpopulations with statistical significance, but because of considerable overlap of results, these tests have not achieved the equivalent position in rhinitis severity evaluations as the corresponding bronchial tests i.e. in asthma diagnosis. Grading of CT findings, both structural and mucosal, do not reflect the rhinosinusitis symptom severity either (264).

Validation of classical overall rating scores for rhinosinusitis against objective criteria is insufficient, but quality of life evaluations of these criteria have been validated.

6-2 Examination

6-2-1 Anterior rhinoscopy

Anterior rhinoscopy alone is inadequate, but remains the first step in examining a patient with these diseases.

6-2-2 Endoscopy

This may be performed without and with decongestion and semi-quantitative scores (237) for polyps, oedema, discharge, crusting and scarring (post-operatively) can be obtained (Table 1). A number of staging systems for polyps have been proposed (264-266). Johansson showed good correlation between a 0-3 scoring system and their own system in which they estimated the percentage projection of polyps from the lateral wall and the percentage of the nasal cavity volume occupied by polyps. However, they did not find a correlation between size of polyps and symptoms. (Level III).

Table 6-1. Endoscopic appearances scores.

Characteristic	Baseline	3 mo	6 mo	1 y	2 y
Polyp left (0,1,2,3)					
Polyp, right (0,1,2,3)					
Oedema, left (0,1,2,)					
Oedema, right (0,1,2,)					
Discharge, left (0,1,2)					
Discharge, right (0,1,2)					
Postoperative scores to be used for outcome assessment only					
Scarring, left (0.1,2)					
Scarring, right (0.1,2)					
Crusting, left (0,1,2)					
Crusting, right (0,1,2)					
Total points					

0-Absence of polyps;
1-polyps in middle meatus only;
2-polyps beyond middle meatus but not blocking the nose completely;
3-polyps completely obstructing the nose.
Oedema: 0-absent; 1-mild; 2-severe
Discharge: 0-no discharge; 1-clear, thin discharge; 2-thick, purulent discharge
Scarring: 0-absent; 1-mild; 2-severe
Crusting: 0-absent; 1-mild; 2-severe. (237, 267)

Table 6-2. Bacteriology of Rhinosinusitis; Correlation of middle meatus versus maxillary sinus.

Author	*No of Samples*	*Type of Rhinosinusitis*	*Technique*	*Concordance*
Gold & Tami, 1997 (271)	21	chronic	Endoscopic tap (MM) v maxillary aspiration during ESS	85.7%
Klossek et al., 1998 (270)	65	chronic	Endoscopic swab (MM) v maxillary aspiration during ESS	73.8%
Vogan et al., 2000 (272)	16	acute	Endoscopic swab (MM) v maxillary sinus tap	93%
Casiano et al., 2001 (273)	29	acute (intensive care)	Endoscopic tissue culture (MM) v maxillary sinus tap	60%
Talbot et al., 2001 (274)	46	acute	Endoscopic swab (MM) v maxillary sinus tap	90.6%

MM: middle meatus; ESS: endoscopic sinus surgery

6-2-3 Nasal cytology, biopsy and bacteriology

A positive nasal smear may be helpful in indicating the aetiology of disease (268, 269) but a negative smear is not conclusive. The advantage of the technique is its cheapness. However, quantification and changes as a result of therapy in chronic rhinosinusitis/nasal polyposis have not been routinely used

A biopsy may be indicated to exclude more sinister and severe conditions such as neoplasia and the vasculitides.

Several microbiology studies (270-273) [Evidence Level IIb] have shown a reasonable correlation between specimens taken from the middle meatus under endoscopic control and proof puncture leading to the possibility of microbiological confirmation of both the pathogen and its response to therapy (Table 6-2).

6-2-4 Imaging

Plain sinus x-rays are insensitive and of limited usefulness for the diagnosis of rhinosinusitis due to the number of false positive and negative results (275-277).

Transillumination was advocated in the 1970 as an inexpensive and efficacious screening modality for sinus pathology (278). The insensitivity and unspecificity makes it unreliable for the diagnosis of rhinosinusitis (279)

CT scanning is the imaging modality of choice confirming the extent of pathology and the anatomy. However, it should not be regarded as the primary step in the diagnosis of the condition but rather corroborates history and endoscopic examination after failure of medical therapy.

Table 6-3. CT scoring system (264).

Sinus System	*Left*	*Right*
Maxillary (0,1,2)		
Anterior ethmoids (0,1,2)		
Posterior ethmoids (0,1,2)		
Sphenoid (0,1,2)		
Frontal (0,1,2)		
Ostiomeatal complex (0 or 2 only)*		
Total points		

0-no abnormalities; 1-partial opacification; 2-total opacification.
*0-not occluded; 2-occluded

MRI is not the primary imaging modality in chronic rhinosinusitis and is usually reserved in combination with CT for the investigation of more serious conditions such as neoplasia.

A range of staging systems based on CT scanning have been described using stages 0-4 and of varying complexity (80, 264, 280-284).

The Lund-Mackay system relies on a score of 0-2 dependent upon the absence, partial or complete opacification of each sinus system and of the ostiomeatal complex, deriving a maximum score of 12 per side (Table 3) (264).

This has been validated in several studies (285) [Evidence Level IIb] and was adopted by the Rhinosinusitis Task Force Committee of the American Academy of Otolaryngology Head and Neck Surgery in 1996 (6). However, the correlation between CT findings and symptom scores has been shown to be consistently poor and is not a good indicator of outcome (286) [Evidence Level IIb]. In addition for ethical reasons a CT scan is generally only performed post-operatively when there are persistent problems and therefore CT staging or scoring can only be considered as an inclusion criterion for studies and not as an outcome assessment.

6-2-5 Mucociliary function

6-2-5-1 Nasomucociliary clearance

The use of saccharin, dye or radioactive particles to measure mucociliary transit time has been available for nearly thirty years (287-289). It allows if altered, to recognize early alterations of rhinosinusal homeostasis. Although a crude measure, it has the advantage of considering the entire mucociliary system and is useful if normal (< 30 minutes). However, if it is prolonged, it does not distinguish between primary or secondary causes of ciliary dysfunction.

6-2-5-2 Ciliary beat frequency

Specific measurements of ciliary activity using a phase contrast microscope with photometric cell (290, 291) have been used in a number of studies to evaluate therapeutic success (292, 293) [Evidence Level IIb]. The normal range from the inferior turbinate is between 12 and 15 Hz but these techniques are available in only a few centres and therefore largely experimental. The final gold standard of ciliary function are culture techniques (294).

6-2-5-3 Electron microscopy

This may be used to confirm the presence of specific inherited disorders of the cilia as in primary ciliary dyskinesia.

6-2-5-4 Nitric oxide

This metabolite found in the upper and lower respiratory tract is a sensitive indicator of the presence of inflammation and ciliary dysfunction. It requires little patient co-operation and is quick and easy to perform but the availability of measuring equipment at present limits its use. The majority of nitric oxide is made in the sinuses (chest < 20 ppb, nose 400-900 ppb, sinuses 20-25 ppm) and therefore may be low even in the presence of normal activity if the sinus ostia are blocked e.g. nasal polyposis (295) [Evidence Level IIb]. It can be used however, as an outcome measure after therapy (296) [Evidence Level IIa]

6-2-6 Nasal airway assessment

6-2-6-1 Nasal inspiratory peak flow

This inexpensive, quick and easy test is a useful estimate of airflow which can be performed at home as well as in the hospital setting. However, it measures both sides together and has little direct role in the assessment of chronic rhinosinusitis. It could be used to assess gross reduction in nasal polyposis and compares well with rhinomanometry (297, 298) [Evidence Level IIb]. Expiratory peak flow is less often used as mucus is expelled into the mask and the technique may be associated with eustachian dysfunction.

6-2-6-2 Rhinomanometry (active anterior and posterior)

The measurement of nasal airway resistance by assessing nasal flow at a constant pressure is again of limited usefulness in chronic rhinosinusitis and nasal polyposis but can be useful in confirming that improvement in nasal congestion is the result of reduction in inflammation in the middle meatus rather than mechanical obstruction (292) [Evidence Level IIb].

6-2-6-3 Acoustic rhinometry
The distortion of a sound wave by nasal topography allows quantification of area at fixed points in the nose from which volume may be derived. It can be used to demonstrate subtle changes, both as a result of medical and surgical intervention (296, 298-300)[Evidence Levels IIa,IIb,III].

6-2-6-4 Rhinostereometry
This also measures subtle changes in mucosal swelling, largely in the inferior turbinates (301, 302) [Level IIb] and is therefore not directly applicable to assessment of chronic rhinosinusitis and nasal polyposis.

6-2-7 Olfaction
6-2-7-1 Threshold Testing
The estimation of olfactory thresholds by the presentation of serial dilutions of pure odorants such as pm carbinol have been used in a number of studies (293, 299, 303-305) [Evidence Levels IIb, III].

6-2-7-2 Other quantitative olfactory testing
Scratch and sniff test using patches impregnated with micro-encapsulated odorants are available (306) and have been utilised in studies of both chronic rhinosinusitis and nasal polyposis (298). A cruder screening test, the Zurich test may also be used and has the advantage of pictorial representation of the items (307, 308). More complex tests exist (309) e.g. 'Sniff 'n' sticks' which limit their application to the research setting. Recently a combined supra-threshold detection and identification test has been devised as a cross-cultural tool in the European population. The results are presented in the appendix (310) [Evidence Level III].

Sources of some commercially available and validated olfactory tests are also mentioned in the appendix.

6-2-8 Laboratory assessments – C-reactive protein (CRP)
Known since 1930, C-reactive protein is part of the acute phase response proteins. Its principal properties are short half-life (6-8 h), rapid response (within 6 hours) and high levels (x500 normal) after injury. It activates the classical complement pathway, leading to bacterial opsonization. Studies have shown that the CRP value is useful in the diagnosis of bacterial infections (311). However, among patients suspected of an infectious disease, CRP levels up to 100 mg/l are compatible with all types of infections (bacterial, viral, fungal, and protozoal) (312).

Sequential CRP measurements will have greater diagnostic value than a single measurement and changes of the CRP values often reflect the clinical course. When used in general practice the diagnostic value of CRP is found to be high in adults with pneumonia, sinusitis and tonsillitis. Measurement of CRP is an important diagnostic test but the analysis should not stand alone but be evaluated together with the patient's history and clinical examination (313).
CRP is most reliably used for exclusion of bacterial infection: two values less than 10 mg/l and 8-12 hours apart can be taken to exclude bacterial infection (312).

6-3 Quality of Life

During the last decade more attention has been paid to not only symptoms but also to patient's quality of life (QoL) (241). However, it is of interest that the severity of nasal symptoms do not always correlate with QoL scales (314) [Evidence Level IIb]. The QOL questionnaires can provide either general (generic) or disease specific health assessment.

6-3-1 General health status instruments
Generic measurements enable the comparison of patients suffering from chronic rhinosinusitis with other patient groups. Of these the Medical Outcomes Study Short Form 36 (SF36) (242) is by far the most widely used and well validated and this has been used both pre- and post-operatively in chronic rhinosinusitis. (296, 315) [Evidence Level IIa,IIb]. It includes eight domains: physical functioning, role functioning physical, bodily pain, general health, vitality, social functioning, role-functioning emotional and mental health. Many other generic measurements are also available (243).

6-3-2 Disease specific health status instruments
Several disease specific questionnaires for evaluation of quality of life in chronic rhinosinusitis have been published. In these questionnaires specific symptoms for rhinosinusitis are included. Such areas include headache, facial pain or pressure, nasal discharge or postnasal drip, and nasal congestion.

6-3-2-1 Rhinosinusitis outcome measure (RSOM)
This contains 31 items classified into 7 domains and takes approximately 20 minutes to complete (316). A modified instrument referred to as the Sinonasal Outcome Test 20 (SNOT 20) is validated and easy to use (260). This has been used in a number of studies both medical and surgical (286, 296) [Evidence Levels Ib, IIb].

The Sinonasal Outcome Test 16 (SNOT 16) is also a rhinosinusitis specific quality of life health related instrument (317) as is the 11 point Sinonasal Assessment Questionnaire (SNAQ-11) (318).

6-3-2-2 Chronic Sinusitis Survey (CSS)
This is a 6 item duration based monitor of sinusitis specific outcomes which has both systemic and medication-based sections (319). In common with other questionnaires, it is rather better at determining the relative impact of chronic rhinosinusitis compared to other diseases than as a measure of improvement following therapeutic intervention but can be a useful tool (241, 320) [Evidence Level IIb].

6-3-2-3 Rhinosinusitis Disability Index (RSDI)
In this 30 item questionnaire the patient is asked to relate nasal and sinus symptoms to specific limitations on daily functioning (240, 321). It is similar to the RSOM 31 in the types of questions it contains. It can be completed easily and quickly but does not allow the patient to indicate their most important symptoms. However, it does have some general questions similar to the SF-36.

6-3-2-4 The Chronic Rhinosinusitis Type Specific Questionnaire
This test contains three forms. Form 1 collects data on nasal and sinus symptoms prior to treatment, Form 2 collects data on the clinical classification of sinus disease and Form 3 data on nasal and sinus symptoms after sinus surgery. Hoffman et al.have used this in combination with an SF-36 to look at patient outcomes after surgical management of chronic rhinosinusitis though it is somewhat time consuming to complete (322).

6-3-2-5 Rhinoconjunctivitis quality of life questionnaire (RQLQ)
This is a well-validated questionnaire but specifically focuses on allergy and is of less relevance in chronic rhinosinusitis and nasal polyposis (323).

6-3-2-6 Rhinitis Symptom Utility Index (RSUI)
This consists of ten questions on the severity and frequency of a stuffy or blocked nose, runny nose, sneezing, itching, watery eyes and itching nose or throat. The two-week reproducibility of the RSUI was weak, probably reflecting the day to day variability of rhinitis (324).

6-3-2-7 General
Most questionnaires concentrate on the duration of the symptoms and not on the severity of the symptoms. A QoL questionnaire developed by Damm et al.includes the severity of the symptom scale (239). The domains in the questionnaire are the overall quality of life, nasal breathing obstruction, post-nasal drip or discharge, dry mucosa, smell, headache and asthmatic complaints.

6-3-3 Results
6-3-3-1 Generic
In a generic SF-36 survey the scores of chronic rhinosinusitis patients were compared to those of a healthy population. The results showed statistically significant differences in seven of eight domains (325). Gliklich and Metson (53) have reported that patients with chronic rhinosinusitis have more bodily pain and worse social functioning than for example patients with chronic obstructive pulmonary disease, congestive heart failure, or back pain.

Winstead and Barrett (315) confirmed a similar degree of impact on general quality of life in chronic rhinosinusitis with the SF-36. Following endoscopic sinus surgery they demonstrated a return to normality in all eight domains six months post-operatively which was maintained at twelve months.

6-3-3-2 Disease specific
In a study by Gliklich and Metson the effect of sinus surgery on QoL was studied (320). After the surgery significant improvements were found in reduction of the symptoms and medications needed. Significant improvements in general health status were noted in six of eight categories, and most attained near-normative levels. A disease-specific questionnaire seems to be more sensitive than a general questionnaire in following patients after ethmoid sinus surgery (319). 76% patients reported relief of the symptoms at least in two of the domains studied after FESS surgery (239).

The Chronic Sinusitis Survey has been used in QoL outcomes after osteoplastic frontal sinus obliteration (326). Most patients were satisfied with the results and had significant improvements in their survey scores. The number of clinic visits and antibiotic use also declined.

Mean scores one year after endoscopic frontal sinus surgery showed a significant improvement in symptoms of pain, congestion, and drainage as measured by the Chronic Sinusitis Survey. Medication use was also significantly reduced (327).

Radenne et al.have studied the QoL of nasal polyposis patients using a generic SF-36 questionnaire (314). Polyposis impaired the QoL more than for example perennial rhinitis. Treatment significantly improved the symptoms and the QoL of the polyposis patients. FESS surgery on asthmatic patients with massive nasal polyposis improved nasal breathing and QoL, and also the use of asthma medications was significantly reduced (328).

In a recent randomised study of patients with chronic rhinosinusitis/nasal polyposis, treatment was either endoscopic sinus surgery or three months of a macrolide antibiotic such as erythromycin (296). Patients were followed up at 3, 6, 9 and 12 months with a variety of parameters including visual analogue scores of nasal symptoms, SNOT 20, SF-36, nitric oxide measurements of upper and lower respiratory tract expired air, acoustic rhinometry, saccharine clearance test and nasal endoscopy. Ninety patients were randomised, with 45 in each arm and at the end of one year, 38 were available for analysis in the medical arm and 40 in the surgical arm. The study showed that there had been improvement in all subjective and objective parameters ($p < 0.01$) but there was no difference between the medical and surgical groups except that total nasal volume as measured by acoustic rhinometry was greater in the surgical group. This study shows the usefulness of objective measurement in confirming subjective impressions (Evidence Level 1b).

Quality of life measurement is quite a new tool evaluating the impact of disease and the efficacy of treatment. In rhinosinusitis studies, when the effect of medical treatment or surgery has been evaluated, QoL has been considered to be an important outcome measurement as distinct from classic rhinosinusitis symptom parameters. In a number of studies, chronic rhinosinusitis has been shown to significantly impair QoL [Level Ib] (260, 329-332) and this has also been shown to improve significantly with treatment [Level IIb] (239, 320, 333, 334).

7. Management

7-1 Treatment of rhinosinusitis with corticosteroids

The introduction of topically administered glucocorticoids has improved the treatment of upper (rhinitis, nasal polyps) and lower (asthma) airway inflammatory disease. The clinical efficacy of glucocorticoids may depend in part on their ability to reduce airway eosinophil infiltration by preventing their increased viability and activation. Both topical and systemic glucocorticoids may affect the eosinophil function by both directly reducing eosinophil viability and activation (207, 335-337) or indirectly reducing the secretion of chemotactic cytokines by nasal mucosa and polyp epithelial cells (208, 338-340). The potency of these effects is lower in nasal polyps than in nasal mucosa suggesting an induced inflammatory resistance to steroid treatment in chronic rhinosinusitis / nasal polyposis (337, 338).

The biological action of glucocorticoids is mediated through activation of intracellular glucocorticoid receptors (GR) (341), expressed in many tissues and cells (342). Two human isoforms of GR have been identified, GR? and GR?, which originate from the same gene by alternative splicing of the GR primary transcript (343). Upon hormone binding, GR? enhances anti-inflammatory or represses pro-inflammatory gene transcription, and exerts most of the anti-inflammatory effects of glucocorticoids through protein-protein interactions between GR and transcription factors, such as AP-1 and NF-?B. The GR? isoform does not bind steroids but may interfere with the GRa function. There may be several mechanisms accounting for the resistance to the anti-inflammatory effects of glucocorticoids, including an overexpression of GR? or a downexpression of GR? . Increased expression of GR? has been reported in patients with nasal polyps (344, 345) while downregulation of GRa levels after treatment with glucocorticoids (346, 347) has also been postulated to be one of the possible explanations for the secondary glucocorticoid resistance phenomenon.

The anti-inflammatory effect of corticosteroids could, theoretically, be expected as well in non-allergic (i.e. infectious) as in allergic rhinosinusitis. Tissue eosinophilia is thus also seen in persistent RS (348).

Potential indications for corticosteroids in rhinosinusitis:

- Acute/Intermittent rhinosinusitis without nasal polyposis (NP);
- Persistent rhinosinusitis without NP;
- Persistent rhinosinusitis with NP;
- Postoperative treatment of persistent rhinosinusitis to prevent recurrences of NP;
- Prophylactic treatment of intermittent rhinosinusitis;
- Oral steroids in persistent rhinosinusitis with NP;
- Oral steroids in acute intermittent rhinosinusitis.

7-1-1 Acute/Intermittent Rhinosinusitis without nasal polyps

Qvarnberg et al. (349) measured the clinical effect of budesonide (BUD)/placebo as a complement to erythromycin and sinus wash out in a randomized, double-blind study on patients referred for sinus surgery due to persistent or intermittent maxillary sinusitis. Three months treatment was given to 20 subjects in 2 groups, all without NP. Treatment with BUD resulted in a significant improvement of nasal symptoms, facial pain and sensitivity. No significant improvement was seen in mucosal thickening on x-ray. The final clinical outcome did not differ between the groups. No side effects of treatment were noted. It is not possible in this study to distinguish intermittent from persistent rhinosinusitis but all cases were reported to have intermittent “episodes of sinusitis for the last two years”.

Melzer et al. (350) gave mometasone furoate (MF) 400 ?g to 200 patients and placebo to 207 patients with acute intermittent RS as adjunctive therapy to amoxicillin/clavulanate potassium for 21 days. Total symptom score and individual symptom scores as congestion, facial pain, headache and rhino rhea improved significantly, but not postnasal drip in the MF group. The effect was most obvious after 16 days treatment. Improvement on CT was seen in MF group but not statistically significant. No side effects of treatment were seen.

Nayak et al. (351) compared MF 200 and 400 ?g to placebo in 325, 318 and 324 patients with intermittent RS (no NP) as adjunctive therapy to amoxicillin/clavulanate potassium for 21 days treatment. Total symptom score (TSS) was improved from day 4 and at the end of the study (21 days) in both MF groups compared to placebo. Improvement compared to the situation before treatment was 50 and 51% for MF groups and 44% in placebo group, $p<0{,}017$. Individual nasal symptom scores such as nasal congestion, facial pain, rhino rhea and postnasal drip improved in both MF-groups compared to placebo. CT was improved, but not statistically significant in MF groups compared to placebo. No side effects of treatment were seen.

In a study by Dolor et al. (352) 200 µg FP daily was used as adjunctive therapy for 3 weeks (to cefuroxime for 10 days and xylometazoline for 3 days) in a double blind placebo controlled multicentre trial (n=47 in FP group and 48 in control group) in patients with acute intermittent rhinosinusitis. Time was measured to clinical success. After two weeks, success was seen in 73.9 and 93.5% in placebo and FP group respectively ($p=0.009$). Time to clinical success was 9.5 and 6.0 days respectively ($p=0.01$)

Barlan et al. (353) used BUD as adjunctive therapy to amoxillin clavulanate potassium for three weeks in a randomized, placebo controlled study in children with acute intermittent rhinosinusitis. Improvement in cough and nasal secretion were seen at the end of the second week of treatment in the BUD group, $p<0.05$ for both symptoms compared to placebo. At the end of week three there were no differences between the groups.

In a multi centre study Meltzer et al. (354) used flunisolide as adjunctive therapy to amoxicillin clavulanate potassium in patients with intermittent or persistent RS for three weeks and an additional four weeks on only flunisolide. The overall score for global assessment of efficacy was greater in patients treated with flunisolide than placebo ($p=0.007$) after 3 weeks and after 4 additional weeks $p=0.08$. No difference was seen on x-ray but inflammatory cells were significantly reduced in flunisolide group compared to placebo.

All these studies were on study groups where intra nasal steroids have been used as an additional treatment to antibiotics and no studies are found where nasal steroids have been compared to antibiotics as a single treatment in intermittent RS. Studies are underway which compare nasal steroids, as a single treatment to antibiotics in patients with acute rhinosinusitis. The first data (only published as abstract) show significant reduction of symptomatology in acute rhinosinusitis over placebo and an antibiotic. The evidence level as adjunctive therapy to systemic antibiotics is I, but as a single therapy no (published) data are available.

7-1-2 Persistent rhinosinusitis without nasal polyps

Parikh et al. (355) performed a randomized, double blind, placebo-controlled trial on patients with persistent RS on two groups with respectively 9 and 13 subjects (2 subjects in each group with nasal polyps) to test fluticasone propionate for 16 weeks. No significant improvement was seen, as measured by symptom scores, diary card, acoustic rhinometry or endoscopy. No side effects were seen in either group.

In another double blind placebo controlled study on patients with persistent RS (without NP) with allergy to house dust mite and who had recently been operated on but still had signs of persistent RS, 256 µg budesonide (BUD) or placebo was instilled into the maxillary sinus once a day through a sinus catheter for three weeks (356). A regression of more than 50% of total nasal symptom scores was seen in 11/13 in the BUD group and 4/13 in placebo group. The effect was more long term in BUD group, i.e. 2-12 months compared with less than 2 months in the placebo group (who had experienced an effect during the catheter period). A significant decrease was also seen in BUD group after three weeks treatment for CD-3, eosinophils and cells expressing IL-4 and IL-5.

In a study by Cuenant et al. (357) tixocortol pivalate was given as endonasal irrigation in combination with neomycin for 11 days in a double blind placebo controlled in patients with persistent RS. Maxillary ostial patency and nasal obstruction was significantly improved in the tixocortol group compared to placebo. Patients with persistent RS without allergy responded better to local steroids than those with allergy.

Sykes et al. (358) looked on 50 patients with chronic mucopurulent RS and allocated them to 3 groups for local treatment with sprays with either dexamethasone + tramazoline + neomycin/dexamethasone + tramazoline/placebo 4 times daily for 4 weeks and evaluation was performed double blinded. Treatment in both active groups was more effective than place-

Table 7-1. Treatment with nasal corticosteroids in acute/intermittent rhinosinusitis without nasal polyposis.

Study	*Drug*	*Antibiotic*	*Number*	*Effect*	*X-ray*
Qvarnberg, 1992 (349)	budesonide	erythromycin	20	significant effect on nasal symptoms, facial pain and sensitivity; final clinical outcome did not differ	mucosal thickening = no effect
Meltzer, 2000 (350)	mometasone furoate	amox/clav	407	significant effect in congestion, facial pain, headache and rhino rhea. no significant effect in postnasal drip	no statistical difference in CT outcome
Nayak, 2002 (351)	mometasone furoate	amox/clav	967	total symptom score (TSS) was improved (nasal congestion, facial pain, rhino rhea and postnasal drip)	no statistical difference in CT outcome
Dolor, 2001 (352)	fluticasone propionate	cefuroxime axetil	95	significant effect. effect measured as clinical success depending on patients self-judgment of symptomatic improvement	not done
Barlan, 1997 (353)	budesonide	amox/clav	89 (children)	improvement in cough and nasal secretion seen at the end of the second week of treatment in the BUD group	not done
Meltzer, 1993 (354)	flunisolide	amox/clav	180	significant effect: overall score for global assessment of efficacy was greater in the group with flunisolide	no effect on x-ray

bo (discharge, blockage and facial pain and x-ray) but no difference was seen with the addition of neomycin to dexamethasone.

A recent multicentre double-blinded placebo-controlled randomised trial of 134 patients with CRS (excluding nasal polyps) treated with topical budesonide for 20 weeks showed significant improvement in a number of parameters including symptom score and nasal inspiratory peak flow (359). Quality of life assessments did not change however.
There is some evidence for an effect of local intranasal steroids in persistent RS, particularly with intramaxillary instillation of steroids. No side effects were seen, including any increased signs of infection with intranasal corticosteroid treatment.

7-1-3 Persistent rhinosinusitis with NP
In studies on the treatment of NP, it is of value to look separately at the effect on rhinitis symptoms associated with polyposis and the effect on the size of nasal polyps per se. Only placebo controlled studies will be referred to.

Mygind et al. (360) showed that beclomethasone dipropionate (BDP) 400?g daily for three weeks reduced nasal symptoms in 19 patients with NP compared to a control group of 16 patients treated with placebo aerosol. Reduction of polyp size did not differ in this short treatment study.

In another study with BDP 400 ?g daily for four weeks (double blind, cross over with 9 and 11 subjects in each group), Deuschl and Drettner (361) found a significant improvement in nasal symptoms of blockage and nasal patency as measured with rhinomanometry. Difference in size of polyps was, however, not seen.

Holopainen et al. (362) showed in a randomized, double blind, parallel, placebo controlled study with 400 mcg budesonide (n=19) for 4 months that total mean score and nasal peak flow were in favour for budesonide. Polyps also decreased in size in the budesonide group.

Tos et al. (363) also showed that budesonide in spray (128 mcg) and powder (140 mcg) were both significantly more effective than placebo (multicentre) concerning reduction of polyp size, improvement of sense of smell, reduction of symptom score and overall assessment compared to placebo.

Vendelo Johansen (364) tested BUD 400µg daily compared to placebo for three months in a multi-centre, randomized, double blind study in patients with small and medium-sized eosinophilic nasal polyps (grade 1-2). Polyps decreased in the BUD group while an increase was seen in the placebo group. The difference in polyp score between the groups was significant ($p<0.01$). Both nasal symptoms (blockage, runny nose, sneezing) and peak nasal inspiratory flow (PNIF) improved significantly in BUD group.

Lildholt et al. (265) compared BUD 400 or 800 µg daily with placebo for four weeks (n=40, 34, 42 resp.). Symptom relief was significant in both BUD groups compared to placebo but there was no significant difference in polyp size between the groups as measured by the investigators. Peak nasal expiratory flow (PNEF) was significantly improved in the BUD groups and increased during the study. No difference was noted for sense of smell. No dose-response correlation was seen.

Holmberg et al. (365) used FP 400µg, BDP 400 µg and placebo for 26 weeks in a double blind, parallel group, single centre study. Patients with bilateral polyps, grade 1-2, n= 19, 18 and18 respectively in each group were investigated. There was a significant improvement in symptoms and PNIF for both steroid groups compared to placebo. No statistically significant differences between the two active groups were seen.

Keith et al. (366) compared fluticasone propionate (FP) nasal drops (FPND) 400 µg daily to placebo in a placebo controlled, parallel-group, multi-centre, randomized study (n=52 in both groups) for 12 weeks. Polyp reduction was not significant but nasal blockage and PNIF were significantly improved in FPND group. A few more cases of epistaxis in the FPND group were seen. No other side effects were reported.

Table 7-2. Treatment with nasal corticosteroids in persistent rhinosinusitis without nasal polyposis.

Study	*Drug*	*Number*	*Time*	*Symptoms*	*Other effects*
Parikh, 2001 (355)	fluticasone propionate	22	16 wks	not significant	acoustic rhinometry not significant.
Lavigne, 2002 (356)	intrasinus budesonide	26	3 wks	total symptom score significant improved	T-cells, eosinophils mRNA for IL-4, and IL-5 significantly improved
Cuenant, 1986 (357)	tixocortol irrigation	60	11 days	nasal obstruction significantly improved	maxillary ostial patency significantly improved
Sykes, 1986(358)	dexametasone + tramazoline	50	4 wks	discharge, obstruction and facial pain significantly improved	plain x-ray and nasal airway resistance and mucociliary clearance significant improved
Lund et al. 2004 (359)	budesonide	134	20 wks	significant symptom improvement	significant improvement in airway using PNIF

Penttila et al. (367) tried FPND 400 and 800 ?g and placebo daily for 12 days in a randomized, double-blind, multi-centre study for a dose-response analysis. Nasal symptoms were significantly reduced in both FP groups as well as PNIF. 800 ?g FP improved PNIF more than the lower dose and reduced polyp size significantly ($p<0.01$) which was not seen in the 400 ?g group.

Lund et al. (298) compared FP 400 ?g, BDP 400?g and placebo (n=10, 10, 9) for 12 weeks in a double-blind, randomized, parallel-group, single-centre study. Polyp score was significantly improved in FP group. Nasal cavity volume measured with acoustic rhinometry improved in both active groups. Morning PNIF improved in both active groups but was quicker with FP. Overall rhinitis symptoms did not differ statistically between the groups after 12 weeks treatment.

Hadfield et al. (368) looked on treatment of NP in patients with cystic fibrosis in a randomised, double-blind, placebo controlled study. Betamethasone drops were used in 46 patients for 6 weeks out of which 22 completed the course. There was a significant reduction in polyp size in the group treated with betametasone but no significant difference was seen in the placebo group.

Local corticosteroids have a documented effect on bilateral NP and also on symptoms associated with NP such as nasal blockage, secretion and sneezing but the effect on the sense of smell is not high. There is a high evidence level (I) for effect on polyp size and nasal symptoms associated with nasal polyposis. For individual symptoms blockage responds best to corticosteroids but improvement in sense of smell is not so obvious.

7-1-4 Postoperative treatment with topical corticoidsteriods for chronic rhinosinusitis with NP to prevent recurrence of polyps

There are a couple of studies on nasal steroids used after surgical resection of polyps.

Drettner et al. (369) used flunisolide 200 mg daily for 3 months in a double-blind, placebo controlled study with 11 subjects in both groups. A statistically significant effect was seen on nasal symptoms but not on polyp score.

Table 7-3. Treatment with nasal corticosteroids in persistent rhinosinusitis with nasal polyposis.

Study	*Drug*	*Number*	*Treatment time (weeks)*	*Effect on nasal symptoms (*stat sig)*	*Objective measures (*stat sig)*	*Effect on polyps*
Mygind, 1975 (360)	beclomethasone dipropionate	35	3	total symptom score*		not seen
Deuschl, 1977 (361)	beclomethasone dipropionate	20	2x4weeks	blockage*	rhinomanometry*	not seen
Holopainen, 1982 (362)	budenoside	19	16	total symptom score*	nasal peak flow* eosinophilia*	yes
Tos, 1998 (363)	budenoside	138	6	total symptom score* sense of smell*		yes
Vendelbo Johansen, 1993 (364)	budenoside	91	12	blockage* sneezing* secretion* sense of smell N.S.	nasal peak inspiratory flow *	yes
Lildholt, 1995 (265)	budenoside	116	4	blockage* sneezing* secretion* sense of smell N.S.	nasal peak expiratory flow*	yes
Holmberg, 1997 (365)	fluticasone propionate/ beclomethasone dipropionate	55	26	over all assessment*	nasal peak inspiratory flow*	yes in beclomethasone dipropionate
Keith, 2000 (366)	fluticasone propionate nasal drops	104	12	blockage* rhinitis* sense of smell N.S.	nasal peak inspiratory flow* olfactory test N.S.	not seen
Penttilä, 2000 (367)	fluticasone propionate	142	12	blockage* rhinitis* sense of smell N.S.	nasal peak inspiratory flow* olfactory test*	yes
Lund, 1998 (298)	fluticasone propionate/ beclomethasone dipropionate	29	12	blockage* rhinitis N.S. acoustic rhinometry*	nasal peak inspiratory flow*	yes fluticasone propionate
Hadfield, 2000 (368)	betametasone	46 CF children	6	not seen		yes

Virolainen and Puhakka (370) tested 400 µg BDP in 22 patients and placebo in 18 in a randomized, double blind study. After one year of treatment 54% in BDP group were polyp free compared to 13% in the placebo group. No statistics were given. 86% in BDP group were free of nasal symptoms compared to 60% in placebo group.

Karlsson and Rundkrantz (371) treated 20 patients with BDP and 20 were followed with no treatment for NP (no placebo treatment) for 2.5 years. BDP was given 400 mg daily for the first month and then 200 mg daily. There was a statistically significant difference between the groups after 6 months in favour of BDP, which increased during the study period of 30 months.

Dingsor et al. (372) used flunisolide 2x25 mcg on both sides twice daily (200 mcg) after surgery in a placebo controlled study for 12 months (n=41). Flunisolide was significantly better than placebo at both 6 and 12 months both with respect to number and size of polyp recurrence.

Hartwig et al. (373) used budesonide 6 months after polypectomy in a double blind parallel-group on 73 patients. In the budesonide group, polyp scores were significantly lower than controls after 3 and 6 months. This difference was only significant for patients with recurrent polyposis and not for those operated on for the first time.

Dijkstra et al. (374) performed a double-blind placebo-controlled randomized study in 162 patients with chronic sinusitis with or without nasal polyps after FESS after failure of nasal steroid treatment. Patients were randomized and given FPANS 400 microg b.i.d., FPANS 800 microg b.i.d. or placebo b.i.d. for the duration of 1 year after FESS combined with peri-operative systemic corticosteroids. No differences in the number of patients withdrawn because of recurrent or persistent diseases were found between the patients treated with FPANS and patients treated with placebo. Also no positive effect was found of FPANS compared with placebo in several subgroups such as patients with nasal polyps, high score at FESS or no previous sinus surgery.

Postoperative effect on recurrence rate of NP after polypectomy with intranasal steroids is well documented and the evidence level is Ib. Only one study describes the effect after FESS in a group of patients who underwent FESS after inadequate response to at least three months local corticosteroid treatment It did not show a positive effect of local corticostoroids over placebo.

7-1-5 Prophylactic treatment of intermittent rhinosinusitis

In a study by Puhakka et al. (375) FP (200 mg four times daily) or placebo were used for 6 days in 199 subjects with an acute common cold, 24-48 hours after onset of symptoms to study the preventive effects of FP on risk for development of acute rhinosinusitis. Frequency of sinusitis at day 7 in subjects positive for rhinovirus, based on x-ray, was 18,4% and 34,9% in FP and placebo group respectively (p=0.07) thus indicating a non significant effect of FP.

Cook et al. randomized, as a continuation of an acute episode of rhinosinusitis, patients with at least 2 episodes of rhinosinusitis in the previous 6 months or at least 3 episodes in the

Table 7-4. Nasal corticosteroids in the post operative treatment of persistent rhinosinusitis with nasal polyps to prevent recurrences of nasal polyps.

Study	*Drug*	*Number*	*Treatment time (weeks)*	*Effect on nasal symptoms (*stat sig)*	*Effect on polyp recurrence (method of test)*
Drettner, 1982 (369)	flunisolide	22	12	total nasal score (blockage, secretion sneezing)*	anterior rhinoscopy not seen
Virolainen, 1980 (no statistics) (370)	beclomethasone dipropionate	40	52	blockage	- yes anterior rhinoscopy
Karlsson, 1982 (371)	beclomethasone dipropionate	40	120	not described	- yes anterior rhinoscopy
Dingsor, 1985 (372)	flunisolide	41	52	blockage* sneezing*	- yes anterior rhinoscopy
Hartwig, 1988 (373)	budenoside	73	26	blockage not seen	- yes anterior rhinoscopy
Dijkstra 2004 (374)	fluticasone propionate	162	52	not seen	nasal endoscopy not seen.

Table 7-5. Treatment with nasal corticosteroids in prophylaxis of intermittent rhinosinusitis.

Study	*Drug*	*Number*	*Time (weeks)*	*Effect*	*Comments*
Puhakka, 1998 (375)	fluticasone propionate	199	1	not seen	common cold
Cook, 2002 (376)	fluticasone propionate	227	7	increased time to first recurrence. decreased frequency of intermittent rhinosinusitis	

last 12 months for a double blind, placebo-controlled study with FP, 200 mcg QD. 227 subjects were included. Additionally cefuroxime axetil 250 mg BID was used for the first 20 days. 39% had a recurrence in the placebo group and 25% in the FP-group (p=0.016) during the seven week-follow-up period. Mean number of days to first recurrence was 97.5 and 116.6 respectively (p=0.011) (376).

There is very low evidence for a prophylactic effect of nasal corticosteroids to prevent intermittent rhinosinusitis.

7-1-6 Systemic steroids in acute/intermittent rhinosinusitis

Gehanno et al. (377) tried 8 mg metylprednisolone three times daily for 5 days as adjunctive therapy to 10 days treatment with amoxicillin clavulanate potassium in patients with acute RS (criteria: symptoms < 10 days, craniofacial pain, purulent nasal discharge with purulent drainage from the middle meatus, opacities of the sinuses in x-ray or CT scan) in a placebo controlled study. No difference was seen in therapeutic outcome at day 14 between the groups (n=417) but at day 4 there was a significant reduction of headache and facial pain in the steroid group. Evidence level: I b. Recently Klossek showed efficacy of a short course of oral prednisone (3 days), versus a placebo, in the treatment of the functional signs of acute maxillary rhinosinusitis with severe pain in adults in addition to an appropriate antibiotic treatment (378).

7-1-7 Systemic steroids in persistent rhinosinusitis with nasal polyps

There are no studies performed on single treatment with systemic steroids in patients with NP without concomitant treatment with topical steroids. Placebo-controlled studies and dose-effect studies are also lacking but there is a clinical acceptance that systemic steroids have a significant effect on NP supported by open studies where a single injection of 14 mg betametasone have been compared with snare polypectomy surgery (267, 379). In these studies effects are seen on nasal polyp size, nasal symptom score and nasal expiratory peak flow but it is difficult to differentiate the effect of systemic steroids from that of local treatment since both treatments were used at the same time. The control groups underwent surgery during the study period.

In another open study oral prednisolone was given in doses of 60 mg to 25 patients with severe polyposis for four days and for each of the following 12 days the dose was reduced by 5 mg daily. Antibiotics and antacids were also given. 72% experienced a clear improvement due to involution of polyps (380)and in 52% a clear improvement was seen on CT. In particular nasal obstruction and the sense of smell were reported to improve. Out of 22 subjects treated, 10 were polyp free based on anterior rhinoscopy 2 weeks –2 months after therapy.

Damm et al. (381) showed a good effect with combined treatment using local steroids (budesonide, unknown doses) and oral treatment with fluocortolone 560 mg or 715 mg in 2 different groups of patients with 20 severe cases of chronic RS with NP. This study was not controlled. A large improvement of symptoms was seen (80%) and improvement on MRI (>30% reduction of MRT-pathology) was observed in 50%.

Systemic steroids are less well documented than intranasal steroids but open studies indicate that they are effective in polyp reduction and nasal symptoms associated with NP, even on sense of smell, in contrast to the effect of intranasal corticosteroids. The effect is reversible. Evidence level :III.

There is also no study available on depot injection of corticosteroids or local injection into polyps or the inferior turbinate. These types of treatment are actually obsolete, because of the risk of fat necrosis at the site of the injection or blindness following endonasal injection.

7-2 Treatment of rhinosinusitis with antibiotics

7-2-1 Acute community acquired rhinosinusitis

Although more than 2000 studies on the antibiotic treatment of acute sinusitis have already been published, only 49, involving 13,660 participants, meet the Cochrane Board criteria for placebo control, statistical analysis, sufficient sample sizes, and the description of clinical improvements or success rates (36).
Primary outcomes were:

a. clinical cure;
b.clinical cure or improvement.

Secondary outcomes were:

a. radiographic improvement;
b. relapse rates;
c. dropouts due to adverse effects.

Major comparisons were antibiotic versus control (n=3) (382-384); newer, non-penicillin antibiotic versus penicillin class (n=10); and amoxicillin-clavulanate versus other extended spectrum antibiotics (n=17), where n is the number of trials. Most trials were conducted in otolaryngology settings. Only 8 trials described adequate allocation and concealment procedures; 20 were double-blinded.

Compared to control, penicillin improved clinical cures [relative risk (RR) 1.72; 95% confidence interval (CI) 1.00 to 2.96]. For the outcome of cure or improvement, 77.2% of penicillin-treated participants and 61.5% of control participants were responders. Individuals treated with penicillin were more likely to be cured [RR 1.72; 95% CI 1.00 to 2.96] or cured/improved [RR 1.24; 95% CI 1.00 to 1.53]. Rates for cure or improvement were 82.3% for amoxicillin and 68.6% for placebo. Participants treated with amoxicillin were not more likely to be cured than with placebo [RR 2.06; 95% CI 0.65 to 6.53] or cured/improved [RR 1.26; 95% CI 0.91 to 7.94] but there was significant vari-

ability between studies. Radiographic outcomes were improved by antibiotic treatment. (36).

Comparisons between newer non-penicillins (cephalosporins, macrolides, minocycline), versus penicillins (amoxicillin, penicillin V) showed no significant differences [RR for cure 1.07; 95% CI 0.99 to 1.17]; Rates for cure or improvement were 84% for both antibiotic classes. Drop-outs due to adverse events were infrequent, and. these rates were not significantly different [RR 0.61; 95% CI 0.33 to 1.11]. Cumulative meta-analysis of studies ordered by year of publication (a proxy for prevalence of beta-lactamase-producing organisms) did not show a trend towards reduced efficacy of amoxicillin compared to newer non-penicillin antibiotics.

Because macrolides are bacteriostatic and cephalosporins bactericidal, subgroup analyses were performed to determine if one of these two classes were superior to penicillins. In the subgroup analyses, cephalosporins and macrolides showed similar response rates compared to penicillins.

Sixteen trials, involving 4,818 participants, compared a newer non penicillin antibiotic (macrolide or cephalosporin) to amoxicillin-clavulantate. Three studies were double-blind. Rates for cure or improvement were 72.7% and 72.9% for newer non-penicillins and amoxicillin-clavulanate respectively. Neither cure rates (RR 1.03; 95% CI 0.96 to 1.11) nor cured/improvement rates (RR 0.98; 95% CI 0.95 to 1.01), differed between the groups. Compared to amoxicillin-clavulanate, dropouts due to adverse effects were significantly lower for cephalosporin antibiotics (RR 0.47; 95% CI 0.30 to 0.73). Relapse rates within one month of successful therapy were 7.7% and did not differ between the groups.

Six trials, of which 3 were double blind, involving 1,067 participants, compared a tetracycline (doxycycline, tetracycline, minocycline) to a heterogeneous mix of antibiotics (folate inhibitor, cephalosporin, macrolide, amoxicillin). No relevant differences were found.

The reviewers conclude that in acute maxillary sinusitis confirmed radiographically or by aspiration, current evidence is limited but supports the use of penicillin or amoxicillin for 7 to 14 days. Clinicians should weigh the moderate benefits of antibiotic treatment against the potential for adverse effects (36).

It is interesting to see that in this review the local differences in susceptibility of micro-organisms to the antibiotics used is not acknowledged, although total cumulative meta-analysis of studies ordered by year of publication did not show a trend towards reduced efficacy of amoxicillin compared to newer non-penicillin antibiotics. Resistance patterns of predominant pathogens like Streptococcus pneumoniae, Haemophilus influenzae and Moraxella catarrhalis, vary considerably (43, 44). The prevalence and degree of antibacterial resistance in common respiratory pathogens are increasing worldwide. The association between antibiotic consumption and the prevalence of resistance is widely assumed (45). Thus the choice of agent may not be the same in all regions, as selection will depend on local resistance patterns and disease aetiology (45, 385). Moreover one might wonder whether the limited benefits of antibiotic treatment outweigh the considerable threat of antibiotic resistance. In 1995, upper respiratory tract infection was the most frequent reason for seeking ambulatory care in the United States, resulting in more than 37 million visits to physician practices and emergency departments (386).

7-2-2 Antibiotics in chronic rhinosinusitis

7-2-2-1 Introduction

It is significantly more difficult to evaluate the efficacy of antibiotic treatment in chronic rhinosinusitis compared to acute sinusitis, because of the conflicts in terms of terminology and definition of the clinical picture of chronic rhinosinusitis in the literature. In most studies, no radiological diagnosis, such as computer tomography, has been performed to confirm the diagnosis of chronic rhinosinusitis. The data supporting the use of antibiotics in this condition, however, are limited and lacking in terms of randomized placebo controlled clinical trials.

7-2-2-2 Available studies

In a retrospective study, McNally et al. (387) reported patient symptoms and physical examination findings in a cohort of 200 patients with CRS who were treated with a combination of 4 weeks of oral antibiotics, as well as topical corticosteroids and other adjunctive medications. All patients subjectively improved in response to therapy after 1 month.

Subramanian et al. (388) retrospectively studied a group of 40 patients with CRS who were treated with a combination of 4 to 6 weeks of antibiotics and a 10-day course of systemic corticosteroids. Outcome measures, including comparison of pre- and

Table 7-6. Treatment with systemic corticosteroids in persistent rhinosinusitis with NP.

Study	*Drug*	*Number*	*Time/Dose*	*Effect symptoms*	*Effect polyps*	*Evidence*
Lildholt, 1997 (267)	betametamethasone/ budesonide	16	14mg/52w	yes	yes	III
Lildholt, 1988 (379)	betametamethasone/ beclomethasone dipropionate	53	?/52w	yes	yes	III
van Camp, 1994 (380)	prednisolone 60 mg	25	2 weeks	72%	yes 10/22	III
Damm, 1999 (381)	budesonide + fluocortolone	20	?	yes	?	III

post-treatment CT scan, as well as patient symptom scores, revealed improvement in both outcome parameters in 36 of 40 patients. In the latter study, 24 of 40 patients had sustained improvement for at least 8 weeks, which would seem to imply that whatever infection was present was fully eradicated in these patients.

In a prospective study by Legent et al. (389), 251 adult patients with CRS were treated in a double-blind manner with ciprofloxacin vs. amoxicillin/clavulanic acid for 9 days. Only 141 of the 251 patients had positive bacterial cultures from the middle meatus at the beginning of the study. At the end of the treatment period, nasal discharge disappeared in 60% of the patients in the ciprofloxacin group and 56% of those in the amoxycillin/clavulanic acid group. The clinical cure and bacteriological eradication rates were 59% and 89% for ciprofloxacin versus 51% and 91% for amoxycillin/clavulanic acid respectively. These differences were not significant. However, amongst patients who had a positive initial culture and who were evaluated 40 days after treatment, ciprofloxacin recipients had a significantly higher cure rate than those treated with amoxycillin/clavulanic acid (83.3% vs. 67.6%, $p = 0.043$). Clinical tolerance was significantly better with ciprofloxacin ($p = 0.012$), largely due to a large number of gastro-intestinal related side-effects in the amoxycillin/clavulanic acid group ($n = 35$). Ciprofloxacin proved to be at least as effective as amoxycillin/clavulanic acid.

The efficacy and safety of amoxycillin/clavulanic acid (AMX/CA) (875/125 mg b.i.d. for 14 days) were compared with that of cefuroxime axetil (500 mg b.i.d. for 14 days) in a multicentre, open, parallel-group, randomized clinical trial in 206 adults with chronic or acute exacerbation of CRS by a polish group. Clinical response was similar, with 95% of AMX/CA-, and 88% of cefuroxime-treated, clinically evaluable patients cured. In bacteriologically evaluable patients, cure rates, defined as eradication of the original pathogen with or without re-colonization with non-pathogenic flora, were also similar, with 65% of AMX/CA- and 68% of cefuroxime-treated patients cured. However, clinical relapse was significantly higher in the cefuroxime group: 8% (7/89) of clinically evaluable patients, compared with 0% (0/98) in the AMX/CA ($p=0.0049$) group (390).

Huck et al. (391) compared in a double-blind, randomized trial compared cefaclor with amoxicillin in the treatment of 56 acute, 25 recurrent, and 15 chronic maxillary sinusitis: Whether treated with cefaclor or amoxicillin, clinical improvement occurred in 86% of patients with acute rhinosinusitis and 56% of patients with recurrent rhinosinusitis. Patients with chronic sinusitis were too few to allow statistical analysis. The susceptibility of organisms isolated to the study drugs was unrelated to outcome.

To summarize, at the moment no placebo-controlled studies on the effect of antibiotic treatment are available. Studies comparing antibiotics have level II evidence and do not show significant differences between ciprofloxacin vs. amoxicillin/clavulanic acid, and cefuroxime axetil. The few available prospective studies show effect on symptoms in 56% to 95% of the patients. It is unclear which part of this effect is regression to the mean because placebo controlled studies are lacking. There is urgent need for randomized placebo controlled trials to study the effect of antibiotics in chronic rhinosinusitis and exacerbations of chronic rhinosinusitis.

7-2-3 Long-term treatment with antibiotics in chronic rhinosinusitis

The efficacy of long term treatment with antibiotics in diffuse panbronchiolitis, a disease of unclear aetiology, characterized by chronic progressive inflammation in the respiratory bronchioles inspired the Asians in the last decade to treat CRS in the same way (392, 393). Subsequently a number of clinical reports have stated that long-term, low-dose macrolide antibiotics are effective in treating chronic rhinosinusitis incurable by surgery or glucocorticosteroid treatment, with an improvement in symptoms varying between 60% and 80% in different studies (20, 392, 394, 395). The macrolide therapy was shown to have a slow onset with ongoing improvement until 4 months after the start of the therapy.

In animal studies macrolides have increased mucociliary transport, reduced goblet cell secretion and accelerated apoptosis of neutrophils, all factors that may reduce the symptoms of chronic inflammation. There is also increasing evidence in vitro of the anti-inflammatory effects of macrolides. Several studies have shown macrolides inhibit interleukin gene expression for IL-6 and IL-8, inhibit the expression of intercellular adhesion molecule essential for the recruitment of inflammatory cells. However, it remains to be established if this is a clinically relevant mechanism (396-402).

There is also evidence in vitro, as well as clinical experience, showing that macrolides reduce the virulence and tissue damage caused by chronic bacterial colonization without eradicating the bacteria. In addition long term treatment with antibiotics has been shown to increase ciliary beat frequency (403). In a prospective RCT from the same group (296) ninety patients with polypoid and nonpolypoid CRS were randomised to medical treatment with 3 months of an oral macrolide (erythromycin) or endoscopic sinus surgery and followed over one year. Outcome assessments included symptoms (VAS), the SinoNasal Outcome Test (SNOT-22), Short Form 36 Health Survey (SF36), nitric oxide, acoustic rhinometry, saccharine clearance time and nasal endoscopy. Both the medical and surgical treatment of CRS significantly improved almost all subjective and objective parameters, with no significant difference between the two groups nor between polypoid and nonpolypoid CRS except for total nasal volume which was greater after surgery and in the polypoid patients.

Table 7-7. "Short Term" Antibiotics in Chronic Rhinosinusitis.

Study	*Drug*	*Number*	*Time/Dose*	*Effect on symptoms*	*Evidence*
McNally et al., 1997 (387)	oral antibiotics + topical steroids + adjunctive therapy	200	4 weeks	yes, subjectively after 4 weeks	III
Subramanian et al., 2002 (388)	antibiotics 10 days corticosteroids	40	4 –6 weeks	yes, pre-/posttreatment CT in 24 patients also improvement after 8 weeks	III
Legent et al., 1994 (389)	ciprofloxacin vs. amoxicillin clavulanate	251	9 days	nasal discharge disappeared: ciprofloxacin 60% amoxicillin clavulanate 56% clinical cure: ciproloxacin 59% amoxicillin clavulanate 51% bacterological eradication: ciprofloxacin 91% amoxicillin clavulanate 89%	no
Namyslowski et al., 2002 (390)	amoxicillin clavulanate vs. cefuroxime axetil	206	875/125mg for 14 days 500mg for 14 days	clinical cured: amoxicillin clavulanate 5% cefuroxime axetil 88% bacterial eradication: amoxicillin clavulanate 65% cefuroxime axetil 68% clinical relapse: amoxicillin clavulanate 0/ 98 cefuroxime axetil 7/89	no
Huck et al., 1993 (391).	ceflaclor vs. amoxicillin	56 acute rhinosinusitis 25 recurrent rhinosinusitis 15 chronic maxillary sinusitis	2x 500mg 3x500mg for 10 days	clinical improvement: acute rhinosinusitis 86% recurrent rhinosinusitis 56% chronic maxillary sinusitis no statistics	no

The benefit of long-term, low-dose macrolide treatment seems to be that it is, in selected cases, effective when steroids fail. The exact mechanism of action is not known, but it probably involves downregulation of the local host immune response as well as a downgrading of the virulence of the colonizing bacteria. Placebo-controlled studies should be performed to establish the efficacy of macrolides if this treatment is to be accepted as evidence-based medicine.

7-2-4 Acute exacerbations of chronic rhinosinusitis: oral antibiotic treatment

In open trials, oral antibiotics have an effect on the symptomatology of acute exacerbations of chronic rhinosinusitis (390, 405). In some of these studies patients with acute or chronic rhinosinusitis are combined with patients with acute exacerbations of chronic rhinosinusitis (406, 407). No studies have shown efficacy of antibiotics in acute exacerbations of chronic rhinosinusitis in a double blind placebo controlled manner.

In conclusion data on the treatment of acute exacerbation of chronic rhinosinusitis are mostly level IV evidence and include oral and local antibiotics. Double-blind data show a positive effect of the addition of local corticosteroid treatment to oral antibiotics in the treatment of acute exacerbation of chronic rhinosinusitis.

7-2-5 Acute exacerbations of chronic rhinosinusitis: local antibiotic treatment

Some studies have compared the effects of local antibiotics in chronic rhinosinusitis and acute exacerbation of chronic rhinosinusitis (357, 408-410).

Desrosiers studied in a randomized, double-blind trial of tobramycin-saline solution versus saline-only solution administered thrice daily to the nasal passages by means of a large-particle nebulizer apparatus for 4 weeks in twenty patients with chronic rhinosinusitis refractory to medical and surgical therapy. He found no significant difference between the groups and concluded that large-particle nebulized aerosol therapy may offer a safe and effective management alternative for patients with refractory rhinosinusitis irrespective of the addition of gentamicin (411).

Sykes found no additional effect with the addition of neomycin to a spray containing dexamethasone and tramazoline four times daily to both nostrils for 2 weeks (358).

However, Mosges and Leonard did find differences between local antibiotics and placebo (408, 410). Mosges showed a positive effect for fusafungine nasal spray as early as the first 24 h of treatment which was not seen in the placebo group. The antimicrobiological effect of this preparation is unclear.

Table 7-8. Long-term treatment with antibiotics in chronic rhinosinusitis.

Study	*Drug*	*Number*	*Time/Dose*	*Effect symptoms*	*Evidence*
Hashiba et al., 1996 (392)	clarithromycin	45	400mg /d for 8 to 12 weeks	clinical improvement in 71%	III
Suzuki et al., 1997 (393)	roxithromycin	12	150mg /d	CT scan pre- and post-therapy: improvement in the aeration of nasal sinuses	III
Nishi et al., 1995 (394)	clarithromycin	32	400mg /d	pre- and post-therapy assessment of nasal clearance	III
Gahdhi et al., 1993 (395)	prophylactic antibiosis details not mentioned	26	not mentioned	19/26 decrease of acute exacerbation by 50% 7/26 decrease of acute exacerbation by less than 50%	III
Ichimura et al., 1996 (20)	roxithromycin roxithromycin and azelastine	20 20	150mg /d for at least 8 weeks 1mg /d	clinical improve-ment and polyp-shrinkage in 52% clinical improve-ment and polyp shrinkage in 68%	III
Scadding et al., 1995 (403)	oral antibiotic therapy	10	3 month	increased ciliary beating	III
Cervin et al., (404)	erythromicin or clarithromycin	17	1 year	increase mucociliary clearance and endoscopic signs	III
Ragab et al., 2004 (296)	erythromycin v ESS	45 in each arm	3 months	improvement in upper & lower RT symptoms, SF36, SNOT-22, NO, Ac Rhin, SCT, nasal endoscopy at 6 & 12 months	Ib

RT: respiratory tract, SF 36: Short Form 36 QoL, SNOT-22: SinoNasal Outcome Test, NO:expired nitric oxide, Ac Rhin: acoustic rhinometry, SCT: saccharine clearance time.

Schienberg et al. studied the effectiveness of aerosol delivery of antibiotics to the sinuses via a nebulizer in 41 patients who had chronic, recurrent rhinosinusitis that had persisted despite endoscopic sinus surgery and that had not responded to multiple courses of oral antibiotics. Following 3 to 6 weeks of treatment, 34 patients (82.9%) experienced either an excellent or good response to treatment. Side effects were infrequent, mild, and transient. They concluded that nebulized antibiotics should be considered for all patients with chronic rhinosinusitis who have undergone functional endoscopic sinus surgery and who have failed to respond to oral antibiotics or who do not tolerate them (412).

Further studies with better characterized patient populations are needed.

7-3 Other medical management for rhinosinusitis

Standard conservative treatment for intermittent and persistent rhinosinusitis is based on short or long-term antibiotics and topical steroids with the addition of decongestants - mostly in a short term regimen and for the intermittent attack itself. Many other types of preparations have been investigated, but substantial evidence for their benefit is poor. These medications include antral washings, isotonic/hypertonic saline as nasal douche, antihistamines, antimycotics, mucolytic agents/phytomedical preparations, immunomodulators/ immunostimulants and bacterial lysate preparations. For selected patients with persistent rhinosinusitis and gastroesophageal reflux, the impact of antireflux treatment on sinus symptom scores has been studied. Topical nasal application of furosemide and capsaicin have also been considered in the treatment of nasal polyposis and prevention of recurrence.

7-3-1 Decongestants

7-3-1-1 Acute/Intermittent Rhinosinusitis

Nasal decongestants are usually applied in the treatment of acute/ intermittent rhinosinusitis, in order to achieve better sinus ventilation and drainage. Experimental trials on the effect of topical decongestants by CT (413) and MRI scans (414) on ostial and ostiomeatal complex patency have confirmed marked effect on congestion of inferior and middle turbinates and infundibular mucosa, but no effect on ethmoidal and maxillary sinus mucosa. Experimental studies suggested beneficial anti-inflammatory effect of xylometazoline and oxymetazoline by decreasing nitric oxide synthetase (415) and anti-oxidant action (416). In contrast to previous in vitro trials on the effect of decongestants on mucociliary transport, a controlled clinical trial (II) by Inanli et al. suggested improvement in mucociliary clearance in vivo, after 2 weeks of oxymetazoline application in acute bacterial rhinosinusitis, compared to fluticasone, hypertonic saline and saline, but it did not show significant improvement compared to the group where no topical nasal treatment was given, and the clinical course of the disease between the groups was not significantly different (417). This is in concordance with previous random-

ized controlled trial in adult acute maxillary sinusitis (Ib), which did not prove significant impact of decongestant when added to antibiotic treatment in terms of daily symptoms scores on headache and obstruction and sinus x-ray scores, although decongestant and placebo were applied through a bellow, which should have enabled better dispersion of the solution in the nasal cavity (418). Decongestant treatment did not prove superior to saline, when added to antibiotic and antihistamine treatment in a randomized double-blind placebo-controlled trial for acute/intermittent paediatric rhinosinusitis (Ib) (419). Clinical experience, however, supports the use of topical application of decongestants to the middle meatus in acute rhinosinusitis (evidence level IV).

7-3-1-2 Chronic/Persistent Rhinosinusitis

The use of decongestants for adult chronic/persistent rhinosinusitis has not been evaluated in a randomized controlled trial. Decongestants and sinus drainage did not prove to be superior to saline in chronic paediatric maxillary sinusitis in terms of subjective or x-ray scores (420).

7-3-1-3 Nasal polyps

No controlled trials were used to test the effect of decongestant treatment in nasal polyposis. CT studies before and after decongestant application in patients with nasal polyposis did not show any densitometric changes in the sinuses or polyps, only decongestion of the inferior turbinates (421).

7-3-2 Mucolytics

7-3-2-1 Acute/intermittent rhinosinusitis

Mucolytics were used as adjuncts to antibiotic treatment and decongestant treatment in acute/intermittent rhinosinusitis in order to reduce the viscosity of sinus secretion. The benefit of such treatment has not been evaluated in many trials. In paediatric rhinosinusitis, a RCT (Ib) did not prove bromhexine superior to saline in inhalation for children with chronic/persistent rhinosinusitis (422).A second RCT (Ib) suggested bromhexine was superior to placebo (423).

7-3-2-2 Chronic/persistent rhinosinusitis

A cohort study in a mixed group of 45 acute and chronic rhinosinusitis patients suggested beneficial effect of adding mucolytic to standard rhinosinusitis treatment in terms of reducing treatment duration (424) (evidence level III).

7-3-2-3 Nasal polyps

No clinical trials have tested the effect of mucolytics in nasal polyp treatment.

7-3-3 Antihistamines, cromones

7-3-3-1 Acute intermittent rhinosinusitis

The beneficial effect of loratadine in terms of symptom reduction for the treatment of acute/intermittent sinusitis in patients with allergic rhinitis was confirmed in a multicentre randomized double-blind, placebo controlled trial (Ib)(425). Patients receiving loratadine as an adjunct to antibiotic treatment suffered significantly less sneezing and obstruction on daily VAS scores, and overall improvement was confirmed by their physicians. Cromolyn did not prove better than saline in a RCT (Ib) for treatment of acute intermittent hyperreactive sinusitis measured by subjective scores and ultrasound scans, leading to 50% improvement in both groups (426). A RCT (Ib) for intermittent paediatric rhinosinusitis did not confirm any benefit of oral antihistamine-nasal decongestant drops (419).

7-3-3-2 Chronic/persistent rhinosinusitis

Although generally not recommended as rhinosinusitis treatment, an evaluation study of chronic rhinosinusits treatment in the USA revealed antihistamines as rather often prescribed medication in patients with chronic rhinosinusitis (an average of 2.7 antibiotic courses; nasal steroids and prescription antihistamines 18.3 and 16.3 weeks, respectively, in a 12-month period) (427). However, no evidence of beneficial effects of antihistamine treatment for persistent rhinosinusitis is found, as there are no controlled trials evaluating such treatment.

7-3-3-3 Nasal polyps

Cetirizine in a dose of 20 mg/day for three months, significantly reduced sneezing, rhinorrhoea and obstruction compared to placebo in the postoperative treatment of recurrent polyposis but with no effect on polyp size (Ib) (428).

7-3-4 Antimycotics

Antimycotics are used as topical and systemic treatment, as an adjunct to sinus surgery, in allergic fungal, and invasive fungal rhinosinusitis, especially in immunocompromized patients (429). Surgery is considered the first line treatment for allergic fungal (430) and invasive fungal rhinosinusitis (431). Although the use of antimycotics in the treatment of allergic fungal rhinosinusitis has not been tested in controlled trials, high dose of postoperative itraconazole, combined with oral and topical steroids in a cohort of 139 patients with AFS reduced the need for revision surgery rate to 20.5% (432). The state-of-art treatment for invasive fungal sinusitis is based on small series of patients and case reports, which do not meet the criteria for meta analysis and may be considered as level IV evidence.

7-3-4-1 Acute/intermittent sinusitis

No controlled trials for antimycotic treatment for acute rhinosinusitis was found on the Medline search.

7-3-4-2 Chronic/persistent rhinosinusitis

The fungal hypothesis, based of the premise of an altered local immune (non-allergic) response to fungal presence in nasal/sinus secretions resulting in the generation of chronic eosinophilic rhinosinusitis and nasal polyposis (124), has led to idea of treating any persistent rhinosinusitis/nasal polyposis with a topical antimycotic. Although the presence of fungus in

sinus secretions was detected in a high proportion (< 90%) of patients with persistent rhinosinusitis, as well as in a control disease-free population in a few study centres (124, 125), it cannot be taken as proof of aetiology. Until now a few case studies (level III) are conducted (433, 434). Ponikau, in a group of 51 patient with chronic rhinosinusitis, including polyposis patients, treated with topical amphotericin B as nasal/sinus washing, without placebo or other control treatment. The treatment resulted in 75% subjective improvement and 74% endoscopic improvement (433). As the authors stated, antifungal treatment should be evaluated in a controlled trial to be justified. In a double blind randomized placebo controlled trial in 60 patients with chronic rhinosinusitis, topical treatment with amphotericine B did not show superior to saline in CT scores (p 0.2) and subjective scores, which were (insignificantly) worse in active treatment group (435). In a recent small randomized, placebo-controlled, double-blind, trial using amphotericin B to treat 30 patients with CRS Ponikau was also not able to show significant effect on symptomatology although he did show a reduced inflammatory mucosal thickening on both CT scan and nasal endoscopy and decreased levels of intranasal markers for eosinophilic inflammation in patients with CRS (436).

7-3-4-3 Nasal polyposis

Another case study (as the previous trials also included patients with nasal polyposis) combined topical steroid treatment with amphotericin B in 74 patients with nasal polyposis for 4 weeks (437) and found 48% disappearance of the polyps at endoscopy in previously endoscopically operated patients.

The effect of amphotericin B on sinus mucosa may be explained by some other modes of action. In common with other polyene antibiotics and antimycotics, amphotericin B acts on cellular membrane permeability, which may reduce the size of nasal polyps by reducing oedema, leading to subjective improvement (438). These studies were not placebo controlled and had short observation periods. Amphotericin B is a cytotoxic drug and long-term topical application may have systemic effect. On the other hand, nasal washings with hypertonic solution (without antifungal medication) offer up to 60% improvement (see under chapter 7-4-7 Nasal and antral irrigation - saline, hypertonic saline).

7-3-5 Bacterial lysate preparations

Altered local (and systemic) immune response to bacterial infection (antigens) may be responsible for frequent recurrence of rhinosinusitis. Beneficial effect of antibiotic treatment is declining together with the increased microbial resistance after repeated treatments. Such patients are usually regarded as difficult-to-treat, and usually unresponsive in the long-term to medical and surgical treatment. As altered immune response is expected to be responsible for frequent recurrence, different immunomodulators or immunostimulants have been tested in such patients. The most common form of medications used are bacterial lysates. Efficacy of bacterial lysate preparations (Enteroccocus faecalis autolysate (439), ribosomal fractions of Klebsiella pneumoniae, Streptococcus pneumoniae, Streptococcus pyogenes, Haemophilus influenzae and the membrane fraction of Kp (440), and mixed bacterial lystate (441) in terms of the reduction of the number of acute relapses in persistent rhinosinusitis, period between the relapses and need for antibiotic treatment, have been tested in multicentre, placebo controlled RCTs (Ib) (439-441).

7-3-5-1 Acute/intermittent rhinosinusitis

Bacterial lysates were tested in the treatment of acute recurrent rhinosinusitis and the outcomes measured were the reduced rate of acute episodes and antibiotic treatment. Enteroccocus faecalis autolysate treatment for 6 months in 78 patients (3x30 drops daily) resulted in 50 relapses during 6 months treatment and 8 months follow-up compared to 79 placebo treated group with 90 recurrences. The time interval to the first relapse was clearly longer in the active arm (513 days) compared with placebo (311 days) (439). A RCT of the effect of 6 months treatment with ribosomal fractions of Klebsiella pneumoniae, Streptococcus pneumoniae, Streptococcus pyogenes, Haemophilus influenzae and the membrane fraction of Kp was compared to placebo in 327 adult patients (168 active and 159 placebo treatment) with recurrent acute infectious rhinitis (the criteria could meet recurrent rhinosinusitis based on symptoms – 4.3 episodes per year) demonstrated 39% reduction of antibiotic courses and 32% of days with antibiotics during the 6 months treatment period (440).

7-3-5-2 Chronic/persistent rhinosinusitis

Six months treatment with mixed bacterial lystate was tested in a multicentre randomized double-blind placebo-controlled trial in 284 patients with CRS (diagnosed by persistent nasal discharge, headache, and x-ray criteria). Reduction in symptom scores and over-all severity score, including cough and expectoration were significant during the treatment period (441).

7-3-5-3 Nasal polyposis

No data could be found on treatment with bacterial lysates in nasal polyposis.

7-3-6 Immunomodulators/immunostimulants

Treatment with filgrastim, recombinant human granulocyte colony stimulating factor, was tested in a RCT (Ib) in a group of persistent rhinosinusitis patients refractory to conventional treatment, which did not confirm significantly improved outcomes after such expensive treatment (331). A pilot study (III) with interferon gamma suggested this treatment may be beneficial in treating resistant persistent rhinosinusitis, but the number of patients was not adequate to provide evidence to justify such treatment (442). Certain groups of antibiotics may be regarded as immunomodulators, like quinolones (443) and macrolides (444).

7-3-7 Nasal and antral irrigation (saline, hypertonic saline)

A number of randomized controlled trials have tested nasal and antral irrigation with isotonic or hypertonic saline in the treatment of acute/intermittent and chronic/persistent rhinosinusitis. Although saline is considered as a control treatment itself, patients in these randomized trials were assigned to different modalities of application of saline or hypertonic saline, or hypertonic compared to isotonic saline. The results between the groups were compared. Most of them offer evidence that nasal washouts or irrigations with isotonic or hypertonic saline are beneficial in terms of alleviation of symptoms, endoscopic findings and HRQL improvement in patients with chronic persistent rhinosinusitis. Hypertonic saline is preferred to isotonic treatment for rhinosinusitis by some authors in the USA, mostly based on a paper indicating it significantly improves nasal mucociliary clearance measured by saccharine test, in healthy volunteers (445).

7-3-7-1 Acute/intermittent rhinosinusitis

A randomized trial (Ib) by Adam et al. (446). with two controls, compared hypertonic nasal saline to isotonic saline and no treatment in 119 patients with common cold and acute rhinosinusitis (predominantly rhinosinusitis). Outcome measures were subjective nasal symptoms scores (congestion, secretion, headache) at day-3, day-8-10 and the day of symptom resolution. Rhinosinusitis patients (98%) were also treated with antibiotics. There was no difference between the groups and only 44% of the patients would use the hypertonic saline spray again. Thirty-two percent noted burning, compared with 13% of the normal saline group.

Antral irrigation (Ib) did not offer significant benefit when added to standard 10-day antibiotic treatment in (4 antibiotics+ decongestants vs. antral washouts; 50 patients per group) acute/intermittent rhinosinusitis, demonstrating approximately 5% better cure rate in each group for washouts than for decongestants, which was not significant (447).

7-3-7-2 Chronic/persistent rhinosinusitis

A randomised controlled trial (RCT) by Bachmann (Ib), comparing isotonic saline and EMS solution (balneotherapeutic water) in the treatment of persistent sinusitis in a double-blind fashion revealed improvement in both groups, with no difference between them (448). In the 7-days follow-up, nasal air flow was not improved significantly. Subjective complaints, endonasal endoscopy, and radiology results revealed a significant improvement in both groups ($P = 0.0001$). A similar RCT by Taccariello et al. (Ib),with a longer follow-up confirmed that nasal washing with sea water and alkaline nasal douche produced benefit over standard treatments. Douching per se improved endoscopic appearances ($p = .009$), and quality of life scores ($p = .008$) (449). These measures did not change in a control group ($n = 22$) who received standard treatment for chronic rhinosinusitis, but no douche. There were significant differences between the two douching preparations - the alkaline nasal douche improved endoscopic appearances but did not enhance quality of life, whereas the opposite was true for the spray. Rabago et al. (Ib) tested benefit from daily hypertonic saline washings compared to standard chronic rhinosinusitis treatment (control) for 6 months in a RCT using subjective scores instruments: Medical Outcomes Survey Short Form (SF-12), the Rhinosinusitis Disability Index (RSDI), and a Single-Item Sinus-Symptom Severity Assessment (SIA). Experimental subjects reported fewer 2-week periods with sinus-related symptoms ($P < .05$), used less antibiotics ($P < .05$), and used less nasal spray ($P = .06$) (450). On the exit questionnaire 93% of study subjects reported overall improvement of sinus-related quality of life, and none reported worsening ($P < .001$); on average, experimental subjects reported 57 -/+ 4.5% improvement measured by Medical Outcomes Survey Short Form (SF-12), the Rhinosinusitis Disability Index (RSDI), and a Single-Item Sinus-Symptom Severity Assessment (SIA). A double blind RCT (Ib) compared the effect of nasal wash with hypertonic saline (3.5%) versus normal saline (NS) (0.9%) for the 4 weeks in treatment of paediatric chronic/persistent rhinosinusitis using cough and nasal secretions/postnasal drip as subjective and a radiology score as objective outcome measures (451). Hypertonic saline demonstrated significant improvement for all the scores (13/15 for cough,13/15 postnasal drip, 14/15 x-ray scores), while saline improved only postnasal drip.

Nebulised hypertonic saline improves mucociliary clearance in short term clinical trials and appears to increase lung function compared to controls in cystic fibrosis patients (Wark, Cochrane Database Syst Rev. 2003;(1):CD001506 – apropos doubt about general harm of hypertonic saline on lung function. However, it does cause bronchocontriction in the asthmatics).

Comparison of treatment with antral washouts in the treatment of persistent adult (452) and paediatric rhinosinusitis (453) did not prove benefit from such treatment. In a RCT by Pang et al. patients received either antral washouts followed by antibiotics and topical nasal steroids or antibiotics and topical nasal steroids alone. In each group 51.6 per cent and 50 per cent of patients respectively improved with treatment (452).

7-3-7-3 Nasal polyps

Nasal saline has been used as a control treatment in trials on nasal polyposis with topical steroid, but there are no controlled trials on saline/hypertonic saline treatment alone in nasal polyposis.

7-3-8 Capsaicin

Capsaicin, the active substance from red hot chilli peppers, is a neurotoxin which depletes substance P with some other neurokinins and neuropeptides, leading to long lasting damage of

unmyelinated axons and thinly myelinated axons when repeatedly applied to the respiratory mucosa. Substance P was found effective in reducing nasal symptoms after cumulative topical applications in the treatment of non-allergic hyperreactive rhinitis, probably acting as desensitizer of nasal mucosa due to depletion of SP and neurokinins. The hypothesis that neurogenic inflammation may play a role in the pathogenesis of nasal polyps has lead to trials on capsaicin treatment of nasal polyposis.

7-3-8-1 Acute/intermittent, chronic/persistent sinusitis
No trials of treatment of acute or chronic rhinosinusitis with capsaicin could be found.

7-3-8-2 Nasal polyps
A case study (III) by Filiaci et al. has demonstrated significant reduction of the size of nasal polyps after five (weekly) topical applications of capsaicin (30 mmol/L) solution in patients with nasal polyposis (454). The authors noted increased nasal eosinophilia after the treatment, which was not correlated to the polyp size. A case study by Baudoin et al. has demonstrated significant reduction of sinonasal polyposis after 5 consecutive days treatment with increasing doses (30-100 mmol/L) of topical capsaicin in massive polyposis measured by CT scans at entry and after 4 weeks (III) (455). ECP in nasal lavage was not influenced by the treatment. Protection of polyp recurrence following endonasal surgery by 5 topical applications of capsaicin in 51 patient after surgery with a 9 months follow-up has confirmed significant recurrence protection and significantly better nasal patency in the active group in a randomized, double blind, placebo controlled trial (Ib) by Zheng et al. (456). The authors used 70% ethanol 3x10-6E ml capsaicin solution, which may explain the high rate of recurrence in the control group after ESS, which received only 70% ethanol. They noted 40% polyp stage 0 (Malm) and 45% stage 1 in the active treatment group, while controls demonstrated 45% stage 2 and 40% stage 3 polyposis following treatment at 9 months observation. The low cost of capsaicin treatment was noted as a certain advantage compared to other postoperative treatments. As capsaicin is NF kappa B antagonist in vitro, some other modes of action may be proposed (457).

7-3-9 Furosemide
The protection of hyperreactive response to different challenges (propranolol (458); metabisulphite (459); exercise (460)) in asthmatics was demonstrated after inhalation of furosemide, suggesting bronchoprotective effects, similar to the effect of cromones. Histamine exocytosis from rat mast cells was protected by furosemide in vitro (461). It exhibited an anti-inflammatory effect through inhibition of production and release of cytokines, interleukin (IL)-6, IL-8, and tumor necrosis factor-alpha from peripheral mononuclear cells in vitro (462).

7-3-9-1 Acute/intermittent, chronic/persistent sinusitis
No trials of treatment of acute or chronic rhinosinusitis with furosemide have been found.

7-3-9-1 Nasal polyps
Protection against nasal polyp recurrence following surgery with 1-9 years follow-up, comparable to the effect of the topical steroid, was demonstrated after topical application of furosemide in 97 patients postoperatively vs. mometasone furoate in 33 patients, in a prospective non-randomized controlled trial (IIa) by Passali et al. (463), previously reported by the same group in a case study. Relapses were recorded in 17.5% in the furosemide, 24.2% in the mometasone and 30% in the no treatment group, suggesting that furosemide, as a much cheaper medication than steroids, might be considered in polyp recurrence protection treatment. Randomized trials however are lacking.

7-3-10 Proton pump inhibitors
7-3-10-1 Acute/intermittent rhinosinusitis
There are no trials with proton pump inhibitors for acute rhinosinusitis

7-3-10-2 Chronic/persistent rhinosinusitis
There is no evidence for benefits in the general population suffering from rhinosinusitis following treatment with proton pump-inhibitors, while subjective improvement was noted in patients with laryngopharyngeal reflux (proved by pH-metry) and rhinosinusitis. Grade C evidence for a positive association between gastroesophageal reflux and rhinosinusitis was found in a meta analysis of the literature for this co-morbidity (57 articles screened, 14 articles included) (464, 465). A number of case trials of rhinosinusitis, especially paediatric (464), has tested the efficacy of antireflux treatment with proton pump inhibitors on the clinical course and symptoms of rhinosinusitis. Increased rates of reflux were detected in persistent rhinosinusitis in adults unresponsive to standard treatment (466). A beneficial effect of proton pump inhibitors on sinusitis symptoms in patients with resistant persistent sinusitis was demonstrated in an open label clinical trial (III) (467). Further research is expected in this field, and such treatment should be justified by randomized controlled trials.

7-3-10-3 Nasal polyps
There are no data on proton-pump inhibitors in nasal polyposis.

7-3-11 Antileukotrienes
The role of leukotriens in the pathogenesis of bronchial asthma has been well documented, and increased levels of these mediators have been detected in patients with rhinosinusitis and nasal polyps. Antileukotrienes have been evaluated in the treatment of asthmatics, especially in those with ASA triad. The effect of leukotrienes was evaluated in a randomized con-

trolled trial of patients with seasonal allergic rhinitis and was not found to be superior to placebo in terms of daily nasal symptoms score, and was significantly inferior to nasal steroid (468).
The effect of antileukotriens was not tested in controlled trials for rhinosinusitis and nasal polyposis. However, a few case-controlled trials indicate that antileukotriene treatment may have beneficial effect on nasal symptoms in patients with chronic/persistent rhinosinusitis and nasal polyposis.

7-3-11-1 Acute/intermittent rhinosinusitis
No trials were done on the antileukotrienes treatment in acute rhinosinusitis.

7-3-11-2 Chronic/persistent rhinosinusitis and nasal polyps
The antileukotriene treatment in 36 patients with chronic rhinosinusitis and nasal polyposis, added to standard treatment, resulted in statistically significant improvement in scores for headache, facial pain and pressure, ear discomfort, dental pain, purulent nasal discharge, postnasal drip, nasal congestion and obstruction, olfaction, and fever. Overall improvement was noted by 72% of the patients and side-effects occurred in 11% of the patients (469). In a selected group of 15 ASA triad patients, addition of antileukotriene treatment resulted in 9/15 with sinusitis experiencing improvement and over-all benefit in 12/15 patients, which was confirmed by endoscopy (470). In a group of patients with nasal polyposis, significant subjective improvement in nasal symptoms occurred in 64% aspirin tolerant patients and 50% aspirin sensitive patients Significant improvement in peak flow occurred only in aspirin tolerant patients, while acoustic rhinometry, nasal inspiratory peak flow and nitric oxide levels did not change (471).

Results of these three studies indicate that there is a need for controlled trials of antileukotriene treatment in chronic persistent rhinosinusitis and nasal polyposis.

7-3-12 Aspirin desensitisation
7-3-12-1 Acute/intermittent and chronic/persistent rhinosinusitis
No controlled trials of systemic aspirin desensitisation or topical aspirin lysine treatment for acute and chronic rhinosinusitis were found.

7-3-12-2 Nasal polyps
Systemic aspirin desensitisation or topical lysine-aspirin treatment may be implicated in protection against chronic rhinosinusitis with nasal polyposis recurrence. However, no randomized controlled trials have been done, and only one non-randomized controlled trial showed doubtful control.

Sixty-five aspirin-sensitive patients with aspirin sensitive asthma underwent aspirin challenge, followed by aspirin desensitization and daily treatment with aspirin over 1 to 6 years (mean, 3.1 years). There were significant reductions in numbers of sinus infections per year and an improvement in olfaction. Numbers of sinus and polyp operations per year were significantly reduced and doses of nasal corticosteroids were significantly reduced. There were reductions in hospitalizations for treatment of asthma per year and reduction in use of systematic corticosteroids (472-474).

Nucera et al. have followed three groups of patients with nasal polyposis (about 50% aspirin sensitive), the first with 76 consecutive nasal polypectomy patients who had a topical lysine-acetylsalicylate-therapy afterwards, the second 49 patients with 40 mg triamcinolone retard ("medical polypectomy") and also further lysine-acetylsalicylate-therapy and the third with 191 control patients who underwent only polypectomy but received no placebo. The group treated with lysine-acetylsalicylate postoperatively had a recurrence rate of 6.9% after 1 year and 65% after six years postoperatively, while controls experienced recurrence in 51.3% at 1 year and 93.5% at six years after the operation, indicating a significant protection against recurrence from the lysine-acetylsalicylate treatment. Systemic corticoid therapy and nasal lysine-acetylsalicylate-therapy resulted in 33% with unchanged polyp size after three years compared to 15% in the operated-not treated group, but this was not statistically significant (475).

A case controlled trial of treatment with lysine aspirin to one nostril and placebo to the other in 13 patients with bilateral nasal polyposis resulted in delayed polyp recurrence and 8 remained symptom free at 15 months observation period, which was significantly better than results of the patients previously treated with steroid for recurrence protection. Endoscopy and acoustic rhinometry indicated minor polyp size on the aspirin treated side (476).

These data indicate that systemic aspirin desensitisation and topical aspirin lysine treatment in nasal polyposis needs to be tested in randomized controlled trials to obtain proper evidence of recurrence protection.

7-3-13 Phytopreparations
Treatment of rhinosinusitis by alternative medicine, including herbal preparations is common in the general population. A study by interview in a random telephone sample population suffering from chronic rhinosinusitis and asthma revealed that 24% were taking herbal preparation (477). Lack of randomized controlled trials comparing such treatment to standard medication in rhinosinusitis patients should be a concern to health care providers.

7-3-13-1 Acute/intermittent rhinosinusitis
A standardized myrtol oil preparation was proven superior to other essential oils, and both were superior to placebo in the randomized placebo controlled trial for uncomplicated acute

rhinosinusitis. A need for antibiotic treatment after myrtol was 23%, compared to 40% for placebo (478).

With andrographis paniculata in a fixed combination Kan Jang showed significantly improved nasal symptoms and headache in acute rhinosinusitis compared to placebo (479).

7-3-13-2 Chronic/persistent rhinosinusitis

Guaifenesin, a phytopreparation known for its mucolytic properties, was tested in a RCT on a selected population of HIV patients with chronic/persistent rhinosinusitis, demonstrating 20% higher improvement in subjective scores compared to placebo in this population (480).

7-3-13-3 Nasal polyps

No controlled trials on nasal polyp treatment with phytopreparations were found.

7-3-14 Conclusion

The results are summarized in table 7-9.

There is research-based evidence (level B) for adjunctive use of hypertonic/normotonic saline in the treatment of persistent rhinosinusitis (<4 controlled trials [CT]), but not intermittent rhinosinusitis.

There is no evidence for the use of decongestants and antral lavage in the treatment of intermittent rhinosinusitis (481). There is research-based evidence (level B) in children for selective use of bacterial lysates in the treatment of recurrent intermittent rhinosinusitis (3 multicentre RCTs). There is level C (limited) evidence for the use of mucolytics in the treatment of intermittent rhinosinusitis (controlled clinical trial, 1 RCT for and 1 RCT against in paediatric rhinosinusitis). There is level B evidence for the use of antihistamines in intermittent rhinosinusitis in patients with allergic rhinitis (1 multicentre placebo controlled RCT).

There is level C (limited) evidence for the use of antimycotics in eosinophilic mucin rhinosinusitis (2 case trials).

There is level B evidence for the use of capsaicin and furosemide in protection against recurrence of nasal polyposis (1 RCT for capsaicin, 2 CT for furosemide). There is also level C evidence for aspirin lysine as a protection against polyp recurrence. There is level C evidence for use of antileukotrienes in patients with nasal polyposis for the alleviation of nasal symptoms.

There is level C evidence for the use of proton pump inhibitors in patients with persistent rhinosinusitis and gastroesophageal reflux.

7-4 Evidence based surgery for rhinosinusitis

7-4-1 Introduction

Nowadays surgery, although minimally invasive, is generally reserved for acute/intermittent rhinosinusitis and chronic/persistent rhinosinusitis un-responsive to conservative medical treatment or where there are complications associated with these conditions. The concept of functional endoscopic sinus surgery (FESS), the Messerklinger technique, spread worldwide by the efforts of Stammberger and Kennedy, was broadly accepted in the 80's and evaluated in numerous prospective and retrospective case controlled studies or non randomized clinical trials. The functional approach to rhinosinusitis hypothesized recovery of the diseased sinus mucosa by enabling ventilation through the natural ostia and restoring mucociliary clearance achieved by minimally invasive endoscopic technique (482, 483).

7-4-2 Surgery in acute /intermittent rhinosinusitis.

To date there are no data available to judge the role of surgery in acute/intermittent rhinosinusitis.

Table 7-9. Other medical management for rhinosinusitis. Results from the treatment studies summarised.

Treatment	*Acute*	*Evidence*	*Relevance*	*Chronic*	*Evidence*	*Relevance*	*Nasal polyp*	*Evidence*	*Relevance*
decongestant	1 RCT, 1 CT	B	no.	no trial			no		
trial									
mucolytic	1 RCT	B	no	1 case	no	no	no trial		
phytomedicine	1 RCT (myrtol)	B	no	1 CT	C	no	no trial		
bacterial lysate	2 RCT recurrent	A	yes	1 RCT	B	no	no trial		
immunomodulation	no trial			1 RCT	B	no	no trial		
antihistamine	1 RCT allergic	B	no	no trial			1 RCT allergic	B	no
antimycotic	no trials			1 case trial	C	no	1 case trial	C	no
antral lavage	1 RCT	B	no	1 RCT	B	no	no trial		
isotonic douche	no trial			3 RCT	A	yes	no trial		
hypertonic douche	1 RCT	B	yes	2 RCT	A	no	no trial		
antileukotriene	no trial			1 case	C	no	3 case	C	no
proton pump inhibitor	no trial			3 case	C	no	no trial		
aspirin lysate	no trial			no trial			1 CT 1 case	B	no
furosemide	no trial			no trial			1 CT 1 case	B	no
capsaicin	no trial			no trial			1 RCT 1 case	B	no

7-4-3 Surgery in chronic /persistent rhinosinusitis and nasal polyposis unresponsive to medical treatment

7-4-3-1 Introduction

Table 7-10 summarizes some of the larger studies with follow up ranging from six months to ten years. Virtually all of these offer only Level III evidence.

Treatment outcomes for ESS were reviewed by Terris and Davidson in 1994 (499), analysing 10 large series (II and III level) with a total of 1,713 patients, which showed a mean 91% (73-97.5%) improvement rate. Subjectively, 63% of patients reported a very good result, 28% a good result, and 9% an unsatisfactory result. Twelve percent of patients required revision surgery and major complications occurred in 1.6% of patients.

7-4-3-2 Comparing ESS and Caldwell/Luc in the short and long term

Some evidence has been provided by studies either comparing different surgical techniques (radical vs. endoscopic sinus surgery (ESS)), or considering the use of new technology- e.g. powered instrumentation applied to the Messerklinger technique. Penttila and co-workers randomized patients to either endoscopic sinus surgery or a Caldwell Luc approach (C-L) and considered outcomes one year following surgery (500); and in the longer term (501) (Level Ib)

Interestingly, the first study revealed significant improvement for obstruction, rhino rhea and improved smell in the ESS group compared to C-L group (global evaluation showed marked improvement in 50.7% of the C-L group and in 76.7% of the ESS group), (500) but the outcomes in the second trial demonstrated a different improvement rate 5-9 years postoperatively, with 82% of the C-L and 76% of the ESS patients respectively deriving benefit. Long term revision surgery was done in 20% of ESS group and 18% of C-L group (501). However, postoperative cheek pain and altered sensation to changes in temperature were noted in 23% of C-L group. The histopathology of similar groups was studied by Forsgren et al. (IIb level), indicating a greater reduction in inflammatory parameters in the mucosa of the maxillary sinus after C-L than ESS one year after the surgery (502). Another randomized controlled (485) clinical study (503) (level Ib), has revealed superiority of ESS (40 patients) to C-L (37 patients) when both CT scans and endoscopy were used as outcome measures (Level III).

7-4-3-3 Comparing inferior antrostomy with middle meatal antrostomy

A cohort controlled trial (38 patients, bilateral disease, sides randomized) comparing outcomes of chronic maxillary sinusitis following middle (MMA) and inferior meatal antrostomy (IMA) did not reveal significant differences, (504) in contrast to the results of Lund, (505) (Level III) who analysed long-term nasal symptoms scores for two types of antrostomies, proving superiority of MMA.

Table 7-10. Subjective results following endoscopic sinus surgery.

First author	*Year reported*	*Number of Patients*	*Improvement*	*Follow-up*
Kennedy et al. (483)	1987	75	92%	0.3-2.75 years
Hosemann et al. (484)	1988	220	81.8%	4.3 years
Hoffman and May (485)	1989	100	98% (10 revised)	0.75 years
Rice (486)	1989	100	83% (7% revised)	2 years
Schaefer et al. (487)	1989	100	83%	0.4 years
Levine (488)	1990	221	80% (CRS) 88% (NP)	1.4 years
Mathews et al. (488 a)	1991	155	91%	1 year
Stammberger and Posawetz (489)	1990	500	95%	0.75-10 years
Wigand and Hosemann (490)	1991	84	83%	1 year
Kennedy (281)	1992	120	85%	1:5 years (mean)
Vleming (491)	1993	92	85%	3.6 years
Schaitkin et al. (492)	1993	100	98%	0.75 years
Lund and Mackay (493)	1994	650	87%	0.5 years
Danielson and Olofsson (494)	1996	226	49% asymptomatic 25% improved 15% slightly improved 0% worse	1-5 yrs mean 3y 5 mo
Weber et al. (495)	1997	170	89%	1.6 - 10 years
Senior et al. (496)	1998	72 (from original cohort of 120 Kennedy)	98% (18% revised)	Mean 7.8 years
Sobol et al. (497)	1998	393	81% 70% (4% revised)	6 months 12 months
Jakobsen and Svendstrup (498)	2000	237	45% totally satisfied 44% improved	1 year

7-4-3-3 Comparing endoscopic sinus surgery with conventional surgery

In a randomized study of 50 patients comparing endoscopic sinus surgery with conventional surgery (506), follow up ranged from 15-33 months with a mean of 19 months, at the end of which 76% of the endoscopic group had complete relief of symptoms, 16% partial relief and 8% no relief as compared to 60%, 16% , 24% in the conventionally treated group. Outcomes for purulent discharge and loss of smell showed significant improvement following ESS when preceded by maxillary sinus irrigation as compared with those obtained by sinus irrigation alone after one year's observation for chronic maxillary sinusitis in a trial (Level III) conducted by Hartog et al. (507). Scores for other sinusitis symptoms did not differ significantly and as sinus irrigation avoided surgery in 58% of the patients at one year follow up, it was suggested that this method, combined with broad spectrum antibiotics should precede ESS.

There are no direct comparisons between endoscopic sinus surgery and conventional intranasal ethmoidectomy and only an historical comparison is possible. In these earlier studies improvement was judged in a fairly crude subjective manner and would appear to be somewhat worse than that reported with endoscopic sinus surgery though that might reflect the predominance of nasal polyposis in these patient groups.

More recently a systematic review of the clinical effectiveness of endoscopic polypectomy was conducted by the University of Exeter in 2002. This considered 33 published studies which had enrolled more than 50 patients, comprising three RCTs, three non-randomised control trials and twenty seven case series including many of the references already discussed. The RCTs and controlled trials reported an overall symptomatic improvement that ranged from 78% to 98% for FESS compared to 43 to 84% for comparative techniques (including polypectomy, Caldwell-Luc and intranasal ethmoidectomy). Disease recurrence was 8% for FESS compared to 14% for Caldwell-Luc and polyp recurrence was 28% for endoscopic ethmoidectomy compared to 35% for polypectomy. The percentage of overall complications was 1.4% for FESS compared to 0.8% for conventional procedures. The case series studies reported overall symptomatic improvement for patients with nasal polyps that ranged from 37% to 99% (median 89%). For the mixed patient groups with and without polypoid disease, overall symptomatic improvement ranged from 40% to 98% (median 88%). The authors concluded that FESS may offer some advantages in effectiveness over comparative techniques but there is enormous variation in the range of results reported and severe methodological limitations (514).

In 2000 the Clinical Effectiveness Unit of the Royal College of Surgeons of England conducted a national comparative audit of the surgery for nasal polyposis and chronic rhinosinusitis covering the work of 538 ENT surgeons (both consultants and trainees) working in 87 hospitals in England and Wales. Patients undergoing surgery were prospectively enrolled and followed up at 3 and 12 month intervals post-operatively using the SNOT-22 as the main outcome measure. Three thousand one hundred and twenty eight patients participated in the audit of whom two-thirds had nasal polyps. This included all forms of surgery though the majority were performed endoscopically. Overall there was a high level of satisfaction with the surgery irrespective of whether it was performed endoscopically or not and clinically significant improvement in the SNOT-22 scores were demonstrated at 3 and 12 months although there was some deterioration during this interval. All polyp patients benefited more from surgery than the chronic rhinosinusitis with benefit increasing as polyp extent increased. 8.7% of patients had or were waiting for revision surgery at 12 months. Overall the surgery was safe with a CSF leak of 0.064% and peri-orbital haematoma rate of 0.2% with no long term visual problems. Patients with aspirin sensitivity and patients with a history of previous surgery tended to derive less benefit from sinonasal surgery in terms of symptom improvement (515) (Level II).

Modifications to standard FESS technique have been studied in several randomized controlled clinical trials. A multicentre study (Ib) compared extended versus limited ESS approach in 65 patients with a long-term follow up evaluating subjective symptom scores, nasomucociliary transit time and endoscopic findings which showed no significant difference between the two groups although the number of patients was small for statistical analysis (516). Nayak et al. have tested so-called functional nasosinusal surgery (FENS – limited ethmoid approach combined with endoscopic septal surgery) for what they described as allergy-associated chronic rhinosinusitis in a randomized controlled trial (Ib) by means of visual analogue symptom scores and endoscopy. The results indicated FENS to be superior to FESS for this selected population with CRS (517). More conservative procedures e.g. minimal invasive sinus surgery (MIST) had similar subjective outcomes as con-

Table 7-11. Subjective results following conventional intranasal ethmoidectomy.

First author	*Year reported*	*Number of Patients*	*Improvement*	*Follow-up*
Eichel (508)	1982	46	83%	3-8 years
Taylor et al. (509)	1982	80	70%	1-10 years
Stevens and Blair (510)	1988	87	75%	0.5-11 ears
Friedman and Katsantonis, 1990 (511)	1990	1037	85%	8 years
Sogg, 1989 (512)	1989	146	69%	6-13 years
Lawson, 1991 (513)	1991	90	73%	3.5 years

ventional ESS, in a prospective non-randomized study in 85 patients with persistent rhinosinusitis (level III) but the results should be validated by a RCT (518).

A randomized controlled trial (Ib) tested the outcomes for holmium-YAG laser in 32 patients with CRS undergoing ESS (randomization - one side conventional, contralateral laser) (519). The use of holmium-YAG laser in ESS resulted in significantly lower blood loss during surgery and less post-operative crust formation than conventional ESS, but long term subjective outcomes did not show significant difference between the methods. Similarly in a prospective randomized study Selivanova et al.were unable to demonstrate an advantage of mechanical debriders over conventional instrumentation (520).

7-4-3-5 Endoscopic surgery in special situations

From a cohort of 650 patients undergoing ESS for CRS, 28 patients suffered for cystic fibrosis and14 from immune deficiency (493) (Level III). Whilst overall subjective improvement was less than in the cohort as a whole (91% improved), 54% of the cystics and 79% of those with immune deficiency derived significant benefit at six month follow-up. No studies specifically focusing on primary ciliary dyskinesia or congenital immune deficiency were found in the literature. However, a number of authors have considered acquired immune deficiency, mainly related to HIV. These have been by definition a relatively small series (98) , (Level III). The bacterial profile may mirror that seen in conventional rhinosinusitis but can also includes pseudomonas aeruginosa and toxoplasma. A range of surgical approaches have been used in this group with high relapse rates reported of 76-81%.

The small number of papers concentrating on cystic fibrosis have mainly concerned the paediatric population. Halvorsen et al. (521) reported 16 adults with cystic fibrosis and chronic rhinosinusitis/nasal polyposis combined with pulmonary complications. The study considered pulmonary function following endoscopic sinus surgery and preliminary findings suggested an improvement in both the symptoms of rhinosinusitis and exercise tolerance (Level III). However, again there was a high chance of relapse, 50% in the study by Rowe-Jones and Mackay (522) (Level III) within two years of the procedure.

The relationship of asthma/aspirin-sensitivity on surgical results and the effects of surgery on the lower respiratory tract are debated. A prospective study of 120 patients maintained that when extent of disease was taken into account, asthma per se did not adversely affect outcome (281) (Level II). However, as a corollary of this, recurrence particularly in the aspirin-sensitive group is likely to be higher (492) (523) (Level III). This may be off-set to some extent in the short term by the extent of surgery (523, 524) The effect of sinonasal surgery on respiratory function has generally been positive.

7-4-4 Conclusion

In conclusion, trials providing high level statements of evidence for efficacy of surgery for rhinosinusitis are lacking, as already concluded by Lund in 2001 (539). Few sinonasal surgical studies are designed as RCTs, and those that are should be of higher quality. Lack of consistency between the studies (inclusion-exclusion criteria, staging, scores, questionnaires etc.) and inadequate numbers for robust statistics are the main drawbacks of these trials. In addition the experience of an endoscopic rhinosurgeon should be established before one can compare results from different studies (540) though there have been some attempts to look at the 'learning curve' through complication rates (Stankiewicz). We have a large amount of low level evidence that ESS is a safe procedure that improves rhinosinusitis symptom scores, HRQL and some objective criteria (see Chapter 7-5-3) in low-risk adult patients. However, at least two studies have shown that aggressive medical therapy offers similar results over a one year period (296, 541) (Level IIb) underlining the need to reserve surgery for those who have failed medical therapy. 'High-risk' patients should be treated with aggressive long-term medication pre- and postoperatively and represent a different group when evaluating studies.

7-5 Surgical treatment vs. medical treatment in CRS /NP

7-5-1 Surgical treatment vs. steroids in NP

In the two open studies by Lildholt et al. (267, 379) single injections of 14 mg betametasone have been compared to intranasal polypectomy without any difference in outcome 12 months after treatment with subsequent local steroids in both groups, as measured by mean nasal score or mean score of sense of smell. In a study by Blomqvist et al. (542) 32 patients were pre treated with systemic steroids (prednisolone for fourteen days) and budesonide for 4 weeks after which unilateral FESS was performed and intranasal steroids given for an additional 12 months to both sides. The sense of smell improved after treatment with systemic and local steroids. Surgery had an additional beneficial effect on nasal obstruction and secretion that persisted over the study period but no additional effect was observed on sense of smell. The authors conclude that surgical treatment is indicated after steroid treatment, if nasal obstruction persists but not if hyposmia is the primary symptom (Level III).

To date there is too little data available to determine if there is any difference between surgery and steroid therapy in the long-term outcome of patients with nasal polyposis.

7-5-2 Surgical vs. steroids in CRS

To our knowledge no studies have been published to date comparing surgery and topical corticosteroids in the treatment of CRS.

Table 7-12. Chronic rhinosinusitis and bronchial asthma: Effects of various paranasal sinus procedures on lung function (Level II/III).

Author	*Patients (age)*	*Procedure*	*Post-operative interval*	*Results*	*Comments*
Brown et al., 1979 (525)	101 patients with ASA triada (10-74y)	polypectomyb	12 mo	clinically[c] 32% better, 53% unchanged, 15% worse.	60% nasal passages free post-operative
Jäntti-Alanko et al., 1989 (526)	34 patients	polypectomy	48 mo	clinically: 59% better, 29% unchanged, 12% worse	
English, 1986 (527)	205 patients with ASA triad[a] (91% adults)	Caldwell-Luc[b]	6-156 mo	lung function: 98% better, 2% unchanged, 0% worse	steroids reduced in 84%
Nishioka et al., 1994 (91)	20 patients (16-72 y)	partial endonasal ethmoidectomy	12 mo	clinically: 95% better	90% nasal obstruction preoperative.
Friedman et al., 1982 (528)	50 patients	endonasal ethmoidectomy	6-36 mo	clinically: 93% cortisone reduced	100% nasal obstruction preoperative
Hosemann et al., 1990 (529)	13 patients (27-75 y)	endoscopic ethmoidectomy	12 mo	lung function/medication: 77% better, 15% unchanged, 8% worse	
Ilberg, 1994 (530)	32 patients	endoscopic ethmoidectomy	36 mo	clinically: 50% better	
Jankowski et al., 1992 (531)	50 patients	endoscopic ethmoidectomy	18 mo	lung function/ clinically: 91% better, 9% unchanged	
Korchia et al., 1992 (532)	25 patients	endoscopic ethmoidectomy	1 y	clinically: 66% unchanged, 29% better, 5% worse	lung function 100% unchanged
Dunlop et al., 1999 (533)	50 patients (17-74 y)	endoscopic ethmoidectomy	1 y	clinically: 40% better 20% less steroid inhaler 28% less bronchodilator sig less oral steroids with hospital admissions	
Goldstein et al., 1999 (534)	13	endoscopic ethmoidectomy	mean 33 months	1/13 showed obj or subj improvement	
Ikeda et al., 1999 (535)	21-15 6	endoscopic sinus surgery controls	6 months	ESS: ?peakflow ? steroids controls: no change	
Palmer et al., 2001 (536)	15	endoscopic sinus surgery	1 y	? steroids ? antibiotics	
Wreesman et al., 2001 (537)	82	Denker's procedure	?	clinical improvement	refractory CRS/polypoids
Batra et al., 2003 (538)	17 9 ASA triad	endoscopic ethmoidectomy	1 y	clinically 76% better FEV_1[d] better 71% less steroid	ASA triad did worse

a ASA triad: asthma + chronic rhinosinusitis + aspirin intolerance; b Additional endonasal procedures to the ethmoidal; c Clinically: clinical investigation (assessment based on questioning of patient, consumption of medication, admissions to hospital etc); d FEV1: forced expiratory volume (1/s);e Variable: various procedures, operating technique unclear, mo: months; y: years

7-5-3 Surgical vs. antibiotics in CRS

Only one recent study in the literature compares surgery versus long term antibiotic treatment in patients with CRS with and without NP (296). Ninety patients with CRS were equally randomized either to medical or surgical therapy. Each patient had three assessments: before starting the treatment, after 6 months, and at 1 year. Both the medical and surgical treatment of CRS significantly improved almost all the subjective and objective parameters of CRS ($P<.01$), with no significant difference being found between the medical and surgical groups ($P>.05$), except for the total nasal volume in CRS with ($P<.01$) and without polyposis ($P<.01$) groups, in which the surgical treatment demonstrated greater changes.

8. Complications of rhinosinusitis and nasal polyps

8-1 Introduction

In the pre-antibiotic era, complications of rhinosinusitis represented extremely common and dangerous clinical events. Today, thanks to more reliable diagnostic methods (CT, MRI) and to the wide range of available antibiotics, their incidence and related mortality have dramatically decreased. In some cases however, if sinus infection is untreated or inadequately treated, complications can still develop (543). In patients affected by acute bacterial rhinosinusitis with intracranial spread despite antibiotic therapy , there still is a high incidence of morbidity and mortality rate, estimated at between 5% and 10% (544).

Complications of rhinosinusitis are classically defined as **orbital**, **osseous** and **endocranial** (544) though rarely some unusual complications can develop (table 2) (545-549).

An extremely useful test, although not specific, is the white cell count which, if elevated in acute rhinosinusitis unresponsive to treatment, is highly suggestive of a complication.

8-2 Epidemiology of complications

Epidemiological data concerning the complications of rhinosinusitis vary widely and there is no consensus on the exact prevalence of the different types of complications. Moreover, the relationship between acute or chronic rhinosinusitis and the various complications is not clearly defined in the literature. This is probably related to the different number and methods of sampling patients in the various studies and no account is taken of local demographics. For these reasons, as table 8-1 clearly shows, an attempt to make a comparison of the different epidemiological data available is difficult.

For example, whilst the percentage is similar in two studies that compared two different groups of selected patients affected with pansinusitis (72.4% and 75% respectively) (472,473), the percentage in another (551) is smaller (37%); this is probably due to the fact that in this sample, both acute and chronic disease were studied, whereas the other two authors focused their attention on acute cases.

In another mixed (acute and chronic) sample, Clayman highlighted the frequency of intracranial complications in patient with complicated rhinosinusitis as about 3.7%, but no data concerning the global prevalence of complications were give in his work (555).

8-3 Orbital complications

8-3-1 Systemic

If there is a complication in rhinosinusitis, the eye is often involved (552) especially in ethmoiditis, whereas this is rare in sphenoidal infection (557). The spread of infection directly via the thin and often dehiscent lamina papyracea (557); or by veins (558) occurs with relative ease.

According to Chandler's classification orbital complications may progress in the following steps (559):
periorbital cellulitis (preseptal edema),
orbital cellulitis,
subperiosteal abscess,
orbital abscess or phlegmon and
cavernous sinus thrombosis (543, 560).

Moreover orbital complications especially in children, often occur without pain (561). Orbital involvement is manifested by swelling, exophthalmos, and impaired extra-ocular eye move-

Table 8-1. Epidemiological data of complications in rhinosinusitis.

Author	*Country*	*Age*	*Pathology*	*Pts*	*Total % of complications*	*Orbital*	*Intracranial*	*Osseous*	*Soft tissue*
Mortimore, 1999 (550)	South Africa	adults	acute pansinusitis	87	72.4% (63/87)				
Ogunleye, 2001 (551)	Nigeria	adults	acute/chronic pansinusitis	90	37% (33/90)	41%	5%	32%	18%
Eufinger, 2001 (552)	Germany	adults/ children	acute pansinusitis	36	75% (27/36)	58% (20+1/36)	11% (3+1/36)		8.4% (3/36)
Kuranov, 2001 (553)	Russia	adults	rhinosinusitis			0.8%	0.01%		
Gallagher, 1998 (554)	USA	adults	rhinosinusitis	176			8.5% (15/176)		
Clayman, 1991 (555)	USA	adults	acute/chronic rhinosinusitis	649			3.7% (24/649)		
Lerner, 1995 (556)	USA	children	rhinosinusitis	443			3% (14/443)		

ments (562). Periorbital or orbital cellulitis may result from direct or vascular spread of the sinus infection. As the spread of sinus infection through the orbit follows a well-described pattern, the initial manifestations are oedema and erythema of the medial aspects of the eyelid. Spread of infection from the maxillary or frontal sinus produces swelling of the lower or upper eyelid, respectively (560).

8-3-2 Periorbital cellulitis

Periorbital cellulitis (inflammation of the eyelid and conjunctiva) (549) involves the tissue anterior to the orbital septum and is readily seen on CT scan as soft tissue swelling. It is the most common complication of rhinosinusitis in children (563) and it manifests itself as orbital pain, blepharal edema and high fever (564). Periorbital cellulitis usually responds to an oral antibiotic appropriate to common sinus organisms but if not aggressively treated, may spread beyond the orbital septum (563).

8-3-3 Orbital cellulitis

As the inflammatory changes spread beyond the orbital septum, proptosis develops together with some limitation of ocular motion, indicating orbital cellulitis. Further signs are conjunctival oedema (chemosis), a protruding eyeball (proptosis), ocular pain and tenderness, and decreased movement of the extra ocular muscles (549, 565).

This complication requires aggressive treatment with intravenous antibiotics.

Any children with rhinosinusitis and proptosis, ophthalmoplegia, or decreased visual acuity should have a CT scan of the sinuses with orbital detail to distinguish between an orbital and periorbital (subperiosteal) abscess. Both conditions cause proptosis and limited ocular movement. Evidence of an abscess on the CT scan or progressive orbital findings after initial i.v. antibiotic therapy are indications for orbital exploration and drainage. Repeated ophthalmologic examination of visual acuity should take place and i.v. antibiotic therapy may be converted into oral when the patient has been afebrile for 48 hours if the ophthalmological symptoms and signs are resolving (563).

8-3-4 Subperiosteal or orbital abscess

The clinical features of a subperiosteal abscess are oedema, erythema, chemosis and proptosis of the eyelid with limitation of ocular motility and as a consequence of extra-ocular muscle paralysis, the globe becomes fixed (ophthalmoplegia) and visual acuity diminishes.

An **orbital abscess** generally results from diagnostic delay or to immunosuppression of the patient (564) with a frequency of 9% and 8.3% (566, 567) in paediatric studies.
A CT scan of the sinuses with orbital sequences to distinguish between orbital and periorbital (subperiosteal) abscess should be performed. Evidence of an abscess on the CT scan or absence of clinical improvement after 24-48 hours of i.v. antibiotics are indications for orbital exploration and drainage. An ophthalmologist should check visual acuity from the early stages of the illness and i.v. therapy should cover aerobic and anaerobic pathogens. It can be converted to an oral preparation when the patient has been afebrile for 48 hours (563).

Blindness may result from central retinal artery occlusion, optic neuritis, corneal ulceration, or pan-ophthalmitis. In such a case the CT usually reveals oedema of the medial rectus muscle, lateralization of the periorbita, and displacement of the globe downward and laterally. When the CT scan shows obliteration of the detail of the extraocular muscle and the optic nerve by a confluent mass, the orbital cellulitis has progressed to an abscess, in which there is sometimes air due to anaerobic bacteria. Sepsis not infrequently can spread intracranially as well as anteriorly into the orbit (568).

8-4 Endocranial complications

These include epidural or subdural abscesses, brain abscess, meningitis (most commonly), cerebritis, and cavernous sinus thrombosis (563, 569, 570).

The clinical presentation of all these complication is non-specific, being characterized by high fever, frontal or retro-orbital migraine, generic signs of meningeal irritation and by various degrees of altered mental state (554) while intracranial abscesses are often heralded by signs of increased intracranial pressure, meningeal irritation, and focal neurological deficits (562). Although an intracranial abscess is relatively asymptomatic, subtle affective and behavioural changes often occur showing altered neurological function, altered consciousness, gait instability, and severe, progressive headache.
Endocranial complications are most often associated with ethmoidal or frontal rhinosinusitis. Infections can proceed from the paranasal cavities to the endocranial structures by two different routes: pathogens, starting from the frontal most commonly or ethmoid sinus, can pass through the diploic veins to reach the brain; alternatively, they can reach the intracranial structures by eroding the sinus bones (554).

All endocranial complications start as cerebritis, but as necrosis and liquefaction of brain tissue progresses, a capsule develops resulting in brain abscess. Studies show a high incidence of anaerobic organisms or mixed aerobic-anaerobic in patients with CNS complications.

A CT scan is essential for diagnosis as it allows an extremely accurate definition of bone involvement, whereas MRI is essential when there are some degrees of soft tissues involvement such as in cavernous sinus thrombosis (554). Moreover, if meningitis is suspected, a lumbar puncture could be useful (554) once an abscess has been excluded.

Table 8-2. Endocranial complications in rhinosinusitis.

Author	*Number of patients with endocranial complications*	*Complications*	*Mortality/Further Defects*
Gallagher 1998 (554)	176 patients	meningitis represented 18% cerebral abscess 14% epidural abscess 23%	Mortality 7% Morbidity 13%
Albu 2001 (571)	16 patients	6 had meningitis 6 frontal lobe abscess 5 epidural abscess 4 subdural abscess 2 cavernous sinus thromb-ophlebitis	
Dunham 1994 (563)		subdural empyema in 18%	Mortality 40% Surviving patients often have neurological disability
Eufinger 2001 (552)		together meningitis, empyema and brain abscess constitute 12% of all the intracranial complications	

High dose long term i.v. antibiotic therapy followed by craniotomy and surgical drainage are usually required for successful treatment (566). Pathogens most commonly involved in the pathogenesis of endocranial complications are Streptococcus and Staphylococcus species and anaerobes (570).

8.5 Cavernous sinus thrombosis

When the veins surrounding the paranasal sinuses are affected, further spread can lead to cavernous sinus thrombophebitis causing sepsis and multiple cranial nerve involvement (563). Such a complication has been estimated at 9% of intracranial complications (554, 571) and is a fortunately rare and dramatic complication of ethmoidal or sphenoidal sinusitis. The main symptoms are bilateral lid drop, exophthalmos, ophthalmic nerve neuralgia, retro-ocular headache with deep pain behind the orbit, complete ophthalmoplegia, papilloedema and signs of meningeal irritation associated with spiking fevers and prostration (560).
The cornerstone of diagnosis is high-resolution CT scan with orbit sequences (572) which show low enhancement compared to normal (573). A mortality rate of 30% and a morbidity rate of 60% remain in the adult population. No data are available for the paediatric population in which the mortality rate for intracranial complications is 10% to 20% (574). The use of anticoagulants in these patients is still controversial (560) but is probably indicated if imaging shows no evidence of any intracerebral haemorrhagic changes (575).

8-6 Osseous complications

Sinus infection can also extend to the bone producing osteomyelitis and eventually involving the brain and nervous system. Even if the most frequent intracranial spread is due to frontal sinusitis, any sinus infection can lead to such a complication (560). The most common osseous complications are osteomyelitis of the maxillary (typically in infancy) or frontal bones (573).

As vascular necrosis results from frontal sinus osteitis, an osteomyelitis of the anterior or posterior table of the frontal sinus is evident. On the anterior wall it presents clinically with "doughy" oedema of the skin over the frontal bone producing a mass (Pott's puffy tumor) whereas from the posterior wall spread occurs directly or via thrombophlebitis of the valveless diploic veins leading to meningitis, peridural abscess or brain abscess (560).

In this context, Gallagher (554) reviewing the files of 125 patients with complicated rhinosinusitis, found that osteomyelitis developed in about 9% of cases. The sinus walls were affected in 32% of patients in Ogunleye's data (551). Lang in 2001 recorded 10 cases of subdural empyema in adults and children secondary to frontal sinus infection: among them 4 had Pott's puffy tumor and 1 had periorbital abscess (544).

Signs and symptoms of intracranial involvement are soft tissue oedema (especially of the superior lid), high fever, severe headache, meningeal irritation, nausea and vomiting, diplopia, photophobia, papilloedema, coma and focal neurological signs. Ocular signs can appear contralaterally. Contrast-enhanced CT scan confirms the diagnosis. A lumbar puncture, though contraindicated if intracranial pressure is elevated, can also be useful.
Therapy includes a combination of i.v. broad-spectrum antibiotics administration and surgical debridement of sequestered bone and drainage (560).

8-7 Unusual complications of rhinosinusitis

Table 8-3. Unusual complications of rhinosinusitis.

Complication	*Author, year*
Lacrimal gland abscess	Mirza 2001 (545)Patel 2003 (546)
Nasal septal perforation	Sibbery 1997 (576)
Visual field loss	Gouws 2003 (548)
Mucocoele or mucopyocoele	Low 1997 (569)
Displacement of the globe	Low 1997 (569)

8-8 Complications of surgical treatment

8-8-1 Introduction

After the introduction of endoscopic paranasal sinus surgery, the indication for operations in this region expanded, the number of operators increased together with an increase in the numbers of operations, but also increasing the absolute number of iatrogenic complications. As a consequence, for a period of time in the United States, paranasal sinus surgery was the most frequent source of medicolegal claims (577).

8-8-2 Complications of sinus surgery

Factors responsible for complications are the variability of the anatomy of this region, the proximity of the brain and orbita and last but not least the ability of the operator to maintain orientation especially in revision surgery. The typical complications are listed in table 8-4.

8-8-3 Epidemiology of complications of sinus surgery using non-endoscopic techniques

Table 8-5. presents the number of complications in several studies using non-endoscopic sinus surgery.

8-8-4 Epidemiology of complications of sinus surgery using endoscopic techniques

The Table (8-6) presents the number of complications in studies using endoscopic sinus surgery and which included a minimum of 100 patients. Meta-analysis of these data suggests major complications occur in about 1% and minor complications in about 5-6% of cases. Further analysis with the available data is not possible because of different classification and data presented in these studies.

8-8-5 Comparison of various techniques

Comparison of non-endoscopic and endoscopic techniques shows similar frequencies of complications. Differences in minor complication rates, with for example more synechiae being seen in endoscopic surgery, could be a result of the more precise follow-up using an endoscope, compared to follow-up with anterior rhinoscopy. On the other hand ecchymosis was not always considered a complication in the pre-endoscopic period.

In a study by Kennedy et al. (594), a survey regarding complications of sinus surgery was mailed to 6969 otolaryngologists; 3933 responses (56.44%) were obtained, and 3043 of these physicians (77.37%) reported that they performed ethmoidectomy. Completed questionnaires were available for review from

Table 8-4. Complications following paranasal sinus surgery.

Location	*Minor complications*	*Major complications*
Orbital	Orbital emphysema Ecchymosis of the eyelid	Orbital haematoma Loss of visual acuity/blindness Diplopia Nasolacrimal duct damage
Intracranial	CSF leak - uncomplicated	CSF leak Pneumcephalus (Tension) Encephalocoele Brain abscess Meningitis Intracranial (subarachnoid) bleeding Direct brain trauma
Bleeding	Small amount of bleeding Stopped with packing No need for blood transfusion	Lesion of anterior ethmoidal artery Lesion of sphenopalatine artery Lesion of internal carotid artery Bleeding which requires transfusion
Other	Synechiae Slight exacerbation of pre-existent asthma Hyposmia Local infection (osteiitis) Post-FESS MRSA infection Atrophic rhinitis Myospherulosis Temporary irritation of infraorbital nerve Hyperaesthesia of lip or teeth	Toxic-shock syndrome Anosmia Severe exacerbation of pre-existent asthma or broncospasm Death

Table 8-5. Epidemiology of complications following paranasal surgery, using non-endoscopic techniques.

Author/Year	*N*	*Orbita*	*Intracranial*	*Bleeding*	*Others*	*Minor*
Freedman and Kern, 1979 (578)	565	4	2	2	1	16
Taylor et al, 1982 (509)	284	1	3	-	-	8
Stevens and Blair, 1988 (510)	87	3	-	3	-	8
Eichel, 1982 (508)	123	1	2	1	-	no numbers
Sogg, 1989(512)	146	-	-	-	-	4
Friedman and Katsantonis, 1990 (511)	1163	-	4	3	-	25
Lawson, 1991 (513)	600	2	3	-	2	5
Sogg and Eichel, 1991 (579)	3000	-	5	2	-	288

Table 8-6. Epidemiology of complications following paranasal surgery, using endoscopic techniques.

Author/Year	*N*	*Orbita*	*Intracranial*	*Bleeding*	*Others*	*Minor*
Schaefer et al., 1989 (487)	100	-	-	-	-	14
Toffel et al., 1989 (580)	170	-	-	1	-	6
Rice, 1989 (486)	100	-	-	-	-	10
Stammberger & Posawetz, 1990 (489)	500	-	-	1	-	22
Salman, 1991 (581)	118	-	-	-	-	28
Wigand and Hoseman, 1991 (490)	500	-	10	-	-	no numbers
Lazar et al., 1992 (582)	210	-	-	-	3	16
Vleming et al., 1992 (583)	593	2	2	2	1	38
Weber and Draf, 1992 (584)	589	20	15	1	-	no numbers
Kennedy, 1992 (281)	120	-	-	-	-	1
May et al., 1993	1165	-	4	3	-	94
Smith and Brindley, 1993 (585)	200	1	-	-	-	16
Dessi et al., 1994 (586)	386	3	2	-	-	no numbers
Cumberworth et al., 994 (587)	551	1	2	-	-	no numbers
Lund and Mackay, 1994 (493)	650	1	1	-	-	no numbers
Ramadan and Allen, 1995 (588)	337	1	3	-	-	34
Danielson and Olafson, 1996 (494)	230	-	-	-	10	6
Castillo et al., 1996 (589)	553	2	2	8	-	36
Weber et al., 1997 (495)	325	4	3	30		no numbers
Rudert et al., 1997 (590)	1172	3	10	10	-	no numbers
Dursum et al., 1998 (591)	415	12	1	12	-	56
Keerl et al., 1999 (592)	1500	2	5	9	-	no numbers
Marks, 1999 (593)	393	1	3	5	-	22
Total amount	10877	53 (0.5%)	63 (0.6%)	82 (0.8%)	14 (0.1%)	399 (3.6%)

42% of all Academy fellows (2942 physicians). The survey confirmed that there has been a marked rise in the frequency of ethmoidectomy and in the amount of training in ethmoidectomy since 1985. At the same time the frequency of microscopic, external or transantral ethmoidectomy seemed to decrease. In 86% a preoperative CT-scan was routinely done.

The study did not demonstrate a clear and consistent statistical relationship between the incidence of complications, the type of surgery performed, and the quality of training. Moreover, physicians who provided data from record review tended to report higher rates than those who estimated responses. The majority of physicians discussed specific potential complications with their patients before surgery and routinely performed preoperative computed tomography. The study demonstrated that physicians who experienced complications at higher rates were more likely to discuss these complications with patients before surgery (76% discussed CSF leak, 63% meningitis, 54% permanent diplopia, 66% intraorbital hematoma, 87% lost of vision, 46% intracranial lesions, 40% death in relation with the operation).

Between 1985 and 1990 the following complication rates were seen: table 8-7.

The complication rate in this study was significantly lower in the hands of experienced operators with 11 to 20 years experience.

In Australia Kane (595) did an similar review, presenting an overall major complication rate of 0.03% (12 major orbital complications and 22 intracranial complications in 10,000 FESS operations).

Table 8-7. Complications comparison of non-endoscopic and endoscopic techniques.

Technique	*Major complications*	*Patients died*
Endoscopic ethmoidectomy	0.4097%	3
Endonasal ethmoidectomy with headlamp	0.3569%	23
External ethmoidectomy	0.5204%	9
Transantral ethmoidecthomy	0.1765%	3

8-8-6 Risk factors for complications in sinus surgery

The risk of complications in sinus surgery depends on several factors:

- extent of the pathology (i.e. requiring infundibulotomy or complete pansinus operation);
- first or revision surgery (loss of landmarks, dehiscent lamina papyracea);
- right- or left sided pathology (right side most often affected);
- operation under local or systemic anaesthesia (feedback from patient!);
- amount of bleeding during the operation;
- expertise of the operator (learning curves).

With respect to the last point, a structured training program for beginners in sinus surgery is recommended, including cadaver dissection, hands-on training and supervision during the first operations.

8-8-7 Conclusion

Sinus surgery is well established. There are several techniques used to adequately treat the pathology. Nevertheless the risk of minor or major complications exists and has to be balanced with the expected result of operative or conservative treatment. The learning curve of less-experienced operators has to be considered, as well as the complexity of the individual case.

A preoperative CT-scan is nowadays standard in the preoperative assessment and especially important in revision surgery.

9. Special considerations: Rhinosinusitis in children

9-1 Introduction

Rhinosinusitis is a common problem in children that is often overlooked. It is a multifactorial disease in which the importance of several predisposing factors change with age. The management of rhinosinusitis in children is a controversial and a rapidly evolving issue.

9-2 Anatomy

In the newborn, the maxillary sinus extends to a depth of about 7 mm, is 3 mm wide and 7 mm high (596). When a child reaches the age of 7-8 years the floor of the maxillary sinus already occupies the same level as the nasal floor. In the newborn, two to three ethmoid cells are found bilaterally, and by the age of four the ethmoid labyrinth has been formed. The sphenoid sinuses are also present in the neonate. Each sphenoid sinus is 4 mm wide and 2 mm high. At birth the frontal sinuses are not present, but they gradually develop from the anterior ethmoid cells into the cranium. When the upper edge of the air cell (cupola) reaches the same level as the roof of the orbit, it can be termed a frontal sinus, a situation that appears around the age of five.

9-3 Epidemiology and pathophysiology

Since the introduction of CT-scanning, it has become clear that a runny nose in a child is not only due to limited rhinitis or adenoid hypertrophy, but that in the majority of the cases the sinuses are involved as well. Van der Veken (173) in a CT scan study showed that in children with a history of chronic purulent rhino rhea and nasal obstruction 64% showed involvement of the sinuses. In a MRI study of a non-ENT paediatric population (597) it was shown that the overall prevalence of sinusitis signs in children is 45%. This prevalence increases in the presence of a history of nasal obstruction to 50%, to 80% when bilateral mucosal swelling is present on rhinoscopy, to 81% after a recent upper respiratory tract infection (URI), and to 100% in the presence of purulent secretions. Also Kristo et al. (598) found a similar overall percentage (50%) of abnormalities on MRI in 24 school children. They included, however, a follow-up after 6 to 7 months, and found that about half of the abnormal sinuses on MRI findings had resolved or improved without any intervention.
Epidemiologic studies on rhinosinusitis in children are limited but reveal the following information on the pathophysiology and clinically relevant factors influencing the prevalence of rhinosinusitis in children.
There is a clear-cut decrease in the prevalence of rhinosinusitis after 6 to 8 years of age. This is the natural history of the disease in children and is probably related to an immature immune system in the younger child (176, 177)
In temperate climates there is a definite increase in the occurrence of chronic rhinosinusitis in children during the fall and in the wintertime, so that the season seems to be another important factor (176).
Younger children staying in day care centres show a dramatic increase in the prevalence of chronic or recurrent rhinosinusitis compared to children staying at home.

Although viruses are uncommonly recovered from sinus aspirates (562, 599), most authors agree (600, 601) that viral infections are the trigger to rhinosinusitis. Although CT scan abnormality can be seen up to several weeks after the onset of a URI, one can assume that only 5 to 10% of the URI in early childhood are complicated by acute rhinosinusitis (602). The time course (i.e. clinical symptoms) of viral to bacterial rhinosinusitis is the same as in adults.

The most common bacterial species isolated from the maxillary sinuses of patients with acute rhinosinusitis are Streptococcus pneumoniae, Haemophilus influenzae, and Moraxella catarrhalis, the latter being more common in children (41, 42).

Since antral punctures are not frequently performed in children anymore, it is interesting to know from the studies that in children there is a good correlation of bacteriology between the maxillary sinus and the middle meatal specimen (83%), and a poor correlation between those of the nasopharynx and the maxillary sinus (45%) (603).

9-4 Symptoms and signs

Several authors studied the presenting symptoms of rhinosinusitis in children (177, 604, 605). Children with acute rhinosinusitis frequently have less specific complaints than adults. Rhino rhea is the most frequent presenting symptom in all forms of rhinosinusitis (71% to 80%). Cough seems to be a frequent symptom (50% to 83%). In acute rhinosinusitis, however, nasal obstruction does not appear to be the most prominent symptom, probably because it is masked by more severe symptoms such as fever (50 to 63%) and pain (29% to 33%). On the other hand, in chronic sinusitis, nasal obstruction and mouth breathing are very frequent (70% to 100%) and is often accompanied by ear complaints (recurrent, purulent otitis media or chronic otitis media with effusion: 40% to 68%). This relationship between rhinosinusitis and otitis is not unexpected, as the middle ear can be considered a kind of specialized paranasal space.

9-5 Examination

Physical examination of a child's nose is often difficult, and only limited anterior rhinoscopy is tolerated by these young patients (606). This examination may be accomplished in a simple way by tilting the tip of the nose upward (young children have wide noses with round nostrils and no vibrissae, allowing easy examination of the condition of the head of the inferior turbinate). Another convenient method is the use of an otoscope (607, 608). Because of the difficulties of performing anterior rhinoscopy in a young child, most studies provide limited information about the condition of the nasal cavity in rhinosinusitis in children. Mostly the nasal (boggy turbinate) and pharyngeal mucosa appears erythematous. Yellow to greenish purulent rhino rhea of varying viscosity can be seen. Lymphoid hyperplasia may be seen in the oropharynx. There may be adenoid and/or tonsillar hypertrophy, cervical lymph nodes may be moderately enlarged and slightly tender (606, 607). The only quantitative data on rhinoscopy in young children is given by Clement et al. (605) showing a postnasal drip in 60% and presence of pus in the middle meatus in 50% and by Riding et al. showing turbinate mucosal swelling in 29% (604).

The value of transillumination and ultrasonography is certainly limited, and these procedures are not recommended for diagnoses of adult rhinosinusitis. The increased thickness of both the soft tissue and bony vault of the palate in children under 10 years of age limits the clinical usefulness of transillumination in the younger age group even more (279).

The value of plain sinus films in assessing the extent of the disease, especially in young children, is questionable. Lusk et al. (607) studied 70 children who had symptoms compatible with chronic rhinosinusitis, and compared plain films with coronal CT scans within a few hours of one another. When all sinuses were evaluated or considered, they found a lack of correlation between both methods in 74% of the patients. Forty five percent of the normal plain radiographs showed abnormalities on CT, and 34% of the abnormal plain radiographs were actually normal on CT. These authors found that plain films both over- and underestimated the amount of sinus disease. Thus, for evaluation of paediatric rhinosinusitis, CT remains the imaging modality of choice, because of its ability to resolve both bone and soft tissue (608). Before defining which CT scan findings are considered abnormal in children, it is interesting to discuss the incidental paranasal sinus abnormalities on CT scans of children and their clinical correlation. A number of authors have shown that radiographic opacification on the CT scan are found in considerable number of asymptomatic children (609).

Looking at the percentage of CT signs of sinus disease in a symptomatic paediatric population, the prevalence of CT abnormalities increases from 64% to 81% (173, 610). Thus most authors are in agreement that an asymptomatic child with an incidental paranasal sinus finding on CT needs no further work-up unless clinical symptoms and signs are elicited (611).
A number of studies suggest that the growth of the maxillary sinus is not impaired by extensive or chronic disease, unlike the temporal bone and it seems that the presence of a hypoplastic maxillary sinus per se is not an indication for surgery (612).

9-6 Systemic disease and chronic rhinosinusitis

The role of atopy in chronic rhinosinusitis is unclear. Many authors attribute a great deal of importance to allergy (73, 604, 608) although others (81, 173, 613) did not find an increased prevalence of rhinosinusitis in allergic children.

All young children have a physiologic primary immune deficiency (608, 614). Defence against polysaccharides encapsulated bacteria via immunoglobulin G subclasses 2 and 4 may not reach adult levels until the age of 10 years (95). IgG subclass deficiency can lead to protracted or chronic rhinosinusitis (74,79,85,94,96). According to Polmar (615) recurrent and chronic rhinosinusitis is the most common clinical presentation of common variable immunodeficiencies. Although not all patients who lack secretory IgA antibodies have an increased number of more severe respiratory infections, the subject who has IgA deficiency and chronic rhinosinusitis is a difficult management problem and replacement therapy cannot be provided (616). Patients with primary or acquired immune deficiencies (e.g. treatment for malignancies, organ transplants, maternally transmitted AIDS or blood-transmitted AIDS in hemophilics, drug induced conditions) are at risk for developing a difficult-to-treat rhinosinusitis with resistant or uncommon micro-organisms and fungi. Also the initial signs and symptoms may be non-specific, such as thin rhino rhea, mild congestion, and chronic cough (608).

Cystic fibrosis is caused by a mutation of the gene FES1 encoding the cystic fibrosis transmembrane conductance regulator (CFTR). This gene contains 27 exans encompassing approximately 252 kb of DNA on chromosone 7q 31.2. The most common mutation, deletion of phenylalanine at position 508 (D F508) accounts for nearly 70% of mutuations in European-derived Caucasian population (617).

In children with cystic fibrosis, sinusitis seems to be a common problem. Although the prevalence of nasal polyposis in children with cystic fibrosis was previously estimated to be between 6 and 20% (618), Yung et al. (619) found it to be over 50% and Brihaye et al. (620) reported that performing rigid endoscopy in 84 patients with cystic fibrosis, revealed inflammatory polyps in 45% (mean age 15 years) and medial bulging of the lateral nasal wall in 12% (mean age 5 years). In patients

with cystic fibrosis and chronic rhinosinusitis, CT showed in 100% (620) opacification of the anterior complex (anterior ethmoid, maxillary and -if developed- frontal sinus) and 57% showed clouding of the posterior complex (posterior ethmoid and sphenoid). In all children with a medial displacement of the lateral nasal wall, there was a soft tissue mass in the maxillary antrum (large quantity of secretions surrounded by polypoidal mucosa, representing a mucopurulent rhinosinusitus). In 80% of these children the displacement was so extreme that the lateral nasal wall touched the septum, resulting in total nasal blockage. In the study by Brihaye et al. (620) massive polyposis was never found before the age of 5 years. Mucopyosinusitis of the maxillary sinus occurs at a younger age (3 months to 8 years) and the maxillary sinus seems to be the first sinus affected by the disease. The youngest child reported with the disease was a 3 months old infant presenting symptoms similar to those of children with bilateral choanal atresia (nasal blockade, stridor, and feeding problems), except that the symptoms occurred only gradually following a symptom-free period after birth.

By definition, patients with Kartagener's syndrome [a hereditary disease involving the classic triad of rhinosinusitis, bronchiectesis, and situs inversus] have chronic rhinosinusitis, but which develops later in life. The neonatal group with Kartagener's syndrome do not have rhinosinusitis and bronchiectesis, and therefore the term "immotile cilia syndrome" was introduced in the seventies. As ultrastructural changes of cilia were also found after chronic infections or polyposis, and situs inversus did not seem to be essential, the name of this autosomal recessive disease was changed to primary ciliary dyskinesia (PCD) (621). One should always consider the diagnosis in any neonate with respiratory or ENT problems of unknown origin. At least half of the PCD patients have symptoms when first born and especially in a term baby with no risk factor for congenital infection showing signs of rhinitis at birth, PCD should be excluded. The same goes for an infant or older child with atypical asthma, unresponsive to treatment, chronic wet cough, and sputum production in the older child who is able to expectorate, very severe gastro-oesophagal reflux, bronchiectasis, rhinosinusitis (rarely with polyposis), chronic and severe secretory otitis media, particularly with continuous, long lasting and diffuse discharge from the ears after grommet insertion.
There are a number of ways to diagnose PCD. Clinically the most useful is the saccharine test, which is a cheap and easy procedure to screen older children and adults. If the child is too young for the test or the results are positive (transport time longer than 60 minutes) or there exists a strong clinical suspicion, the ciliary beat frequency can be tested from a nasal epithelial biopsy.

If the direct inspection of the ciliary beat frequency is abnormal (less than 11-16 Hz) an ultrastructional study of cilia is needed. The most common ciliary abnormalities in PCD are: dynein arm defects (absence or reduced number of inner, outer or both dynein arms), tubular defects (transposition and extra microtubules), radial spokes defects or absence, ciliary dysorientation (suspected if mean standard deviation of angle is larger than 20°), abnormal basal apparatus, ciliary aplasia, abnormally long cilia (622). Many of these abnormalities on TEM (transmission electron microscopy), however, can be transient or occur secondarily after infection. In cilia with patients with PCD specific ultrastructural abnormalities are present, such as dynein and/or spoke deficiency, and absence of the central pair of microtubules. Secondary ciliary dyskinesia, the acquired form (infections, inflammatory or toxic) is mostly correlated with other anomalies, such as microtubular abnormalities and composed cilia. However, there exists a great overlap of ultrastructural abnormalities between both (294). Therefore the study of cilia after sequential monolayer-suspension culture technique avoids the acquired form (623).

The parallel existence of upper airway inflammation with ensuing problems of intractable rhinosinusitis, otitis, and gastro-oesophageal reflux (GER) has been observed and suggests a causal relationship. Barbero found in a group of patients with upper airway disease and GER, that anti-reflux measures may permit a greater well-being and that GER maybe among the variables leading to refractory chronic upper airway disease (624). The otolaryngologist should be suspicious of GER in children complaining of chronic nasal discharge and obstruction combined with chronic cough, hoarseness and stridulous respiration. The endoscopic appearance of the laryngeal and tracheal areas are of considerable importance in conjunction with oesophageal examination, in determining potential relationship between GER and otolaryngologic abnormalities. The author found in 17 patients: 1 or more of these endoscopic signs: cobblestoning of the mucosa of the laryngopharynx, inflammation of the upper airway, sinus involvement, rhino rhea, subglottic stenosis, velopharyngeal insufficiency, pharyngeal tracheitis and tracheomalacia. In most of the patients the oesophagus on examination was erythematous. The diagnosis needs to be confirmed by oesophageal 24 hours pH monitoring. In 30 children with chronic sinus disease found after 24 hour pH monitoring in 63% oesophageal reflux and 32% had nasopharyngeal reflux (466).

9-7 Management

9-7-1 Introduction
In 1994 Poole stated that chronic rhinosinusitis in the young child does not necessary have to be treated, as spontaneous resolution is the norm (625). With regard to the natural history of the disease and the growing resistance and b-lactamase production of many microorganisms, one should refrain from overtreating a runny nose in a young child. One should not treat every common cold with antibiotics or smash any minor

self-limiting infection of a common cold with the sledge hammer of broad spectrum antibiotics. Some physicians prescribe antibiotics for minor respiratory infections in the hope of preventing serious complications and/or avoid medical/legal litigations. Van Buchem et al. followed 169 children with a runny nose for 6 months, treating them only with decongestants or saline nose drops. They did not find a single child who developed a clinically serious disease with general symptoms such as marked pain, pressure on sinuses, local swelling, or empyema, which proved that complications of rhinosinusitis in a child are uncommon (177).

9-7-2 Treatment of rhinosinusitis

9-7-2-1 Medical treatment of rhinosinusitis

The data on specific treatment of children are very limited.

In a short-term follow-up study Furukawa (626) showed a superior result from erythromycin-sulfisoxazole plus topical decongestants compared with placebo + topical decongestants, and Rachelefsky et al. (85) studying 84 children, demonstrated on the basis of radiographs and clinical response a better result in the group treated with amoxicillin, although trimethoprim-sulfamethoxazole was an adequate alternative, while erythromycin was not any better than an antihistamine-decongestant combination. The only long-term follow-up in the treatment of children with chronic maxillary sinusitis (n=141) comparing oral amoxicillin combined with decongestant nose drops, drainage of the maxillary sinus (antral lavage), a combination of the two previous regimen, and placebo was performed by Otten et al. (627) showing that the therapeutic effects of these four forms of treatment did not differ significantly or have a significant curative effect The usual duration of antimicrobial therapy is 10 to 14 days. This recommendation is based on experience in adults.

One study suggest that topical corticosteroids may be a useful ancillary treatment to antibiotics in childhood rhinosinusitis, effective in reducing the cough and nasal discharge earlier in the course of acute sinusitis (353). There are a large number of studies showing that local corticosteroids are effective and safe in children with rhinitis (628-632).

Additional therapy consists of topical or oral decongestants. Most authors prefer topical a2 agonists (xylo- and oxymetazoline) in appropriate concentrations. Careful dosage is important when treating infants and young children, to prevent toxic manifestations.

Saline nose drops or nasal douches are popular with paediatricians (606, 608, 616). As long as the saline is isotonic and at body temperature, it can help in eliminating nasal secretions and it can decrease nasal oedema.

In children with chronic rhinosinusitis and proven gastro-oesophageal reflux (GER) after 24 hours of pH monitoring Phipps et al. (466) showed that most children showed improvement of sinus disease after GER treatment and Bothwell et al. (633) suggests that in 89% of the children (25 out of 28) surgery could be avoided. These studies indicate that GER could be evaluated and treated in children with chronic sinus disease before sinus surgical intervention.

9-7-2-2 Surgical treatment of rhinosinusitis

The effectiveness of adenoidectomy in the management of paediatric rhinosinusitis is still a controversial issue. It is difficult to differentiate between the symptoms typical for chronic rhinosinusitis and those of adenoid hypertrophy. Hibert (634) showed that nasal obstruction, snoring and speech defects occur more frequently in children with adenoid hypertrophy while symptoms of rhino rhea, cough, headache, signs of mouth breathing, and abnormalities on anterior rhinoscopy occur as frequently in children with chronic rhinosinusitis as in children with adenoid hypertrophy.

Wang et al. e.g. didn't find any significant correlation between the size of the adenoid and the presence of purulent secretions in the middle meatus on fiberoptic examination in 420 children between the age of 1 and 7 years, while there was a very significant correlation between the size of the adenoid and the complaints of mouth breathing ($p<0.001$) and snoring ($p<0.001$) (635). The size of the adenoid and associated diseases seem to be factors for consideration. Adenoidectomy was included in the stepwise protocol for the treatment of paediatric rhinosinusitis proposed by Don et al. (636). Recently Ungkanont et al. proved adenoidectomy to be effective in the management of paediatric rhinosinusitis. They suggest performing an adenoidectomy as a surgical option before endoscopic sinus surgery (ESS), especially in younger children with obstructive symptoms (637).

Antral lavage: with the introduction of antroscopy at the end of the 1970s antral lavage in children became popular. As a trocar of the endoscope has a 4 mm diameter, it was easy to leave a ventilation tube in position, making frequent irrigations of the maxillary sinus possible in children, without any need for repetitive anaesthesia. It was shown, however, that in children with chronic rhinosinusitis, irrigation of the maxillary sinus does not lead to a better cure after 3 weeks, compared with a control group (638) or is not statistically significantly more successful (607).

Inferior antrostomy: as it had been demonstrated that the results of antral lavage in children were not long lasting; the logical consequence in children who required continuous antral lavage was to resort to a permanent antrostomy or nasal antral window in the inferior meatus. Lund (639), however, demonstrated that -especially in children under the age of 16 years there is a higher rate of closure of these antral windows. She concluded that the inferior meatus in children is smaller than in adults, making it impossible to create an adequately sized antrostomy. As a consequence Lusk (607) was able to

show that in a six-month follow-up the success rate of the nasal antral window procedure dropped to 27%. All patients remained symptomatic, and 28% needed further functional endoscopic sinus surgery. So the only current indication for a naso-antral window in the inferior meatus is therefore mainly limited to PCD where one hopes to achieve a kind of gravitational drainage.

Sinus surgery: the Caldwell-Luc operation is contra-indicated in children as it can cause damage to the unerrupted teeth (608, 616). Most of the controversies seem to centre on the indications for functional endoscopic sinus surgery in children. (FESS or paediatric FESS=PESS). The "functional" in FESS stands for the restoration of the function of the ostiomeatal complex i.e. ventilation and drainage. In 1998 an international consensus was reached concerning the indications of FESS in children (11):

a. absolute indications:
   1. complete nasal obstruction in cystic fibrosis due to massive polyposis or by medialization of the lateral nasal wall
   2. orbital abscess
   3. intracranial complications
   4. antrochoanal polyp
   5. mucocoeles or mucopyocoeles
   6. fungal rhinosinusitis
b. possible indications:
   in chronic rhinosinusitis with frequent exacerbations that persist despite optimal medical management and after exclusion of any systemic disease, endoscopic sinus surgery is a reasonable alternative to continuous medical treatment. Optimal management includes a 2-6 weeks of adequate antibiotics (IV or oral) with treatment of concomitant disease.

Surgery for chronic rhinosinusitis with frequent exacerbations that persist despite optimal medical management is mostly limited to a partial ethmoidectomy: removal of the uncinate process, with or without a maxillary antrostomy in the middle meatus, and opening of the bulla is often sufficient. In other cases such as in cystic fibrosis with massive polyposis, extensive sphenoidectomy may be necessary.

Most results are judged on symptomatic relief and not include endoscopic examination or CT scan. Lusk et al. (640) found a success rate of 88% in 24 children who had only one procedure. They saw a 24% improvement of the purulent rhino rhea (from 100% tot 64%), 33% improvement of fever, usually low grade (from 55% to 22%), and a 13% improvement of cough (from 48% to 35%).

A meta-analysis performed by Hebert et al. (641) focusing on the number of patients per study, length of follow-up, prospective versus retrospective, a separation or exclusion of patients with significant underlying systemic disease, showed in 8 published articles (832 patients) positive outcome rates going from 88 to 92%. The average combined follow-up was 3.7 years. Thus they concluded that FESS is a safe and effective treatment for chronic rhinosinusitis that is refractory to medical treatment.

Similar results were published in a more recent study by Jiang et al. (642) and Fakhri et al. (643) showing a postoperative improvement in 84% of the FESS (n=121). For this indication Bothwell et al. (644) found no statistical significant difference in the outcome of facial growth between a retrospective age-matched cohort outcome study between 46 children who underwent FESS surgery and 21 children who didn't, using qualitative antropomorphic analysis of 12 standard facial measurements after a 13.2 years follow-up.

As already mentioned before in a cystic fibrosis population of 48 children, 12% showed on endosocpy a medialisation of the lateral nasal wall and 45% nasal polyps coming out of the middle meatus (620). Initially polyps were removed as they appeared. When nasal obstruction occurred polypectomy was the rule. Regrowth, however, was sometimes observed within 3 weeks and many patients had multiple polypectomies ranging from 1 to 12 procedures per child. Crockett et al. (645) was the first to stress the importance of a long-term follow-up (average 5 years) and showed that when intranasal ethmoidectomy and Caldwell-Luc procedures were combined with polypectomy, fewer recurrences and longer symptom-free intervals resulted. Unfortunately Caldwell-Luc procedures can only be performed in older children and adults. With the introduction of FESS, however, a new approach was possible to achieve radical surgery. Duplechain (646) reported for the first time the results of this kind of surgery in cystic fibrosis children which was soon followed by many more (522, 619, 647, 648).

10. Socio-economic cost of chronic rhinosinusitis and nasal polyps

10-1 Direct Costs

Chronic rhinosinusitis, which can be debilitating for patients and imposes a major economic cost on society in terms of both direct costs as well as decreased productivity. To better evaluate the socioeconomic impact of chronic rhinosinusitis, the current English literature has been reviewed. Data from outside the USA are very limited. In a 1999 publication, Ray et al. (3) estimated the total direct (medical and surgical) costs of sinusitis to be a staggering $5.78 billion in the US. This figure was extrapolated from governmental surveys such as the national health care survey and medical expenditure data. The cost of physician visits resulting in a primary diagnosis of sinusitis was $3.39 billion, which does not reflect the complete cost of radiographic studies, medication, or productivity losses.

Acknowledging that other airway disorders are closely tied to rhinosinusitis, Ray et al. (3) used the Delphi method to quantify how often rhinosinusitis is a secondary diagnosis contributing to the primary diagnosis assigned by physicians. An expert panel examined the co-incidence of rhinosinusitis in diseases such as asthma, otitis media, and allergic rhinitis, and determined that 10-15% of the cost of these other diseases was attributable to rhinosinusitis, increasing the economic burden of rhinosinusitis to the often quoted $5.78 billion sum. Ray's paper relied on data collected by the National Centre for Health Statistics and did not attempt to distinguish acute rhinosinusitis from the chronic form of this disease.

In 2002, Murphy et al. (649) examined a single health maintenance organization to evaluate the cost of chronic rhinosinusitis. The authors compared the costs of healthcare for members with a diagnosis of CRS to the cost of those without the diagnosis during 1994 and were able to determine the direct medical costs of the disease based on reimbursements paid rather than charges submitted. According to Murphy's study, patients with a diagnosis of CRS made 43% more outpatient and 25% more urgent care visits than the general population (p=0.001). CRS patients filled 43% more prescriptions, yet had fewer hospital stays than the general HMO adult population. In total, the cost of treating patients with CRS was $2,609 per year, 6% more than the average adult in the HMO. Because patients received all healthcare services in one integrated system, this figure includes the costs of radiography, hospitalization, and medication. Chronic rhinosinusitis care specifically cost $206 per patient per year, thus contributing to a calculated nationwide direct cost of $4.3 billion annually based on the 1994 statistic of 20.9 million individuals seeking care for CRS. Using the more recent value of 32 million affected (56) the overall cost would increase to $6.39 billion annually.

Addressing the cost of pharmacologic management of chronic rhinosinusitis, Gliklich and Metson's (650)1998 study reported an annual expenditure of $1220. This figure is the sum of OTC medications ($198), nasal sprays ($250), and antibiotics ($772).

Only one study in Europe has been found which considers the costs of CRS. This study was done in patients with severe chronic rhinosinusitis visiting a university hospital in the Netherlands (651). The direct cost of the CRS of these severe patients was €1,861,- per year.
No data are available distinguishing costs of nasal polyps from CRS.

In conclusion we can deduce from these limited data that the average direct costs of CRS per patient per year is between €200,- and €2,000,- depending on the severity of the disease.

10-2 Indirect Costs

The studies of direct medical costs demonstrate the social economic burden of the disorder. However, the total costs of CRS are greater. With 85% of patients with CRS of working age (between 18-65 years old) indirect costs such as missed workdays and decreased productivity at work significantly add to the economic burden of disease(56).

Goetzel et al. (2) attempted to quantify the indirect costs of rhinosinusitis. Their 2003 study resulted in rhinosinusitis being named one of the top ten most costly health conditions to US employers. A large multi-employer database was used to track insurance claims through employee health insurance, absentee days, and short-term disability claims. Episodes of illness were linked to missed workdays and disability claims, accurately correlating absenteeism to a given disease.

In a large sample size (375,000), total healthcare payments per employee per year for rhinosinusitis (acute and chronic) were found to be $60.17, 46% of which came from the cost of absenteeism and disability. These figures approximate the cost to employers, disregarding the cost incurred by other parties, and therefore tremendously underestimate the entire economic burden of the disease.
In his 2003 study, Bhattacharyya (427) used patient-completed surveys to determine the direct and indirect costs of chronic rhinosinusitis. Patients completed a survey assessing symptoms of disease, detailing medication use, and quantifying missed worked days attributable to CRS. According to Bhattacharyya, the cost of treating CRS per patient totaled $1,539 per year. Forty percent of these costs were due to the indirect costs of missed work; the mean number of missed

workdays in this sample of 322 patients was 4.8 days (95% CI, 3.4-6.1). Bhattacharyya's study attempts to analyze both the direct and indirect costs of CRS and the final figures are enormous. Assuming a cost of $1,500 per patient per year, and assuming CRS affects 32 million Americans, the overall cost of the disease would be $47 billion if the severity of disease was similar to that assessed in the study for all patients with the disorder. However, this would appear to be an unlikely assumption.

It should be noted that in this last study, the patient population evaluated were generated through visits to an otorhinolaryngologist. Therefore, this patient population had already failed initial therapy by primary care givers and possibly by other otolaryngologists. The therapeutic interventions by the specialist are therefore likely to be biased toward more aggressive and thus more expensive therapy.

The cost burden of absenteeism is enormous, and yet it is only the beginning. The general health status of patients with CRS is poor relative to the normal US population (53). This decreased quality of life not only leads to absenteeism, but also contributes to the idea of "presenteeism" or decreased productivity when at work. Ray et al.estimated by the 1994 National Health Interview Survey, that missed worked days due to rhinosinusitis was 12.5 million and restricted activity days was 58.7 million days (3). Economic loss due to presenteeism cannot be easily quantified, but surely increases the cost burden of the disease.

11. Outcomes measurements in research

For transparent and equal outcome results, the collection of some specific details is recommended by the Task Force on "Rhinosinusitis".

For acute rhinosinusitis recommended information collection includes:

a. symptoms;
b. endoscopic signs;
c. fluid level or total opacification on a plain x-ray;
d. medication used;
e. dropouts.

For CRS and NP, the following minimum data set describing outcome measures of research should include:

a. Symptoms as above (VAS) for Chronic Rhinosinusitis (CRS); and for Nasal polyps (NP);
b. QOL – general health (SF36) for CRS and NP;
c. Endoscopy – polyps 0-4 (pictures & description) based on the worst detected side for CRS and NP
   0 = no polyps
   1 = cobblestoned mucosa
   2 = pendunculated polyps only visible endoscopically
   3 = pendunculated polyps not protruding under the middle turbinate (equivalent to the back of the inferior turbinate when the middle turbinate is (partially) resected or absent
   4 = pendunculated polyps below the middle turbinate (see 3);
d. CT scan description – following the system of Lund/Mackay for CRS and NP;
e. Smell (validated) for NP;
f. medication used for CRS and NP;
g dropouts for CRS and NP;
h. information about asthma and other lower airway disease for CRS and NP.

Additional information for all types of rhinusinusitis is required on:

a. medication pre/post therapeutic intervention;
b. smoking history;
c. allergy (history and test);
d. history of aspirin intolerance.

Additional tests may be done eg. cells, mediators, mucociliary clearance, microbiology, haematology.

12. Evidence based schemes for diagnostic and treatment

12-1 Introduction

The following schemes for diagnosis and treatment are the result of a critical evaluation of the available evidence.
The tables give the level of evidence and grade of recommendation for the available therapy. Under relevance it is indicated whether the group of authors think this treatment to be of relevance in the indicated disease.

12-2 Level of evidence and grade of recommendation

Table 12-1. Therapy in acute/intermittent rhinosinusitis.

Therapy	*Level*	*Grade of recommendation*	*Relevance*
antibiotic (36).	Ia (49 studies)	A	yes: after 5 days, or in severe cases
topical steroid	1b (1 study not yet published)	B	yes
addition of topical steroid to antibiotic (350-353)	Ib	A	yes
oral steroid (377, 378)	no evidence (1 study +, one -)	D	no
addition of oral antihistamine in allergic patients (425)	2b	B	no
nasal saline douche (446, 447)	no evidence	D	no
decongestion (417-419)	no evidence	D	yes as symtomatic relief
mucolytics (422, 423)	no evidence	D	no
bacterial lysates (439, 440)	2b	B	no
phytotherapy (478, 479)	2b	B	no

Table 12-2. Therapy in chronic rhinosinusitis *.

Therapy	*Level*	*Grade of recommendation*	*Relevance*
oral antibiotic therapy short term < 2 weeks (387-391)	III	C	no
oral antibiotic therapy long term ~ 12 weeks (20, 296, 392, 394, 395, 403)	III	C	yes
antibiotics – topical (412, 358, 408, 410, 411)	III	D	no
steroid – topical (355-359)	Ib	A	yes
steroid – oral	IV	D	no
nasal saline douche (448-451)	III no data on single use	C	yes, for symptomatic relief
decongestant oral / topical	no data on single use	D	no
mucolytics (424)	III	C	no
antimycotics - systemic	no data	D	no
antimycotics – topical (433, 435, 436)	Ib (-)	D	no
oral antihistamine added in allergic patients	no data	D	no
allergen avoidance in allergic patients	IV	D	yes
proton pump inhibitors (464, 466, 467)	III	C	no
bacterial Lysates (441)	2b	C	no
immunotherapy	no data	D	no
phytotherapy	no data	D	no

* Some of these studies also included patients with nasal polyposis in addition to CRS.
* Acute exacerbations of CRS should be treated like acute rhinosinusitis

Table 12-3. Postoperative treatment in chronic rhinosinusitis *.

Therapy	*Level*	*Grade of recommendation*	*Relevance*
oral antibiotics short term <2 weeks (390, 405-407)	IV	D	immediately post-operative, if pus was seen during operation
oral antibiotics			
long term ~ 12 weeks (20, 392, 394, 395)	III	C	yes
topical steroids (374)	1b (negative)	D	yes: immediately post-operative no: long term therapy
oral steroids	no data available	D	yes: immediately post-operative no: long term therapy
nasal douche	no data available	D	yes: immediately post-operative no: long term therapy

* Some of these studies also included patients with nasal polyposis in addition to CRS.

Table 12-4. Therapy in nasal polyposis.

Therapy	*Level*	*Grade of recommendation*	*Relevance*
oral antibiotics short term <2 weeks	no data available	D	no
oral antibiotic long term ~12 weeks (296, 403)	III	C	yes
topical antibiotics	no data available		no
topical steroids (360, 367, 368)	I b (>10)	A	yes
oral steroids (267, 379-381)	III	C	yes
nasal douche	III no data in single use	D	yes for symptomatic relief
decongestant topical / oral	no data in single use	D	no
mucolytics	No data	D	no
antimycotics – systemic	No data	D	no
antimycotics – topical (437, 438)	III (2)	D	no
oral antihistamine in allergic patients (428)	Ib (1)	B	no
capsaicin (454-456)	II	B	
proton pump inhibitors (463)	II	C	no
immunotherapy	no data	D	no
phytotherapy	no data	D	no

Table 12-5. Postoperative care in nasal polyposis *.

Therapy	*Level*	*Grade of recommendation*	*Relevance*
oral antibiotic short term <2 weeks	no data available	D	immediately postoperative, if pus was seen during operation
oral antibiotic long term ~ 12 weeks (296)	III	C	yes
topical antibiotics	no data available	D	no
topical steroid after polypectomy (369-373)	Ib	A	yes
topical steroid after FESS (374)	Ib (negative)	D	yes
oral steroid (652)	III	C	short time in high dose long time low dose
nasal douche	no data available	D	yes, for immediante use no for long time use
decongestant - topical /oral	no data available	D	no

12-3 Evidence based diagnosis and management scheme for GP's

12-3-1 Scheme for GP for adults with acute/intermittent rhinosinusitis

Diagnosis

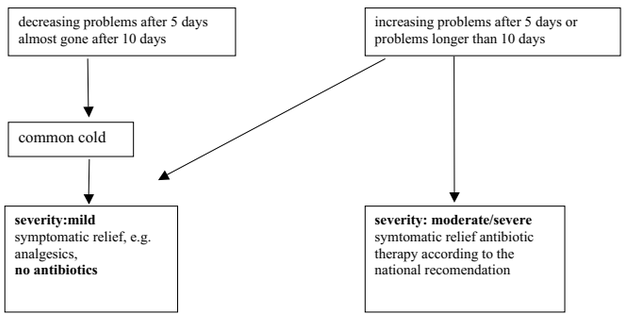
Symptoms

- facial pain or headache (for adults) especially unilaterally,
- plus one or more of the following:
- nasal obstruction;
- smell disturbance.

Treatment

- mild: start with symptomatic relief, analgesics;
- moderate / severe: additional topical steroids.

Treatment scheme for GP for adults with acute/intermittent rhinosinusitis



Failure of treatment for moderate/severe disease:

- persistence of symptoms after 5 days of therapy;
- or increasing symptoms for 2 days during therapy.

Signs of potential complications requiring immediate referral:

- eye swollen/red eyelids;
- displaced globe;
- double vision;
- ophthalmoplegia
- unable to test vision
- reduced vision acuity;
- severe unilateral or bilateral frontal headache;
- frontal swelling;
- signs of meningitis or focal neurologic signs.

12-3-2 Scheme for GP for CRS /NP in adults

Diagnosis

Symptoms present longer than 12 weeks

- nasal obstruction;
- plus one or more of following symptoms:
- discoloured discharge
- frontal pain;
- smell disturbance.

Additional diagnostic information

- questionnaire for allergy should be added and, if positive, allergy testing should be performed.

Not recommended: plain x-ray.

CT-Scan is also **not** recommended **unless** additional problems such as:

- very severe disease;
- immuncompromised patient;
- signs of complications;
- operation recommended.

Severity of symptoms

- (following the VAS score for the total severity) mild/moderate/severe.

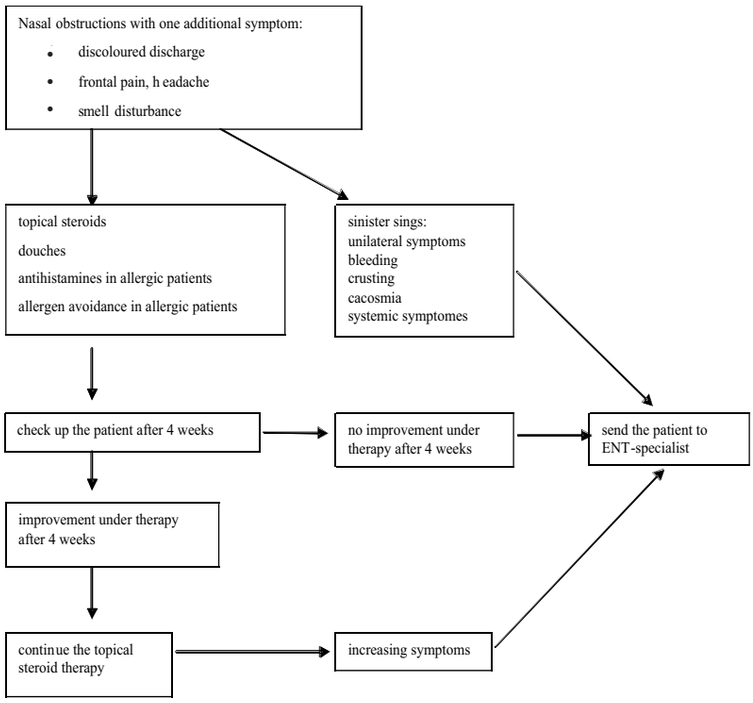
Signs of potential complications requiring immediate referral:

- swelling of eye or lids/eye redness;
- displaced globe;
- double vision;
- reduced vision;
- severe unilateral frontal headache;
- frontal swelling;
- signs of meningitis or focal neurologic signs.

Therapy

- topical steroids;
- nasal douches;
- antihistamines in allergic patients;
- allergen avoidance in allergic patients.

Scheme for GP: therapy for CRS/NP in adults



12-4 Evidence based diagnosis and management scheme for Non-ENT specialist for adults with CRS/NP

Diagnosis

Symptoms present longer than 12 weeks

- nasal obstruction;
- plus one or more additional symptom:
- discoloured discharge;
- frontal pain, headache;
- smell disturbance.

Additional diagnostic information

- anterior rhinoscopy, inspection with otoscope or ideally nasal endoscopy (if available);
- review primary care physician's diagnosis and treatment;
- questionnaire for allergy should be added and, if positive, allergy testing should be performed, if it is not done yet.

Not recommended: plain x-ray.

CT-Scan is also **not** recommended **unless** additional problems such as:

- very severe disease;
- immuncompromised patients;
- signs for complications.

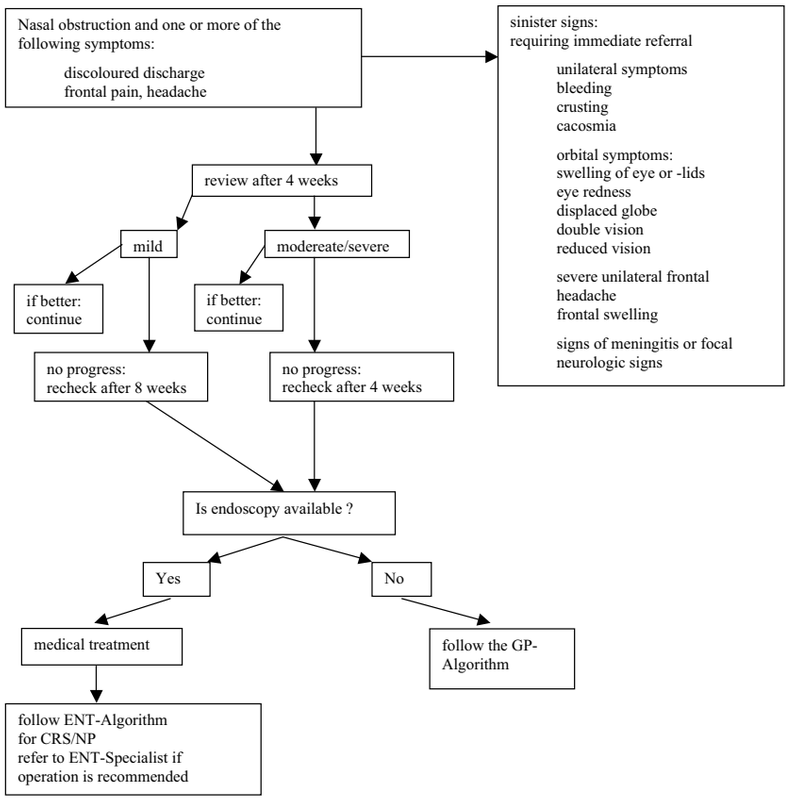
Severity of symptoms

- (following the VAS score for the total severity) mild /moderate /severe.

Treatment

- topical steroids;
- nasal douches;
- antihistamines and allergen avoidance in allergic patients.

Treatment scheme for Non-ENT specialists: therapy for CRS/NP in adults



12-5 Evidence based diagnosis and management scheme for ENT specialists

12-5-1 Scheme for ENT-Specialist for adults with acute rhinosinusitis

Diagnosis

Symptoms

- facial pain (for adults) especially unilaterally; plus one or more of the following symptoms:
- nasal obstruction;
- smell disturbance;
- nasal discharge.

Signs

- nasal examination (swelling, redness, pus);
- oral examination: posterior discharge;
- exclude dental infection.

ENT-examination including nasal endoscopy.

Not recommended: plain x-ray.

CT-Scan is also **not** recommended **unless** additional problems such as:

- very severe diseases,
- immuncompromised patients;
- signs for complications.

Severity of symptoms

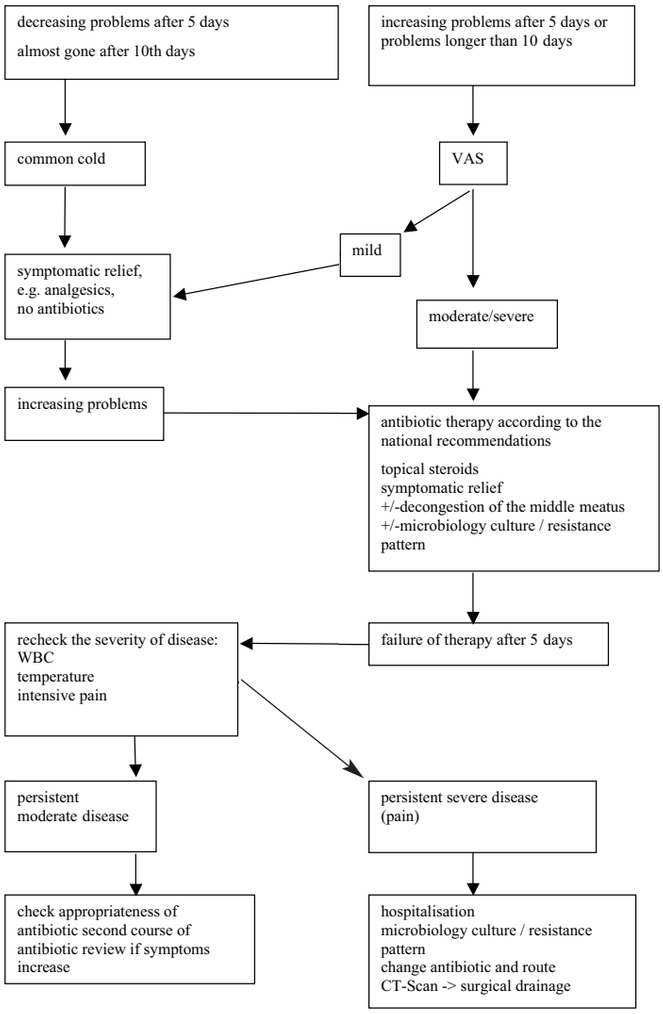
- mild /moderate /severe.

Treatment

Initial treatment depending on the severity of the disease:

VAS: mild -> follow initial treatment for common cold;
moderate -> follow initial treatment for common cold with short follow up;
severe -> follow initial treatment as listed below.

Treatment scheme for ENT specialists: therapy for acute rhinosinusitis in adults



Signs of potential complications requiring immediate intervention:

- eye swollen / red eye or lids;
- displaced globe;
- double vision;
- ophthalmoplegia
- unable to test vision
- reduced vision;
- severe unilateral frontal headache;
- frontal swelling;
- signs of meningitis or focal neurologic signs.

12-5-2 Scheme for ENT-Specialists for adults with CRS

Diagnosis

Symptoms present longer than 12 weeks

- nasal obstruction;
- plus one or more of the following symptoms:
- discoloured discharge;
- frontal pain, headache;
- smell disturbance.

Signs

- ENT examination, endoscopy;
- review primary care physician's diagnosis and treatment;
- questionnaire for allergy and if positive, allergy testing if it has not already been done.

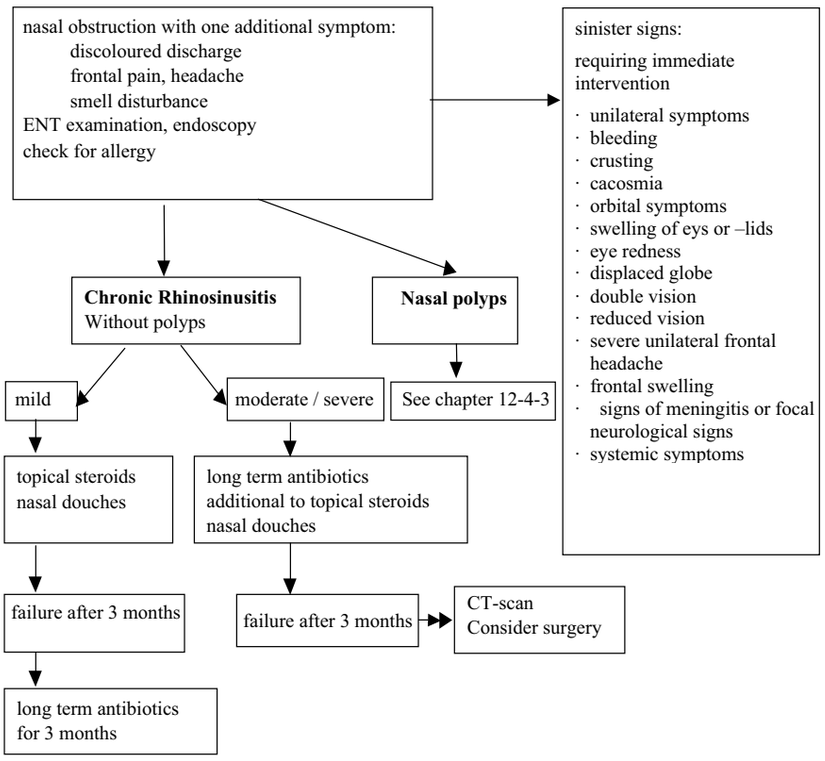
Severity

- (following the VAS score for the total severity) mild / moderate / severe.

Treatment

- topical steroids;
- douches;
- antihistamines in allergic patients;
- allergen avoidance in allergic patients.

Treatment scheme for ENT-Specialists: therapy for CRS in adults



12-5-3 Scheme for ENT-Specialists for adults with NP

Diagnosis

Symptoms for longer than 12 weeks

- nasal obstruction;
  plus one or more of the following symptoms:
- discolourered discharge;
- frontal pain;
- smell disturbance.

Signs

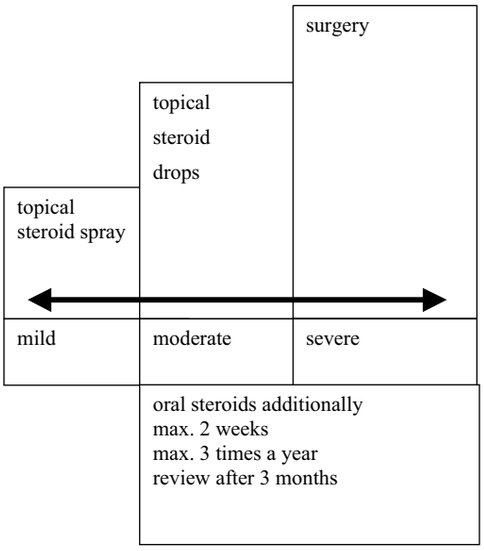
- ENT examination, endoscopy;
- review primary care physician's diagnosis and treatment;
- questionnaire for allergy and if positive, allergy testing if not already done.

Severity of the symptoms

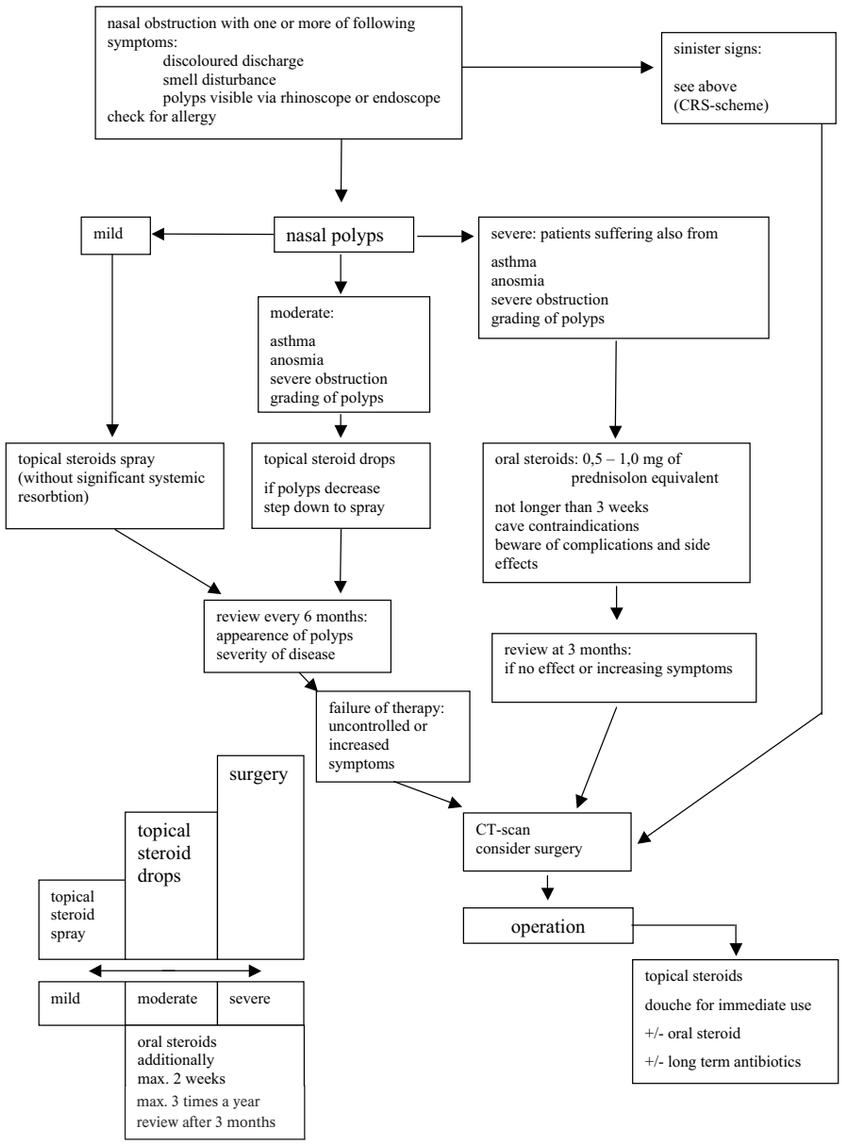
- (following the VAS score for the total severity) mild/moderate/severe.

Treatment

- topical steroids (drops preferred);
- nasal douches;
- antihistamines in allergic patients;
- allergen avoidance in allergic patients.



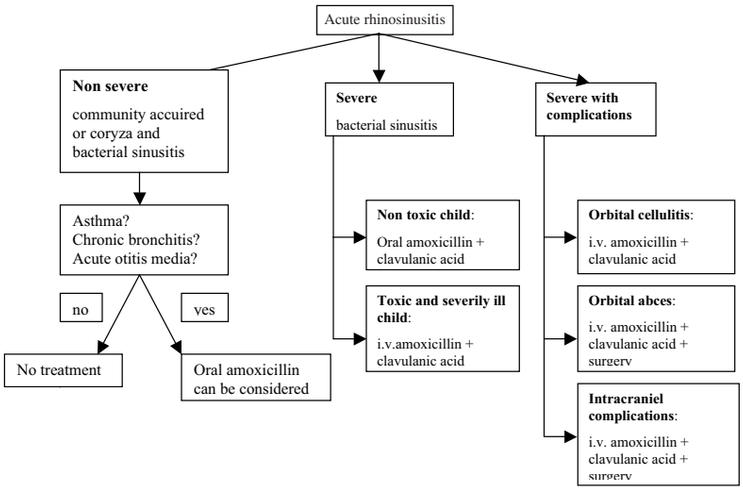
Treatment scheme for ENT-Specialists therapy for nasal polyps in adults



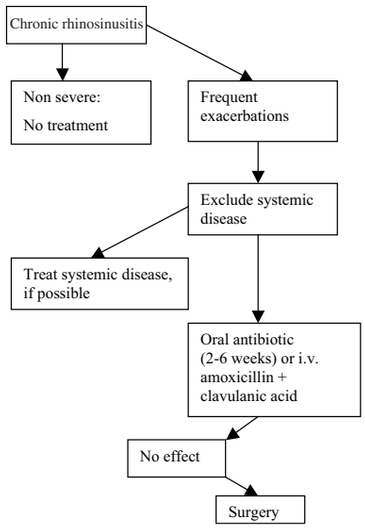
12-6 Evidence based schemes for therapy in children

The following scheme should help different disciplines in the treatment of rhinosinusitis in children. The recommendations are based on the available evidence, but the choices need to be made depending on the circumstances of the individual case.

Treatment scheme for Non-ENT Specialists: therapy for acute rhinosinusitis in children



Treatment scheme for Non-ENT Specialists: therapy for chronic rhinosinusitis in children



13. Research needs and priorities

Although much work has been done on chronic rhinosinusitis and nasal polyps there are many questions still unanswered.

The following suggestions should highlight some areas of interest for further research.

A prospective population study of a group of age- and sex-matched controlled atopic and non-atopic individuals to consider the incidence of all upper respiratory tract symptoms including acute and chronic rhinosinusitis over a 5 year period.

A long-term follow-up of a cohort of patients with nasal polyposis to study the natural history of the condition (a randomised medical and surgical arm could be done at the same time).

A study of the benefit of long term macrolide therapy in nasal polyposis and chronic rhinosinusitis (this needs repeating to verify the work already published on this).

Studies should be performed to compare nasal steroids as a single modality of treatment with antibiotics in patients with intermittent or persistent rhinosinusitis.

There is an urgent need for randomized placebo controlled trials to study the effect of antibiotics in chronic rhinosinusitis and exacerbations of chronic rhinosinusitis.

To provide good evidence for the use of local antibiotic treatment in acute exacerbations of chronic rhinosinusitis, further studies with better characterized patients are needed.

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15. Appendix

15-1 Survey of published olfactory tests

Author(s)	Year	Test name	Test-Time	Country	Sample size	Test retest	Subject differences	Method
Cain	1983 1988 1989	CCCRC	35 min	USA	>700		Age, gender, diseases, olfactory disorders.	1/ Threshold. N-butanol. 2AFC 4-correct-in-a-row method. Separate nostrils. Odours in squeeze bottles 2/Identification. 10 odours (score on &+1). Forced choice from 20 (or 16) descriptors. Odours in jars. Separate nostrils. Feedback.
Doty et al.	1984 (a,b) 1985	UPSIT	15 min	USA	>3000	r=0.981	Age, gender, culture, smoker, disease, olfactory disorder, malingering.	Identification of 40 encapsuated odours. 4AFC. Scratch-and-sniff-technique
Wright Kurtz et al.	1987 2001	Odourant Confusion Matrix (OCM)	15 min	USA	480		Disease.	Identification of 10 odours each presented once (100 stimuli or 121 if a blank is added). Forced choice from list of 10 names. Pattern of odorant identification and misidentification.
Hendriks	1988	GITU		Netherlands	221		Age, gender, olfactory disorders.	Identification of 18 or 36 odours. Forced choice either from 4 alternatives or from a list of 24 for 18 odours to identify. “Everyday life” odours. Odours in jars.
Corwin	1989 1992	YN-OIT		USA			Age, disease	Based on 20 UPSIT odours. Yes or no matching of a descriptor to a proposed odour.

Author(s)	Year	Test name	Test-Time	Country	Sample size	Test retest	Subject differences	Method
Takagi	1989	T&T Olfacto-meter		Japan	>1000		Olfactory disorders.	Thresholds of detection and recognition for 5 odorants. Odours on slips of filter papers. Separate nostrils.
Anderson et al.	1992	SDOIT		USA	Young children		Age.	Identification of 10 odours. Forced choice using an array of 20 visual stimuli. Odours in jars.
Eloit and Trotier	1994			France	84		Olfactory disorder, disease.	Odours in bottles. 1/Threshold to 5 odorants. 2/Identification of 6 odorants. Odours in bottles.
Doty et al.	1995 1996	CC-SIT MOD-SIT	5 min	USA Europe Asia	>3000	r=0.71	Age, gender, olfactory disorders.	Identification of 12 encapsulated odours. 4AFC. Scratch and sniff technique.
Kobal et al.	1996		5 min	Germany	152	r=0.73	Gender, olfactory disorder, age.	Identification of 7 odours in pens. Forced choice from 4 alternatives.
Robson et al.	1996	Combined olfactory test	UK and New Zealand	227			Olfactory disorder.	1/Threshold for n-butanol. Odours in plastic containers. 2/Identification of 9 odours. 4AFCE. Odours in jars.
Hummel et al. Kobal et al.	1997 2000	Sniffin'Sticks		Germany, Switzer-land, Austria, Australia, Italy, USA	>1000	r=0.72	Age, olfactory disorder. 1/Threshold for n-butanol.	Odours in pens. Triple forced choice paradigm. Single staircase method. 2/Discrimination: 16 odorant triplets. Identify the pen with the different smell. Forced choice. 3/Identification: 16 odours. 4AFC

Author(s)	Year	Test name	Test-Time	Country	Sample size	Test retest	Subject differences	Method
Davidson and Murphy	1997	AST	5 min	USA	100		Olfactory disorder.	Detection of isopropanol. Measure as distance from nose.
Ahlskog et al.	1998	CA-UPSIT		Gua-manian Cha-morro	57		Neuro-degnerative disease. Educational level.	Identification of 20 encapsulated odours. 4AFC. Scratch-and-sniff technique.
Nordin	1998 2001	SOIT	15 min	Sweden Finland	>600	r=0.79	Age, gender, olfactory disorder.	Identification of 16 odours in bottles. 4AFC
Kremer et al.	1998		4 min	Germany Netherlands	>200		Hyposmia.	6 aromas sprayed into open mouth. Odours in nasal sprays.
McCaffrey et al.	2000	PST		USA	40		Discrimination between Alzheimer's dementia and major depression.	Identification of 3 encapsulated odours. 4AFC. Scratch-and-sniff technique.
Kobal et al.	2001	"Random" test	10 min	Germany	273	r=0.71	Gender, olfactory disorder.	Labelling of 16 concentrations of two odorants randomly presented.
Hummel et al.	2001	"Four-minute 4 min odour identification test"	4 min	Germany	1,012	r=0.78	Age, olfactory disorder.	Identification of 12 odours. 4AFC. Odours in pens.

15-2 Source of some olfactory tests

University of Pennsylvania Smell Identification Test (UPSIT)
Sensonics Inc
125 White Horse Pike
Haddon Heights
New Jersey 08035
USA

Tel: (International +1 609 547 7702
Fax No: (Intrnational +1 609 547 5665
www.smelltest.com.usa

Sniffin' Sticks
Burghart medizintechnik
Tinsdaler weg 175
Tel: +49 (0) 103 800 76-0
Fax: +49 (0) 4 103 800 76-29
Email: sniffin@burghart.net
www.burghart.net

Zurich Test
UniversitätsSpital Zürich
Klinik für Ohren-, Nasen-, Hals- und Gesichtschirugie
Frauenklinikstr 24
CH-8091 Zürich
Tel: +44 1 255 5860
Fax: +41 1 255 4556
Email: simmen@jorl.usz.ch

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Pediatric Rhinosinusitis

Keegan Smith, MD

March 17, 2005

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GOALS

- Present a clinically useful definition reflecting the current literature
- Review the Anatomy
- Review the Pathogenesis
- Present clinically useful diagnostic criteria in primary care setting
- Present treatment guidelines based on current literature

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Case

- BP is a 17 yo female with history of allergic rhinitis who presented to her PCP with c/o persistent cough for over 1 month.
- Cough worse at night while lying down. Not improved by fexofenadine and nasal steroid.
- Denies fever, sore throat, sinus pressure, or headache.
- PE remarkable for inflammed nasal mucosa with copious discharge.
- Pt. was treated with 2 weeks of Amox/clav for presumptive sinusitis

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Case

- 2 weeks later patient developed shortness of breath while marching in the band. PCP diagnosed exercise-induced asthma and prescribed albuterol.
- Symptoms worsened after finishing antibiotic, still with persistent cough and shortness of breath when marching.
- PCP referred to pulmonologist to eval chronic cough. Pt. was seen in pulmonology clinic 2 months after onset of symptoms, still with persistent cough and nasal congestion.
- A sinus CT scan was obtained…

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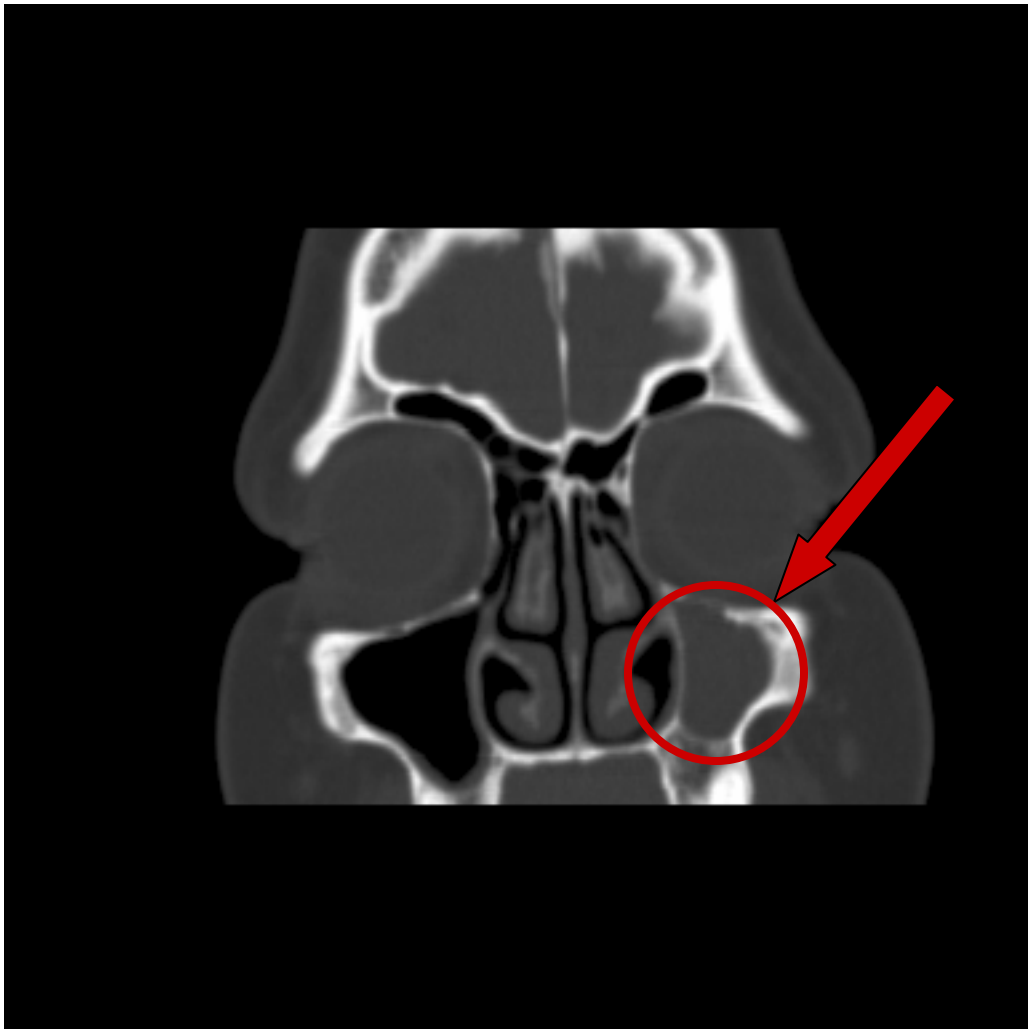
Case



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Definition

- **"Rhinosinusitis"** is preferred term because sinusitis is accompanied by nasal airway inflammation and frequently preceded by rhinitis.

- **"A group of disorders characterized by inflammation of the nasal mucosa and paranasal sinuses"**

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Epidemiology

- Maxillary RS complicates 0.5-2% of all URIs.[1]
- Children average 3-8 URIs each year, more if in daycare.[1]
- This translates to **20 million cases** of acute bacterial *maxillary* RS annually[1]

[1]Poole, Am J Med, 2004, 117 (3A) 29S-38.

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Disease Burden

- Children with chronic RS have been documented to have alterations in physical and psychosocial function exceeding that of children with asthma, JRA, and other chronic conditions.[2]

- Sinusitis accounted for 9% of all pediatric antibiotic prescriptions written in 2002, and costs approx. $3.5 billion per year in the U.S.[3]

[2]Cunningham et al, Arc Otolaryngol Head Neck Surg, 2000;126:1363-8.

[3]Sinus and Allergy Partnership, Otolaryngol Head Neck Surg, 2004;Jan Supp.

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Comorbidity

- **Rhinosinusitis and Asthma-The Unified Airway Hypothesis**
  - A study of 35 severe, steroid-dependent patients with asthma found 100% of them had abnormal sinus CT.[4]
  - Another study showed 79% of children with asthma were able to discontinue bronchodilators after their RS was treated. PFTs normalized in 67% of them.[6]
  - There are numerous studies showing medical or surgical management of RS improves the control of pediatric asthma.[5]

[4]Bresciani et al, *J Allergy Clin Immunol* 2001;107:73-80.

[5]Smart et al, *Immunol Allergy Clin N Am* 2005; 25:67-82.

[6]Rachelefsky et al, *Pediatrics* 1984; 73:526-9.

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Anatomy

- Ethmoid and Maxillary sinuses form in the 3rd to 4th months of gestation and are therefore present at birth
- Shah et al[7] reviewed 91 CT scans of 66 patients ranging in age from birth to 12 years. Ethmoid sinuses were the first to fully develop followed sequentially by maxillary, sphenoid, and frontal sinuses.

[7]Shah et al, *Laryngoscope*, 2003;113(2): 205-9.

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Anatomy

Sinus	Development	Age Visible on Plain Film
Ethmoid	In Utero (Full size at 12 yrs)	1 year
Maxillary	In Utero (Expands until 18 yrs)	4-5 months
Sphenoid	Begins at 3 yrs (Full size at 18 yrs)	Never
Frontal	Begins In Utero (Full size by adolescence)	5-6 years

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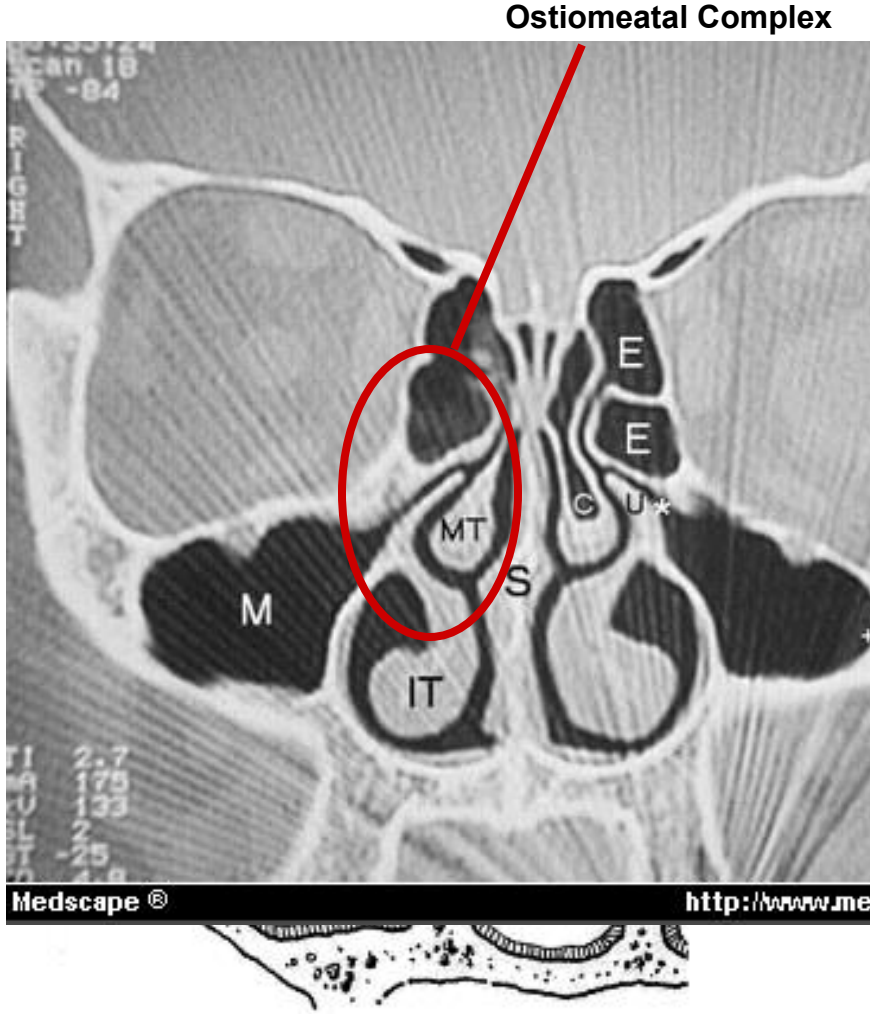
Anatomy

- **Normal ventilation of the sinuses depends on:**
  - Intact mucociliary clearance
  - Ostia patency
  - Quality of the secretion
- The sinuses are normally sterile but transiently colonized with nasal bacterial flora.
- A single nose blow can propel 1mL of nasal fluid into the maxillary sinus.[8]



[8]Meltzer et al, Journal Allergy, Clinical Immunology 2004; 114: S155-211.

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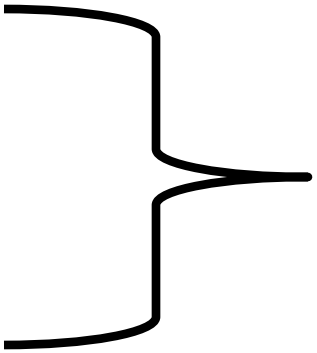
Pathogenesis

- **Factors Predisposing to Rhinosinusitis:**
  - Viral URI
  - Allergic Rhinitis
  - GERD
  - Immunologic Defects



Ostia Patency

  - Ciliary dysfunction → **Mucociliary Clearance**
  - Cystic Fibrosis → **Quality of Secretion**

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Pathogenesis

- **Factors Predisposing to Rhinosinusitis:**
  - **Viral URI- most common predisposing factor[9]**
  - Inflammation of sinus ostia→stasis/poor ventilation→absorption of O_2→negative pressure→movement of bacteria and nasal contents into the sinus.
  - Viruses have a toxic effect on sinus cilia

[9]Goldsmith et al, *Pediatric Clinics N America* 2003; 50.

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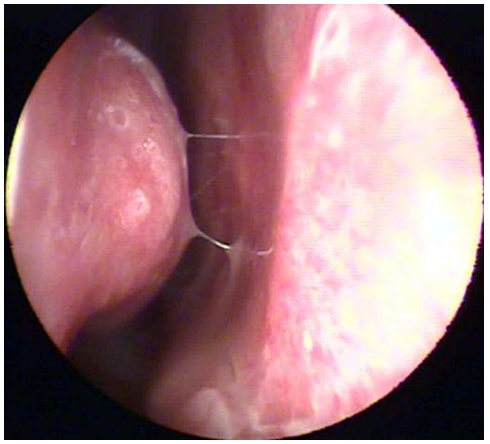
Pathogenesis



- **Factors Predisposing to Rhinosinusitis:**
  - **Allergic Rhinitis**
    - >80% of children with RS have a family history of allergy compared to a general population frequency of 15-20%[10]
    - Obstruction of sinus ostia due to swelling AND a direct effect on the sinus epithelium[8]

[10]Holtzmann et al, *Am J Rhinol* 2001;15: 387-90.

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Pathogenesis

- **Factors Predisposing to Rhinosinusitis:**
  - **GERD**
    - GERD has been shown to extend to the nasopharynx[9]
    - Nasopharyngeal reflux→mucosal edema→obstruction of ostia.
    - In a study of 30 children referred for refractory chronic RS, GERD treatment prevented sinus surgery in 90%.[11]
    - In another study of 30 children with chronic RS,GERD treatment decreased sinus symptoms in 79%.[12]

[11]Bothwell et al, *Otolaryngol Head Neck Surg* 1999;121:255-62.

[12]Phipps et al Arch *Otolaryngol Head Neck Surg*. 2000 Jul;126(7):831-6.

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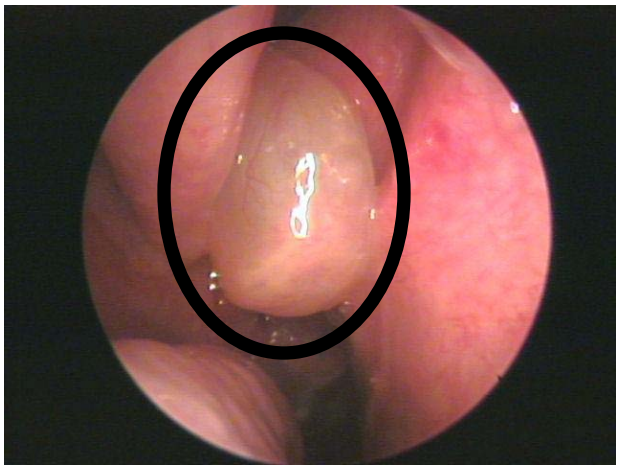
Pathogenesis

- **Factors Predisposing to Rhinosinusitis:**
  - **Immunologic Defects** (Humoral Immunity)
  - **Ciliary Dysfunction**
    - Primary Ciliary Dyskinesia
      Kartagener's syndrome
  - **Cystic Fibrosis**
    - Quality of secretion
    - Most common life threatening genetic disorder in Caucasians



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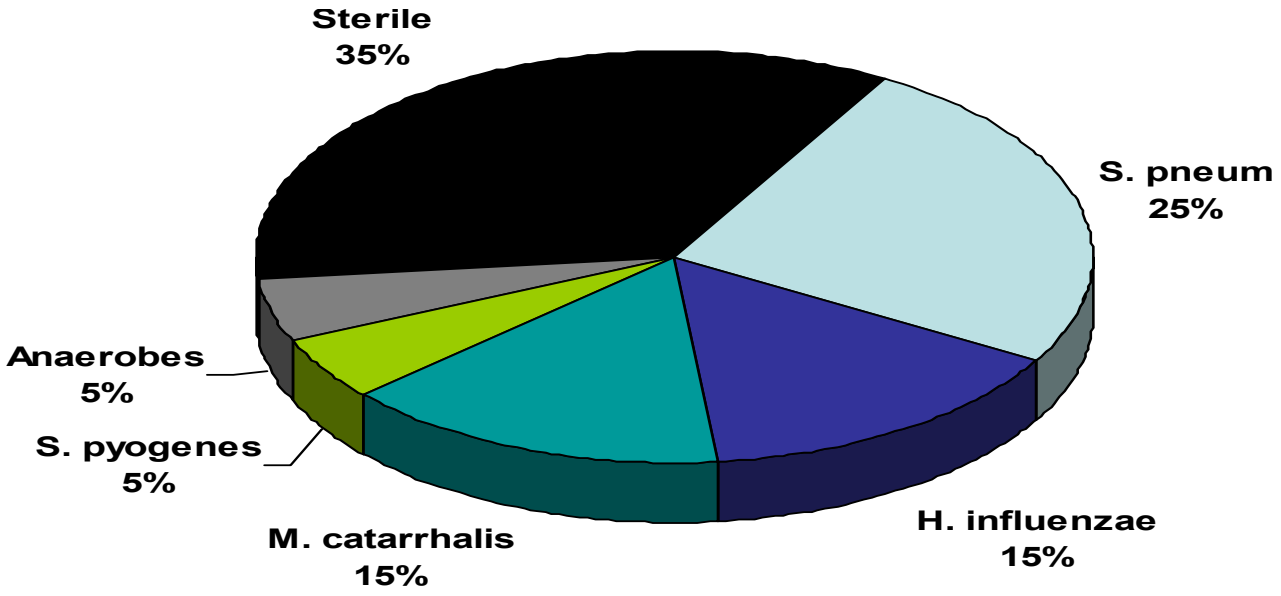
Pathogenesis

- **Microbiology**
  - Acute RS caused by same pathogens in adults and children.
  - Strep. pneumo, H. influenzae, M. catarrhalis
  - Wald et al[13] study found:
    - Pneumococcus>M. cat>H. flu>>anaerobes

Don't Forget the Viruses!



[13]Wald et al, *J Allergy Clin Immunol* 1992;90:452-56.

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Pathogenesis

- **Microbiology**
  - **Chronic RS (Symptoms >3 months)**
    - Infection or Inflammation or both? Much Controversy.
    - 9 studies of microbiology of CRS between 1981 and 2001, transnasal maxillary sinus aspiration in all but 1 study.[8]
      - 2 studies→normal flora (coag neg staph, viridans)
      - 7 studies→H.flu, S. pneumo, M. cat
    - Fungus?

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Classification System

- Recently, a group of 30 physicians met to create evidence-based guidelines for rhinosinusitis.[8]
- Allergy/Immunology, Otolaryngology, Infectious Disease, Radiology

Consensus Definitions Put Forth:

- Acute Presumed Bacterial Rhinosinusitis
- Chronic Rhinosinusitis without polyps
- Chronic Rhinosinusitis with polyps
- Classic Allergic Fungal Rhinosinusitis

[8]Meltzer et al, Journal Allergy, Clinical Immunology 2004; 114: S155-211.

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Acute Bacterial RS

- Symptoms lasting longer than 10-14 days but less than 3 months

OR

Severe symptoms **(fever ≥ 102F, purulent nasal discharge, ill-appearing child)** for at least 3-4 consecutive days

- Gold standard for diagnosis is recovery of bacteria in high density (>10^4 CFUs/mL)

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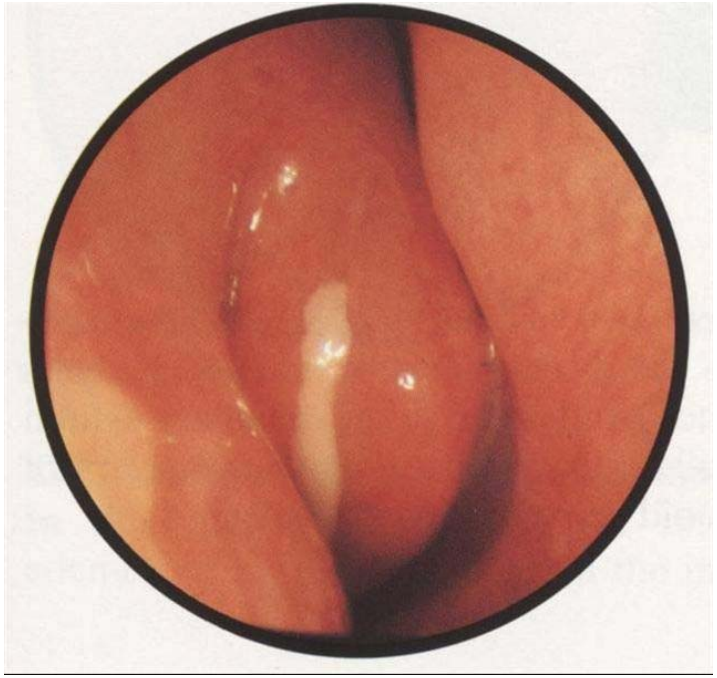
Acute Bacterial RS

- **Physical exam generally does NOT contribute substantially.**
  - Overlap of findings with viral RS
  - TTP over sinus that is reproducible may be helpful in older children/adolescents
  - Anterior rhinoscopy shows same findings in viral illness
  - Nasal endoscopy is useful but not practical.



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Viral vs. Bacterial

	Viral	Bacterial
FEVER	• Early in absence of nasal discharge	• Usually late and in presence of nasal discharge
DURATION	• 7-10 days	• >10 days
SEVERITY	• Improving after 4-5 days	• Worsening at 7-10 days **OR** 3 consecutive days of high fever (≥ 102F) with purulent nasal discharge
SYMPTOMS	SAME	
COLOR OF DISCHARGE	SAME	
RADIOLOGY (including CT)	SAME	**Up to 90% of pts with viral RS will have CT scan involvement of sinuses**
PHYSICAL EXAM	SAME	

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Acute Bacterial RS

- Imaging in Acute RS
  - **NOT indicated in the majority of cases**
  - Sinus CT can look the same in viral URI vs. Acute RS
  - Plain films (Water's view) are **NOT** indicated in children ≤ 6 years
    - a positive history equally predicts a positive sinus aspirate as positive history with abnormal radiographs.[14]
  - Plain films in older children are controversial, but plain films in adolescents and adults are **NOT** indicated.
  - The American College of Radiology says diagnosis of acute uncomplicated RS should be made on clinical grounds alone.

[14]Wald et al, *Pediatrics* 1986;77:795-800.

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Acute Bacterial RS

- **Treatment**
  - Should you treat?
    - Predicted spontaneous resolution rate in children is 63%.[15,16]
    - Garbutt et al study[17]
      - Randomized, placebo controlled trial of antimicrobial treatment for children with clinically diagnosed acute RS.
      - Improvement occurred in 79% Amox, 81% Amox/Clav, 79% placebo
      - Problems:
        - » Larger cohort of older children
        - » Exclusion of sicker children (fever >102F, facial pain)
        - » **Used low dose amox (45mg/kg) and amox/clav (40mg/kg)**

[15]Madgy et al, *Curr Opin Otolaryngol Head Neck Surg* 2000;8:469-76.

[16]Carron et al, *Curr Opin Otolaryngol Head Neck Surg* 2001;9:61-6.

[17]Garbutt et al, *Annals of Emergency Medicine* 2002;40(1).

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Acute Bacterial RS

- **Treatment**
  - Should you treat?
    - Cochrane Database Review 2004
      - Abx vs. placebo for children with persistent nasal discharge over 10 days
    - 6 studies, 562 children
    - Number needed to treat to achieve 1 additional cure over placebo = 8

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Acute Bacterial RS

– Multiple studies[14,18,19,20] suggest that antibiotics allow earlier resolution and may prevent recurrence, therefore…

The AAP consensus guidelines are to treat acute bacterial RS

[18]Sinus and Allergy Health Partnership, *Otolaryngol Head Neck Surg* 2000;123(Supp 1):S1-32

[19]Agency for Health Care Policy and Research, *Otolaryngo Head Neck Surg* 1999; AHPRC.

[20]Brook et al, *Ann Otol Rhinol Laryngol* 2000; 109:2-20.

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Acute Bacterial RS

- **Treatment**

  – There are very few recent evidence-based antimicrobial treatment guidelines.

  – Older studies do not reflect changes in antimicrobial resistance. Many newer studies have methodologic limitations.

S. pneumo
H. influenzae
M. catarrhalis

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Acute Bacterial RS

– Sinus and Allergy Health Partnership 2004

Used a therapeutic outcomes model as a tool

- **Takes into account multiple variables including:**
  - The proportion of patients with clinical dx. and positive sinus aspirate
  - Clinical resolution of disease in culture negative group
  - Distribution of frequently encountered pathogens
  - Rate of spontaneous resolution
  - In vivo susceptibility of pathogens to antimicrobial agents
    - » Pharmacokinetics/pharmacodynamics

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Acute Bacterial RS

- **Treatment**

Mild disease
AND
No abx past 4-6 weeks

•High dose Amox (90mg/kg/day)

Alternatives:

•High dose Amox/Clav (90mg/kg/day)
•Cefpodoxime
•Cefuroxime
•Cefdinir

•Clarithromycin
•Azithromycin

Limited effectiveness

Bacterial failure rate of 20-25% is possible

Mod. disease
OR
Abx in past 4-6 weeks

•High dose Amox/Clav (90mg/kg/day)

Alternatives:

•Cefpodoxime
•Cefuroxime
•Cefdinir

•Clarithromycin
•Azithromycin

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Acute Bacterial RS

- **Treatment**
  - Duration of therapy:
    - Should see response (decrease symptoms) in 48-72 hours
    - There are no studies examining duration of therapy
    - Consensus recommendations are **at least 10 days, then 7 days beyond resolution of symptoms.**[21]
    - BP required more than 2 weeks of antibiotics to resolve her symptoms.

[21]Wald et al, *Pediatrics* 2001;108(3):supp.

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Acute Bacterial RS

- **Treatment**
  - Adjunctive treatments:
    - No evidence for use of H1 blockers in non-allergic patients[22]
    - No evidence for use of nasal steroids[23]
    - No trials have examined the use of mucolytics.

[22]McCormick et al, *Clin Pediatr (Phila)* 1996;35:457-460.

[23]Meltzer et al, J *Allergy Clin Immunol* 1993;92:812-23.

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Acute Bacterial RS

- **Treatment**
  - Adjunctive treatments:
    - Nasal Saline
      - Generally accepted as appropriate
      - One study compared antibiotics with nasal saline (5 drops each naris QID) and found saline was nearly twice as effective as abx based on clinical and radiographic improvement. [24]
    - Topical Decongestants?
      - Paucity of data, but shouldn't be used longer than 3 days

[24]Topal et al, *Yeni Tip Dergisi* 2001;18 (suppl):58-60.

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Acute Bacterial RS

- **Treatment**
  - Adjunctive treatments:
    - Dr. Hummell's nasal saline irrigation:

1. ½ tsp non-iodized table salt dissolved in 8 oz boiled water
2. Fill 10 mL syringe, insert into nostril with head sideways, syringe nostril down
3. Fill nostril with saline until saline drains out of the opposite nostril
4. Gently blow nose, turn head so opposite side is down, and blow nose into tissue
5. Repeat with the other nostril

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Chronic Rhinosinusitis

- Poorly understood disease with much controversy and in need of much additional study.

- **Symptoms (cough, congestion, nasal discharge, halitosis, behavior problems, headache) lasting 3 months or longer without improvement.**

- Recent studies support dividing chronic RS into 2 categories:
  - **CRS with nasal polyps**
  - **CRS without nasal polyps**

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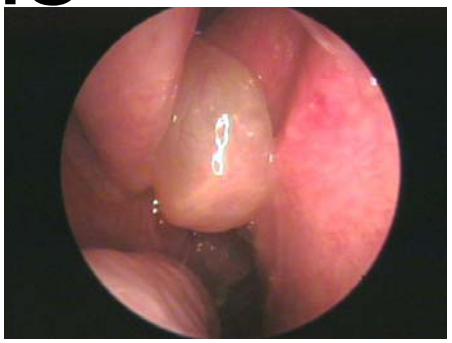
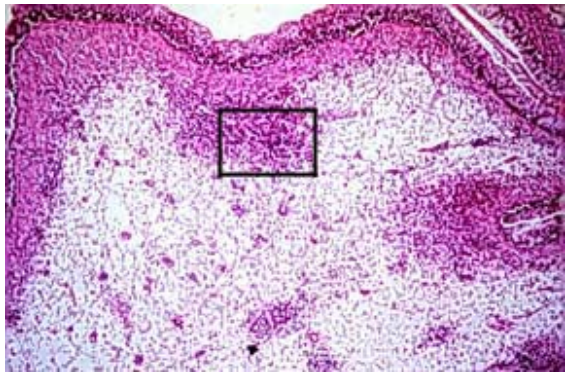
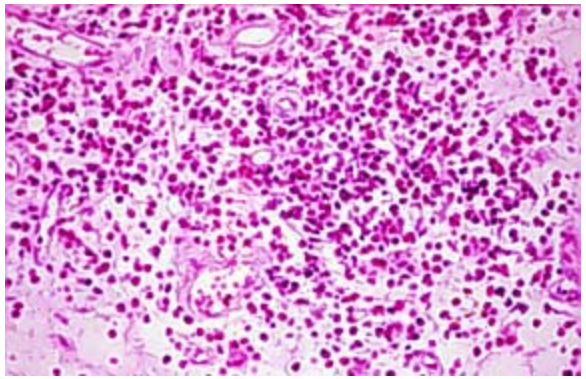
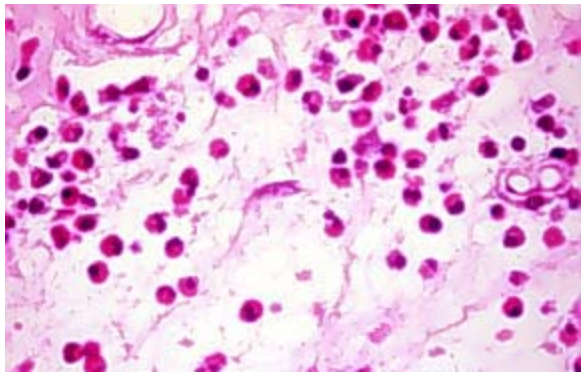
Chronic Rhinosinusitis



- **Nasal Polyposis-What is it?**
  - Histology of a mature polyp:[8]
    - Edematous stroma with supporting fibroblasts
    - Infiltrating inflammatory cells around empty pseudocyst formations







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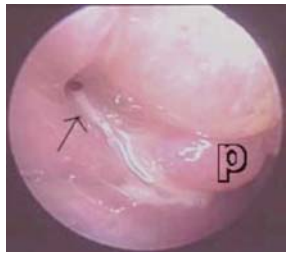
Chronic Rhinosinusitis



- **CRS WITHOUT Polyps**
  - Histology shows less eosinophilic infiltration
  - More likely to have positive cultures
  - More likely to respond to medical therapy
  - Less likely to have disease recurrence
- **CRS WITH Polyps**
  - Prominent eosinophilic infiltration
  - Rarely able to obtain positive cultures
  - Rarely respond to medical therapy alone
  - Disease recurrence common

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Chronic Rhinosinusitis

- **Diagnosis**
  - Based on symptoms and duration of illness (3 months)
  - Determine presence of nasal polyps based on exam/imaging studies
  - **Sinus CT can be useful for 2 reasons:**
    - Define the anatomy prior to surgery
    - Define the extent of disease, follow the course of disease.

    Coronal plane has been shown to best correlate with endoscopy.

  - **Don't forget your differential diagnosis!**
    - Foreign body, unilateral choanal atesia, dental abscess, neoplasm.

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Chronic Rhinosinusitis

- **Other Suggested workup:**
  - Sweat chloride, especially if polyps are present
  - GERD workup and/or treatment
  - Allergy skin testing
  - Immunologic workup?
    - Just 1 time.

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Chronic Rhinosinusitis

- **Medical Treatment**
  - Short term abx use in CRS has shown no benefit[25,26]
  - A longer course, 3-6 weeks, may be considered
  - Since most patients will have failed first line therapy, it is reasonable to progress to 2nd line therapy.
  - Positive culture would be very helpful, but must be obtained by ENT
  - Nasal steroids are recommended, however there is no scientific data.[9] They have been shown to decrease polyp size prior to surgery.
  - Nasal decongestants may be beneficial to ventilate the sinuses.
  - GERD treatment
  - Oral steroids?

[25]Otten et al, *Clin Otolaryngo* 1994;19:215-7.

[26]Otten et al, *Acta Otorhinolaryngol Belg* 1997;51:173-5.

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Chronic Rhinosinusitis

- **Surgical Treatment**
  - Adenoidectomy is first line after failed medical management
    - Adenoids thought to be bacterial reservoir.
    - Expected rate of improvement is 70-80%[8]
    - **How do you evaluate the adenoids?**
      - If older than 4 years: Lateral soft tissue film of neck
      - If less than 4 years: Flexible endoscopy
  - Second line surgical management is Flexible Endoscopic Surgery to open the sinus ostia.

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Chronic Rhinosinusitis

- **Treatment summary:**
  - Long course antibiotics (3-6 weeks)
  - Nasal Steroid
  - Oral Steroids
  - Nasal decongestant
  - Nasal saline irrigation
  - GERD treatment

  - If failure of maximum medical therapy, consider referral for surgical evaluation.

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Fungal Rhinosinusitis

- **Disease spectrum greatly influenced by host immunity**
  - Allergic fungal RS caused by abnormal host response to fungus.
  - Chronic, non-invasive fungal RS is rare in children.
  - Invasive disease almost exclusively in immunocompromised individuals.

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Fungal Rhinosinusitis

- **Sinus Mycetoma (fungus ball)**
  - **Symptoms:** **Nasal obstruction, chronic RS, facial pain, fetid smell**
    - Maxillary sinus most commonly involved, calcifications on CT
    - Aspergillus, Dematiaceous fungi
    - Usually immunocompetent or only mildly compromised, sometimes atopic
    - No fungal invasion of bone/vessels
    - **Treatment:** Debridement, no need for antifungals, good prognosis

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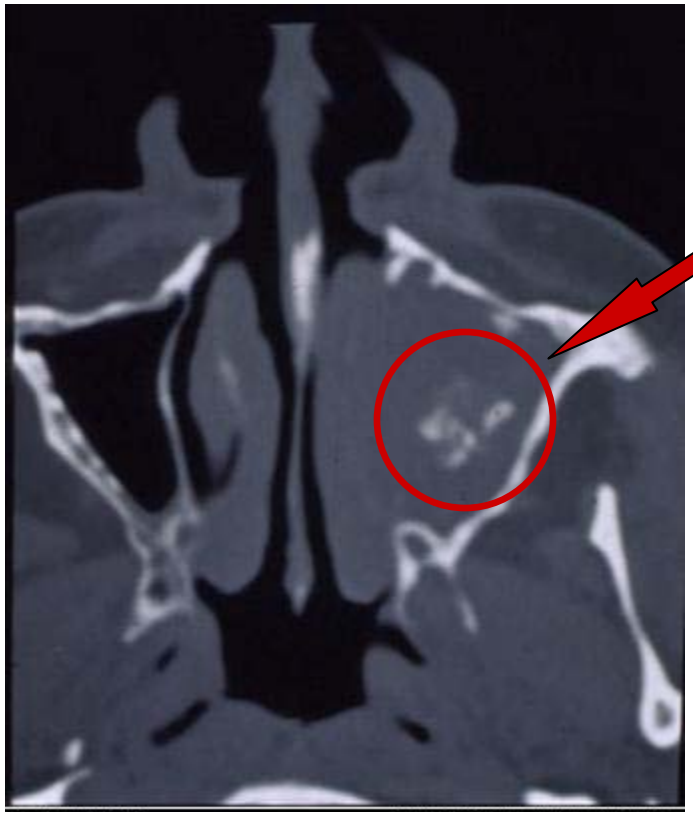
Fungal Rhinosinusitis



Sinus Mycetoma (fungus ball)

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Fungal Rhinosinusitis

- **Invasive disease**
  - Rhinocerebral mucormycosis
  - **Symptoms:** **RS plus painless, necrotic/black palatal or septal ulcer/eschar, mental status changes**
  - Saprophytic fungi: Rhizopus, rhizomucor, absidia, etc.
  - Immunocompromised individuals
  - Histology shows invasion of bone/blood vessels by hyphae
  - **Treatment:** Radical debridement until clear margins, treat underlying disease, ampho B for at least 14 days.

MEDICAL EMERGENCY!

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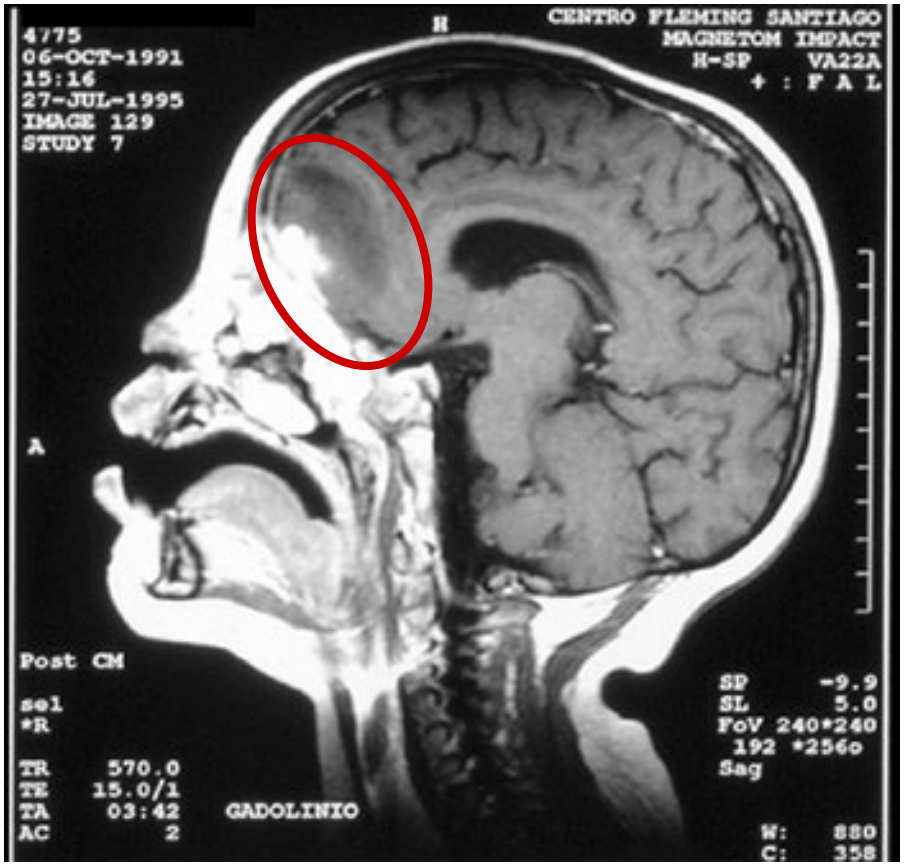
Fungal Rhinosinusitis



Rhinocerebral mucormycosis

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Allergic Fungal Rhinosinusitis

- **Description**
  - Thought to be allergic reaction to aerosolized environmental fungi in an immunocompetent host.[27]
  - **5 Characteristics:**
    - Gross production of eosinophilic mucin containing non-invasive fungal hyphae.
    - Nasal polyposis
    - Characteristic radiographic findings
    - Immunocompetence
    - Allergy to the cultured fungus

[27]McClay et al, *Laryngoscope* 2002;112:565-9.

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Allergic Fungal Rhinosinusitis

- **Epidemiology is unknown**
  - Mean age 23 years[28]
  - More common in warm humid climates
  - Atopy is common (50% of AFRS patients have asthma[29])
  - Prevalence in chronic RS patients who require surgery is 5-10%.[28]

[28]Houser et al, *Otolaryngol Clinics N America* 2000;33(2).

[29]Johnston et al, *Thorax* 1981;36:710.

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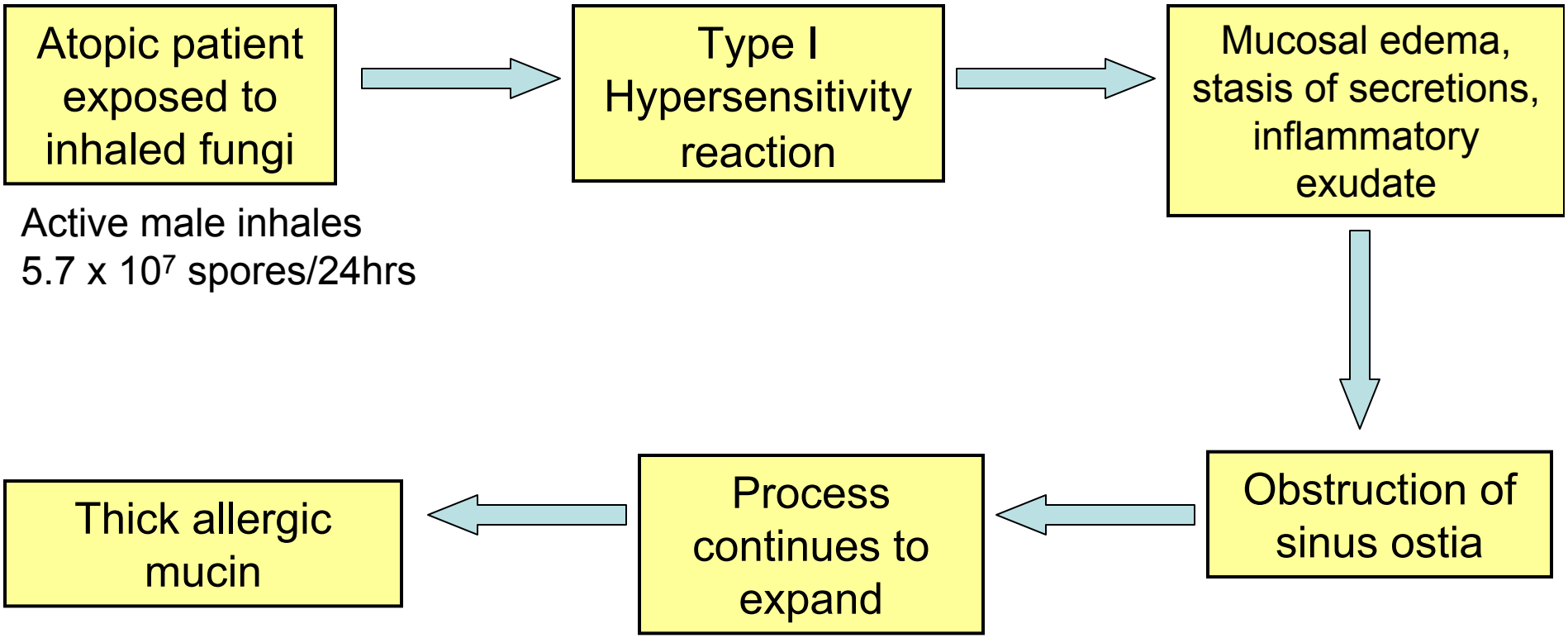
Allergic Fungal Rhinosinusitis

- **Pathogenesis – speculative[30]**
  - Thought to be similar to allergic bronchopulmonary aspergillosis



[30]Marple et al, *Curr Allergy and Asthma Reports* 2004;4:465-70.

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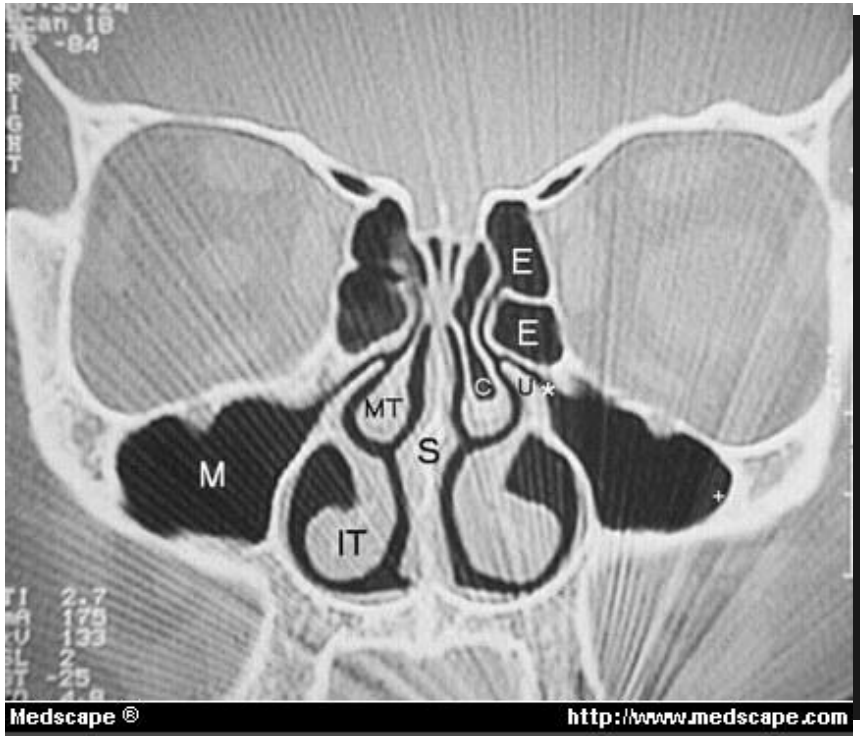
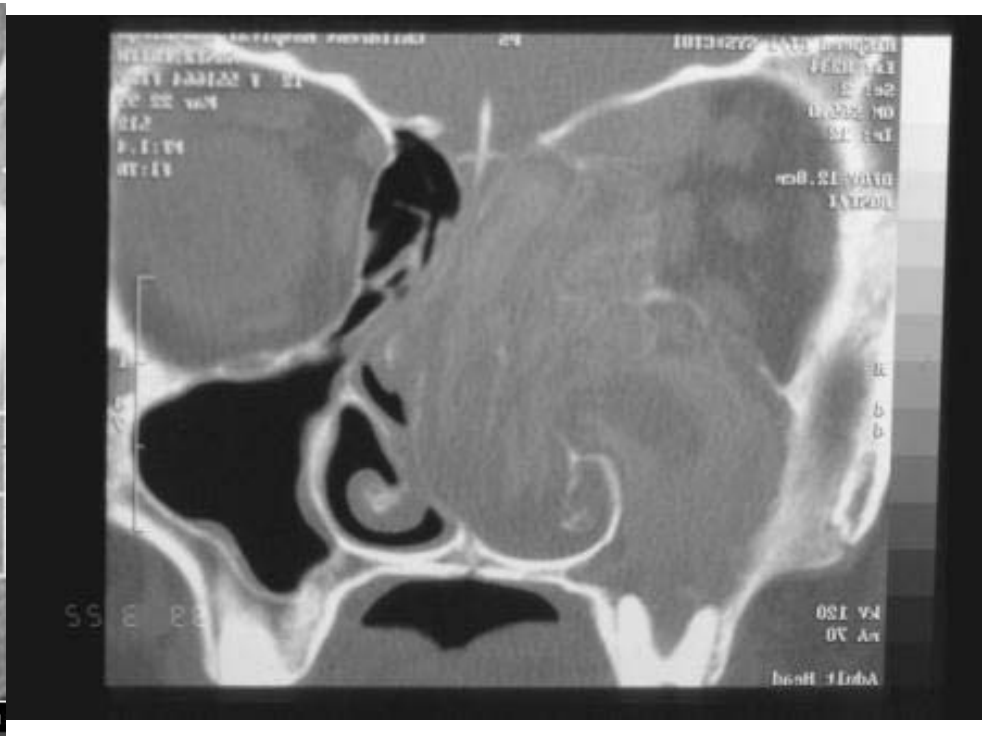
Allergic Fungal Rhinosinusitis



Normal Sinus CT



Allergic Fungal RS CT

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Allergic Fungal Rhinosinusitis

- **Symptoms**
  - Similar to other chronic rhinosinusitis
  - Usually a history of nasal polyps
  - Pain is uncommon unless there is a super-imposed bacterial process
  - 75% of patients describe dark-colored rubbery nasal casts (consistent w/ gross description of allergic mucin)[31]
  - Rarely presents with dramatic symptoms:

    acute vision loss, gross facial dysmorphia, complete nasal obstruction.

[31]Schubert et al, *J Allergy Clin Immunol* 1998;102:387-394.

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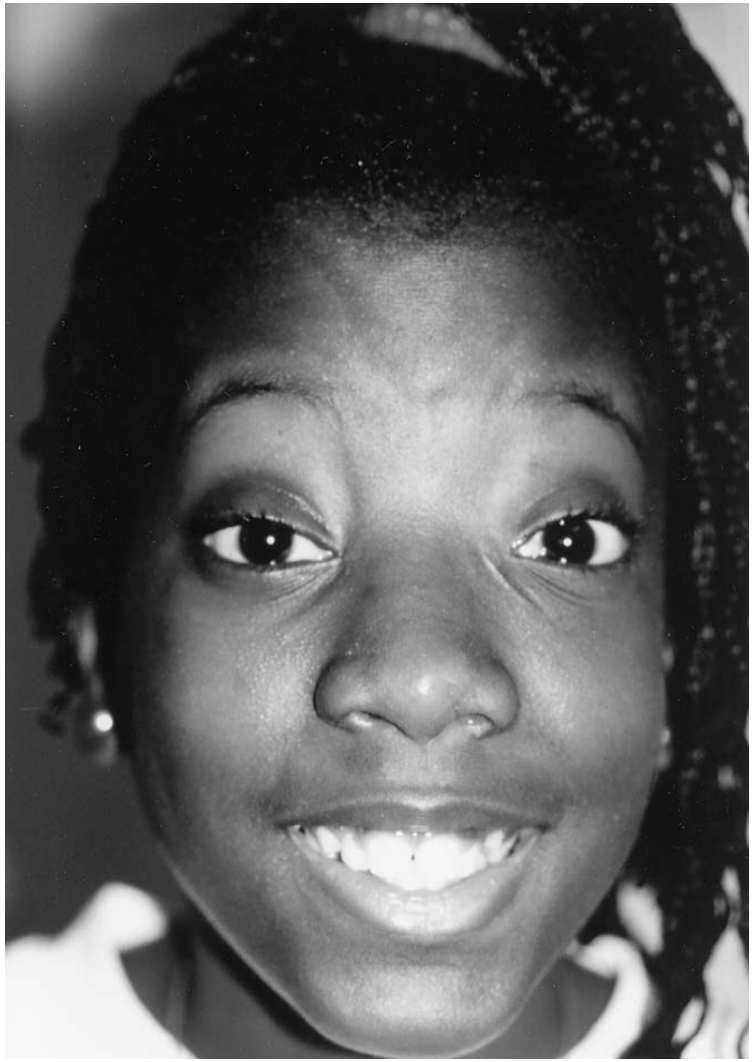
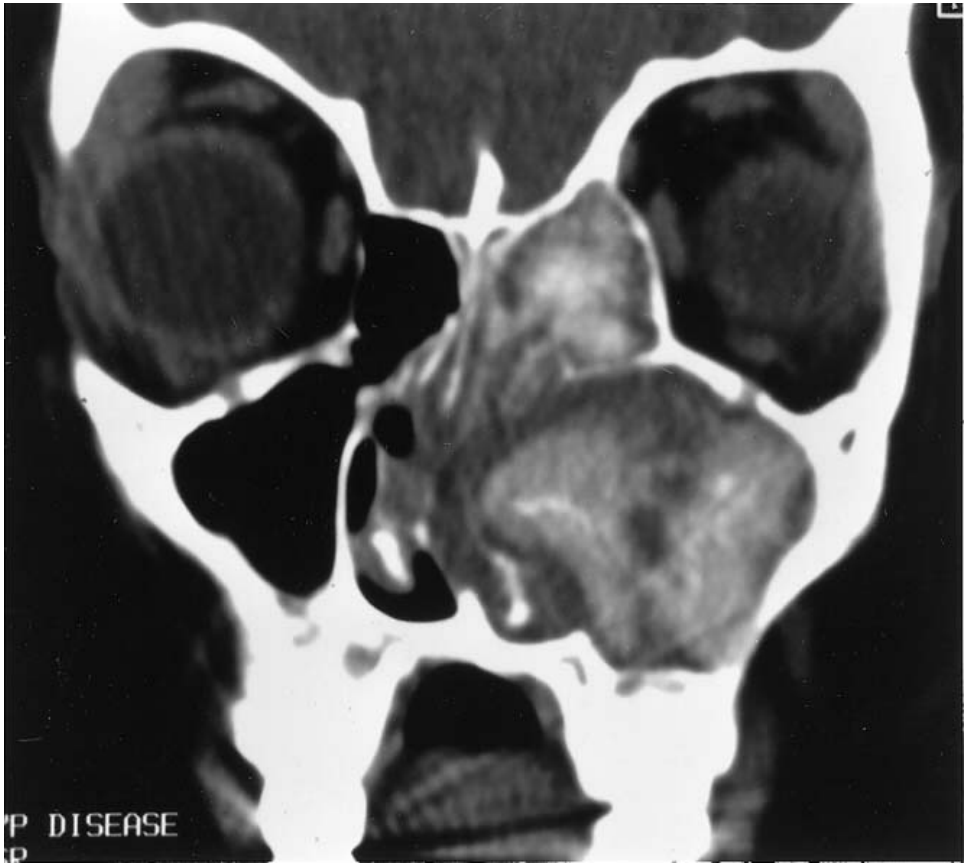
Allergic Fungal Rhinosinusitis





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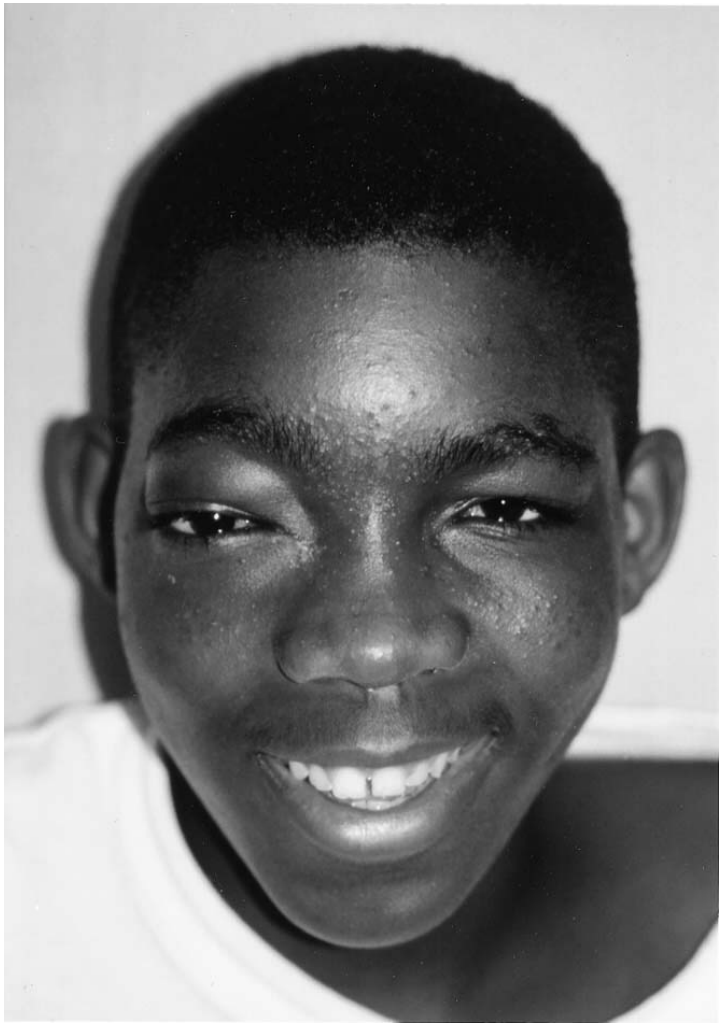
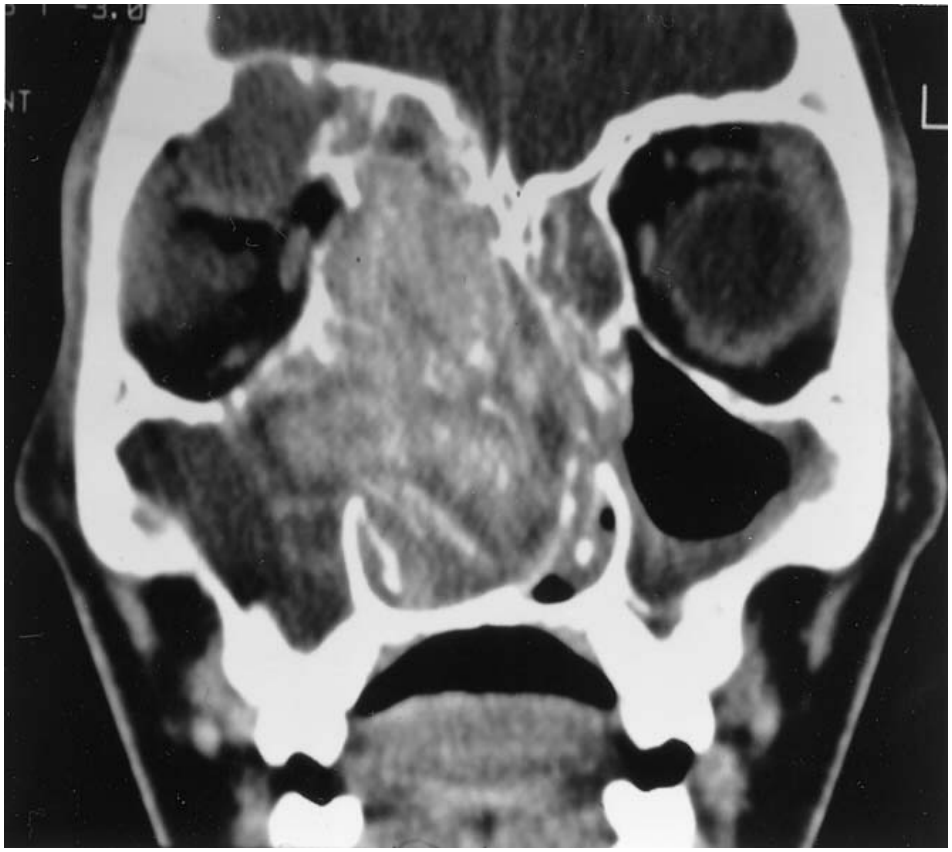
Allergic Fungal Rhinosinusitis





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Allergic Fungal Rhinosinusitis

- **Diagnosis**
  - **Bent and Kuhn Criteria:**
    - Type 1 Hypersensitivity (positive skin test, RAST)
    - Nasal Polyps
    - Allergic Mucin with fungal elements **(pathognomonic)**
    - Characteristic radiographic (CT) findings
      - Central areas of hyperattenuation in the sinus cavity (allergic mucin)
      - Bony loss
    - +/- positive fungal culture

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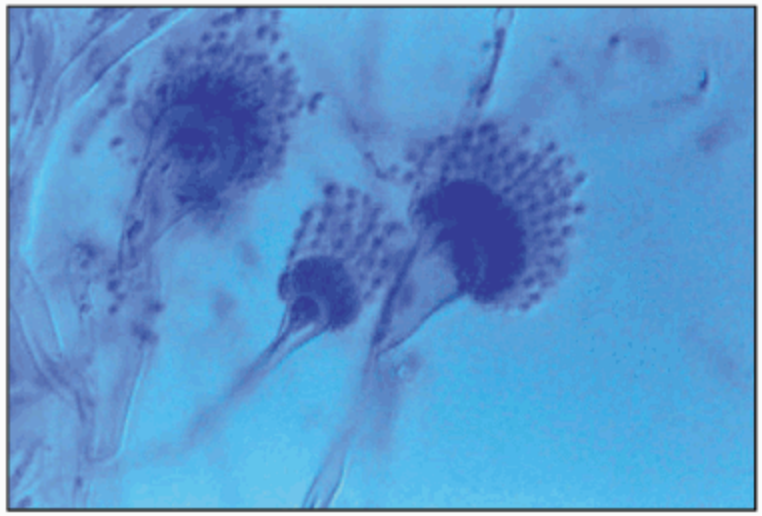
Allergic Fungal Rhinosinusitis

- **Organisms[30]**
  - Dematiaceous fungi
    - Bipolaris, Curvularia, Exserohilum, Alternaria, Dreschslera, etc.
  - Aspergillus



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Allergic Fungal Rhinosinusitis

- **Treatment**
  - Surgical
    - Removal of allergic mucin, provide permanent drainage/ventilation for the affected sinuses.[30]
  - Recurrence is high after surgery, so medical therapy is necessary.
    - Allergen Immunotherapy patients have decreased mucosal edema and increased quality of life as well as decreased disease recurrence[30]
    - Nasal steroids (no studies, but generally accepted)
    - Systemic antifungals are NOT used to prevent recurrence
    - Systemic steroids can delay need for repeat surgery but have side effects.

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Some Pearls…

- Dr. Cofer requests ordering "brain lab protocol" for sinus CT because this data can be used for stereotactic guidance during surgery. No additional costs or radiation.
- Sphenoid disease warrants aggressive treatment/referral because of risk of invasion of nearby vessels, optic nerve.
- Headache with a negative sinus CT scan is NOT a headache caused by sinusitis.
- The Amox/Clav suspensions ending in "00" (e.g. 200, 400, 600/5mL) are prepared so that you can give the high dose of Amox divided BID without overdosing on the clav component.

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SUMMARY

- Rhinosinusitis is a costly disease with significant burden.
- The most common cause of rhinosinusitis is viral infection
- 63% of cases of pediatric RS will resolve without treatment
- The AAP recommends treating pediatric RS to shorten disease course and prevent recurrence.
- Chronic RS is a poorly understood disease in need of much study.
- Sinus CT is useful in chronic RS, but not necessary in uncomplicated acute RS.
- Rhinosinusitis can present as uncontrolled asthma, and treating it can improve asthma symptoms.

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Thanks…

- Dr. Donna Hummell
- Dr. Shelagh Cofer
- Dr. Paul Moore
- Dr. Paige Smith

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[5]Smart et al, *Immunol Allergy Clin N Am* 2005; 25:67-82.

[6]Rachelefsky et al, *Pediatrics* 1984; 73:526-9.

[7]Shah et al, *Laryngoscope*, 2003;113(2): 205-9.

[8]Meltzer et al, Journal Allergy, Clinical Immunology 2004; 114: S155-211.

[9]Goldsmith et al, *Pediatric Clinics N America* 2003; 50.

[10]Holtzmann et al, *Am J Rhinol* 2001;15: 387-90.

[11]Bothwell et al, *Otolaryngol Head Neck Surg* 1999;121:255-62.

[12]Phipps et al Arch *Otolaryngol Head Neck Surg*. 2000 Jul;126(7):831-6.

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[16]Carron et al, *Curr Opin Otolaryngol Head Neck Surg* 2001;9:61-6.

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[22]McCormick et al, *Clin Pediatr (Phila)* 1996;35:457-460.

[23]Meltzer et al, J *Allergy Clin Immunol* 1993;92:812-23.

[24]Topal et al, *Yeni Tip Dergisi* 2001;18 (suppl):58-60.

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[26]Otten et al, *Acta Otorhinolaryngol Belg* 1997;51:173-5.

[27]McClay et al, *Laryngoscope* 2002;112:565-9.

[28]Houser et al, *Otolaryngol Clinics N America* 2000;33(2).

[29]Johnston et al, *Thorax* 1981;36:710.

[30]Marple et al, *Curr Allergy and Asthma Reports* 2004;4:465-70.

[31]Schubert et al, *J Allergy Clin Immunol* 1998;102:387-394.

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Couldn't Resist…

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Viral vs. Bacterial

	Viral	Bacterial
FEVER	• Early in absence of nasal discharge	• Usually late and in presence of nasal discharge
DURATION	• 7-10 days	• >10 days
SEVERITY	• Improving after 4-5 days	• Worsening at 7-10 days **OR** 3 consecutive days of high fever (≥ 102F) with purulent nasal discharge
SYMPTOMS	SAME	
COLOR OF DISCHARGE	SAME	
RADIOLOGY (including CT)	SAME	**Up to 90% of pts with viral RS will have CT scan involvement of sinuses**
PHYSICAL EXAM	SAME	

Efficacy of daily hypertonic saline nasal irrigation among patients with sinusitis: A randomized controlled trial

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KEY POINTS FOR CLINICIANS

- Nasal irrigation improved sinus symptoms and decreased sinus medication use.
- Patient satisfaction and compliance were high for nasal irrigation.
- Patient training in nasal irrigation technique should be provided.

■ OBJECTIVES To test whether daily hypertonic saline nasal irrigation improves sinus symptoms and quality of life and decreases medication use in adult subjects with a history of sinusitis.
■ STUDY DESIGN Randomized controlled trial. Experimental subjects used nasal irrigation daily for 6 months.
■ POPULATION Seventy-six subjects from primary care (n = 70) and otolaryngology (n = 6) clinics with histories of frequent sinusitis were randomized to experimental (n = 52) and control (n = 24) groups.
■ OUTCOMES MEASURED Primary outcome measures included the Medical Outcomes Survey Short Form (SF-12), the Rhinosinusitis Disability Index (RSDI), and a Single-Item Sinus-Symptom Severity Assessment (SIA); all 3 were completed at baseline, 1.5, 3, and 6 months. Secondary outcomes included daily assessment of compliance and biweekly assessment of symptoms and medication use. At 6 months, subjects reported on side effects, satisfaction with nasal irrigation, and the percentage of change in their sinus-related quality of life.
■ RESULTS No significant baseline differences existed between the 2 groups. Sixty-nine subjects (90.8%) completed the study. Compliance averaged 87%. Experimental group RSDI scores improved from 58.4 ± 2.0 to 72.8 ± 2.2 ($P \leq .05$) compared with those of the control group (from 59.6 ± 3.0 to 60.4 ± 1.1); experimental group SIA scores improved from 3.9 ± 0.1 to 2.4 ± 0.1 ($P \leq .05$) compared with those of the control group (from 4.08 ± 0.15 to 4.07 ± 0.27). The number needed to treat to achieve 10% improvement on RSDI at 6 months was 2.0. Experimental subjects reported fewer 2-week periods with sinus-related symptoms ($P < .05$), used less antibiotics ($P < .05$), and used less nasal spray ($P = .06$). On the exit questionnaire 93% of experimental subjects reported overall improvement of sinus-related quality of life, and none reported worsening ($P < .001$); on average, experimental subjects reported 57 ± 4.5% improvement. Side effects were minor and infrequent. Satisfaction was high. We found no statistically significant improvement on the SF-12.
■ CONCLUSIONS Daily hypertonic saline nasal irrigation improves sinus-related quality of life, decreases symptoms, and decreases medication use in patients with frequent sinusitis. Primary care physicians can feel comfortable recommending this therapy.
■ KEY WORDS Sinusitis, nasal irrigation, quality of life. (*J Fam Pract 2002; 51:1049–1055*)

Sinusitis is a common clinical problem with significant morbidity and often refractory symptoms that accounted for approximately 26.7 million office and emergency visits and resulted in $5.8 billion spent in direct costs in 1996.[1] Sinusitis was the fifth most common diagnosis for which antibiotics were prescribed from 1985 to 1992.[2] In 1992, 13 million prescriptions were written for sinusitis, up from 5.8 million in 1985.[2] The number of US chronic sinusitis cases in 1994 was estimated at 35 million, for a prevalence of 134 per 1000 patients.[3] The effect of sinusitis on patients' quality of life (QOL) is significant and can rate as high as back pain, congestive heart disease, and chronic obstructive pulmonary disease on some measures.[4]

Hypertonic nasal irrigation is a therapy that flushes the nasal cavity with saline solution, facilitating a wash of the structures within. Originally part of the Yogic tradition, this technique is anecdotally regarded as safe and effective; it has been suggested as adjunctive therapy for sinusitis and sinus symptoms.[5–7] Potential efficacy is supported by the observation that hypertonic saline improves mucociliary clearance,[8] thins mucus,[9,10] and may decrease inflammation.[8] Optimal irrigant salinity

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and pH are unclear.[10,11] Several small trials examining nasal irrigation have suggested that nasal irrigation is safe, improves nasal symptoms, and is physically tolerable, but inclusion criteria, intervention protocols, and methodological quality vary.[12–18] Improvement of QOL scores[12–14] and several surrogate measures[14–16] have been reported. No study has rigorously evaluated nasal irrigation over a longer period for its effect on QOL, antibiotic and nasal medication use, symptom severity, compliance, and side effects.

We conducted a randomized controlled trial to test the hypotheses that daily hypertonic saline nasal irrigation improves symptoms, decreases antibiotic and nasal medication use, and improves QOL in adult subjects with a history of sinusitis.

METHODS

The study protocol was approved by the University of Wisconsin Health Sciences Human Subjects Committee. Subjects were enrolled from May to August 2000 and, after a study period of 6 months, were exited from November 2000 to February 2001. No prior studies existed at inception to guide sample size estimation. Power calculations performed before study initiation indicated that a sample size of 60 subjects would provide 80% power to detect a 10% difference in the Rhinosinusitis Disability Index (RSDI) between study groups. Due to the high patient burden of this study, we assumed a 25% dropout rate.

Randomization

The randomization scheme was prepared by the Investigational Drug Services of the University of Wisconsin Hospital and Clinics. Subjects were stratified by smoking status and then randomized by using an approximate 2:1 block design, with 10 subjects per block. Therefore 68% of subjects were assigned to the experimental group and 32% to the control group. A 2:1 scheme favoring the experimental group was selected due to resource limitations.

Eligibility criteria and subject recruitment

The recruitment and subject participation scheme is shown in Figure W1 (available on the JFP Web site: http://www.jfponline.com). The billing databases for the University of Wisconsin primary care and Ear, Nose, and Throat (ENT) practices were screened for acute and chronic sinusitis (codes 461 and 473, respectively, from the *International Classification of Diseases, Ninth Revision*). Patients 18 to 65 years old with 2 episodes of acute sinusitis or 1 episode of chronic sinusitis per year for 2 consecutive years (n = 602) were sent a letter explaining the study and inviting participation, along with an opt-out postcard. If no card was returned, potential subjects were phoned. Exclusion criteria included pregnancy and comorbidity significant enough to preclude travel to an informational meeting or performance of the nasal irrigation technique. Patients indicating "moderate to severe" impact of sinus symptoms on their QOL on a Likert scale of 1 to 7 were invited to attend an informational meeting involving enrollment, randomization, and training (n = 128). Of those potential subjects, 44 declined the meeting or were ineligible; 84 agreed to attend the meeting, 77 attended, and 76 enrolled. Of the initial group of 602 potential subjects, 375 were not contacted because the study census reached intended sample size.

One of us (D.R., R.M., or A.Z.) facilitated each informational meeting of 1 to 6 persons. Sealed envelopes containing the patient's randomized group assignment were distributed to subjects in the order they entered the room. The group assignment was unknown to the investigator. Subjects broke the seal and learned their assignment. Thereafter, investigators were not blind to subjects' group assignment. Persons managing and analyzing data also saw unblinded data but had no contact with subjects. Participants heard a brief presentation about sinus disease and its treatment. Nasal irrigation theory and technique were explained. Seventy-six subjects consented and were allocated by their randomized group assignments to experimental (n = 52) or control (n = 24) groups. Control subjects continued treatment of sinus disease in their usual manner. Experimental subjects saw a brief demonstration film, witnessed nasal irrigation by the facilitator, and demonstrated proficiency with the nasal irrigation technique before departure. Subjects were provided all ingredients and materials for 6 months of daily nasal irrigation. Experimental subjects also continued usual care for sinus disease.

Intervention

Subjects in the experimental group were asked to irrigate the nose (150 mL through each nostril) daily for 6 months with the SinuCleanse[19] nasal cup containing 2.0% saline buffered with baking soda (1 heaping teaspoon of canning salt, one half teaspoon of baking soda, and 1 pint of tap water; Figure 1). Solution was mixed fresh every 1 to 2 days. All subjects were phoned at 2 weeks to assess initial compliance with study protocols and thereafter if assessment instruments were not returned promptly.

Outcome measures

The primary outcomes were QOL scores from 2 validated questionnaires: the general health assessment Medical Outcomes Survey Short Form (SF-12)[20] and the RSDI,[21] a disease-specific instrument assessing QOL in emotional, functional, and physical domains. We reworded the phrase *my problem* to *my sinus symptoms* on several RSDI items. Consensus within the research group and

TABLE 1

Baseline patient characteristics*

Variable	Control group (n = 24)	Experimental group (n = 52)
Age, y†	41.4 ± 2.4	42.4 ± 1.4
RSDI score†	59.6 ± 3.0	58.4 ± 2.0
SF-12 score†	59.3 ± 4.0	60.3 ± 3.0
SIA score†	4.1 ± 0.2	3.9 ± 0.1
Female‡	18 (75)	37 (71)
Caucasian race‡	23 (96)	49 (94)
Smokers‡	1 (4)	3 (6)
Education‡		
≤High school	6 (25)	11 (21)
Some college	10 (42)	18 (35)
≥College degree	8 (33)	23 (44)
Seasonal allergies‡	17 (71)	34 (66)
Medication allergies‡	12 (50)	29 (56)
ENT history‡		
Nasal surgery	7 (29)	19 (37)
Nasal polyps	3 (13)	9 (17)
Deviated septum	7 (29)	12 (23)
Nasal fracture	4 (17)	7 (13)
Asthma‡	4 (17)	14 (27)
ICD-9 code‡		
461 (acute sinusitis)	20 (83)	34 (65)
473 (chronic sinusitis)	2 (8)	11 (21)
Both (acute and chronic sinusitis)	2 (8)	7 (14)
Clinic type‡		
Primary care	24 (100)	46 (89)
ENT	0 (0)	6 (12)

*At baseline, there were no statistically significant ($P > .05$) differences between the experimental and control groups.
† Data are presented as mean ± standard error.
‡ Data are presented as number (%) of subjects.
ENT, Ear, Nose, and Throat; ICD-9, *International Classification of Diseases, Ninth Revision*; RSDI, Rhinosinusitis Disability Index; SF-12, Medical Outcomes Survey Short Form 12; SIA, Single-Item Symptom Severity Assessment.

among consulted experts was that this minor change facilitated more accurate reading and reporting. We also measured overall sinus symptom severity with a Single-Item Symptom Severity Assessment (SIA): "Please evaluate the overall severity of your sinus symptoms since you enrolled in the study"; higher scores on the Likert scale SIA indicated increased severity. Scales for RSDI and SF-12 ranged from 0 to 100 points, with higher scores indicating better overall QOL. Each was completed at baseline and at 1.5, 3, and 6 months; at the 6-month assessment, subjects were shown their baseline answers for comparison because they had told us they needed to recall answers to past questions. They believed they knew whether they felt better or worse and wanted their later answers to reflect this change. Allowing subjects to view previous scores is an accepted research practice.[22] However, because we did not allow subjects to see their baseline answers at 1.5 and 3 months, scores must be interpreted in light of the availability of the baseline data to the subjects.

Secondary outcomes were assessed with multiple methods. Compliance with nasal irrigation was recorded in a daily diary. The presence or absence of sinus symptoms (headache, congestion, facial pressure, facial pain, nasal discharge), antibiotic use, and nasal-spray use was assessed every 2 weeks. An exit questionnaire asked subjects to report categorically whether their sinus-related QOL had gotten worse, stayed the same, or improved, and to estimate the percentage of change (scale from 0 to ±100%). Overall satisfaction and side effects were reported at 6 months.

Statistical methods

Baseline characteristics of experimental and control groups were compared to assess randomization. Analysis, performed on an intention-to-treat basis, involved all 76 subjects randomized into the

TABLE 2

Primary outcomes: RSDI, SF-12, and SIA baseline scores and mean score changes*

Status	Baseline score	Baseline vs score change at 1.5 mo	3 mo	6 mo
RSDI				
Experimental	58.4 ± 2.0	8.2 ± 1.2	14.0 ± 2.0†	14.4 ± 1.7‡
Control	59.6 ± 3.0	5.6 ± 1.4	7.7 ± 1.9	0.9 ± 1.0
SF-12				
Experimental	60.3 ± 3.0	6.7 ± 2.1	8.2 ± 2.9	12.7 ± 3.6
Control	59.3 ± 3.9	5.4 ± 3.9	2.9 ± 4.0	2.2 ± 3.5
SIA				
Experimental	3.9 ± 0.1	-0.8 ± 0.2†	-1.2 ± 0.2†	-1.6 ± 0.2‡
Control	4.1 ± 0.2	-0.02 ± 0.21	-0.3 ± 0.2	-0.005 ± 0.2

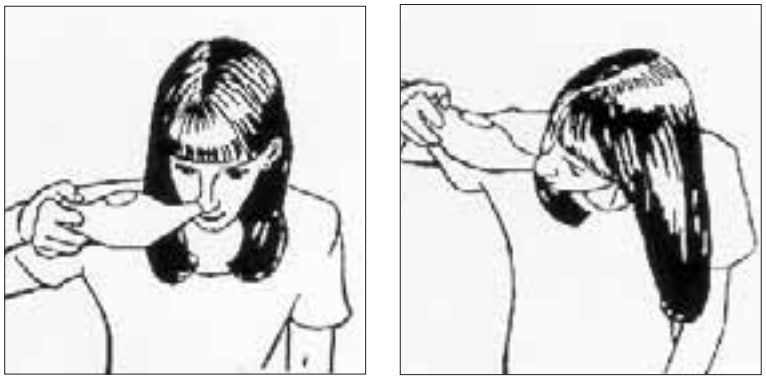
*Data are presented as mean ± standard error.
† Statistically significant at $P < .05$.
‡ Statistically significant at $P < .001$.
RSDI, Rhinosinusitis Disability Index; SF-12, Medical Outcomes Survey Short Form 12; SIA, Single-Item Symptom Severity Assessment.

study. As dictated by the intention-to-treat model, the few missing values were imputed with multiple regression. Repeated measures analysis of variance contrasted the primary outcomes, that is, QOL status and sinus symptom scores within each group at baseline and subsequent periods. Differences between experimental and control groups were analyzed at each point in the repeated measures model and comprehensively for the entire time frame of the study. Statistical significance was assessed with 2-tailed tests. Data are presented as mean values with range of standard error, unless otherwise indicated.

RESULTS

FIGURE 1

Position of nasal cup for nasal irrigation therapy



A B

The study sample (Table 1) consisted of 76 subjects (55 female) randomized to experimental (n = 52) and control (n = 24) groups. Subjects' ages ranged from 19 to 62 years, with a mean age of 42 years. Sixty-nine subjects (46 experimental and 23 control) completed the study. Seven subjects dropped out of the study at 1.5 months or earlier. A phone questionnaire was completed by 3 experimental dropouts; 2 of the 3 identified "lack of time" as the main reason for leaving the study; the remaining subject did not specify a reason. All 3 identified nasal irrigation as "helpful," and none identified side effects as significant. The remaining 4 subjects were lost to follow-up. Dropouts tended to have slightly better baseline RSDI scores than nondropouts, 66.8 vs 58.1 points, but this difference was not significant ($P = .15$).

No significant baseline differences were found between the groups of mostly white, female, well-educated subjects (Table 1). Baseline RSDI, SF-12, and SIA scores were similar in both groups. Although ENT subjects tended to have slightly worse baseline RSDI and SIA scores and improved slightly more during the study than other experimental subjects, the effect of clinic type (ENT vs primary care) was not statistically significant. By chance all subjects from ENT clinics (n = 6) and a disproportionate percentage of subjects

with chronic sinusitis were randomized to the experimental group. Neither variable was statistically significant.

Experimental subjects showed a significant improvement in RSDI scores: 58.4 ± 2.0, 66.6 ± 2.2, 72.4 ± 2.2, and 72.8 ± 2.2 points at baseline, 1.5, 3, and 6 months, respectively (Table 2, Figure 2). Although the difference was not significant (P = .08), experimental subjects whose initial RSDI score was less than 50 points improved the most, with an average score change of 17.8 ± 4.4, and comparable control subjects had an average RSDI score change of 8.8 ± 2.9 points. Emotional and functional RSDI domains were not significantly related to score change; however, the physical domain of the survey was significant (P = .05).

SIA scores for experimental subjects improved (P < .05) at all follow-up points compared with control subjects; scores for the experimental group were 3.9 ± 0.1, 3.1 ± 0.2, 2.7 ± 0.2, and 2.4 ± 0.1 points at baseline, 1.5, 3, and 6 months, respectively (Table 2, Figure 2).

SF-12 score showed no significant differences between groups at any follow-up point but by 6 months trended toward significance (P = .06; Table 2).

Forty-one (93%) experimental subjects completing the exit questionnaire reported improvement. Most (n = 16, 73%) control subjects reported no change, but 18% reported worsening (P < .001; Table 3). Experimental subjects reported an average of 57 ± 4.5% improvement (range, 0–100%), whereas control subjects reported an average of 7 ± 5.9% worsening (range, -80% to 50%; P < .001).

Experimental subjects reported using nasal irrigation on 87% of days during the study; 31 subjects reported using nasal irrigation on 91% or more days, 13 subjects on 76% to 90% of days, and 5 subjects on 51% to 75% of days. Only 3 subjects used nasal irrigation on 50% or fewer days; these 3 subjects had relatively good baseline RSDI and SIA scores compared with other experimental subjects. Compliance was not significantly associated with changes in SIA or RSDI scores. The average survey completion rate was 96% at each assessment by each group.

Experimental subjects spent fewer 2-week blocks with nasal congestion, sinus headache, and frontal pain and pressure and used antibiotics and nasal sprays in fewer blocks (Table 3).

Forty-four experimental subjects answered questions about satisfaction and side effects. Forty-two stated they "will continue to use" nasal irrigation; the remaining 2 subjects found nasal irrigation less helpful but did not experience side effects. All 44 subjects "would recommend" nasal irrigation to friends or family with sinus problems. Ten subjects (23%) experienced side effects; 8 identified nasal irritation, nasal burning, tearing, nosebleeds, headache, or nasal drainage as occurring but "not significant." Two subjects identified nasal burning, irritation, and headache as "significant," but this did not change their high satisfaction rating. Of the 10 subjects who experienced side effects, 4 reduced or eliminated the side effects by temporarily alternating treatment days or decreasing salinity by 50%.

TABLE 3

Secondary outcomes

Secondary outcome	Experimental	Control
Sinus symptoms*		
Sinus headache†	57 ± 0.05	76 ± 0.06
Frontal pain‡	55 ± 0.05	82 ± 0.05
Frontal pressure‡	53 ± 0.05	86 ± 0.05
Nasal congestion†	67 ± 0.04	83 ± 0.05
Nasal discharge	65 ± 0.05	69 ± 0.07
Medication use*		
Antibiotics†	10 ± 0.02	19 ± 0.04
Nasal sprays§	4 ± 0.01	8 ± 0.02
EQ: sinus symptoms related to QOL‖		
Better‡	41 (93)	2 (9)
Same‡	3 (7)	16 (73)
Worse‡	0 (0)	4 (18)

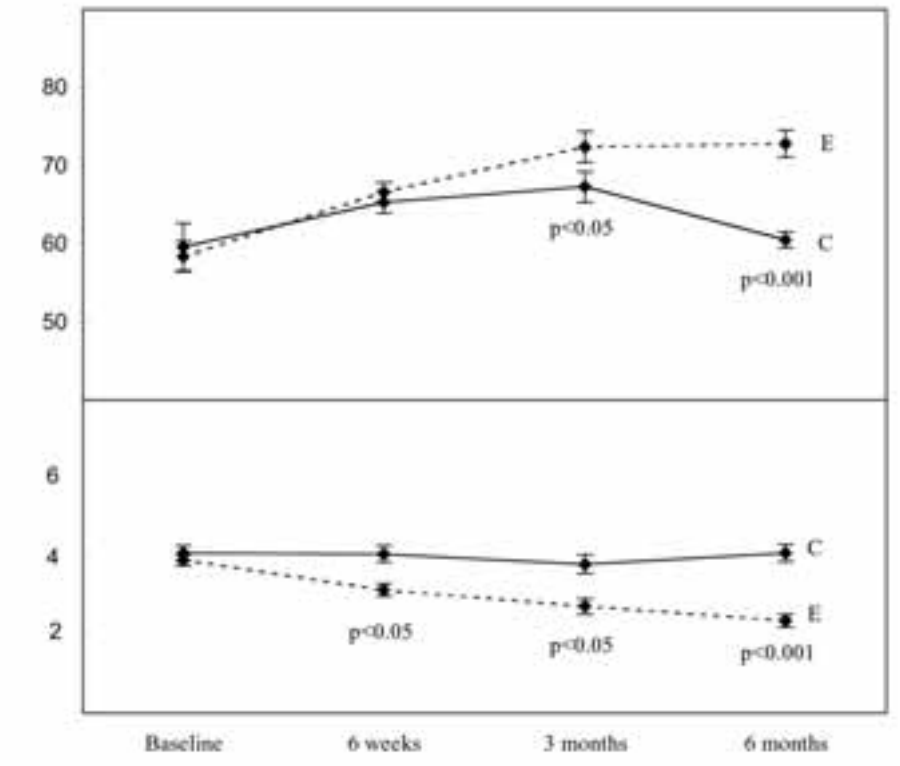
*Data are presented as the percentage of 2-week blocks ± standard error during the study.
† Statistically significant difference between groups: P < .05.
‡ Statistically significant difference between groups: P < .001.
§ Not statistically significant, difference between groups: P = .06.
‖ Data are presented as number (%) of subjects.
EQ, exit questionnaire (Is your quality of life with respect to sinus symptoms better or worse since the beginning of the study?); QOL, quality of life.

DISCUSSION

Our trial of daily hypertonic nasal irrigation produced several significant findings. We found consistent, statistically significant improvements in QOL (RSDI) and overall symptom severity (SIA). This was consistent with QOL improvement previously reported over short periods with the use of disease-specific measures.[12–14] The RSDI is a moderately well-developed and validated disease-specific QOL instrument.[21–23] The "minimal clinically important difference," defined as the average score improvement needed to justify costs and risks,[24–26] has not been established for sinusitis. However, it has been estimated for other disease states. For example, a half-point change on a 7-point Likert scale corresponds to estimates of important change in patients with chronic heart and lung disease.[22,27]

FIGURE 2

Mean RSDI and SIA scores in control and experimental subjects



Values are ± standard error of change in score. C, control; E, experimental; RSDI, Rhinosinusitis Disability Index; SIA, Single-Item Symptom Severity Assessment.

Others have found similar relationships.[28–31] In our study, RSDI scores among treated subjects averaged 6.0 and 15.5 points better than controls at 3 and 6 months, respectively. On the SIA, treated subjects averaged 0.6, 0.9, and 1.6 points better. Extrapolating from these findings, these differences appear to be clinically significant. By using 10% improvement of the RSDI, our data showed numbers needed to treat of 9, 5, and 2 at 1.5, 3, and 6 months, respectively (95% confidence interval at 6 months, 1.4–2.6). Numbers needed to treat for SIA, symptom frequency, and medication use were similar. SF-12 improvement, although not statistically significant in this small trial, may represent clinically significant improvements in general health-related QOL.

"Percentage change" is used often by clinicians to gauge therapeutic progress. Ours is the first study to document such change in sinusitis patients using nasal irrigation. Ours is also the first trial to show decreased symptom frequency over a 6-month period. Shorter trials have documented improvement in patients with nasal symptoms[12,13,17,18] or with chronic sinusitis in adult[14,15] and pediatric[16] populations. Consistent with improved symptoms and QOL, experimental subjects decreased their use of antibiotics and nasal sprays, as previously reported in a short trial.[12]

Side effects have not been carefully assessed in previous trials. Although generally safe, daily hypertonic nasal irrigation was associated with some clinically minor side effects. Interestingly, subjects were able to decrease side effects by adjusting irrigation schedule or salinity. Side effects were not sufficiently bothersome to stop therapy. Compliance with daily therapy was very high and is previously unreported. Although this was consistent with a positive effect on relatively severe symptoms, we believe high compliance also was related to teaching, demonstrated proficiency with nasal irrigation, and close telephone follow-up. One prior study reported subjects' observation of the first nasal irrigation[15]; several studies reported providing some education.[12–14,18]

Our study has several limitations. It was not blinded or placebo controlled. Blinding subjects to a physical therapy is inherently difficult. Investigators who have tried to use normal saline

placebos probably affected outcomes.[14–16] One trial using a fresh water (0% saline) placebo was stopped early when several control subjects developed otitis media.[32] The investigators also were unblinded, possibly creating observer bias.

Methodologic and recruitment strengths of this study included effective randomization, matched control group, intention-to-treat analysis, low missing data rates, high compliance rate, and low dropout rate. Clinical strengths included significant findings on most parameters assessed. Particularly intriguing was the decreased use of antibiotics in the experimental group. This study offered strong evidence that nasal irrigation is a safe, effective, and inexpensive (nasal pot, $15; daily therapy, <$1/month) therapy for sinus disease that properly trained patients will use. Although questions about the protocol (schedule, concentration, and buffering) and indications require further study in a more diverse patient population, clinicians may confidently recommend nasal irrigation; it offers significant hope for symptomatic relief and QOL improvement for millions of individuals with sinus disease who often have few therapeutic options.

CONCLUSIONS

Daily hypertonic saline nasal irrigation improves sinus-related QOL, decreases symptoms, and decreases medication use in patients with frequent sinusitis. Primary care physicians can feel comfortable recommending this therapy.

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JFP

Current Concepts

Fungal Sinusitis

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UNTIL recently, there has been no consensus on the classification of or the diagnostic criteria for fungal sinusitis. Many case reports and series have lacked the histopathological data necessary to distinguish invasive from noninvasive disease, used similar terms to describe different syndromes, or included patients with noninvasive disease in studies of invasive fungal sinusitis. Thus, the literature has provided only limited guidance with respect to the care of patients with these conditions. A number of recent investigations have addressed these problems and led to both a histopathologically based classification and criteria for diagnosis.[1-5] Since the newer surgical techniques and therapeutic approaches are likely to improve the prognosis of patients with fungal sinusitis, a review of this topic seems timely.[6-10]

DIAGNOSIS

Fungal sinusitis should be considered in all patients with chronic sinusitis, especially in association with certain clinical features that serve as clues to the diagnosis (Table 1). Patients with noninvasive forms have intractable sinusitis that fails to respond to repeated courses of antibiotics and, unfortunately, often results in multiple operations before the diagnosis is recognized.[4] Invasive fungal sinusitis usually occurs in immunocompromised patients with acute onset of fever, cough, nasal mucosal ulceration or eschars, epistaxis, and headache. Commonly associated conditions include malignant diseases, especially leukemia; other causes of neutropenia; and diabetes, hemochromatosis, or protein-calorie malnutrition. More chronic forms of invasive disease may present as proptosis or orbital apex syndrome. Left untreated, any of the invasive forms can lead to fungal invasion of cerebral blood vessels, with ischemic infarction or direct infection of the brain.

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DISTINGUISHING BETWEEN INVASIVE AND NONINVASIVE SINUSITIS

Fungi are the chief aeroallergens in many areas. In some locales, airborne spore counts are a thousand times those of pollens.[11] Host defense mechanisms for fungi have not been clearly elucidated, but the pathophysiology of fungal sinusitis probably involves compromised sinus aeration, altered immune responses to fungi, and bad luck.[12]

Invasive and noninvasive syndromes of fungal sinusitis share many features. They both may occur in immunocompetent or immunocompromised persons, may have an acute or chronic course, and may extend beyond the thin walls of the sinuses into the orbit, structures of the eye, and the brain. Purulent, pasty, often foul-smelling material is present within affected sinuses and may contain few or many fungal elements, which often fail to grow in culture.[13] This fungal material is commonly associated with dense polyposis and calcification that results in areas of focal or diffuse radiodensity on computed tomographic imaging of the sinuses[14] (Fig. 1) and decreased signal intensities on T_1- and T_2-weighted magnetic resonance imaging. There have been no controlled trials of the treatment of any of the syndromes of fungal sinusitis.

Aspergillus is the most common reported cause of fungal sinusitis.[15] Since noninvasive and invasive forms have been thought to represent a continuum, reports of "aspergillosis of the sinuses," including those focusing on clinical management, often include both as a single entity.[13] It is now clear that invasive fungal sinusitis can be distinguished from noninvasive disease with the use of clinical criteria that include radiologic diagnosis of sinusitis and histopathological examination of tissue from sinuses (Table 2). Radiologic findings associated with fungal sinusitis include those also seen with isolated bacterial sinusitis, such as air–fluid levels or more than 8 mm of mucoperiosteal thickening, and those more specific for fungal sinusitis, such as calcifications and loss of bony sinus margins. Fungal cultures of the nasal mucus are unreliable in the diagnosis of any form of fungal sinusitis.[16] Stainable hyphae are not present in the mucosa of patients with chronic bacterial sinusitis; they are present solely in mucopurulent material within the sinus in noninvasive disease.[5] Hyphae penetrate the sinus mucosa into submucosa, blood vessels, or bone in invasive disease.

To distinguish between these two forms, adequate quantities of sinus contents and biopsy specimens of diseased and healthy mucosa and bone adjacent to areas of frank necrosis must be obtained for histopathological analysis. Since fungi do not stain well with routine stains (such as hematoxylin and eosin), silver-impregnation fungal stains and fungal cultures of surgical specimens are necessary whenever fungal sinusitis is considered.

TABLE 1. KEY CLINICAL POINTS IN THE DIAGNOSIS AND TREATMENT OF FUNGAL SINUSITIS.

TYPE	CLINICAL CLUES	MOST COMMON CAUSES	DIAGNOSIS	INITIAL MANAGEMENT
Noninvasive fungal sinusitis	Immunocompetent patient Intractable symptoms despite adequate treatment for bacterial sinusitis Allergic rhinitis, asthma Nasal polyps Calcifications in sinus on computed tomography Proptosis in children	Hyaline molds Aspergillus species Fusarium species Dematiaceous molds Bipolaris species *Curvularia lunata* *Pseudallescheria boydii*	Aspiration of sinus contents should be followed by silver-impregnation staining and culture of aspirate. Sinus contents often have the consistency of peanut butter or cottage cheese. In patients with diabetes or other conditions involving immunocompromise, biopsy of healthy and diseased mucosa and bone should be considered to rule out tissue invasion.	Surgery is necessary to establish drainage and to remove impacted mucus, polyps, or fungus ball.
Invasive fungal sinusitis	Fever, headache, epistaxis, and cough in an immunocompromised patient Diabetes, hemochromatosis, protein-calorie malnutrition Nasal mucosal ulcer or eschar Calcifications in sinus on computed tomography Orbital apex syndrome Proptosis in adults	Hyaline molds Zygomycetes *Rhizopus oryzae* *Cunninghamella bertholettiae* Aspergillus species Fusarium species Dematiaceous molds *P. boydii*	Early endoscopic evaluation should be followed by biopsy of healthy and diseased mucosa and bone. Sinus contents should be cultured. All surgical specimens should be stained with silver-impregnation stains. If the results of endoscopic evaluation are negative, open biopsy should be performed immediately.	Emergency surgery is necessary to remove necrotic and devitalized tissue. Treatment with amphotericin B should be initiated on demonstration of tissue invasion and before culture results become available. Immunosuppression should be reversed, including discontinuation of corticosteroids and treatment of iatrogenic neutropenia.

NONINVASIVE FUNGAL SINUSITIS

Allergic Fungal Sinusitis

Allergic fungal sinusitis should be suspected in patients with atopy and chronic, often intractable, sinusitis and nasal polyposis. Most have pansinusitis, and many have had multiple sinus operations by the time of diagnosis.[2,17] At surgery, involved sinuses contain brown or greenish-black material with the consistency of peanut butter or cottage cheese. This material has been called "allergic mucin" and contains laminated accumulations of intact and degenerating eosinophils, Charcot–Leyden crystals, cellular debris, and sparse hyphae rarely visualized without fungal stains.[18] The adjacent sinus mucosa has a mixed cellular infiltrate of eosinophils, plasma cells, and lymphocytes (Fig. 2). The allergic mucin and polyps may form a partially calcified expansile mass that obstructs sinus drainage and perpetuates the bacterial sinusitis often associated with allergic fungal sinusitis. Growth of the mass may lead to pressure-induced erosion of bone, rupture of sinus walls, and occasional leakage of sinus contents into adjacent orbit or brain. In children with incompletely calcified cranial bones, involvement of the frontal or ethmoid sinuses may lead to hypertelorism or proptosis.[17]

The most common causes of allergic fungal sinusitis are the dematiaceous (pigmented) fungi, including curvularia, bipolaris, and pseudallescheria, and the hyaline molds, such as aspergillus and fusarium.[2,19] These fungi are also common causes of allergic rhinitis.[2] Patients with allergic fungal sinusitis often have asthma and usually have allergic rhinitis, eosinophilia, and elevated total and fungus-specific IgE concentrations — the latter detected by skin tests or radioallergosorbent testing. Allergic fungal sinusitis appears to represent an IgE-mediated hypersensitivity reaction to fungi resembling that occurring in the bronchi in allergic bronchopulmonary aspergillosis.[20]

The diagnostic criteria for allergic fungal sinusitis consist of five clinical features: radiologically confirmed sinusitis; the presence of allergic mucin within a sinus; the demonstration of fungal hyphae in the allergic mucin; the absence of fungal invasion of submucosa, blood vessels, or bone; and the absence of diabetes, immunodeficiency disease, or recent treatment with immunosuppressive drugs.[2,3] Allergic fungal sinusitis does not become invasive. Like other syndromes of fungal sinusitis, allergic fungal sinusitis must be distinguished from other infectious, neoplastic, and inflammatory conditions causing sinusitis.[21]

Endoscopic removal of polyps and inflammatory material to establish aeration and drainage of involved sinuses is an essential first step in treatment. Repeated endoscopic surgery obliterates anatomical landmarks and increases the risk of complications with additional procedures, necessitating open sur-

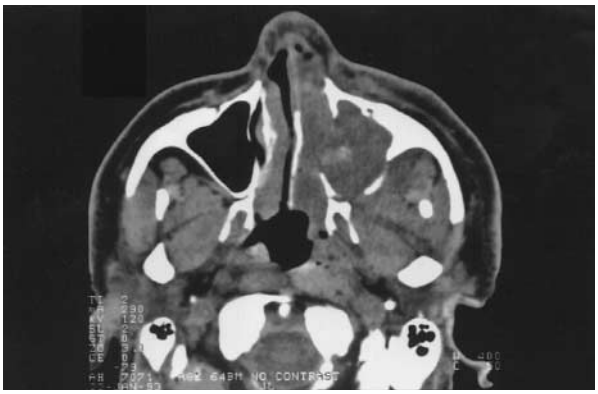

Figure 1. Axial Computed Tomographic Image of the Sinuses in a Patient with Diabetes and Chronic Sinusitis.

There is opacification of the left maxillary sinus with expansion of the sinus contents through the medial wall of the sinus into the nose. The flocculent calcifications in the sinus are common in fungal sinusitis, with values on densitometry ranging from 1870 to 3070 Hounsfield units (average, 2868). Biopsy of the diseased mucosa showed vascular invasion by hyphae, and a diagnosis of invasive fungal sinusitis was made. Cultures subsequently grew *Aspergillus fumigatus.* Despite vigorous treatment, the fungus spread from the similarly affected left ethmoid sinus superiorly into the orbital apex, causing the orbital apex syndrome, and posteriorly into the cavernous sinuses, causing cavernous venous thrombosis and death.

gical procedures in some patients. Therapy with amphotericin B, with its attendant toxicity, is not indicated, and newer, less toxic antifungal agents have not been shown to be useful. Since allergic fungal sinusitis usually recurs after treatment with either sinus surgery or surgery plus antifungal agents, additional measures aimed at prevention are being evaluated.[22] For instance, twice-daily sinus irrigation with warm isotonic saline with a bulb irrigator or a Water Pik device with a Grossan Sinus Irrigator Tip can prevent impaction of mucus. The concept that corticosteroid therapy prevents the recurrence of sinus inflammation and polyps was derived from experience with allergic bronchopulmonary aspergillosis.[17,23] Postoperatively, oral prednisone in a dose of 10 to 20 mg per day is given for a minimum of two weeks, followed by the same dose on alternate days for an additional two weeks or longer. Full-dose, short-acting intranasal corticosteroids are prescribed on a long-term basis.[24] Postoperatively, patients benefit from regular nasal endoscopy to remove any synechiae or polyps that develop. Allergen immunotherapy to down-regulate the production of fungus-specific IgE and decrease the inflammatory reaction appears useful.[25]

Sinus Mycetoma

Patients with sinus mycetomas (fungus balls) usually seek medical attention because of nasal obstruction, chronic sinusitis, facial pain, or a fetid smell (cacosmia). Some patients have presented with a seizure disorder of recent onset.[4] Mycetomas predominantly — and often exclusively — involve the maxillary sinus. Nasal polyps and bacterial sinusitis may be associated conditions. Fungi frequently fail to grow from the hyphae-rich material obtained at surgery, since fungal elements in mycetomas have a low viability.[26] Although point sources of infection are infrequently identified, a poorly cleaned continuous positive-airway-pressure device infected one patient with *Aspergillus fumigatus,* the most common reported cause of mycetomas.[4]

The criteria for the diagnosis of sinus mycetoma consist of five features.[4] Radiologic studies show sinus opacification, often associated with flocculent

TABLE 2. FEATURES OF NONINVASIVE AND INVASIVE FUNGAL SINUSITIS.

SYNDROME	COMMON CAUSES	GEOGRAPHIC DISTRIBUTION	CHARACTERISTICS OF HOST	ASSOCIATED CONDITIONS
Allergic fungal sinusitis	Bipolaris species, *Curvularia lunata*, and *Aspergillus fumigatus*	Humid areas, especially coastal United States	Immunocompetent, frequently atopic	Chronic sinusitis, nasal polyps
Sinus mycetoma (fungus ball)	*A. fumigatus* and dematiaceous fungi	Humid areas, especially coastal United States	Immunocompetent, sometimes atopic	Chronic sinusitis, nasal polyps
Acute (fulminant) invasive fungal sinusitis	Fungi of the order Mucorales and *A. fumigatus*	No specific geographic location	Immunocompromised; rarely immunocompetent	Diabetes mellitus, malignant conditions, immunosuppressive therapy
Chronic invasive fungal sinusitis	*A. fumigatus*	No specific geographic location	Immunocompromised	Diabetes mellitus
Granulomatous invasive fungal sinusitis	*A. flavus*	Predominantly North Africa	Immunocompetent	None

*There is no evidence that oral antifungal agents are helpful.

calcifications. Mucopurulent, cheesy, or clay-like material is present at the time of surgery. Histopathological evaluation shows no allergic mucin but a matted, dense conglomeration of hyphae separate from but adjacent to the respiratory mucosa of the sinus. This mucosa is characterized by a chronic, nongranulomatous, inflammatory response of variable intensity to adjacent fungal elements.[27] There is no fungal invasion of mucosa, associated blood vessels, or bone.

Allergic conditions and fungus-specific IgE are less common in patients with mycetoma than in those with allergic fungal sinusitis, but like patients with allergic fungal sinusitis, they are immunocompetent. Radiologic results are often interpreted as showing bony erosion, which actually reflects pressure-induced necrosis of bone like that seen in allergic fungal sinusitis, rather than invasiveness. A single patient has been described with histopathological evidence of a mycetoma and allergic fungal sinusitis in the same sinus.[4]

Removal of the fungus ball with aeration and drainage of the affected sinus usually resolves this condition without the need for antifungal agents.[28]

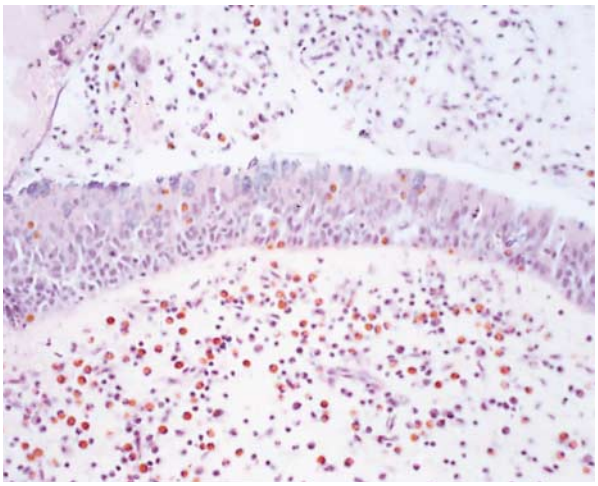

Figure 2. Biopsy Specimen of Sinus Mucosa in a Patient with Allergic Fungal Sinusitis (Hematoxylin and Eosin, ×40).

There is a dense mucosal and submucosal infiltrate of eosinophils, lymphocytes, and plasma cells. The cellular composition is similar in the mucin above the epithelium. Staining with Gomori's methenamine silver stain revealed small numbers of hyphae in this material, which is sometimes referred to as "allergic mucin." Histopathological demonstration of allergic mucin is essential for the diagnosis of allergic fungal sinusitis.

INVASIVE FUNGAL SINUSITIS

Acute (Fulminant) Invasive Fungal Sinusitis

Rhinocerebral mucormycosis is a syndrome characterized by sinusitis and a painless, necrotic black palatal or nasal septal ulcer or eschar. Without early treatment, the fungus may rapidly disseminate by the vascular route, causing death within days. Although most common in patients with diabetes and other immunosuppressed patients, it occasionally occurs in previously healthy persons.[7,29] Saprophytic fungi of the order Mucorales, including rhizopus, rhizomucor, absidia, mucor, cunninghamella, mortierella, saksenaea, and apophysomyces, have caused this syndrome, which is also called zygomycosis.

Histopathological studies show hyphal invasion of blood vessels, including the carotid arteries and cavernous sinuses; vasculitis with thrombosis; hemorrhage; and tissue infarction. The inflammatory response has not been well characterized. There may be an acute neutrophilic infiltrate,[30] but one report

TABLE 2. CONTINUED.

HISTOPATHOLOGICAL FINDINGS	CLINICAL PRESENTATION	TREATMENT	PROGNOSIS
Sparse fungal elements in dense, eosinophil-rich, mucoid material ("allergic mucin") containing rare hyphae; lymphoplasmocytic and eosinophilic response in adjacent mucosa	Chronic pansinusitis, nasal polyps, calcification within sinus on computed tomography, proptosis or eye-muscle entrapment in children	Débridement, aeration, oral and topical corticosteroids, and (?) allergen immunotherapy*	Recurrence common
Dense accumulation of fungal elements in a mucoid matrix forming an expansile mass; low-grade chronic inflammatory response in adjacent mucosa	Rhinosinusitis (often unilateral), nasal obstruction, green-brown nasal discharge, calcification in sinus on computed tomography	Débridement, aeration; antifungal agents not required	Excellent
Fungal elements in mucosa, submucosa, blood vessels, or bone, with extensive tissue necrosis and neutrophilic inflammation	Fever, cough, crusting of nasal mucosa, epistaxis, headache, mental-status changes	Radical débridement until histopathologically normal tissue is evident, antifungal agents, treatment of underlying conditions	Fair when disease is limited to sinus; poor with intracranial involvement
Necrosis of mucosa, submucosa, bone, and blood vessels, with low-grade inflammation	Orbital apex syndrome	Radical débridement, antifungal agents	Poor
Granuloma with multinucleated giant cells and palisading histiocytes	Unilateral proptosis	Débridement, aeration, and itraconazole therapy	Good, but disease can recur

described a "centrifugally spreading, necrotizing reaction with only minimal inflammation, thrombosis, mycotic aneurysms and ischemic infarction of tissues."[31]

An identical syndrome, which includes nasal septal ulceration, has been described with aspergillus, fusarium, and *Pseudallescheria boydii* infections and has been called fulminant invasive sinusitis.[7,32,33] Fever, cough, crusting of nasal mucosa, epistaxis, and headache are the most common presenting symptoms.[33] The condition usually involves patients with the acquired immunodeficiency syndrome or systemic lupus erythematosus and those receiving immunosuppressive therapy for cancer or after bone marrow transplantation.[33-37] Since the syndromes of fulminant invasive sinusitis and rhinocerebral mucormycosis are the same, both are better termed "acute (fulminant) invasive fungal sinusitis."[4]

When symptoms and signs of invasive fungal sinusitis are present, emergency surgery should be performed to obtain material for histopathological evaluation and to débride aggressively the devitalized tissue supporting fungal growth. When histopathological studies confirm tissue invasion, treatment with amphotericin B (1.0 to 1.5 mg per kilogram of body weight per day) should be initiated immediately, without waiting for the results of fungal cultures, and continued for a minimum of 14 days. Total doses of 2500 to 4000 mg of amphotericin B may be necessary if the patient is immunosuppressed.[10,29,38] Liposomal amphotericin B, azole antifungal agents, and combinations of antifungal agents will also probably prove useful in the treatment of invasive fungal sinusitis.[39] The liposomal forms of amphotericin B appear to have greater effectiveness and lower toxicity. Azole antifungal agents lack activity against Mucorales species. The combination of surgical and antifungal treatment has a cure rate of 30 to 80 percent; the lowest rate of cure is associated with intracranial involvement.[40] In immunosuppressed patients who respond to initial treatment, frequent endoscopic evaluation with biopsies and cultures, periodic computed tomographic imaging, and protracted antifungal therapy are usually required. Close collaboration between medical and surgical specialists is essential in the care of these patients.

Granulomatous Invasive Fungal Sinusitis

Primary paranasal granuloma is a curious syndrome of chronic sinusitis associated with proptosis that has been also called indolent fungal sinusitis.[41,42] Reports of this condition have come primarily from Sudan, but also from India, Pakistan, and the United States.[43,44] Patients appear to be immunocompetent and are infected almost exclusively with *A. flavus*. There is profuse fungal growth with regional tissue invasion, noncaseating granulomas with giant cells, and plasma cells. Central microgranulomata of eosinophils, fibrinoid necrosis, fibrosis, and vasculitis have also been noted.[45] Unless removed surgically, the resulting fibrous fungal mass may spread into the orbit, dura, and brain. Treatment with itraconazole at a dose of 8 to 10 mg per kilogram per day appears to decrease the high postoperative relapse rate.[46]

Chronic Invasive Fungal Sinusitis

Chronic invasive fungal sinusitis can be distinguished from the other two forms of invasive fungal sinusitis by its chronic course, dense accumulation of hyphae resembling a mycetoma, and association with the orbital apex syndrome, diabetes mellitus, and corticosteroid treatment. The orbital apex syndrome is characterized by decreasing vision and ocular immobility resulting from a mass in the superior portion of an orbit.[47-49] The mass results from bony erosion and the spread of fungal material from an ethmoid sinus.[5] The condition may be misdiagnosed as inflammatory pseudotumor, and corticosteroid therapy may be initiated before appropriate orbital exploration and biopsy are performed. Biopsy and orbital exploration show vascular invasion by fungal elements and only a sparse chronic inflammatory infiltrate. Involvement of the cavernous sinuses often leads to death (Fig. 1). The condition may begin as a sinus mycetoma and become invasive, perhaps as a result of the immunosuppression associated with diabetes mellitus or corticosteroid treatment. The poor prognosis of this condition suggests that it should be treated as aggressively as acute (fulminant) invasive fungal sinusitis.

CONCLUSIONS

Fungal infection should be considered in all patients with chronic sinusitis. Early diagnosis of noninvasive fungal sinusitis may prevent multiple surgical procedures and lead to effective treatment. Invasive fungal sinusitis should be suspected in immunocompromised patients with acute sinusitis, inflammation of nasal septal mucosa, unexplained fever or cough, or the orbital apex syndrome. All three forms of invasive fungal sinusitis are associated with reasonable rates of response if diagnosed and treated early.

Clarification of the classification of these syndromes and the criteria for their diagnosis should facilitate the clinical trials necessary to establish appropriate treatment. The most immediate need is to establish the respective roles of surgery and antifungal therapy. Clinical trials are under way to compare the efficacy of the newer forms of amphotericin B, azole antifungal agents, other antifungal agents, and biologic-response modifiers with amphotericin B deoxycholate, which is currently the gold standard of treatment.[50]

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the study by Yağcıoğlu et al., this study does not suggest that the negative findings of the Honer study resulted from an inadequate dose of risperidone. I apologize for my mistake. I found no evidence of bias in terms of pharmaceutical-industry sponsorship on the efficacy data from the randomized, controlled trials comparing second-generation with first-generation antipsychotic agents. All these drugs are effective, but randomized, controlled trials establish clozapine as the most efficacious.[1,2] However, the initial European experience found clozapine associated with agranulocytosis in about 1 to 2 percent of the patients (one third of cases were fatal). I agree with Dr. Gerson's conclusions. Mandatory monitoring of white-cell counts does indeed greatly minimize the risk of this complication.

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Hypertonic Saline for Cystic Fibrosis

TO THE EDITOR: We question the selection by Elkins et al.[1] and Donaldson et al.[2] (Jan. 19 issue) of 7 percent hypertonic saline, which can result in bronchoconstriction, in these studies of therapy for cystic fibrosis. Elkins et al. report a fall of 94 ml in the forced expiratory volume in one second (FEV_1) after the first dose of medication, which is greater than the reported final improvement in FEV_1 of 68 ml. Conversely, Donaldson et al. do not specify any change in FEV_1 with the use of 7 percent hypertonic saline. Robinson et al.[3] have compared mucociliary clearance with the use of different concentrations of hypertonic saline and did not find any difference in efficacy between solutions of 3 percent and 7 percent hypertonic saline solutions. We have shown that the use of 3 percent hypertonic saline is effective and has the additional advantage of not causing a substantial change in FEV_1, oxygen saturation, or symptom score.[4] Hence, the choice of the strength of the hypertonic saline solution administered should be based on the potential effects of hypertonic saline on pulmonary function, oxygen saturation, palatability, and the patient's preference.

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TO THE EDITOR: Donaldson and colleagues report that hypertonic saline after pretreatment with amiloride did not result in a sustained increase in mucus clearance or improvement in lung function or respiratory symptoms because of inhibition of apical membrane water permeability. Animal airways have a moderate osmotic water permeability and express aquaporin water channels, one of which is aquaporin-3.[1-3] In Table 1 of their article, the authors report that 50 percent of the patients in each of the two study groups received inhaled steroids concomitantly. Corticosteroids have been found to induce the expression of aquaporin-3 in A549 cells, a human airway epithelial-cell line derived from lung adenocarcinoma, in vitro.[3] In addition, hypertonicity induces the expression of aquaporin-3 in Madin–Darby canine-kidney cells, a renal epithelial-cell line, in vitro.[4] Perhaps patients receiving concomitant treatment with inhaled steroids should have been studied separately, in order to identify the possible contribution of aquaporin-3 overexpression to hypertonic saline treatment.

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TO THE EDITOR: The importance of the volume of the airway surface liquid in the pathophysiology of cystic fibrosis lung disease is supported by the findings of Elkins et al. and Donaldson et al. As pointed out in the accompanying editorial by Ratjen,[1] the mechanism of the prolonged action of inhaled hypertonic saline remains to be elucidated. We suggest that one mechanism pertains not to the volume of the airway surface liquid but, rather, to the effect of sodium ions on the viscosity of the mucus gel. Studies of gastrointestinal mucins have shown that calcium is the main cation that binds to mucins; the interaction increases the viscosity of the mucus gel.[2] Calcium binding to mucin is displaced by hypertonic sodium chloride.[3] Whether these observations pertain to airway mucins in patients with cystic fibrosis requires further investigation. Since mucus hyperviscosity has been implicated in the intestinal, hepatobiliary, and pancreatic manifestations of cystic fibrosis, hypertonic saline might be useful for the prevention of complications in these organs as well.

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DRS. BYE AND ELKINS REPLY: Drs. Aziz and Kastelik question the selection of a concentration higher than 3 percent in our phase 3 trial of inhaled hypertonic saline for cystic fibrosis. On the basis of the single-intervention studies they cite, we agree that a single dose of 3 percent saline increases the weight of sputum expectorated and improves mucociliary clearance to a degree similar to 7 percent saline. However, the primary outcome of our trial was lung function, which was chosen because it correlates with mortality in patients with cystic fibrosis.[1] When designing the trial, we therefore also considered the data from phase 2 trials that examined the effect of the regular use of hypertonic saline on lung function. We were unable to find evidence of an improvement in lung function with 3 percent saline. At higher concentrations, however, there was evidence of a benefit in both mucociliary clearance and lung function.[2] Our observations that 7 percent saline did not result in excessive side effects in clinical practice and in previous trials were supported by others.[3] We therefore chose 7 percent saline as the intervention for our trial. Further studies comparing various concentrations, as well as dosages and delivery systems, would help to refine the treatment protocol.

Drs. Aziz and Kastelik also express concern that the 94-ml fall in FEV_1 after the first dose of hypertonic saline was greater than the final improvement in FEV_1, of 68 ml. As stated in the article, premedication with a bronchodilator resulted in a 60-ml improvement in FEV_1 that limited the effective fall from baseline. We also stated that the final improvement of 68 ml was relative to baseline. Thus, any initial fall in FEV_1 was recovered, and then an additional average improvement of 68 ml was achieved.

Drs. Kuver and Lee suggest that a possible mechanism of action of hypertonic saline in the lungs is the effect of sodium ions on the viscosity of the airway mucus gel. Other authors have examined this possibility, as mentioned in our article and as reviewed more comprehensively by King.[4] Our trial did not provide any data to indicate whether hypertonic saline would have an effect on mucins from other organs.

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DR. DONALDSON AND COLLEAGUES REPLY: Mr. Zarogiannis et al. point out that corticosteroids and hypertonicity up-regulate aquaporin-3 and speculate that the use of inhaled corticosteroids could have influenced responses to amiloride, hypertonic saline, or both. Because the effect of amiloride on water transport was discovered only after the completion of our clinical trial, we neither excluded nor studied separately patients receiving inhaled corticosteroids. Reassuringly, inhaled corticosteroid use was balanced in the randomized groups, and all subjects were exposed to hypertonic saline, making it unlikely that an effect on aquaporin-3 greatly influenced the trial outcomes. Finally, recent in vitro experiments in our laboratory (unpublished data) suggest that water transport by means of aquaporin-3 is not attenuated by amiloride.

Drs. Aziz and Kastelik question the selection of 7 percent (as compared with 3 percent) saline. They refer to their own study, which reported safety with a single dose of 3 percent saline used for sputum induction. Because the mass of salt deposited on airway surfaces determines the magnitude of the increase in the volume of airway surface liquid, we sought to use the highest concentration of hypertonic saline that would be safe and well tolerated. Robinson et al.[1] provided good evidence for a dose–effect relationship between hypertonic saline and mucociliary clearance, despite the absence of a significant difference between the 3 percent and 7 percent groups. Twelve percent saline was poorly tolerated, however, because of oropharyngeal irritation. Therefore, 7 percent saline was selected on the basis of the study by Robinson et al. and other short-term studies of hypertonic saline in cystic fibrosis. In our study, we report FEV_1 values at two hours after administration of the first dose of hypertonic saline — values that, in fact, increased from baseline, further supporting the assertion that 7 percent saline is well tolerated in patients with cystic fibrosis.

Drs. Kuver and Lee propose an alternative mechanism linking the use of hypertonic saline and stimulated mucociliary clearance. Displacement by sodium of the calcium ions that bind mucins is postulated to explain the expulsion of mucins during exocytosis, and may influence the rheologic properties of mucus once secreted.[2] In fact, we did invoke the "electrostatic effects" of hypertonic saline to explain acutely stimulated mucociliary clearance after amiloride plus inhalation of hypertonic saline, because in vitro data suggested that little increase in airway surface liquid volume occurs in this situation because amiloride blocks water transport. During treatment with hypertonic saline without amiloride, however, isotonicity is restored rapidly (in approximately two minutes) in the airway lumen,[3] suggesting that both the acute and the sustained effects on mucociliary clearance of placebo or hypertonic saline were due to improved hydration of secretions, rather than to the persistence of a high salt environment.

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DR. RATJEN REPLIES: Drs. Kuver and Lee propose that the beneficial effect of inhaled hypertonic saline in cystic fibrosis may be due to the displacement by sodium of calcium ions bound to mucins, thereby reducing the viscosity of airway mucus. Hypertonic saline has indeed been shown to improve sputum rheology, and it is conceivable that changes in mucin ion composition contribute to this finding.[1] However, changes in the mechanical properties of mucus would not explain the prolonged effect of hypertonic saline on airway surface liquid height in vitro, since these experiments were performed in the absence of a mucus layer. In addition, agents that merely change the rheology of airway secretions do not affect mucociliary clearance in cystic fibrosis. This is highlighted by studies with recombinant human DNase, which reduces sputum viscosity but, unlike hypertonic saline, does not increase mucociliary clearance.[2,3] These observations would therefore support the concept that hypertonic saline, rather than acting primarily as a mucolytic agent, improves mucociliary clearance through an increase in airway surface liquid height.

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Illness in Returned Travelers

TO THE EDITOR: Freedman et al. (Jan. 12 issue)[1] has called attention to hazards for travelers. As the authors state, the study does not reflect the full epidemiology of travelers' diseases. There is a great danger that patients and practitioners who anticipate and strive to prevent the serious threats to health for travelers will mistakenly consider only infectious diseases. Physicians advising patients who are planning travel to tropical countries must warn them of the real burden of illness: premature death from injury.

In earlier studies of deaths of Americans overseas, some 10,000 deaths were analyzed according to cause, age, and place of occurrence.[2,3] There were 601 deaths from injuries and only 25 deaths caused by infectious diseases. Death rates from injuries in developing countries were considerably higher than those in the United States. Similar findings came from an earlier study involving Peace Corps volunteers.[4]

Travel clinics would be seriously remiss if they did not counsel travelers on the dangers of injuries. Advice to avoid motorcycles, small vehicles, unscheduled aircraft, and swimming in unfamiliar waters is essential to help protect travelers.[5]

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THE AUTHORS REPLY: We concur with the point made by Bishai and Baker. The literature indicates that about 25 percent of overseas deaths are from injury, with the remainder largely from natural causes.[1,2] MacPherson et al. estimated that about 36 percent of all overseas deaths are preventable.[1] As travel patterns have changed and adventure travel has increased, new studies are needed. An unanswered question is whether the risk of dying from causes other than natural ones while traveling overseas is different from that while staying home.

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Unprofessional Behavior among Medical Students

TO THE EDITOR: The real shocker in the report by Papadakis et al. (Dec. 22 issue)[1] regarding disciplinary action by medical boards is the enormous prevalence of unprofessional behavior among medical students in the control group (nearly 20 percent). If unprofessional students become unprofessional doctors, then we face a real crisis, with huge numbers of unprofessional physicians currently in practice.

Medical students are reflective of society at large. Lack of professionalism among medical students is hardly surprising when high schools

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Pediatric chronic rhinosinusitis

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Abstract

Purpose of review: Pediatric sinusitis is prevalent, and the debate continues regarding how best to care for these children. Although acute sinusitis is commonly associated with an upper respiratory infection, the focus of this paper is on chronic rhinosinusitis in children. Research is often more difficult in children than adults, so many times one can learn from the adult literature and determine whether there can be application to the childhood population.

Recent findings: This paper looks at both medical and surgical treatment of chronic rhinosinusitis. Maximal medical management is often cited in the literature, but what this should consist of has never been clearly proved in the literature. Alternative medicine approaches as well as irrigation as an adjunct to care are discussed. Biomaterials are also be discussed. Recent outcome data are put in perspective.

Summary: Hopefully the reader will find the presentation stimulating. The paper does not promote surgery as a cure all, and in the end, analysis will hopefully leave the reader more cautious but with a better understanding of this complex disease.

REVIEW

Relation Between Rhinosinusitis and Bronchiectasis

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The nose and lungs have both histological and functional similarities and differences. Sinonasal and bronchial involvement are associated in many diseases. Cystic fibrosis, primary ciliary dyskinesia, Young's syndrome, and α-1 antitrypsin deficiency are diseases in which bronchiectasis and rhinosinusitis are both present. This review considers the diseases in which bronchiectasis occurs along with sinonasal manifestations. We propose examining sinonasal disease from a new perspective by observing it in patients with bronchiectasis.

Key words: *Rhinitis. Sinusitis. Bronchiectasis.*

Relaciones entre rinosinusitis y bronquiectasias

La nariz y el bronquio presentan similitudes y diferencias tanto histológicas como funcionales. Son muchas las enfermedades en que se asocian la afección nasosinusal y la bronquial. La fibrosis quística, la discinesia ciliar primaria, el síndrome de Young y el déficit de alfa-1-antitripsina son enfermedades en las que se asocian bronquiectasias y rinosinusitis. En este artículo se realiza una revisión de las bronquiectasias y de las enfermedades que las asocian junto a afección nasosinusal. El propósito es dar un nuevo enfoque de la patología nasosinusal observada en los pacientes afectados de bronquiectasias.

Palabras clave: *Rinitis. Sinusitis. Bronquiectasias.*

Introduction

Diseases that until recently were regarded as exclusively pulmonary or bronchial are increasingly being shown to occur in association with nasal and paranasal disease. The concept of rhinobronchitis has introduced the idea that the upper and lower airways are in fact a single airway and that diseases affect the whole respiratory system.[1] Many epidemiological studies have examined and confirmed this association, giving rise to the concept of "one airway, one disease," (Figure). The clearest example of this association is with rhinitis and asthma[2]; most asthmatics present both disorders and the treatment of rhinitis can be beneficial for asthma.[3]

The upper and lower respiratory airways have the common function of conditioning and channeling external air into the lungs. Within this shared function there are specific functions performed by different sections: humidifying, heating, filtering, phonation, and gas interchange.[4]

Nasal and Bronchial Mucosa

The epithelium and lamina propria of the nasal and bronchial mucosa are similar. A major function of the nose is to filter out harmful substances, both infectious and noninfectious ones. The nose also conditions inspired air, heating and humidifying it. The function specific to the nose and that most distinguishes it from the lower airways is, without doubt, olfaction, involving the pituitary gland, and located in the roof of the nasal cavity.[5]

The squamous epithelium of the nasal valve is transformed in the rest of the nose into a ciliated pseudostratified columnar respiratory epithelium. In the nose this columnar epithelium is formed by ciliated, nonciliated, basal, and goblet cells, and it differs from the epithelium of the lower airway by the absence of serous cells, Clara cells, or brush cells.[6] The basement membrane is composed of type IV collagen, proteoglycans, laminin, and fibronectin. The lamina reticularis is found below the membrane and is evenly thicker in asthmatic patients.[7] Focal thickening of the membrane is observed in patients with bronchiectasis, tuberculosis, and chronic rhinosinusitis[8] but no changes in this part of the structure have been observed in patients with rhinitis.[9]

In the submucosa, there are glands, blood vessels, nerves, extravascular cells, and extracellular matrix. One of the major structural differences is found here: the bronchial submucosa has smooth muscle whereas the nasal submucosa does not.[6]

Glands and blood vessels predominate in the nose. Apart from arterial vessels, nasal vasculature is formed by capillary beds, arteriovenous shunt, sinusoids, and venous vessels. The veins that drain the sinusoids have

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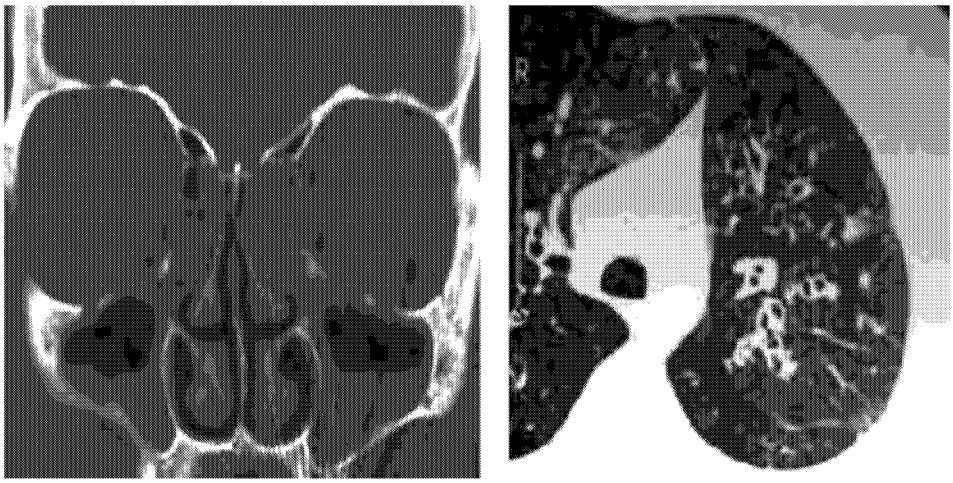

Figure. Chronic rhinosinusitis in the bilateral maxillary ethmoidal region (computed tomography scan of the sinus) beside a bilateral bronchiectasis (lung scan) in the same patient.

smooth muscle. When the veins contract, the sinusoids expand, increasing the size of the turbinates (erectile tissue), facilitating nasal flow. This does not occur in the bronchi where smooth muscle contraction increases flow resistance.

Mucociliary Transport

The mucociliary system is formed by many cilia, which protrude from the surface of the pseudostratified columnar epithelial cells. Each ciliated cell contains about 200 to 300 cilia which beat about 500 times per minute. Beat frequency decreases distally,[10] so frequency is lower in middle airways. Malfunction in this zone can lead to pooling of secretions and predisposition to local infections, possibly contributing to the development of bronchiectasis in this part of the respiratory airways.[11] Ultrastructural abnormalities in the cilia interfere with and prevent normal motility predisposing an individual to chronic and recurrent nose and sinus infections (chronic rhinosinusitis) and lung infections that lead to bronchiectasis.

Approximately 70% to 80% of asthma patients present rhinitis and recent studies have shown rhinitis to be a predisposing factor of asthma.[12] This has led to the performance of studies that aim to prevent asthma by providing early treatment of rhinitis.

Nasal polyposis is detected in 2% to 4% of the population but the prevalence rises to 7% among asthmatic patients. Polyposis is uncommon among patients with mild asthma but as the severity of the disorder increases, sinus infections and polyps become much more common to the extent that it is unusual to find a patient with asthma and intolerance to aspirin who does not have nasal polyposis.[13]

Relation between chronic obstructive pulmonary disease (COPD) and rhinitis has also been observed.[14] Biopsies of nasal mucosa in COPD patients have been found to contain similar inflammatory abnormalities to those of bronchial biopsies in the same patients.[15]

The association between respiratory symptoms and anterior and posterior rhinorrhea, adenoids, nasal congestion, and loss of smell reinforces the concept that upper and lower respiratory airways are related.[16]

Bronchiectasis

Bronchiectasis is the abnormal dilatation and destruction, permanent and irreversible, of one or more medium or small bronchi (from the fourth to the ninth generation), produced by the destruction of the muscular and elastic components of the bronchial wall. The prevalence in the general population is unknown and the natural history of the condition has not been studied from the beginning of the process and with posterior analysis of its progression.[17]

Laennec[18] first described bronchiectasis in 1819, noting that it was caused by the retention of bronchial secretions with secondary destruction of the wall and posterior weakening and dilatation of the same. This interpretation is still valid and bronchial inflammation is thought to play a central role. After contrast bronchography was introduced by Sicard in 1922, bronchiectasis could be seen with more precision.[19]

Etiology and Pathogenesis

Bronchiectasis is not a single disease but rather the result of the damage that can be caused by several different processes acting on the bronchial wall and which can interfere directly or indirectly with its defenses. Bronchiectasis can be diffuse or focal. Medium sized bronchi are usually dilated but often small bronchi can be enlarged or destroyed too. Sections of bronchial wall are destroyed and chronically inflamed, ciliated cells are damaged or destroyed, and mucus production is enhanced, the normal tone of the wall being lost. Increased mucus production encourages bacterial growth, obstructs the bronchi, and leads to pooling of infected secretions, with subsequent damage to the bronchial

wall.[20] The inflammation can spread to the alveoli and produce bronchopneumonia, formation of scar tissue, and loss of healthy lung tissue. Moreover, inflammation of the blood vessels in the bronchial wall can cause blood-stained sputum or frank hemoptysis. Examination by the pathologist reveals bronchial dilatation, mucosal hypertrophy sometimes with squamous metaplasia, lymphocytic infiltrates in the bronchial wall, and loss of cartilage, muscle, and elastic fibers—these last structures being replaced by scar tissue.[21]

Focal bronchiectasis is usually caused by stenosis of some bronchi through inflammatory processes, neoplasms, or foreign bodies.[22] Any circumstance that produces absorption collapse in the zone and fibrosis of the adjacent lung tissue contributes to the formation of bronchiectasis through compensatory dilatation of the bronchi.

Diffuse bronchiectasis has many possible causes (Table), in particular congenital diseases, which affect mucociliary function and include cystic fibrosis and dyskinesia (Kartagener's syndrome, Young's syndrome). It can also be associated with defects in defense mechanisms, which can lead to recurrent bronchial infections (common variable immunodeficiency, defective antibody formation). Some bronchiectases seem to have developed from infectious bronchiolitis in childhood (measles, syncytial respiratory virus). Bronchiectasis can also be associated with systemic diseases (rheumatoid arthritis, Sjögren syndrome) or inflammatory intestinal diseases (ulcerous colitis, Crohn's disease). In a few cases it is the consequence of aspiration of toxic substances, which damage the bronchi.

Bronchiectasis is classified into 3 types according to shape: cylindrical, varicose, and saccular (the last 2 tend to be clinically more severe).

Biopsy of the bronchial mucosa reveals infiltration by neutrophils and T lymphocytes,[21] as well as an increase in the elastase content of the sputum[23] and an increase in the interleukin-8 concentrations,[24] tumor necrosis factor-α,[25] and prostanoids.[26]

The most common complication of bronchiectasis is recurrent infection,[27] usually by *Haemophilus influenzae* (55%) and *Pseudomonas* species (26%).[28] Less common infectious agents are metastatic abscesses, mainly in the central nervous system (12%-16%), and amyloid type AA accumulations (6%). Other complications are pulmonary hypertension and chronic cor pulmonale. In saccular bronchiectasis, clubbing of the fingers is often found.

Clinical Manifestations

Although bronchiectasis can occur at any age, it usually starts in the first 20 years of a patient's life. The symptoms may not appear until much later or never, in some cases a radiologic diagnosis is made while the bronchiectasis is still asymptomatic. Common signs are cough with abundant expectoration (bronchorrhea), which is occasionally blood-stained. The quantity and type of sputum depends on the extent of the disease and the presence of an active infection. In some cases massive hemoptysis can occur. Pneumonia is relatively common and, in some patients, recurrent. Diffuse bronchiectasis can cause respiratory failure, pulmonary hypertension, and cor pulmonale.[29]

Diagnosis

Diagnosis is made on clinical and radiological evidence. A simple chest x-ray may show images such as tram lines, cysts, and bronchi filled with mucus (gloved fingers image) all of which are indicative of bronchiectasis although more often images are normal or show nonspecific signs such as an increase in bronchovascular markings. Nowadays, computed tomography (CT) of the chest allows certain diagnosis at the same time as it determines the location and extension of disease.[30] Since the introduction of CT, bronchography is no longer used in the diagnosis of bronchiectasis.

Lung function testing can reveal varying degrees of obstruction according to the extent of the disease, although mixed patterns are often seen, caused by loss of volume through the collapse of some lobes associated with the obstruction. Impaired gas exchange due to the existence of shunt zones can cause severe hypoxemia.[31]

Treatment

The main objective of treatment is to control infections and secretions and thus avoid airway obstruction and its complications. Effective respiratory physiotherapy is essential to expel the bronchial secretions. The reduction of some childhood viral

TABLE
Etiology of Bronchiectasis

Focal Bronchiectasis
Bronchial obstruction: foreign body aspiration, diseased lymph nodes, lung tumors, and mucus plug
Diffuse Bronchiectasis
Congenital: primary ciliary dyskinesia (Kartagener's syndrome), cystic fibrosis, α_1-antitrypsin deficiency, tracheobronchomegaly (Mounier-Kühn syndrome), cartilage deficiency (Williams-Campbell syndrome), Marfan syndrome, and pulmonary sequestration
Postinfectious: viral (paramyxovirus, adenovirus, influenza virus, human immunodeficiency virus); bacterial (*Haemophilus, Pseudomonas, Klebsiella, Staphylococcus, Bordetella, Mycobacterium [M tuberculosis], Mycoplasma [M pneumoniae]*); and fungal (*Aspergillus*)
Immune system disorders: primary (hypogammaglobulinemia, complementary deficiencies) and secondary (chronic lymphocytic leukemia, chemotherapy)
Toxic: inhalation of noxious fumes, aspiration of gastric content.
Systemic diseases: rheumatoid arthritis, systemic lupus erythematosus, Sjögren syndrome, recurrent polychondritis.
Others: inflammatory intestinal diseases (ulcerative colitis, Crohn's disease), yellow nail syndrome.

infections through vaccination has lowered the risk of bronchiectasis. Vaccination against pneumococcus and *Haemophilus* species and the annual influenza vaccination very likely reduce the number of serious infectious episodes.[32]

Diseases That Lead to Bronchiectasis and Associated Nasal Disease

Cystic Fibrosis

Cystic fibrosis is an autosomal recessive genetic disorder found above all among Caucasian peoples. One in 25 individuals carries the gene.[33,34] It is estimated to affect about 1 in every 3000 to 10 000 live births per year. The gene responsible for cystic fibrosis is found in a simple locus on the long arm of chromosome 7. The deletion of 3 pairs of bases or mutation delta F508 occurs in about 70% of all cystic fibrosis chromosomes. The defective protein—the cystic fibrosis transmembrane regulator—codified by this abnormal gene has a structure similar to that of a class of proteins known for being active in epithelial transport.[35] The defective protein contributes to the poor function of the chloride channels, causing an increase in mucus viscosity, which makes its elimination difficult and encourages the colonization of *Staphylococcus aureus* and mucoid *Pseudomonas aeruginosa.*

Many other mutations have been identified near the locus involved. Patients with cystic fibrosis present recurrent infections in the respiratory tract, pancreatic exocrine insufficiency, and infertility. In the early stages, chest x-rays show upper lobe involvement,[36] which spreads as the disease progresses. Lung function can be normal or display an obstructive or mixed pattern. Adult patients have often had symptoms of the disease for many years but, because they were moderate, they went unnoticed. Adults may present bronchiectasis, rhinosinusitis, pancreatic failure, acute pancreatitis, cholelithiasis, and infertility. Nasal obstruction is the most common symptom among cystic fibrosis patients, and more than 20% present nasal polyposis. There are several patterns of rhinosinusitis: nasal polyposis, chronic purulent nasal and sinus infection, and pyogenic mucus impaction of the maxillary antrum with bulging of the lateral nasal wall; this last type has been called maxillary pseudomucocele.[37] The sweat test is important in diagnosis,[38] as sodium or chloride concentrations are 60 mmol/L in cystic fibrosis patients whereas healthy individuals and cystic fibrosis gene carriers have concentrations of 30 mmol/L. Also important are genotyping and pulmonary and sinus CT. The treatment objectives are to reduce obstruction, control infections,[39] reduce inflammation, and improve nutritional status. Nasal treatment consists of lavage with saline solution, intranasal corticosteroid therapy, antibiotic therapy, and, when necessary, functional endoscopic surgery on the sinuses.

Primary Ciliary Dyskinesia

Primary ciliary dyskinesia (PCD) is a congenital disease which affects, totally or partially, the function of the ciliated cells.[40] It is an autosomal recessive disorder, which affects 1 in every 16 000 live births and presents clinically as rhinosinusitis, bronchiectasis, and less often, sterility among men. In the primary ciliary dyskinesia syndrome (dyskinesia refers to difficulty of movement) there is structural and functional impairment in the cilia microtubules, which are responsible for motility. This dysfunction prevents the cilia from clearing the mucus, causing purulent bronchial infections and bronchiectasis. All ciliated structures can be involved: epithelia of the respiratory airways, paranasal sinuses, the eustachian tube, and spermatozoids (asthenospermia).[41]

About 50% of patients present Kartagener's syndrome, characterized by the triad of bronchiectasis, rhinosinusitis, and situs inversus (dextrocardia).[42,43] Rhinitis with anterior rhinorrhea is found in all PCD patients, accompanied in some by nasal polyps and the reduction or complete loss of the sense of smell. A sinus CT scan often shows invasion of ethmoidal and maxillary sinuses, together with hypoplasia of the frontal sinus. Diagnosis is based on a battery of tests: saccharin time, nasal nitric oxide, and nasal biopsy in which ciliary beat and density is observed with an electronic microscope.[44] The mainstays of PCD treatment are respiratory physiotherapy with postural drainage and antibiotic therapy for exacerbations of respiratory infections. Endoscopic polypectomy or functional surgery of the sinuses is beneficial in patients with chronic rhinosinusitis which does not respond to treatment.

Diagnosis is established by the study of the ultrastructure of nasal mucosal samples, in which absence of the dynein arms or abnormal position of the microtubules can be seen. Recent studies have shown low concentrations of nasal nitric oxide in those patients.[45]

Young's Syndrome

Young's syndrome is characterized by the triad of bronchiectasis, chronic rhinosinusitis, and infertility. Patients present normal ciliary activity and highly viscous mucus. Nasal biopsy material does not show changes in ciliary structure under an electronic microscope.[46] The azoospermia causes infertility by obstructing the epididymis, although spermatogenesis is completely normal. Diagnosis is based on clinical signs (chronic sinopulmonary disease, azoospermia), and the exclusion of cystic fibrosis and immotile-cilia syndromes.[47]

α_1-Antitrypsin Deficiency

α_1-antitrypsin, a glycoprotein produced by liver cells, inhibits proteases (elastase), particularly those released by neutrophils while repairing and cleaning agents

outside the lung. The inhibition of proteases prevents the destruction of healthy tissue in the organism.[48] The codifying gene is located on chromosome 14. α_1-antitrypsin deficiency of the lung produces emphysema by progressively destroying the alveoli in individuals aged 30 to 50 years. Tobacco smoke contributes to lung destruction by increasing elastase activity, decreasing α_1-antitrypsin activity by oxidation, and stopping elastin synthesis, preventing lung repair. Cessation of smoking should consequently be high priority for patients diagnosed with α_1-antitrypsin deficiency.[49]

Emphysema produced by α_1-antitrypsin deficiency is panacinar, destroying the entire acinus, and is usually found in the bases. Lung compliance increases. Reduction of α_1-antitrypsin concentrations produces an imbalance between this protein, an antiprotease, and elastase, a protease. α_1-antitrypsin deficiency enables elastase to progressively destroy the elastin in the alveolar walls.[50] Normal rates of α_1-antitrypsin protein in blood are considered to be between 150 and 350 mg/dL or 20 and 53 μM and at concentrations of less than 80 mg/dL or 11 μM there is risk of developing one of the deficiency diseases.[51] The second most affected organ is the liver, especially in newborn babies and children. Patients present a history of α_1-antitrypsin deficiency or lung disease including emphysema, chronic bronchitis, bronchiectasis, asthma resistant to treatment, and recurrent pneumonia. Quantitative α_1-antitrypsin measurement is recommended in patients with precocious emphysema, a family history of the condition, dyspnea or cough in several members or generations of the same family, adults with bronchiectasis of unknown etiology, obstructive pulmonary disease, liver disease of unknown origin, asthma which does not respond to treatment, and panniculitis of unknown origin.[52] Allergic rhinitis and recurrent rhinosinusitis are also common even in the absence of obstructive pulmonary disease.[53]

Conclusions

Consistent with the concept of "one airway, one disease," bronchiectasis patients often present sinonasal involvement. The prevalence of the association is not known as systematic studies have not been carried out. It is not known, for example, whether the microbes which colonize the lower airways are responsible for the nasal process or whether the characteristics of the lower airway inflammatory process are similar to nasal and sinus processes. Given that the nose is more accessible for examinations (endoscopy, biopsy, nasal secretion collection) compared to the lower airways, which must be examined by fiberoptic bronchoscopy, monitoring the nose might offer an easier and less invasive way to follow lung disease progression. The treatment of allergic rhinitis and nasal polyposis has been shown to improve asthma progression, but it is not known if there is a similar relation between sinusitis and bronchiectasis. Demonstrating the similarity of infectious and inflammatory processes in the upper and lower airways of patients with bronchiectasis would allow studies to be performed to clarify the mechanisms responsible for the origin of this disease.

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Nonpathogenic, Environmental Fungi Induce Activation and Degranulation of Human Eosinophils[1]

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Eosinophils and their products are probably important in the pathophysiology of allergic diseases, such as bronchial asthma, and in host immunity to certain organisms. An association between environmental fungal exposure and asthma has been long recognized clinically. Although products of microorganisms (e.g., lipopolysaccharides) directly activate certain inflammatory cells (e.g., macrophages), the mechanism(s) that triggers eosinophil degranulation is unknown. In this study we investigated whether human eosinophils have an innate immune response to certain fungal organisms. We incubated human eosinophils with extracts from seven environmental airborne fungi (*Alternaria alternata, Aspergillus versicolor*, *Bipolaris sorokiniana*, *Candida albicans*, *Cladosporium herbarum*, *Curvularia spicifera*, and *Penicillium notatum*). *Alternaria* and *Penicillium* induced calcium-dependent exocytosis (e.g., eosinophil-derived neurotoxin release) in eosinophils from normal individuals. *Alternaria* also strongly induced other activation events in eosinophils, including increases in intracellular calcium concentration, cell surface expression of CD63 and CD11b, and production of IL-8. Other fungi did not induce eosinophil degranulation, and *Alternaria* did not induce neutrophil activation, suggesting specificity for fungal species and cell type. The *Alternaria*-induced eosinophil degranulation was pertussis toxin sensitive and desensitized by preincubating cells with G protein-coupled receptor agonists, platelet-activating factor, or FMLP. The eosinophil-stimulating activity in *Alternaria* extract was highly heat labile and had an M_r of ~60 kDa. Thus, eosinophils, but not neutrophils, possess G protein-dependent cellular activation machinery that directly responds to an *Alternaria* protein product(s). This innate response by eosinophils to certain environmental fungi may be important in host defense and in the exacerbation of inflammation in asthma and allergic diseases. *The Journal of Immunology,* **2005, 175: 5439–5447.**

Eosinophils are implicated in the pathophysiology of allergic diseases, such as bronchial asthma and atopic dermatitis, and in host immunity to helminth infections (1). During such inflammatory reactions, soluble mediators released by immune cells induce eosinophil recruitment from the bloodstream into sites of inflammation, where as yet unknown stimuli trigger the release of eosinophil granule proteins (2). Eosinophil granule major basic protein (MBP)[3] and eosinophil peroxidase are toxic to respiratory epithelial cells, pneumocytes, and tracheal epithelium in vitro (3–6). MBP augments the contraction of tracheal smooth muscle induced by acetylcholine in vitro (7), and instillation of MBP causes airway hyper-responsiveness in primates (8). These observations suggest potential roles for these proteins in the pathophysiology of human diseases related to eosinophils. Indeed, marked extracellular deposition of released eosinophil granule proteins is found in specimens from patients who died of asthma and patients with chronic rhinosinusitis and atopic dermatitis (9–11). However, the presence of eosinophils per se, as in normal intestinal mucosa (12), does not lead to disease pathology. Thus, a fundamental and important question still remains: what triggers eosinophil activation and proinflammatory mediator release in human disease?

Unlike mast cells and basophils, there is no or only minimal surface expression of FcϵRI in eosinophils, and eosinophil mediator release is not triggered through the IgE/FcϵRI interaction (13, 14). In vitro, eosinophil degranulation follows engagement of the IgG and IgA receptors and follows stimulation with soluble inflammatory mediators such as IL-5, GM-CSF, RANTES, eotaxin, IFN-γ, platelet-activating factor (PAF), C5a, and plasma-activated zymosan (15–21). It is not known whether these factors are responsible for eosinophil mediator release in vivo.

Fungi are ubiquitous in the environment, and as saprophytes or commensals, they may coexist without effect in the host with normal cellular immunity (22). Nonetheless, these airborne fungi and their products may contribute to the development and exacerbation of allergic airway diseases. For example, fungal products, e.g., proteins, induce immunologic and inflammatory reactions, resulting in a Th2-like cytokine response and the destruction of mucosal barrier functions (23–25). Clinically, an association between fungal exposure and asthma has been widely recognized (26). Increased spore counts and fungal Ag levels correlate with allergic symptoms (27–29). Moreover, exposure to *Alternaria* is a risk factor for respiratory arrest in patients with asthma (30). The general consensus at present is that Th2 cell-dependent, Ag-mediated immune responses are probably central mechanisms directing eosinophilic inflammation and disease exacerbations in these conditions. However, direct activation of eosinophils by fungal products may provide another explanation.

In this study we hypothesized that when eosinophils recognize the products of certain common environmental fungi, these cells

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[3] Abbreviations used in this paper: MBP, eosinophil granule major basic protein; $[Ca^{2+}]_i$, intracellular concentration of Ca^{2+}; EDN, eosinophil-derived neurotoxin; PA, protease activated; PAB, PBS containing 0.1% NaN_3 and 1% BSA; PAF, platelet-activating factor; PAR-2, protease-activated receptor 2; PTX, pertussis toxin.

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release their inflammatory mediators. Our results suggest that eosinophils, but not neutrophils, are equipped with innate cellular activation machinery that responds to the products of *Alternaria* and *Penicillium.* Exposure of humans to and subsequent activation of eosinophils by these common environmental fungi may provide an important mechanism for exacerbation of eosinophil-related airway disorders, such as asthma.

Materials and Methods

Materials

Culture filtrate extracts from seven different fungi (*Alternaria alternata, Aspergillus versicolor*, *Bipolaris sorokiniana*, *Candida albicans*, *Cladosprium herbarum*, *Curvularia spicifera*, and *Penicillium notatum*) and mycelium extract (cellular extract) of *A. alternata* were purchased from Greer Laboratories. Culture filtrate extracts are derived from the media in which the fungi were grown; as they grow, they excrete proteins into the media. After removing the medium components, the culture filtrates are concentrated, dialyzed, and lyophilized. Mycelium extract was prepared by extracting the acetone-washed crude mycelium material in a buffer solution; this solution was then lyophilized. RPMI 1640 medium was purchased from Protide Pharmaceuticals. EGTA, thapsigargin, and Nonidet P-40 were obtained from Sigma-Aldrich. Pertussis toxin (PTX) and PMA were obtained from Calbiochem; PAF was purchased from BIOMOL. Stock solutions of thapsigargin (20 mM) were prepared in DMSO; aliquots were stored at −20°C; stock solutions were diluted in HBSS medium with 25 mM HEPES and 0.01% gelatin (Sigma-Aldrich) immediately before use. Anti-CD11b, anti-CD63, and control Ab were purchased from BD Biosciences. Anti-TLR2 and anti-TLR4 Abs were obtained from eBioscience.

Eosinophil and neutrophil isolation

Human eosinophils were isolated from normal volunteers or patients with histories of asthma, allergic rhinitis, or both by Percoll density gradient centrifugation and MACS using MACS anti-CD16 microbeads as described previously (31). The purity of eosinophils was regularly >98%. Isolated granulocytes (before addition of anti-CD16) were used as neutrophils with purities regularly >92%; neutrophils were further gated electronically during flow cytometric analysis (see below). The Mayo Clinic Rochester institutional review board approved the protocol to obtain blood from volunteers; all provided informed consent.

Eosinophil degranulation assays

To monitor eosinophil function in response to extracts from fungi, IL-5, PAF, or PMA, we measured degranulation of human eosinophils by quantitating released eosinophil-derived neurotoxin (EDN) and MBP (one set of experiments), as described previously (32). In brief, freshly isolated eosinophils were suspended in HBSS with 25 mM HEPES and 0.01% gelatin at 5×10^5 cells/ml. Eosinophils and stimuli were incubated in 96-well tissue culture plates for 3 h at 37°C and 5% CO_2. Cell-free supernatants were stored at −20°C. A specific RIA quantitated eosinophil degranulation by measuring the concentration of EDN in the supernatants (32). MBP release was also measured by two-site immunoradiometric assay (33). Because MBP attaches to plastic and is difficult to detect in the supernatants at neutral pH, after stimulation, MBP was measured by lysing the cell pellet with Nonidet P-40. The percentage of total MBP was calculated as follows: % of total MBP = (total MBP in lysate of eosinophils before incubation − MBP in lysate after stimulation)/total MBP in lysate of eosinophils before incubation × 100%.

To examine the calcium dependency of eosinophil degranulation, cells were preincubated with 1 mM EGTA or 0.5 μM thapsigargin for 15 min at 37°C before stimulation with fungal extracts. To investigate the roles of TLR, PTX-sensitive G proteins, and G protein mediation in the eosinophil response to fungi, we preincubated the cells with blocking Abs (10 μg/ml) to TLR2 or TLR4 for 30 min, with 100 ng/ml PTX for 2 h at room temperature, or with suboptimal concentrations of PAF (0.3 μM) or FMLP (0.1 μM) for 15 min before stimulation with fungal products, respectively. To investigate the effects of temperature on *Alternaria,* the extract and IL-5 solutions were exposed to 4, 37, 56, or 100°C for 30 min and were restored to 37°C before use as stimulants for degranulation. To investigate the degranulation capabilities of the retentates, filtrates, and fractions from the *Alternaria* characterization experiments (see below), portions of these solutions were incubated with eosinophils for 3 h at 37°C in 5% CO_2, and EDN release was quantitated as described above.

Eosinophil morphology

We used transmission electron microscopy to examine eosinophil morphology after culture with *Alternaria* extract. Isolated eosinophils were incubated with 100 μg/ml fungal product in HBSS buffer with gelatin for 3 h at 37°C in 5% CO_2. After overnight fixation in 4% formaldehyde and 1% glutaraldehyde in 0.1 M phosphate buffer (pH 7.2), the cell pellet was rinsed, postfixed with 1% phosphate-buffered osmium tetroxide for 60 min, and stained en bloc with 2% aqueous uranyl acetate at 60°C. After dehydration in ethanol, the cells were infiltrated with Spurr resin/ethanol mixtures (1/1 and 3/1) for 60 min each, resuspended in fresh Spurr resin overnight, and embedded in polyethylene capsules. Thin sections were examined with a transmission electron microscope (JEOL 1200).

IL-8 production by eosinophils

Purified eosinophils (1 ml at 1×10^6 cells/ml) were cultured for 24 h at 37°C in 5% CO_2 in RPMI 1640 with 10% bovine calf serum and *Alternaria* extract. Levels of IL-8 in the cell-free supernatants were measured using an ELISA kit (Quantikine IL-8 Immunoassay Kit; R&D Systems); the threshold sensitivity was 4 pg/ml.

Flow cytometric analyses for CD11b and CD63 expression

Purified eosinophils or granulocytes (1×10^6cells) were suspended in RPMI 1640 with 25 mM HEPES, 1% BSA, and 0.1% NaN_3 and were incubated with *Alternaria* extract (50 μg/ml) or PAF (1.0 μM) as a positive control for 1 h at 37°C. After washing with PBS containing 0.1% NaN_3 and 1% BSA (PAB buffer), cells were incubated for 30 min at 4°C with anti-CD11b, anti-CD63, or control Ab, followed by incubation with PE-conjugated goat anti-mouse IgG. After washing with PAB buffer, cells were fixed with 1% paraformaldehyde in PAB buffer (pH 7.4). The fluorescence intensity of individual cells was measured with a FACScan (BD Biosciences). In the granulocyte preparation, neutrophils were identified by their weaker green autofluorescence and side scatter, as previously described (13)

Measurement of intracellular Ca^{2+}

Real-time changes in intracellular Ca^{2+} ($[Ca^{2+}]_i$) were measured in a flow cytometer (34) using the calcium indicator indo-1 (35). To load the eosinophils, a 1-ml suspension (1 to 2×10^6 cells/ml) was incubated with 3 mM indo-1-AM (Molecular Probes) in phenol red-free RPMI 1640 with 10% α calf serum and 10 mM HEPES for 30 min at 37°C. After washing, cells were suspended in RPMI 1640 with 0.1% human serum albumin and 10 mM HEPES. To measure $[Ca^{2+}]_i$, cells were stimulated, and fluorescence was analyzed by a FACS analyzer with an ion-argon laser (BD Biosciences). $[Ca^{2+}]_i$ was monitored on the basis of the ratio of the fluorescence of the calcium-bound indo-1 emission (401 nm) and the free indo-1 emission (475 nm).

Size exclusion chromatography of Alternaria *culture extract*

To probe the components in *Alternaria* extract that are involved in eosinophil activation, we used size exclusion chromatography with a Superdex 200–10/30 column (Amersham Biosciences). A vial of *A. alternata* culture filtrate Ag (38 mg/vial; 15.4% protein) was mixed with 1 ml of 0.05 M PO_4 buffer, pH 6.8, sonicated in a water bath for 2 min at 22°C, and applied to a YM100 Centricon membrane system (100-kDa cutoff; Millipore). After centrifugation at 3000 × *g* for 1 h at 4°C, the resulting filtrate was applied to a YM10 Centricon membrane system (10-kDa cutoff). After centrifugation at 3000 × *g* for 6 h at 4°C, the retentate was applied to the column and eluted with 0.05 M PO_4 at a flow rate of 0.5 ml/min; 0.5-ml fractions were collected. The UV absorbance of fractions was measured by SpectraMAX plate reader (Molecular Probes), and their abilities to induce eosinophil degranulation were determined by EDN release (see above).

Statistics

Data from three or more experiments using eosinophil preparations from different donors were summarized as the mean ± SEM. Statistical analyses (two-tailed) used Student's *t*, Mann-Whitney *U*, or Wilcoxon test.

Results

Alternaria *induces exocytotic degranulation of human eosinophils*

We investigated whether the culture extracts of seven common environmental fungi (*A. alternata, A. versicolor*, *B. sorokiniana*, *C. albicans*, *C. herbarum*, *C. spicifera*, and *P. notatum*) induce

degranulation of human eosinophils in vitro. Instead of live fungi, we used commercial, lyophilized products; this minimized experimental variability from day-to-day differences in the growth stages of each fungus. Both *Alternaria* and *Penicillium* induced concentration-dependent EDN release, as a marker of eosinophil degranulation (Fig. 1). Other fungi, including *Aspergillus*, *Bipolaris*, *Candida*, *Cladosporium*, and *Culvularia* up to 200 μg/ml, induced no or minimal EDN release. The *Alternaria*- and *Penicillium*-induced degranulation increased with time (results not shown). After 3-h incubation, *Alternaria* (50 μg/ml) and *Penicillium* (200 μg/ml) induced maximal EDN release (263 $\pm$ 60 and 237 $\pm$ 60 ng EDN/2.5 $\times$ 10^5 cells, respectively) or ~30% of total cellular EDN. As potent eosinophil secretagogues, PAF (1 μM) and PMA (1 ng/ml) induced 547 $\pm$ 32 and 402 $\pm$ 35 ng EDN/2.5 $\times$ 10^5 cells of EDN release, respectively. *Alternaria* also stimulated the release of another eosinophil granule protein, MBP; eosinophils incubated for 3 h with *Alternaria* (100 μg/ml) released 52 $\pm$ 5% of their total MBP (mean $\pm$ range; $n = 2$).

By electron microscopy, eosinophils incubated at 37°C for 3 h with *Alternaria* extract (100 μg/ml) showed granule fusion and electron-lucent granule cores and matrices (Fig. 2), consistent with the extracellular release of both core (MBP) and matrix (EDN) granule proteins (see above). The plasma membranes remained mostly intact, suggesting that *Alternaria* induced compound exocytosis (36) of eosinophils. In contrast, most eosinophils incubated in medium maintained their cytoplasmic granules with characteristic core and matrix structures and intact plasma membranes.

Although the molecular mechanisms for eosinophil exocytosis are incompletely understood, increased $[Ca^{2+}]_i$ is a key triggering step in the coupling of stimulus to secretion (36). Therefore, we studied the roles of $[Ca^{2+}]_i$ and extracellular Ca^{2+}. Both culture and cellular extracts of *Alternaria* induced eosinophil EDN release, but eosinophils that were preincubated with 1 mM EGTA did not degranulate (Fig. 3*A*), suggesting that *Alternaria*-induced eosinophil degranulation is highly dependent on extracellular Ca^{2+}. We next investigated the priming effects of a well-defined agonist that increases $[Ca^{2+}]_i$. Thapsigargin inhibits the endoplasmic reticulum Ca^{2+}-ATPase and allows influx to the cytoplasm, thus elevating $[Ca^{2+}]_i$ from intracellular stores (37). Eosinophils pretreated with suboptimal concentrations of thapsigargin showed synergistic and dramatic increases in *Alternaria*-induced degranulation (Fig. 3*B*). Thus, extracellular Ca^{2+} and $[Ca^{2+}]_i$ probably play key roles in *Alternaria*-induced eosinophil degranulation.

Alternaria induces eosinophil exocytosis, but is this response limited to *Alternaria*-sensitized individuals? Acid stripping of eosinophils with lactic acid to remove cell-bound IgE and IgG (13) did not affect *Alternaria*-induced eosinophil degranulation (data not shown). Furthermore, *Alternaria* induced degranulation of eosinophils isolated from normal individuals ($p < 0.01$; $n = 10$; Fig. 4), suggesting that this response to *Alternaria* is not limited to sensitive patients. However, eosinophils from patients with clinical allergy or asthma released ~70% more EDN compared with normal individuals ($p < 0.05$; $n = 8$ and $n = 10$, respectively). No difference was observed in IL-5-induced EDN release between these groups.

Alternaria *induces IL-8 production in and CD11b up-regulation on eosinophils*

Other effector functions of eosinophils include the production and release of various proinflammatory cytokines and chemokines, including IL-8 (38). Eosinophils incubated with *Alternaria* for 24 h produced IL-8 in their supernatants (Fig. 5*A*), but IL-5-stimulated cells did not. Lysates from freshly isolated eosinophils (prepared using 0.5% Nonidet P-40) showed no detectable IL-8 (data not shown), suggesting de novo synthesis of IL-8 when stimulated with *Alternaria*.

Stimulation of eosinophils with their agonists, such as PAF and FMLP, up-regulates surface expression of a β_2 integrin, CD11b,

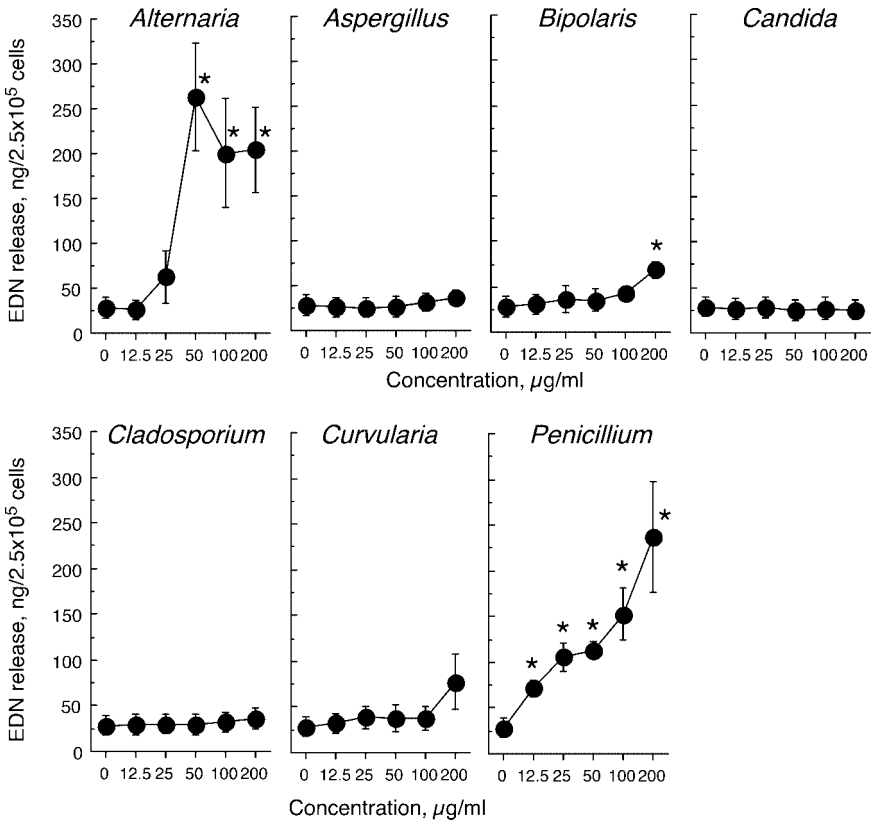

FIGURE 1. Effects of fungi on eosinophil degranulation. Eosinophils were incubated in duplicate with different concentrations of culture extracts from fungi (*A. alternata*, *A. versicolor*, *B. sorokiniana, C. albicans*, *C. herbarum*, *C. spicifera*, or *P. notatum*) for 3 h at 37°C. EDN concentrations in the cell-free supernatants were measured by RIA, as described in *Materials and Methods.* Results show the mean $\pm$ SEM from six different eosinophil preparations. *, Significant differences compared with medium alone ($p < 0.05$).

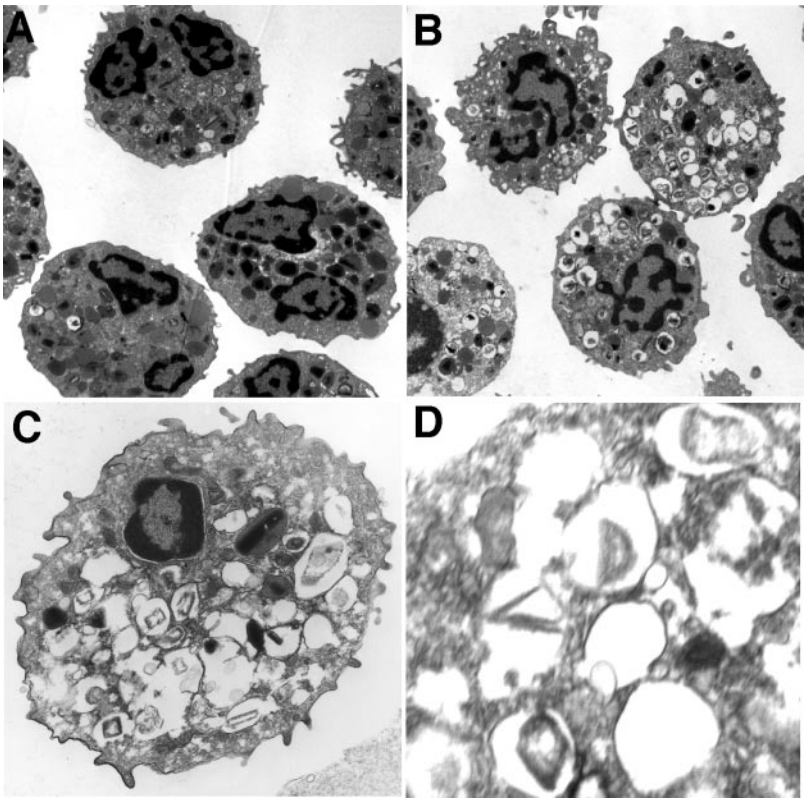

FIGURE 2. *Alternaria*-induced eosinophil degranulation appears regulated and exocytotic. Transmission photomicrographs show eosinophils after 3 h at 37°C of incubation with medium or *Alternaria* extract. *A*, Eosinophils incubated in medium only; note the well-maintained cytoplasmic granules containing characteristic electron-dense core and matrix structures and intact plasma membranes. *B*, Eosinophils stimulated with 100 μg/ml *Alternaria* culture extract show granule fusion and electron-lucent granules, but plasma membranes are intact. *C* and *D*, Higher magnification views of eosinophils incubated with *Alternaria* show the intact plasma membrane and emphasize the granule fusion and loss of electron-dense material from granules. Original magnification: *A* and *B*, ×6000; *C*, ×20,000; *D*, ×60,000.

and this increased CD11b expression is an activation marker for eosinophils (39). We next investigated the effects of *Alternaria* on eosinophil CD11b expression. Cells stimulated with 50 μg/ml *Alternaria* or 1 μM PAF, as a positive control, showed increased expression of eosinophil CD11b compared with medium (Fig. 5*B*, *left panel*). A summary of three experiments (Fig. 5*B*, *right panel*) shows that *Alternaria* highly increased the expression of CD11b, even more than PAF. *Alternaria* probably triggers various effector functions of eosinophils, including exocytosis, chemokine production, and integrin expression.

Alternaria *stimulates CD63 expression by eosinophils, but not by neutrophils*

Both eosinophils and neutrophils share a number of cellular receptors for microbial products (e.g., zymosan and FMLP), and some receptors are preferentially expressed by neutrophils (e.g., TLR2, TLR4, and TLR5) (40). Therefore, we compared the eosinophil and neutrophil cellular responses to *Alternaria*. CD63 is a well-established component of the late endosomal and lysosomal membranes (41) and is used as a surface marker for exocytosis in both eosinophils and neutrophils (19, 42). Both 50 μg/ml *Alternaria* and 1.0 μM PAF increased eosinophil surface expression of CD63 (Fig. 6*A*). In contrast, PAF, but not *Alternaria,* increased the expression of CD63 in neutrophils (Fig. 6*B*). Thus, the activation response to *Alternaria* occurs in eosinophils, but it is unlikely in neutrophils.

Potential role of heterotrimeric G protein(s) in the eosinophil response to Alternaria

We next investigated how eosinophils recognize *Alternaria* products. Initially, we examined the effects of blocking Abs, including

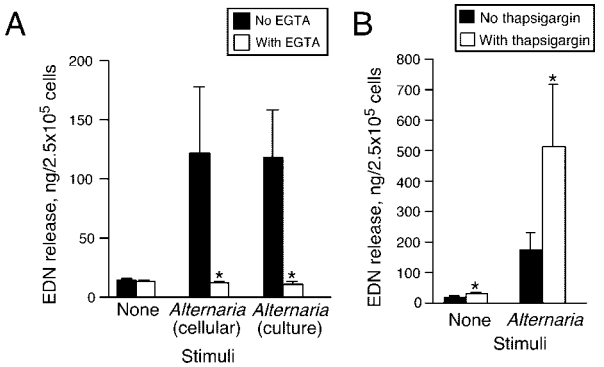

FIGURE 3. Effects of calcium on *Alternaria*-induced eosinophil degranulation. Eosinophils were preincubated with 1 mM EGTA (*A*) or 0.5 μM thapsigargin (*B*) for 15 min at 37°C and stimulated with medium, 100 μg/ml *Alternaria* cellular, and culture extracts for 3 h at 37°C. Results show the mean ± SEM from five (*A*) and six (*B*) different eosinophil preparations. ∗, Significant differences compared with no EGTA (*A*) or no thapsigargin (*B*; $p < 0.05$).

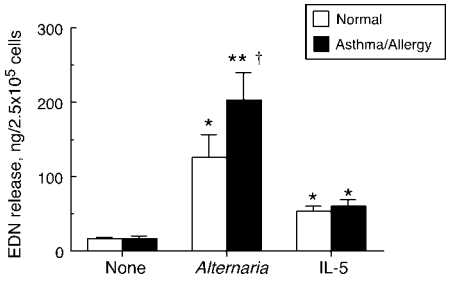

FIGURE 4. Comparison of eosinophil degranulation with cells from healthy donors and from patients with asthma or allergy. Purified eosinophils from 10 normal volunteers and eight volunteers with asthma or allergy or both were incubated with 100 μg/ml *Alternaria* or 10 ng/ml IL-5 for 3 h. EDN concentrations in the cell-free supernatants were measured by RIA, as described in *Materials and Methods*. Results show the mean ± SEM. ∗, $p < 0.05$; ∗∗, $p < 0.01$ (significant difference compared with medium). †, $p < 0.05$ (significant difference, normal compared with asthma/allergy).

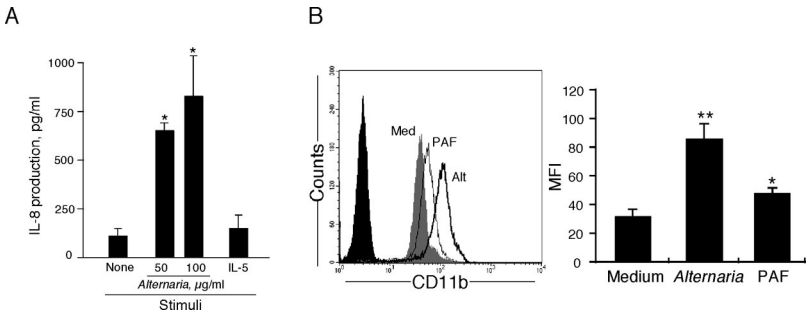

FIGURE 5. *Alternaria* induces IL-8 from and CD11b on eosinophils. *A*, Eosinophils were incubated with 50 or 100 μg/ml *Alternaria* extract or 10 ng/ml IL-5 for 24 h at 37°C. The levels of IL-8 in the supernatants were measured by ELISA. Results show the mean ± SEM from three different eosinophil preparations. *, $p < 0.05$ (significant difference compared with medium). *B*, Eosinophils were incubated with 50 μg/ml *Alternaria* extract, 1.0 μM PAF, or medium for 1 h. A representative histogram illustrates the differences in surface expression for cells stimulated with *Alternaria* (thick line), PAF (thin line), medium (light gray area), and isotype control Ab (dark gray area). Bar graphs show the results of three independent experiments. *, $p < 0.05$; **, $p < 0.01$ (significant differences compared with medium).

anti-TLR2 and anti-TLR4. These Abs inhibited *Alternaria*-induced degranulation by ≤10% (data not shown), suggesting that TLR involvement is unlikely. Ca^{2+} is strongly implicated in eosinophil exocytosis (20) (see Fig. 3); thus, exposure to *Alternaria* might induce increased $[Ca^{2+}]_i$. After loading cells with the calcium-sensitive fluorescent dye, indo-1, we monitored the $[Ca^{2+}]_i$ changes in stimulated eosinophils by flow cytometry. Eosinophils incubated with 10 ng/ml IL-5 or medium showed no change in $[Ca^{2+}]_i$ (Fig. 7). In contrast, eosinophils stimulated with 100 μg/ml *Alternaria* showed rapid increases in $[Ca^{2+}]_i$ within 200 s; the increased $[Ca^{2+}]_i$ persisted for up to 500 s, suggesting the involvement of a calcium-mobilizing receptor(s), such as a G protein-coupled receptor(s). Next, we preincubated eosinophils with PTX for 2 h and stimulated cells with *Alternaria* for 3 h. Because the PAFR is coupled to PTX-sensitive G protein in human eosinophils (43), 1.0 μM PAF was used as a positive control. PTX treatment significantly inhibited both PAF- and *Alternaria*-induced EDN release (60% ($p < 0.05$; $n = 5$) and 80% ($p < 0.01$; $n = 5$), respectively; Fig. 8*A*). PMA acts independently of G proteins, and 1 ng/ml PMA was used as a second positive control; PTX had no effect on PMA-induced eosinophil degranulation. We next investigated whether the eosinophil's response to *Alternaria* is consistent with G protein mediation by manifesting the phenomenon of heterologous desensitization (44, 45). Eosinophils were preincubated with suboptimal concentrations of PAF or FMLP for 15 min and then stimulated with medium or 100 μg/ml *Alternaria* for 3 h. Cells incubated with PAF or FMLP without *Alternaria* showed small, but significant, EDN release (~70 ng EDN/2.5 × 10^5 cells; $p < 0.05$; $n = 4$; Fig. 8*B*). Without PAF or FMLP pretreatment, *Alternaria* induced the release of ~225 ng EDN/2.5 × 10^5 cells. Pretreatment with PAF decreased this *Alternaria*-induced EDN release to ~90 ng EDN/2.5 × 10^5 cells ($p < 0.05$; $n = 4$), a level

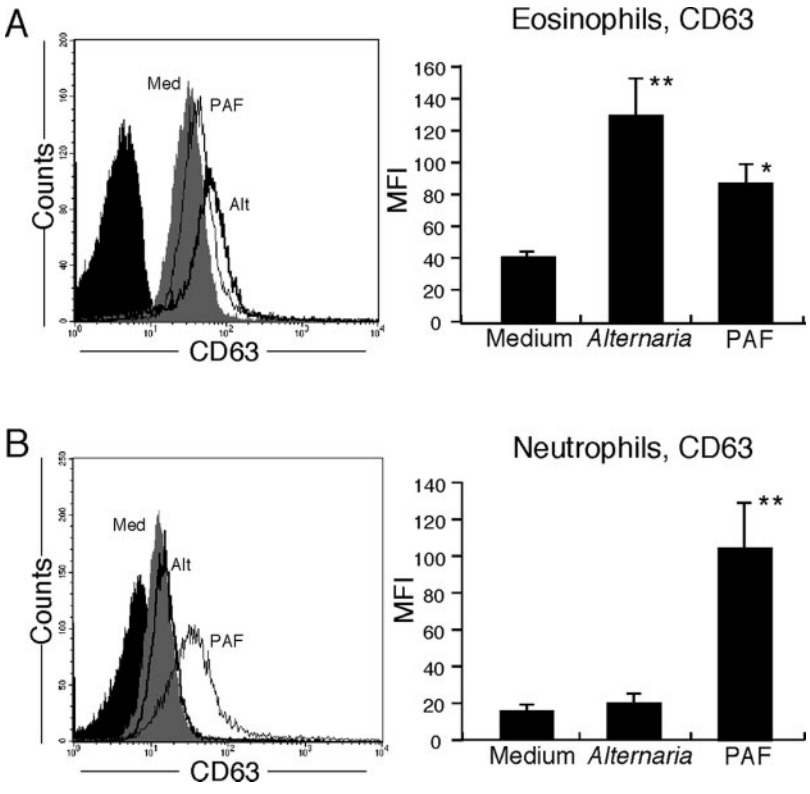

FIGURE 6. *Alternaria*-induces CD63 expression on eosinophils and not neutrophils. Purified eosinophils (*A*) or purified neutrophils (*B*) were incubated with 50 μg/ml *Alternaria* extract and 1.0 μM PAF or medium for 1 h. Representative histograms are described in Fig. 5. Bar graphs show the results of three independent experiments. *, $p < 0.05$; **, $p < 0.01$ (significant differences compared with medium).

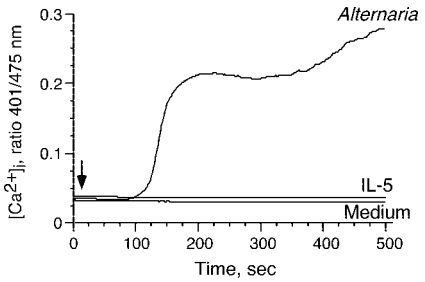

FIGURE 7. Changes in $[Ca^{2+}]_i$ in eosinophils stimulated with medium, *Alternaria* culture extract, or IL-5. Eosinophils were pretreated with the calcium-sensitive fluorescent dye indo-1-AM, loaded onto the FACS analyzer, and stimulated after 20 s with medium, 100 μg/ml *Alternaria* culture extract, or 10 ng/ml IL-5. $[Ca^{2+}]_i$ is shown as the ratio of the calcium-bound indo-1 fluorescence emission (401 nm) to the free indo-1 emission (475 nM). The arrow indicates the time of addition of medium, *Alternaria* culture extract, or IL-5.

comparable to that after PAF pretreatment without *Alternaria*. Similarly, pretreatment with FMLP partially decreased the *Alternaria*-induced EDN release ($p < 0.05$). Thus, a G protein-coupled receptor(s), probably a PTX-sensitive $G_i\alpha$-coupled receptor(s), is likely to be involved in the eosinophil's response to *Alternaria*.

Partial characterization of Alternaria *extract*

We used three strategies to begin characterizing the *Alternaria* products involved in eosinophil degranulation. First, the *Alternaria* extract was subjected to membrane filtration. After filtration with a YM100 Centricon membrane, the filtrate stimulated eosinophil degranulation, but the retentate did not (results not shown). After filtration with a YM10 Centricon membrane, the retentate stimulated eosinophil degranulation, but the filtrate did not. Thus, the eosinophil stimulatory activity in the *Alternaria* extract is probably between 10 and 100 kDa. Second, *Alternaria* extracts, which had been treated at 56 or 100°C for 30 min, did not induce EDN release (Fig. 9*A*), but extracts treated at 4 or 37°C for 30 min did induce EDN release, suggesting that it is a heat-labile protein(s) or glycoprotein(s). The activity of a cytokine, IL-5, to induce EDN release was abolished by treatment at 100°C, but not by treatment at 56°C or lower temperatures. Third, we used size exclusion chromatography (Fig. 9*B*) and tested the column fractions for their abilities to induce eosinophil degranulation. Although the absorbance profile showed a broad peak from fractions 32–37, the most potent eosinophil degranulation activity appeared in fraction 32 with an M_r of ~60 kDa.

Discussion

Although recent studies by several investigators have elucidated innate immune responses of various inflammatory cells to microorganisms, the innate immune responses of human eosinophils remain unknown. Unlike macrophages or neutrophils, the reported TLR expression on eosinophils is limited, except for TLR7 (40). Our report is the first to show that products of fungi (i.e., *Alternaria* and *Penicillium*) induce in vitro activation and degranulation of human eosinophils. This *Alternaria*-induced exocytosis of eosinophils is highly dependent on extracellular Ca^{2+} and $[Ca^{2+}]_i$ and is mediated by PTX-sensitive G proteins. In addition, *Alternaria* culture extract induced synthesis of IL-8 and increased the expression of CD11b and CD63, suggesting that a series of activation events, including exocytosis, integrin expression, and cytokine production, follows the exposure of eosinophils to *Alternaria* products. Together, human eosinophils probably react with certain fungi, such as *Alternaria* and *Penicillium,* as part of their role in innate immunity.

The potential implications of our study in understanding the mechanisms of asthma and other allergic diseases may be substantial. Previous studies suggest that T cell-mediated immune responses to exogenous Ags, such as mite and cockroach, and coordinated actions by cytokines, chemokines, and adhesion molecules recruit eosinophils to the airways (2); however, the triggers of proinflammatory mediator release by eosinophils in the airways are unknown. Importantly, unlike mast cells and basophils, the expression of IgE receptors on eosinophils is extremely limited (13, 14). Our observations suggest that products of certain environmental fungi, such as *Alternaria* and *Penicillium*, may directly induce exocytotic release of granule proteins from eosinophils in the absence of other immune cells or Igs. An association between fungal exposure and asthma has long been recognized clinically (26, 27). Furthermore, an accumulating body of evidence suggests that sensitivity to fungi, particularly *Alternaria*, is associated with asthma (26). *Alternaria* is ubiquitous both outdoors and indoors (46) and is known for the high rate of its spore germination and Ag release (47). Sensitization to *Alternaria* has been associated with asthma in various countries and in regions of the United States (48, 49). Moreover, exposure to *Alternaria* is a risk factor for respiratory arrest in patients with asthma (30). Similar reports have indicated that sensitivity to fungal proteins is a significant risk factor for life-threatening asthma (50). Therefore, the orchestration of both the acquired immune response (e.g., Th2 cytokine response) to

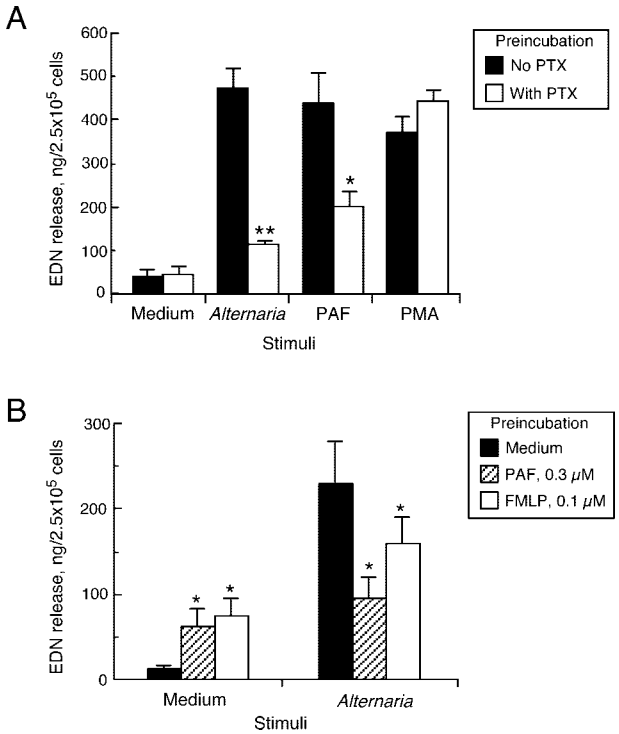

FIGURE 8. *Alternaria*-induced eosinophil activation involves a PTX-sensitive, G-protein-coupled receptor. *A*, After a 2-h preincubation with 100 ng/ml PTX or medium, eosinophils were stimulated for 3 h with 100 μg/ml *Alternaria*, 1.0 μM PAF, or 1.0 ng/ml PMA. *B*, After a 15-min preincubation with suboptimal concentrations of PAF or FMLP or with medium, eosinophils were stimulated with 100 μg/ml *Alternaria* for 3 h. Results show the mean ± SEM from five (*A*) and four (medium and PAF) or three (FMLP; *B*) different eosinophil preparations. *, ($p < 0.05$; **, $p < 0.01$ (significant differences compared with no PTX (*A*) or medium only (*B*) preincubation).

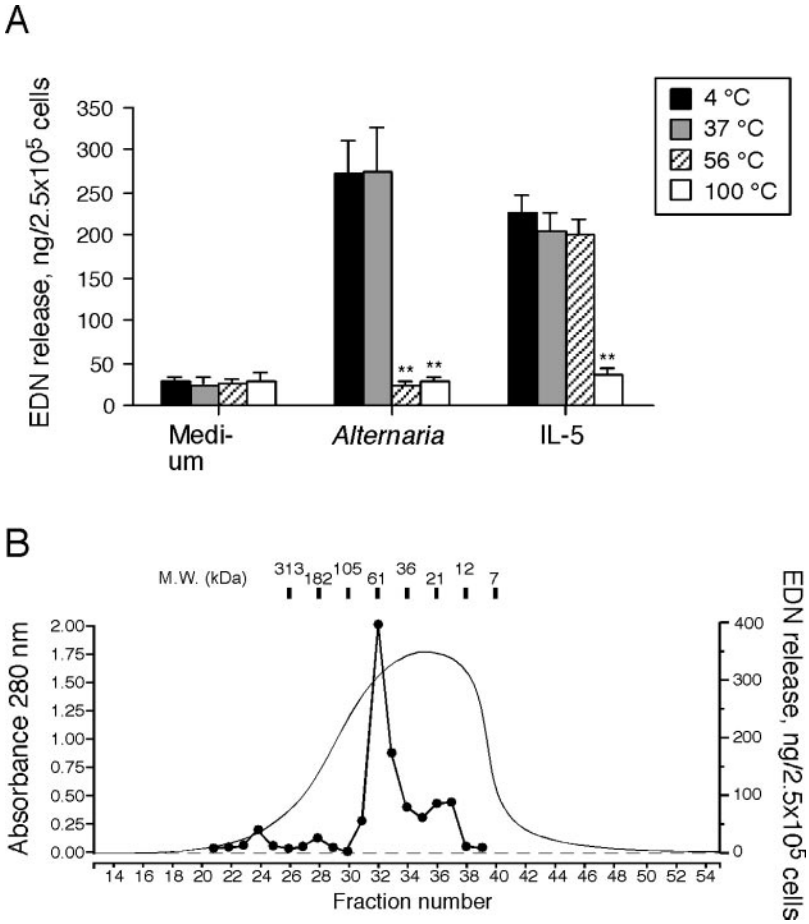

FIGURE 9. Partial characterization of *Alternaria* extract. *A*, Before incubation with eosinophils, aliquots of 100 μg/ml *Alternaria* and 10 ng/ml IL-5 were heated at 37, 56, or 100°C for 30 min or were treated at 4°C for 30 min. Eosinophils were incubated in duplicate with these treated stimuli for 3 h at 37°C. Results show the mean ± SEM from five different eosinophil preparations. **, $p < 0.01$ (significant differences compared with no heat treatment of extract). *B*, Size exclusion chromatography used a Superdex 200–10/30 column and produced a broad absorbance peak (smooth line) of the *Alternaria* culture extract. The dots connected by lines show the levels of EDN release when portions of fractions 21–39 were incubated with eosinophils. The M_r calibration of the column is shown above the elution profile.

certain fungi (e.g., *Alternaria*), which mobilizes eosinophils, and the innate direct response by eosinophils to the same fungi, which induces mediator release, may have important implications in the pathophysiology and exacerbation of asthma and other eosinophil-related airway diseases.

We also investigated which component(s) in *Alternaria* extracts stimulates eosinophils. Because fungal extracts contain large quantities of proteases (51), they could be potential candidates. Although information on fungal proteases is limited, they potently induce epithelial cell desquamation and the production of proinflammatory cytokines (51). Recently, we demonstrated that human eosinophils express functional protease-activated receptor 2 (PAR-2), and that serine proteases, such as trypsin, activate effector functions of human eosinophils through this receptor (52). PARs are coupled to a heterotrimeric G protein(s), and the increase in $[Ca^{2+}]_i$ is an activation hallmark of these receptors (53). In the present study the stimulatory activity of *Alternaria* extract was present in an ~60-kDa fraction and was very heat labile, suggesting that it is probably a protein(s). The rapid increase in $[Ca^{2+}]_i$ in eosinophils stimulated with *Alternaria* (Fig. 7), the PTX sensitivity (Fig. 8*A*), and the heterogeneous desensitization by PAF or FMLP (Fig. 8*B*) are all consistent with the involvement of a G protein-coupled receptor(s). Furthermore, in preliminary studies we found that *Alternaria*-induced increases in $[Ca^{2+}]_i$ and EDN release were inhibited ~60% by a PAR-2 peptide antagonist, LSIGKV (54) (data not shown). In contrast, no trypsin-like activity was detectable in our *Alternaria* extract, and an *Aspergillus* extract did not stimulate eosinophils, but it did contain trypsin-like activity (data not shown). Alternatively, because β-D-glucans have been reported to stimulate immune function and proinflammatory activity, perhaps β-D-glucan, a primary component of fungal cell walls or secreted products of various fungi, might trigger eosinophil degranulation (55). However, preliminary results showed that various concentrations of β-D-glucan did not induce eosinophil degranulation or superoxide production in vitro (data not shown). Finally, certain microorganisms, such as HIV and fungi, might directly interact with or produce a molecule(s) that binds to a cell's chemokine receptors (e.g., CCR5), which are coupled to certain G proteins (56, 57). Additional studies are needed to identify the stimulatory component(s) in *Alternaria* extract and its receptor(s) on eosinophils.

The majority of previous studies of antifungal immune responses used the following models: animal infection in in vivo systems (e.g., *C. albicans* and *A. fumigatus)* or entire fungal hyphae or conidia (e.g., *C. albicans* and *A. fumigatus*), a yeast model (e.g., zymosan), or isolated fungal macromolecules (e.g., β-glucan and mannan) in in vitro systems (58). These studies pointed to critical roles for TLRs, in particular TLR2 and TLR4, and to other pattern recognition receptors that recognize fungal pathogens and their cell wall components by immune cells, such as macrophages and neutrophils. Our unique approach used the secreted products of fungi, namely culture extracts, rather than fungal organisms. We found that certain environmental fungi, such as *Alternaria* and *Penicillium*, but not *Candida* or *Aspergillus*, secrete products that stimulate eosinophils through a G protein-dependent mechanism, leading to cellular activation and effector functions; neutrophils did not show a similar response. These findings suggest a novel innate immunological pathway, other than TLRs, that eosinophils use to recognize certain microorganisms and their products. Questions

remain regarding the specific microbial molecules and cellular receptors involved in this interaction. Additional questions include describing the conditions for fungi to release such bioactive products and whether innate immune cells other than eosinophils (e.g., mast cells) can recognize these products. The physiologic importance of this pathway in human immunity and in disease processes also needs to be elucidated. A better understanding of the interactions between eosinophils and fungi could provide a basis for new therapeutic strategies to prevent the development and exacerbation of asthma and other chronic airway diseases.

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Disclosures

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Relationships Among Bacteria, Upper Airway, Lower Airway, and Systemic Inflammation in COPD

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Relationships Among Bacteria, Upper Airway, Lower Airway, and Systemic Inflammation in COPD*

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Study objective: **The upper and lower airways are continuous. While upper airway symptoms are common in COPD patients, with accumulating evidence to suggest increased nasal inflammation, the relationships among upper airway, lower airway, and systemic inflammatory indexes have not been studied. We aimed to confirm that there is heightened nasal inflammation in COPD patients, to test the hypothesis that the degree of upper airway inflammation relates to the degree of lower airway inflammation, and to investigate the underlying associations with bacterial carriage and the systemic inflammatory response.**
Design: **Prospective cohort study.**
Setting: **Outpatient Department, London Chest Hospital, London, UK.**
Participants: **Forty-seven patients with COPD and 12 control subjects of similar age, sex, and smoking status.**
Measurements: **Serum, nasal wash fluid, and sputum samples were obtained from 47 stable patients with COPD for the analysis of inflammatory indexes and bacterial colonization. Nasal wash fluid specimens were obtained from 12 control subjects.**
Results: **COPD patients had an increased nasal interleukin (IL)-8 concentration compared to control subjects (difference, 97.2 pg/mL; $p = 0.009$). The nasal IL-8 concentration in COPD patients correlated with that in sputum ($r = 0.30$; $p = 0.039$). In both the upper and lower airways of patients with COPD, the IL-8 concentration was associated with indexes of bacterial colonization. Patients colonized with a sputum potentially pathogenic microorganism had a higher total nasal bacterial load (difference, 1.5 log cfu/mL; $p = 0.016$). We did not find significant relationships between the degree of upper or lower airway inflammation, or bacterial carriage, and the systemic inflammatory response.**
Conclusions: **COPD is associated with an increased nasal concentration of the neutrophil chemoattractant protein IL-8, the degree of which reflects that present in the lower airway. A relationship between lower airway bacterial colonization, postnasal drip, and higher nasal bacterial load may suggest a mechanism underlying this finding. This study is the first to report a correlation between the degree of upper and lower airway inflammation in COPD.**
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Key words: bacterial colonization; COPD; cytokines; inflammation; nose

Abbreviations: IL = interleukin; IQR = interquartile range; PPM = potentially pathogenic microorganism

COPD is a condition that is characterized by airflow obstruction that is largely irreversible and is associated with an abnormal inflammatory response in the lung.[1] This focus on the lung ignores the fact that there is anatomic continuity between the lower and upper airway and that both components act together as a single physiologic unit showing similar reactions to noxious stimuli.[2]

Interactions between the upper and lower airway have been extensively studied in patients with asthma. Asthma and rhinitis commonly coexist,[3] nasal allergen challenge in asthmatic patients results

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in heightened bronchial reactivity,[4] and bronchial allergen challenge in patients with rhinitis results in a nasal inflammatory reaction.[5] Therefore, there has been increasing interest in the phenomenon of inflammatory "cross-talk" between the nose and lung,[6] suggesting the concept of a "united airways disease" in which rhinitis and asthma are the upper and lower airway manifestations of the same disease process.[7] In contrast, little is known about possible upper airway involvement in COPD patients, in whom cigarette smoke provides the pan-airway exposure in contrast to the allergen stimulation of allergic disease.

We have previously reported[8] a high prevalence of chronic nasal symptoms in patients with COPD and have gone on to show[9] that these contribute to impairment in quality of life. In our initial study,[8] 75% of patients with moderate-to-severe COPD experienced persistent daily nasal symptoms, most commonly rhinorrhea. More recently, an analysis[10] of matched nasal and bronchial biopsy specimens has suggested that nasal and bronchial inflammation coexist in COPD patients. Lower airway inflammation in COPD patients is known to be modulated by bacterial colonization.[11] In contrast, the mechanisms underlying upper airway involvement in COPD patients have not been described, and, in particular, it is not known whether the degree of upper airway inflammation reflects that occurring in the lower airway or systemic circulation. Since lower airway inflammation is known to be associated with important clinical variables including FEV_1[12] and exacerbation frequency,[13] a link between upper and lower airway inflammation in COPD patients could result in modulation of the lower airway disease and affect clinical outcomes. This has implications for the development of novel therapeutic strategies.

We aimed to confirm that stable COPD is indeed associated with up-regulated nasal inflammation, to test the hypothesis that the degree of this upper airway inflammation correlates with the degree of lower airway inflammation, and to investigate the underlying relationships with bacterial colonization and the systemic inflammatory response. This is the first study to investigate the inflammatory profile of upper airway, lower airway, and serum samples taken at a single time point from stable patients with COPD. A control population of similar age, sex, and smoking status was included to enable a comparison between nasal inflammatory indexes in adults with and without COPD. The use of the well-characterized East London COPD cohort allows a unique opportunity to relate upper airway indexes to important prospectively collected clinical variables, including exacerbation frequency.

Materials and Methods

Study Subjects

Forty-seven patients with COPD who were enrolled in the East London cohort were studied during the period October 2002 through July 2003. These patients with well-characterized disease recorded daily peak expiratory flow rate and any increase in symptoms on diary cards, and attended the Outpatient Clinic of London Chest Hospital for a quarterly review that included spirometry and clinical sampling. This prospectively collected daily diary card data allowed the calculation of an exacerbation frequency according to our previously published methodology.[14] The entry and exclusion criteria have also been previously described[15] and, in brief, consisted of a postbronchodilator FEV_1 of $<80\%$ predicted, an FEV_1/FVC ratio of $< 70\%$, β_2-agonist reversibility on baseline FEV_1 of <200 mL and/or 15%, and the absence of clinical asthma or other significant respiratory pathology. In particular, given the recognized association between bronchiectasis and sinusitis, none of the patients had clinical findings that were suggestive of bronchiectasis (such as the production of large volumes of purulent sputum or coarse inspiratory crepitations). FEV_1 was assessed as the best of three consecutive attempts using a rolling seal spirometer (SensorMedics; Yorba Linda, CA). Three of the 47 patients (6%) reported a history of physician-diagnosed rhinosinusitis. None were receiving therapy with nasal corticosteroids or antihistamines. Forty-four of the 47 patients were receiving regular therapy with inhaled corticosteroids. Samples of sputum, nasal wash fluid, and serum were obtained at a single clinic visit during a period of clinical stability at least 3 months after any preceding exacerbation.

Twelve control patients were recruited from an otolaryngology clinic. Inclusion criteria were no history of atopy, significant lung or nasal disease, and freedom in the preceding 3 months from upper respiratory tract infection. The patients were attending the clinic for a variety of reasons including assessment for hearing aids (n = 4), tinnitus (n = 1), and Ménière disease (n = 1), or surveillance of previous mastoid cavity surgery (n = 4) or otitis externa (n = 2), which had been judged to be clinically quiescent and did not require ongoing therapy. None of the patients were receiving inhaled or intranasal therapies, or treatment with oral antihistamines or corticosteroids. None of the control subjects were current smokers. Four of the 12 subjects had never smoked, and the remaining 8 subjects had smoked a mean of 21.1 pack-years (SD, 11.2 pack-years) and had been abstinent for a mean period of 27.1 years (SD, 16.5 years). A medical history was recorded, spirometry was performed, and the nasal wash fluid sample taken. All participants gave written informed consent, and the study was approved by the local (East London and The City) Research Ethics Committee.

Nasal Symptoms

A simple nasal score, as used in our previous work,[8] was used to assess the severity of chronic nasal symptoms. The presence or absence on most days of the week of the five principal nasal symptoms (*ie*, rhinorrhea, postnasal drip, nasal congestion, sneezing, and impaired sense of smell) were binary coded as 1 or 0, respectively, and the scores were summed to yield a total score between 0 and 5.

Sputum Samples

A single sample of sputum, either spontaneous or induced, was obtained and processed according to techniques that we have

previously reported.[16] In brief, each sample was divided into three aliquots. One portion was processed with 0.1% dithiothreitol, and was centrifuged to produce a cell-pellet for a leukocyte count using a hemocytometer and the trypan-blue exclusion method. A second sample was homogenized with glass beads in phosphate-buffered saline solution and centrifuged, and aliquots of supernatant were stored at –70°C for later cytokine analysis. The third aliquot was used for quantitative bacteriologic culture. This portion was incubated for 30 min at 37°C with an equal weight of 0.1% dithiothreitol. Tenfold serial dilutions were then made in Brain Heart infusion broth, and 100-μL aliquots were plated onto the surface of a range of culture media, including blood, chocolate, MacConkey medium, and cysteine lactose electrolyte-deficient agars. These were incubated for 18 h at 37°C in air that was enriched to 5% CO_2, and bacterial colonies were counted and subcultured for identification using standard morphologic and biochemical assessments, as used in our previous studies.[17]

Nasal Wash Procedure and Samples

Nasal wash was performed using a technique adapted from Hilding.[18] Briefly, a 12F Foley catheter (Bard; Crawley, UK), modified by removal of the tip distal to the balloon, was inserted into the nostril and inflated with sufficient air to form a comfortable seal (typically, 7 to 10 mL). With the patients head flexed 45° forward, 7 mL warmed 0.9% saline solution was instilled through the catheter, and was washed in and out of the nasal cavity three times. A portion of the pooled wash fluid from both nostrils was processed for quantitative bacteriology, and the remainder was centrifuged to yield a cell-pellet for leukocyte count and a supernatant for analysis of inflammatory cytokines, as described above for the sputum specimens. We assessed the validity of our nasal wash methodology by repeating the procedure a mean time of 118 days (SD, 34 days) later in 12 of the COPD patients. Concentrations of interleukin (IL)-6, IL-8, and the log bacterial load were reassayed with resultant intraclass correlation coefficients of 0.7, 0.6, and 0.7, respectively. These values indicate good reproducibility.

Serum Samples

A 5-mL sample of serum was collected into a sterile vacutainer and centrifuged, and the supernatant was stored for later analysis of IL-6 as described above for sputum specimens.

Sample Analysis

The inflammatory cytokines IL-6 and IL-8 were quantified using commercial sandwich enzyme-linked immunosorbent assay kits (R&D Systems; Abingdon, UK). Concentrations of cytokine are expressed in picograms per milliliter, and for sputum samples this represents a 10-fold dilution by weight of the original sample. The limits of detection were 0.7 pg/mL for IL-6 and 10 pg/mL for IL-8.

Bacteriology data are expressed as the total bacterial count (in colony forming units [cfu] per milliliter of nasal wash fluid or sputum supernatant, in logarithmic units) and the presence or absence of a range of potentially pathogenic microorganisms (PPMs) associated with exacerbations of COPD. For the purposes of this study, we defined PPM to include *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Haemophilus parainfluenzae*, *Moraxella catarrhalis*, *Klebsiella pneumoniae*, and *Pseudomonas aeruginosa*.

Statistical Analysis

Data were analyzed using a statistical software package (STATA-5 software; Stata Corporation, Austin, TX). Clinical data with normal distribution are described by mean (SD), and differences between groups were tested by unpaired *t* test. Nasal wash fluid, blood, and sputum sample data are all reported for clarity as median and interquartile range (IQR). The Kolmogorov-Smirnov test of normality was employed, and relationships between groups used the Pearson or Spearman rank correlation as appropriate. Comparisons between independent groups were made with a Mann-Whitney *U* test, and frequency distributions were tested by χ^2 analysis. A probability of ≤ 0.05 was considered to be statistically significant.

Results

Baseline Clinical Characteristics

The clinical characteristics of the 12 control subjects and 47 COPD patients are reported in Table 1. The control subjects, none of whom were current smokers, were compared with the 35 ex-smoking

Table 1—*Clinical Characteristics of the 12 Control Subjects (6 Men), 35 Ex-Smoking COPD Patients (20 Men), and 12 Currently Smoking COPD Patients (7 Men)

	Control Subjects		Ex-Smoking COPD Patients		Smoking COPD Patients	
Characteristics	Mean	SD	Mean	SD	Mean	SD
Age, yr	71.8	7.1	71.1	7.2	68.8	6.4
FEV_1						
L	2.3	0.6	0.9	0.4	0.9	0.2
% predicted	96.6	12.7	38.7	14.3	35.7	11.6
FVC, L	2.7	0.7	2.1	0.9	2.4	0.6
FEV_1/FVC ratio, %	86.1	8.7	47.6	13.1	39.6	15.0
Pa_{O_2}, kPa			8.8	1.1	8.5	0.9
Pa_{CO_2}, kPa			5.6	0.8	6.0	0.7
Smoking, pack-yr	14.0	13.7	46.8	26.5	44.0	27.4
Nasal score	1.0	1.5	1.2	0.8	1.6	1.6

*Control subjects, no current smokers, were of similar age and sex distribution to the 35 ex-smoking COPD patients. There were no significant differences between the COPD patients who did and did not continue to smoke. Arterial blood gas analysis was not performed in the Control subjects.

COPD patients to avoid any effect of active cigarette smoking on nasal symptoms, inflammatory markers, or bacterial carriage. Subjects in the control population were of similar age and sex distribution to those of the ex-smoking COPD patients but had a lower total pack-year smoking history. There were no significant differences in the clinical variables between the 12 COPD patients who continued to smoke and the 35 ex-smokers (who had stopped smoking a median of 8 years previously; IQR, 3 to 15 years). The subsequent analysis, within the COPD patients, of inflammatory indexes and bacterial carriage in the upper airway, lower airway, and systemic circulation, therefore includes data from all 47 patients.

Comparison of Nasal Inflammatory Markers in Control Subjects and COPD Patients

The results of the nasal wash fluid leukocyte count and cytokine analysis for the 12 control subjects and 35 matched (ex-smoking) COPD patients are reported in Table 2. The median nasal wash fluid IL-8 concentration was significantly higher in the COPD patients than in the control subjects as illustrated in Figure 1 (COPD patients, 156.1 pg/mL; control subjects, 58.9 pg/mL; $p = 0.009$). The differences in leukocyte count, bacterial load, and IL-6 concentration, although higher in the COPD patients, did not reach statistical significance. Two of the 47 COPD patients (4.3%) and 1 control subject (8.3%) were colonized with a nasal PPM. These organisms consisted of one isolate each of *K pneumoniae* and *P aeruginosa* in the COPD patients, and an *M catarrhalis* isolate in the control subjects. Four of the 47 COPD patients (8.5%) were colonized with *Staphylococcus aureus*, and the remainder of the nasal wash fluid cultures in the COPD patients and control subjects grew a mixed growth of upper respiratory tract commensal organisms.

Interrelationships Among Nasal Wash Markers

We found significant correlations between the individual nasal wash fluid inflammatory markers in both the control subjects and COPD patients. In the control subjects, but not in the COPD patients, the nasal wash fluid leukocyte count correlated with the total nasal bacterial load ($\rho = 0.60$; $p = 0.050$). In the COPD patients, the nasal leukocyte count correlated with the nasal IL-8 concentration ($\rho = 0.55$; $p < 0.001$), and the IL-8 concentration correlated with that of IL-6 ($\rho = 0.59$; $p < 0.001$). There was a trend to correlation between the nasal IL-8 concentration and the nasal bacterial load that just failed to reach conventional statistical significance ($\rho = 0.27$; $p = 0.067$).

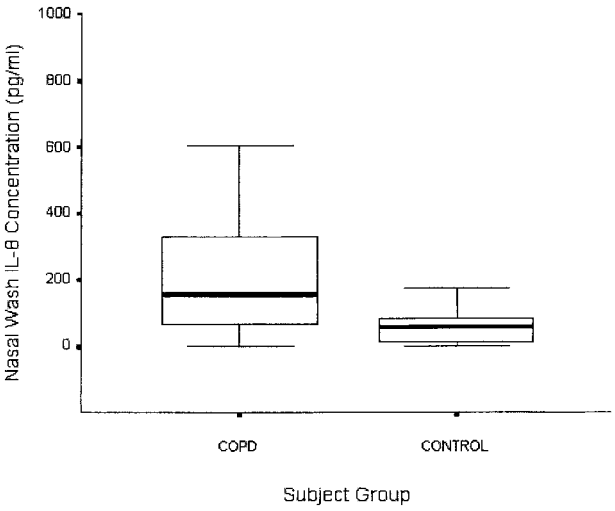

FIGURE 1. Comparison of nasal wash fluid IL-8 concentration in 35 patients with COPD and 12 control subjects of similar age, sex, and smoking status. Box plot represents median, IQR, and range ($p = 0.009$).

Interrelationships Among Sputum Markers

There was a significant correlation between the sputum IL-8 and IL-6 concentration in the patients with COPD ($r = 0.41$; $p = 0.004$). Twenty of the 47 COPD patients (43%) had lower airway colonization with a PPM. Of those with a PPM, 43% had *H influenzae*, 19% had *H parainfluenzae*, 14% had *S pneumoniae*, and 14% had *M catarrhalis*. One isolate each of *P aeruginosa* and *K pneumonia* was identified. Patients in whom the lower airway was colo-

Table 2—*Nasal Wash Inflammatory Markers in 12 Control Subjects and 35 Ex-Smoking COPD Patients*

	Control Subjects		Ex-Smoking COPD Patients		
Markers	Median	IQR	Median	IQR	p Value
IL-8, pg/mL	58.9	13.8–81.6	156.1	63.3–339.5	0.009
IL-6, pg/mL	1.9	1.5–2.6	2.7	0.8–7.3	0.335
Leukocyte count, cells/mL	6,250	3,714–12,500	12,500	3,750–43,182	0.142
Bacterial load, log cfu/mL	2.3	2.0–2.7	2.7	1.4–3.7	0.446

nized with a PPM had a significantly higher median sputum IL-8 concentration than those who were not colonized (PPM group, 4,907.1 pg/mL; no-PPM group, 3,784.3 pg/mL; p = 0.041).

Relationships Among Nasal Wash Fluid, Sputum, and Serum Markers

The results of the nasal wash fluid and sputum analyses for the 47 COPD patients are reported in Table 3. The nasal IL-8 concentration correlated positively with that in sputum, as illustrated in Figure 2 ($r = 0.30$; p = 0.039). No significant relationships were observed for the leukocyte count, IL-6 concentration, or total bacterial load. However, lower airway colonization with a PPM was associated with a higher total nasal bacterial load (difference, 1.5 log cfu/mL; p = 0.016) [Fig 3]. Both COPD patients with a nasal PPM had the same species isolated in their sputum at the same visit.

The median serum IL-6 concentration was 4.7 pg/mL (IQR, 3.1 to 8.3 pg/mL). The serum IL-6 concentration did not correlate significantly with inflammatory indexes or markers of bacterial colonization in either the upper or lower airway samples.

Relationships Among Nasal Wash Fluid, Sputum, and Clinical Parameters

The mean nasal score was higher, but not significantly so, in COPD patients than in the control subjects and was highest in those COPD patients who continued to smoke (Table 1). The nasal score did not correlate with nasal inflammatory markers, but the presence of postnasal drip was associated with both a higher sputum cell count (p = 0.043) and the presence of a sputum PPM (p = 0.049).

We found no significant relationships between nasal inflammatory markers and clinical indexes, including smoking status, FEV_1, or exacerbation frequency, over the previous 12 months. Sputum bacterial load correlated positively with exacerbation frequency, as has been previously reported ($\rho = 0.32$; p = 0.029).[17]

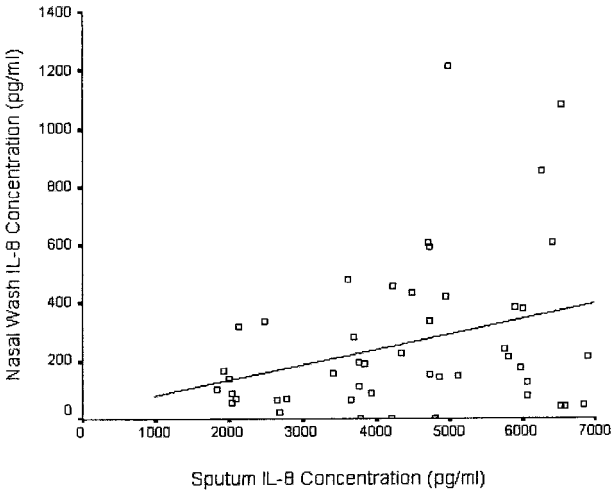

FIGURE 2. Relationship between IL-8 concentration in paired nasal wash fluid and sputum samples from 47 patients with COPD ($r = 0.30$; p = 0.039).

DISCUSSION

This study has demonstrated increased levels of the neutrophil chemoattractant protein IL-8 in the upper airway of COPD patients when compared to control subjects of similar age, sex, and smoking status. The upper airway IL-8 concentration correlated with that in the lower airway, and at both sites the concentration was related to indexes of bacterial colonization. Furthermore, lower airway colonization with a PPM was associated with both postnasal drip and a higher nasal bacterial load. This study is therefore the first to suggest a correlation between the degree of upper and lower airway inflammation in COPD patients. We did not find significant relationships between upper or lower airway inflammatory cytokines, or bacterial colonization, and a marker of systemic inflammation.

We have previously described[8] a high prevalence of chronic nasal symptoms in a cohort of patients with well-characterized COPD. The basis for these nasal symptoms has not been explained. Nihlen and colleagues[19] have recently reported that COPD patients, particularly those with nasal symptoms, have an exaggerated nasal neutrophil response to histamine challenge. IL-8 is a potent chemotactic factor and activator of neutrophils.[20] Our finding of a raised IL-8 concentration in the nasal wash fluid of COPD patients, and the highly significant correlation between nasal wash fluid IL-8 concentration and leu-

Table 3—*Inflammatory Markers in Nasal Wash Fluid and Sputum From 47 Patients With COPD*

	Nasal Wash		Sputum	
Markers	Median	IQR	Median	IQR
IL-8, pg/mL	168.5	76.1–359.4	4,472.6	3,406.6–5,903.7
IL-6, pg/mL	2.6	1.0–6.1	190.5	122.9–376.4
Leukocyte count, cells/mL	12,500	3,693–35,231	781,893	325,380–1,473,684
Bacterial load, log cfu/mL	2.3	1.8–3.7	7.4	7.0–8.0

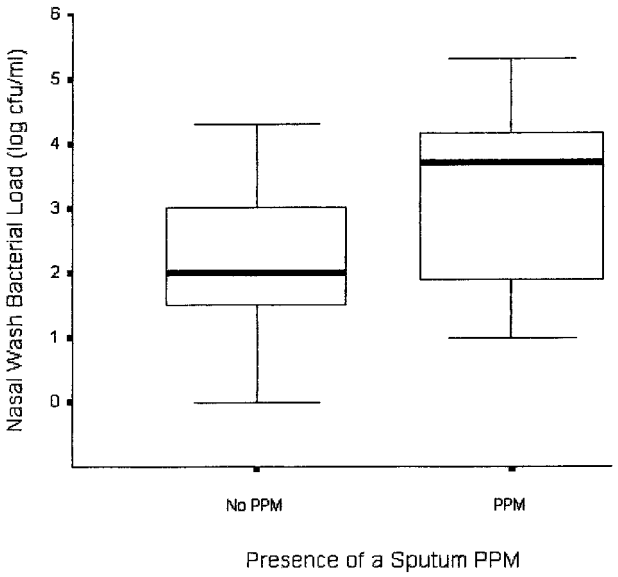

FIGURE 3. Comparison of nasal bacterial load in 47 COPD patients with and without a lower airway colonizing PPM. Box plot represents median, IQR, and range ($p = 0.016$).

kocyte count, also suggests the presence of a neutrophilic inflammatory process in the upper airways of these patients. Although we did not demonstrate a direct relationship between nasal symptoms and IL-8 concentration, neutrophilic inflammation remains a plausible cause of nasal symptoms. In experimental rhinovirus infection, the nasal IL-8 concentration was related to the severity of symptoms,[21] and the intranasal administration of IL-8 can induce rhinorrhea.[22]

A recent study by Vachier et al[10] has also suggested the presence of neutrophilic inflammation in the nasal airways of patients with COPD. However, all of these patients continued to smoke, a behavior that is known to affect both nasal symptoms[23] and cytokine concentrations.[24] We therefore compared control subjects, none of whom were active smokers, with the subgroup of COPD patients who were ex-smokers. The finding of a raised IL-8 concentration in the nasal wash fluid of COPD patients even after prolonged smoking cessation is novel and suggests the presence of ongoing upper airway inflammation in these patients. This phenomenon is known to occur in the lower airway,[25] and our results suggest that the upper and lower airways are behaving in a similar manner.

In both the COPD patient and control subject populations the degree of upper airway inflammation was related to indexes of bacterial colonization. In the COPD patients, there was a trend to correlation between the nasal bacterial load and the IL-8 concentration in nasal wash fluid that suggested a relationship between the neutrophilic response and bacterial carriage. It has been previously reported[11] that lower airway bacterial colonization modulates lower airway inflammation. The demonstration of a relationship between upper airway bacterial colonization and heightened nasal inflammation is further evidence of the similarity between upper and lower airway pathology in COPD patients.

This is the first study to demonstrate a significant relationship between the degree of upper and lower airway inflammation in COPD patients, as assessed by nasal and sputum IL-8 concentration. However, while statistically significant, the correlation coefficient of 0.3 suggests that only 9% of the variance in inflammation at one site is accounted for by the degree of inflammation at the other. Other local mechanisms must therefore contribute to airway inflammation, which, as discussed above, are likely to include bacterial carriage.

There is a considerable volume of work exploring the relationships between the upper and lower airways in asthma patients. In addition to the strong epidemiologic links between rhinitis and asthma,[3] there are many pathophysiologic similarities.[26] This has resulted in the concept of an inflammatory "cross-talk" between the nose and the lung,[6] which becomes of clinical relevance with the suggestion that treating the rhinitis of patients with asthma may improve their asthma symptoms.[27] Our results suggest that in patients with COPD there is also a pan-airway inflammatory response, reflecting the pan-airway exposure to cigarette smoke. This has important implications. First, the nose may provide new therapeutic targets that could result in the modulation of lower airway inflammation, in addition to reducing nasal symptoms. Second, our findings of a similar inflammatory process in the upper and lower airways suggest that the nose deserves further study and that it may provide a more accessible site for future COPD airway research.

A number of mechanisms have been suggested to explain the link between the upper and lower airway in asthma, including the direct passage of mediators along the respiratory mucosa, blood-borne passage, and neural responses.[26] Our finding of higher nasal bacterial load in patients with lower airway colonization suggests a possible mechanism for the relationship between upper and lower airway inflammation in COPD patients. We hypothesize that patients with a higher nasal bacterial load (and associated greater nasal inflammation) may be more likely to pass bacteria into the lower respiratory tract where colonization is known to be associated with increased lower airway inflammation. The demonstration of a relationship between postnasal drip and the presence of a lower airway PPM provides further evi-

dence to support this hypothesis. Although only two patients with COPD were colonized with a nasal PPM, nasal bacterial carriage is dynamic. It is also possible that the discrepancy in colonization rates between the upper and lower airway samples could be accounted for by the nasal wash technique that was employed, which samples the nasal cavity but not, for example, the posterior nasopharynx. Since lower airway bacterial load is known to relate to clinically important variables such as the rate of decline in FEV_1[28] and exacerbation frequency,[17] it is possible that strategies aimed at reducing nasal bacterial carriage could provide new therapeutic strategies in COPD patients.

In contrast to the relationships described between the upper and lower airway, we did not find a significant correlation between either upper or lower airway inflammation and the systemic inflammatory response, as assessed by the serum IL-6 concentration. We measured IL-6 because this cytokine is known to mediate the hepatic production of fibrinogen, which may represent a mechanism underlying the link between COPD and increased cardiovascular mortality.[29] The current data suggest that in stable patients with COPD the degree of systemic inflammation is independent of airway IL-8 concentration and bacterial colonization. This is in contrast to data from a recent report by Banerjee et al[30] describing a relationship between the presence of a lower airway PPM and higher serum fibrinogen level. The latter study used a different definition of PPM from that in the current study, which may explain the apparent discrepancy, and which serves to highlight that the links among the degree of airway inflammation, systemic inflammation, and cardiovascular morbidity also require further investigation.

In this study, we have compared soluble mediators in nasal wash fluid and sputum. An alternative approach for studying the upper and lower airways would be with matched nasal and bronchial biopsy specimens. This has been performed in asthma patients[31] and, more recently, in patients with relatively mild COPD.[10] However, the morbidity and mortality in COPD patients is most pronounced in those with more severe underlying disease. In these patients, biopsy studies are more difficult to perform because the greater severity of airflow obstruction precludes volunteer research bronchoscopy procedures for reasons of safety.

We have used a nasal wash technique adapted from that of Hilding.[18] In contrast to sputum analysis, in which standard protocols have been developed,[32] a variety of methods may be used to assess the upper airway.[33,34] For the analysis of soluble mediators, the three main approaches are the collection of spontaneous secretions, absorption, or dilutional nasal wash techniques.[35] Collecting spontaneous secretions directly or by absorption may not provide enough secretion for analysis, and we therefore elected to use a dilutional nasal wash technique. The major concern with the nasal wash technique is that the collected nasal secretion is diluted to an unknown degree.[36] Our data suggest good reproducibility of this nasal wash methodology. A number of methods of correcting for dilution have been suggested including dividing the cytokine concentration by the total protein level.[36] In preliminary experiments, we found that the total protein level itself correlated with IL-6 and IL-8 concentrations in nasal wash fluid, and the bacterial load, perhaps because of increased protein transudation in the inflamed noses of these patients with COPD. Correcting the cytokine concentration using total protein measurement did not enhance the differences between the control subjects and COPD patients, and diminished reproducibility between the repeat washes. Our results therefore remain uncorrected.

In conclusion, we have demonstrated that COPD is associated with an increased nasal concentration of the neutrophil chemoattractant protein IL-8 and, furthermore, that this upper airway IL-8 concentration was related to that present in the lower airway. A relationship between lower airway bacterial colonization and both higher nasal bacterial load and postnasal drip may suggest a possible mechanism for cross-talk between the upper and lower airways in COPD patients. This study is the first to report a correlation between the degree of upper and lower airway inflammation in COPD patients. These findings have implications for the use of the nose as a model of the lower airway in COPD patients, and in suggesting novel therapeutic targets to treat this common and debilitating condition.

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Qualitative Aspects of Nasal Irrigation Use by Patients With Chronic Sinus Disease in a Multimethod Study

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ABSTRACT

PURPOSE We qualitatively assessed attitudes regarding use of hypertonic saline nasal irrigation (HSNI) for frequent rhinosinusitis and chronic sinonasal symptoms in a 3-part, multimethod study.

METHODS We conducted semistructured, in-depth interviews with 28 participants who recently used nasal irrigation in studies assessing HSNI.

RESULTS Four themes emerged: (1) HSNI improved self-management of sinus symptoms, creating a sense of empowerment; (2) HSNI produced rapid and long-term improvement in quality of life; (3) participants identified discomfort, time, and mild side effects as barriers to HSNI use; and (4) participants identified aspects of training and at-home use that overcame these barriers.

CONCLUSION HSNI is a safe, well-tolerated, inexpensive, effective, long-term therapy that patients with chronic sinonasal symptoms can and will use at home with minimal training and follow-up. Success with HSNI will likely be improved by patient education.

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INTRODUCTION

Rhinosinusitis[1] is a common clinical problem with considerable morbidity and often-refractory symptoms, accounting for approximately 26.7 million office and emergency department visits and resulting in $5.8 billion in direct costs for 1996.[2] Rhinosinusitis was the fifth most common diagnosis for which antibiotics were prescribed from 1985 to 1992.[3] The Centers for Disease Control and Prevention has estimated the 1994 number of cases of chronic rhinosinusitis in the United States to be 35 million, a prevalence of 134/1,000.[4] The impact on patients' quality of life is significant.[5]

Originally part of the Yogic and Ayurvedic traditions, hypertonic saline nasal irrigation (HSNI) is an adjunctive therapy for rhinosinusitis and sinus symptoms[6-8] that flushes the nasal cavity, facilitating the evacuation of potentially allergen- and irritant-containing mucus[9] (Figure 1). Several randomized controlled trials examining HSNI suggest that it is a safe, effective, and tolerable therapy for rhinosinusitis and sinus symptoms.[10-17] Previous randomized controlled trials have reported improvement of quality-of-life scores,[10-12,17] and improvement of several surrogate measures.[12-14,17] In a closely monitored 6-month randomized controlled trial (phase 1, Figure 2),[17] our group found that daily HSNI using 2% saline is associated with high patient satisfaction, improved quality of life, decreased antibiotic and nasal spray use, and improved sinus symptoms in adult participants with a history of frequent rhinosinusitis and chronic sinus complaints. In a 12-month follow-up study (phase 2),[18] we found that patient education

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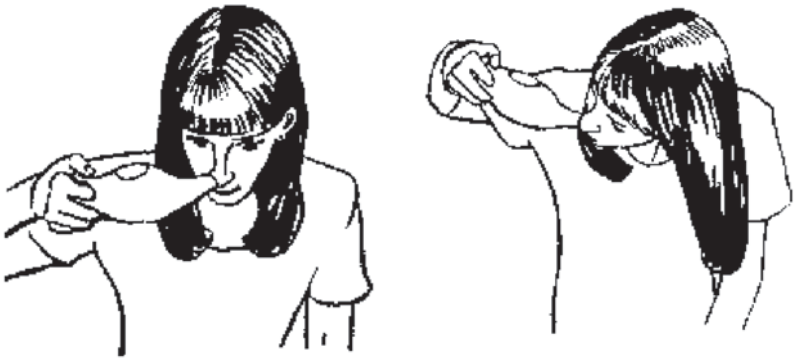
Figure 1. Nasal irrigation technique.



without close monitoring enabled phase 1 control participants to initiate and maintain identical HSNI use patterns, and that control participants had the same significant and clinically meaningful improvements in quality of life. HSNI has received attention in the lay press[19] and was recently identified as "an important component in the management of most sinonasal conditions" that is "effective and underutilized."[20]

Successful use of even proven therapy is often difficult for patients, however.[21] Clinicians may be hesitant to prescribe unfamiliar therapy, and misunderstandings between clinician and patient often occur.[22] HSNI is associated with difficult adherence issues because rinsing the nasal cavity is not intuitive. Clinicians and patients would be well served by descriptive information of successful HSNI use, but no study has assessed the natural history of long-term use of HSNI and its incorporation into daily life. We therefore undertook a qualitative study (phase 3) to assess perceptions, experiences, and strategies regarding successful HSNI use at the conclusion of phases 1 and 2.

METHODS

The study protocol was approved by the University of Wisconsin Health Sciences Human Subjects Committee. The inclusion criterion was being an HSNI-user in either the phase 1 randomized controlled trial or the phase 2 follow-up study (Figure 2). The primary inclusion criteria of phase 1 was having either 2 episodes of acute sinusitis or 1 episode of chronic sinusitis per year for 2 consecutive years, and a moderate-to-severe overall daily quality-of-life burden of sinus disease. Participants randomized to HSNI in phase 1 received an educational intervention that included a brief discussion of rhinosinusitis, a demonstration of HSNI, and coaching to facilitate each participant's proficiency. All participants in phase 1 were monitored frequently with validated questionnaires.[23] In phase 2, phase 1 control participants were given the same patient-education and pooled into 1 HSNI use group. All phase 2 participants were thereafter assessed less frequently. The mean HSNI use frequency at the time of the interviews was 2.4 irrigations per week after at least 12 months of assessment.[18] For the current study, we contacted phase 1 and phase 2 HSNI users sequentially from a randomized list of all 66 possible participants (Figure 2). Study personnel tape-recorded interviews of 21 participants in person and 7 participants by telephone at our institution from April to July 2002. We followed a standard qualitative research method of transcribed, in-depth, long interviews.[24] The semistructured 30-minute interview consisted of open-ended questions with several prompts that the interviewer could use to encourage salient discussion (Table 1). Transcripts were stripped of all identifiers except a code number. All interviews were completed and transcribed before being analyzed. Each transcript was reviewed individually by each of the first 4 authors and was then discussed by all of the first 4 authors in 6 meetings over 2 months using a consensus approach to identify major themes.

RESULTS

Consent from 28 participants was obtained from the first 35 HSNI users queried; 7 participants declined to participate, stating they did not have time, resulting in a 28-member sample similar to the 66 HSNI users in phases 1 and 2 in sex, age, and quality-of-life scores at the beginning and end of the studies. One participant had completed phase 1 only, 27 had completed both phases 1 and 2 (Table 2). The 28 transcribed interviews were analyzed in 6 meetings. Four major themes emerged (Table 3).

Major Themes

Empowerment

Among the major themes, participants reported several ways in which use of HSNI improved their ability to control sinus symptoms and their treatment, a major aspect of their health and health care. We have termed this *empowerment*. Participants expressed a strong sense of satisfaction with the ability to use, monitor, and adjust several aspects of HSNI themselves (eg, water temperature, salinity, timing, frequency) as opposed to making multiple office visits with a clinician. This attitude was commonly reflected in such comments as,

"I've learned that I can take care of a lot of this [sinus symptoms] by myself, so I do," and "… [HSNI] makes me feel more in control of my own health and my own sinus condition." Participants also expressed satisfaction in their perception that at-home use of HSNI greatly reduced the number of trips to their physician and the number of antibiotic prescriptions.

Improvement in Quality of Life

Participants confirmed the results of phases 1 and 2; use of HSNI improved short- and long-term sinus symptoms and sinus-related quality of life. Many participants were enthusiastic, reporting improvements with the first or second use: "… my results were immediate," and "… almost instant relief of the congestion." Most participants also confirmed positive long-term effects of HSNI on sinus-related quality of life, and noted a deep sense of satisfaction associated with the diminution of their sinus symptoms, often reflected in moving comments, such as, "It just made a world of difference in my life," and "… when you suffer from a chronic illness for so long and then you don't, … it's such a big relief … (to) enjoy things that people take for granted." Participants

Table 1. Open-Ended Questions for Participant Discussion

1. What were your sinus problems like before using nasal irrigation, and how did nasal irrigation affect you?
2. Did you experience any problems from using nasal irrigation?
3. How did you fit nasal irrigation into your life?
4. Did you get any reactions about using nasal irrigation from those around you?
5. How do you feel about nasal irrigation now?
6. What was the informational meeting like for you?
7. Is there anything else you'd like to tell us about your experience with nasal irrigation or this study?

Figure 2. Subject participation in phase 1, randomized controlled trial; phase 2, follow-up study; and phase 3, current study.

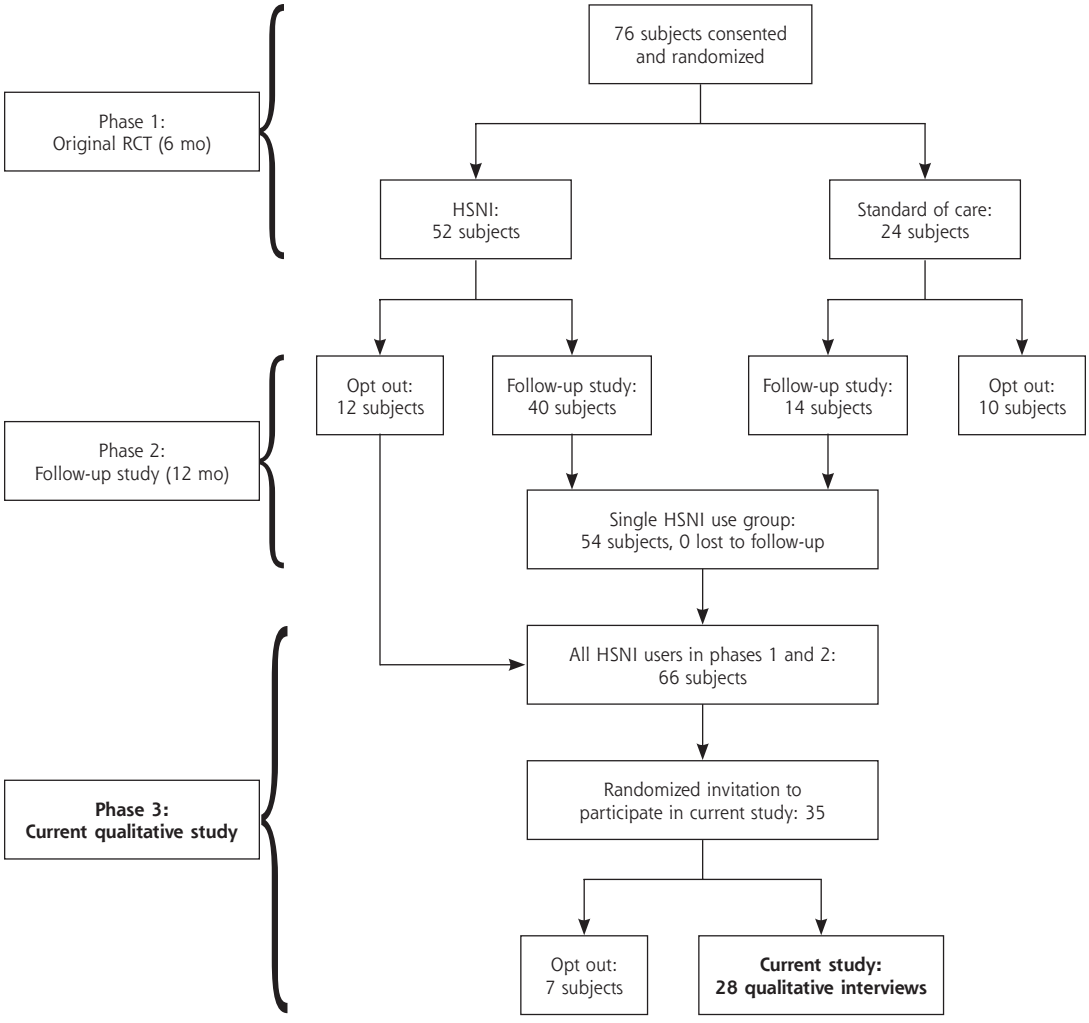


Table 2. Baseline Demographic, Medical Characteristics, and Quality-of-Life Scores of All HSNI Users and Current Study Participants

Characteristic	Phase 1 and 2 HSNI Users (n = 66)	Current Study/ Phase 3 Participants (n = 28)
Age, y ± SEM	42.4 ± 1.3	44.8 ± 1.8
Female, No. (%)	48 (73)	19 (68)
Baseline RSDI,* No. ± SEM	58.8 ± 1.8	57.2 ± 2.9
Baseline SIA,† No. ± SEM	3.95 ± 0.12	4.02 ± 0.20
Seasonal allergies, No. (%)	44 (67)	21 (75)
Asthma, No. (%)	16 (24)	7 (25)
Nasal surgery, No. (%)	25 (38)	12 (43)
Nasal polyps, No. (%)	11 (17)	3 (11)
Deviated septum, No. (%)	16 (24)	8 (29)
Quality-of-life scores at end of phase 2		
End of phase 2 RSDI, No. ± SEM	77.9 ± 1.8	80.1 ± 2.9
End of phase 2 SIA, No. ± SEM	2.36 ± 0.13	2.29 ± 0.18

HSNI = hypertonic saline nasal irrigation; RSDI = Rhino Sinusitis Disability Index; SIA = single-item assessment.

* Using a 30-item validated multidimensional disease-specific assessment instrument, participants scored their sinus symptoms: 0 = maximal impact of sinus symptoms on quality of life, 100 = no impact.

† Using a 1-7 Likert scale, where 1 = no impact, and 7 = maximal impact, participants responded to the statement: "Please evaluate the overall severity of your sinus symptoms since enrolled in the study."

also expressed satisfaction with a perceived association with decreased allergy symptoms and with the naturalness and economy of HSNI.

Barriers to HSNI Use

While HSNI was effective for many participants, many also reported substantial barriers to initial and consistent use of HSNI. These barriers included fear of having water in the nasal cavity, initial unpleasant sensation of water in the nasal cavity, having to learn how to perform HSNI effectively, taking time at home to do HSNI, and experiencing occasional mild side effects. Consistent with phases 1 and 2, such side effects as saline drainage, nasal burning, or irritation were noted but not identified as important enough to stop HSNI.

Strategies to Overcome Barriers to HSNI Use

Participants identified how they overcame barriers to using HSNI. Participants identified each element of the teaching strategy used in the introductory meeting as important in their use of HSNI. These 30-minute meetings were made up of 2 to 6 participants per meeting; they involved a sequence of activities starting with a group discussion of participants' sinus disease histories, a 5-minute film and discussion of nasal irrigation, and a demonstration and coached practice of HSNI. Participants identified coached practice as the single most important element of the enrollment meeting. Each participant was able to perform the procedure before leaving the enrollment meeting.

Participants also noted several at-home strategies that facilitated regular use, which included incorporating HSNI into an already-existing daily hygiene routine, placing HSNI materials in convenient and accessible locations, adjusting the HSNI use schedule and salinity to decrease or eliminate discomfort, and using warm water. Social concerns were also addressed by our interviewers. Because HSNI therapy is novel for most patients and could engender stigma or embarrassment, we wondered whether social issues played a part in the tendency to regular use. Participants reported reactions from family and friends that included encouragement, surprise, or amusement; none reported that negative reactions from family or friends limited their use of HSNI.

The themes and quotations illustrate participants' range of experience. The overall story of using HSNI, however, may be better told using an extended quotation. An abbreviated transcript of a representative participant whose narrative provides a more personal view of the major themes can be found in Table 3. Her reporting was neither especially negative about the initial aspects of nasal irrigation nor overly effusive about her success. It is consistent with the data from this group of participants who had a debilitating condition (chronic sinus symptoms), who were introduced to a nonintuitive therapy, the mastery of which required work and insight (performing HSNI), and who achieved therapeutic success (improved quality of life). Her transcript identified the core themes in a matter-of-fact manner. Bracketed words are the authors' interpretation of the participant's original intent; they are used to link ideas or abbreviate wordiness.

DISCUSSION

This study is the third of a 3-phase study assessing HSNI for frequent rhinosinusitis and chronic sinus complaints. Phases 1 and 2 found that participants in both a fastidious[25] randomized controlled trial[17] and pragmatic follow-up setting[18] experienced improved quality of life, reduced sinus symptoms, and decreased use of sinus medications, including antibiotics. The current study is the first to assess the perceptions, experiences, and strategies surrounding use of HSNI and thereby bridge

Table 3. Major Themes and Representative Narrative Emerging From the Qualitative Survey

Theme	Descriptive Comments
Empowerment	"It's really truly a wonderful opportunity for me to get what I needed health-wise that makes me feel more in control of my own health and my own sinus condition."
	"What's different is that I don't anymore feel like there's no relief."
	"It's so simple, whenever you want, you can do it."
	"I've learned that I can take care of a lot of this by myself, so I do."
	"You don't have to run to the doctor every few months to get on antibiotics again."
	"The best thing is not having to go to the doctor. Not having to use antibiotics."
Quality of life	" ... almost instant relief of the congestion...."
	"... my results were immediate. I went from being congested to breathing, and I would stay clear all day."
	"I could actually feel ... the pressure—kind of a dam held, and then it whooshed out the other side."
	"It just made a world of difference in my life."
	"For me this is the magic cure for my sinuses."
	"Best thing I've ever had. Better than any medication. It's amazing. I would recommend it to anybody."
	"When you suffer from a chronic illness for so long and then you don't have problems with it anymore: I think it's such a big relief and I can't explain it, it's such a big change where you can enjoy things that people take for granted."
	"I was so desperate to get some relief from my sinuses and not have to go back and have surgery again. Planting my flower beds was just terrible, I would just have hay fever and then I'd be plugged up and then I'd have to go to the doctor. (Now) I can go outdoors ... and not worry about my sinus' plugging up on me and causing the great facial pain. I really couldn't believe that that one simple thing could have changed my life, but it has."
Barriers to use of HSNI	"It was [initially] uncomfortable and it kind of burned."
	"... the first time that you use it, it's a strange sensation—that feeling of water...."
	"... it was kind of strange—kind of like you're drowning, almost ..."
	"Pure and simple: it was gross. It took a while to get used to it. It felt really funky."
	"The hardest part was creating a habit of doing it and doing it all the time."
	"I thought it was not a very graceful thing. Not a very easy thing to do."
Strategies for overcoming barriers	
Teaching strategies	"It helped to hear that there were other people going through those reactions and stuff, and I didn't realize that I was feeling isolated until I met some of the other people."
	"(The part of the first meeting I liked most ... was) being around other people that are having trouble with their sinuses."
	"It needs to be not just prescribed: It needs to be taught with a video or some type of informational packet with it."
	"I think the demonstration that the doctor had with us was the most helpful part."
	"The hands-on was critical."
	"The actual instruction when we went to the [sink] and you showing us directly how to use it made all the difference in the world."
At-home strategies	"I just established a habit."
	"I learned to adjust the temperature and salt content to what felt best."
	"I guess when I was in the shower it was a lot easier."
	"I don't know if I was more relaxed and the steam or whatever..., but it seemed to be a lot more effective in the shower."
	"After you do it a few times, it's nothing anymore"
Representative narrative	"I spent a lot of time in the doctor's office for sinus infections or being frustrated with sinus symptoms ... and [had] frequent sinus headaches–as many as 3-4 per week. [The first time I used HSNI] it felt like warm water running down my nose and some of it into my throat ... I did it wrong. My initial thought was 'Oh my God, this is not going to work.' But I did it ... when we were coached ... and I ... worked at it ... about 20 minutes in the bathroom that night. When I got it to work, it felt wonderful. I'd say it took a week before I got it down to a fine art. The first evening, I could already tell I was cleaning something out.... I was blowing all this junk out of my head. By the third evening, it was clear that there was definitely a point to this, less sinus drainage, and that it was going to help me. I also notice that I've been able to smell things [better]. I haven't had a sinus infection in I can't remember how long. I use it about 3 days out of 7, when my nose puffs up ... or my sinuses start swelling. I don't wait until I get severe [sinus symptoms] to go back to use [HSNI] every day. [The worst thing about nasal irrigation] is having to occasionally clean my face, not a big deal. For me warm water is more comfortable and seems slightly more effective. I use [HSNI] in the shower [or by the sink], clean the face, brush the teeth. I store the materials tucked in a closet in the bathroom and [leave] the water bottle and nasal pot sitting on the counter. I leave it out [as a reminder]. In the winter I'll do it twice per day ... in the summer [once]. [I use] gentle variations of the positions they taught us. [The mixing of the solution] is the easiest part; I generally do that [with each use]. My partner has been supportive. My family says [HSNI] is 'bohemian' and roll their eyes a little, but they never bothered me."
	"[I will continue to use nasal irrigation] and have several friends who have sinus and allergy troubles to whom I've introduced [HSNI], and recommend it to others. Small-group demonstration is the best way to teach [it]. You get a demonstration from someone who knows [it. They tell you] 'you will feel the water here and there.' That alleviates the [concern of drowning, or the water getting in the wrong place]. One person [should train] 2 to 3 people, [and] actually do [HSNI]."
	"I'm amazed and a bit humbled. There ought to be a way to [find] ... people with [sinus problems] and send them information about this treatment. More ... people are beginning to say, 'OK, what alternatives are there to antibiotics?'"

the gap between clinical effectiveness of HSNI in formal studies and success with at-home use. We found that participants receiving clear and focused instruction can overcome initial barriers to HSNI use and can create at-home strategies to facilitate long-term HSNI use.

Effective teaching combined with a positive clinical outcome led to improved quality of life and sense of empowerment for these participants. The introductory meeting set the stage for participants' use of a therapy by establishing a relationship with research staff and trust in the overall research plan. Group discussion of clinical histories promoted an esprit de corps regarding use of HSNI and participation in the study. Group interaction and discussion have been used to facilitate understanding and acceptance of one's condition, and the notion that active involvement in therapy can facilitate improved clinical outcomes. Group discussion also served to decrease the alienation and stress that participants may have felt in isolation. Hearing others' clinical stories likely increased bonds with fellow participants and may have helped participants feel that their own story was heard and valued. Positive effects of group behavior programs have resulted in improved outcomes in other treatment settings.[26-28]

Early demonstration and coached practice of HSNI ensured proficiency before the participants' first at-home use. Patient education and coached practice have been identified as important aspects of successful care of chronic illness[29] and have been linked to successful treatment of chronic conditions such as asthma and COPD.[30]

Given that the immediate effect of HSNI under supervision was generally positive, and side effects were limited, participants were able to adapt the scheduling, location, and materials handling to best suit their personal and social context in the long term. This ability to manage their own treatment likely contributed to the reported sense of empowerment and personal control of their chronic symptoms, further enabling continued use. A sense of empowerment among users of complementary medical therapy is consistent with recent findings that characterize patients' views about complementary medical therapy compared with conventional therapy.[31]

Because 3 of us (DR, BB, RM) were co-researchers on phases 1 and 2, we anticipated that the comments would be positive, but several aspects of the results surprised us. First was the passion and drama of many reports. Sinus disease, HSNI, and clinical improvement are clearly important to these participants and deeply affect the quality of their lives. Also surprising was the uniform reporting about 2 issues. First, most participants expressed the need to overcome the oddness of pouring water through the nasal cavity, Second, it was worth the effort of doing so, because HSNI truly improved quality of life for this group of participants, most of whom had had less success with multiple previous therapies.

Our study has several limitations. These results may not generalize well to patients who have uncomplicated acute bacterial rhinosinusitis, less-frequent rhinosinusitis, sinus symptoms that are less chronic, or have undergone less HSNI coaching. Recollection of initial experiences and feelings toward HSNI may have been inaccurate, because participants were interviewed 12 to 18 months after starting phase 1. We did not use an iterative process to guide the formulation of interview questions and may have missed issues important to participants. The researchers may have been biased in favor of HSNI because 3 coauthors were familiar with the positive quantitative HSNI results of phases 1 and 2.

Implications for Clinicians

This study has important implications for clinicians. HSNI can be confidently and safely prescribed to patients with chronic sinonasal symptoms. Adherence to HSNI will likely be improved by a patient-education encounter that includes coached practice of HSNI. Consideration should be given to grouping several patients into a single class for patient education. In our clinical practice, we describe the rationale for HSNI as part of the treatment plan for patients with chronic sinonasal complaints; if the patient is interested, we explain the technique with an illustrated patient handout, as shown in Supplemental Appendix, which can be found online at http://www.annfammed.org/cgi/content/full/4/4/295/DC1, and at http://www.fammed.wisc.edu/research/projects/nasalirrigation-instructions.pdf), before we proceed with guided practice. We recommend using nasal irrigation once daily at the onset of sinus symptoms until resolution, and thereafter for maintenance as needed. The materials are inexpensive, and nasal irrigation cups are increasingly available at local pharmacies nationwide.

Implications for Researchers

This study has implications for future HSNI research. Questions remain about the basic science of HSNI, clinical protocol (eg, irrigation schedule, irrigant concentration, buffering, and irrigant delivery system), specific indications, and optimal training techniques and context. These issues require study in a larger patient population with more identified subgroups, including acute bacterial rhinosinusitis, vasomotor rhinitis, and asthma.

In addition, the current study also has implications for primary care research. Integrated, multi-

method research techniques in primary care have been described and advocated.[32,33] Taken together with phases 1 and 2, the current study is an example of such an approach. By using both qualitative and quantitative methods, a broader and deeper picture of HSNI use emerges than if either were used alone. Phases 1 and 2 used a conventional, quantitative hypothesis-testing approach that produced internally consistent conclusions; HSNI is an effective therapy for patients with recurrent rhinosinusitis and chronic sinonasal complaints. In phase 3, we asked participants to describe and interpret the experience of HSNI. Such qualitative data brings the use of HSNI closer to real clinical life by making the quantitative findings easier to act upon for physicians and patients.

Participants confirmed positive results from 2 previous studies. HSNI is an effective, safe, well-tolerated, inexpensive therapy that patients with frequent rhinosinusitis and chronic sinus symptoms can learn in the office and use at home over the long term with minimal training and follow-up. Clinical success with HSNI will likely be improved by brief patient education, HSNI demonstration, in-person coaching, and the ability to tailor HSNI use to individual needs.

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Key words: Nasal irrigation; sinusitis/therapy; rhinosinusitis; chronic sinus symptoms; quality of life; qualitative study

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Respiratory syncytial virus (RSV) SH and G proteins are not essential for viral replication *in vitro*: Clinical evaluation and molecular characterization of a cold-passaged, attenuated RSV subgroup B mutant

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ABSTRACT **A live, cold-passaged (*cp*) candidate vaccine virus, designated respiratory syncytial virus (RSV) B1 *cp*-52/2B5 (*cp*-52), replicated efficiently in Vero cells, but was found to be overattenuated for RSV-seronegative infants and children. Sequence analysis of reverse-transcription–PCR-amplified fragments of this mutant revealed a large deletion spanning most of the coding sequences for the small hydrophobic (SH) and attachment (G) proteins. Northern blot analysis of *cp*-52 detected multiple unique read-through mRNAs containing SH and G sequences, consistent with a deletion mutation spanning the SH:G gene junction. Immunological studies confirmed that an intact G glycoprotein was not produced by the *cp*-52 virus. Nonetheless, *cp*-52 was infectious and replicated to high titer in tissue culture despite the absence of the viral surface SH and G glycoproteins. Thus, our characterization of this negative-strand RNA virus identified a novel replication-competent deletion mutant lacking two of its three surface glycoproteins. The requirement of SH and G for efficient replication *in vivo* suggests that selective deletion of one or both of these RSV genes may provide an alternative or additive strategy for developing an optimally attenuated vaccine candidate.**

Respiratory syncytial virus (RSV), the leading cause of severe viral respiratory illness in pediatric populations throughout the world (reviewed in ref. 1), accounts for approximately 90,000 hospitalizations in infants and children in the United States each year (2). The importance of RSV as a respiratory pathogen makes development of a safe and effective RSV vaccine a public health priority (3). Although a number of approaches to RSV vaccine development have been taken, live RSV vaccines may provide the best alternative for immunizing young infants, because a live vaccine would mimic natural infection, induce a balanced cellular and humoral immune response, and be unlikely to produce enhanced disease (4).

RSV exists as two antigenically distinct subgroups, A and B, and both RSV A and RSV B infections are capable of inducing severe lower respiratory tract disease (5–7). For this reason, a bivalent live RSV vaccine containing attenuated RSV A and RSV B components would be most desirable. Recently, a live attenuated RSV A candidate vaccine has been identified that appears to be safe and immunogenic in infants and children over 6 months of age (8). In addition, a cold-passaged (*cp*) RSV B candidate vaccine, designated RSV B1 *cp*-52/2B5 (*cp*-52), was derived by passage of the RSV B1 wild-type (wt) virus 52 times at low temperature (21–32°C) (9). *Cp*-52 was shown to be restricted in replication *in vivo* but still able to induce RSV serum-neutralizing antibody responses in cotton rats, African green monkeys, and chimpanzees (9). Also, it was found to be phenotypically stable after prolonged replication in cotton rats (9). Here, we describe the phase I evaluation of the *cp*-52 candidate vaccine in adults, children, and infants. Although this virus mutant grew to high titer ($>10^{7.0}$ plaque-forming units (pfu)/ml) in Vero cell culture, it was poorly infectious and overattenuated for humans. When we sought to elucidate the genetic basis for its overattenuation, we made an unexpected discovery that this *cp*-52 virus, which is replication competent *in vitro*, contains a large deletion that ablates the synthesis of two of its three virion glycoproteins, namely the small hydrophobic (SH) and attachment (G) glycoproteins.

MATERIALS AND METHODS

Clinical Studies. The isolation and characterization of RSV B1 wt and *cp*-52 have been described elsewhere (9). Virus suspensions of the wt (lot RSV B1) and *cp*-52 mutant (lot RSV B-10) were grown in Vero cell culture and were found to be free of adventitious agents by Louis Potash (Dyncorp/PRI, Rockville, MD). The titers of the wt RSV B1 strain and RSV B1 *cp*-52 were $10^{5.0}$ and $10^{5.5}$ pfu/ml, respectively. When necessary, the viruses were diluted in L-15 medium (BioWhittaker) immediately before use.

Guidelines for human experimentation of the Joint Committee for Clinical Investigation of the Johns Hopkins University School of Medicine were followed in the conduct of clinical studies in adults, infants, and children. The RSV B1 wt virus and *cp*-52 each were evaluated in open-label, nonrandomized trials in healthy adults between 18 and 45 years of age. Evaluation of the wt RSV B1 virus was performed in the Johns Hopkins University Center for Immunization Research (CIR) isolation unit, and evaluation of the vaccine strain was performed in outpatient studies at the CIR, both as previously described (8). Nineteen volunteers in the inpatient study received $10^{4.7}$ pfu of RSV B1 wt, and 17 volunteers in the

Abbreviations: *cp*, cold-passaged; RSV, respiratory syncytial virus; wt, wild type; pfu, plaque-forming unit; moi, multiplicity of infection.

Data deposition: The sequences reported in this paper have been deposited in the GenBank database [accession nos. AF013254 (RSV B1) and AF013255 (RSV B1 *cp*52/2B5)].

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outpatient study received 10^5 pfu of RSV B1 *cp*-52. Both viruses were administered intranasally in a 0.5-ml inoculum.

After *cp*-52 was shown to be well tolerated in adults, it was evaluated in randomized, double-blind, placebo-controlled phase I trials in infants and children 6–59 months of age at the Johns Hopkins University Center for Immunization Research (CIR). The candidate vaccine was evaluated at a dose of 10^4 or 10^5 pfu in 22 RSV-seropositive children and 26 RSV-seronegative children, who were screened for level of RSV serum-neutralizing antibody by a 60% complement-enhanced plaque reduction assay as previously described (8). Each subject received 0.5 ml of vaccine or placebo intranasally. In the pediatric studies, the ratio of vaccinees to placebo recipients was approximately 2:1. Seropositive study participants and seronegative study participants were evaluated at the CIR for respiratory and febrile illnesses as previously described (8, 10).

Nasal wash specimens for virus isolation were obtained on each day of observation from all subjects who participated in these studies. Fresh undiluted nasal wash specimens were titered by plaque assay on Vero cell monolayer cultures maintained under a semisolid overlay at 32°C, and results were expressed as $\log_{10}$ pfu/ml (9). Nasal wash samples also were inoculated into tubes containing Vero cell monolayers and were identified as RSV-positive by using an indirect immunofluorescence assay (Bartels Microscan, Baxter Healthcare, Bellevue, WA). For purposes of calculation, samples in which virus was not detected or did not produce plaques were assigned an infectivity titer of $10^{0.6}$ pfu/ml.

Sera for measurement of RSV-specific antibodies were obtained from adults and RSV-seropositive children before and 4 weeks after inoculation of virus, and from RSV-seronegative children before and 8 weeks after inoculation. Sera were tested for antibodies to RSV by the plaque-reduction neutralization assay (11, 12), and the RSV antibody titers were expressed as reciprocal mean $\log_2$. Laboratory evidence of infection with RSV wt or vaccine strain was defined as isolation of RSV and/or a 4-fold or greater rise in serum RSV neutralizing antibody titer. The Fisher's exact test (two-tailed) was used to compare the percent of adults shedding wt and candidate vaccine virus.

Sequence Analysis. Vero cell monolayer cultures were infected with either the RSV B1 wt parent or *cp*-52 mutant virus at a multiplicity of infection (moi) of 0.2. After development of cytopathic effect at 3–5 days postinfection, infected cultures were frozen and thawed, and genomic RNA was extracted from clarified supernatants by using Trizol-LS reagent (Life Technologies, Grand Island, NY). Reverse transcription–PCR amplifications spanning the RSV genome were performed by using the GeneAmp XL RNA PCR Kit (Perkin–Elmer) and primer pairs specific to the RSV subgroup B strain 2B, which is highly related to B1 (unpublished observations). Briefly, reverse transcription was performed for 1 hr each at 55°C and 60°C, followed by hot start PCR with initial denaturation at 94°C for 3 min and 40 cycles of 94°C for 1 min, 55°C for 0.5 min, and 70°C for 5 min, followed by extension at 70°C for 10 min. A consensus sequence for the PCR amplified products was generated by using the Applied Biosystems-PRISM fluorescent dye terminator cycle sequencing kit with AmpliTaq DNA polymerase, FS and the Applied Biosystems 377 DNA sequencer (Perkin–Elmer). Sequences were analyzed by using the MacVector gene analysis program (Oxford Molecular, Oxford, UK).

Analysis of Gene Transcription Products. Total cell-associated RNA was isolated from Vero cells 48 hr after infection with either RSV B1 or *cp*-52 virus at a moi of 2. RNA was extracted with Trizol-LS reagent and analyzed by Northern blotting by using RSV B1-specific M, SH, G, and F gene probes (see Fig. 1*A*) as described in the Fig. 2 legend. Two G gene-specific probes designated G and Gsm were used: the G gene probe contains ≈380 nucleotides from the central portion of the G gene transcription unit, and the Gsm probe contains ≈300 nucleotides derived from the 3′ end of the mRNA (Fig. 1*A*).

Identification of G Glycoprotein by Western Blot. Vero cell monolayer cultures were infected with either B1 or *cp*-52 virus at an moi of 1, or were mock-infected. Cells were harvested at 30 hr postinfection into lysing buffer (1% Nonidet P-40/0.4% deoxycholic acid/66 mM EDTA/10 mM Tris·HCl, pH 7.4), and cell nuclei were removed by centrifugation (1,000 × *g*). Proteins from crude cell lysates were separated by electrophoresis on 8–16% gradient polyacrylamide-SDS gels under denaturing, but nonreducing conditions and analyzed by Western blotting with RSV G protein-specific mAb K6 purified from murine ascites fluid (13). A biotinylated horse anti-mouse IgG was used with an avidin DH and biotinylated horseradish peroxidase H detection system.

Identification of F or G Glycoproteins in Viral Plaques by Immunostaining. Viral plaques that developed on Vero cell monolayer cultures were immunostained by using a mouse anti-RSV F or G mAb-immunoperoxidase system as described previously (14). mAbs used to identify the RSV F and G glycoproteins in the plaques formed by B1 wt or the *cp*-52 mutant were kindly provided by Larry Anderson, Centers for Disease Control and Prevention, Atlanta, GA (mAbs 131–2 g, 130–5f, 92–11C, and 102–10B) and Edward Walsh, University of Rochester School of Medicine, Rochester, NY (mAb L9).

Analysis of Viral Growth at Low Temperature. To generate multicycle growth curves for RSV B1 wt and *cp*-52 viruses, Vero cell monolayers were infected with either virus at a moi of 0.01, and growth was assessed at 25°C. Aliquots of the supernatant were removed daily for 14 days postinfection, and virus was quantitated by plaque titration on Vero cell monolayer cultures incubated at 32°C.

RESULTS

Response of Adults and Children to wt RSV B1 and RSV B1 *cp*-52. The RSV B1 wt virus infected 53% of the adult volunteers and caused upper respiratory tract illness in 5 of the 10 infected adults. This degree of virulence of the wt virus in adults allowed us to assess the effect of the *cp*-52 mutations on attenuation. In contrast to individuals who received wt virus, only 6% of adults who received *cp*-52 shed virus [$P = .003$, Fisher's (two-tailed) exact test, Table 1]. This indication of attenuation of the *cp*-52 virus in adults suggested that it was safe to evaluate this candidate vaccine mutant in seropositive children, and subsequently in seronegative children. The *cp*-52 vaccine candidate infected seropositive and seronegative children, but the frequency and magnitude of virus shedding were low, especially compared with RSV subgroup A vaccines that had been evaluated similarly (8). In adults and children, vaccine virus was shed between days 3 and 10 after inoculation, likely the result of viral replication rather than recovery of the inocula. The limited shedding of *cp*-52, coupled with the absence of a serum antibody response by infected vaccinees (Table 1), indicated that *cp*-52 was infectious but overattenuated for susceptible humans. The *cp*-52 virus therefore had sustained one or more host-range mutations that did not restrict replication in Vero cells, but nonetheless were attenuating for humans.

Genetic and Immunologic Analysis of wt RSV B1 and RSV B1 *cp*-52. To understand the genetic basis of the host-range mutation(s), the nucleotide sequence of the B1 wt parent and *cp*-52 viruses was determined. The full RNA genome of B1 virus was amplified by reverse transcription–PCR as four overlapping fragments (I-IV) of ≈3.9-, 4.7-, 3.9-, and 4.7-kb length (data not shown). These amplified products were sequenced directly on both strands by using RSV 2B-specific primers. Consensus sequence of the full-length RSV B1 was

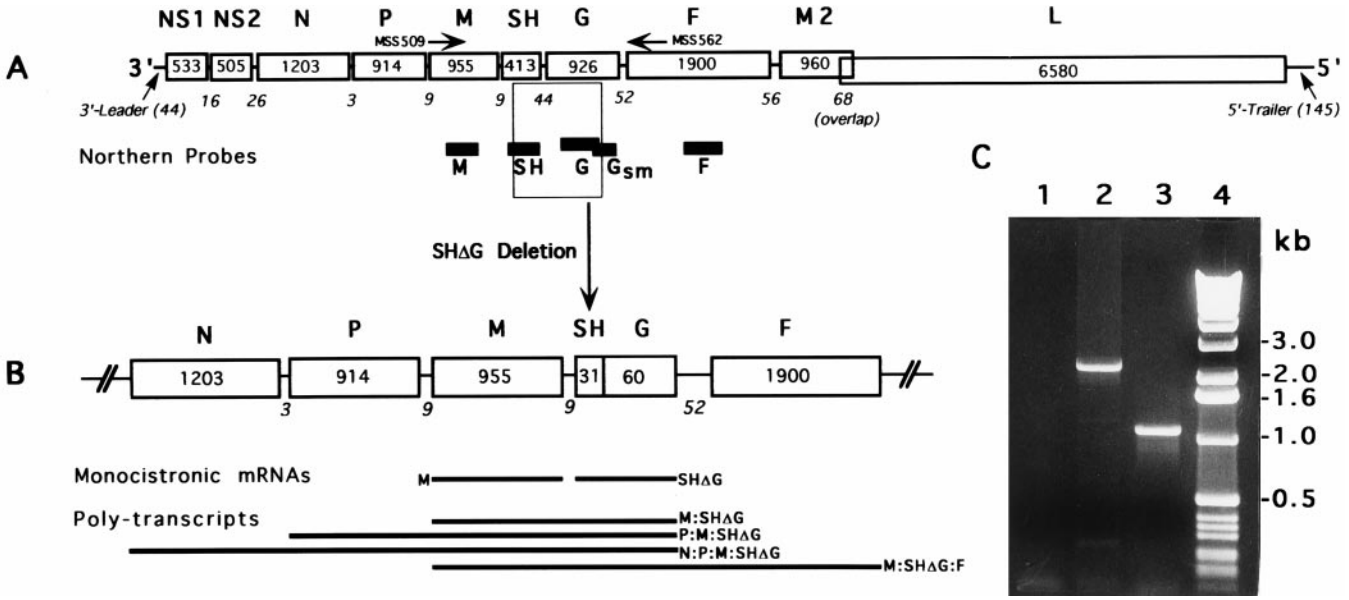

FIG. 1. Genetic map of the RSV B1 parental strain (15,225 nts) and its deletion mutant, *cp*-52 (13,933 nts). Genes are listed on top according to encoded proteins: NS1 and NS2, nonstructural proteins; N, nucleocapsid protein; P, phosphoprotein; M, matrix protein; SH, small hydrophobic protein; G, attachment protein; F, fusion protein; M2, second matrix protein; L, large polymerase protein. The numbers in boxes are gene lengths and numbers below are the length of the intergenic regions with the exception of M2:L, which has a 68-nt overlap rather than an intergenic region. Map is not to scale. (*A*) Genetic map of wt B1. Noncoding 3′-leader (44 nt) and 5′-trailer (145 nt) are the potential genomic and antigenomic promoters. A primer pair (MSS509/MSS562) used for amplification of fragment IIa across the deleted region of *cp*-52 virus is depicted by arrows. Genomic location of the RNA probes used for Northern analysis is depicted by solid bars under the RSV B1 genome. (*B*) Genetic map of *cp*-52 with deleted SH and G gene regions. Two monocistronic gene products, M and SHΔG, detectable by M and Gsm gene probes, respectively, and several polycistronic transcription products identically detectable by both of these probes are depicted at the bottom. (*C*) Ethidium bromide-stained 1% agarose gel showing reverse transcription–PCR amplification products generated by primers MSS509 and MSS562 that used RSV B1 or *cp*-52 genomic RNAs. PCR product amplified from *cp*-52 RNA (lane 3) was found to be ≈1.3 kb smaller than that from B1 RNA (lane 2). Lane 1 is a reagent control and lane 4 shows size markers (1-kb ladder, Life Technologies).

determined and used for the amplification and sequence analysis of its *cp*-52 derivative. Reverse transcription–PCR of the *cp*-52 genomic RNA failed to amplify full-length fragment II (≈4.7 kb), which spans the M, SH, G, and F genes. Primer pairs were designed to amplify this region as two smaller fragments, from nucleotide 3,287 to 5,679 (IIa) and 5,465 to 7,707 (IIb). Fragment IIb that spanned the F gene was successfully amplified. Attempts to amplify fragment IIa that spanned the M, SH, and G genes (Fig. 1*A*) yielded a truncated product of ≈1.1 kb, which was ≈1.3 kb shorter than the full-length IIa fragment (Fig. 1*C*). Several other primer pair combinations spanning the IIa region also failed to produce a full-length product (data not shown), suggesting that a portion of this region was deleted in the *cp*-52 virus. Sequence analysis of the truncated IIa fragment revealed that most of the region spanning the SH and G genes of the *cp*-52 virus was deleted (Table 2, Fig. 1*B*), retaining only the first 31 nucleotides of the SH gene (including the gene-start signal) and the last 60 nucleotides of the G gene (including the gene-end signal). The remaining SH:G region could encode a chimeric transcript of ≈91 nucleotides that lacked a predicted ORF. In addition to the long deletion, *cp*-52 virus contains seven point mutations (Table 2), five of which code for amino acid changes (one in the F gene and four in the L gene), one that is silent (F gene), and one that is in the noncoding G:F intergenic region (Table 2).

Northern blot analysis confirmed that the *cp*-52 virus lacked intact SH and G genes (Fig. 2). In contrast, identical monocistronic M and F gene products were produced, as expected, by the B1 and *cp*-52 viruses (Fig. 2, compare lanes 1 and 2 and 9 and 10). The patterns of RSV B1 RNA bands hybridizing with the G and Gsm probes (Fig. 2, lanes 5 and 7) were identical and were consistent with those predicted for the normal G gene transcription products. The M and Gsm probes detected unique and identical bands consistent with the predicted SHΔG-containing polytranscripts, namely, M:SHΔG, P:M:SHΔG, N:P:M:SHΔG, and/or M:SHΔG:F (Fig. 1*B*) in the *cp*-52 virus (Fig. 2, lanes 2 and 8). These bands were not seen with the wt B1 virus (Fig. 2, lanes 1 and 7). These polytranscripts could have been produced only as a consequence of the SHΔG chimeric gene structure that juxtaposes the M gene with the truncated G gene and removes the SH:G intergenic region, allowing read-through across the RSV SH:G gene junction. In addition, the Gsm probe identified the predicted SHΔG gene fusion transcript of ≈91 nucleotides (Fig. 2, lane 8), which also was authenticated by ribonuclease protection studies that used a *cp*-52 probe specific to the SH:G gene boundary (data not shown). Further evidence to support the G gene deletion in *cp*-52 virus was provided by Northern blot analysis of genomic RNA extracted from virions. A positive-sense B1-specific G gene probe that hybridized to full-length B1 RNA failed to react with *cp*-52 genomic RNA, whereas genomic RNA from both viruses hybridized with a control probe containing 3′-leader and NS1 gene sequences (data not shown).

Immunologic confirmation of the deletion of RSV G from *cp*-52 was provided when RSV-infected cell cultures were analyzed by Western blot (data not shown) and plaque immunostaining that used G protein-specific mAbs. As shown in Table 3, RSV-B *cp*-52 plaques were stained with mAbs specific for RSV F protein but not with those specific for RSV G protein. The failure of broadly reactive G protein-specific mAbs to detect G protein in *cp*-52 virus-infected cells by two different assays thus provides further evidence that an intact RSV G protein is not produced by this mutant virus.

Growth of RSV B1 wt and *cp*-52 at 25°C. As shown in Fig. 3, titers of *cp*-52 in infected Vero cell culture supernatants were approximately 10- to 100-fold higher than RSV B1 throughout the course of replication. It is likely that *cp*-52 emerged as the dominant strain during cold passage because of this growth advantage.

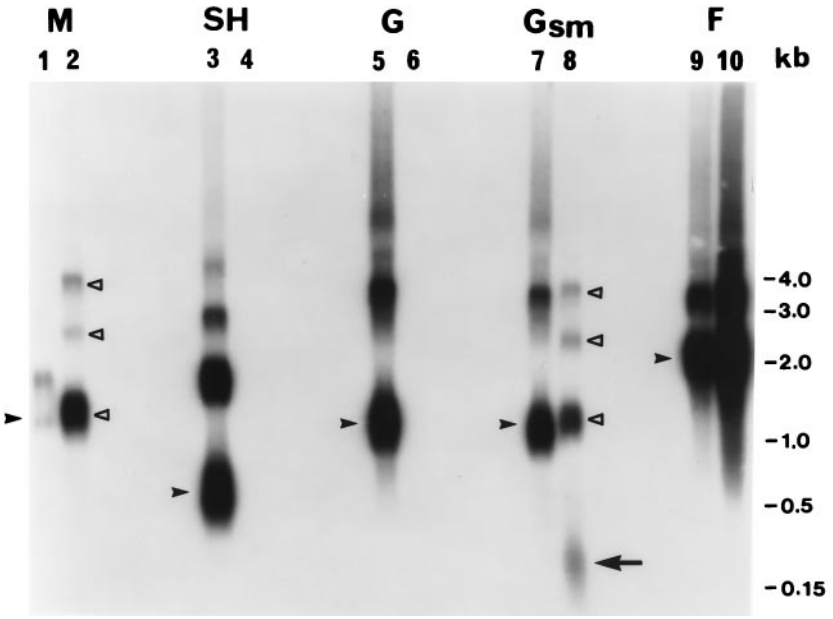

FIG. 2. Northern blot hybridization of total intracellular RNA extracted from B1 and *cp*-52 virus-infected Vero cells. Replicate RNA samples (5 μg) were fractionated by electrophoresis for 3.5 hr at 90 V in a 1.2% agarose-2.2 M formaldehyde gel in 1× Mops buffer (pH 7.0). RNA was transferred in 20× SSC (1× SSC is 0.15 M NaCl and 0.015 M sodium citrate) to 0.2 μm Nytran nylon membrane with a TurboBlotter system (Schleicher & Schuell), and then was fixed by UV crosslinking. Negative-sense riboprobes (≈300 to 400 nt) labeled with [α-^{32}P]UTP were prepared by *in vitro* transcription of B1 virus-specific PCR products (containing T7 promoter sequence) by using a MAXIscript T7 kit (Ambion, Austin, TX). Probe map positions on the RSV B1 genome are shown in Fig. 1*A*; 1.25 × 10^7 cpm of each probe were used for hybridization at 65°C in Rapid-hyb buffer (Amersham). Stringency washes of 15 min each were done twice in 2× SSC, 0.1% SDS at room temperature and twice in 0.2× SSC, 0.1% SDS at 65°C. The 65°C washes were separated by room temperature treatment with 1 μg/ml RNase A in 2× SSC for 15 min to remove nonspecifically bound probe (Promega). The blot was exposed to x-ray film for 6.5 hr. B1, lanes 1, 3, 5, 7, and 9; *cp*-52, lanes 2, 4, 6, 8, and 10. RSV B1-specific monocistronic mRNA transcripts corresponding to M, SH, G, and F genes are indicated by filled arrowheads. Identical polytranscripts unique for *cp*-52 virus that were detected independently by the M and Gsm probes are marked by open triangles in lanes 2 and 8 (see Fig. 1*B* for identification). The predicted SHΔG transcript is identified by the long arrow in lane 8. It should be noted that a short exposure revealed that the *cp*-52 M-specific signal in lane 2 (marked by the open triangle closest to the bottom) consists of two RNA species of similar size: a monocistronic M mRNA that is identical to the RNA identified by the filled arrowhead in B1 lane 1, and an M:SHΔG read-through transcript. The weak monocistronic M signal for B1 virus (lane 1) that was consistently observed in independent experiments indicates inefficient transcription termination and/or mRNA instability in RSV B1 virus.

DISCUSSION

The serial passage of wt respiratory viruses at low temperature to select attenuated mutant viruses has been used to produce live attenuated influenza and human parainfluenza type 3 (PIV-3) candidate vaccines (15, 16), and most recently, a live attenuated RSV A candidate vaccine (8). Each of these candidate vaccines (cold-adapted influenza, *cp*-45 PIV-3, and RSV A 248/404) contain temperature-sensitive and non-temperature sensitive attenuating mutations that act in concert to restrict replication in rodents, primates, and humans (8, 17, 18), yet permit sufficient replication to induce virus-specific systemic and mucosal antibody responses. Although the genetic basis of attenuation of these candidate vaccines has not been fully defined, each possess a series of point mutations in the coding or regulatory regions of the genomes that specify

Table 1. Response of adults to RSV wild-type or to RSV B1 *cp*-52 mutant virus and of infants and children to RSV B1 *cp*-52 or placebo

					Virus isolation, nasal wash		% with indicated illness					Serum neutralizing antibody titer, reciprocal mean (SD) $\log_2$		
Subjects	RSV B1 administered	Dose ($\log_{10}$ pfu)	No. of subjects	% Infected	% Shedding virus	Peak titer, mean (SD) $\log_{10}$ pfu/ml	Febrile	URI	LRI	OM	Any RSV-like	Pre	Post	% with rise
Adults	wt	4.7	19	53	53	3.1 (1.3)	5	21	0	0	26	10.2 (1.2)	10.6 (0.9)	6
	cp-52	5.0	17	6	6	1.9†	6	0	0	0	6	9.3 (0.8)	9.4 (0.9)	0
Sero +	*cp*-52	4.0	4	25	25	≤0.6*	75	50	0	0	75	9.1 (0.8)	8.5 (0.7)	0
children	*cp*-52	5.0	11	45	45	0.9† (0.6)	9	18	0	0	27	9.9 (1.6)	9.7 (1.4)	0
	Placebo	0.0	7	0	0	≤0.6	14	0	0	0	14	10.2 (1.9)	9.7 (1.8)	0
Sero −	*cp*-52	4.0	7	14	14	1.3†	28	14	0	14	28	4.3 (0.1)	4.3 (0.1)	0
children	*cp*-52	5.0	9	11	11	1.9†	22	56	0	22	67	4.4 (0.3)	4.4 (0.3)	0
	Placebo	0.0	10	0	0	≤0.6	20	30	0	10	50	4.3 (0.1)	4.4 (0.2)	0

Healthy adults, 15- to 59-month-old RSV seropositive and 6- to 24-month-old RSV seronegative children were enrolled in these studies. For the purposes of this study, seropositive children were those with an RSV serum plaque reduction neutralizing antibody titer >1:40. URI, upper respiratory tract illness; LRI, lower respiratory tract illness; OM, otitis media.

*This patient shed vaccine virus that did not plaque.

†One adult, one seropositive child, and two seronegative children shed vaccine virus in titers ranging from $10^{1.3}$ to $10^{2.1}$ pfu/ml. Attempts to recover vaccine virus from snap-frozen nasal wash specimens by serial passage in Vero cell culture were unsuccessful, probably because low titers of virus were shed.

Table 2. Sequence comparison of RSV B1 and *cp*-52

Gene	Genomic position	Nucleotide*		Amino acid change	
		B1	*cp*-52†	B1 → *cp*-52	
G:F	5626	C	A	Noncoding intergenic	
F	6318	A	G	Glu → Gly	218‡
	6460	U	C	Silent	265
L	10973	G	A	Arg → Lys	822
	13492	A	C	Asn → His	1662
	14164	U	A	Leu → Ile	1886
	14596	U	C	Phe → Leu	2030

*Positive (+) sense.
†*cp*-52 also sustained a deletion of nucleotides 4249-5540 spanning the SH and G genes that is not shown in the table.
‡Number indicates position of amino acid in the indicated protein.

the mutant phenotypes (19–21). In the present study, passage of RSV B1 at low temperature selected for a host-range mutant that was able to replicate efficiently in Vero cells, but was highly restricted in replication and poorly immunogenic in seronegative vaccinees. In contrast, seronegative vaccinees who received RSV A candidate vaccines in previous studies shed a moderate amount of virus and developed a high level of serum neutralizing antibodies (8). Thus, *cp*-52 appears to be overattenuated and is unlikely to prove useful as a vaccine strain.

Sequence analysis and *in vitro* studies indicated that the *cp*-52 virus sustained a large deletion that ablated synthesis of the SH and G surface glycoproteins. It is perhaps not completely surprising that an RSV lacking an SH gene can replicate effectively *in vitro*, because many paramyxoviruses lack this membrane glycoprotein and a recent report describes the absence of SH in the Enders strain of mumps virus despite its presence in other mumps strains (22). However, the mechanism by which an RSV lacking the attachment (G) glycoprotein can initiate infection remains to be determined. It is possible that naturally occurring cell surface lectins could serve as an alternate receptor for *cp*-52, and that the F protein might serve as a ligand for this receptor, as has been previously described for Sendai virus (23, 24). Whether the host range phenotype of *cp*-52 might result from a difference in lectins on the surface of Vero cells and human respiratory epithelium requires further study.

The mechanism by which this replication-competent deletion mutant arose was not clear initially, but because the *cp*-52 mutant was recovered after multiple cold passages, we considered the possibility that this mutant may have had a growth advantage over wt RSV in Vero cell culture at low temperature. The multicycle growth curve analysis indicated that *cp*-52 grew to significantly higher titer than wt virus in cell cultures incubated at low temperature, suggesting it may replicate more efficiently and/or be less cell-associated than wt virus. Hence,

Table 3. Cells infected with the *cp*-52 mutant virus do not bind murine mAbs directed at epitopes shared by subgroup A and subgroup B RSV G glycoproteins

mAb	Protein specificity of mAb	Subgroup specificity of mAb	Reactivity of indicated RSV with Ab		
			A2 wt	B1 wt	*cp*52
131-2g	G	A,B	+	+	−
130-5f	G	A,B	+	+	−
L9	G	A,B	+	+	−
92-11C	F	A	+	−	−
102-10B	F	B	−	+	+

Plaque immunostaining was performed as previously described (14). Vero cell monolayers in 24-well plates were inoculated with 50 pfu of indicated virus, incubated for 5 days at 37°C, fixed with methanol, and stained with RSV F- or G-specific mAbs. Each G-specific mAb was used at a dilution of 1:200. Each F-specific mAb was used at a dilution of 1:1,000.

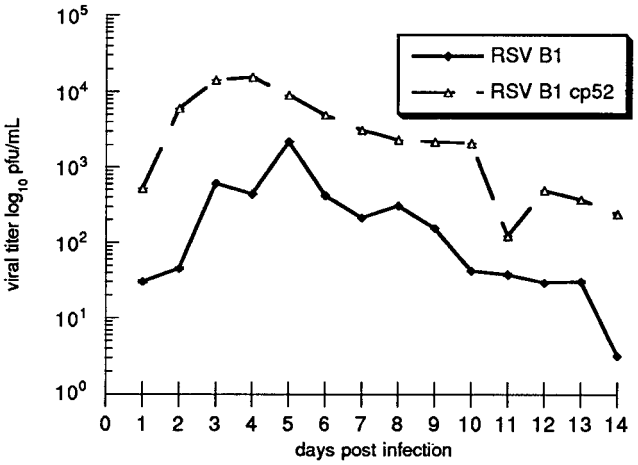

FIG. 3. Multistep growth curves for RSV B1 wt and *cp*-52 viruses. Vero cell monolayer cultures were infected with either B1 or *cp*-52 at an moi of 0.01. Cultures were maintained at 25°C, and aliquots of supernatant were removed daily for 14 days postinfection, snap-frozen, and stored at −70°C. Thawed aliquots were titered by plaque assay on Vero cell monolayer cultures maintained under a semisolid overlay at 32°C as previously described, and results were expressed as $\log_{10}$ pfu/ml (8). Each point represent the mean ± SE of three experiments. The titers of the input viruses were 2.5×10^4 pfu/ml for RSV B1 wt and 2.3×10^4 pfu/ml for *cp*-52.

cp-52 is likely to have emerged during repeated cold passage of virus-infected culture fluids because of its growth advantage over wt virus. In addition, replication of *cp*-52 may have interfered with replication of the wt virus, as has been previously described for cold-adapted influenza and wt influenza viruses (25, 26). Recently, it has been shown that RSV with an engineered insertion exhibited decreased replicative capacity (27). Therefore, it also is possible that *cp*-52 may replicate more efficiently than wt virus because of its truncated genome. In addition, the *cp*-52 virus is clearly a host-range mutant, because its replication is highly restricted in rodents, nonhuman primates, and humans despite its efficient replication in Vero cell culture. Whether these host-range properties are the result of the five point mutations resulting in amino acid substitutions, the large SH:G deletion, or both awaits additional study.

Although the *cp*-52 mutant virus is not an appropriate RSV B vaccine candidate for RSV seronegative infants and children, we have learned that a large mutation involving the deletion of the RSV SH and G genes is compatible with efficient replication in cell culture. It is possible that deletion of a nonessential viral gene (such as SH) might contribute to the attenuation of future candidate vaccines. The use of cDNA technology (28) will allow the construction of a series of diverse recombinant viruses to assess the individual contribution of the point mutations and the SH and G deletions to the attenuation phenotype of *cp*-52. Once the critical mutations are identified, recombinant viruses containing these mutations can be produced and evaluated in preclinical and clinical trials for their usefulness in RSV vaccine development.

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How Does Patient Education and Self-management among Asthmatics and Patients with Chronic Obstructive Pulmonary Disease Affect Medication?

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The effect of patient education on steroid inhaler compliance and rescue medication utilization in patients with asthma or chronic obstructive pulmonary disease (COPD) has not been previously investigated in a single study. We randomized 78 asthmatics and 62 patients with COPD after ordinary outpatient management. Intervention consisted of two 2-h group sessions and 1 to 2 individual sessions by a trained nurse and physiotherapist. A self-management plan was developed. We registered for 12 mo medication dispensed from pharmacies according to the Anatomical Therapeutic Chemical (ATC) classification index. Steroid inhaler compliance (SIC) was defined as (dispensed/prescribed) $\times$ 100 and being compliant as SIC $>$ 75%. Among asthmatics 32% and 57% were compliant ($p = 0.04$) with a median (25th/75th percentiles) SIC of 55% (27/96) and 82% (44/127) ($p = 0.08$) in the control and intervention groups, respectively. Patient education did not seem to change SIC in the COPD group. Uneducated patients with COPD were dispensed double the amount of short-acting inhaled β_2-agonists compared with the educated group ($p = 0.03$). We conclude that patient education can change medication habits by reducing the amount of short-acting inhaled β_2-agonists being dispensed among patients with COPD. Educated asthmatics showed improved steroid inhaler compliance compared with the uneducated patients, whereas this seemed unaffected by education in the COPD group. Gallefoss F, Bakke PS. How does patient education and self-management among asthmatics and patients with chronic obstructive pulmonary disease affect medication?

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Medication regimens for patients with asthma or chronic obstructive pulmonary disease (COPD) are particularly vulnerable to adherence problems because of the chronic nature of the diseases, the use of multiple medications, and the periods of symptom remission. Rates of noncompliance in the treatment of asthma may vary from 20 to 80% (1). Factors leading to poor compliance are not fully understood, but lack of education may be one cause (1).

Previous surveys in asthmatics examining the effect of education programs on compliance have shown conflicting results. Windsor and coworkers (2) reported from a study in 267 adult asthmatics that patient education consisting of one individual and one group session gave significantly improved medication adherence compared with the control group after a 1-yr follow-up. In a controlled intervention study of 116 asthmatics Allen and coworkers (3) observed an increased compliance 12 mo after a 2.5 $\times$ 4 h group session. The Grampian Asthma Study of Integrated Care (GRASSIC) did not show any change in the use of bronchodilators or inhaled steroids after an enhanced education program (4). In two of the studies cited (2, 3) the compliance was self-reported, whereas the third study (4) based the compliance data on medication prescribed by the patients' doctors. Only one of the studies presented data on inhaled steroid compliance (4). No data are available regarding the effect of patient education on medication adherence in the Nordic countries. To our knowledge data are lacking on the effect of patient education on compliance in patients with COPD as well as comparable studies on asthma and COPD.

We performed a randomized, controlled intervention study in patients with mild to moderate asthma or COPD using a standardized education program and a self-management plan. The objectives of the present report are to assess the effect of patient education on antiobstructive medication dispensed from pharmacies.

METHODS

Study Design

Between May 1, 1994 and December 1, 1995, 140 consecutive patients were included in the study after having received ordinary consultation care at our outpatient chest clinic at Central Hospital of Vest-Agder, Kristiansand, Norway. At inclusion they signed a written consent and were then randomized to an intervention group or a control group. The control group were followed by their general practitioners, and the intervention group received an education program and were then

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also transferred to a 1-yr follow-up by their general practitioners (Figure 1).

Eligible subjects were patients with bronchial asthma or COPD between 18 and 70 yr of age, not suffering from any serious disease, such as unstable coronary heart disease, heart failure, serious hypertension, diabetes mellitus, kidney or liver failure.

Subjects with stable asthma were to have a prebronchodilator FEV_1 equal to or higher than 80% of predicted value (5). Furthermore we required either a positive reversibility test (5), a documented 20% spontaneous variability (peak expiratory flow [PEF] or FEV_1), or a positive methacholine test (provocative dose causing a 20% decrease in FEV_1 [PD_{20}]) (6). A positive reversibility test required at least a 20% increase (FEV_1 or PEF) after inhalation of 400 μg salbutamol. Because we wanted to include those with mild COPD, subjects with COPD were to have a prebronchodilator FEV_1 equal to or higher than 40% and lower than 80% of predicted (7). Among patients with COPD 32% were reversible to ipratropium bromide 80 μg and/or salbutamol (8, 9). These measures were obtained from the participants' charts.

Of the eligible patients, the inclusion rate was 92% (78 of 85) and 91% (62 of 68) for the asthma and COPD group, respectively.

Educational Intervention

The educational intervention has been thoroughly described (10). Briefly, it consisted of a specially constructed patient brochure, two 2-h group sessions (separate groups for asthmatics and patients with COPD) concentrating on pathophysiology, antiobstructive medication, symptom awareness, treatment plans, and physiotherapy. One or two 40-min individual sessions were supplied by both a nurse and a physiotherapist (Figure 1). With regard to antiobstructive medication the following was emphasized: The components of obstruction were explained together with the site of action of the actual medication. The patient's pulmonary symptoms were registered and discussed with emphasis on the early symptoms experienced at exacerbations. The individual factors causing attacks/exacerbations and concerns regarding adverse effects of medication were discussed and inhalation technique was checked. At the final teaching the patients received an individual treatment plan on the basis of the acquired personal information and 2 wk of peak flow monitoring (10). The personal understanding of the treatment plan with regard to changes in PEF and symptoms was discussed and tested (Table 1).

All patients received treatment plans aimed at making early changes in medication at exacerbations. Among the educated asthmatics, 94% received standard treatment plans incorporating peak flow monitoring (Table 1). In the COPD group 12 of 26 (46%) received standard treatment plans. Nonstandard treatment plans incorporated the use of oral steroids as the first line of action in the yellow zone if, for example, the patient already used high dosages of inhalation steroids as maintenance therapy or could tell that a double or triple increase in inhalation steroids previously had marginal effect on the course of attacks/exacerbations. Among those 14 patients with COPD receiving nonstandard treatment plans, eight patients did not want to or were not able to use peak flow monitoring as a basis for change in medication. For those patients, only symptom-based treatment plans were issued (Table 1).

Outcome Variables

All medication was coded to Defined Daily Dosages (DDD) according to the Anatomical Therapeutic Chemical (ATC) classification index (11, 12) for comparison of medication within the same chemical–therapeutic groups, thus allowing us to compare those using, for instance, beclomethasone and budesonide. Prescribed Defined Daily Dosage (PDDD) of regular medication (11, 12) is expressed as the regular dosage recommended by the lung clinic at baseline. Short-acting β_2-agonist inhalations were in this study categorized as rescue medication because it was not recommended as regular medication. Dispensed medication was reported from all local pharmacies through monthly print-outs from the pharmacy data registers. At the 1-yr follow-up all patients were asked whether they had received medication elsewhere. Only one individual reported this and the data were included.

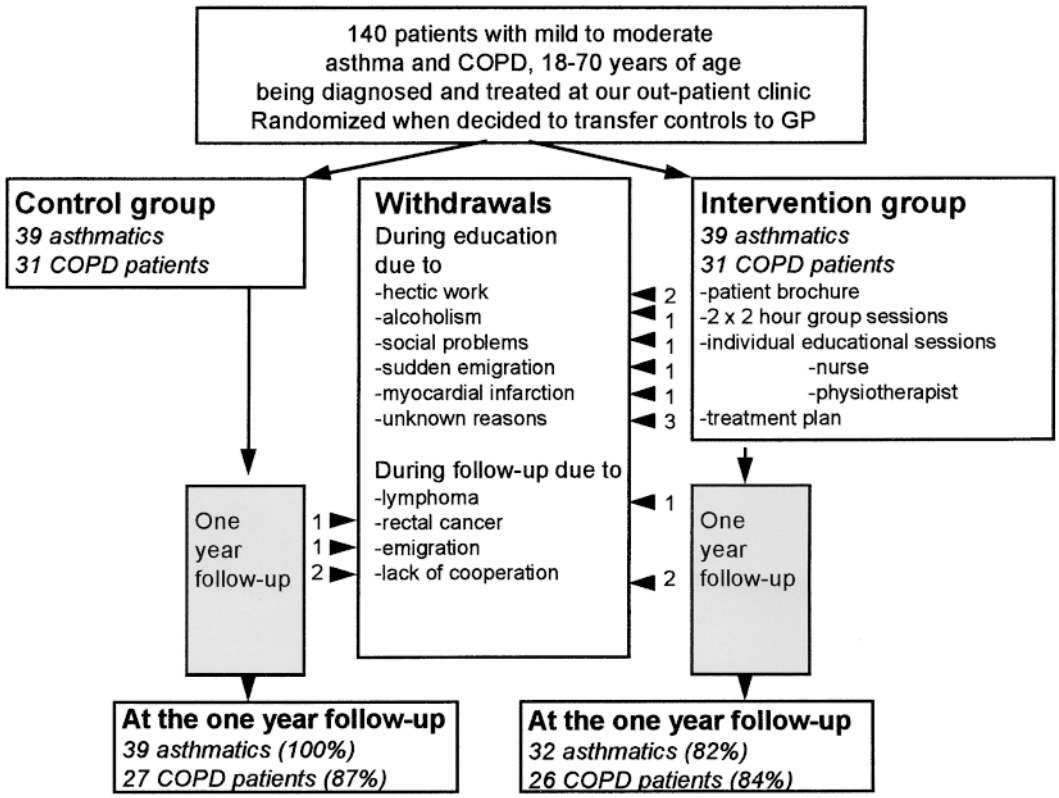

Figure 1. Study design and withdrawals.

TABLE 1

MODEL FOR THE STEPWISE TREATMENT PLAN

Color Code	PEF*	Symptoms	Treatment
Green	> 80%	No symptoms; occasional use of inhaled β_2-agonist	Maintenance treatment
Yellow	80–60%	Start of a cold; night symptoms; cough; or increased use of inhaled β_2-agonists	Double or triple dosage of inhalation steroids until back in green zone, then continue double or triple dosage for as long a time as outside green zone
Orange	60–40% or > 150 L/min	The effect of inhaled β_2-agonists lasts < 2 h; shortness of breath on exertion	Prednisolone 30–40 mg/d until back in green zone, then 10–20 mg/d for as long a time as outside green zone
Red	< 40% or < 150 L/min	Inhaled β_2-agonists of little help or effect lasts < 30 min; shortness of breath when talking	Take prednisolone 40 mg and high-dose inhaled β_2-agonist and contact doctor immediately

* In relation to personal best.

Compliance of regular medication was calculated as a percentage: (dispensed DDD/PDDD) × 100 during the 1-yr follow-up. Standard definition of compliance differs in the literature and is variably defined to values from 70% (13, 14) to 90% (3). We defined *a priori* the patient as compliant when dispensed regular medication was greater than 75% of prescribed regular medication during the study period (15).

Number of prednisolone courses was retrospectively self-reported at 12 mo follow-up. Prebronchodilator spirometry was performed before randomization and at 12 mo follow-up by standard methods (5) using a Jaeger MasterLab Body Box (Würzburg, Germany). The technical staff did not know whether the patients belonged to the control or intervention groups.

Statistics

A number of the outcome variables showed skewed distribution as judged by normality plots, and Lilliefors' test for normality with $p < 0.05$ and then median (the value that separates the highest 50% of the scores from the lowest 50%) values are shown as a measure of central tendency with the 25th and 75 percentiles (the interquartile range) as a measure of dispersion. For normally distributed data the measures of central tendency and dispersion are mean and standard deviation (SD), respectively. The nonparametric Mann-Whitney U test was applied when comparing continuous, skewed variables between groups. Chi-square test was applied for categorized dependent variables also giving the odds ratio. All tests were done two-sided. An alpha < 0.05 was considered statistically significant.

When testing the correlation between the change in FEV_1 over the study period and steroid inhaler compliance (SIC) and between dispensed β_2-agonist inhalation DDD and SIC, bivariate nonparametric correlation analysis (Spearman's correlation coefficient rho [ρ]) was applied.

All analyses were performed on Compaq computers applying SPSS version 7.5 (SPSS Inc., Chicago, IL). Permission to establish a person register was given from the National Data Supervision Center. The methodological procedures were in accordance with the ethical standards of the Helsinki Declaration as approved by the regional ethical committee.

RESULTS

The study population consisted of 140 patients, with 39 patients randomized to each asthma treatment group and 31 to each COPD treatment group. The baseline parameters are shown in Table 2.

Table 3 shows the mean PDDD per year at randomization in the control and intervention groups. In the asthma group 96% used inhalation steroids at randomization amounting to a mean (± SD) steroid inhaler PDDD of 313 ± 164. The corresponding numbers in the COPD group were 92% and 439 ± 216, respectively. Eighty-one percent and 14% of the asthmatics used one and two regular medications, respectively compared with 60% and 23% in the COPD group.

Among the asthmatics the proportion of patients with SIC above 75% in a 1-yr follow-up (Figure 2) was almost twice (57/32 = 1.8) as large in the educated group as in the control group ($p = 0.04$). The odds ratio for having a SIC > 75% were 2.8 (95% confidence interval: 1.1 to 7.7) in the educated group

TABLE 2

BASELINE CHARACTERISTICS OF PATIENTS INCLUDED IN THE STUDY

	Asthma		COPD	
	Control Group	Intervention Group	Control Group	Intervention Group
	(*n* = 39)	(*n* = 39)	(*n* = 31)	(*n* = 31)
Sex, women, n (%)	31 (79)	24 (62)	15 (48)	16 (52)
Age, yr, mean ± SD	44 ± 12	41 ± 12	58 ± 10	57 ± 9
Smoking habits				
Current smokers, n (%)	13 (33)	9 (23)	12 (39)	12 (39)
Pack-years, median*	11	6	17	17
Ex-smokers, n (%)	11 (28)	14 (36)	19 (61)	15 (48)
Never-smokers, n (%)	15 (39)	16 (41)	0	4 (13)
Current use of peak flow meter, n (%)	12 (31)	16 (41)	4 (13)	9 (29)
FVC% pred, mean ± SD	105 ± 15	104 ± 12	90 ± 12	88 ± 14
FEV_1% pred, mean ± SD	95 ± 17	93 ± 13	56 ± 11	59 ± 9
PEF% pred, mean ± SD	107 ± 25	106 ± 19	70 ± 19	69 ± 20

* Median (the value that separates the highest 50% of the scores from the lowest 50%) values are shown as a measure of central tendency for non-normally distributed data.

TABLE 3

BASELINE MEDICATION CHARACTERISTICS AT RANDOMIZATION

	Asthma				COPD			
	Control (*n* = 39)		Intervention (*n* = 39)		Control (*n* = 31)		Intervention (*n* = 31)	
	n (%)	PDDD*	n (%)	PDDD*	n (%)	PDDD*	n (%)	PDDD*
Inhalation steroids	38 (97)	335 ± 161	37 (95)	294 ± 164	27 (87)	476 ± 216	30 (97)	406 ± 200
Long-acting β_2-agonist inhalations	3 (8)	425 ± 105	10 (26)	383 ± 134	8 (26)	387 ± 152	11 (36)	373 ± 193
Ipratropium bromide inhalations	2 (5)	364 ± 171	2 (5)	486 ± 0	12 (39)	455 ± 75	12 (39)	455 ± 105
Xanthine derivative tablets	1 (3)	638	0		3 (10)	577 ± 105	3 (10)	638
β_2-Agonist tablets	0		1 (3)	365	0		1 (3)	486
Steroid tablets	2 (5)	182 ± 128	1 (3)	97	2 (7)	227 ± 64	3 (10)	151 ± 52

* PDDD/patient/year is shown as mean ± SD. Mean and SD values are calculated only for those using the medications. Short-acting β_2-agonist inhalations are not included because we only recommended their use as rescue medication.

compared with the control group. No significant difference was observed between the COPD treatment groups. Table 4 shows the median compliances for the regular medication. In the asthmatics the median SIC was higher in the intervention than in the control group, the difference being of borderline statistical significance ($p = 0.08$). For the compliances of the other regular medications no overt differences were observed between the intervention and control groups, but the small numbers did not allow sound statistical analyses and should be interpreted with caution.

Among the asthmatics 26 of 71 (37%) did not collect short-acting β_2-agonist inhalations (rescue medication) at the pharmacies; in the COPD group the corresponding ratio was six of 53 (11%) ($p = 0.001$, chi-square test). Figure 3 shows the amount of short-acting β_2-agonist inhalations being dispensed during a 1-yr follow-up. The educated patients with COPD received less than half the amount of rescue medication compared with the control group. In the asthmatics a similar tendency was observed, but the difference was not statistically significant. Nine subjects in both asthma treatment groups ($p = 0.63$, chi-square test) reported a median (25th/75th percentiles) number of two (1/2) steroid courses ($p = 0.86$, Mann-Whitney U test) during the 1-yr follow-up. Eighteen of 26 (69%) educated COPD patients reported steroid courses compared with 12 of 27 (44%) in the control group ($p = 0.07$, chi-square test) among which a median (25th/75th percentiles) of three (1/4) and four (1/7) steroid courses were recorded, respectively ($p = 0.42$, Mann-Whitney U test). The COPD control patients who needed steroid tablets were dispensed a median (25th/75th percentiles) of 100 (58/181) DDD compared with 200 (100/288) DDD in the educated group ($p = 0.02$), but then steroid tablets as a rescue medication (being dispensed in advance as a "just in case" medication) was included for the educated group. If rescue medication was subtracted, the median (25th/75th percentiles) number of reported steroid courses for the COPD intervention group was 125 (100/425) DDD, and the difference was no longer statistically significant ($p = 0.21$).

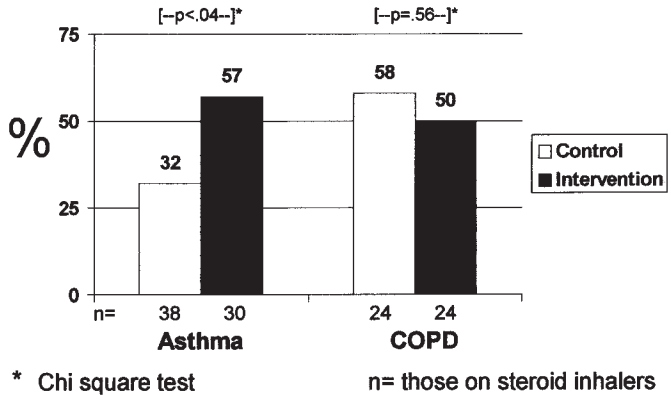

Figure 2. Proportion of patients with steroid inhaler compliance > 75% during a 1-yr follow-up.

Bivariate nonparametric correlation analysis between SIC and dispensed β_2-agonist inhalation DDD showed a weak association for the asthma group (Spearman's $\rho = 0.36$, $p = 0.03$), the higher the DDD of steroid inhalers received, the higher the received DDD of short-acting β_2-agonist inhalations (rescue medication). This correlation tended to be stronger in the educated asthma group (Spearman's $\rho = 0.49$, $p = 0.006$) than in the control group (Spearman's $\rho = 0.27$, $p = 0.11$). No such correlation was found for the COPD group (Spearman's $\rho = 0.16$, $p = 0.29$).

Bivariate nonparametric correlation analysis between change in FEV_1 as dependent variable and SIC showed no correlation (Spearman's $\rho = 0.04$ and 0.22, $p = 0.75$ and 0.13) for the asthma group and patients with COPD, respectively.

Withdrawals

Of the 140 included patients, nine withdrew in the educational period for reasons listed in Figure 1; during the 12-mo follow-up, four and three patients withdrew in the control and intervention groups, respectively. Details about withdrawals have been described previously (10).

DISCUSSION

Our study showed that patient education emphasizing self-management and control of exacerbations in asthmatics gave a better SIC when compared with traditional treatment at our outpatient clinic with general practitioner (GP) follow-up. SIC seemed unaffected by patient education in the COPD group, while the need for short-acting β_2-agonist inhalations as rescue medication was doubled in the uneducated group. Use of oral steroids did not differ significantly between the intervention and control group, neither among the asthmatics nor in the patients with COPD.

Evaluation of compliance in the present study was based on the dispensed DDD from pharmacies. The method is regarded as useful for measuring compliance with long-term medication regimens (16). It is unobtrusive, not reminding the patients of the registration going on, thereby reducing the bias of the study itself. However, the method provides no informa-

TABLE 4

MEDIAN COMPLIANCES FOR REGULAR MEDICATIONS IN CONTROL AND INTERVENTION GROUPS DURING A 1-yr FOLLOW-UP*

	Asthma							COPD						
	Control Group (*n* = 39)			Intervention Group (*n* = 32)				Control Group (*n* = 27)			Intervention Group (*n* = 26)			
	n	Median	25th/75th Percentiles	n	Median	25th/75th Percentiles	p Value	n	Median	25th/75th Percentiles	n	Median	25th/75th Percentiles	p Value
Steroid inhaler	38	55	27/96	30	82	44/127	0.08	24	82	31/134	24	85	51/110	0.94
Long-acting β_2 inhaler	3	90	44/90	9	74	37/97	0.93	6	82	47/115	7	99	74/99	0.94
Ipratropium bromide inhaler	2	134	103/165	1	134		1.00	10	62	50/100	12	81	57/109	0.37

* Median (the value that separates the highest 50% of the scores from the lowest 50%) values are shown as a measure of central tendency with the 25th and 75th percentiles (the interquartile range) as a measure of dispersion. Compliance data for xanthine derivative, β_2-agonist, and steroid tablets are not shown owing to small numbers.

tion about daily patterns of medication use (medication adherence) and gives a coarse and probably overestimated measure of compliance, since return of issued medication was not measured.

There are several alternative methods available for measuring compliance. First, self-reported medication/asthma diaries could have been used giving more exact knowledge, especially about change in medication, but this method has highly variable validity (16). Patient adherence to asthma diaries over time is frequently poor. Asthma diary data are also vulnerable to patient deceit (16). Second, medication monitors (electronic monitors recording date and time of medication use) could be an applicable alternative, but this is an expensive method. In addition, we would have had to adjust this type of equipment to many different devices. Patients could also react on the presence of a monitoring device, altering natural patterns of medication use (16). In our setting the retrospective interpretation of such data for 12 mo would be difficult and would necessitate more frequent controls for safe interpretation of data, which again would increase the bias on compliance in the study.

Regarding inhaled steroids, we found a higher degree of complying (compliance > 75%) subjects among educated compared with uneducated asthmatics. The educated asthmatics were almost two times as likely to be steroid inhaler compliant compared with the uneducated. This finding is in alignment with previous self-management studies (2, 3). However, the present study is the first to show such a finding when compliance is not self-reported. There might be several reasons for this observation. It could reflect a basically better adherence to recommended regular medication, but could also have been influenced by compliance to the self-management plan which recommended higher doses during exacerbations, as found by others after patient education (17, 18). It is likely that both factors influenced our result. The degree of noncompliance in the educated asthma group was, however, still unsatisfactory.

As many as 90% of the patients with COPD used inhaled steroids. These high figures reflect the liberal use of such medication for the patients with COPD in Norway when the study was conducted (19). Patient education did not alter SIC in the COPD group. However, the results should be interpreted with caution owing to limited ability to detect these differences in the COPD groups. There may be several reasons for the pre-

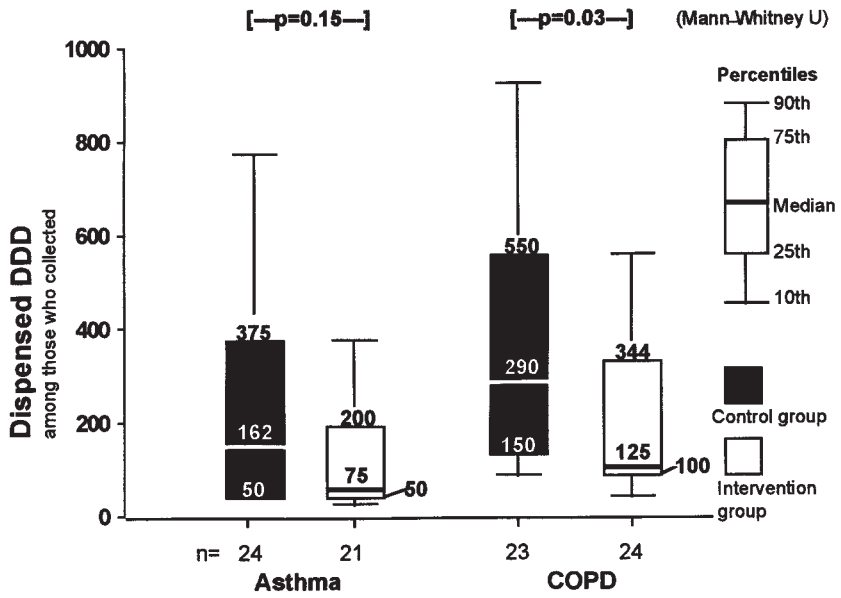

Figure 3. Dispensed short-acting β_2-agonist inhalations as DDD during a 12-mo follow-up stratified by treatment group.

sumed lack of difference in SIC between groups: The educational method, the rationale for regular use of medication, and a stepwise self-management plan may all be more easily adjusted, incorporated, and justified for asthmatics than for patients with COPD. SIC was equivalent in both the COPD control and intervention group to the compliance attained in the educated asthma group; this finding could be explained by the fact that patients with COPD might have experienced more daily symptoms than asthmatics, which may have reinforced the use of regular medication. To our knowledge, the effect of an education program on SIC in patients with COPD has not been previously investigated. Prescription charges are not likely to have influenced our results because the maximum amount a Norwegian citizen must pay from his or her own pocket per year for medication and total medical treatment (hospital included) is approximately $US 150.

The short-acting β_2-agonist inhalations dispensed to the uneducated groups were approximately twice as high as in the educated groups, but the difference was only statistically significant for the COPD group. These figures imply that the uneducated COPD patient took approximately two extra inhalations of either salbutamol 0.2 mg/d or terbutaline 0.5 mg compared with the educated. There could be several reasons for this finding: Educated patients with COPD might have had less daily symptoms than uneducated patients or might have treated their exacerbations more effectively. A greater tolerance to symptoms without the use of rescue medication could also partly explain the figures for the educated COPD group.

The short-acting β_2-agonist results dispensed to the asthma group should be interpreted with caution because seven more persons in the educated group were on long-acting β_2-agonists at randomization compared with the uneducated group. The reduced use of β_2-agonists in the educated asthma group could theoretically be explained by the higher SIC, but an opposite correlation was found. Among asthmatics increased SIC was correlated to increased use of β_2-agonists. Interpretation of this finding should be cautious, but could support a theory that those who needed more inhalation steroids presumably were sicker and so might also have used more β_2-agonists. Patient education seemed to strengthen this correlation.

We cannot explain what part of the education influenced compliance, but we emphasized the regular use of steroid inhalations to avoid the daily use of β_2-agonists. An overall impression was that the educated group had been more aware of their symptoms and the effect of their change in medication according to their self-management plan.

We conclude that patient education can change medication habits toward more desirable goals by reducing the collection of short-acting inhaled β_2-agonists among patients with COPD. Educated asthmatics showed improved SIC while this seemed unaffected by education in the COPD group.

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July 27, 2006

Licensing Agreement for a Nasal Drug Delivery Technology "New Hopes for Infertility and Osteoporosis; Countermeasures to Address the Declining Birthrate and the Aging Population"

Translational Research, Ltd. (TRL), a 100% subsidiary company of SNBL, has signed an agreement with Tokai Pharmaceuticals, Inc., for the license to use TRL's nasal drug delivery technology. The license is for Tokai's exclusive use of TRL's technology to research, develop, manufacture, and market products of specific pharmaceutical compounds, including Follicle Stimulating Hormone (FSH), Parathyroid Hormone (PTH), Parathyroid-related Protein (PTHrP), and Growth Hormone Releasing Peptide (GHRP).

In the recent years, there is an increasing trend in cases of infertility. Around 15% of all couples in the conceivable age are being treated after 2 years of infertility. The current infertility treatment market in the USA is reported to reach as high as US$20 Billion. FSH is an effective drug to treat infertility; however it requires about 2 weeks of going to the hospital daily for subcutaneous or intramuscular injections of FSH until the ovum become mature. Also, there is a considerable amount of discomfort felt by the patient, because the location of the injections must be changed each time due to possible irritation and infections. Also, cases of osteoporosis have also been increasing each year. In the year 2000, the number of patients in major countries was reported to be around 35 million. The market size, in the USA alone, was reported to be US$8.5 Billion in the year 2003 and is expected to increase to around US$200 Billion by the year 2014. PTH and PTHrP are both known to effectively induce bone formation; however, the treatment currently requires a patient to take injections for an extended period. For these reasons, an alternate drug delivery method has been sought after for the treatment of infertility and osteoporosis without needle injections… one that is painless and more convenient to use.

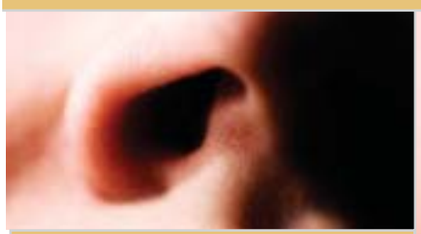
Through this partnership, Tokai aims to apply TRL's nasal delivery technology to pharmaceutical compounds, including FSH, PTH, PTHrP and GHRP, for future manufacturing and marketing. The application of these pharmaceutical compounds using nasal delivery will add therapeutic value to the patients, by relieving them of the pain felt with injections and, ultimately, contributing the increase in their quality of life. According to this agreement, TRL has received an initial licensing fee of US$50,000 and will receive additional total licensing fee of US$475,000 over the next 4 years. TRL will also receive royalty fees according to the sales of Tokai's products.

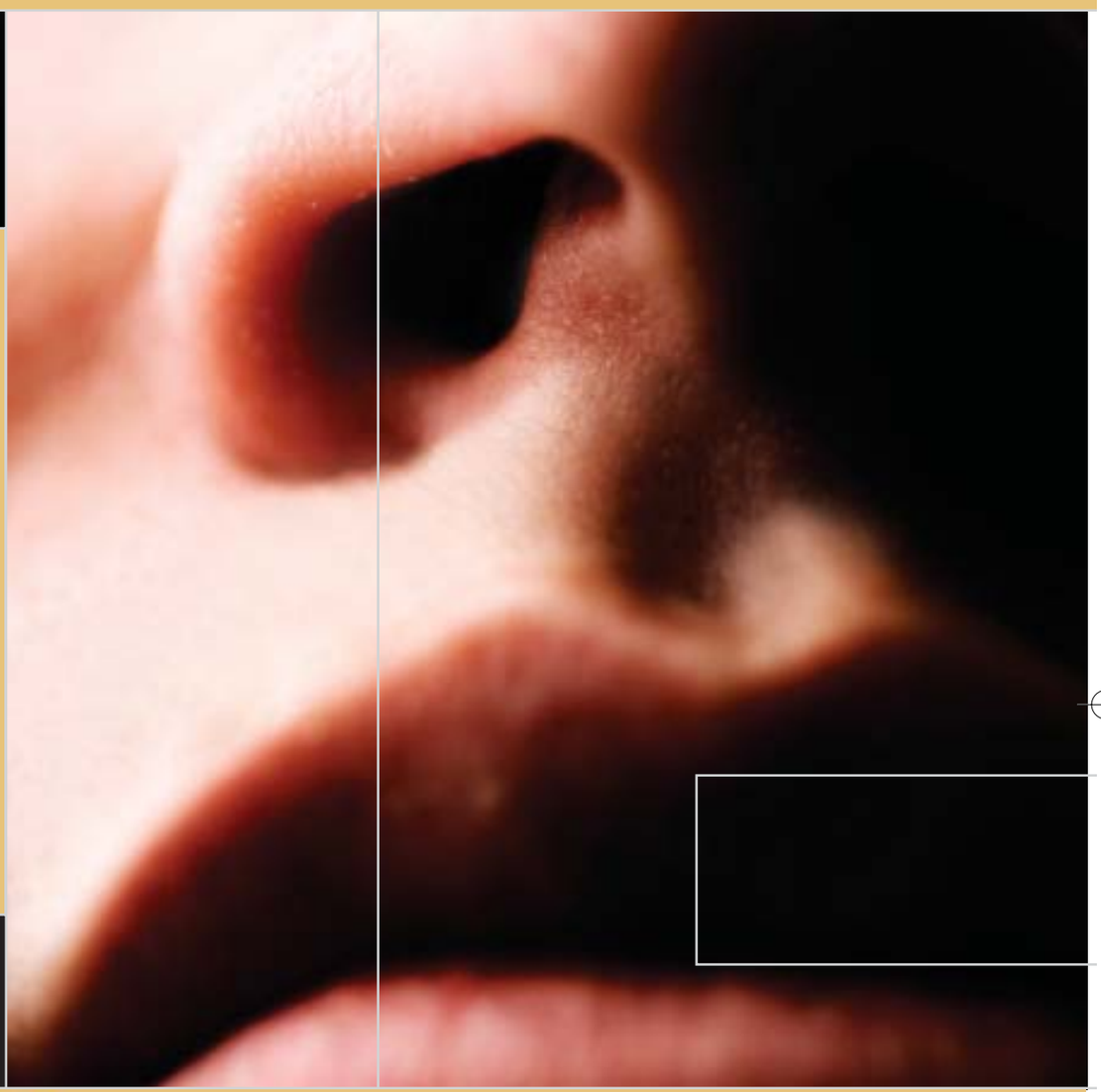
Other than this partnership with Tokai, TRL is currently developing nasal delivery formulations of morphine (pain reliever) and granisetron (anti-emetics) in-house and, at the same time, proceeding to aggressively research/develop applications of the nasal delivery technology to other therapeutic compounds, as well as negotiating other licensing agreements.

The effect of this partnership on the performance of SNBL group in this fiscal year is minimal.

NASAL DRUG DELIVERY

RAPID ONSET VIA A CONVENIENT ROUTE





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INTRODUCTION

Welcome to this, the third edition in ONdrugDelivery's novel series of sponsored publications, each of which focuses exclusively on one specific area within the field of drug delivery.

Nasal drug delivery, the topic of this edition, is undoubtedly becoming an increasingly attractive consideration in many quarters. The scientific, technological and medical factors that are promoting current interest are discussed briefly below, and in closer detail in the articles that follow.

It is important first to highlight one quality of nasal delivery technologies that is capturing the interest of potential partners in both the pharmaceutical industry and the investment community. The word is on the lips of many delivery industry commentators these days – products!

There are a number non-invasive delivery routes – pulmonary, transdermal, needle-free, buccal and others – for which optimised technologies are under development to a) enhance the performance of products that have already been delivered with some success via that route and b) access larger markets by enabling the effective delivery of a broader range of compounds – particularly those compounds which have previously only been suitable for injection.

Among these routes, the proven track record of nasal drug delivery technologies to pass the concept stage in this quest, and go on to facilitate the development and launch of viable product candidates, stands out. Many nasal products for the topical treatment of conditions such as rhinitis and sinusitis have of course been marketed for decades. More recently, several systemic nasal formulations of, for example, hormones, vaccines and compounds for the treatment of migraine, have also reached the market – and more still are progressing through clinical development. As Michael Sheckler of Javelin Pharmaceuticals (formerly IDDS) reports herein, Greystone Associates predicts that the nasal drug delivery market will enjoy annual growth of 24% between 2004 and 2007, increasing the market value from around US$2 billion to US$4.3 billion.

Nasal anatomy and physiology play a crucial role in making it such an appealing administration route. The details of structures within the nose are described in this issue but, in general terms, it is clear that no other portal so close to the exterior gives such ready access to a range of systems, without the need to cross barriers such as the stratum corneum, which hinders transdermal delivery.

Chief among the systems that intranasal administration can reach is the systemic circulation, which is made accessible by the rich vasculature of the nasal mucosa. But the lymphatic and immune systems, the sinuses, and the adenoids can also all be accessed through intranasal delivery. Furthermore, for direct "nose-to-brain delivery", by-passing the blood-brain barrier, the olfactory region enables drugs to enter the cerebrospinal space, for effective treatment of the central nervous system.

"As aging-population demographics and managed-care initiatives drive growth in home health care and self-administration of drug therapies for chronic conditions such as diabetes, arthritis, and hormone replacement therapy, drug developers are showing increased interest in routes of administration that are patient friendly and cost effective," says Greystone Associates. "Intranasal administration is well positioned to take advantage of these trends."

Of course, nasal drug delivery research faces significant challenges. They include: accurately targeting the correct sites within the nose; avoiding unwanted deposition in the stomach and lungs; microbial contamination of multi-use devices; successful development of preservative-free formulations; and the incorporation of dose-counting mechanisms.

There is a view that available nasal delivery technologies have not advanced in a meaningful way for perhaps more than a decade, meaning that a technology gap has opened up. The sector is waiting to take advantage of the opportunities the nasal route presents but cannot do so until a suitable nasal delivery technology becomes available. A read of the articles that follow would suggest that the wait is over.

The leading players in the nasal drug delivery field that have contributed to this publication are developing technologies that aim to meet these challenges and products that have the potential to prove it. Looking ahead, we hope to be able to update you with more news of progress and success from these companies and others when we cover nasal drug delivery again in May 2006.

Guy Furness
Managing Director, ONdrugDelivery Ltd

ADVANCED SIMPLIFICATION OF NASAL DELIVERY TECHNOLOGY:

ANATOMY + INNOVATIVE DEVICE = ADDED VALUE OPPORTUNITY

Direct-Haler A/S has invented and developed a novel nasal delivery device and nasal delivery principle. The innovation takes advantage of the patient's anatomy to improve nasal delivery effectiveness and convenience. The integrated nasal device and delivery method enables nasal delivery of very fine particles, without the risk of pulmonary deposition. Dr Troels Keldmann, Managing Director, Direct-Haler A/S, explains.

The DirectHaler Nasal device has successfully been used in clinical trials, and has confirmed patient acceptability. The single-use, disposable device is for both mono and bi-dose delivery, in a pre-metered, prefilled dose format. The device offers effective, accurate, repeatable and hygienic dosing, and is intuitively easy-to-use. Furthermore, the straightforward device design possesses unequalled cost-effective manufacturability.

DELIVERY METHOD INNOVATION *AND* DEVICE INNOVATION

When air is being blown out of the mouth against a resistance, the airway passage between the oral and nasal cavities automatically closes. The same reflex is activated when a person blows up a balloon; none of the air escapes through the nose. This anatomical feature is activated when the patient uses DirectHaler Nasal for blowing their nasal dry-powder dose into their nostril. Thus, the dose is captured in the nasal cavity, where it is intended to act or to be absorbed into the systemic circulation. After completion of the dose delivery blow, the nasal/oral connection returns to its normal open state (see figure 1).

This delivery method holds the potential to become the dominant delivery principle in nasal drug delivery. Direct-Haler is the first drug delivery company to take advantage of this device-dependent reflex for enhancing nasal drug delivery. Naturally, the increased interest in this principle for enhanced nasal delivery has recently led other companies to seek exploitation of the same delivery principle. However, Direct-Haler has broadly issued device and delivery method patents for this area. Patents are issued in more than 40 countries, with priority dates going back to 1997.

REMOVING DISADVANTAGES OF CURRENTLY AVAILABLE SYSTEMS

A range of nasally delivered products has been on the market during recent decades. These products belong to therapeutic areas such as allergic rhinitis treatment, migraine relief, hormone replacement therapy (HRT) and common cold relief. The products have applied nasal delivery systems based primarily on four different formulation/device technology types: liquid nasal drops; liquid nasal sprays; pressurised metered-dose inhalers (HFA, CFC); and dry-powder inhalers and insufflators. Performance and characteristics of these nasal delivery systems have been studied widely (see figure 2), and various disadvantages have been identified. The DirectHaler Nasal device and delivery method can solve or significantly reduce these problems.

Liquid nasal sprays and drops are currently the most widely used nasal delivery systems. Among the drawbacks with which they have been associated are:

- Risk of liquid dose dripping out from nostril after dose delivery.[1]
- Risk of liquid dose being swallowed immedi-

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ately after delivery – giving limited absorption time and unpleasant taste.[2]

- Complicated device priming procedure before first use, and if many days pass between uses.[3,4,5]
- Risk of small delivered dose for the last actuations as container begins to empty; no dose counter, patient has to keep records to ensure the product is discarded before the dose size becomes insufficient.[3,4,5]
- Acceptability problems for liquid formulations with preservatives, for chronic use.[6]
- Multi-dose containers include risk of contamination, necessitating preservatives in formulation and frequent device cleaning.[6,7]

Dry-powder formulations can offer important advantages over liquid formulations such as: enabling higher drug payload per dose delivered; prolonging absorption time in nasal cavity; reducing temperature sensitivity during product distribution and storage. Further to these advantages, DirectHaler Nasal eliminates the risk of contamination and thereby eliminates the need for preservatives. It also removes the need for priming and cleaning.

The pressurised metered-dose inhaler (pMDI) technology, widely used in pulmonary administration, has also been applied for nasal delivery. However, patient acceptability has not been impressive with the unpleasant "cold-blow" and "hard-blow" of medication from pMDI being one of the commonly reported problems. [8]

In contrast, when using DirectHaler Nasal, the patient contributes the blow energy using their own breath. Therefore, the nasal dose blow is naturally at the correct temperature for high patient acceptability.

Dry-powder nasal formulations have historically been used mostly for locally acting drugs, in rhinitis treatment, for example. Several of these delivery devices comprise pulmonary dry-powder inhalers with a nostril piece instead of a mouthpiece.

Such devices are activated by the patient snorting in the medication. This means that the patient is effectively breathing in the formulation through the nose, by use of the lungs. Unfortunately, therefore, while some of the dose will be trapped in the nasal mucosa en route, the lungs will inevitably be the final delivery site for part of the dose.[9]

The DirectHaler Nasal device and method automatically activates the anatomical reflex that closes the airway passage between the nasal and oral cavities. This activated reflex removes the risk of pulmonary deposition of drug particles.

In summary, DirectHaler Nasal provides a novel opportunity for overcoming the recognised problems, described above, associated with currently marketed nasal delivery device concepts (see figure 2).

NEW HORIZONS FOR NASAL DELIVERY

New opportunities in nasal drug delivery include the possibility for direct nose-to-brain delivery, requiring dose particle deposition in the olfactory region. However, researchers working in this area currently face a dilemma. Traditionally, nasal formulations ideally have particle sizes above 20-30 μm to minimise the degree of deposition in the lower airways, which increases as particle size decreases. But at the same time, to reach the olfactory region requires dose particle sizes below 5 μm.

Figure 1: DirectHaler Nasal: Device innovation and delivery method innovation.

tive results gathered during the development of Direct-Haler's dry-powder pulmonary delivery technology. With DirectHaler Nasal the ambition was to develop a disposable dry powder delivery device offering effective, accurate and repeatable dosing and in addition being compact and easy-to-use. Our ambition also included making it possible for pharmaceutical companies to manage their own manufacture, filling and device packaging. The innovative result of breakthrough required to overcome this issue.

Disadvantages reported on current nasal delivery systems	Solved by DirectHaler Nasal
Risk of liquid dose dripping out from nostril after dose delivery. [1]	Dry powder formulations adhere to the nasal mucousa.
Risk of liquid dose being swallowed immediately after delivery – giving limited absorption time and unpleasant taste. [2]	No risk of immediate swallowing. Reduction of taste sensation.
Complicated device priming procedure before first use, and if many days pass between uses [3,4,5]	Primeless.
Risk of small delivered dose for the last actuations as container begins to empty; no dose counter, patient has to keep records to ensure the product is discarded before the dose size becomes insufficient [3,4,5]	Pre-metered, pre-filled unit dose/bi-dose device system. No risk of reduced dose.
Acceptability problems for liquid formulations with preservatives, for chronic use [6]	No preservatives.
Multi-dose containers include risk of contamination, necessitating preservatives in formulation and frequent device cleaning. [6,7]	Hygienic single-use, disposable. No contamination risk.
Unpleasant "cold-blow" and "hard-blow" of medication from pMDI. [8]	Tempered & pleasant blow.
Risk of pulmonary dose deposition for "snorting-in" DPI devices. [9]	No risk of pulmonary deposition.

Figure 2: DirectHaler Nasal overcomes disadvantages of currently marketed nasal delivery device systems.

A new nasal delivery method is therefore needed to prevent deposition of fine particle nasal dose in the lower airways. Working in concert with the patient's anatomy, DirectHaler Nasal's delivery method represents the type of

BASED ON PROVEN TECHNOLOGY APPLIED IN PULMONARY DELIVERY

The R&D program for DirectHaler Nasal was initiated on the basis of the expertise and posi-

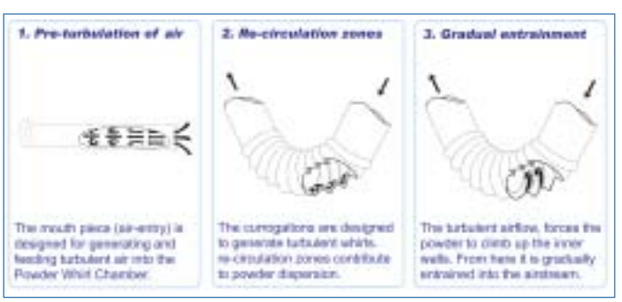

Figure 3: Three powder dispersion principles are applied simultaneously in DirectHaler Nasal.

Figure 4: Applying DirectHaler Nasal.

Figure 5: New device cap types for DirectHaler.

our nasal R&D is patent protected worldwide.

The nasal device comprises an engineered curved and bendable inhaler tube with a "mouth-to-nose" optimised corrugated flexible bend, and a double cap that seals each end of the device's tube. As DirectHaler Nasal is intended for nasal delivery of dry-powder formulations, it takes advantage of the PowderWhirl chamber for dispersion, and powder entrainment. The PowderWhirl chamber was originally developed for pulmonary delivery applications, where powder dispersion and gradual entrainment into the airflow is important.

Three principles governing airflow and powder dispersion are applied in the design (see figure 3), so that DirectHaler Nasal delivers the complete dose gradually over one administration blow as a well-dispersed powder.

First, the mouthpiece is designed for generating and feeding in turbulent air to the PowderWhirl chamber. Secondly, the corrugations of the PowderWhirl chamber are designed to generate turbulent whirls. These recirculation zones contribute to powder dispersion. Finally, the turbulent airflow forces the powder up on the inner walls of the corrugations. From here, it is gradually entrained into the blown air stream until the device is completely empty.

EASY-TO-USE MEANS EASY-TO-INSTRUCT AND CHECK

DirectHaler Nasal is intuitively easy to use, which minimises the instruction task – and makes it easy to check the patient's technique. The pre-metered and pre-filled powder dose in the DirectHaler Nasal, is always visible due to device transparency. This allows the patient to have visual contact with the dose – ensuring confirmed "dose ready" before delivery and "dose taken" after delivery. The compact device dimensions ensure portability and discretion in using the device.

To use DirectHaler Nasal, the cap is taken off leaving both ends of the tube open and the dose resting at the bottom of the "U". Holding and pressing the mouthpiece between the thumb and forefinger, facilitated by the flexible bend, the patient inserts the nostril piece into a nostril and the mouthpiece into their mouth. They then blow into the mouthpiece and thereafter completely release the finger pressure on the tube (see figure 4). The blow of the patient will close the airway passage between the nasal and oral cavities, and then disperse the powder dose and transport it via the nostril piece to the nasal mucosa.

ACCOMMODATING SENSITIVE POWDERS AND SPECIAL APPLICATIONS

Special therapeutic applications require delivery of two nasal doses – one to each nostril. Two DirectHaler Nasal devices can be "clicked" together to constitute such a compact bi-dose. Further, we have developed additional types of device caps to accommodate bi-dose requests, and APIs/formulations which have variable sensitivities to moisture, light, temperature and mechanical impact.

Examples of such new cap types are shown in figure 5, along with the original cap. Such new caps enable bi-dose storage and dose encapsulation, along with customised device appearance – both designed for optimal ease of use.

Type 1 (left side): the powder dose is sealed inside the cap with a foil strip, which is easily torn off for dose loading to the PowderWhirl chamber, before removing the cap and delivering the dose.

Type 2 (centre): the isolated dose inside the cap is loaded by pressing the two cap parts together until a "click" is heard.

HOW CAN THE DEVICE APPEAR SO STRAIGHTFORWARD?

The high degree of function-integration in only two device components (with a total weight of 0.6 g) has been achieved by an R&D philosophy focusing on identifying the essential device functionality requirements, and on sophisticated engineering.

The analysis of previous nasal delivery device concepts shows that these possess a range of mechanisms which make the devices complicated to use and/or expensive to manufacture. As a new and innovative device concept, the DirectHaler Nasal device eliminates the need for a number of the common device mechanisms. This has allowed us to focus on new principles for nasal delivery.

Figure 6 shows our identification of the most essential functional elements for a powder based nasal device technology. Moving from left to right, the diagram progresses from overall aims to detailed functional elements.

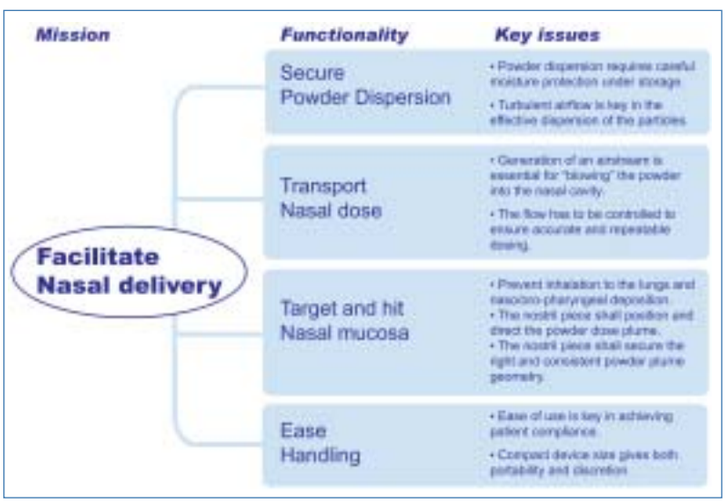

Figure 6: Defining the key device functionality for facilitating nasal delivery.

UNIQUE MANUFACTURABILITY

DirectHaler Nasal is extremely straightforward and cost effective to manufacture, fill and assemble using high-speed standard mass production technology. The device tube is manufactured using extrusion and roll forming and the device cap by injection moulding.

Figure 7: Equipment for integrated filling and assembly of DirectHaler Nasal.

Figure 8: Combining an oral dose with DirectHaler Nasal.

The device's initial design was partly inspired by the design of a standard drug capsule. Thus, powder-dose filling is carried out using modified high-speed capsule filling equipment supplied by MG2 (see figure 7), ensuring high-precision pre-metered doses.

The overall extremely straightforward DirectHaler manufacturing process – rare in the inhaler market – adds flexibility when it comes to choosing a device supply strategy.

One option for DirectHaler technology licensees is to select local suppliers for manufacturing the device components, and keep in-house complete filling and packing lines. Such lines could be placed locally for regional supply of the finished product. Another option is for pharmaceutical companies to take advantage of the straightforward and efficient production process, which allows them to manage device manufacture, filling and packing in house, without the usual contract manufacture and filling link in the supply chain.

BUILDING FURTHER ON THE ADVANTAGES OF NASAL DELIVERY...

The manufacturing simplicity and compactness of the DirectHaler Nasal opens new opportunities to address future needs for combination therapy. The DirectHaler device can be considered as the basic building block in any combination therapy or dosing sequencing involving nasal delivery. This means that the DirectHaler device could be the nasal component in a combination therapy consisting of, for instance: one nasal dose + one oral dose in the same blister pack (see figure 8).

Such innovative combination therapy options for the use of two delivery routes at the same time would enable design of delivery systems for achieving for example:

- Local action (nasal) + systemic action (oral)
- Rapid onset of action (nasal) + delayed and sustained release (oral)

... AND TARGETING THE COMPLETE RESPIRATORY SYSTEM

The building block characteristic of DirectHaler Nasal can be exploited further, as this characteristic is shared with our pulmonary device technology, DirectHaler Pulmonary.

Dosing to the complete respiratory system has previously only been possible by special nebulizers with facemasks, and limited portability. Such highly specialised equipment is expensive, complicated, and mainly suitable for stationary use.

The DirectHaler technologies do away with these limitations, and open a completely new option for drug delivery to the whole respiratory system with dry-powder formulations. DirectHaler Pulmonary and DirectHaler Nasal are the first unit-dose devices that can be clicked together as one device (see figure 9), enabling specific dosing to the nasal and pulmonary airways, and thereby targeting the complete airway system. Such targeting can be highly relevant in treatment of respiratory diseases, and in prevention/treatment of respiratory infections (also in relation to biodefence).

The two devices are packed together but applied separately, allowing separate formulation technologies for reaching the nasal airways and the pulmonary airways. This is important, as nasal delivery and pulmonary delivery each have specific optimal powder formulation characteristics.

CONCLUSION

The DirectHaler Nasal technology offers advanced nasal delivery characteristics, in a straightforward, patent protected and cost-effective device embodiment. The DirectHaler Nasal device not only removes the disadvantages of currently available nasal delivery technologies, but it enables new therapeutic approaches exploiting the nasal route of administration to be pursued.

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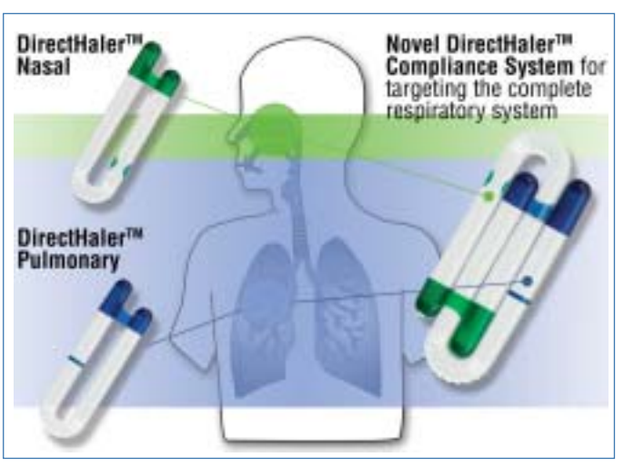

Figure 9: DirectHaler CombinationUnit for pulmonary and nasal delivery.

NASTECH
PHARMACEUTICAL COMPANY INC.

PHARMACOKINETIC ATTRIBUTES OF INTRANASAL DELIVERY:
CASE STUDIES AND NEW OPPORTUNITIES

Intranasal drug delivery represents a non-invasive route with the potential (particularly for large molecule drugs) to improve convenience, patient comfort, compliance and hence the overall efficacy of pharmacological interventions. Here, Henry R Costantino, PhD, Director, Formulations; Paul H Johnson, PhD, Senior Vice President, Research & Development and Chief Scientific Officer; and Anthony P Sileno, MS, Senior Director, Clinical Affairs & Toxicology (all of Nastech Pharmaceutical Company) present a series of case studies illustrating these attributes. The technologies they describe demonstrate the versatility of IN drug administration, ranging from straightforward formulations of small molecules, to advanced formulations that leverage the ability to modulate epithelial tight junctions and enable delivery of peptides and proteins.

Intranasal (IN) delivery is suitable for the local and systemic delivery of diverse therapeutic compounds.[1-2] Attributes of this approach include a large surface area for introduction of drug to the bloodstream, rapid onset of therapeutic drug levels, potential for direct-to-central nervous system delivery, no first-pass metabolism, and non-invasiveness to maximise patient comfort and compliance. Although the nasal mucosa poses a permeation barrier to high-molecular-weight therapeutics such as peptides and proteins, the tight junctions that form this barrier to paracellular drug delivery can be reversibly and safely opened.[3] Owing to these and other factors, marketed IN formulations exist for a variety of low- and high-molecular-weight drugs (for example, peptides), and additional products are under development. Examples of intranasal formulations Nastech has developed are presented in figure 1.

The following series of case studies describe a range of IN formulations, from simple small molecules that are established, marketed products, to developmental tight junction-modulating formulations of peptides and proteins. Through this series of case studies, various attributes of intranasal administration are demonstrated.

CASE STUDY: BUTORPHANOL

Butorphanol tartrate is an analgesic possessing mixed agonist-antagonist activity at opiate receptors. Its therapeutic uses include management of pain when the use of an opioid analgesic is appropriate. Butorphanol is extensively metabolised upon first pass through the gastro-intestinal (GI) tract and as a result has very poor oral bioavailability (5-17%). The intravenous (IV) and intramuscular (IM) routes provide improved bioavailability and rapid drug onset but at the cost of invasiveness, pain and inconvenience. IN butorphanol offers a convenient alternative to IV and IM delivery and has been successfully developed commercially (marketed as STADOL NS®). [4]

Representative human pharmacokinetic data generated by Nastech comparing IM and IN butorphanol tartrate are depicted in figure 2. As can be seen, IN delivery can achieve similar or greater drug levels in the blood (at the same dose) and is as fast or faster compared with IM dosing. Rapid drug onset is a key attribute for many pain management applications. It is important to note that human clinical testing demonstrated that rhinitis conditions did not significantly impact intranasal pharmacokinetics. [4]

CASE STUDY: GALANTAMINE

Dementia affects approximately 5% of people over 65 years of age, primarily due to Alzheimer's disease. Currently, the first-line treatments for Alzheimer's disease symptoms are acetylcholinesterase inhibitors such as galantamine.

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Drug Form	MW (Da)	Comments
butorphanol tartrate	478	Marketed as STADOL NS®
cyanocobalamin gel	1355	Marketed as NASCOBAL®
cyanocobalamin spray		FDA Approved
scopolamine hydrobromide	384	For an example human clinical testing reference, see Admed *et al* [6]
galantamine	368	For an example human clinical testing reference, see Leonard *et al* [9]
apomorphine hydrochloride	304	For an example human clinical testing reference, see Brandt *et al* [7]
morphine gluconate	433	Phase II clinical trials
salmon calcitonin	3432	ANDA filing accepted
human parathyroid hormone 1-34	4118	Phase I clinical trials
human peptide YY 3-36	4050	Phase I clincial trials
human interferon-beta	22.5k	For an example human clinical testing reference, see Vitkun *et al* [8]
undisclosed macromolecules	~1-50k	Various feasibility stages, preclinical testing

Figure 1. Examples of various Nastech IN formulations

Similar to other orally delivered acetylcholinesterase inhibitors, galantamine has a clinically significant level of mechanism-based GI side effects including nausea and vomiting. Thus, it was of interest to explore IN galantamine and evaluate the potential for reducing such undesirable effects.

Nastech has previously reported on the feasibility of IN galantamine.[9] A key challenge was increasing drug solubility in order to deliver a therapeutically relevant dose given the limitations of IN dose volume. A more than 12-fold improvement in solubility was successfully achieved by exchanging drug salt form. Having established the feasibility of an IN formulation, the pharmacokinetics and emetic responses were evaluated in an animal model. [10]

A much more rapid drug onset was observed for IN administration (Tmax = 5 min) compared with oral dosing (Tmax = 240 min). The emetic response data depicted in figure 3 confirms that IN delivery can reduce the GI and related side effects associated with oral administration.

CASE STUDY: SCOPOLAMINE

Scopolamine, an antimuscarinic agent used for the treatment of motion sickness, is another good candidate for IN delivery. This compound has very low oral bioavailability due to an extensive first-pass metabolism. Transdermal delivery provides an option, but this route results in a very slow drug onset, while rapid onset has obvious benefits for the treatment of motion sickness. Furthermore, unnecessarily prolonged drug levels result in a significant side-effect profile including dry mouth, drowsiness and blurred vision.

In a previous publication, Nastech researchers reported on the clinical pharmacokinetic and side-effect profile of various IN scopolamine formulations.[6] IN scopolamine, compared with transdermal dosing, exhibited a more rapid onset. Although a variety of side effects have been reported for transdermal scopolamine, no significant adverse effects were observed for the various IN formulations tested.

CASE STUDY: APOMORPHINE

Apomorphine is a dopamine receptor agonist with high affinity for D1 and D2 receptor subtypes in sites within the brain known to be involved in the mediation of erection. The compound is currently approved for several indications and uses including: as a diagnostic aid in predicting a patient's responsiveness to levodopa for treating early-morning motor dysfunction in late-stage Parkinson's disease and "off" episodes; and as an emetic in acute oral poisoning and drug overdoses.

Various *in vivo* studies have shown that the erectile effects of apomorphine are mediated at dopamine receptors in various nuclei of the hypothalamus and midbrain.

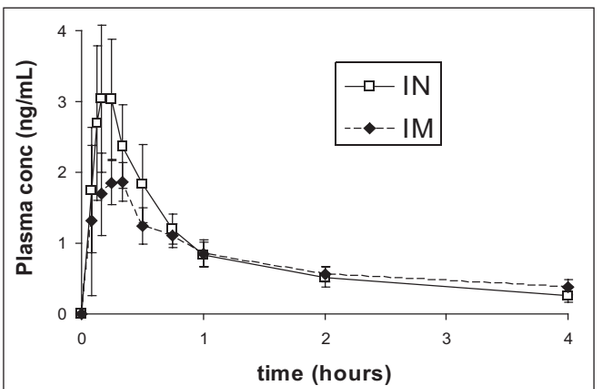
When administered intranasally, apomorphine hydrochloride is absorbed as rapidly as the subcutaneously injected preparation. Compared with sublingual preparation, IN delivery resulted in increased absorption. Indeed, the bioavailability of sublingual apomorphine was only 56% that of IN apomorphine.

Nastech has investigated the uptake of IN apomorphine into human cerebrospinal fluid (CSF) as compared with sublingual dosing. The data revealed an approximately five-fold increase in the ratio of apomorphine levels in the CSF to plasma (see figure 4).

Interestingly, we have observed that the rates of significant adverse events were reduced dramatically after changing the route of administration to IN even though the systemic drug exposure was similar. For sublingual apomorphine delivery, the rates of nausea and vomiting observed are about 18-22% and 1-4%, respectively. In contrast, following IN delivery of a dose corresponding to about the same AUC as the sublingual dose, the incidence of nausea (3%) was nearly an order of magnitude less compared with sublingual delivery and there were no incidences of vomiting.

CASE STUDY: MORPHINE GLUCONATE

Nastech has developed an IN formulation of the opioid, morphine, as a gluconate salt.[11] Similarly to butorphanol and scopolamine discussed above, morphine has relatively low oral bioavailability due to extensive first-pass metabolism. For this reason, IN delivery is a highly attractive dosing route. The additional benefit of IN delivery described previously –



Time to maximal drug concentration (Cmax) was 3.37 ±1.04 ng/mL and 2.11 ±0.60 ng/mL, respectively; time to maximal drug concentration (Tmax) was about 11.3 ± 3.4 and 13.0 ± 5.7 min, respectively.

Figure 2. PK for IN versus IM butorphanol tartrate (1.0mg dose) in humans

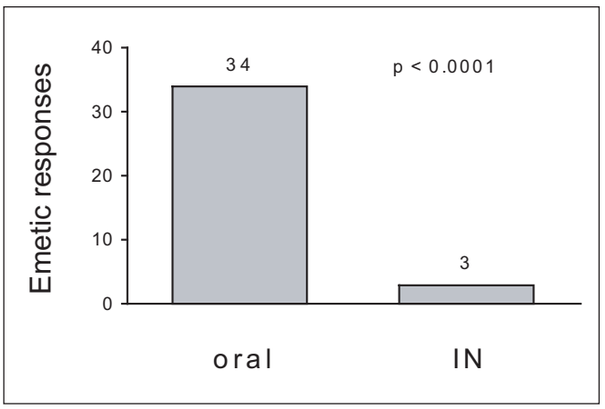


Figure 3. Emetic response for oral versus IN galantamine (Source: Leonard *et al* [10])

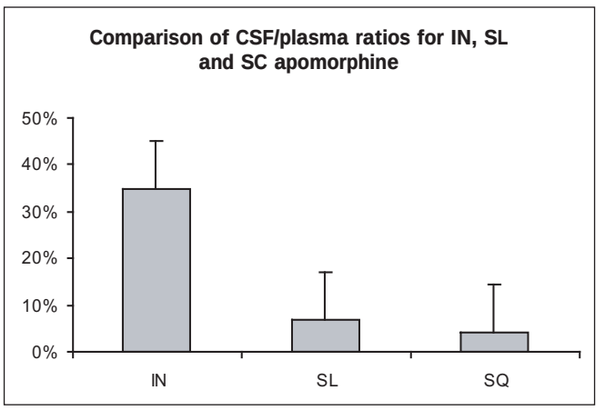


Figure 4. Human clinical testing of IN apomorphine. Sublingual and subcutaneous dosing in 12 subjects

relieving pain as rapidly as the injected product – serves only to add to its appeal.

The patented gluconate salt enables a therapeutic level of morphine to be delivered to opioid-tolerant patients in volumes associated with nasal delivery. Figure 5 illustrates the pharmacokinetics of the IN formulation compared with the traditional IM and oral routes. The data show that IN dosing achieves a similarly fast drug onset (Tmax = 15 minutes) compared with IM dosing, and is much faster than oral dosing (Tmax = 50 minutes).

As is the case with butorphanol, speed of onset for morphine is a highly desired attribute, particularly for the treatment of breakthrough pain in cancer where rapid onset of meaningful pain relief is critical. IN morphine has achieved such meaningful pain relief in 2.2 minutes (data not shown).

PROTEIN/PEPTIDE DELIVERY VIA TIGHT JUNCTION-MODULATING EXCIPIENTS

Recent trends in drug discovery methods and the continuing emergence of biotechnology products, have meant that IN delivery of peptides and proteins is becoming an ever more attractive therapeutic option, receiving increased attention from the industry.

Such macromolecules have extremely poorly bioavailability due to enzymatic digestion in the GI tract. Therefore, delivery by injection is the predominant route for commercial applications. Even so, some peptide products have successfully reached the market as IN formulations, albeit as simple formulations with relatively low bioavailability due to the permeation barrier presented by the nasal mucosa.

In order to improve IN delivery of macromolecules and expand the possibilities for future development, Nastech has devised strategies to increase permeability of the nasal mucosa safely and reversibly.

Specifically, we have focused on transient modulation of the nasal (and other) epithelial tight junctions, allowing for their safe and reversible opening and to improve paracellular transport. A variety of compounds, from small-molecule permeation enhancers to tight junction-modulator (TJM) peptides[3], illustrate beneficial effects.

Figure 6 depicts a specific example of improved IN absorption of a peptide by comparing plasma levels when using small molecule versus peptide tight junction-modulating excipients. The data show a dramatic improvement in bioavailability (50- to 70-fold improvement in Cmax and AUC) of the therapeutic peptide when dosed with 50 μM of a TJM peptide. Notably, the effect was superior even when a much higher concentration (39.2 mM) of low-molecular-weight permeation enhancers was used. These data demonstrate the promise of developing such potent TJM peptides for enhancing IN delivery of macromolecules.

CONCLUSIONS

For many drugs, intranasal administration offers an effective alternative both to oral delivery, with its associated problems with poor bioavail-

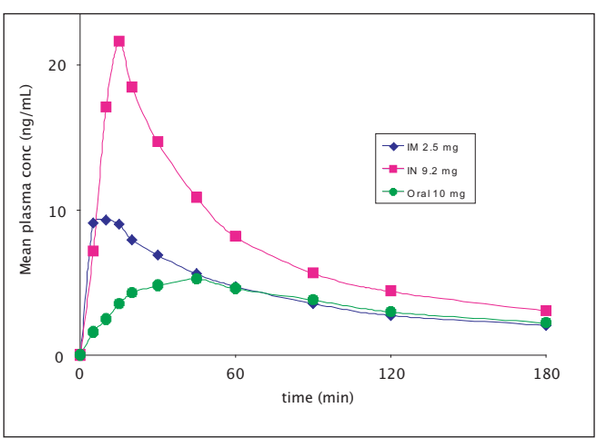


Figure 5. Clinical testing of IN morphine gluconate compared with traditional IM and oral products. AUClast ng/mL.min: IM = 765; IN = 1359; oral = 747

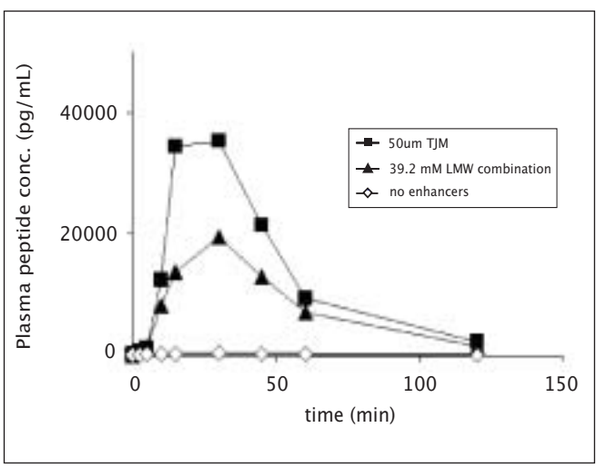


Figure 6. IN dosing of a therapeutic peptide (rabbit pharmacokinetic data) (Source: Chen *et al* [12])

ability, and invasive injections. This article has illustrated how IN delivery may be preferred for various applications.

Currently, an active area of development at Nastech is to optimise IN delivery of peptides and proteins by modulation of epithelial tight junctions. Nastech employs a rational, molecular biology-based approach to this end, which includes the use of relevant and predictive *in vitro* models to identify optimal combinations of existing and/or novel excipients. Nastech uses its Tight Junction Modulator technology to isolate and develop mechanism-based compounds or excipients that can effect reversible responses in tight junctions.

These technologies are the foundation of Nastech's drug delivery platform. The results as demonstrated here, and in ongoing clinical and research projects, are safe and effective drug formulations. Nastech believes this work will significantly advance the development of non-invasive large-molecule products that do not require injection, and may further mitigate other undesirable consequences of traditional pharmaceutical modalities. Progress to date suggests that IN delivery can continue to expand and become an increasingly important delivery route.

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CONTROLLED PARTICLE DISPERSION™:

EFFECTIVE NASAL DELIVERY FROM A VERSATILE, FLEXIBLE TECHNOLOGY PLATFORM

Today's nasal delivery technology – the spray pump – has been the status quo for over 25 years. Despite the fact that up to 90% of the drug ends up in the stomach, somehow spray pumps became accepted as nasal drug delivery devices. Increasing demands for targeted deposition, less peripheral delivery, fewer side effects, compliance monitoring and dose counting, render spray bottle technology ever more inadequate. Clearly, says Marc Giroux, Chief Executive Officer of Kurve Technology, the pharmaceutical industry needs a comprehensive, versatile technology platform that addresses the inevitable paradigm shifts coming in nasal drug delivery.

Figure 1: The ViaNase™ electronic atomizer

INTRODUCING CONTROLLED PARTICLE DISPERSION™

Controlled Particle Dispersion (CPD) is a technology platform that pharmaceutical companies can use to deliver most compounds regardless of characteristics or target conditions. Whether the applications are systemic or topical, solutions or suspensions, CPD meets the demands of today and tomorrow's full nasal delivery product line. CPD offers a vast improvement in efficacy and performance while presenting design flexibility for maximum compliance.

Building a more efficient nasal drug delivery device requires not only better device design but a far more versatile technology platform; one that delivers optimal nasal deposition, with formulation flexibility to work successfully with the many variables of the formulation itself.

Rather than build a single device, Kurve Technology developed CPD – a comprehensive nasal drug delivery technology platform. Using new principals such as vortical flow, CPD effectively disrupts inherent nasal cavity airflows to deliver compounds to the entire nasal cavity, the olfactory region and the paranasal sinuses. CPD optimises droplet size and trajectory to saturate the nasal cavity, lengthens compound residence time, and minimises deposition to the lungs and stomach. This leads to more effective and efficient treatments than delivery via traditional nasal spray bottles that deliver compounds only as far as the anterior portion of the nasal cavity.

CPD's adjustable variables include:

- droplet size variability from 3 to 50 μm
- atomisation rate
- delivery of solutions, suspensions and dry powder
- small and large molecules
- proteins and peptides
- preservative-free, unit-dose ampoules
- targeted deposition including to the paranasal sinuses and the olfactory region
- variable medication volumes in the device and in the nasal cavity
- wide viscosity range
- vortex characteristic variability
- electronics and power (compliance monitoring, dose counters, etc)

CPD powers ViaNase™ – Kurve Technology's electronic atomiser (see figure 1). Understanding the flexibility of these parameters as it pertains to ViaNase is key to appreciating the versatility of CPD.

DROPLET SIZE VARIABILITY

As a nasal drug delivery company, Kurve's goal is to get close to 100% of the drug into the nasal cavity and onto the nasal mucosa. To accom-

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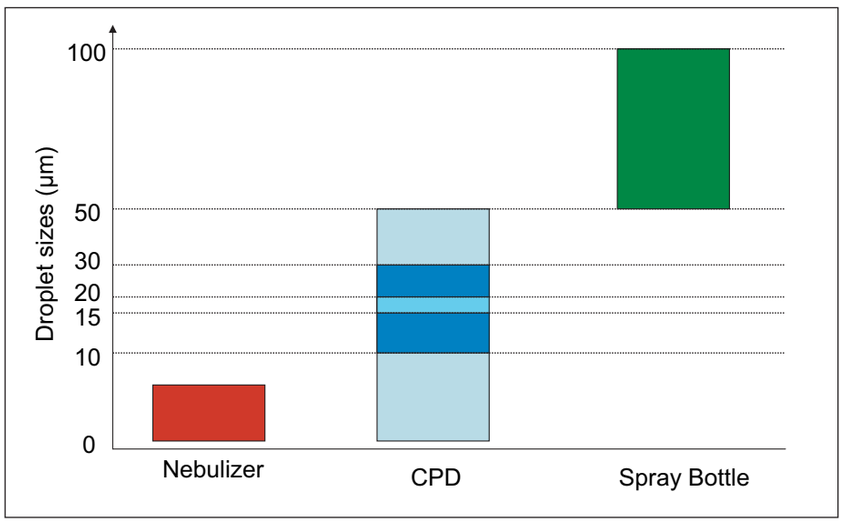


Figure 2: Droplet size comparison (CPD, nebulizers, and spray bottles)

plish this, ViaNase delivers droplets ≥ 8 µm in order to avoid pulmonary deposition. In fact, ViaNase is capable of generating narrow droplet distributions from 3-50 µm. However, for optimal nasal drug delivery device, Kurve uses a size range between 10 and 30 µm.

The upper limit of 30 µm was determined because larger droplets are more difficult to control in vortical flow and deposition is reduced. CPD's ability to generate a range of droplets in tight distribution curves allows for small incremental changes in the mass median aerodynamic diameter (MMAD), so slight adjustments can be made to optimise performance of a particular formulation.

In early tests, droplet sizes of 15-20 µm consistently performed well across many compounds. CPD produces a droplet distribution curve with droplets at a Dv10 of 9 µm, a Dv50 of 19 µm and a Dv90 of 29 µm. This distribution not only leaves all of the droplets within a controllable range, but virtually eliminates peripheral deposition in the stomach and lungs.

Figure 2 compares droplet sizes from CPD, nebulizers, and spray bottles.

ATOMISATION RATE

CPD can control the rate at which the droplets are created and how quickly they will exit the device. Kurve designed its unique droplet generator for short treatment times – a characteristic necessary to improve compliance in patients frequently using the device.

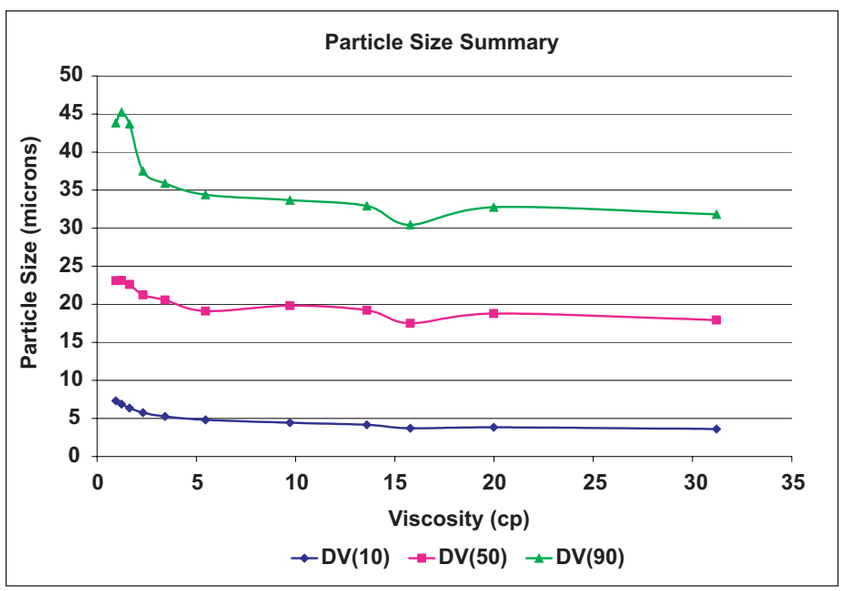


Figure 3. Droplet size versus formulation viscosity at three points along the volume diameter distribution curve

While a typical atomisation rate would be 1 ml/min, the droplet generator can achieve a volume rate of over 4 ml/min. This offers increased output capacity should a formulation warrant a larger volume to be delivered in a short treatment time. The rate at which the device generates droplets does not affect the droplet size to any measurable degree.

SOLUTIONS, SUSPENSIONS AND DRY POWDER

CPD can effectively deliver solutions and suspensions, and conceptual designs and development are already underway for dry-powder delivery. Of the current technologies available, none are capable of delivering all three formulation types. All the principles of CPD will be applied to dry powder delivery.

SMALL AND LARGE MOLECULES, PROTEINS AND PEPTIDES

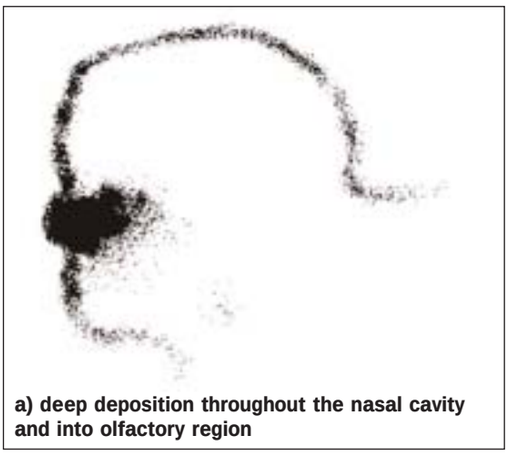
CPD can deliver more than small molecules. A potential pharmaceutical partner independently tested ViaNase with one small molecule and two large peptides (>20 amino acids). In each instance the droplets exiting the machine were 98% pure. In addition, Kurve also tested salmon calcitonin exiting the device and found minimal degradation. It is well known that salmon calcitonin is fairly durable, but one of the peptides tested was more fragile and it faired as well as the others. While ViaNase's droplet generator is fast, it is not overly harsh on compounds.

VISCOSITY

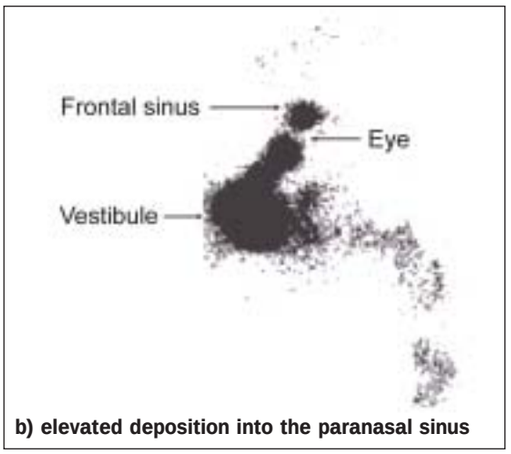
Viscosity of a formulation is not a limiting factor with CPD. Viscosities ranging from 1 to 30 centipoise were tested with no significant change in droplet size (see figure 3). The atomisation rate changed slightly, but droplet sizes remained consistent.

PRESERVATIVE-FREE PACKAGING

The pharmaceutical industry is shifting away from preservatives given the inherent difficulties with side effects and production. Kurve designed ViaNase to use form, fill and seal unit-dose ampoules. Filled sterile and used within minutes of opening, unit-dose ampoules are the least expensive packaging for formulations. Ampoules eliminate the need for costly preservatives and minimise preservative-induced side effects.



a) deep deposition throughout the nasal cavity and into olfactory region



b) elevated deposition into the paranasal sinus

Figure 4: Scintigraphy studies showing CPD's ability to target deposition in different areas of the nasal cavity

TARGETED DEPOSITION

Published scintigraphy studies show CPD's capability to reach the paranasal sinuses[1] and the olfactory region[2]. Kurve found that manipulating CPD's many available parameters resulted in significantly different deposition patterns (see figures 4a & 4b). While testing continues in vivo, a large test result database allows adjustment of parameters to optimise deposition regions for any compound.

VOLUME

Delivering greater medication volumes to the nasal cavity often provides an added therapeutic effect. Unlike current methods, CPD allows the formulator to deliver these larger volumes. This is particularly important for relatively insoluble compounds

ViaNase's droplet generator requires only minimal space in the device housing. This allows a large volume in the chamber itself. As much as 5-6 ml is possible in the existing device while even more volume is possible with a slight retrofit.

VORTEX CHARACTERISTICS

CPD induces a vortical flow on the droplets as they exit the device. The induced vortical flow characteristics can be altered in circular velocity and direction to achieve different droplet trajectories. Variations can be added to the vortical flow characteristics involving rate of spin, series of vortices and combinations of vortices. Deposition differences are noticeable with vortex variation and testing is ongoing.

THE FUTURE – ELECTRONICS AND POWER

With the US FDA advocating dose counting and compliance monitoring, new methods of nasal drug delivery are a must for the device industry. Physician monitoring and web-based downloads also are under discussion. With built-in electronics and power, the ViaNase device offers these functions upon request.

CONCLUSION

From its inception, CPD was designed as a technology platform. With its many controllable parameters, CPD offers pharmaceutical partners a nasal drug delivery device that meets industry needs – today and tomorrow.

Although used for 25 years, the spray pump, was never a viable system. When 90 percent of the drug delivered is swallowed, nasal drug delivery is at best, a misnomer. Spray pumps in fact use the nose as an alternative route to the stomach. Most of the devices available today are simply variations on this single theme – and most of the compound still ends up in a region other than the nasal cavity.

Based on the CPD technology platform, ViaNase is a truly viable nasal drug delivery device, demonstrating that the key to effective nasal drug delivery is a flexible technology platform upon which a product line can be built and expanded. After 25 years of falling far short of the intended target – saturation of the entire nasal cavity – the future of nasal drug delivery brings change. This much needed paradigm shift is Controlled Particle Dispersion.

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JAVELIN

NASAL DELIVERY OF ANALGESICS

A number of high-profile drugs important to the management of pain have received negative press in the past few months, from the withdrawal of COX-2 inhibitors to the withdrawal of Palladone. The unfortunate demise of these agents has left a short-term void in the marketplace. Overlooked in this spate of bad publicity, though, is the crucial long-term story that the pain market will experience significant, sustained growth due to the current under-treatment of acute, chronic and cancer-related pain and the need to close these gaps. In this article, Michael Sheckler, MBA, Vice-President, Business Development; Fred Mermelstein, PhD, President; Douglas Hamilton, BSc, MBA, Chief Operating Officer and Chief Financial Officer; and Daniel Carr, MD, Chief Executive Officer and Chief Medical Officer, all of Javelin Pharmaceuticals (formerly Innovative Drug Delivery Systems), describe the important place that intranasal analgesics have in this growing market.

Valued at nearly US$21 billion in 2004, the entry of new drugs for the treatment of neuropathic pain, acute and breakthrough cancer pain, and postoperative pain, will grow the pain management market to US$30 billion by 2008, says Navigant Consulting. Like the pain management market, nasal drug delivery is also projected to grow significantly over the next few years. Greystone Associates is forecasting 24% annualised growth from 2004 to 2007, which will increase the value of the nasal drug delivery market from slightly less than US$2 billion to US$4.3 billion. More specifically, the global 2007 forecast for analgesics delivered nasally is US$535 million, up from US$110 million in 2003.

A number of small, innovative companies are now addressing the unmet need for nasal analgesics. In the July 2005 update of BioPharm Insight (Infinata), 16 INDs were cited for nasally delivered pain drugs. This activity speaks to the attractiveness of the nasal delivery of analgesics. With ease of administration, rapid absorption and onset of action, generally low dose requirements, and safety, it is easy to understand why so much attention is being paid to this route of administration.

Two nasally delivered analgesics are the focus of this article – morphine and ketamine. Morphine remains the gold standard of opioids and is often considered the prototype μ-agonist. With its good safety profile, widespread usage and historical record of efficacy, it is highly unlikely that it will ever be withdrawn from the market. It has been used extensively in the management of both acute and chronic pain. Ketamine, a non-opioid, is an N-methyl D-aspartate, or NMDA, receptor antagonist that has been in clinical use as a general anesthetic for the past 30 years. It has been administered to tens of thousands of patients and has an established safety record.

INTRANASAL MORPHINE

With a successful track record as an intramuscularly (IM) and intravenously (IV) delivered drug (oral preparations are available, but have a slow onset of pain relief and variable bioavailability), why do we need or want a nasal form of morphine?

As can be seen in figure 1, there are several advantages to intranasal morphine, perhaps the most significant of which is getting rid of the requirement for a needle and syringe.

Of the advantages outlined in figure 1, perhaps the most important is that the pharmacokinetic performance of nasal formulations approaches that of IV administration. After all, IV delivery offers the most rapid absorption and onset of action of all routes of administration. Figure 2 clearly depicts the kinetic superiority of intranasal morphine to oral morphine and its similarity to that of injectable kinetics.

Several other advantages are available to both the patient and healthcare professional. There is patient/staff familiarity with both morphine (as a "gold standard" in pain management) and the nasal route. The duration of action makes it ideal for large target markets, including, orthopaedic, post-operative, procedural and burn pain. There is a low risk of misuse of residual controlled substances, such as the scavenging of residual materi-

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Rapid Onset	→	Onset of action in under 10 min
Immediate release of morphine	→	• 1st order delivery comparable to IV morphine • Easy to calculate equi-analgesic doses to layer on top of baseline medication
Ease of Administration	→	Patient controlled dose titration
Bypasses GI metablolism	→	• Fewer GI side-effects • Lower levels of metabolites involved in side-effects (M6G, M3G)
Desirable Safety Profile	→	• No nasal irritation or deposition on lungs • Can be used in opioid naïve patients

Figure 1: Intranasal morphine product profile

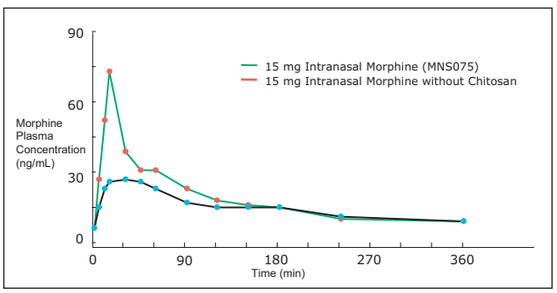

Figure 2: Phase I Trial - Mean plasma concentration curves of 15mg intranasal morphine with and without chitosan

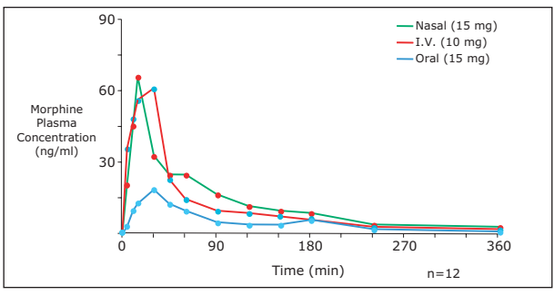

Figure 3: Intranasal morphine - intranasal kinetics similar to injectable kinetics

	Javelin Intranasal morphine	Oral morphine sulphate	I.V. Morphine	Actiq®
Onset of action	<10 min	20-40 min	<10 min	15 min PD[2]
Time until peak efficacy	30 min	60 minutes	30 min	45 min
Ability to titrate	Easy titration	Difficult titration	Easy titration	Difficult titration
Patient ease of use	Easy to use	Easy to use	Requires a nurse	Easy to use
Duration of effect	2 to 2.5 hrs	4 to 6 hrs	4 hrs	4 hrs

[1] Physicians' Desk Reference, 58th edition, 2004
[2] PD = post dose, on average it takes 15 minutes to consume a single dosage unit

Figure 4: Competitive product comparison[1]

al from used units. Finally, if implemented for PCA (patient-controlled analgesia) delivery, safety is an important factor since, according to Alaris Medical Systems (San Diego, CA, US), a typical 350-bed hospital will average one life-threatening IV error every 2.6 days.

The nasal morphine product in this article is formulated with chitosan. Chitosan is a cationic polysaccharide derived from the shells of crustaceans. It is synthesised by the deacetylation of chitin and has been found to be both biocompatible and biodegradable. Much information can be found in published literature supporting the use of chitosan as a bioadhesive in transmucosal delivery systems. The benefit of using chitosan as a formulation enhancer is seen in figure 3, where the greater mean plasma concentration curves of 15 mg intranasal morphine with chitosan is clearly demonstrated.

Given the uniqueness of route of administration and the advantages of intranasal morphine, how does it compare with competitive products? Figure 4 outlines the comparison using the criteria set forth in the product profile found in figure 1.

INTRANASAL KETAMINE

With the documented success of ketamine as an anaesthetic, one can ask the same question as that for morphine: Why the need for an intranasal form? Low doses (one sixth the dose needed to induce anaesthesia) of intranasal ketamine have been found to be effective in the treatment of moderate-to-severe acute pain. It has a rapid onset of action (4-8 minutes) and its duration (up to 2.5 hours of analgesia) matches the timeframe for breakthrough pain & procedural pain episodes.

Ketamine enjoys a wide margin of safety. It is not physically addictive, does not cause respiratory depression, hypotension or gastro-intestinal or genito-urinary dysfunction and, at lower doses, is not associated with the dissociative side effects such as hallucination or psycho-mimetic effects sometimes associated with higher doses. Like intranasal morphine, it is easily titrated for effective nasal dosing.

Ketamine can be used as an alternative to opioids, yet can be used in combination. In so doing, the compound becomes a valuable tool to healthcare providers, enabling them to minimise opioid side effects, and treat opioid dependent/tolerant patients and patients unable to take opioids.

An additional benefit that can be conferred is that when ketamine is used in a multimodal regimen, post-operative pain and analgesic consumption are both reduced. The US Department of Defense is very interested in intranasal ketamine as an alternative to IM morphine for battlefield analgesia and a variety of severe pain indications such as trauma, burn wound care and procedural pain. It is financially supporting the development of intranasal ketamine.

As an example of the pain relief intranasal ketamine can provide, the following graphs outline the plight of a hypothetical patient with breakthrough cancer pain. Figure 5 shows the several episodes/day of breakthrough pain. Regardless of the reason, it can be seen that the pain overcomes the baseline medicine.

In figure 6, we see that if there is an increase in the opioid regimen, meaning an increase in the controlled release form, it will blanket more of the pain episodes, but will only do so at the expense of opioid side effects, such as constipation, respiratory depression sedation and an overall decrease in the quality of life.

Lastly, in figure 7, we see the introduction of intranasal ketamine. This is the approach that most guidelines recommend where the baseline regimen stays as it was and the physician adds a quick-onset, short-duration medication for those episodes. Baseline opioid consumption is reduced and quality of life improves.

A CLOSER LOOK AT SAFETY AND RISK MANAGEMENT

At the heart of the delivery of any opioid or non-opioid analgesic is the consideration of safety and risk and how to ensure the former and minimise the latter. In the case of intranasal morphine, the drug's developer has taken numerous steps to accomplish both.

A valuable lesson learned early on in the nasal delivery of potentially addictive drugs was that of the abuse of butorphanol.

Sold in a multidose sprayer (up to 12-13 doses after priming) with no lock-out mechanism, this product was easily abused. Regrettably, it required the death of the child of a high-profile individual to draw attention to the dangers of an abusable drug in a multidose sprayer. While such dosage forms are still available, prescription drugs that are being delivered today are more likely to be found in unit dose sprayers such as that used for Imitrex and Zomig nasal migraine products.

This device is the same one chosen by the developer of intranasal morphine and ketamine. Because it contains only 120μL of drug and the delivered amount is 100μL, there is very little residual to scavenge after actuation.

An intrinsic safety mechanism is the capacity of the nasal passages. Each nostril can hold only 150-200μL of administered drug. It requires approximately 15 minutes for the drug to clear the nasal passages, so attempting to introduce additional drug will result in either the drug being swallowed or dripping out of the nose.

Ketamine, even as a non-opioid and with its wide safety profile, is not immune to abuse and will have to be handled and managed as a controlled substance. However, when one examines trend data from the Drug Abuse Warning Network (DAWN) that reports those drugs associated with emergency department visits, the ketamine-related visits occur at only 1% of the rate of visits related to hydrocodone.

Both intranasal morphine and ketamine have been shown to be non-irritating to the nasal mucosa. Chitosan, the naturally occurring bioadhesive that improves the mean plasma concentration of intranasal morphine, is also a non-irritant. It would seem that the preferred bio-adhesive would be an agent like chitosan, that is generally recognised as safe, rather than unproven agents that may cause irreversible damage to the nasal mucosa.

CONCLUSION

The fields of pain management and nasal drug delivery clearly combine to meet the needs of a growing and underserved marketplace. Help-ing to drive the growth will be the approval of new nasal products for pain management, a trend toward self-administration, an aging population, managed healthcare initiatives and growth in the home healthcare population.

The convergence of pain management and nasal drug delivery may prove to be very fortuitous to those who are suffering with acute, moderate-to-severe and breakthrough pain. In an era when people are recognising that they can talk with their healthcare provider about their pain rather than simply try to ignore and live with it, nasal delivery of analgesics will offer a non-invasive, fast-acting, efficacious means to relieve that pain.

FOOTNOTE

Javelin Pharmaceuticals has been awarded government contracts from the US Department of Defense, which are used to subsidise the company's research and development projects.

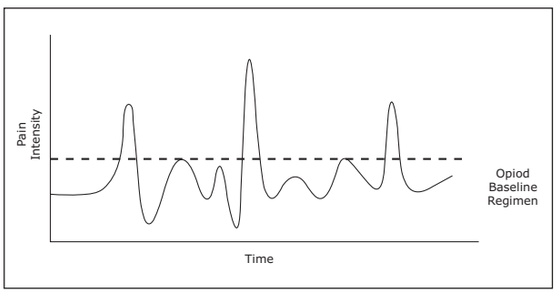

Figure 5: Cancer pain = baseline plus breakthrough episodes

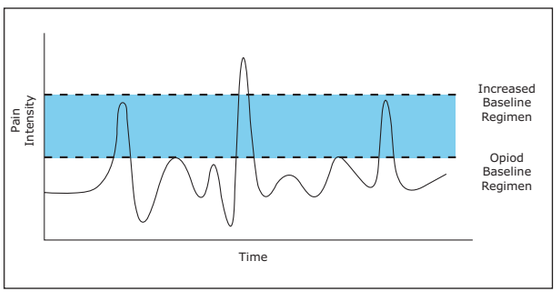

Figure 6: Controlling breakthrough pain episodes by increasing the fixed-dose, baseline opioid regimen increases side effects (sedation, constipation, respiratory depression...) and decreases quality of life

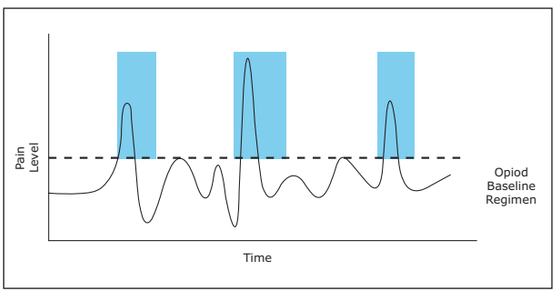

Figure 7: Adding ketamine as needed for breakthrough pain episodes avoids the need to increase the fixed-dose, baseline opioid regimen and improves quality of life.

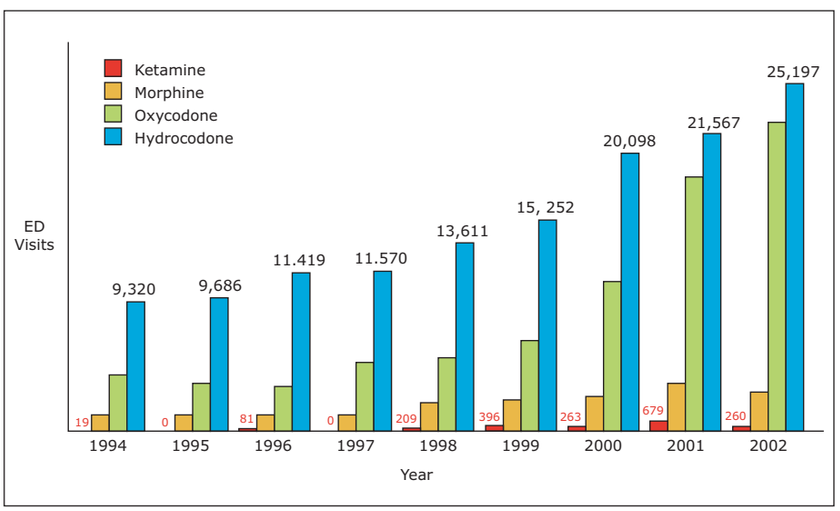

Figure 8: DAWN trends for selected drugs - emergency department visits 1994-2002

BREATH-ACTUATED BI-DIRECTIONAL DELIVERY SETS THE NASAL MARKET ON A NEW COURSE

Nasal drug delivery is already a thriving market but there is still a wide gap between what has been achieved in the past and what could be achieved were the full potential of this highly attractive administration route released. This article describes a technological breakthrough by OptiNose that has allowed the company to make that hitherto elusive step of achieving truly optimal nasal drug delivery.

Compiled by ONdrugDelivery on behalf of OptiNose.

The advantages of delivery via the nasal route are numerous. It is clearly a convenient, non-invasive administration route but this is not what sets it apart. Where other routes often offer such benefits at the expense of desirable pharmacokinetics, nasally administered formulations have true potential for rapid onset of action, high bioavailability and direct "nose-to-brain" delivery.

This potential arises predominantly because of the complicated structure of the nasal cavity, which has evolved to carry out multiple functions. They include physical protection of the lower airways (by filtering out large particles), immune protection, and optimisation of the temperature and humidity of air before it enters the lungs. What is more, the nose is an amazing and delicate sensory organ, able to detect minute traces of countless substances in the air via the olfactory nerves that enter the roof of the nose through the cribiform plate.

Despite the success of conventional nasal sprays there is still significant room for improved delivery

Of course previous systems have not been without their benefits – indeed, today several topical and systemic nasal products can be found on the market. However, the crux of the issue, and the point of this article, is that so much more can be accomplished. A simple yet remarkable technological leap offers to bridge the gap between previous nasal products with their limited efficacy and applications, and success in the pharmaceutical market for future nasal formulations on a scale that could exceed even the most optimistic expectations.

With an elegant adaptation to the mechanism of nasal delivery devices, OptiNose has successfully taken this step. In-depth knowledge of the nasal anatomy and physiology, reinforced by detailed studies, have provided the information enabling OptiNose to understand how to optimise drug delivery while reducing or eliminating side effects. The result is nothing short of a medical breakthrough. The nose is now set to take its place as an ideal delivery route for any number of pharmaceutically active compounds for the treatment and prevention of diseases across the board.

WHY THE LONG WAIT?

To get to the core of why earlier nasal delivery systems only managed a degree of success within a narrow market, it is necessary to take a closer look at the complex structures and geometry that give the nose its exceptional functional properties.

Between the anterior third of the nose (roughly equivalent to the visible part of the nose on your face) and the posterior two thirds (deep inside your head above the roof of the mouth) the nasal valve disrupts the airflow to facilitate trapping and the filtering of particles. The posterior two thirds, beyond the nasal valve, is divided into slit-like passages by the nasal turbinates. Slowing of the airflow as it passes over the turbinates allows time for inhaled air to be heated and humidified before reaching the lungs and, crucially, causes particles to sediment out on the nasal mucosa.

The true nasal mucosa beyond the nasal valve is lined by a single cell-thick columnar epithelium, similar in structure to the respiratory epithelium that lines the lungs. As well as being rich in immunologically active cells, den-

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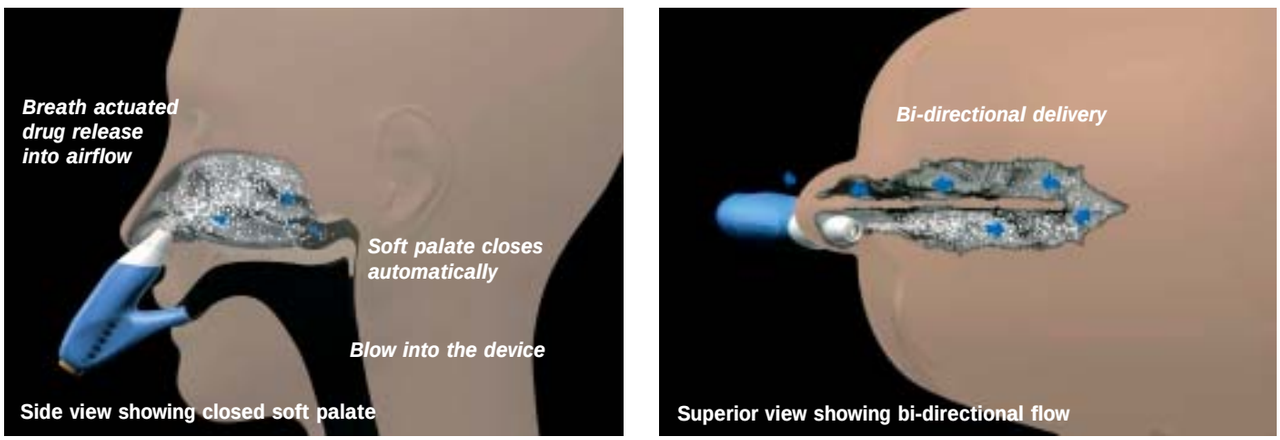

Figure 1: Two interlinked anatomical principles underlying bi-directional drug delivery

dritic cells and organised lymphatic tissues, the nasal mucosa is also highly vascularised making it an ideal target for optimal drug absorption.

The riddle that standard nasal delivery systems have been unable to solve is that if a dose consists of large particles, a significant proportion does not reach the true nasal mucosa beyond the valve but remains in the anterior region, which is not the target site. Absence of cilia in this region means that particles will largely remain stationary or will drip out or be wiped off, leaving large portions of the nasal surface unexposed to drug and thereby limiting their clinical effects. Pressurised metered-dose inhalers adapted for nasal use, nasal powder inhalers and mechanical spray pumps, have all been shown to suffer from this shortcoming.

Furthermore, sniffing too sharply during or after actuation causes the spaces between elastic tissues within the nasal valve to narrow, trapping more of the dose in the anterior segment. Particles that pass through the nasal valve during a strong sniff are sucked along the floor of the nose to the back of the mouth and swallowed.

The obvious solution to the problems encountered by large particles is to reduce particle size, but this is equally unsatisfactory since small particles (less that 5-10 μm) may travel beyond the nasal turbinates and be inhaled into the lungs. Clinical testing of nasal nebulisers delivering particles of 6 μm resulted in better delivery to the mucosa but 33-56% of the dose was deposited in the lung.[1]

It is tempting to reason that it might be satisfactory for most of the dose to be delivered to the target site with some reaching the lungs. However, for both systemic and topical nasal products there is a risk of adverse side effects in the lung, and the variability of the dosing increases. Lung deposition of nasal formulations is unacceptable, to the extent that the guidelines from regulatory authorities in major markets such as the US require nasal spray pumps to limit the respirable fraction to 5%. For conventional technologies, this equates to a mean particle size of approximately 30-50 μm, which represents a true challenge for efficient and controlled delivery to the nasal mucosa.

One type of formulation – nasal drops – has been shown to achieve improved delivery beyond the nasal valve without lung deposition. However, correct administration requires the patient to carry out complex manoeuvres involving contorted head movements not acceptable to most patients. Any deviation from this process can preclude effective delivery, and thus nasal drop formulations result in poor compliance.

BI-DIRECTIONAL DELIVERY: AN ELEGANT SOLUTION

So, it seems that every approach to achieving efficient delivery via the nasal route that has been tried so far has one deficiency or another. Yet the particle-size riddle does have a solution. Once realised, the solution is strikingly simple and highly effective. The concept has been termed breath-actuated bi-directional delivery by OptiNose.

It is somehow appropriate that anatomical features of the nose have been the root of the tribulations of previous nasal delivery systems, and yet it is by harnessing two interlinked functional anatomical nasal features, that bi-directional delivery achieves its aim.

The first of these features is that during exhalation against a resistance the soft palate closes, separating the nasal and oral cavities (see figure 1a). Thus if nasal delivery can be achieved whilst exhaling against a resistance the previously insurmountable problem of lung deposition following nasal inhalation of smaller particles is immediately and completely avoided.

The second anatomical feature is that during closure of the soft palate there is a communication pathway that remains between the two nostrils, located behind the nasal septum. Under these circumstances, it is possible for air to enter via one nostril, turn through 180˚ passing through the communication pathway, and leave by the other (see figure 1b).

OptiNose's breath actuated bidirectional delivery couples together the act of blowing out and the use of a sealing nozzle to direct the airflow into the nose. The sealing nose piece allows control over pressure and flow conditions and, together with optimisation of particles size characteristics and the use of a breath-actuation mechanism, controlled and targeted nasal delivery of both liquid and powders can be achieved. At the same time lung deposition is avoided.

In a study of 16 healthy subjects using 99mTc-labelled nebulised particles with a mean particle size of 3.5 μm, bi-directional delivery prevented lung deposition, whereas significant fractions (12-39%) were deposited in the lungs in all 16 subjects following conventional nasal inhalation. The study concluded that bi-directional nasal delivery minimises the risks and problems related to lung deposition.[2]

FULLY FUNCTIONAL DEVICES

Bi-directional drug delivery has already made the transition from concept to reality. With the key to effective nasal delivery in its possession, OptiNose is proceeding rapidly with the development of several groundbreaking breath-actuated bi-directional nasal drug delivery devices for both liquid and powder.

All of these systems apply bi-directional drug delivery in the same way. A sealing nozzle is inserted into one nostril and the patient blows into the mouthpiece. The blowing action closes the soft palate and creates an airflow, which carries the formulation out of the device through

Figure 2: The single-use device

the sealing nozzle into one nostril to the target sites. The airflow passes through the communication pathway between the nostrils and back out through the other nostril.

An additional benefit of the positive pressure created as the patient blows into the sealing mouthpiece is the expansion of the narrow passages and opening of obstructed segments. This potentially improves distribution of delivered particles – the reverse of what happens during a sharp sniff.

The lead bi-directional device manufactured in collaboration with Ing Erich Pfeiffer GmbH, Germany, is a single-dose liquid spray technology, intended for the delivery of high-value drugs for systemic and "nose-to-brain" delivery, as well as vaccines. The value of bi-directional drug delivery in these applications is discussed in more detail below.

The device, which is shown in figure 2, is supplied pre-assembled with a single-dose vial and applicator from Pfeiffer located inside. The user primes the device by pushing the orange handle, positions the nosepiece and mouthpiece, and begins to exhale. The drug is released when the correct pressure-flow relationship is reached, and is carried to the desired site within the nose.

User studies have shown a clear preference for the bi-directional delivery format compared with traditional nasal sprays, probably due to three separate effects. First, the bi-directional device is more comfortable because of its fixed position during use, compared with a traditional spray pump, which tends to move during actuation. Second, the devices are breath actuated. Third, the airflow through the nose at actuation reduces the discomfort often experienced when the spray is released. Finally, there may be a reduction in the aftertaste at the back of the throat due to a different deposition and clearance pattern.

MULTI-DOSE AND POWDER DEVICES

Two other types of device under development by OptiNose are a multi-dose liquid reservoir device, shown in figure 3, and a powder delivery device.

The multi-dose liquid device has been designed to incorporate existing nasal spray pump technology and to incorporate proven breath actuation technology in order to reduce risk. Device design is currently being finalised and injection-moulded devices will be available in 2006.

Recent clinical studies comparing delivery from a traditional spray pump with delivery from an initial multi-use liquid bi-directional delivery device design (with the same spray pump incorporated inside), have shown significantly improved delivery beyond the nasal valve and in particular to the upper remote and clinically important nasal segments (see figure 4). Reproducibility of dosing was also improved with the bi-directional delivery device.

The powder device, which is at a slightly earlier stage of development, is designed for single- or multi-dose use and will allow the development of powder formulations with greater opportunity for stability to be delivered without the risk of pulmonary deposition.

THE NEW VISION FOR NASAL DRUG DELIVERY

Like all true breakthroughs, the implications of breath-actuated, bi-directional drug delivery reach far beyond simply addressing the predominant shortfall of existing systems – the particle size riddle. Indeed, bi-directional drug delivery is aptly named since the array of new opportunities it opens up for the nasal delivery market can be said to stretch in two directions.

In one direction, it allows a look back at standard nasal delivery devices and overcomes some of their other disadvantages, such as lack of consistency over dosing, local irritation, nosebleeds and uncomfortable taste from concentrated drugs reaching the mouth, as well as the failure to achieve optimal local and systemic absorption. Furthermore, breath actuation is likely to contribute strongly to improved patient compliance and acceptability as well as more consistent performance. When breath actuation was introduced to pulmonary delivery two decades ago it transformed the pulmonary drug delivery market.

Looking in the other perhaps more interesting direction – forwards – bi-directional drug delivery expands the possible applications of nasal administration into new areas not previously considered as viable markets for conventional nasal technology.

For example, once the nasal circuit is isolated from the lungs during administration, nasal drug delivery is freed from other restrictions. Particle size – along with flow-rate and direction – can of course be optimised to target the nasal mucosa effectively. However, the ability of bi-directional delivery to deliver to structures not reached by traditional nasal sprays has been verified through gamma scintigraphy studies. As well as significantly reduced deposition in the anterior region and prevention of lung deposition, they have shown significantly improved and more targeted delivery to the parts of the nose where the olfactory nerves pass and, the entrances to the sinuses, middle ears and the adenoid are located.

In addition to delivery to specific structures within the nose for topical delivery, these findings present two further major opportunities.

The first of these is in the area of nasal vaccination. Bi-directional delivery of diptheria and influenza antigens has shown a significant improvement in both the local and systemic immune response when compared with traditional spray pumps.

Figure 3: The multi-use liquid reservoir device

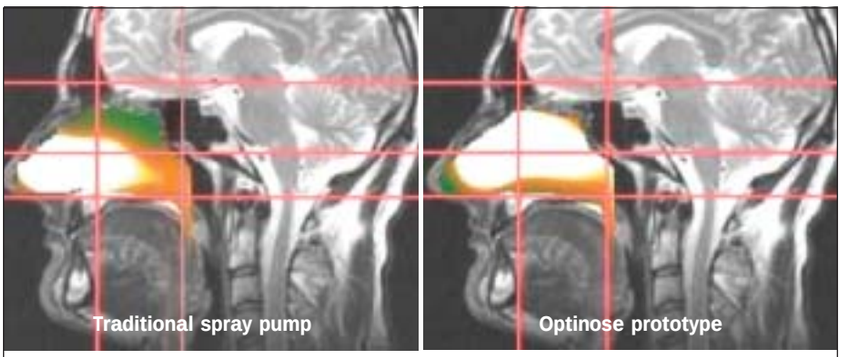

Figure 4: Gamma scintigraphy images comparing deposition following traditional and bi-directional delivery

The second opportunity is the real possibility of effective nose-to-brain drug delivery, an area in which OptiNose has taken a keen interest.

NOSE-TO-BRAIN DRUG DELIVERY

There is a growing body of evidence supporting the existence of a delivery route for pharmaceutically active compounds from the olfactory region of the nose directly into the central nervous system.

The olfactory epithelium is located just below the cribiform plate in the upper posterior quadrant of the nasal cavity. It contains olfactory receptor cells, which have a single dendrite that extends to the apical surface of the epithelium. At the basal end, the cell ends in an axon that joins into a bundle surrounded by glial cells and cerebrospinal fluid, and penetrates into the cranial cavity through the cribiform plate. To access this route of absorption, drug molecules must be delivered to the olfactory epithelium in meaningful quantities.

Nose-to-brain delivery offers two important benefits in the treatment of CNS disorders. First, it avoids the blood-brain barrier, which prevents the majority of compounds delivered via other routes – even injections – from gaining access to the cerebrospinal space.

Secondly, nose-to-brain drug delivery can achieve therapeutic levels in the cerebrospinal space while maintaining minimal systemic concentrations. Neuropeptides are one class of molecules whose usefulness could be greatly enhanced, as Born et al explained. "Biologically effective concentrations of neuropeptides can be achieved in the human brain without strong, systemic, hormone-like side effects. Such effects limit the systemic administration of peptides to amounts too small to have substantial effects in the brain."

Another interesting aspect of nose-to-brain drug delivery arises because the effects of some compounds differ in the brain compared with in the rest of the body. The potential that nose-to-brain delivery has for maintaining high drug concentrations in the CNS relative to the systemic circulation means that this route could take advantage of these diverse pharmaceutical activities.

Stockhurst et al give insulin as an illustration of this interesting phenomenon. "The intranasal route is a practicable way to reach the brain while maintaining euglycaemia. Additionally, the localization of insulin receptors in the olfactory bulb makes insulin interesting for the nose-to-brain pathway. Promising initial results have been reported with intranasal insulin corresponding to the diverse actions of insulin within the brain. Interestingly, initial data indicate that states of central insulin deficiencies (dopamine transporter [effects] and obesity) are accompanied by olfactory deviations. Thus, the nose-to-brain pathway deserves further attention." [4]

A recent Phase I clinical trial compared pharmacokinetics and subjective sedation from the same dose (3.4 mg) of midazolam delivered intravenously, intranasally using a traditional pump spray, and intranasally using OptiNose's bi-directional delivery device.

The speed of onset and level of sedation following iv administration were comparable with those achieved by OptiNose's device, and the duration of sedation was longer from OptiNose's device, compared with iv delivery. However, the bioavailability of the bi-directionally delivered formulation was only 68%, compared with 100% from iv.

The traditional intranasal device achieved significantly lower subjective sedation score compared with iv, despite achieving a bioavailability and Cmax comparable with the formulation delivered by OptiNose's device with the same dose.[5]

The discrepancy between the pharmacokinetic data and sedation results can be explained by a significant proportion of the dose having access to the CNS via a route that does not involve systemic absorption following administration via OptiNose's device, rather than entering the systemic circulation.

CONCLUSION

Earlier on in the article, it was noted that OptiNose had successfully converted bi-directional drug delivery from a concept into a functioning technology. However, in delivery to the CNS as well as the other applications, the company is in fact going a stage further – applying its technology in a range of product development projects.

OptiNose is partnering its technology with pharmaceutical companies for indications where significant therapeutic benefits could arise from bi-directional delivery as well as progressing a number of in-house applications for indications such as rhinosinusitis, migraine and Parkinson's disease.

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Association of Expired Nitric Oxide with Occupational Particulate Exposure

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Particulate air pollution has been associated with adverse respiratory health effects. This study assessed the utility of expired nitric oxide to detect acute airway responses to metal-containing fine particulates. Using a repeated-measures study design, we investigated the association between the fractional concentration of expired nitric oxide (F_ENO) and exposure to particulate matter with an aerodynamic mass median diameter of ≤ 2.5 μm ($PM_{2.5}$) in boilermakers exposed to residual oil fly ash and metal fumes. Subjects were monitored for 5 days during boiler repair overhauls in 1999 (n = 20) or 2000 (n = 14). The Wilcoxon median baseline F_ENO was 10.6 ppb [95% confidence interval (CI): 9.1, 12.7] in 1999 and 7.4 ppb (95% CI: 6.7, 8.0) in 2000. The Wilcoxon median $PM_{2.5}$ 8-hr time-weighted average was 0.56 mg/m^3 (95% CI: 0.37, 0.93) in 1999 and 0.86 mg/m^3 (95% CI: 0.65, 1.07) in 2000. F_ENO levels during the work week were significantly lower than baseline F_ENO in 1999 (p < 0.001). A significant inverse exposure–response relationship between log-transformed F_ENO and the previous workday's $PM_{2.5}$ concentration was found in 1999, after adjusting for smoking status, age, and sampling year. With each 1 mg/m^3 incremental increase in $PM_{2.5}$ exposure, log F_ENO decreased by 0.24 (95% CI: –0.38, –0.10) in 1999. The lack of an exposure–response relationship between $PM_{2.5}$ exposure and F_ENO in 2000 could be attributable to exposure misclassification resulting from the use of respirators. In conclusion, occupational exposure to metal-containing fine particulates was associated with significant decreases in F_ENO in a survey of workers with limited respirator usage. *Key words:* **air pollutants, epidemiology, nitric oxide, occupational, particulate matter.** *Environ Health Perspect* **111:676–680 (2003). doi:10.1289/ehp.5880 available via *http://dx.doi.org/* [Online 31 October 2002]**

Residual oil fly ash (ROFA) is an emission source air pollutant resulting from the combustion of fuel oil. Previous epidemiologic studies have shown that exposure to ROFA particulates is associated with adverse respiratory health effects (Hauser et al. 1995a, 2001; Lees 1980; Williams 1952; Woodin et al. 2000). Individuals occupationally exposed to high levels of ROFA particulates for extended periods of time experienced a reduction in pulmonary function (Hauser et al. 1995a; Lees 1980) and frequent, severe respiratory symptoms (Woodin et al. 2000). Other studies found an increase in proinflammatory cytokines and polymorphonuclear cells in the nasal lavage fluid of these workers, indicating the presence of upper airway inflammation after ROFA exposure (Hauser et al. 1995b; Woodin et al. 1998). Although many previous studies have shown that exposure to ROFA particulates adversely affects respiratory health, few sensitive early indicators of airway response have been used in these studies.

This study evaluated the utility of expired nitric oxide (NO) to detect acute airway responses to occupational particulate exposure. Endogenous NO is produced when the enzyme NO synthase (NOS) catalyzes the conversion of L-arginine to L-citrulline and NO (Marletta 1993). Of the three types of NOS, neuronal NOS and endothelial NOS generally have constitutive activity, whereas inducible NOS is immunoactivated (Michel and Feron 1997). Endogenous NO plays a crucial role in the airways because NO is a potent neurotransmitter of bronchodilator nerves (Belvisi et al. 1992). In addition, NO produced from inducible NOS expression is important in nonspecific host defense of the respiratory tract (Moncada and Higgs 1993). Expired NO has been found to be a sensitive and noninvasive marker for the assessment of inflammatory lung diseases (Silkoff 2000). Individuals with asthma, bronchiectasis, or airway infections have increased levels of expired NO compared with healthy individuals (Kharitonov and Barnes 2000; Kharitonov et al. 1994).

The use of expired NO in the assessment of acute airway responses is not limited to the clinical setting. Previous studies have shown that various components of air pollution are associated with increased levels of expired NO (Steerenberg et al. 2001; Van Amsterdam et al. 1999). In particular, urban children experienced a significant increase in expired NO with increasing particulate and black smoke exposure (Steerenberg et al. 2001). In one animal study, exposure to diesel exhaust particles (DEP), another component of ambient air, resulted in increased expired NO in mice (Lim et al. 1998). In contrast, exposure to cigarette smoke, both active and passive, has been shown to decrease expired NO levels in epidemiologic studies (Kharitonov et al. 1995; Yates et al. 2001). Cigarette smoke has been found to reduce NO production by inhibiting NOS expression or activity (Su et al. 1998).

The measurement of expired NO has been used frequently in clinical and research settings to characterize acute airway responses, yet its use in an occupational environment has been limited. In this short-term prospective cohort study, we investigated the association between the fractional concentration of NO in mixed expired gas (F_ENO) and exposure to fine particles with an aerodynamic mass median diameter of ≤ 2.5 μm ($PM_{2.5}$) in a group of boilermakers who were performing maintenance and repairs on oil-fired boilers. The boilermakers were monitored during a 5 day work period using a repeated-measures study design. Occupational $PM_{2.5}$ exposure resulted mainly from the ROFA inside the boilers and the various work tasks of the boilermakers, which included welding and burning. ROFA and metal fumes contain significant levels of soluble transition metals such as vanadium and nickel, making their chemical compositions distinct from that of ambient air pollution or DEP. Previous studies have shown that the change in F_ENO depends on the specific type of exposure. In this study, we examined the direction of change in F_ENO to metal-containing fine particulates.

Materials and Methods

Study population. The study was approved by the Institutional Review Board of the Harvard School of Public Health. Written informed consent was obtained from each subject. The study population consisted of 32 boilermakers working at a power plant during the overhaul

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of oil-fired boilers. Twenty subjects were monitored in June 1999, and 14 subjects, including two from 1999, were monitored in October 2000. Self-administered questionnaires were used to obtain information on medical history, including respiratory symptoms and diseases, smoking history, and occupational history.

F_ENO collection. F_ENO samples were collected before and after work shifts each day during a 5-day sampling period. Baseline F_ENO samples were collected before the work shift on the first day of the work week, after 1–2 days away from work. The offline collection and measurement of F_ENO were in accordance with American Thoracic Society (ATS) recommendations (ATS 1999). Subjects were asked to refrain from smoking in the 1 hr preceding NO sampling. Subjects wore nose clips and tidal breathed for 30 sec through an apparatus containing two one-way valves with a NO-scrubbing filter attached to the intake limb to prevent sample contamination by ambient NO. Subjects then inhaled to total lung capacity and expired their entire vital capacity into a Mylar balloon attached to the expiratory limb while maintaining an oropharyngeal pressure of 12.5 cm H_2O. Three F_ENO samples were taken at each collection time. To minimize NO loss in the Mylar balloons, we measured the NO levels within 4 hr of sample collection. NO levels in the balloons were measured using a calibrated Sievers (Boulder, CO) NOA 280 chemiluminescence analyzer. The median NO concentration of the three samples was used in the statistical analysis because it was insensitive to any aberrant observations while providing a measure of central value.

Spirometry. Spirometry was conducted before the work shift on the first and last day of sampling using a MicroPlus spirometer (Micro Direct Inc., Auburn, ME). Subjects performed a minimum of three acceptable forced vital capacity (FVC) maneuvers. The reproducibility standards required that the two highest forced expiratory volume in 1 sec (FEV_1) values be within 10% or 0.2 L of each other. The highest FEV_1 and FVC values from any of the maneuvers were used in the analysis.

Exposure assessment. Subjects were randomly selected to wear personal exposure monitors (PEMs) during their work shift. Workplace particulate samples were collected from 19 of the 20 subjects in 1999 and from all 14 subjects in 2000. The number of workdays each subject wore the PEM varied from 5 study days to none. On average, each subject was monitored 2 to 3 times throughout the week. The model 200 PEM (MSP Corp., Minneapolis, MN) with a 2.5 µm impactor cutsize was used in line with a Gilian GilAir5 pump (Sensidyne Inc., Clearwater, FL) calibrated at a flow rate of 4 L/min. The air sample was collected on a polytetrafluoroethylene membrane filter (Gelman Laboratories, Ann Arbor, MI) placed within the PEM. The PEMs were placed on the lapels of the subjects, near their breathing zone. The mass collected on the filter was divided by the air volume sampled to calculate the gravimetric $PM_{2.5}$ concentration.

Statistical analysis. Statistical analyses were performed using SAS version 6.12 (SAS Institute Inc., Cary, NC) and S-Plus2000 for Windows (MathSoft Inc., Cambridge, MA). Two-sample *t*-tests and Wilcoxon rank-sum tests were performed to compare the baseline characteristics of the population in the 2 sampling years. Paired *t*-tests were performed to compare prework F_ENO and spirometry values from baseline (day 1) to day 5 of sampling, days where corresponding F_ENO and spirometry measurements were both collected. The strength of the association between the changes in prework F_ENO and the changes in spirometric values from baseline to day 5 was determined using the Spearman rank correlation coefficient.

Linear models were constructed to investigate the association between log-transformed F_ENO values and $PM_{2.5}$ exposure. A linear model with independent and identically distributed errors was used because the repeated within-subject F_ENO measurements were found to be uncorrelated (Kleinbaum et al. 1998). Although F_ENO data collection was complete, $PM_{2.5}$ concentration data were missing. However, the $PM_{2.5}$ sampling data were missing at random because subjects were randomly selected each day to wear exposure monitors. Therefore, all analyses were restricted to subjects who had both F_ENO and the corresponding $PM_{2.5}$ concentrations on a given day. Including baseline data, there were a total of 50 complete measurements in 1999 and 46 complete measurements in 2000. F_ENO values were log-transformed to improve normality. The models were adjusted for self-reported current cigarette smoking status (yes/no), age, and sampling year. In addition, an interaction term between sampling year and $PM_{2.5}$ exposure was included in the model. The level of significance for all analyses was 0.05.

Results

Description of study population. Population demographic data are summarized in Table 1. The study population consisted of 32 men, 31 of whom were white (97%). Thirteen of the 32 subjects (41%) were current cigarette smokers. Their ages ranged from 18 to 59 years, with 2 weeks to 40 years of boilermaking experience. Twenty subjects were sampled in 1999, and 14 subjects, including two that were monitored in 1999, were sampled in 2000. Of the 32 subjects, six subjects entered the cohort on the second day of sampling because they had not attended work the previous day. Three subjects dropped out of the study after the fourth day of sampling; two subjects were transferred to a different work shift, and one subject did not come to work on the last day of sampling.

Six of the 32 subjects (19%) had chronic obstructive pulmonary disease (COPD), as defined by ATS (1995). Five subjects had chronic bronchitis, as diagnosed by a physician or with symptoms as defined by ATS (1995). One subject had emphysema diagnosed by a physician. None of the subjects with COPD were on medications that could influence expired NO levels. All analyses were performed initially with the total cohort, and then analyses were rerun after excluding the subjects with COPD. Because the results from the two analyses did not differ significantly, the final results included all 32 subjects.

The baseline spirometry results are summarized in Table 1. Only subjects with reproducible FEV_1 on both days that spirometry was performed were included in the spirometry analyses. None of the demographic information was significantly different between those who had reproducible spirometry and

Table 1. Study population characteristics by sampling year.

Study population characteristics	1999	2000
Number of subjects	20	14[a]
Number (%) of current smokers	9 (45%)	5 (36%)[b]
Number (%) of subjects with COPD	4 (20%)	2 (14%)
Age, years		
Mean ± SD	45.4 ± 12.0	41.5 ± 11.1
Range	18–59	20–55
Years as boilermaker		
Mean ± SD	21.7 ± 12.9	17.4 ± 13.5
Range	0.04–40	0.08–36
Number (%) of subjects with complete spirometry data[c]	14 (70%)	9 (64%)
Mean ± SD baseline percent predicted FEV_1[c,d]	95.8 ± 11.3	92.8 ± 9.2
Mean ± SD baseline percent predicted FVC[c,d]	95.4 ± 14.6	93.6 ± 8.1
Mean ± SD baseline percent FEV_1/FVC[c]	79.5 ± 7.0	79.3 ± 9.9

[a]Includes two subjects that were also monitored in 1999. [b]Includes one subject that was also monitored in 1999. [c]Includes only subjects with reproducible spirometric values on both days that spirometry was performed. [d]Spirometric predictions were based on predicted normal values by Hankinson et al. (1999).

those who did not. The mean baseline percent predicted FEV_1 was 95.8% (SD 11.3) in 1999 and 92.8% (SD 9.2) in 2000. The mean baseline percent predicted FVC was 95.4% (SD 14.6) in 1999 and 93.6% (SD 8.1) in 2000. The mean baseline percent predicted FEV_1 and FVC values were not statistically different in the two sampling years ($p > 0.2$).

Baseline measurements of F_ENO. The baseline measurements of F_ENO are shown in Table 2. Baseline measurements were taken on average after 2 days away from work in 1999 and 1 day away from work in 2000. Wilcoxon confidence intervals (CIs) and corresponding medians are presented because of the positively skewed distribution of F_ENO. In the 1999 cohort, the median baseline F_ENO was 8.8 ppb (95% CI: 7.0, 13.6) for smokers and 12.2 ppb (95% CI: 9.8, 15.9) for nonsmokers. In the 2000 cohort, the median baseline F_ENO was 7.6 ppb (95% CI: 6.5, 8.3) for smokers and 7.4 ppb (95% CI: 6.2, 8.6) for nonsmokers. The median baseline F_ENO across the two sampling years was significantly different for nonsmokers ($p = 0.002$) but not for smokers ($p < 0.20$).

Exposure assessment. The occupational $PM_{2.5}$ exposures for the 1999 and 2000 survey periods are shown in Table 3. The mean sampling time was 8.8 hr (SD 1.2) in 1999 and 10.9 hr (SD 1.3) in 2000. The difference in the average time monitored in the two sampling years was due to the difference in work shift length. During the overhaul in 1999, the boilermakers worked 10-hr shifts, whereas in 2000 most of the boilermakers worked 12-hr shifts. To account for this difference in work shift length, $PM_{2.5}$ concentrations were standardized to 8-hr time-weighted averages (TWAs). The Wilcoxon median $PM_{2.5}$ 8-hr TWA was 0.56 mg/m^3 (95% CI: 0.37, 0.93) in 1999 and 0.86 mg/m^3 (95% CI: 0.65, 1.07) in 2000. The median $PM_{2.5}$ 8-hr TWAs were marginally different in the two sampling years ($p = 0.06$).

In 1999, 85% of the subjects stated in the questionnaires that they wore respirators while performing boiler maintenance and repair. However, it was noted by the field team that the actual use of respirators while working was limited because of the high temperatures and limited ventilation inside the power plant. Data from the National Weather Service, Boston Weather Forecast Office (Taunton, MA), indicated that the maximum temperature in Boston, Massachusetts, was 92°F (33°C) to 97°F (36°C) during the first half of the 1999 sampling period. In the 2000 sampling period, 85% of the subjects also stated that they wore respirators while working. In contrast to 1999 observations, the field team observed that respirator use was more common in 2000. The maximum temperature in Boston during the 2000 sampling period ranged from 53°F (12°C) to 65°F (18°C). The cooler temperature may have made use of respirators more tolerable. The respirators typically used were the half-mask particulate respirators equipped with a high-efficiency particulate air (HEPA) filter, which has a particle filter efficiency of 99.97% for particles with an aerodynamic mass median diameter of 0.3 μm (NIOSH 1996).

Changes in F_ENO and spirometric parameters. The changes in F_ENO and spirometric parameters after occupational particulate exposure were calculated as the difference in the prework measurements from baseline (day 1) to day 5 of sampling. Measurements from day 5 were used to compare with the baseline levels because day 5 was the only workday during which both spirometry and F_ENO samples were collected. The changes in F_ENO and spirometric measurements are shown in Table 4. The mean change in F_ENO was –5.5 ppb (95% CI: –8.8, –2.1) for 1999 subjects and +1.0 ppb (95% CI: –0.2, 2.2) for 2,000 subjects. The changes in F_ENO for each individual are shown in Figure 1.

A similar trend was seen in the mean change in FEV_1 and FVC. The mean change in FEV_1 was –0.17 L (95% CI: –0.24, –0.09) for 1999 and –0.05 L (95% CI: –0.19, 0.09) for 2000. Likewise, the mean change in FVC was –0.14 L (95% CI: –0.23, –0.04) for 1999 subjects and +0.02 L (95% CI: –0.18, 0.22) for 2000 subjects. Compared with baseline levels, the F_ENO, FEV_1, and FVC values were significantly lower on day 5 in the 1999 subjects ($p < 0.01$). In contrast to 1999 data, the F_ENO, FEV_1, and FVC values from day 5 did not differ statistically from the baseline measurements in 2000. The changes in F_ENO, FEV_1, and FVC values did not differ by smoking status.

Baseline-adjusted changes were used to determine the correlation between F_ENO and spirometric parameters. In both 1999 and 2000, the changes in F_ENO were significantly correlated to the changes in FEV_1 ($r = 0.51$, $p = 0.01$) and moderately correlated with changes in FVC ($r = 0.39$, $p = 0.07$).

Association between F_ENO and $PM_{2.5}$ exposure. There was a weak correlation between $PM_{2.5}$ 8-hr TWA exposure and the postshift F_ENO on the same day ($r = –0.06$, $p = 0.60$). Furthermore, the linear models did not indicate a significant association between postshift F_ENO and the $PM_{2.5}$ exposure from the same day after adjusting for preshift F_ENO. However, there was a stronger lagged association between preshift F_ENO and $PM_{2.5}$ exposure from the previous workday ($r = –0.22$, $p = 0.03$). Therefore, analyses were restricted to regressing preshift F_ENO on $PM_{2.5}$ exposure the previous day.

Linear models indicated that $PM_{2.5}$ exposure was associated with a decrease in log F_ENO in the sampling year 1999. With each 1 mg/m^3 increase in $PM_{2.5}$ exposure, log F_ENO decreased by 0.24 (95% CI: –0.38, –0.10) after adjusting for dichotomized cigarette smoking status, age, and sampling year. Cigarette smoking was significantly associated

Table 2. Baseline F_ENO measurements (ppb) by sampling year and cigarette smoking status.

Sampling year	No. subjects	Median[a]	95% CI
1999	20	10.6	(9.1, 12.7)
Current smokers	9	8.8	(7.0, 13.6)
Nonsmokers[b]	11	12.2	(9.8, 15.9)
2000	14	7.4	(6.7, 8.0)
Current smokers	5	7.6	(6.5, 8.3)
Nonsmokers[b]	9	7.4	(6.2, 8.6)

[a]Wilcoxon median. [b]Nonsmokers include ex-cigarette smokers and never smokers.

Table 3. Occupational $PM_{2.5}$ exposure by sampling year.

	1999	2000
Number of samples	30	33
Mean ± SD sampling time, hr	8.8 ±1.2	10.9 ±1.3
$PM_{2.5}$ 8-hr TWA, mg/m^3		
Median[a]	0.56	0.86
95% CI	(0.37, 0.93)	(0.65, 1.07)

[a]Wilcoxon median.

Table 4. Changes in F_ENO and spirometric parameters from baseline (day 1) to day 5 by sampling year.[a]

	1999 ($n = 14$)[b] Mean (95% CI)	2000 ($n = 9$)[b] Mean (95% CI)
Change in F_ENO (ppb)	–5.5 (–8.8, –2.1)	+1.0 (–0.2, 2.2)
Change in FEV_1 (L)	–0.17 (–0.24, –0.09)	–0.05 (–0.19, 0.09)
Change in FVC (L)	–0.14 (–0.23, –0.04)	+0.02 (–0.18, 0.22)

[a]Change = day 5 – day 1. [b]n = number of subjects. Includes only subjects with complete data (F_ENO and reproducible spirometric values on both days 1 and 5).

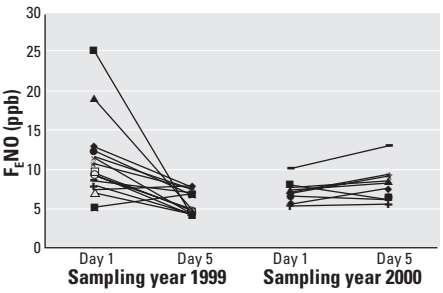

Figure 1. F_ENO measured on day 1 (baseline) and day 5 of the monitoring period by sampling year. The F_ENO values on day 1 were significantly different from those on day 5 in sampling year 1999 ($p < 0.001$) but not in 2000 ($p > 0.3$).

with a change of –0.22 (95% CI: –0.36, –0.08) in log F_ENO. Residual analysis indicated that there were two subjects with standardized residuals greater than 2. After excluding the two potential statistical outliers, log F_ENO decreased by 0.19 (95% CI: –0.32, –0.05) for each 1 mg/m^3 of $PM_{2.5}$ exposure. Although the two outlying subjects increased the magnitude of the association between $PM_{2.5}$ exposure and log F_ENO, their influence was marginal.

For the subjects sampled in year 2000, there was no association between $PM_{2.5}$ exposure on the previous workday and preshift log F_ENO. After adjusting for cigarette smoking status, age, and sampling year, the $PM_{2.5}$ regression coefficient was 0.02 (95% CI: –0.15, 0.18).

Discussion

In the present study, short-term occupational exposure to particulates was associated with a significant decrease in F_ENO and spirometric indices. A significant inverse exposure–response association between log F_ENO and $PM_{2.5}$ 8-hr TWA exposure was found. However, these associations were seen only in subjects tested in 1999. In the group of boilermakers sampled in 2000, there was no change in F_ENO or spirometric indices, and no exposure–response relationship between log F_ENO and $PM_{2.5}$ exposure.

A possible explanation for the lack of change in F_ENO and spirometric parameters, and lack of an exposure–response relationship between $PM_{2.5}$ exposure and F_ENO in the 2000 subjects could be attributable to respirator use. During the sampling week in June 1999, temperatures neared 100°F (38°C) inside the power plant because of a heat wave and limited ventilation. The difficult environmental conditions might have prevented the boilermakers from wearing their respirators. In contrast, the climate was much cooler during the sampling period in October 2000, making the use of respirators more tolerable. Because the half-mask respirators used by the boilermakers had a particle filter efficiency greater than 99% for particles with an aerodynamic mass median diameter of 0.3 μm, respirator use would have significantly decreased the exposure to particulates during the sampling year 2000. The reduced particulate exposure might explain the lack of a difference between baseline F_ENO, FEV_1, and FVC measurements and measurements taken during the work week in 2000.

During both sampling years, the PEMs were placed on the lapels of the subjects, near their breathing zones. Based on observations made in 1999, no modifications were made in the exposure assessment procedure to adjust for respirator use in 2000. Because the subjects in 2000 were more likely to wear respirators, the $PM_{2.5}$ measurements during this sampling year were less likely to represent true exposure. The $PM_{2.5}$ measurement error might be responsible for the lack of an exposure–response relationship between $PM_{2.5}$ and F_ENO in 2000. We were unable to estimate the effect of respirator use on $PM_{2.5}$ exposure because usage was inconsistent and the fit of the respirators was unknown because of factors such as the presence of facial hair.

Changes in F_ENO from baseline to day 5 were strongly correlated with changes in FEV_1 ($r = 0.51$, $p = 0.01$) and moderately correlated with changes in FVC ($r = 0.39$, $p = 0.07$) in subjects from both sampling years 1999 and 2000. Other studies have also examined the relationship between F_ENO and spirometric indices. Jones et al. (2001) showed a negative correlation between changes in F_ENO and changes in FEV_1 ($r = –0.35$, $p < 0.002$) across weeks. The conflicting results between the Jones et al. study and our study may be attributable to the difference in the study populations. The population in our study generally consisted of healthy subjects, whereas Jones et al. studied asthmatics. The relationship between expired NO and FEV_1 may be dependent on the subjects' states of airway inflammation. Although an increase in F_ENO indicates loss of asthma control in asthmatics (Kharitonov et al. 1994; Massaro et al. 1996), a decrease in F_ENO from normal levels in healthy individuals may be considered an adverse response, as in the case of smokers (Kharitonov et al. 1995). In the present study, a decrease in F_ENO was associated with a decrease in FEV_1, both adverse respiratory responses in healthy individuals.

In our study, a significant inverse exposure–response association between the previous workday's $PM_{2.5}$ 8-hr TWA exposure and the next day's preshift log F_ENO was found in the subjects in 1999. With the median $PM_{2.5}$ exposure of 0.56 mg/m^3, F_ENO declined by 13% from baseline after adjusting for current cigarette smoking status, age, and sampling year.

Previous studies have shown that particulate air pollution is associated with an increase in expired NO levels (Steerenberg et al. 2001; Van Amsterdam et al. 1999). In a study by Steerenberg et al. (2001), exposure to particulate air pollution was associated with an increase in F_ENO. Although the results of our study are inconsistent with the results from Steerenberg et al., there are several important differences in the two studies. First, Steerenberg et al. used particulate matter with an aerodynamic mass median diameter of ≤ 10 μm (PM_{10}) as the marker for particulate exposure, whereas we used $PM_{2.5}$. Our study chose $PM_{2.5}$ because fine particles have been found to have a stronger association with respiratory health effects than coarse particles with larger aerodynamic mass median diameters (Schwartz and Neas 2000). Another difference between the studies is that Steerenberg et al. studied the effects of particulate exposure from urban air pollution, whereas we studied the effects of particulates from ROFA and various boilermaking tasks such as welding and burning. Unlike ambient air, ROFA and metal fumes contain significant amounts of transition metals, including vanadium, nickel, and iron. In addition, the levels of exposure from the two aerosols were different. Typical urban air has a $PM_{2.5}$ concentration of approximately 10–30 μg/m^3, whereas the median $PM_{2.5}$ level from the occupational particulate exposure in our study was 560 μg/m^3.

Other studies have observed that exposure to DEP, another component of ambient air, was associated with increased expired NO levels in mice (Lim et al. 1998; Sagai and Ichinose 1995). Lim et al. found that DEP exposure increased the level of constitutive NOS in the airway epithelium and inducible NOS in the macrophages of mice. However, another study observed that DEP reduced endothelial NOS activity in the bronchi of healthy rabbits (Muto et al. 1996). The source of the increased NO is relevant because the effect of NO may differ depending on whether it is produced by inducible or constitutive NOS. Takano et al. (1999) showed that NO produced from inducible NOS might enhance the DEP-induced inflammatory response, whereas NO derived from constitutive NOS might play a protective role against airway inflammation.

Exposure to cigarette smoke also is known to induce acute airway inflammation. However, in contrast to the results from air pollution and DEP, cigarette smoking consistently results in decreased expired NO levels (Kharitonov et al. 1995; Yates et al. 2001). One hypothesis for the reduction in expired NO is that the levels of NOS are reduced from decreased transcription of NOS. A study by Su et al. (1998) observed that cigarette smoke specifically affected constitutive NOS activity. After exposure to cigarette smoke extract, the presence of endothelial NOS and endothelial NOS mRNA was reduced in the pulmonary artery endothelial cells from pigs. The decrease in endothelial NOS activity caused by cigarette smoke extract was found to be time and dose dependent.

A recent study by Huang et al. (2002) found that ROFA instilled intratracheally into isolated perfused rabbit lungs resulted in reduced NO production, as determined by decreases in nitrite/nitrate accumulation. Huang et al. also observed that NO production was reduced after exposure to vanadium, indicating that the transition metal component of ROFA may be responsible for the decreased NO production. Huang et al.

hypothesized that the inhibition of NO production by ROFA might be related to reduced NOS activity, as shown in studies with cigarette smoke exposure. Therefore, the decrease in F_ENO observed in the boilermakers in our study might be due to a reduction in constitutive NOS activity resulting from ROFA and other metal-containing fine particulate exposure. Given the potential protective role of NO from constitutive NOS, the decreased NO levels might have been a contributing factor to the increased airway inflammation and respiratory symptoms seen in our previous studies on boilermakers exposed to ROFA and other particulates (Hauser et al. 1995a; Woodin et al. 2000).

In conclusion, we found an inverse exposure–response relationship between F_ENO and $PM_{2.5}$ in exposed workers. The results from our study show greater consistency with the studies on exposure to cigarette smoke than to those of ambient air pollution. Cigarette smoke contains a significant concentration of transition metals, similar to ROFA and metal fumes (Chiba and Masironi 1992; Dreher et al. 1997). Further studies are needed to determine if the metal component of $PM_{2.5}$ is specifically responsible for the decline in F_ENO.

Expired NO previously has been found to be a sensitive and practical marker in the assessment of inflammatory lung diseases in a clinical setting. This study shows that F_ENO can be used to detect acute airway responses to metal-containing fine particulate matter in an occupational setting.

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Management of malignant tumors of the anterior and anterolateral skull base

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Object. Malignant tumors of the skull base represent a group of diverse and infrequent lesions. Comprehensive oncological management requires a multidisciplinary team of neurological surgeons, otolaryngologists, radiation oncologists, plastic surgeons, and medical oncologists. The authors describe an institutional experience in performing 54 combined anterior–anterolateral cranial base resections for malignant disease.

Methods. The technical considerations for preoperative workup, surgical approach, resection, and reconstruction are outlined and illustrated. Considerations for complication management and avoidance are detailed.

Conclusions. Overall mortality (0%) and morbidity rates (18%) are acceptable. The influence on the natural history of the disease process is an ongoing study.

KEY WORDS • skull base tumor • multidisciplinary approach • complication analysis

The vast majority of malignant cranial base tumors arise in the anterior or anterolateral skull base, originating in the paranasal sinuses or nasal cavity. Examples of these include esthesioneuroblastoma, sinonasal carcinoma, adenocarcinoma, squamous cell carcinoma, neuroendocrine carcinoma, sarcoma, chondrosarcoma, and other sinonasal malignancies. All are relatively rare, constituting approximately less than 1% of all malignant tumors. Because of their presenting locations and often indolent initial course, their surgical management is challenging.

The orbital regions, optic apparatus, anterior cranial base dura, brain, cavernous sinus, and their neurovascular components are often involved. Patients frequently present late in the disease process, with complaints of symptoms secondary to the indolent course of the lesions. Depending on the lesion type and location, symptom complexes often involve nasal obstruction, epistaxis, sinus headache, nasal pain, trismus, facial numbness or pain, tooth pain, and ocular complaints of pain, exophthalmos, and ophthalmoplegia.

Optimum management of this diverse group of patients and lesions is not universally accepted. We present our institutional approach based on experience performing 100 anterior and anterolateral cranial-based operations, 54 of which were to treat malignant disease (Table 1).

Abbreviations used in this paper: CSF = cerebrospinal fluid; CT = computerized tomography; MR = magnetic resonance.

CLINICAL MATERIAL AND METHODS

Management of Skull Base Malignant Tumors

Workup and Evaluation. Patients who are referred to the cranial base service are evaluated by both the neurological surgeon and otolaryngologist sequentially. Radiological evaluation consisting of contrast-enhanced MR imaging and coronal/axial CT scanning of the frontal sinus is performed. A thorough head and neck examination with flexible endoscopy is performed.

Whenever possible, a transnasal biopsy sample is obtained. Once malignancy is confirmed, a staging metastatic workup consisting of chest, abdomen, and pelvis CT scans is performed. The results of these studies are considered in conjunction with whether an en bloc resection with tumor margins can be performed; these factors are used to determine the roles of surgical management and perioperative chemo- and radiotherapy. Overall management of malignant skull base lesions requires a coordinated effort by an otolaryngologist, neurological surgeon, head and neck radiation oncologist, solid-tumor medical oncology specialist, and a plastic surgeon experienced in microvascular free-tissue transfer reconstruction.

Surgical Management. The goal of surgery is an oncological en bloc resection defined as the lesion plus normal margin. Presently, with the advent of computer-assisted surgical navigation and radiosurgery/therapy/intensity-modulated radiotherapy, this definition is considered anew. The limitation of undertaking this surgical approach is often the functional consideration of the marginal anatomy.

TABLE 1
Summary of malignant skull base lesions treated at our institution

Tumor Type	No. of Cases
myoepithelial carcinoma	2
esthesioneuroblastoma	13
chondrosarcoma	1
squamous cell carcinoma	7
adenocarcinoma	9
neuroendocrine carcinoma	1
melanoma	3
sinonasal carcinoma	3
adenoid cystic	8
hemangiopericytoma	1
malignant paraganglion	1
sarcoma	1
spindle cell carcinoma	1
malignant meningioma	3
total	54

The ability to deliver high doses of radiation extends the margin if radiosensitive structures—for example, optic nerve—can be juxtaposed away from the margins by transposition or separation of the defects by using small adipose tissue spacers. Furthermore, the ability to reconstruct the defects by using durable vascularized tissue enhances the delivery of optimum adjuvant therapies.

Surgery-Related Considerations

Surgery consists of three components: approach, definitive resection, and reconstruction. The three main approaches are craniofacial,[1,3,6,7,13] extended subfrontal,[21,24,25] and transfacial.[8,19,27] Approach-related complications are common and in general are related to bridging the interface between the paranasal sinuses and intracranial/intradural spaces.

Transfacial approaches consist of combinations of transoral, transpalatal, transmaxillary, lateral rhinotomy, and midface degloving. As stand-alone procedures for malignancy, their use is limited to cases in which the superior margin of the lesion can be safely attained.

The standard surgical procedures are the craniofacial resection (combining a bifrontal or orbitozygomatic craniotomy with a transfacial approach) and the extended subfrontal approach in which a bifrontal craniotomy is perfromed in conjunction with a very low aggressive bilateral supraorbital osteotomy.

All patients undergoing resection receive counseling regarding the loss of smell and its effect on the perception of taste. The possibility of a temporary tracheostomy is also detailed, although it is seldom required.

Perioperative antibiotic therapy consists of ceftriaxone (1g/hour for 8 hours). Clindamycin (900 mg) irrigation[2] is administered prior to dural opening and once the dura is reconstituted.

On the operating table patients are positioned supine in three-point pin fixation placed behind the ears. The head is extended and the table angled head-up to optimize drain autoretraction. Tarsorrhaphy is performed for temporary eyelid closure. Prior to pin fixation, a spinal drain is placed but kept closed during all extradural procedures. The head, face, abdomen (for potential fat graft and rectus flap), and thigh (for potential fascia lata graft) are prepared and draped to accommodate multiple approach and reconstructive scenarios.

Patient Population

Fifty-four patients (32 males and 22 females, mean age 49 $\pm$ 3 years) harbored malignant lesions. Frameless stereotaxis[20] was performed preoperatively as an adjuvant for navigation in 48 (88%) cases. Registration was performed prior to preparation and draping. Reregistration divots were placed on the skull after the skin incision was made. Using both anatomical and registration landmarks, accuracy was checked prior to skin incision. The merging of preoperative MR images and CT scans was performed whenever possible. Craniofacial resection was performed in 41 cases (76%), extended subfrontal in 12 (22%), and transfacial only in the remaining case (2%). Primary operations were performed in 46 cases (85%), and reoperations in eight cases (15%). Six orbital exenterations and 11 rectus muscle–fat free flap procedures were performed.[4] Pericranium-assisted or fascia lata–assisted dural reconstruction[9,23,31] was performed in 48 cases (88%); cranial base reconstruction was conducted using vascularized pericranial flap transposition sutured to the remnant base in 48 cases (88%). Temporalis muscle transpositions were conducted in seven cases (13%). Cranial closures were reinforced superiorly using fibrin glue. Drains were placed in the epidural and subgaleal spaces and in any site at which graft material had been harvested.

At the completion of each procedure, the nasal cavity was inspected endoscopically and reinforced using fat, fibrin glue, packs, and nasal trumpets. The patient was kept in the operating room if the epidural drain did not hold suction. This test demonstrated adequate sealing of the intracranial space. In cases in which the seal was not held, additional transnasal endoscopic packing was performed. Spinal drainage was discontinued in the operating room. If necessary, a feeding tube was passed through one nasal trumpet. The neurosurgical approach has been described in detail elsewhere.[16–18,26]

Patients are managed postoperatively in a neurosurgical intensive care unit. Follow-up CT scanning is performed within 24 hours to determine the presence of epidural air and occult hemorrhage and edema. Dilation is maintained for 2 weeks. Epidural drains are removed within 24 to 48 hours, after which the subgaleal drain is extracted. Nasal packings are slowly discontinued beginning on Day 4. Patients are released from the hospital between Days 5 and 7.

Outpatient follow up is conducted in a multidisciplinary clinic. Patients undergo weekly endoscopic surveillance to assess healing and facilitate debridement and sinus drainage. Evaluations to determine the need for postoperative radio- and chemotherapy are performed simultaneously. It is important to continue endoscopic surveillance during and after radiotherapy to avoid complications secondary to radiation-induced sinusitis.

RESULTS

There were no surgery-related deaths. Complications occurred in 10 patients (18%). All patients underwent postoperative radiotherapy. A summary of complications

is provided in Table 2. Primary operations were associated with eight complications (17%) and reoperations with two complications (25%). Complications occurred between Days 1 and 14 (mean postoperative occurrence 7 ± 3 days).

ILLUSTRATIVE CASE

History. This 30-year-old man had a several-month history of nasal congestion, as well as right airway obstruction treated using over-the-counter nose sprays and allergy medications. Subsequently, he began to develop right-sided orbital pain and headache. He underwent endoscopy of the sinus, and an intranasal mass was demonstrated.

Examination. Examination revealed mild exophthalmos of the right eye, double vision, and decreased visual acuity of the right eye (Fig. 1). Sinonasal endoscopy demonstrated a large friable granular mass filling the posterior and superior right nasal cavity. A biopsy sample was obtained, and examination revealed basaloid–squamous cell carcinoma. A CT study of the sinuses revealed a soft-tissue mass and erosion of the medial wall of the right orbit and cribriform plate (Fig. 2). An MR imaging study suggested orbital and cranial invasion (Fig. 3). A systemic workup demonstrated no abnormal findings.

Operation. The patient was taken to the operating room, and endotracheal anesthesia was induced. A standard tracheostomy was performed to secure the airway, provide excellent postoperative pulmonary toilet, and to allow for patient comfort. A lumbar spinal drain was placed. The patient was placed on a three-point pin fixation, and stereotactic registration was performed. Tarsorrhaphy was performed for temporary eyelid closure. The head, face, neck, and abdomen were prepared and draped in a sterile fashion.

TABLE 2

*Surgery-related complications in patients treated for malignant skull base lesions**

Case No.	Complication	Postop Day	Management
1	tension pneumocephalus	4	endoscopic nasal packing, epidural drain
	transverse sinus thrombosis	8	heparinization
2	tumor bed hematoma	1	reop
3	pericranial flap failure, pneumocephalus	14	reop
4	overpacking of free flap	4	flap liposuction recontouring
5	pericranial flap failure, pneumocephalus, infection	10	reop
6	overdrainage, prolong neuromuscular blockade	2	discontinue spinal drain, blood patch
7	pericranial flap failure, pneumocephalus, epidural hematoma	7	reop
8	pericranial flap failure, pneumoencephalocele, epidural hematoma	3	reop
9	vasospasm	7	triple-H therapy
10	distal free flap failure	10	debridement on distal, nonviable flap

* Triple-H = hypertensive hypovolemic hemodilution.

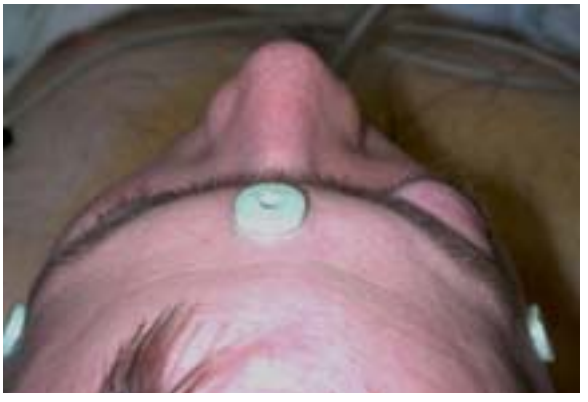

Fig. 1. Preoperative photograph demonstrating exophthalmos of the right eye.

A bicoronal skin incision was performed down to, but not including, the temporalis fascia or pericranium. A large vascularized pericranial flap was lifted from temporal line to temporal line and extended 8 to 10 cm posteriorly. The temporalis fasciae bilaterally were cut to the muscle and brought forward, exposing the entire zygomatic processes. Care was taken to preserve the supraorbital neurovascular structures.

A standard Weber–Fergusson incision was then made; the lip was split, a lateral rhinotomy was made in the nose, and the incisions extended into the conjunctival fornix superiorly and inferiorly, preserving the eyelids for orbital reconstruction. The flap was turned anteriorly, allowing for skeletonization of the hemimaxilla on the right. The flap was then taken laterally to the maxillary tuberosity, and then medially across the hard–soft palate junction, which was divided.

We performed a bifrontal craniotomy, which was followed by a bifrontal supraorbital osteotomy with right zygomatic osteotomy in continuum (Fig. 4). Via a subfrontal extradural approach, microscopic visualization allowed us to observe a tumor breeching the cribriform plate and affixed to the dura. The bone surrounding the right optic canal and medial/superior orbit was drilled away. The dura and the circumferential margin around the por-

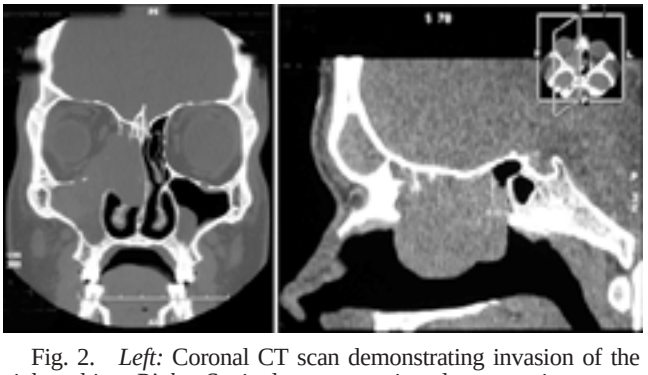

Fig. 2. *Left:* Coronal CT scan demonstrating invasion of the right orbit. *Right:* Sagittal reconstruction demonstrating tumor affixed to the cribriform plate.

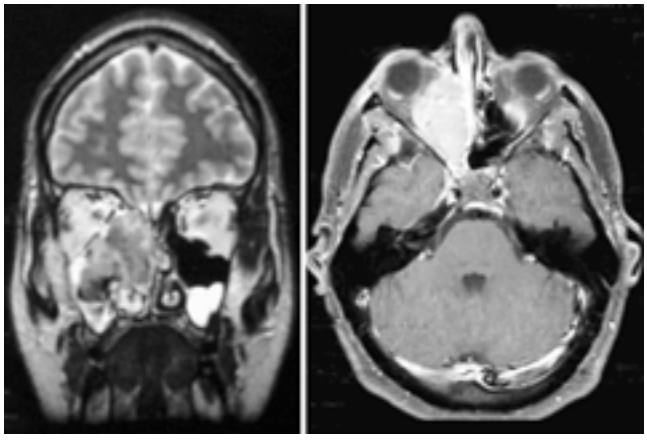

Fig. 3. *Left:* Coronal T_2-weighted MR image revealing tumor against the dura of the anterior cranial fossa. *Right:* Axial contrast-enhanced T_2-weighted MR image demonstrating invasion of the orbit.

tion of the affixed tumor were opened. The olfactory tracts were cut. Duraplasty of the pericranium was performed. The optic nerve was cut distally in the canal and the dura oversown to avoid CSF leakage. The pericranium was brought down and sutured to the remnant bone (Fig. 5). The distal superior orbital fissure was then transected.

The right superolateral, inferior orbital walls were all resected en bloc with the maxilla, tumor, hard palate, and greater wing of sphenoid (Fig. 6). The excised specimen represented the entire orbitocranial–orbitomaxillary complex (Fig. 7).

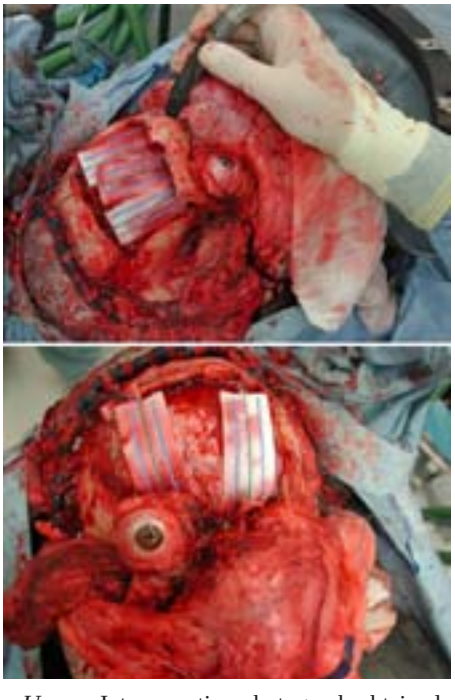

Fig. 4. *Upper:* Intraoperative photograph obtained after soft-tissue takedown and bifrontal craniotomy. *Lower:* Exposure after bifrontal orbital osteotomies and circumferential removal of orbital bone.

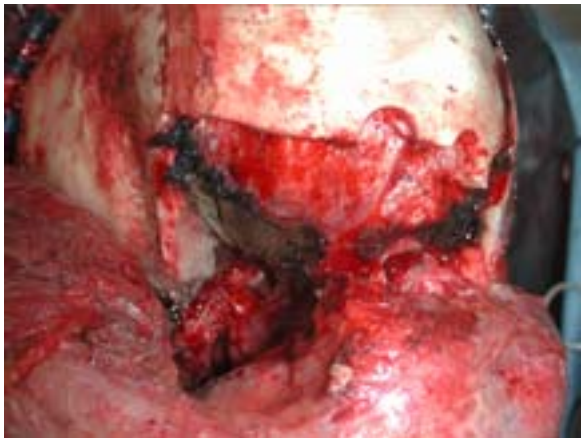

Fig. 5. Intraoperative photograph obtained after resection and prior to pericranial flap rotation.

Microplates and screws were used to close the craniotomy. A rectus abdominus free flap was harvested. De-epithelialization of the skin over the flap was performed, and the skin was placed inward to reconstruct the oral/nasal wall. Microvascular arterial and venous connections to the facial artery and veins were made in an end-to-end fashion. The flap was positioned and contoured to permit placement of an orbital prosthesis in the future.

Hospital Course. The patient was treated for the first 3 days in the neuroscience intensive care unit and stepdown unit, where use of the drains was discontinued. On Day 4 he was transferred to the floor, and on Day 5 the tracheostomy was decannulated. He was discharged to home on Day 7. The patient then underwent 6 weeks of intensity-modulated three-dimensional conformal radiotherapy (Fig. 8) and concurrent chemotherapy.

DISCUSSION

Complication Analysis, Avoidance, and Management

Complication rates for craniofacial resection range from 18 to 63% and mortality rates from 0 to 4.7%.[5,10–12,14,15,22,28–30,32–36] The ability to avoid and manage the associated complications is critical for the successful management of

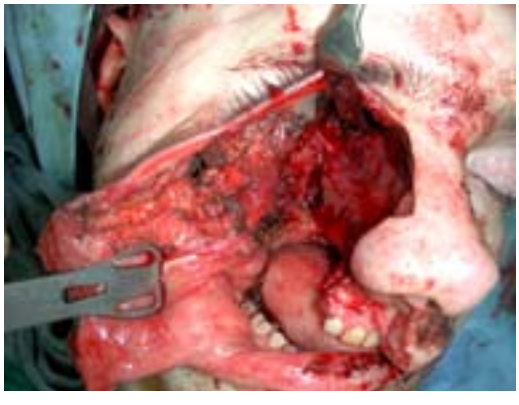

Fig. 6. Intraoperative photograph demonstrating the surgical defect that requires free-flap reconstruction.

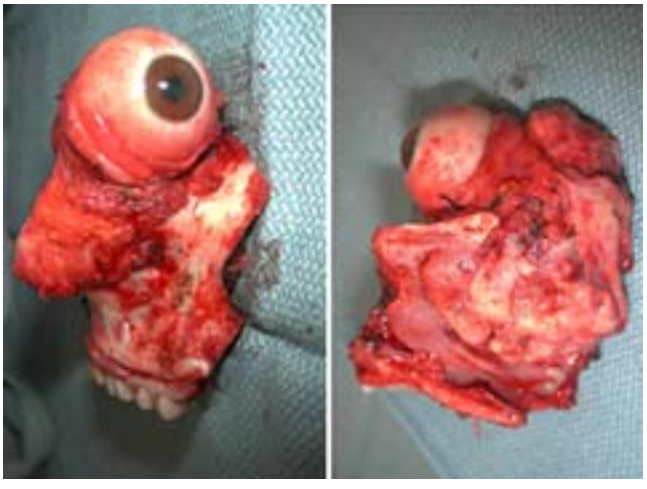

Fig. 7. *Left* and *Right:* Photographs showing the entire orbitocranial–orbitomaxillary complex after en bloc resection.

patients with these neoplasms. Common to all approaches is the crossing of the aerodigestive tract–intracranial space interface during the operation. This results in a common set of complications.

Brain Injury. When the supraorbital ridges have been removed, access is provided to a low region at the base of the brain. Keeping the spinal drain closed, and thus the subarachnoid space filled with CSF, confers a concussion buffer during the extradural procedure. Appropriate head extension allows the brain to fall back against gravity, avoiding frontal lobe retraction. Once the cisterns have been microsurgically dissected the frontal lobes are released, and tumor removal and dural closure are facilitated.

Infection. Whenever possible, the intradural compartment prior to gross containment should be sequestered with the aerodigestive tract. The craniotomy should be designed to be superior to the sinus, permitting elevation of the dura and sequestration with antibiotic-soaked Telfa during the orbital and sinus osteotomies. Antibiotic therapy is undertaken using clindamycin irrigation and intravenous ceftriaxone. Epidural and subgaleal drains are placed to close dead space and prevent potential fluids from becoming culture media.

Only after completion of adjuvant therapy should any synthetic materials such as bone cements be considered for use in reconstruction. The operations are lengthy, and highly contaminated fields are exposed. In delaying cosmetic reconstruction, the risk of foreign body contamination is decreased and correction of late cosmetic changes is permitted. Postoperatively, vigilant endoscopic surveillance and nasal hygiene, which should be continued until completion of radiotherapy, allows the onset of late infection complications to be avoided.

Pneumocephalus (Tension)/Dural Banding/CSF Leak

The use of spinal drainage should be minimized to avoid excessive collapse of the brain. The spinal drain should be removed at the end of the procedure. A patulous overlapping watertight duraplasty should be performed. This allows for free expansion of the brain. If the duraplasty is too tight or the lateral tenting sutures ill placed, brain reexpansion can be restricted. Closure should be reinforced using fibrin glue. The pericranial flap should be positioned inferior to the supraorbital osteotomy and sutured directly to the bone whenever possible. Our experience has taught that in all cases in which there is failure of the pericranial flap, the flap had been brought superior to the ridge and appeared to have undergone infarction secondary to venous outflow obstruction. Pericranial flap failure generally occurs 3 to 7 days postoperatively, manifesting as a new onset of pneumocephalus and presence of epidural blood. An epidural drain should be placed and brought through a separate stab wound. Endoscopic nasal packing composed of fat and fibrin glue is applied, after which nasal trumpets are placed. An epidural drain that holds suction indicates reconstitution and sequestration of the intracranial space; after this has been demonstrated the patient may be taken from the operating room.

Should there be a delayed loss of closure or late-onset pneumocephalus, needle aspiration may be performed through a burr hole. Patients should be returned to the operating room, where endoscopy can be used to guide repacking and placement of an epidural catheter. Intubation or tracheostomy can be used to create airway diversion but this is rarely necessary.

Fig. 8. *Left, Center,* and *Right:* Demonstration of three-dimensional conformal intensity-modulated radiotherapy planning.

CONCLUSIONS

Acceptable rates of morbidity and mortality are achieved in the surgical oncological management of malignant skull base neoplasms. The surgery-related impact on the natural history of the disease remains under investigation, as do the roles of adjuvant chemo- and radiotherapy. Cranial base approaches provide robust exposure to malignancies of the skull base, allowing for resection. The defects created require complex transfers of adjacent tissue and free flap procedures to restore the immunological barriers, sequester the intracranial compartment, and yield satisfactory volumetric and cosmetic results. Successful management requires a multidisciplinary approach and a postoperative environment in which aggressive management of the associated complications can be performed.

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Rhinitis Is Associated with Increased Systolic Blood Pressure in Men

A Population-based Study

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An association between impaired lower respiratory function and cardiovascular risk factors, such as hypertension, is often reported but it is unknown whether there is a relationship between upper airway disorders and cardiovascular risk factors, despite evidence that upper and lower respiratory tract disorders are closely linked. Our objective was to assess whether rhinitis is associated with arterial blood pressure and hypertension. In a population-based study of 330 adults aged 28–56 years, as part of the European Community Respiratory Health Survey, rhinitis was assessed by means of a questionnaire, and cardiovascular data were obtained using a questionnaire and by measuring blood pressure. Systolic blood pressure (SBP) was higher in men with rhinitis than in men without rhinitis (130.6 ± 12.7 mm Hg versus 123.5 ± 13.9 mm Hg; p = 0.002), and it was still the case after adjustment for cardiovascular and respiratory confounding factors. Hypertension was more frequent in men with rhinitis than in men without rhinitis, even after multivariate adjustment (odds ratio = 2.6, 95% confidence interval = [1.14–5.91]). The observation of SBP levels according to whether men have no rhinitis, seasonal rhinitis, or perennial rhinitis was compatible with a dose–response relationship (p for trend = 0.02). In conclusion, rhinitis is strongly associated with SBP and hypertension in men. Blood pressure should be regularly checked in men with rhinitis.

Keywords: rhinitis; blood pressure; hypertension

Numerous epidemiologic studies have suggested that impaired lower respiratory function (expressed by the FEV_1 and/or the peak expiratory flow) is associated with some cardiovascular risk factors (1) and with atherosclerosis (2), arterial stiffness (3), cardiovascular diseases, and mortality (4, 5). However, the physiopathologic mechanisms underlying these associations are not known.

In contrast, no studies have assessed the association between upper airway disorders, such as rhinitis, and cardiovascular alterations, although many epidemiologic studies have shown that lower and upper airway disorders are associated (6–8).

In addition, rhinitis might be related to cardiovascular risk factors, particularly hypertension (9), as rhinitis is associated with snoring and obstructive sleep apnea (OSA) (8–12) and as snoring and OSA are associated with hypertension (13–16).

The high prevalence of both rhinitis and hypertension—approximately 25% of the population living in industrialized countries (17, 18)—intensifies the interest to know whether there is actually an association between rhinitis and arterial blood pressure. The present study was performed with this purpose.

METHODS

Study Participants

Data were collected in Hôpital Bichat (Paris, France), between October 1999 and May 2001, as part of the follow-up phase of the European Community Respiratory Health Survey (ECRHS-II). The methods used in this study have been described elsewhere (19). Briefly, 660 subjects aged 20–44 years were randomly selected from the electoral rolls of the 18th district of Paris. These subjects were examined at the hospital between 1992 and 1993 (ECRHS-I). Three hundred and thirty subjects could be contacted again and accepted to be examined a second time between 1999 and 2001 for ECRHS-II.

Study Protocol

During the second examination, each subject answered a standardized questionnaire administered by trained interviewers and underwent lung function tests. Subjects who answered "yes" to the question: "Do you have any nasal allergies including 'hay fever'?" were considered to suffer from rhinitis (6, 20, 21). Subjects with rhinitis who reported that they "got a runny or stuffy nose or started to sneeze" when they were "near trees, grass or flowers, or when there is a lot of pollen about" were considered to have seasonal nasal symptoms. Rhinitic subjects who reported that they "got a runny or stuffy nose or started to sneeze" when they were "near animals, such as cats, dogs or horses, near feathers, including pillows, quilts or duvets, or in a dusty part of the house" were considered to have perennial nasal symptoms (6, 22–24). Subjects with both perennial and seasonal symptoms were grouped with the subjects with perennial symptoms. Subjects who answered "yes" to both "Have you ever had asthma?" and "Was it confirmed by a doctor?" were considered to suffer from asthma. Smoking status was defined by the cumulative smoking exposure. It was assessed as pack-years (number of packs smoked per day multiplied by the number of years of smoking).

FVC and FEV_1 were measured with a water-sealed bell spirometer (Biomedin, Padova, Italy). Lung function was assessed by FEV_1 %pred and FEV_1 %FVC. Predicted FEV_1 values were calculated according to sex, height, and age (25).

In addition to the general ECRHS-II protocol, the participants were asked to complete a standardized questionnaire on conventional cardiovascular risk factors, and their arterial pressure was measured. Both systolic and diastolic blood pressures (SBP and DBP) were measured with a digital electronic tensiometer (Model CP750, Omron Electronics SARL, Fontenay sous Bois, France). Two independent measurements were taken with a 5-minute interval, with the subjects in a lying position. We used the second values for the statistical analyses. Subjects were classified as being hypertensive when their SBP was at least 140 mm Hg, and/or their DBP was at least 90 mm Hg, and/or they reported using an antihypertensive treatment (26). Patients were considered to have hypercholesterolemia if they answered "yes" to at least one of the

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TABLE 1. CHARACTERISTICS OF THE SUBJECTS INCLUDED IN THE ANALYSIS IN 2000–2001 SORTED BY SEX

	Men (*n* = 146)	Women (*n* = 170)	p
Age, yr*	45.6 ± 7.2	44.6 ± 7.4	0.20
BMI, kg/m²*	24.9 ± 3.1	23.1 ± 4.3	< 0.001
Smoking status, %			
Never smokers	39.6	45.8	
<20 pack-years	33.3	35.1	0.20
⩾20 pack-years	27.1	19.1	
Asthma ever, %	11.0	17.1	0.10
FEV_1 %pred*	103.9 ± 15.7	102.5 ± 13.9	0.40
FEV_1 %FVC*	84.1 ± 6.5	84.2 ± 6.7	0.90
Total serum cholesterol, g/L*	2.30 ± 0.5	2.28 ± 0.5	0.70
Hypercholesterolemia, %	26.7	24.7	0.70
Rhinitis, %	38.4	44.1	0.30
SBP, mm Hg*	126.2 ± 13.9	114.1 ± 15.4	< 0.001
DBP, mm Hg*	80.6 ± 9.2	75.2 ± 10.0	< 0.001
Hypertension, %	23.3	14.7	0.05

Definition of abbreviations: BMI = body mass index; SBP = systolic blood pressure; DBP = diastolic blood pressure.
* Mean ± SD.

following questions: "Have you ever been told your cholesterol level was too high?" and "Do you currently use any lipid-lowering drugs?" Body mass index (BMI) was calculated as weight in kilograms divided by the square of height in meters. Nonfasting total serum cholesterol levels were determined using standard methods.

The protocol was approved by the French Ethics Committee for Human Research and by the National Committee for Data Processing and Freedom. Written informed consent was obtained from each subject before inclusion in the study.

Statistical Analysis

Respiratory and/or cardiovascular data were not available for 14 of the 330 subjects who attended the follow-up assessment. Consequently, the study population consisted of 316 subjects, 146 men and 170 women. The characteristics of the excluded subjects (n = 14) were similar to those of the subjects in the study sample, in particular with regard to FEV_1 %pred, rhinitis, asthma, SBP, DBP, and smoking status.

Data were analyzed with version 8.1 of SAS (SAS Institute, Cary, NC). All analyses were performed in men and in women separately. In univariate analyses, with rhinitis or hypertension as the dependent variable, chi-square tests and *t* tests were used to compare qualitative and quantitative variables, respectively. The relationships between SBP or DBP and quantitative variables were assessed with Pearson's correlation coefficient (r). In multivariate analyses, where all potential confounding factors were taken into account, the mean arterial blood pressures (± SD) of subjects with and without rhinitis were compared using analysis of covariance. Univariate and multivariate logistic regressions were used to analyze the relationship between rhinitis and hypertension. p Values below 0.05 were considered to be significant.

RESULTS

Study Population

Table 1 shows the characteristics of the study population according to sex. BMI was higher among men than among women. Asthma and rhinitis tended to be less frequent in men than in women. SBP and DBP were higher in men, and hypertension was more frequent.

Associations between Blood Pressure and Demographic, Respiratory, and Cardiovascular Risk Factors, by Sex

Age was significantly associated with SBP in women ($r = 0.27$, $p < 0.001$) and tended to be so in men ($r = 0.14$; $p = 0.08$). SBP was positively associated with BMI in both men and women ($r = 0.32$, $p < 0.001$ and $r = 0.33$, $p < 0.001$, respectively) and with total serum cholesterol level ($r = 0.20$, $p = 0.02$ and $r = 0.24$, $p = 0.002$, respectively). SBP was not associated with cumulative smoking exposure (in pack-years) among men ($p = 0.8$) but tended to be negatively so among women ($p = 0.07$). SBP was higher in men with asthma than in men without asthma (133.4 ± 11.9 mm Hg versus 125.3 ± 13.9 mm Hg; $p = 0.03$). SBP was not associated with either FEV_1 %pred or FEV_1 %FVC in men ($r = -0.009$, $p = 0.90$ and $r = -0.10$, $p = 0.20$). In women, SBP tended to be negatively associated with FEV_1 %pred ($r = -0.13$, $p = 0.08$) but was not associated with FEV_1 %FVC ($r = 0.05$, $p = 0.50$). Similar patterns of results were observed for DBP and for hypertension.

Associations between Rhinitis and Demographic, Respiratory, and Cardiovascular Risk Factors, by Sex

Associations between rhinitis and potential confounding factors are shown in Table 2. There was no association between rhinitis and age, cumulative smoking exposure, FEV_1 %pred, FEV_1 %FVC, or cholesterol either in men or in women. An association between rhinitis and BMI was observed in women. As expected, rhinitis was significantly associated with asthma both in men and women.

Associations between Rhinitis and Arterial Blood Pressure, by Sex

Men with rhinitis had a higher SBP than did men without rhinitis (130.6 ± 12.7 versus 123.5 ± 13.9 mm Hg, $p = 0.002$) (Table 3). This result remained similar when common potential confounding factors (age, BMI, hypercholesterolemia, and smoking status) were taken into account (129.9 ± 13.2 versus 123.6 ± 13.3 mm Hg, $p = 0.006$). Additional adjustment for asthma and/or FEV_1 (FEV_1 %pred or FEV_1 %FVC) did not alter this result. In the models including asthma and rhinitis simultaneously, the association between SBP and asthma observed in the univariate analysis disappeared. No association was found between rhinitis and SBP in women either before or after adjustment for common potential confounding factors (Table 3). Rhinitis was not associated with DBP in men or in women (Table 3).

When the analysis was performed in men without asthma alone, SBP was still higher among subjects with rhinitis than among ones without rhinitis (129.2 ± 13.0 versus 123.5 ± 14.0 mm Hg, $p = 0.03$). This result remained similar after adjustment for the potential confounding factors (128.2 ± 13.1 versus 123.6 ± 13.0 mm Hg, $p = 0.07$).

Furthermore, when men were stratified according to their smoking status, SBP was always higher in men with rhinitis than in men without rhinitis in each stratum, before and after multivariate adjustment, although statistical significance was not always reached (Table 4).

Treatment was also taken into account. Eighteen of the men had used corticoids in the last 12 months (10 subjects used steroid nasal sprays alone, 5 used inhaled steroids alone, 2 used nasal sprays plus inhaled steroids, and 1 used nasal sprays plus oral steroids). In the 127 men who had not been treated with steroids, a higher SBP was still observed among men with rhinitis than among men without rhinitis (129.8 ± 12.8 versus 123.9 ± 14.0 mm Hg, $p = 0.02$). This result remained similar after adjustment for the potential confounding factors (128.8 ± 12.6 versus 124.1 ± 12.6 mm Hg, $p = 0.05$).

Lastly, we studied SBP according to whether the men had seasonal or perennial rhinitis (Figure 1). SBP was higher as symptoms of rhinitis were more frequent (p for trend = 0.02 in univariate analysis and 0.03 after adjustment for confounding factors).

TABLE 2. ASSOCIATIONS BETWEEN RHINITIS AND DEMOGRAPHIC, RESPIRATORY, AND CARDIOVASCULAR RISK FACTORS, BY SEX

	Men			Women		
	No Rhinitis (*n = 90*)	Rhinitis (*n = 56*)	p	No Rhinitis (*n = 95*)	Rhinitis (*n = 75*)	p
Age, yr*	45.1 ± 7.2	46.4 ± 7.2	0.30	44.9 ± 7.4	44.2 ± 7.5	0.50
BMI, kg/m²*	24.8 ± 3.1	24.9 ± 3.3	0.90	23.9 ± 5.0	22.2 ± 2.9	0.007
Smoking habits, %						
Never smokers	40.0	38.9		43.0	49.3	
<20 pack-years	30.0	38.9	0.50	36.6	33.3	0.70
⩾20 pack-years	30.0	22.2		20.4	17.3	
Asthma ever, %	1.1	26.8	< 0.001	8.4	28.0	< 0.001
FEV_1 %pred*	104.1 ± 15.6	103.6 ± 16.1	0.90	102.4 ± 13.6	102.6 ± 14.3	0.90
FEV_1 %FVC*	84.6 ± 6.3	83.3 ± 6.8	0.20	84.5 ± 6.5	83.8 ± 7.0	0.50
Cholesterol, g/L*	2.30 ± 0.5	2.31 ± 0.4	0.90	2.26 ± 0.5	2.31 ± 0.4	0.50
Hypercholesterolemia, %	23.3	32.1	0.20	22.1	28.0	0.40

Definition of abbreviation: BMI = body mass index.
* Mean ± SD.

Hypertension

Hypertension was more frequent in men with rhinitis than in men without rhinitis (35.7 versus 15.6%, p = 0.005; odds ratio = 3.0, 95% confidence interval = [1.37–6.64]), and this was still the case after adjustment for the potential confounding factors (odds ratio = 2.6, 95% confidence interval = 1.14–5.91). A similar trend was observed among men without asthma, after stratification according to smoking status, and in men who had not received steroids.

There was also a positive association between the frequency of hypertension and the frequency of symptoms of rhinitis: hypertension was present in 15.6% of the men without rhinitis, 30.8% of the men with rhinitis with seasonal symptoms, and 34.4% of the men with rhinitis with perennial symptoms (p for trend = 0.02).

DISCUSSION

Main Findings

We found that SBP was higher in men with rhinitis than in men without rhinitis, even after adjustment for major known confounding factors. Furthermore, SBP was higher in men with rhinitis than in men without rhinitis in the subgroup of men without asthma and in men who had not received steroids, and tended to be higher in each stratum of cumulative smoking exposure. Hypertension was more frequent in men with rhinitis than in men without rhinitis.

Data Validity

The validity of our results is supported by the quality of the data collected in the ECRHS (19, 27). Rhinitis was defined as in several other population-based studies (20–24). The epidemiologic definition of ECRHS is also referenced in the latest recommendations from "Allergic Rhinitis and its Impact on Asthma" and the World Health Organization (28). Of the 131 patients who reported that they had rhinitis, all except 23 (11 men and 12 women) also reported that they got seasonal or perennial symptoms of rhinitis (*see* the definition in METHODS). There was a strong association between the self-reported rhinitis of ECRHS-II and those of ECRHS-I (p < 0.0001). Moreover, atopy (assessed by means of skin prick tests and IgE levels) was strongly associated with self-reported rhinitis in ECRHS-I (6).

TABLE 3. ASSOCIATION BETWEEN RHINITIS AND SBP AND DBP, BY SEX

	SBP (*mm Hg, mean ± SD*)			
	Men		Women	
	Unadjusted	Adjusted*	Unadjusted	Adjusted*
Rhinitis				
No	123.5 ± 13.9	123.6 ± 13.3	114.4 ± 16.0	113.6 ± 15.4
Yes	130.6 ± 12.7	129.9 ± 13.2	113.6 ± 14.8	114.5 ± 14.7
p	0.002	0.006	0.70	0.70
	DBP (*mm Hg, mean ± SD*)			
	Men		Women	
	Unadjusted	Adjusted*	Unadjusted	Adjusted*
Rhinitis				
No	80.1 ± 9.2	80.2 ± 9.5	75.3 ± 9.4	75.1 ± 9.6
Yes	81.4 ± 9.3	81.1 ± 8.1	75.0 ± 10.8	75.2 ± 9.5
p	0.40	0.50	0.80	1.0

Definition of abbreviations: BMI = body mass index; SBP = systolic blood pressure; DBP = diastolic blood pressure.
* For age, BMI, hypercholesterolemia, smoking status.

TABLE 4. ASSOCIATION BETWEEN RHINITIS AND SBP, IN MEN, ACCORDING TO SMOKING STATUS

	SBP (*mm Hg, mean ± SD*)	
	Unadjusted	Adjusted*
Never smokers		
Rhinitis		
No (36)	124.4 ± 10.5	124.8 ± 10.8
Yes (21)	131.3 ± 12.3	130.7 ± 11.0
p	0.03	0.06
<20 pack-years		
Rhinitis		
No (27)	120.8 ± 13.4	121.9 ± 13.0
Yes (21)	129.8 ± 11.5	128.4 ± 12.8
p	0.02	0.10
⩾20 pack-years		
Rhinitis		
No (27)	124.9 ± 18.0	123.3 ± 16.1
Yes (12)	128.7 ± 16.0	132.2 ± 16.6
p	0.50	0.10

Definition of abbreviation: SBP = systolic blood pressure.
Smoking status was available for 144 men.
* For age, BMI, and hypercholesterolemia.

Finally, the factors we found to be associated with rhinitis are usually reported to be so in the literature (6, 7, 29). We also found that arterial blood pressure (SBP, DBP, and hypertension) was associated with the expected cardiovascular risk factors such as sex, age, BMI, and cholesterol (30).

We did not find any relationship between cumulative smoking exposure and blood pressure. This result is consistent with previously published studies that showed that smoking is not a cause of persistent hypertension. This relationship is indeed much debated: some authors reported a positive association between smoking and hypertension whereas others reported a lower arterial blood pressure in current smokers than in nonsmokers or found a higher rate of hypertension in former smokers—rather than current smokers—compared with nonsmokers (31, 32).

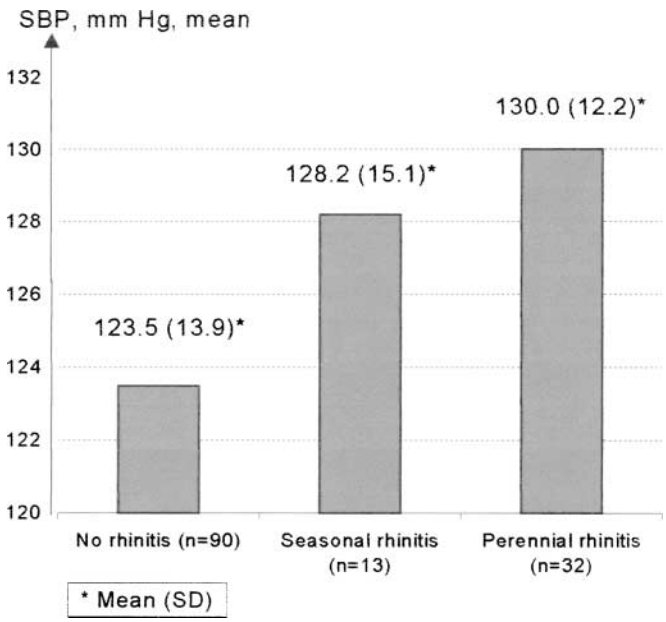

Figure 1. SBP values (mm Hg; mean [SD]) of men with no rhinitis, seasonal rhinitis, or perennial rhinitis (p for trend = 0.02). Categories of rhinitis were assessed for 45 of 56 men with rhinitis. SBP = systolic blood pressure.

Strength of the Relationship between Rhinitis and SBP and Hypertension

The association between rhinitis and SBP in men appeared to be strong. The magnitude of the difference between men with rhinitis and men without rhinitis, approximately 7 mm Hg—more than half the difference between men and women—is clinically relevant. In fact, recent meta-analyses of clinical trials comparing treatments in patients with hypertension have reported tight differences in SBP, often smaller than in our study, and pointed out that reductions in blood pressure, rather than baseline values of blood pressure, accounted largely and independently for most differences in the outcome of cardiovascular events (33, 34).

We also found that rhinitis was associated with hypertension, even after multivariate adjustment. This finding emphasizes the potential clinical relevance of our study as hypertension identifies a category of patients with a high cardiovascular risk profile.

We checked the association between rhinitis and blood pressure among men without asthma, as asthma was associated with both rhinitis—in our study and in the literature (6, 7)—and blood pressure. Associations between asthma and cardiovascular diseases (35), SBP (36), and hypertension (36, 37) have previously been suggested in some studies. The fact that in our study the association between asthma and SBP disappeared only when rhinitis was taken into account suggests that this association could be partly explained by rhinitis.

We also analyzed men who had not received steroids because corticosteroids may increase blood pressure (38). In the different subgroups (i.e., subjects without asthma and men who had not been treated with steroids), SBP was still higher in men with rhinitis than in men without rhinitis. In each smoking stratum, SBP was also higher in men with rhinitis than in men without rhinitis, but statistical significance was not always reached, probably because of the small number of subjects.

The results of our additional analysis of SBP level according to whether rhinitis was seasonal or perennial are consistent with the possibility of a dose–response relationship.

Possible Mechanisms

To our knowledge, no studies have ever been performed on the relationship between rhinitis and blood pressure. The mechanisms of this relationship are thus completely unknown. It is possible that rhinitis is associated with an increased blood pressure partly due to snoring or OSA. This hypothesis has been evoked in a previous review of all potential and known complications of rhinitis (9).

Rhinitis has previously been shown to be associated with both the main symptoms of OSA (snoring and daytime sleepiness) and OSA itself (10, 12). This is probably due to partial or complete nasal obstruction being inherent in rhinitis (11). In turn, OSA and surrogate markers, like snoring, are associated with arterial blood pressure and/or hypertension (13, 15, 16), and there is strong evidence that the mechanisms of blood pressure regulation are severely affected by OSA and consequent hypoxia (14).

Rhinitis was found to be associated with SBP but not with DBP. It is well known that measurement errors and intra-individual variability are greater for DBP than for SBP. In addition, SBP and DBP do not depend on the same hemodynamic mechanisms. In contrast to DBP, which is primarily due to the vascular resistance of small peripheral arteries, SBP may increase due to three main factors: an increase in the velocity of ventricular

ejection and/or stroke volume, a reduction in the viscoelastic properties of the large arteries, and a modification in the timing of the reflected waves within the arterial tree (39). Thus, elevated SBP is not systematically combined with elevated DBP (40). In addition, it has been shown that SBP is a stronger predictor of adverse cardiovascular events and total mortality than is DBP (41). Nevertheless, the mechanisms that might explain the differential association of SBP and DBP with rhinitis are unknown. Further studies are thus needed to investigate the nature of the association between rhinitis and arterial blood pressure.

Why in Men and Not in Women?

The association between rhinitis and SBP or hypertension was not found in women. This may be partly due to the fact that women are protected from cardiovascular morbidity before menopause (42). Furthermore, after menopause, SBP increases slowly, approaching that in men by 60 to 80 years age (43, 44). This increase in blood pressure takes on average 5 to 20 years to develop (44). The women in our study sample were rather young (median age 45 years, range 28–55 years) and still have relatively low blood pressures (i.e., compared with men and with the threshold used to define hypertension).

In addition, *if* OSA is actually implicated in the association between rhinitis and hypertension, this is consistent with the absence of this association in the women in our sample. Indeed, before menopause, women are protected from OSA. A recent study, performed on a large random sample of the general population, reported that the prevalence of OSA is quite low in premenopausal women compared with that in men and postmenopausal women (45).

Conclusion

Rhinitis was strongly associated with SBP and hypertension among men in our population-based study. The high prevalence of both rhinitis and hypertension emphasizes the importance of such results. These findings open up a field of investigations and may have easy-to-implement repercussions in clinical practice. To begin with, men with rhinitis, both with seasonal and perennial symptoms, should have regular blood pressure checks.

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Report on a Pilot Study into

The Effects of Saline Nasal Irrigation (SNI) Upon Nasal Symptoms in Woodworkers

By Swami B. Saraswati and Dr Steve Rabone.

ABSTRACT

Aims

1. To determine if SNI decreases prevalence and/or severity of nasal and general symptoms amongst woodworkers
2. To determine woodworkers' acceptability of SNI.
3. To determine the effects of SNI upon: snoring, predisposition to and recovery from colds, sense of smell, nasal airflow patterns, mouth breathing.
4. To discover: the participants' reasons for trialing SNI and attainment of these reasons; any unexpected benefits or side effects; personal experiences of the technique; problems in learning and performing the technique; usage patterns; usual location and times of nasal cleansing; time taken to perform; lifestyle impositions caused by the method; likelihood of longer term usage.

Methods

A group of 46 volunteer woodworkers were randomly divided into 2 groups. One group used the intervention technique twice daily for 8 weeks whilst the other group was the control. Groups were crossed-over after the 8 weeks. At 16 weeks all participants were free to choose to cease or continue usage of the technique for a further 12 months follow-up period. Self reporting questionnaires were filled in by all participants at the beginning, cross-over, and at the end of the follow-up periods of the trial.

Results

1) The procedure of SNI was shown to be significantly ($p=0.0001$) associated with a perception of decreased nasal problems during both the cross-over period and the one year follow up period. Beneficial changes in other aspects of health and well being appeared to associated with the procedure but inconsistently.

2) Acceptability of the procedure indicates that 21 of the 46 subjects were still using the procedure regularly after 1 year. Additionally, perceived usefulness of SNI showed a favourable response with 34 subjects saying they found the procedure quite useful or very useful.

3) Data was weak and inconclusive on the effects of SNI upon snoring and its effects upon catching and recovering from colds. There was strong evidence for improvements in the sense of smell, gross nasal airflow, nasal airflow imbalances and reduction in mouth breathing.

4) Most participants attained their intentions for entering the study group. There was a high number (124) of unexpected benefits. Side effects were shown to be minimal and overcome by time and experience with the procedure. Nearly all subjects had favourable impressions prior to and after first learning the technique with some apprehension and difficulties showing up whilst first learning SNI. Overall satisfaction after 16 months was 90%. Difficulties with the technique at some stage were reported by between 30 and 54% of users. Average usage of the practice varied from a high frequency of 10.8 times weekly at the beginning to a low of 2.8 times weekly by the end of the trial. When optional, 57% of the subjects adopted regular use, 28% as needed and 15% not at all. Usual location of nasal cleansing was at home for 95% of users. The average time taken to perform SNI was 4.3 minutes. 87 – 97% of users found the technique to be of no inconvenience to their usual lifestyle. Intention of usage beyond the 16 month study period was 41% on a regular basis, 30% on a need to basis, 29% not at all.

Summary & Conclusions

(Rabone) The study provides reasonable evidence that SNI significantly improves nasal symptoms in volunteer woodworkers. It shows that most woodworkers who wish to try the procedure will regard it is a useful aid and will adopt the technique with varying usage according to their own needs.

(Saraswati) The study also gives indications of SNI's potential usefulness in other areas of health and well being. The effects of SNI upon wood dust in woodworkers should be the starting point from which to explore the wider ramifications of a clean and well functioning nasal system.

THE RESEARCHERS

Swami Bhavchaitanya Saraswati is a yoga teacher and yoga therapist of some 15 years experience. Over his years of teaching experience, he has noticed the health benefits gained by people who have been using a particular method of self-administered Saline Nasal Irrigation (SNI), well known by practitioners of the traditional yoga disciplines as a method of daily personal hygiene as well as an aid to meditation. The historical yoga texts; Swami's teacher's experience of some 50 years; his own personal experiences, observations and studies; as well as reports from other yoga teachers and students; all give weight to the anecdotal reports that regular practise of SNI can be a very effective method for both prevention and cure of many common upper respiratory ailments and their associated symptoms.

Swami believes that this particular technique should be investigated in a proper medical and scientific way, and that the findings of such trials should subsequently be presented to the broader community to encourage wider acceptance of the practice and also to find appropriate applications for it within public health management. He approached Dr Rabone for assistance in developing the first proper study of this kind upon SNI in Australia.

As a practising yoga therapist, he uses the methods of yoga for treating many common ailments. He has travelled the country extensively, giving lectures, seminars, workshops and residential retreats on many aspects of yogic science. He has produced a series of videos and cassette tapes on yoga and is the author of 5 books on Integral Yoga and associated topics. Although having no formal training in medical research, he has written several previous papers on SNI which include a 3 year survey on the effects of SNI on 200 yoga students in Western Sydney and rural NSW. He is the director of Nunyara Yoga Ashram near Wisemans Ferry NSW, where he currently resides and teaches.

Dr Steve Rabone is a medical practitioner who developed an interest in wood dust when working in research for Worksafe Australia (The Commonwealth Occupational Health and Safety Commission) between 1992 and 1996. Following surveys of the timber industry in Western Australia he became aware of the high prevalence of nasal symptoms amongst woodworkers. He was interested in exploring techniques to improve nasal symptoms amongst woodworkers. He is the author of published scientific papers on asthma detection and indoor air quality. Prior to Worksafe he worked in general rural practice for 10 years in the Riverland of South Australia and on the NSW far north coast. He graduated from Sydney University in 1974 with honours. His experience and counsel helped Swami Bhavchaitanya initiate this pilot study on SNI in woodworkers and to provide scientific analysis for some of its collected data.

INTRODUCTION & BACKGROUND

(By Rabone)

Exposure to wood dust is associated with nose problems such as blocked nose, dry nose, runny nose, nose bleeds and sinusitis[12] as well as being suspected for other general ailments such as eye problems, snoring, headaches, tiredness, frequent colds, disturbed sleep patterns. Wood dust is also a Group 1 carcinogenic according to the criteria of the International Agency for Research on Cancer (IARC) [3] causing nasal adenocarcinoma. The proposed mechanism for carcinogenesis is based on the knowledge that wood dust contains many chemicals which have been demonstrated to be irritant, genotoxic and/or mutogenic [4,5,6] and that the dust in high concentration inhibits normal mucociliary clearance [7,8]. It is postulated that inhaled wood dust remains in the nose and then carcinogenesis occurs [9,10]. Exposure standards are based on the concentration of wood dust likely to cause mucostasis [11,12], yet compliance with exposure standards and wearing of protective equipment is probably variable in many workplaces. In an unpublished survey of volunteers from the timber industry in Western Australia in 1993, one author found a high prevalence (25%) of self reported nasal symptoms amongst sawmill employees, variable exposures and variable use of personal protection. It is logically accepted that zero exposure to wood dust is the best way to prevent nasal symptoms and cancer. There is however little information about what measures are appropriate once exposure has occurred.

This study tested the hypotheses that cleansing of the nose using Saline Nasal Irrigation (SNI) will reduce nasal symptoms in wood workers. The process of cleansing the nose is directly analogous to cleaning dust and chemicals from the skin after work - a normal procedure to avoid skin irritation.

To test the hypothesis, this study trialed SNI in a group of wood workers. It asked whether the procedure of nasal irrigation affected the frequency and severity of nasal symptoms commonly experienced amongst groups of this type. It asked whether other aspects of health and well being were affected by the procedure. The trial asked for a measure of acceptability of the procedure by determining whether or not subjects would continue to use it beyond the initial compulsory phase.

If SNI proved to be acceptable, and if it was shown to be effective in relieving nasal irritation, then theoretical arguments could be constructed that it could be of use in the preventing nasal cancer. Removal of the carcinogenic should logically decrease cancer risk. The issue of nasal cancer could not, however, be directly assessed by this study.

THE HISTORY OF SNI (known as Jala Neti in the yoga tradition)

(By Saraswati)

It could never be ascertained exactly how, when or where such a concept as saline nasal irrigation originated since as long as man has been living near the oceans and swimming in them, people would have realised the health giving attributes of sniffing saline water and vapours.

In the ancient yogic scriptures from the Indian sub-continent, as far back as 600 BC, mention is made of a method of nasal purification known as Sutra Neti. In the Hatha Yoga Pradipika it states - *"Neti removes diseases of the body in the regions above the shoulders. It purifies the region of the skull and makes the sight capable of seeing subtle things"*. Here the texts point to both its physical as well as meta-physical healing attributes.

The definition of Neti given in those times was the use of cotton threads or Sutras which were skilfully threaded in through the nasal passages and out of the mouth. The use of warm saline water (Jala Neti) was also adopted as an alternative method. It is known that even preceding such writings, these techniques had been passed on orally from guru to disciple in the traditional spiritual lineages. On other continents as well, evidence has been found of ancient civilisations which used

body cleansing rituals including SNI. The traditional medical systems of India, China, Europe, Africa and the Americas, have all used saline irrigation in a wide variety of ways for thousands of years.

More recently, in the western medical regimes of this century, SNI has been used in the otolaryngological profession (ear, nose & throat) upon patients.

Within the general populace, use of saline water is known as one of "grandma's old remedies" just for staying healthy in the head, throat and chest area. Saline gargling is also a part of these traditions. Often in our yoga classes, when we introduce the yogic method of SNI, people say that they have heard about, or actually perform themselves, a similar thing, by sniffing up salty water from their hand or a bowl. Many report that it gives them great protection and recovery from colds.

So, from all of the above, we see that neither the concept nor the practise of SNI is anything new, but rather, that it is both an ancient and universal practice and that it has a reputation with both medical and lay persons Eastern and Western for a range of health benefits. Surprisingly however, acceptance of the concept and practice of a nasal wash-out varies greatly in modern Western culture, with impressions ranging from “Yuk! That’s absolutely disgusting” to “Oh yeah, that makes perfect sense”.

AIMS OF THE STUDY

The 2 researchers differed in their general approach to the study and therefore in the details of their aims and results. Each had different sets of questionnaires, with some cross-over of intention and results. Rabone narrowed the examination of the intervention technique to 2 main quantifiable occupational health issues.

1. To determine if SNI decreases prevalence and/or severity of nasal and general health symptoms amongst woodworkers
2. To determine woodworkers’ acceptability of SNI.

Saraswati had, in addition to Rabone’s aims, a broader focus. He wanted to test several other hypotheses relating to SNI and its effects on upper respiratory functions in general, and to possibly validate the anecdotal reports about its benefits on more subtle areas other than its effects on wood dust in the nostrils. Saraswati’s questionnaires were more general and exploratory, and his analysis is more descriptive of responses rather than formulaic. He also aimed to entice interest in further research of SNI’s possibilites beyond occupational health. These additional issues for investigation were:

3. To determine the effects of SNI upon: snoring, predisposition to and recovery from colds, sense of smell, nasal airflow patterns, mouth breathing.
4. To discover: the participants’ reasons for trialing SNI and attainment of those reasons; unexpected benefits or side effects; personal experiences of the technique; problems in learning or performing the technique; usage patterns; usual location and times of nasal cleansing; time taken to perform; lifestyle impositions caused by the method; likelihood of longer term usage.

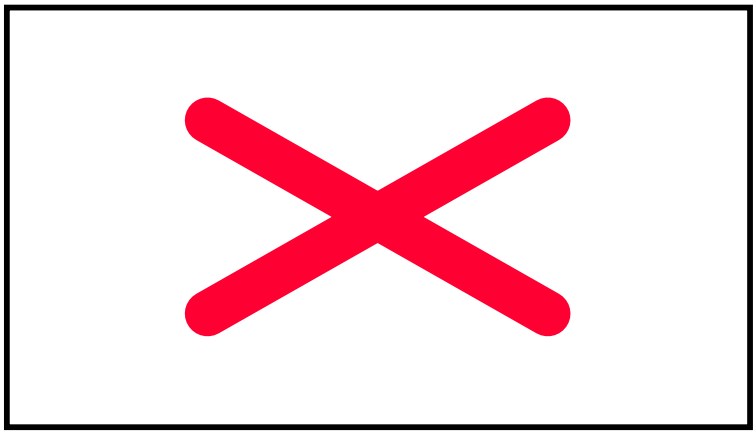
CHRONOLOGY

Study Commenced	5th March 1996
8 week cross-over point	6th May 1996
End of 16 week cross over period	6th July 1996
12 month follow-up period	Commenced 6th July 1997 Completed 10th Dec 1997

METHODS

The Procedure of Saline Nasal Irrigation

A special, purpose-built pot, not unlike a small tea pot, is filled with warm, normal saline solution. A conical nozzle on the end of the spout is inserted into one nostril with enough pressure to seal and prevent water leakage. The angle of the head and pot is adjusted so that the water flows into one nostril, into the nasal passages and then out the other nostril. Half a pot is let flow in one direction and then the direction of the flow is reversed. Breathing is sustained through the mouth whilst water flows through the nose. After emptying the pot, the nose must be properly dried.



Study Design

The study was designed by Rabone and Saraswati at Worksafe Australia including approval by Sydney University Ethics Committee. It was decided to be a randomised cross-over design with 2 months exposure to SNI and 2 months of no intervention. Due to the nature of the intervention technique, it was not possible for a placebo nor blinding to be considered in the design. There were to be 2 phases. A 16 week randomised cross-over period with twice daily application of the SNI intervention technique followed by a 12 month follow-up phase where usage was optional. Self reporting questionnaires were to be the method of measurement.

The final list of 46 volunteers was randomly divided into 2 groups of equal size. Appointments were made for all participants to attend the laboratory at Worksafe Australia to fill in questionnaires and for those in the first intervention group (Group 1) to be taught the technique of SNI. The intervention group were supplied free with stainless steel nasal cleansing pots, given all the relevant back up literature and sent home to perform the SNI technique twice daily for a period of 8 weeks. The first control group (Group 0) was instructed to continue their wood working activities in their usual manner with no intervention methods.

After 8 weeks, all participants were again called to appointments after which the groups crossed-over. The previous control group was instructed in the technique and supplied with the pots recovered from the previous intervention group (after sterilisation of course!). Questionnaires were collected again at this point.

At the end of 16 weeks all participants were again called to appointments, and questionnaires were again collected. From this point on, all participants were free to choose their own rate of usage of the technique (if at all). Those wishing to continue use of the technique were able to purchase their own nasal cleansing pot at their own expense ($45). After 12 months, all participants were requested to attend appointments again where questionnaires were collected.

Measurements were performed by a series of questionnaires at the beginning (t=0), the cross-over point (t=8 weeks), end of the cross-over period (t=16 weeks) and 12 months later (t=68 weeks). Potential confounders included smoking habits, acute and chronic upper respiratory infection, other dust inhalation, drugs and medications that potentially affect nasal function and nasal allergy. If confounders were not able to be dealt with by the randomisation process they were to be adjusted for by using multivariate regression.

Analysis has been hampered by the low power of the study. To gain higher power would have entailed more participants and it was felt that too much was unknown about the methodology of SNI to commit larger resources to the project. Nevertheless it was decided that descriptive analysis of the responses coupled with formal statistical analysis would provide enough information to consider the potential of SNI.

Selection of Participants

The researchers attended 3 meetings of NSW woodworking groups. These groups contained both full time and part-time wood workers. A presentation was given outlining current knowledge about the health effects of wood dust. A demonstration of the SNI procedure was given. The study design was explained and volunteers requested. 50 volunteers were obtained. Prior to commencement of the study, four volunteers withdrew. Thus 46 subjects commenced the study.

Eligibility

To lessen possible confounding factors we excluded: those recovering from recent nasal surgery; those who has serous doubts about compliance; those who intended to dramatically change their work practices and location during the cross-over stage of the study.

Characteristics of Participants

Sex:	42 male, 4 female
Age:	From 24 to 71 (mean 43)
Alcohol:	17 did not drink alcohol
	29 drank less than 3 standard drinks per day.
Smoking:	5 smokers
	23 ex smokers
	18 never smokers.
Work Hours:	34 subjects worked greater than 10 hours per week
	10 worked 4 – 10 hours per week
	2 worked 1 – 4 hours per week.
Exposure:	2.8 years on average potentially exposed to wood dust
Workplace:	Average dustiness of 44, where 100= “ultra clean” and 0= “the dustiest”.
	No general dust controls were used at work by 23 people
	wetting was used by 14
	extraction ventilation by 7
	fans by 3
Protection:	16 used personal protection most of the time (from wood dust that is!)
	27 sometimes
	3 never
Exercise:	24 reported 0 hours per week of sport or fitness activity
	6 reported 1 – 2 hours per week
	5 reported 2 – 4 hours per week
	11 reported greater than 4 hours per week.

Data Collection

Questionnaires were all self-reporting, being posted out in advance of the appointments so as to be filled-in and then brought to each visit. Questionnaires obtained basic demographic data, records of SNI usage, measures of the perceived usefulness, and general comments. In most questions, recorded responses were on 0 – 100 linear scales with prompts written below the scales. Throughout the study, there were a considerable number of non-responses in the questionnaires. Being self reported and not checked through upon presentation, ambiguities and blank answers were not picked up until later. Some of the missing responses were gained by phone later and some could be

safely deduced from other answers given. Over the period of the study, with several participants becoming disinterested in responding, the number of questionnaires recovered diminished as in the following table.

Questionnaires (Total of 10)	A & 1	B	C & 2	D	E & 3	F & 4
Time (in weeks from t=0)	0	0	8	8	16	68
Number of questionnaires received	46	46	46	46	44	38

Where: (A, B, C, D, E, F) belong to Saraswati (1, 2, 3, 4) belong to Rabone

Statistical Analysis

Formal statistical analysis was performed by Rabone upon his own 4 questionnaires as follows: Saraswati reports only the gross numerical responses and simple percentile figures as collected in his 6 questionnaires.

Analysis of crossover trial data was performed according to Armitage and Berry[15.] Analyses used two sample t-tests to test for SNI effect, period effects and period x SNI interaction. SNI x period interaction was assessed using control readings. (The t-tests indicated no detectable period effect or period interaction effect). To assess one year follow up changes, results were subtracted from control (0 months) results and the differences analysed using one sample t-tests.

Repeatability[14] of the questionnaire was estimated by subtracting results from the first response (prior to the study) from the responses after 2 months of not using SNI. Standard deviation of the measurement error ("s") was calculated as $s = \sqrt{(1/2n)\sum (x_1 - y_1)^2}$

For nasal problems s = 16.0, mean = 9.0.
For eye problems s = 15.1, mean = 5.7
For general problems s = 12.8, mean = 3.8.
Results for all other variables in Table 1 were generally comparable with these.

RESULTS - 1 & 2 (as per Rabone)

1. The procedure of SNI was shown to be significantly (p=0.0001) associated with a perception of decreased nasal problems during both the cross-over period and the one year follow up period. Table 1 shows the mean perceptions for the 4 measurement periods as well as statistical significance of the changes.

Beneficial changes in other aspects of health and well being appeared to associated with the procedure but inconsistently (Table 1). There was lack of consistency between the cross over period and the follow up period as well as between some variables that ought to be similar (eg general health, general problems). Because of this, some results are difficult to interpret.

2. The trial asked for a measure of acceptability of the procedure. The reported usage at one year follow up is summarised in Table 2. These results indicate that 21 of the 46 subjects were still using the procedure regularly after 1 year. Additionally, one year follow up responses to perceived usefulness of SNI showed a favourable response (Figure 1) with 34 subjects saying they found the procedure quite useful or very useful.

Comments of the participants were requested on the questionnaires and these were not particularly focussed. They are presented in Table 3 as information about the group's experience with SNI.

RESULTS – 1, 2, 3, 4 (as per Saraswati)

(1)……
Saraswati's data for nasal symptoms and general health benefits shows similar results to Rabone's but with less accuracy. In general terms, there were 37 reports of improved specific nasal symptoms by 49% (22) of the participants during their first 8 week usage period and 28 reports of further improvements by 26 subjects over the 12 month period.

These included: clearer nostrils, clearer head, better breathing, improved sense of smell, better sleep, discontinued nasal sprays, clearer sinuses, less nose bleeds, no colds, clearer head, better thinking, fresh & clean feeling, less sneezing, better sleep, more relaxed, peace of mind, well being. There were 3 negative effects reported: worsening of sinus, increased nasal blockage, cold symptoms. There were 4 reports of no effects.

(2)……
Acceptability
Overall acceptability can best be gauged by a combination of the subjects' choices for using the procedure at 4 occasions during the trial.

(i) Out of all the people addressed in the initial seminars, about 30% became volunteers for the study of which 38 (82%) were hoping to lessen nasal symptoms by doing so.
(ii) In the short term (during the twice daily cross over period) overall average compliance was 77%, that is a total average for all subjects of 10.8 times per week (f = 10.8). For exact distribution see Table 12.
(iii) At the beginning of the optional 12 month phase, 39 out of the 46 subjects bought pots intending to be users. By the end of that period 32 (69%) were still using at some frequency, with 14 having stopped use. During that year, the overall weekly average usage dropped to f = 3.0. Details of usage patterns for the 12 months are shown in Table 14.
(iv) When asked about their future intent beyond the 16 month study, 38 intended to use SNI again at some stage, 1 never again and 7 no responses. See Table 11.

If the intentions of remaining users can be believed (as in Table 11), it makes the total and overall perpetual acceptability for SNI: (71% of 30%) = 21% of woodworkers exposed to knowledge about the technique.

(3)…….
Snoring
1 subject reported their snoring had reduced after 8 weeks of usage
1 subject reported their snoring had ceased after 12 months of usage
1 subject reported their snoring had reduced after 12 months of usage
This reportage of snoring was made only incidentally in general comment and not by measurement scales over the whole group. Rabone's Table 1 shows better statistical significance based on his linear graph responses for the cross-over but not so the 12 month follow up.

Predisposition to and recovery from colds

Such issues as these may seem extremely difficult to assess in just 8 - 16 weeks (irrespective of any particular climatic season) and may even be hard to show even after 1 year of season cycles. None the less, I felt that people's own medical history, compared with instinct and recent recollection could still give them a record for some amount of self assessment after 16 months of use.

Saraswati's responses on linear graph lines showed an overall average of 7.5% reduction in the number of colds contracted during the 16 week cross-over period with a further 8% improvement reported in the 12 month follow up.

An overall average of 3% better recovery from colds was reported during the 16 week cross-over period with 6% reported in the 12 month follow up.

Rabone's responses to this same symptom showed 4 improvements out of 44 in 8 weeks of usage and 7 out of 36 in 12 months.

These are small figures and there was a large variation between the groups which may make the results too inaccurate for evidence of any effect. In addition to the self assessment scale, there were comments made confidently by 4 people that they had definitely had less colds in 16 months since starting SNI.

To assess this reputed benefit of SNI more thoroughly, a study would need to involve people who have a very long history of regular colds, who performed the practice regularly for at least one year, and who had a lesser collection of confounding factors eg smoking, wood dust.

Sense of Smell

Improvement reported in both groups was 25% and 23% overall in the short term with only a further small improvement over long term. However Rabone's figures showed 9 out of 36 improved in the 12 month period. Variations such as these were caused by different forms of questioning. Ecstatic comments such as "Hooray! I can smell again" and "I am enjoying the smell of breakfast again for the first time in many years" gave some indication of the unexpected pleasure arising from improved sense of smell. Details see Table 4.

Nasal Airflow Blockages

Definite improvements were shown in the ability of SNI to improve nasal airflow. Blockages in nasal airflow would most likely be the first symptom noticed arising from excessive wood dust and should therefore be the most immediate and obvious factor showing improvement. One application of SNI can give immediate relief from nasal congestion lasting for many hours depending on the level of airborne particles or infectious causes. As a general question, without considering factors such as structural blockage, responses showed an improvement in both groups (60% and 52%) during their 8 weeks of intervention usage and a further 39% overall in the following 12 months. A definite worsening was shown in Gp 1 when the procedure was withdrawn after the usage period. Ecstatic comments such as "I can breathe again!" were common from many workers. Details see Table 5.

Normalisation of Nasal Airflow Patterns

SNI is said to be able to restore and maintain the normal circadian rhythms of nostril airflow by removing non-structural blockages such as dirt particles and the build up of mucus. The hypothesis was explored that by clearing nasal airflow, normal circadian cycles of the nostril airflow could be restored in those who had imbalances in it. Yogis believe that (in a healthy individual) about each 90 mins, the predominance of nostril airflow will change. For about 4 minutes at the time of change over, there will be an even flow at the nostrils. Immediately after a session of SNI the nostril airflow

flow should, in a healthy person, be balanced for a far longer period of time, the length of which is dependent upon subsequent activity (such as food, work, relaxation, sleep) and environmental factors (such as temperature, humidity etc.) Since, in a healthy person, nostril airflows are seen to be properly fluctuating, and in unhealthy people these flows are more frequently imbalanced, the corollary follows that to restore normal airflow patterns by decreasing foreign particles, mucus and bacteria accumulated in the nose will therefore create better health.

Structural nasal problems such as deviated septum, polyps, along with lifestyle activities like use of nasal drugs, smoking, excessive alcohol and strong environmental pollutants present serious confounding factors for this question. It would have been preferred for each participant to have had a proper nasal examination prior to the trial to establish whether or not they had any structural nasal deformities. In responses, only 2 people mentioned these and thus we would expect less possibility of airflow normalisation in their cases. Others may not have known of such conditions or may have considered their condition not relevant to the study. From the data, it can be deduced that at least another 5 participants had such problems.

The results of Table 6 which asked the question "how often would you notice an imbalance in your nasal airflow?" show that during their 8 week intervention period overall 70% of respondents noticed an average 22% decrease in nasal airflow imbalance (an effect of unblocking one or more congested nostrils) and 63% recorded a further 22% decrease in the next 12 months.

Responses in Table 7 are the sum of data from the above question plus the question "which nostril predominantly has the lesser airflow?" to examine which subjects had normal, abnormal and fluctuating airflow rhythms. It shows that 16 people (35%) did not record abnormal circadian nasal airflow patterns; SNI appeared to make a positive change to 9 out of 46 people (20%); whilst 5 (11%) had a permanent one nostril blockage and 5 (11%) had a fluctuating nasal blockage upon which SNI appeared to make no noticeable difference.

Longer term monitoring of those people who noticed normalisation of nasal airflow patterns would, I believe, show an improvement in their upper respiratory health in particular, as well as in their general health. Much larger study numbers with proper examination would be required to prove more clearly such a hypothesis.

<u>Mouth Breathing</u>

Similar to the previous question on nasal airflow imbalance, yogis maintain that to reduce mouth breathing, is to improve respiratory and general health. Responses to this question may not be wholly accurate since awareness of mouth breathing often takes some time (months) to establish. Responses can only be as accurate as one's own self knowledge, so, for chronic mouth breathers, especially those working where strenuous activity demands high volume breathing, mouth breathing may not be seen as problematic and therefore awareness of mouth breathing would have been low prior to the study. Such an awareness is gained very quickly when SNI is undertaken since the cleanliness of the nose and its normalised function after a wash-out can be quite long lasting.

Table 8 shows improvements in the frequency of mouth breathing during each of the intervention periods with a worsening effect in Gp1 after ceasing the procedure. The groups showed a 16% and 13% lessening of mouth breathing during the 16 week cross-over period with both groups reporting no appreciable difference long term. These responses were obtained from a linear graph.

Responses in Table 9 give a stronger indication of perceived improvement (experienced over time) averaging 28% and 24%. These responses were obtained by pick-a-box "worse/same/better".

(4)……..

Reasons for Joining the Study

I was interested to know what motivates people into joining a medical research trial such as this where the intervention technique is untested and unusual and whether, after 16 months of trialing SNI, participants would consider they gained what they hoped to. The great majority (34/46) hoped to gain either relief from specific nasal ailments which they listed on their symptoms sheets or else general health gains. 8 kind souls volunteered to join the study, at least partly, for altruistic reasons of helping medical research and their fellow industry workers. Four were seriously concerned about the dangers of wood dust and hoped the study might reveal more about the likelihood of nasal cancer and indicate whether SNI might be a possible preventative method for nasal cancer.

Attainment of Reasons for Joining the Study

Yes - 33 participants out of all 46 had a combination of responses which indicated that their primary reason(s) for joining the study were in fact satisfied at some level. Of the 21 who started out with desires for improvement in specific nasal symptoms, all 21 of them (100%) were not disappointed in that they reported definite improvements in the symptoms they mentioned at the beginning of the trial. For the 14 who hoped for more general health benefits 11 (79%) reported gaining benefits along those same lines.

No - 5 did not report at any stage any perceived benefits from participation in the study and had not listed any benefits as having been gained.

Maybe - 8 participants either had stated desires or reasons for joining the study which were not attainable or quantifiable (eg to reduce the risk of nasal cancer and to help out medical research) or had benefits stated which were not comparable with their stated desires.

It may seem pointless to "study the study" but I was interested to assess whether people gained their primary reason for joining the study. Outcomes from this question could help the researchers to ascertain if participants had desires and expectations towards the technique and whether those expectations were realistic. It is also my aim to discover how people "take to" a technique such as SNI (that is - if their reasons for trying it are different to their satisfaction gained by it) and how their initial, intermediate and final attitudes to it change over time.

Unexpected benefits

In addition to the desired relief from certain symptoms listed at the beginning of the trial (n=52), many participants also reported additional unexpected or undesired benefits arising from use of the technique (n=124). Experience of SNI teachers has previously shown that in addition to obvious nasal therapy, there are many other tangential and indirect benefits which users find they have gained. The reports in this study seem to back this up. This may also indicate that the unexpected benefits are less subject to "imagined" outcomes and Hawthorn Effect.

Side effects

During the first 8 weeks of usage 34 users (74%) reported no adverse side effects at all with 12 users (26%) reporting a total of 16 minor difficulties with the procedure which are considered the usual "teething problems" associated with inexperience. 7 subjects chose not to buy pots to continue use after the cross over period, 4 stating their reasons as intolerable side effects with no noticeable benefits, 1 stating he used water from his hand just as effectively, 1 stating she would share a pot with her flatmate and 1 stating he was just too lazy to be bothered doing it for no noticeable benefits.

During the 12 month follow up period, only 1 user (out of 34 respondents) experienced only one negative side effect, possibly due to over use of the procedure. It can be deduced from other questionnaire responses that the 12 missing respondents therefore dropped out of usage due to either no benefits worth the effort (8) or intolerable negative side effects (4).

The side effects reported can be seen in Table 10 which shows the incidence of all reported difficulties experienced during the trial.

The issue of contra-indications for the procedure was not thoroughly dealt with in design of the study. I found close correlation between those who had chronic nasal problems (the usual contra-indications which require closer guidance); the incidence of difficulties experienced and the incidence of dropping out of usage. It is felt that medical history and likelihood of negative side effects are issues which need to be examined more closely in future trials of SNI so that data gained is more closely indicative of the average person's side effects or else can be related to specifically defined ailments and the effect of SNI upon them.

Personal experiences of the technique

Upon first hearing about it	92% of impressions were positive
	5% of impressions were negative
	2% of impressions were neutral
Approaching the first lesson	82% reported positive feelings
	11% reported negative feelings (nervous)
	7% reported neutral feelings
During the first lesson of SNI	43% reported positive experiences
	39% reported neutral experiences
	17% reported negative experiences
Straight after the first lesson in SNI	80% reported a positive experience
	11% reported a neutral experience
	9% reported a negative experience
After their first 8 weeks of usage	83% had an overall impression of SNI as positive
At the end of the 12 month period	90% rated their impression as positive

Whilst it can be seen that nearly all subjects were positive about the idea and theory of SNI, upon approaching the first lesson apprehension and "nerves" lessen that positivity. Problems arose for many during the first attempt but the immediate after effect was highly positive. Technical "teething problems" were solved in the first week at home and then the appreciation rate rose again with long term usage.

Problems or difficulties in learning or performing the technique

At the first lesson	21 (=46%) reported no difficulties at all
In their first week at home	32 (=70%) reported no difficulties at all
In the rest of the 8 week period	31 (=67%) reported no difficulties at all
During the next 12 months	30 (=65%) reported no difficulties at all

Table 10 shows the details of difficulties experienced at the different stages of the trial

The rate of difficulties experienced is highest at the beginning when first learning, lessening after a week or two and then remains fairly constant over time. This indicates that those users encountering problems with the technique are in fact encountering their own problems (ie structural nasal deformities and chronic mucus blockage). The types of difficulties reported are all very familiar to teachers of SNI. Any procedural problem has a simple solution and most users discover these solutions quickly, however, for some individuals, certain nasal pathologies are best excluded from the technique unless under close medical and yogic guidance. These are the users who have constant hassles with SNI and eventually give up on it.

Usage patterns and reasons for changes

Intended and actual usage patterns were examined at each stage of the trial and are shown in Table 11. As can be expected of human nature intention and actual performance were somewhat different realities.

During the 16 week cross-over period when SNI was recommended twice daily, the average compliance rate for both groups was 77% which equates to an average weekly usage rate for the whole group of f = 10.8. See Table 12. Reasons for fluctuations in compliance during this period are in Table 13.

Following their first 8 weeks of usage, subjects were asked their intention for usage in the 12 month follow up. Their actual usage during the 12 month follow up when compliance was optional is in Table 14. Overall average weekly usage frequency by subjects still using at the end was f = 3.02 or f = 2.3 for all 46 subjects who had commenced the trial.

Over the 12 month period, usage by those (39) who had bought pots at the end of the cross-over period to continue usage was

23 (=57%) on a regular basis (greater than or equal to 3 x weekly)
11 (=28%) on an as needed basis (less than 3 x weekly)
6 (= 15%) not at all.

Usual location of nasal cleansing

95% of users preferred place of performing SNI was at home. 26% of these worked at their home. Initially it was presumed that SNI users might perform the technique at a combination of their workplace and their home. It was assumed that the morning SNI would be done at home, and that some might then take their pot to and from work (if it was different to home) like their lunch pack, brief case or tool box and that the after-work cleansing might be done straight after exposure at the workplace. Due to the number of participants who worked at their home location (14 out of 46), and the impression that people prefer to keep their nasal cleansing for the domestic bathroom, very few workers (only 2 out of 46) ever performed SNI at the workplace – that is where it was different to the home place. A future senario was envisaged where SNI might become a recommended occupational health routine, possibly sponsored by the employer, where workers would use SNI (their own pots of course, kept in their locker) in the bathroom at work before going home. Indications from this study seem to show that the technique is considered too personal and private to be used widely in the workplace and that transportation of the SNI pot between home and work would not be widely adopted.

Usual Time of Performing SNI

The aim was to discover the times of day when SNI was performed following dusty work. There were such a high number of non-responses to this question rendering it useless for analysis. This was probably due to ambiguity of the question and also that users may have been inconsistent in their woodworking times and hence couldn't decide upon an accurate response.

Time taken to perform

The average time taken to perform the procedure was 4.3 minutes. There was an enormous range of times reported (0.5 – 17.5 mins).. Possible reasons are as follows:

For users who stated that they take less than 3 minutes, it can be concluded that they may be:

(i) underestimating the actual time taken
(ii) only stating the time for water flow-through and not the mixing and drying processes
(iii) not drying their nose properly in the instructed manner.

For users who take much longer than 5 minutes they may be:

(i) overestimating the time taken
(ii) having troubles getting the water to flow through due to mucus or structural blockage
(iii) keeping the materials needed for the technique (pot, water, salt, basin) in different locations
(iv) using several pots full of water to do a "double wash" due to an impression that they may not be totally cleansed in the nostrils after only one pot
(v) having to repeat the drying process several times due to water left in the passages.

Lifestyle impositions caused by the method

87% of subjects considered SNI to be of no inconvenience to their lifestyle during the twice daily phase. 97% found it of no inconvenience during the 12 month optional phase. There were a few humourous responses such as "Yeah, now we have to go to the bathroom for the salt when cooking!" and "Yeah, we run out of shower hot water more often!" which we took as negatives.

Likelihood of longer term usage

The intended future usage by the 33 users remaining (out of 46) at the end of 16 months was:
19 (=58%) on a regular basis (equates to 41% of all original participants)
14 (=42%) when needed. (equates to 30% of all original participants)
We must assume that the balance who stopped using (13 out of the original 46, = 29%) intend not to use at all.

SUMMARY & DISCUSSION

(Rabone)

The study provides reasonable evidence that SNI significantly improves nasal symptoms in volunteer woodworkers. It shows that most woodworkers who wish to try the procedure will regard it as a useful aid (Figure 1). They will continue to use it, with varying regularity according to their own needs (Table 2). They are most likely to use it after exposure to wood dust (Table 2). The perception of symptoms measured using the questionnaires, is subject to a large measurement error, yet the results strongly indicate a reduction of nasal symptoms using SNI. The behaviour of the woodworkers by continuing to use SNI when optional is the strongest evidence of SNI's efficacy, but it is of note that the additional, if weaker questionnaire evidence supports the original hypothesis the SNI decreases nasal symptoms.

The results must apply only to volunteers and are not generalisable. It is recognised that many woodworkers (and people in general) would not wish to try it and therefore could not benefit from its use.

Potentially, 20% of people exposed to wood dust would benefit from knowing about the procedure. Volunteers were used in this study after a recruiting presentation detailing information about nasal cancer and nasal symptoms. It is estimated that only one third of those who listened volunteered for the study. Comments in the questionnaires indicated that 35 volunteers did so because of recurrent nasal symptoms and 4 because of a fear of developing nasal cancer. Obviously the study excluded wood workers who were not adventurous enough to attempt SNI or couldn't be bothered to join a 16 month study regime. The authors feel that this mimics what would occur in industry if information were to be advertised.

If tolerated, the procedure is cheap, convenient, and probably harmless. Present therapeutic options for woodworkers include vasoconstrictors (which produce tolerance and rebound phenomena) and nasal steroids. Both are expensive and use medical resources. Therapeutic options for those with nasal cancer are quite limited.

Nasal cancer questions remain unanswered. Reports from participants indicates that SNI helps removes wood dust from the nose and reduces symptoms. There is therefore reason to believe that regular SNI might reduce nasal cancer risk. The answer might not be forthcoming because this proof would require a longitudinal study of very large numbers of people over decades.

It is possible that this procedure would be of use in removing dust from the nose in other dusty occupations.

The effects of SNI on other aspects of health were not conclusively determined by this study. Results during the cross-over period were not consistent with those obtained at 1 year follow up. The questionnaires did not measure with great accuracy. In the absence of a direct physiological explanation for symptoms, results must be regarded with caution.

The study concludes that the procedure of SNI deserves more attention from industry and training groups. Maybe the technique could be introduced to woodworkers during apprenticeships or training as an option to try if nasal symptoms become a problem, if compliance with wearing of personal protection is difficult or if development of nasal cancer is of concern.

SUMMARY & DISCUSSION

(Saraswati)

Whilst not analysing the responses to my own questionnaires to the degree of Dr Rabone and showing statistical outcomes for all the hypotheses stated, many responses obtained from the participants do give indication to positive outcomes in a number of areas not covered by Rabone's analysis as well as indicating other interesting possibilities about SNI warranting more investigation and study.

I consider the main issue not successfully covered in the study was the failure of ascertaining the most beneficial frequency of a nasal wash out so as to be more sure of its causes and effects. The twice daily frequency requested during the 16 week cross-over was considered, in my experience, to be the maximum usage which could be sustained on a regular basis and which should definitely show results in its users. It is my contention that the benefits gained during that phase of the trail can be assumed (but not proven by this study) to be the result of this high usage rate (compliance of 77%, average weekly frequency of $f = 10.8$). Traditionally, the technique is advised at least once, preferably twice daily. The usage rates in the follow up year dropped dramatically when usage was optional to (on average) less than one third of this ($f = 3.02$). I believe the inconsistent results gained during this second phase are directly attributable to the frequency of usage dropping below the daily minimum of one application of SNI per day. Perhaps the study has shown how a decrease in usage renders the technique less effective??? Unfortunately no cross checks were made between frequency of usage and benefits gained. Such small numbers would probably make such endeavours meaningless. The reasons for the drop off in usage was caused by a combination of:- lack of prescriptive guidance, changes in working regime, unattended side effects, as well as human forgetfulness and busyness.

The subjects were not given any data feedback about the results of their 8 week usage. They were led to believe that the study's main focus and SNI's main purpose was to reduce wood dust in the nose. They were therefore choosing usage rates based purely on their own experiences of the technique and their own woodworking regimes. Therefore the acceptability factor as judged by the longer term usage should be treated as a minimum range indicator.

This issue needs to be closely examined in all future trials for, without a recommended "dosage", no therapeutic substance or technique can be assured of releasing its potential healing qualities. Without a recommended frequency of usage, users and potential users would have no idea of the effectiveness their actions may have which will reduce the attraction to as well as implementation of the therapy.

It would seem obvious that workers in many other dusty occupations could benefit from SNI, perhaps in an even greater way than the woodworkers have indicated here. Given the relatively large particle size of wood dust compared with say plaster dust, coal dust, fibreglass insulation, ceiling dust, or pollen, and considering that many in the wood working shops have dust extraction systems and personal protection gear on hand, it does seem likely that an even greater acceptance of nasal irrigation may be found elsewhere in industry.

A controversial area is the issue of dangers to health arising from mouth breathing. The participants reported great improvement in nasal airway clarity with a corresponding reduction in mouth breathing. Although not shown in this study the known and suspected effects of mouth breathing could indirectly be lessened by use of SNI. Common cervical and thoracic ailments may be found to benefit indirectly from clearer nostrils.

One design fault leading to weakness for data interpretation was the omission of a suitable "wash-out period" between the intervention cross overs. Certain effects of SNI may well have a "carry over effect" beyond ceasing usage.

One disadvantage of SNI in terms of its accessibility to the many people for whom it may be useful, is the need for hands on tuition. Contrary to the opinion of some users and some yoga teachers, Jala Neti (saline nasal irrigation) is not always an easy thing to learn (or rather, some noses are not easy to teach it to)! For reasons previously stated in the sections on side effects and contra-indications, an experienced instructor (or else a long time user whose own experience has conquered likely difficulties) should always demonstrate the technique firstly, and then help the new student through their first application. Depending on ease of learning, days or even weeks of follow up assistance by phone or sometimes a second lesson may be required to help those with nasal quirks gain competence with the procedure. The proportion of the total populace to whom this may apply is estimated to be 30%. Sometimes professional diagnosis of the cause of problems is needed and an instructor may need to refer the student to a GP or ENT specialist for appraisal. So therefore, it is the opinion of this teacher, and this is backed up by data in this particular research effort, that a nasal cleaning pot should only ever be sold inclusive of an instruction session and subsequent access to follow up assistance. Consequently this would make learning SNI far less commonplace. As a teacher of SNI as well as manufacturer and distributor of the nasal cleaning pots, I would not be recommending sales of nasal cleansing pots through outlets like chemist shops, health food stores or unrestricted mail order but rather through medical practitioners, naturopaths, yoga schools, hospitals, travelling instructors and other places where the time and expertise is available to offer the proper learning method.

The study gives indications of SNI's potential usefulness in other areas of health and well being. I think that the effects of wood dust upon woodworkers is only a starting point from which to explore the wider ramifications of a clean and well functioning nasal system. The technique could well be made known in medical education and community health as a cheap, easy and effective aid to better breathing and other connected faculties.

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Table 1: Perceptions of participants during the trial on a scale of 0 to 100.

	mean perception without (with) SNI	p value	mean perception control (1 year)	p value
Eye problems (Total)	27 (28) N=44	0.6271	33 (23) N=38	0.0240
Burning/itching	15 (12) N=44	0.1502	21 (10) N=36	0.0085
Dryness	16 (13) N=45	0.1458	20 (18) N=34	0.6832
Watering	12 (11) N=42	0.8878	12 (6) N=34	0.0322
Blurred vision	11 (11) N=42	0.4386	14 (13) N=35	0.6513
Puffiness	8 (7) N=42	0.6294	10 (9) N=34	0.9121
Redness	17 (16) N=44	0.4055	17 (14) N=36	0.2407
Grittiness	21 (20) N=45	0.7185	24 (19) N=34	0.0960
Nose problems (Total)	51 (37) N=44	0.0001	59 (39) N=37	0.0001
Dryness	18 (14) N=43	0.0560	15 (9) N=37	0.0183
Blocked/congested	39 (31) N=44	0.0078	40 (32) N=37	0.1065
Sinus problems	30 (19) N=44	0.0010	30 (21) N=35	0.1101
Runny nose	24 (21) N=44	0.3129	27 (15) N=37	0.0053
Nose bleeds	8 (9) N=43	0.8830	12 (7) N=37	0.0821
Post-nasal drip	14 (12) N=42	0.4536	15 (12) N=33	0.1230
Itchy/sneezing	25 (21) N=44	0.0915	35 (17) N=38	0.0001
Poor sense of smell	22 (20) N=44	0.2106	26 (17) N=36	0.0275
General problems (Total)	25 (21) N=44	0.0504	37 (20) N=31	0.0003
No energy	18 (14) N=44	0.0518	28 (19) N=36	0.0245
Headaches	18 (14) N=44	0.1221	17 (12) N=36	0.0582
Snoring	25 (22) N=43	0.1135	27 (17) N=34	0.0126
Fuzzy thinking	19 (18) N=44	0.6299	21 (16) N=37	0.0778
Sore throat	19 (13) N=44	0.0898	17 (11) N=36	0.0088
Emotional ups /downs	2 (14) N=44	0.0274	20 (18) N=37	0.5379
Frequent colds	16 (12) N=44	0.0671	16 (9) N=36	0.0263
General Health	34 (30) N=46	0.2238	28 (25) N=37	0.2393
Going to sleep	19 (21) N=44	0.3283	19 (21) N=37	0.4358
Waking up	51 (47) N=43	0.2397	49 (44) N=37	0.2275
Waking at night	48 (40) N=45	0.0193	42 (47) N=37	0.2756

Legend:

Nose, eye,	No problem=0		Some problem=50		Lots of problems=100
General problems					
Getting to sleep	Easy 0				Difficult=100
Waking at night	Never=0	Sometimes=33		Often=67	Always=100
Waking up	Refreshed=0				Tired=100
Specific symptoms	No prob1em=0	Minor problem=25	Quite annoying=50	V. annoying=75	Require treatment=100

Table 2: SNI Usage of 46 subjects after 1 Year

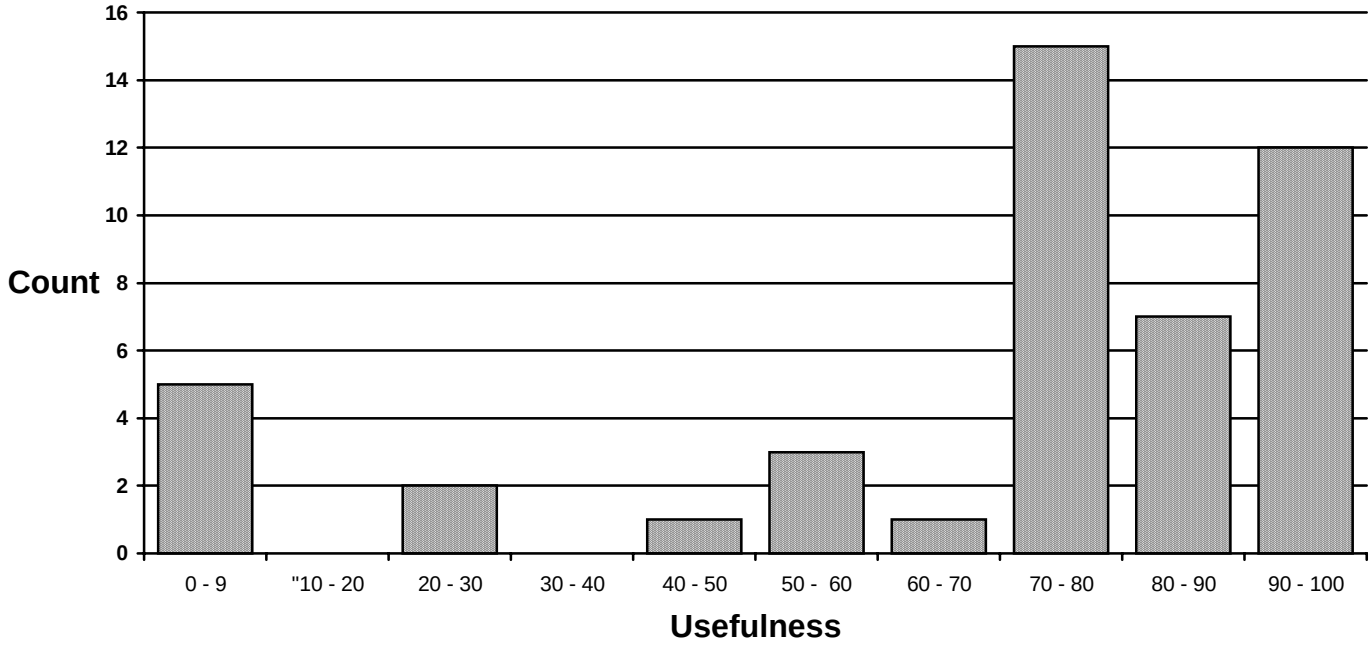
Never	Rarely	After dust exposures, occasionally	After dust exposures, Regularly	For other reasons, occasionally	For other reasons, regularly	Every day
9	4	9	12	3	2	7

Table 3: Comments of participants

ID	Comments
1	It did remove wood-dust from my nose. I didn't buy a pot. I do much less woodwork now I changed jobs."
3	"SNI definitely keeps the nasal passages clean. I don't use it as often as I should. If it was shown to have a positive effect on nasal cells I would use it more."
4	"I use it as required. It usually gives me good relief of my wood dust symptoms. I had chemotherapy and found it brilliant for headaches during that."
5	"I'm lazy. I do use it after a long dusty day or if my nose feels irritated."
6	"No adverse effects but not able to make a habit of it. Use as required."
7	"I use it every day. It suits me and helps."
8	"I am amazed how much dust gets into my nose by just being in the workshop. A lot cones out with SNI."
9	"After my stroke this year I didn't use SNI. As soon as I got back to dusty conditions it was a relief to use the pot again."
10	"Time and convenience diminished its use. I use it after very dusty days."
11	"I use it every day. I get wood dust in my nose despite he fans and mask. SNI removes the dust, my nose feels clean and I feel I am less likely to get cancer."
12	"It's great. I would benefit from doing it more often but it's still worthwhile a few times a week."
13	"Nice to do but easy to forget. I haven't managed to fit it into my daily routine but I remember to use it before and after a big day in the workshop."
14	"I only use it after being in the workshop but it helps clean my nose."
15	"I use SNI about 1-3 times a week after I do woodwork. I find SNI most pleasant to do. I like the clean 'after' feeling."
16	"Masks hurt my neck so SNI has been helpful as another option."
17	"It is useful and I use it."
18	"I find that when I use the pot after working in wood-dust it really does clean out my nose and makes sleeping and breathing easy."
19	"I have found SNI is great especially after being in any dusty environment."
21	"Wonderful beneficial. My asthma is improved."
23	"I now wash my nose out with tap water. SNI was really good but I can get the same result with tap water."
29	"Love it and will continue."
30	"I had problems using it when my nose was very blocked. I take medication which doesn't help much."
31	"I will continue using SNI as part of my after work routine. I shower and use it. It has particularly helped when I'm blocked up."
32	"No adverse effects. I use it once a week or so on days when there is significant dust."
34	"I feel lucky to have been made aware of this procedure by the study and it has now become part of my everyday life."
35	"I definitely think its a good idea. I had a series of colds and I have used it less since then. This prompting might kick me back into it.
36	"It made my head heavy. I couldn't dry my nose. Also I'm too lazy."
37	"I have not been word working much this year so I don't use it."
38	"Thumbs up!"
39	"Sorry I lost interest."
40	"It is good to see all the dust coming out. I can’t dry all the inside of my nose properly."
41	"My wife says my shoring has improved and I sleep better."
42	"It helps"
45	"I have been irregular in use but I will continue. It seems to me SNI frees nasal passages and prevents build up in nose which 'crusts'. It assists uninterrupted sleep, maintains clear sinus passages and improves my well-being."
46	"I use it when I have a stuffy nose to clear out mucous."
49	"I still use it and its there if I want it mainly for stuffy nose."
50	"I had sinus problems for a few years and they went after SNI. I changed jobs and use it now for cement dust."

No response from ID’s number 2, 20, 22, 25, 26, 33, 43, 44

Figure 1 – Perceived usefulness of SNI at 1 year follow up (n = 46)



where: 0=no use, 25= little use, 50= some use, 75=quite useful, 100=very useful

	Table 4 – Change in sense of smell								
	at 8 week crossover			At 16 wk crossover			after 16 months		
	improve	same	worse	improve	same	worse	improve	same	worse
Gp 0	0	20	2	**9**	13	1	4	14	1
Gp 1	**11**	10	1	1	15	4	1	17	0
% imp. in user group	**25**			**23**			**13**		

Table 5 – Changes in Nasal Airflow Blockages									
	First 8 weeks			Second 8 weeks			12 month period		
	Imp.	Same	Worse	Imp.	Same	Worse	Imp.	Same	Worse
Gp 0	0	20	2	**13**	8	1	7	12	1
Gp 1	**15**	4	3	2	5	13	7	11	0
All	15	24	5	15	13	14	**14**	22	1
Improvement in intervention group	**60%**			**52%**			**39%**		

Table 6 – Changes in Frequency of Nasal Airflow Imbalance				
	After 8 weeks of usage		After 12 months more of usage	
	decrease	**no change or increase**	**decrease**	**no change or increase**
Gp 0	13 responses (56%) had an av. 22% decrease	10 responses (44%)	16 responses (70%) had an av. 18% decrease	7 responses (30%)
Gp 1	19 responses (83%) had an av. 22% decrease	4 responses (17%)	13 responses (56%) had an av. 23% decrease	10 responses (44%)
All	32 responses (70%) had an av. 22% decrease	14 responses (30%)	29 responses (63%) had an av. 22% decrease	17 responses (37%)

Table 7 – Summary of Nasal Imbalance		
Number Out of 46	**Comments**	**Summary of effect**
16	Respondents had healthy nasal airflow patterns at the beginning and throughout the whole trial, to which SNI made no reported difference	No effect
9	SNI appears to have normalised nasal airflow patterns, either within 8 weeks of usage or during 12 month follow up	Good effect
5	Respondents had fluctuating nasal airflow patterns (most probably caused by chronic nasal mucus blockages) which seemed unaffected by SNI	No effect
5	Respondents had an unchanging nasal airflow blockage (always on the same side) throughout the whole trial indicating a structural nasal blockage upon which SNI made no difference	No effect
4	Respondents recorded a bad response to the technique (ie adverse nasal airflow reactions)	Adverse effect
7	non-specific results due to incomplete data	Undefined effect
46	**TOTAL**	

Table 8 – Changes in Frequency of Mouth Breathing				
	At beginning of trial	At 8 week crossover	At 16 wk crossover	After 16 months
Gp 0 av	43	40	**30**	38
Gp 1 av	47	**31**	34	32
All av	45	36	32	35
% decrease in user group		**16%**	**13%**	

Table 9 – Perceived Change in Frequency of Mouth Breathing									
	At 8 week crossover			At 16 wk crossover			After 16 months		
	Improve	Same	Worse	Improve	Same	Worse	Improve	Same	Worse
Gp 0	0	21	2	**8**	13	1	5	13	1
Gp 1	**6**	13	1	2	12	5	6	12	0
All	6	33	3	10	25	6	**11**	25	1
% of respondents improved	**24**			**32**			**24**		

Table 10 – Difficulties Experienced					
		On first occasion	During first week	During first 8 weeks	During 12 months
(a)	no problems	21	32	31	30
(b)	water running into mouth	9	3	4	0
(c)	slow flow caused by blocked nostril(s)	5	3	6	3
(d)	finding correct head angle	8	0	0	0
(e)	dry nose properly	1	3	2	2
(f)	stinging from wrong salt & water mix	0	3	3	0
(g)	sealing pot at nostril	1	0	0	0
(h)	nose bleed	1	3	1	0
(i)	Pain/pressure in sinuses	1	0	1	1
(j)	Other	1 tender nostril 1 worry of infection	3 Headache 1 bad congestion	1 sinus infection 1 heavy flu	2 water in ears
	No Response	0	0	0	8

Table 11 - Overall Intended and Actual Usage Rates in Whole Trial and Beyond									
	8 week phase	During the 12 month phase				Beyond the study's 16 months			
Freq.	2 x daily	Not at all	Need to basis	Regular basis	No Response	Not at all	Need to basis	Regular basis	No Response
Intended	46 (100%)	1 (2%)	8 (18%)	33 (72%)	4 (9%)	1 (2%)	18 (39%)	20 (43%)	7 (15%)
Actual	(av) 70%	3 (7%)	28 (61%)	7 (15%)	8 (17%)	?	?	?	?

Table 12 –
User compliance during the 16 week cross over phase
(where 100 = 2 x daily unfailingly)

0	10	40 40 40	45	49	50 50 50 50	60	70	75 75 75 75 75	80	85 85 85	90 90 90 90 90 90 90 90	91	92	93	95 95 95 95 95 95	98 98 98	99	100 100 100	**T O T A L**
1	1	3	1	1	4	1	1	5	1	3	8	1	1	1	6	3	1	3	**46**
Overall average compliance = 77%																			

Table 13 – Reasons for Fluctuation in Usage & Lack of Compliance In the 8 week Cross over period	
Occasionally did it late due to social engagements	just a bit busy
woke late and rushed off to work	a few times a bit bothersome
forgot towards end of 3 days off woodwork	forgot a few mornings in the rush
running late	in a hurry
forgot evenings after a night out	forgot when nose felt clear
didn't take pot when away from home	unsure about 4 hour rule so didn't do it
forgot (when not woodworking)	didn't do it when camping.
forgot on busy mornings	unavoidable problems at times
forgot 2 mornings, gave up when camping 3 days	forgot when away or home very late
forgot and sometimes not enough time	missed occasionally after a late night out
forgetting to take pot away on weekends	forgot when in a rush to go out
forgot to pack the pot on weekend trips	not always necessary
herpes at nasal opening for 2 weeks and didn't do it	sometimes forgot the morning session
forgot sometimes when rushing for work	when away on weekends
Didn't do when nose felt clear	rushed to gym early
lack of time	forgetfulness
when routine broken eg away from home	forgot some afternoons
has the flu twice so didn't do it	too preoccupied to do it before teatime
reduced to 1x daily, but twice when dusty	mornings disagreed with me
since not in workshop 1x daily was enough	had breakfast by mistake
used only once per day for 5 days and then not used since week 7 due to severe head cold	stopped doing regularly due to nose bleeds but continued from time to time
seemed to be more prone to catch colds	only did it once a day for 5 weeks
I found when I use it 2x day I got head cold symptoms and I'm sure I dried my nose properly	tried for 1st week and gave up

Table 14 – Usage During 12 month follow up					
	Beginning	Trend	End	Average	Comments on usage during 12 months
abruptly stop		2			- Did not use when nose very blocked or forgot
lessen then stop		10			- Use only after dusty or paint fumes when nose is blocked or irritated
lessen but continue		20			- Only used with irregular exposure to wood dust
stayed the same		12			- SNI decreased as exposure to wood dust decreased
increased		0			- Stopped working with wood
fluctuated		2			- Use it dependent on time in the workshop
not at all	4		13	3	- Would like to use more
less weekly	7		10	12	- Out of nose, out of mind
1 - 3 x week	10		8	8	
3 - 4 x wk	6		7	8	
1 x day	5		5	5	
1 - 2 x day	5		2	2	
reg 2 x day	1		0	0	
No Response	8		1	8	
Total	**46**	**46**	**46**	**46**	

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(54) **NASAL-NASOPHARYNGEAL CLEANING SYSTEM**

(76) Inventor: **Jin-Zhou Liu**, 462 Burns Dr. North, Westerville, OH (US) 43082

(*) Notice: This patent issued on a continued prosecution application filed under 37 CFR 1.53(d), and is subject to the twenty year patent term provisions of 35 U.S.C. 154(a)(2).

Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: **09/071,459**

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Related U.S. Application Data

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(51) **Int. Cl.**[7] **A61M 35/00**

(52) **U.S. Cl.** **604/289**; 604/94.1

(58) **Field of Search** 604/289, 290, 604/313, 315, 316, 94, 35, 36, 73; 128/207.18, 200.24, 200.11; 606/162, 196, 199; 600/538

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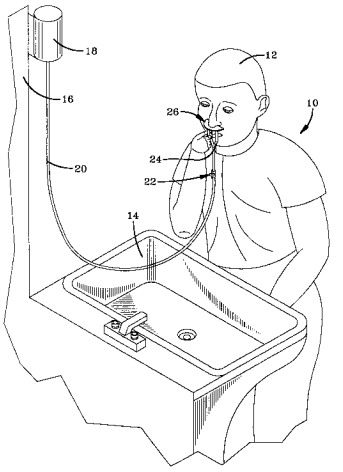
(57) **ABSTRACT**

A nasal-nasopharyngeal-cleaning (NNC) system is disclosed for removing harmful substances from a human's nasal and nasopharyngeal cavities. Harmful substances herein include infectious agents, chemicals, dust, small particles and dirt deposits in nasal cavities and in the nasopharynx. The NNC system includes a NNC solution, a solution container, a liquid transfer tube, a valve means and a flat-head nostril fitting. The two-step cleaning process comprises cleaning the nasal cavity first with the NNC system and then cleaning the nasopharyngeal cavity with the NNC system.

14 Claims, 3 Drawing Sheets



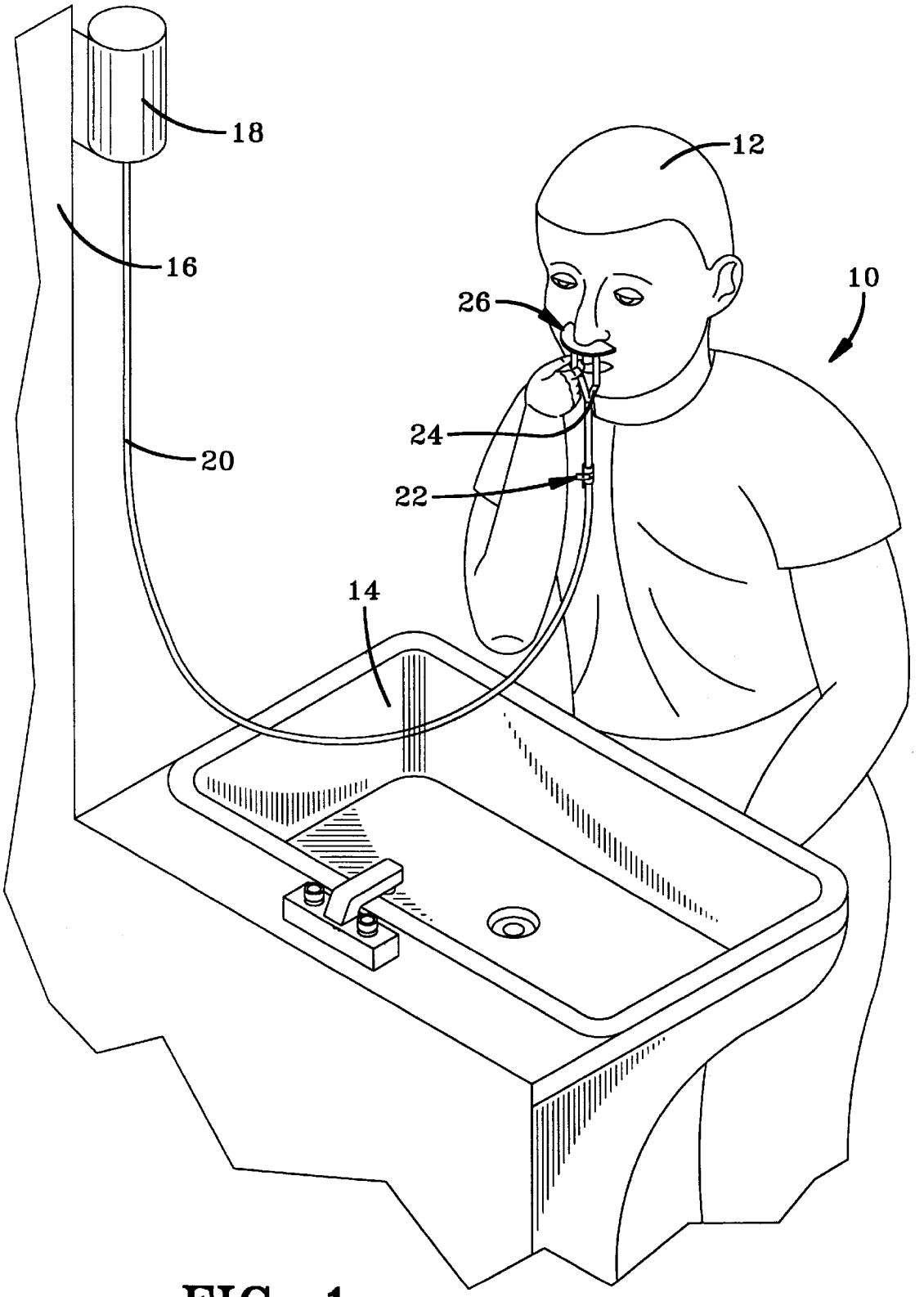
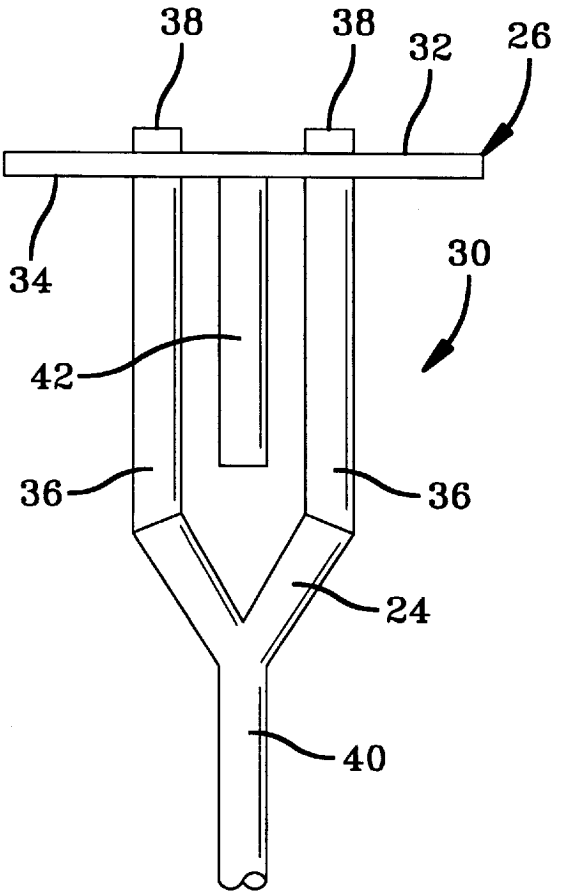
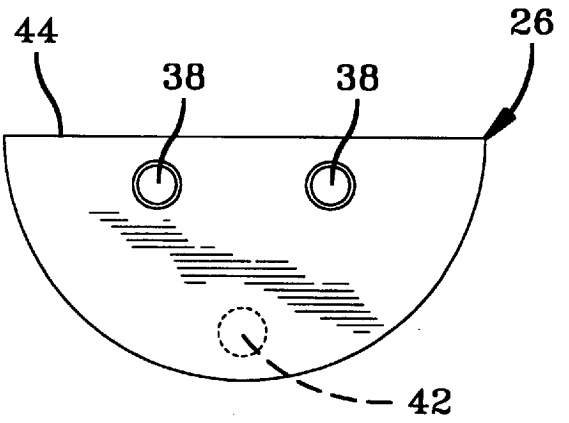


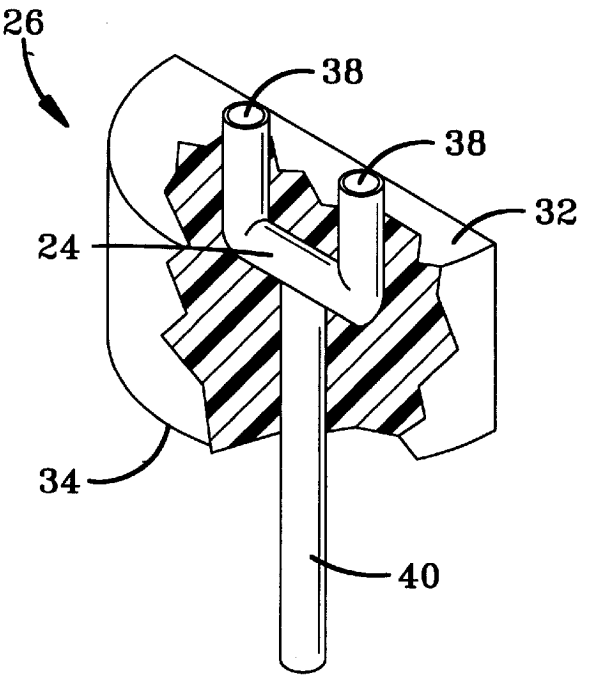
FIG-1



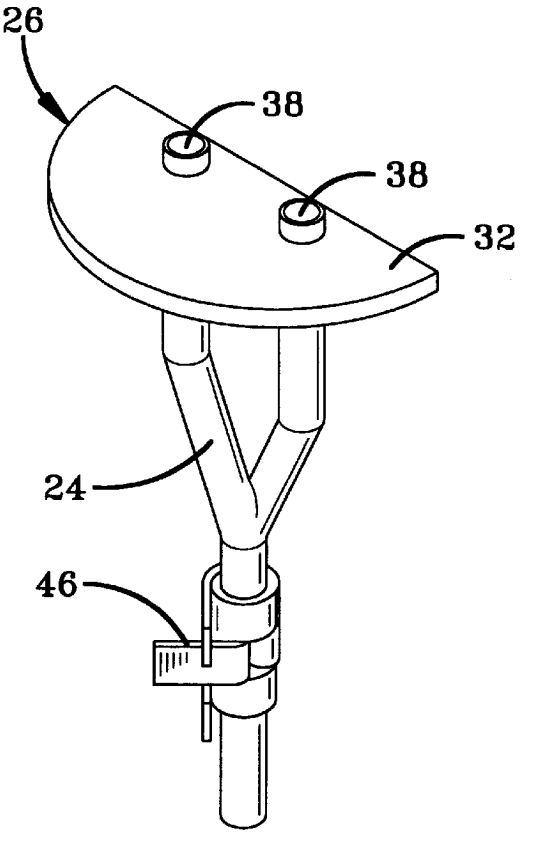
FIG–2



FIG–3



FIG–4



FIG–5

NASAL-NASOPHARYNGEAL CLEANING SYSTEM

RELATED APPLICATIONS

This application is a continuation-in-part application of U.S. Ser. No. 08/788,329 filed Jan. 27, 1997, now abandoned.

TECHNICAL FIELD OF THE INVENTION

The present invention relates generally to a nasal-nasopharyngeal-cleaning (NNC) system to be used in removing harmful substances from a human's nasal and nasopharyngeal cavities. Harmful substances include infectious agents, chemicals, dust, solidified mucous and dirt which adhere to the nasal cavities and the nasopharynx. The NNC system of the present invention comprises the NNC solution and its container, a liquid transferring tubing system, optionally, a valve for controlling the NNC solution flowing through the NNC system and a flat-head nostril fitting which optionally comprises a means for holding the nostril fitting against the nostrils. A two-step method of using the NNC system is also provided.

BACKGROUND OF THE INVENTION

Influenza viruses A, B and C; respiratory syncytial viruses A and B; parainfluenza viruses and the like are common causes for respiratory tract infections in humans. Presently, there are no effective drugs or vaccines to treat or prevent these viral infections. Human adults and school children are constantly exposed to these infectious agents at work and/or at school and may also be carriers of these infectious agents to and from the home. A practice of nasal and nasopharyngeal cleaning can reduce the microbial load of those tissues and reduce the chance of spreading these disease-causing microorganisms at home, school and at work.

Many disease-causing agents exist in the nasal and nasopharyngeal cavities. The shedding of communicable infectious microorganisms in the nasal and nasopharyngeal cavities causes spreading of the disease from the upper respiratory tract to the lower respiratory tract of the carrier. Shedding also causes the spreading these infectious agents to other people through sneezing and/or coughing (Hall, C. B., Douglas, R. J., in an article entitled: "Quantitative shedding patterns of respiratory syncytial virus in infants", *Journal of Infectious Diseases,* 132: 151–156, 1975; and Hall, C. B., Geiman, J. M., Breese, B. B., and Douglas, R. J., in an article entitled "Parainfluenza virus infections in children: Correlation of shedding with clinical manifestations", *Journal of pediatrics,* 91: 194–198, 1977). For most viral infections, antibiotic prevention and/or treatment is generally ineffective. It would thus be beneficial to have a practical system and/or method to remove these disease causing agents from the human body. In a manner similar to brushing one's teeth, nasal and nasopharyngeal cleaning in the general population will have a number of healthy benefits.

Nasal washes, nasopharyngeal swabbing and nasopharyngeal aspiration have previously been used to obtain specimens from patients for the determination of microbial pathogens (Hall, C. B., Douglas, R. J., in an article entitled: "Clinically useful method for the isolation of respiratory syncytial virus", *Journal of Infectious Diseases,* 131: 1–5, 1975). However, these procedures and devices were used only to obtain samples and are not effective in removing the infectious agents from the nasal and nasopharyngeal cavities of a human.

Ephedrine nasal washes have been used in the treatment of sinusitis and other nasal and paranasal symptoms and allergic rhinitis, (Shaikh, W. A., in the *Journal of Allergy Clinical Immunology*, Vol. 96, No. 5, part 1: 597–600, 1995). The Shaikh procedure uses a 1% ephedrine hydrochloride solution in a normal saline solution and a Higginson's rubber syringe. After the rubber syringe was filled with the wash solution, the nozzle of the syringe was introduced into one nostril and the bulb of the syringe was pressed to push the fluid into the nasal cavity. As described by the author, most of the fluid exited from the same nostril, but some fluid exited through the other side of the nose after passing through the nasopharynx. This procedure was performed once every forty-eight (48) hours for a four (4) week period and caused a significant improvement in symptom scores and peak nasal inspiratory flow rates in patients with perennial allergic rhinitis as compared to those treated with a placebo wash (normal saline only). This procedure, however, has the following disadvantages:

(1) ephedrine was the key factor for the effectiveness of this procedure, but this chemical is not suitable for use by the general public on a daily basis;

(2) this procedure was performed only on patients with perennial allergic rhinitis;

(3) this procedure was mainly washing of the nasal cavity, the nasopharyngeal cavity was largely uncleaned;

(4) the apparatus used was clumsy and uncomfortable to use; and

(5) this procedure was performed once every forty-eight (48) hours which is not frequent enough to remove harmful materials from the nasal and nasopharyngeal cavities on a daily basis.

The Shaikh procedure would permit the infectious microorganisms to be brought into and spread around at home, office, school, or day care center. Therefore, there is a need to develop a generally acceptable and more effective nasal and nasopharyngeal cleaning system.

Nasal and nasopharyngeal cavities are common places for holding environmental allergens, such as pollen, fungal spores, animal body-originated dustings and volatile chemicals. These harmful agents cause allergic reactions and other ill consequences. Nasal and nasopharyngeal secretions combine with environmental particles to form big matters (solidified mucous) in the nasal cavity. These big matters narrow the airway and make the individual feel uncomfortable. Prior to the present invention, an apparatus and method to easily and effectively remove harmful agents from the nasal cavity and to prevent the formation of and remove the big matters in the nasal cavity has not been available to medical professionals and to the general public.

The human body is the only natural host for many kinds of pathogenic microorganisms. Nasopharyngeal mucous is one of the prominent places of viral shedding. These pathogens include, but are not limited to, influenza viruses, respiratory syncytial viruses and the like. The nasopharyngeal shedding of these pathogens is the major cause of person-to-person transmission. One skilled in the art will appreciate that those communicable pathogenic microorganisms present in the nasal and nasopharyngeal cavities will be decreased in quantity after the cavities have been cleaned. After nasal and nasopharyngeal cleaning, these infectious agents will be less likely to spread horizontally to non-carriers and/or vertically to the lower respiratory tract of the carrier.

Environmental pathogens can be encountered by inhalation. *Legionella pneumophila*, the causative agent of

Legionnaire's disease presents in aerosols. It is generated from air conditioning cooling towers, cold water taps, showers and other water systems. Depending upon wind speed, *Legionella pneumophila*, in these aerosols, can be carried up to 500 meters and infect a large number of individuals. Promptly removing these aerosols from the nasal and nasopharyngeal cavities will greatly reduce the incidence of infection.

Several methods have been reported to be useful in cleaning nasal and nasopharyngeal cavities. Grossan invented a nasal irrigation system (NASAL IRRIGATION SYSTEM, U.S. Pat. No. 3,047,145, issued Nov. 12, 1974) which provided for an isotonic saline solution under pressure flowing into one nostril, passing through the nasolacrimal duct, where the solution passes, sequentially, into the ostia of the frontal sinus, the ethnoids, the maxillary and the sphenoid. The solution then moves past the outlet of the eustachian tube and then through the nasopharynx to the upper posterior portion of the other nostril and outwardly therethrough, passing the same ducts and ostia, in reverse sequence, before being discharged from the second nostril. This system has numerous and serious shortcomings. First, the cleaning solution cannot be completely drained from the deep regions of certain sinuses due to their cavity structure. Second, certain infectious agents might be moved from one place to another and stay there to cause a new infection. Third, some dried or hard matters in the nasal cavity might be carried inward to the sinuses. Fourth, hard matters might cause a blockage when they are forced to flow into narrow spaces, such as the eustachian tube. Therefore, the reported nasal irrigation system of Grossan cannot be widely used by the general public for cleaning nasal and nasopharyngeal cavities.

A method of administrating a pharmacological solution into the nasal cavity of a patient was described by Löfstedt (METHOD FOR DRUG ADMINISTRATION, U.S. Pat. No. 5,116,311, issued May 26, 1992). Although the author mentioned that there was a possibility to use the reported method to irrigate the nasal cavity, the method and device of this patent were designed to administer pharmacological solutions into the nasal cavity, not to provide a flow of fresh cleaning solution continually into the nasal cavity, since the compressible container of Löfstedt not only forced the solution into the nasal cavity, but also aspirated the solution with nasal secretions and other contaminants back into the container. The effectiveness of the drug administration method was also heavily dependent on the patient's head bending angle. This method and device was designed to administer drugs into the nasal cavity for treating diseases over a short period of time. The Löfstedt device was not designed for and would not be useful to clean nasal and nasopharyngeal cavities by the general public on a daily basis.

Pena invented a device for treating infections of the nasal fossae (DEVICE FOR CIRCULATING TREATING FLUID THROUGH THE NASAL FOSSAE, U.S. Pat. No. 4,029,095 issued Jun. 14, 1977). The Pena device was designed to be used by patients to treat diseases, not for the general public to clean nasal and nasopharyngeal cavities.

Babbitt et al. invented a portable device used to aspirate and remove fluids from nasal and sinus cavities (SINUS EVACUATOR APPARATUS, U.S. Pat. No. 4,403,611 issued Sep. 13, 1983). Since this device only aspirates the sinus fluids from the nasal and sinus cavities, the dirts and pathogenic microorganisms adhering to the surface of the nasal and nasopharyngeal cavities cannot be removed if they are not dissolved in a washing fluid.

The above systems and methods described in Grossan, Löfstedt and Babbitt et al. all utilize a conical nostril fitting. The conical nostril fitting creates a certain amount of "dead space" between the inserted part of the nostril fitting and the wall of the nasal cavity, which a cleaning solution cannot reach (if used in the Grossan et al. devices). To improve the efficiency of nasal cleaning, a new type of nostril fitting is needed. The prior art has failed to suggest a NNC system that is simple in construction and easy to use and that allows for the cleaning of the nasal and nasopharyngeal cavities in the separated steps. Since the nasal cavity: (1) is naturally in the lowest position as compared to the nasopharyngeal cavity and the other sinus cavities; (2) collects secretions from other sinus cavities; and (3) is the first place to meet and store the foreign matters, it is obvious that the first step of the nasal and nasopharyngeal cleaning method should be to initially clean the nasal cavity. Therefore, a new step-by-step cleaning method is disclosed in this invention.

BRIEF DESCRIPTION OF THE DRAWINGS

These and other objects of the present invention will be apparent to those skilled in the art from the following description of the invention. The invention is described with reference to the following Figures:

FIG. **1** is a perspective view of a person using the NNC system of the present invention, shown leaning over a lavatory or washbasin, and holding the inventive device to the bottom of his nose;

FIG. **2** shows a frontal plan view of the flat-head nostril fitting, "Y" fitting (fluid division means) and handle;

FIG. **3** is a top plan view of one embodiment of the flat-head nostril fitting, the handle being shown in dotted lines;

FIG. **4** is a perspective view of the flat-head nostril fitting wherein the fluid division means (in this embodiment, a "T" fitting) is embedded in the flat-head nostril fitting; and

FIG. **5** is a perspective view of the flat-head nostril fitting with a valve means disposed between the "Y" fitting and the NNC solution container (not shown).

DETAILED DESCRIPTION OF THE DRAWING

In FIG. **1**, there is indicated generally at **10** a patient using the NNC system of the present invention. It will be noted that the patient's body is bent so that his head **12** is slightly bent over a conventional lavatory or washbasin indicated generally at **14** for receiving the discharge of the NNC solution from a nasal cavity. Adjacent to the washbasin **14**, and here shown as mounted on a wall **16**, is a container **18** of NNC solution. The solution is fed by gravity through a flexible hose **20** which is connected to a valve means **22** which is then connected to the fluid division means fitting **24** (here shown as a "Y" fitting). The "Y" fitting is in connective relationship to the flat-head nostril fitting **26**. FIG. **1** shows the patient's right hand holding the flat-head nostril fitting **26** to the underside of the patient's nostrils through holding the handle **42** shown in FIG. **2**.

FIG. **2** indicates generally at **30** one embodiment of the NNC system wherein the flat-head nostril fitting **26** has upper surface **32** and lower surface **34**. The flat-head nostril fitting is connectively engaged with the fluid division means shown here as a "Y" fitting **24**. The two arms of the "Y" fitting **36** extend through the flat-head nostril fitting **26** to create projections **38** above the flat-head nostril fitting upper surface **32**. The fluid transfer tubing **40** is in connective engagement with container **18** (not shown). Handle **42** extends from the lower surface **34** of the flat-head nostril fitting **26**.

FIG. **3** is a top plan view of one embodiment of the flat head nostril fitting **26**. In this embodiment, the flat-head nostril fitting is generally semi-circular in shape. The straight edge **44** of the flat-head nostril fitting **26** is intended for engagement against the patient's upper lip. Projections **38** result from the extension of the arms of the fluid division means through the flat-head nostril fitting. The spacing of projections **38** relative to straight edge **44**, and to one another are such that most human beings upon placement of a device against their upper lip, will find projections **38** inserted into each nostril. While this embodiment is semi-circular in configuration, it should be understood that other shapes such as squares, rectangulars, triangles, hexagons and the like can also be used. The feature of the flat-head nostril fitting that is most critical is that straight edge **44** be of sufficient length and configuration so that proper sealing of the nostrils can be accomplished with top surface **32** of the flat-head nostril fitting **26** while projections **38** enter each nostril of the patient.

FIG. **4** is a perspective view in partial cross section of yet another embodiment of the invention wherein the fluid division means **24**, seen here as a "T" fitting, is embedded within the flat-head nostril fitting **26**. The nostril fitting in this embodiment possesses top surface **32** with projections **38** extending therefrom. Bottom surface **34** of the flat-head nostril fitting **26** may have a handle means adapted thereto (not shown). The tubing **40** is connected to a valve means (not shown).

FIG. **5** is a perspective view of another embodiment of the NNC system wherein the flat-head nostril fitting **26** possesses projections **38** through its top surface **32**. The fluid division means **24**, shown here as a "Y" fitting, is connectively engaged with a valve means **46**. This valve means may be any valve type known in the art and may be a squeeze type or push/pull type valve known to those in this field. Other valve means would include those associated with enteral nutrition feeding sets wherein a clamp flow regulator on the tubing permits easy, accurate flow rate adjustment. Preferably, the valve means **46** is configured such that it is closed in normal position and that only upon manual activation would the valve be open, allowing NNC solution to flow from the container **18** through tubing **20** into "Y" fitting **24** through projections **38** and into the nostrils of the patient.

BRIEF SUMMARY OF THE INVENTION

The present invention provides a nasal and nasopharyngeal cleaning (NNC) system which is used to reduce the load of disease-causing agents; to reduce the concentration of infectious agents in the nasal and nasopharyngeal secretions; to prevent these infectious agents from presenting in aerosols/droplets; and to reduce the duration of environmental allergens and other harmful materials staying in nasal and nasopharyngeal cavities. The NNC system includes a washing solution and its container, a liquid transferring tube system and an all-purpose nostril fitting. The NNC system of the invention is portable and constructed of readily available and inexpensive materials. The NNC system is to be used in a method wherein the nasal cavity is cleaned first and then the nasopharyngeal cavity is cleaned thereafter. The method disclosed for using the NNC system may be applied by an individual to him or herself as often as required or deemed convenient.

Thus, there is disclosed a nasal and nasopharyngeal-cleaning (NNC) system comprising a NNC solution, a container for said NNC solution, a tubing system, a valve means and a flat-head nostril fitting. The NNC system may additionally comprise a fluid division means between the valve means and the flat-head nostril fitting. The fluid division means may take the form of a "Y" fitting, a "T" fitting and the like. Numerous variations are possible. Further, the fluid division means may be disposed within the flat-head nostril fitting.

There is further disclosed a nasal and nasopharyngeal cleaning (NNC) system for use by a patient comprising:

1) a container with a volume of at least 100 ml connected via tubing to a valve means;
2) said valve means being in the closed position nominally and open upon manual actuation;
3) said valve means connected via tubing to a fluid division means, wherein said fluid division means is selected from "Y" fittings and "T" fittings;
4) said fluid division means passing through a flat-head nostril fitting, said flat-head nostril fitting comprising a handle and two openings for passage of said fluid division means;
5) said flat-head nostril fitting comprising at least one straight edge for engagement with the upper lip of said patient and said two openings being positioned relative to said straight edge and to each other such that said fluid division means passing through said opening will insert into the nostrils of said patient.

DETAILED DESCRIPTION OF THE INVENTION

The present invention provides a new nasal and nasopharyngeal cleaning (NNC) system and a method of cleansing the nasal and nasopharyngeal cavities. In general, the NNC system comprises:

(1) a nasopharyngeal cleaning solution comprising at least 0.9 gms of NaCl per 100 ml of water;
(2) a container for said NNC solution, said container comprising a hanging means and a means for connection to tubing;
(3) a valve;
(4) a fluid division means; and
(5) a flat-head nostril fitting comprising a handle and at least two openings.

The NNC solution is provided to the nostril fitting through the force of gravity or by a manual and/or mechanical pump. In the embodiment where a pump is used, the pump may be a motor driven pump unit, preferably driven by way of a suitable micromotor. However, the pump means can also be a manually operable pump means in the form of an elastic bulb capable of being manually compressed, and capable of expanding when released by the operator; this particular pump means having at its suction inlet and pressure outlet, respectively, a pair of one way valves which permit the fluid to flow only from the suction tubular means into the plastic bulb when the latter expands and from the elastic bulb only into the pressure tubular means when the elastic bulb is compressed by the operator.

The NNC solution useful in the system and method according to the current invention may be water or an aqueous solution. The most common isotonic solution is a normal saline solution, which contains 9 g of sodium chloride in 1 liter of water (0.9% by weight). This solution can be used as a basal cleaning solution. It has been experienced that a phosphate buffered water solution (pH 7.4) containing sodium chloride at a concentration 1.5 times higher than 0.9% normal saline, resulted in a more comfortable nasal and nasopharyngeal cleaning. Thus, a phosphate buffered

aqueous solution containing about 1.35 g of sodium chloride per 100 mL water is a preferred NNC solution. The NNC solution may also contain an appropriate amount of an anti-attachment agent. Representative anti-attachment agents include various carbohydrates which prevent or reduce the attachment of microbial pathogens to the nasal and nasopharyngeal cavities. The solution may also contain anti-allergy agents, or suitable detergents to improve the cleaning efficiency. The NNC solution may also contain corticosteroids, antibiotics, antihistamines, and/or mucolytic agents. The NNC solution may also contain a suitable decongestant such as phenylephrine hydrochloride. Pharmaceutically active agents should be employed in the NNC solution only under the direction of a physician. The temperature of the NNC solution, when administered, is typically about 20 to 40° C. and more preferably about 30 to 37° C.

The container for NNC solution can be made of any convenient material and may take almost any shape. The container can hold up to 50,000 mL of solution, preferably it can hold 100 to 10,000 mL solution and more preferably, it can hold at least 100 mL of NNC solution. This container can be made from all kinds of safe materials which do not release any chemicals into the solution and do not absorb any chemicals from the solution. The common materials include, but are not limited to, plastic, rubber, glass, metals, china, etc. One end of the container preferably has a means to hang the container above the head of the patient and the other end is open with means to be connected to the tubing system.

A flexible tubing system is used to transfer the NNC solution to the flat-head nostril fitting and into the patient. The tubing may be from 30 cm to 2 meters in length. Preferably, it is between 0.5 to 1 meter in length. The inner diameter of the tubing is between 2 to 10 mm. Preferably, the inner diameter is between 3 and 7 mm. The material of the tubing may include, but is not limited to, plastic, rubber or any other suitable inert material. One end of the tubing is connected to the container of the NNC solution and the other end is connected to the valve means.

Disposed between the NNC container and the flat-head nostril fitting is a valve and a fluid division means. The valve allows the patient to control the flow of NNC solution from the container, through the nostril fitting and into his or her nasal cavity. In a preferred embodiment, the valve, which may be of any known and convenient design, is near to or incorporated into the flat-head nostril fitting as will be further discussed below.

The flexible tubing system may also comprise a fluid division means such as a "Y" fitting disposed between the valve means and the nostril fitting. The "Y" or "T" fitting takes the NNC solution and divides it so that each nostril is afforded simultaneous essentially equal irrigation. In one embodiment of the invention, the "Y" or "T" fitting is integrated into the flat-head nostril fitting.

The two arms of the fluid division means will have the same diameter enabling the smooth connection of the tubing system to the nostril fitting. The connection between the tubing, the valve and the nostril fitting may be formed by contraction force of the elastic tubing or by a plastic or metal screw connection. The combination of the NNC container, the tubing system, the valve and the connections are similar to the apparatus used in hospitals for intravenous infusion or the apparatus for gastric tube feeding.

One important aspect of the NNC system according to this invention is the flat-head nostril fitting. The nasal fitting substantially prevents the NNC cleaning solution from leaking from the nostril during the irrigation step of the process. It has been observed that different people have different shaped nostrils and that not all people have round nostrils. Some people have an irregular opening, like a long narrow channel. Therefore, it is impossible to use the conical shaped nostril fitting of the prior art to prevent the liquid from leaking from the nostrils of these people. Additionally, the conical shaped nostril fittings of the prior art always create a certain amount of dead space between the inserted part of the nasal fitting and the wall of the nasal cavity. The newly invented nostril fitting, as shown in FIGS. **2–5**, is called a "flat-head nostril fitting". The flat-head nostril fitting has the following characteristics in a preferred embodiment:

(1) It has a semi-circle head with a diameter of from 2.0 to 8.0 cm and a thickness of 0.1 to 0.5 cm. The function of the straight edge of the semi-circle (or any other shape) is for placement against the upper lip of the patient. The upper surface of the fitting is placed against the bottom of the nose so as to reduce liquid leakage from the nasal cavity during the cleaning process.

(2) The flat-head nostril fitting has 2 openings therethrough which allow passage of the tubing from the fluid division means. The openings have a diameter which is identical or slightly less than the outside diameter of the tubes penetrating through the head so as to provide for frictional engagement. The distance from the center of one opening to the center of the other opening is from 0.2 to 1.0 cm and is preferably about 0.5 cm so as to match the average distance between the center of each nostril of the patient.

(3) The length of the two tube-arms of the fluid division means is from 5 to 20 cm. A 10 cm or less length is preferred. In another embodiment of the nasal fitting, the fluid division means is embedded in the flat-head nasal fitting, as set forth in FIG. **4**. In this embodiment, the thickness of the head is increased to accommodate the fitting. The embedded "T" shaped configuration is preferred so as to keep the thickness of the head to a minimum.

(4) The outside diameter of the tubes penetrating through the nostril fitting head is preferably from 0.2 to 0.5 cm.

(5) The length of the tubing projecting above the nostril fitting head, items **38** in FIGS. **2–5**, is from 0.0 to 0.5 cm, preferably 0.1–0.4 cm. The tube will preferably have a diameter smaller than the diameter of the patient's nostrils. This is important so as to prevent the creation of any dead space, as discussed above, during the cleaning process.

(6) The nostril fitting may optionally comprise a handle means. While the NNC system is easily used by the patient without a handle means, it has been found convenient for the patient to have some feature attached to the nostril fitting to facilitate holding of the nostril fitting to the bottom of the nose. In one embodiment, the handle means comprises a rod projecting form the bottom surface of the head. The handle may have a diameter of about 1.0 cm and a length of about 2.0 cm. This handle may also be square or rectangular in shape. This handle, no matter what configuration, is to provide ease for the cleaner to hold the nostril fitting against the nostrils to introduce and to release the NNC solution during the cleaning process.

(7) Plastic, rubber, stainless metal materials or other safe materials can be used to make the flat-head nostril fitting. Soft, biocompatible silicons are preferred.

A driving force for the NNC solution flowing through the NNC system must be provided. Natural gravity force or a manual and/or a mechanical pump can be used to force the NNC solution into the nasal and nasopharyngeal cavities. Preferably, the force used to move the fluid through the tubing to the nostrils is produced by hanging the container

of NNC solution at a position of at least 0.1 meter above the patient's forehead. The force used to move the solution may be also produced by a hand or foot operated pump or an electrically operated pump.

EXAMPLE I

Cleaning of the Nasal and Nasopharyngeal Cavities

The method of using the NNC system is simple and readily accomplished by the patient. The NNC solution was made by dissolving 2.7 g of table salt into 200 ml of warm drinkable water. One minute before use, the solution was measured to be 37° C. 100 ml of this solution was charged to the NNC solution container. The container was suspended form a hook projecting from the wall of the bathroom at about 50 cm above the patient's forehead.

Cleaning was accomplished as follows:

Step 1:

The patient was in an upward position with the upper part of the body bending slightly forward to have the face above the washbasin, similar to a "teeth brushing" position. The patient used one hand to open the valve to allow the NNC solution to flow through the NNC system. The other hand held the flat-head nostril fitting against the bottom of the nose to allow the NNC solution to reach the nasal cavity. After the NNC solution filled the nasal cavity, the patient withdrew the nostril fitting from the bottom of his nose, after closing the valve, to allow the solution combined with the nasal cavity secretions to flow/fall into the washbasin. He repeated this liquid in-and-out process several times. The patient then closed the valve of the NNC system after his nasal cavity was filled with the NNC solution. While one hand held the nostril fitting in position, he used the other hand to gently rub his nose to allow the dried and hard matters to be released from the nasal cavity. Then the washing solution in the nasal cavity was released into the washbasin. He repeated this in-depth cleaning process several times. Through the mirror, he saw his nasal cavity was very clean. The cleaning result was verified by a medical examiner (physician).

Step 2: Cleaning of the Nasopharyngeal Cavity

The same patient proceeded to the next step in the process; cleaning of his nasopharyngeal cavity. He was in an upward standing position. After his nasal cavity was cleaned, he placed the nostril fitting against his nose and let the NNC solution fill the nasal cavity without releasing it. When the nasal cavity was full of the NNC solution, he bent his head slightly backward to let the solution naturally flow through the nasopharyngeal cavity. The patient felt that there was some liquid in his mouth. When his mouth was filled with a comfortable amount of solution, he turned off the NNC solution supply (closed the valve) and returned his head to the teeth brushing position. The washing solution was then released from the mouth to the washbasin. This process was continued for two (2) minutes. The medical examiner/physician found that the patient's nasopharyngeal cavity was clean. During Steps 1 and 2, the patient did not feel any pressure from any sinus cavity, because the liquid did not flow into any of the sinuses above his nose.

EXAMPLE II

Cleaning the Nasal Cavity by an Adult

The NNC solution contained sodium chloride at a concentration of 1.35% by weight. One minute before use, the NNC solution was measured to be 37° C. The patient added this solution into the NNC solution container. This container was hung from the wall of the bathroom at about 60 cm above the patient's forehead. The patient placed the nasal fitting under his nose. After opening the valve, the NNC solution flowed through the tubing and the nostril fitting and filled the nasal cavities of the patient. The patient removed the nostril fitting to let the solution flow out of his nasal cavities. By repeating this procedure, several big matters were removed from the nasal cavity. This procedure was repeated several times and the patient's nasal cavities were then examined. The medical examiner/physician could not see any dirty materials left in the patient's nasal cavities.

EXAMPLE III

Cleaning the Nasopharyngeal Cavity by an Adult

The same patient as mentioned in Example II, continued with the method to clean his nasopharyngeal cavity. After cleaning his nasal cavity, he placed the nostril fitting against the nose and allowed the NNC solution to flow through the nasopharyngeal cavity until the solution reached the patient's oral cavity. The patient simply spit this solution into the washbasin. By repeating this procedure, his nasopharyngeal cavity was cleaned. He felt that the air he inhaled was much fresher than before he cleaned his nasopharyngeal cavity.

EXAMPLE IV

Cleaning Nasal and Nasopharyngeal Cavities by a Child

The washing solution was made and used the same way as set forth in Example I. A nine (9) year old child performed the cleaning process. The procedure took 5 minutes to clean both the nasal and nasopharyngeal cavities. As seen by the medical examiner/physician, no dirty materials were left in the child's nasal and nasopharyngeal cavities.

INDUSTRIAL APPLICABILITY

Through the use of the NNC system and process of this invention, the general population now has available to it a simple and inexpensive device that can be used to clean the nasal and nasopharyngeal cavities. As mentioned previously, this will reduce viral loads and thereby reduce the spread of infection and the opportunity for the disease to reach the lower respiratory tract. The medical community and the general population will greatly benefit from the device and method disclosed herein.

Those skilled in the art will appreciate that changes and modifications can be made to the device and the methods disclosed herein without departing from the spirit and scope of the present invention as set forth in the appended claims.

I claim:

1. A nasal and nasopharynegeal-cleaning (NNC) system comprising a NNC solution, a container for said NNC solution, a tubing system, a valve, and a flat-head nostril fitting, wherein said flat-head nostril fitting comprises at least two openings in spaced relationship to accommodate the nostrils of a human, and a branched fluid division tube, for simultaneously receiving substantially equal portions of said solution, in connective relationship with said flat-head nostril fitting.

2. The NNC system of claim **1** wherein said NNC solution is a phosphate buffered aqueous solution containing sodium chloride at a concentration of at least 0.9 g per 100 ml.

3. The NNC system of claim **1** wherein said NNC solution comprises anti-microbial agents.

4. The NNC system of claim 1 wherein said NNC solution comprises anti-allergy agents.

5. The NNC system of claim 1 wherein said NNC solution comprises detergents suitable for use in cleaning nasal and nasopharyngeal cavities.

6. The NNC system of claim 1 wherein said flat-head nostril fitting comprises a semi-circular head.

7. The NNC system of claim 1 wherein said nostril fitting consists of materials which are safe to contact the inside and outside of a human nose.

8. The NNC system of claim 1 wherein said system comprises a gravity system or a mechanical liquid pumping system.

9. The NNC system of claim 1 which is a portable facility or a stationary facility.

10. The NNC system of claim 1 wherein said branched fluid division tube comprises a "Y" shaped fitting.

11. The NNC system of claim 1 wherein said branched fluid division tube comprises a "T" shaped fitting.

12. A method for the cleansing of the nasal and nasopharyngeal cavities of a human, said method comprising the steps of:

a) obtaining a NNC system in accordance with claim 1;

b) cleaning the nasal cavities of the human with said NNC system while said human is positioned in the tooth-brushing position; and

c) cleaning the nasopharyngeal cavities of the human with said NNC system while the human is positioned in an upright position.

13. A nasal and nasopharyngeal-cleaning (NNC) system for use by a patient comprising:

a) a container with a volume of at least 100 ml connected via tubing to a valve means;

b) said valve means being in the closed position nominally and open upon manual actuation;

c) said valve means connected via tubing to a fluid division means, wherein said fluid division means is selected from "Y" fittings and "T" fittings;

d) said fluid division means passing through a flat-head nostril fitting, said flat-head nostril fitting comprising a handle and two openings for passage of said fluid division means; and

e) said flat-head nostril fitting comprising at least one straight edge for engagement with the upper lip of the patient and said two openings being positioned relative to said straight edge and to each other such that said fluid division means passing through said opening will insert into the nostrils of the patient to simultaneously deliver equal portions of said solution.

14. A NNC system comprising:

(1) a nasopharyngeal cleaning solution comprising at least 0.9 gms of NaCl per 100 ml of water;

(2) a container for said NNC solution, said container comprising a hanging means and a means for connection to tubing;

(3) a valve;

(4) a fluid division means; and

(5) a flat-head nostril fitting comprising a handle and at least two openings to simultaneously receive equal portions of said solution.

* * * * *

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(12) **United States Patent**
Liu

(10) **Patent No.: US 6,736,792 B1**
(45) **Date of Patent: May 18, 2004**

(54) **NASAL-NASOPHARYNGEAL-CLEANING SYSTEM**

(76) Inventor: **James Zhou Liu**, 462 Burns Dr., Westerville, OH (US) 43082

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 280 days.

(21) Appl. No.: **09/598,522**

(22) Filed: **Jun. 21, 2000**

Related U.S. Application Data

(63) Continuation-in-part of application No. 09/071,459, filed on May 1, 1998, now Pat. No. 6,238,377, which is a continuation-in-part of application No. 08/788,329, filed on Jan. 27, 1997, now abandoned.

(51) **Int. Cl.**[7] **A61M 31/00**; B65D 37/00; B67D 3/00

(52) **U.S. Cl.** **604/94.01**; 222/211; 222/212; 222/481.5; 222/482

(58) **Field of Search** 604/289, 94.01, 604/73, 35, 36, 315, 313, 316; 600/538; 128/207.18, 200.24, 200.11; 606/162, 196, 199; 222/206, 207, 211, 212, 215, 481.5, 482

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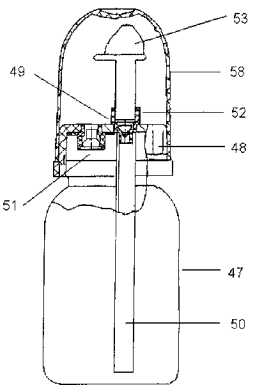
Assistant Examiner—Linh Truong
(74) *Attorney, Agent, or Firm*—Standley Law Group LLP

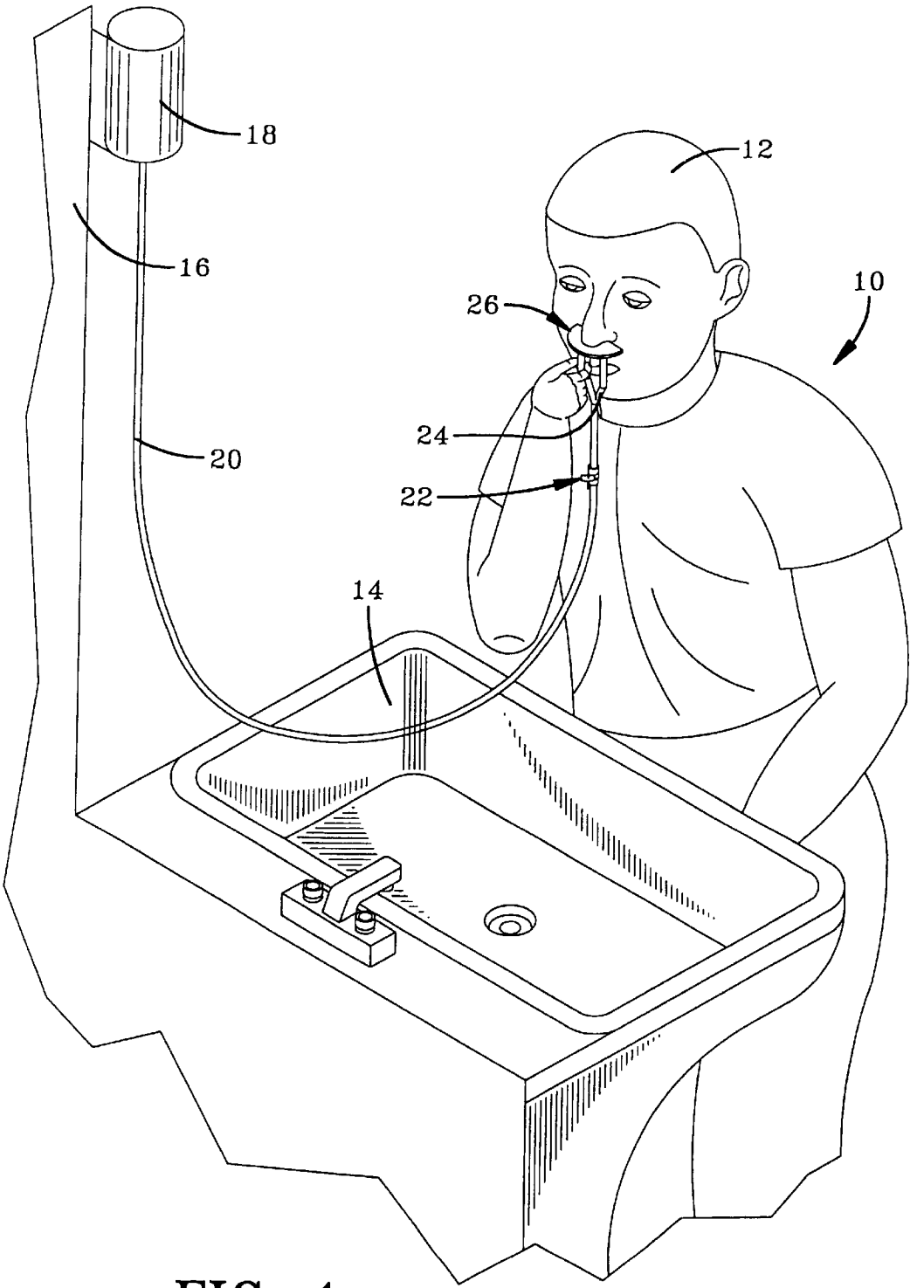
(57) **ABSTRACT**

A nasal-nasopharyngeal-cleaning (NNC) system is disclosed for removing harmful substances from a human's nasal and nasopharyngeal cavities. Harmful substances herein include infectious agents, chemicals, dust, small particles and dirt deposits in nasal cavities and in the nasopharynx. The NNC system includes a NNC solution, a solution container, a liquid transfer tube, a valve means and a flat-head nostril fitting. The two-step cleaning process comprises cleaning the nasal cavity first with the NNC system and then cleaning the nasopharyngeal cavity with the NNC system. The NNC system is also used to prevent snore.

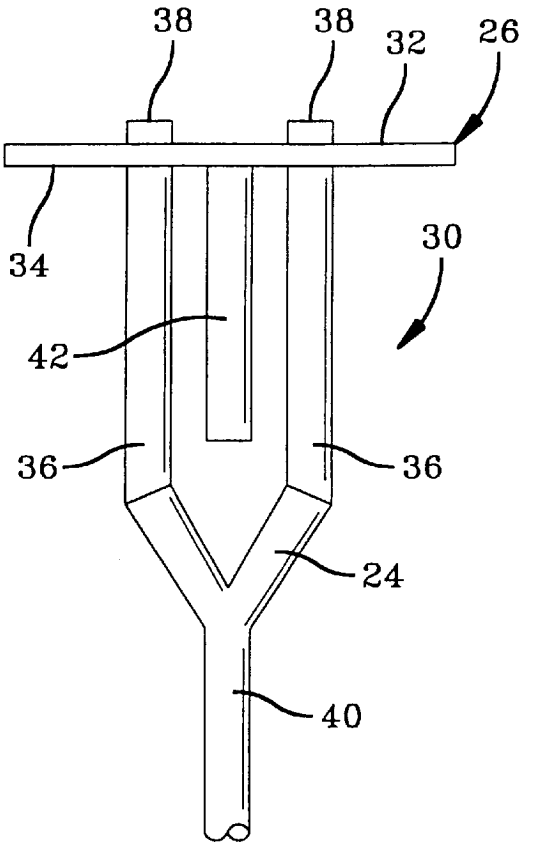
7 Claims, 4 Drawing Sheets



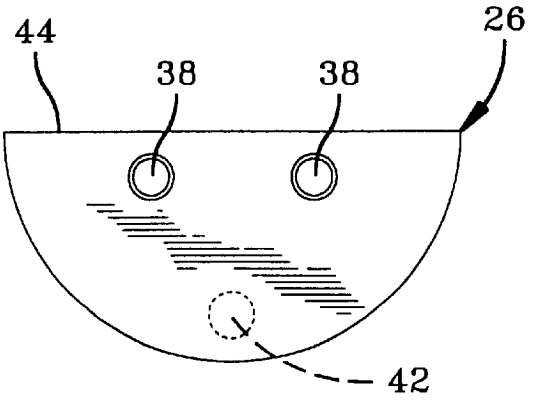
The Portable NNC System



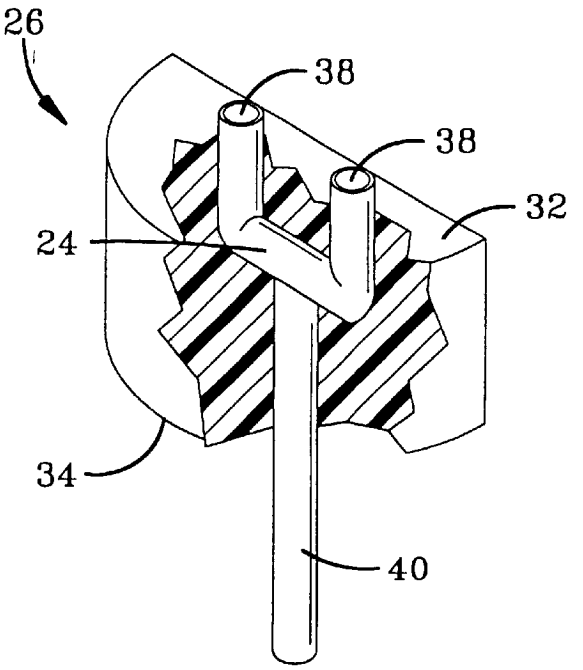
FIG–1



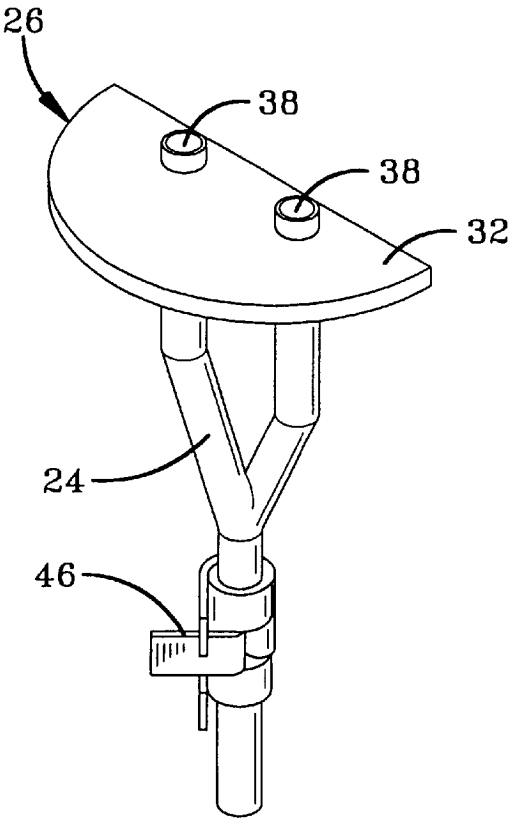
FIG–2



FIG–3



FIG–4



FIG–5

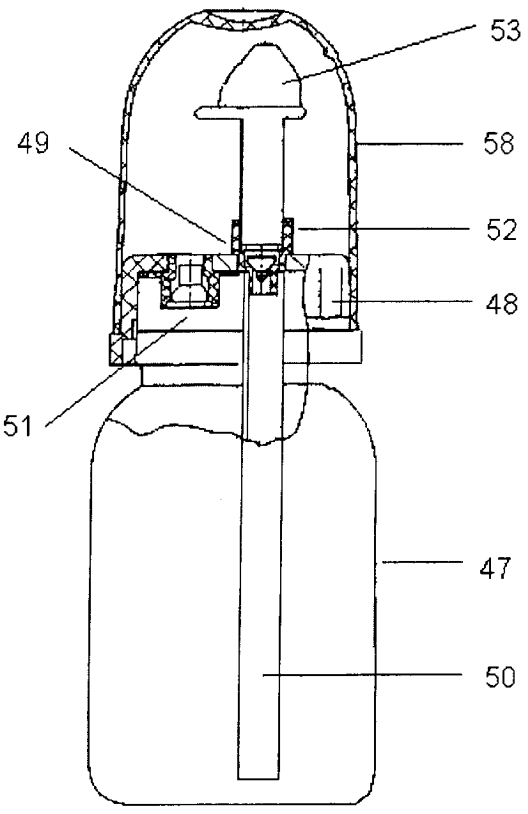


FIG - 6. The Portable NNC System

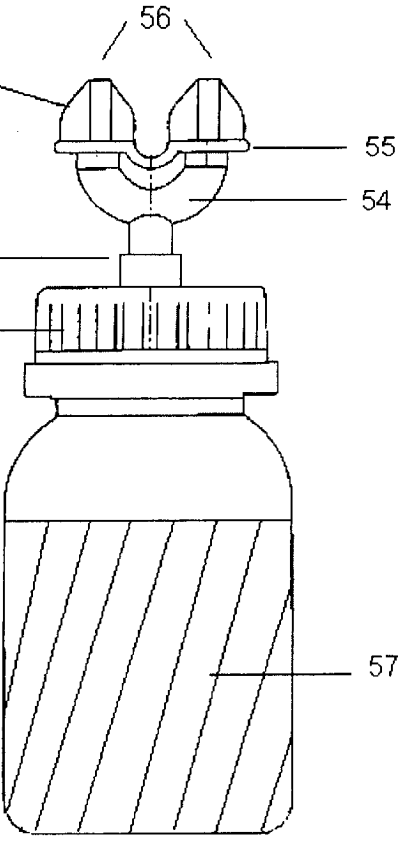


FIG - 7. The Portable NNC System

NASAL-NASOPHARYNGEAL-CLEANING SYSTEM

RELATED APPLICATIONS

This application is a continuation-in-part application of U.S. Ser. No. 09/071,459, filed on May 1, 1998, now U.S. Pat. No. 6,238,377, issued May 29, 2001, which itself is a continuation-in-part application of U.S. Ser. No. 08/788,329, filed Jan. 27, 1997, now abandoned.

TECHNICAL FIELD OF THE INVENTION

The present invention relates generally to a nasal-nasopharyngeal-cleaning (NNC) system to be used in removing harmful substances from a human's nasal and nasopharyngeal cavities. Harmful substances include infectious agents, chemicals, dust, solidified mucous and dirt which adhere to the nasal cavities and the nasopharynx. The NNC system of the present invention comprises the NNC solution and its container, a liquid transferring system, and a flat-head nostril fitting which optionally comprises a means for holding the nostril fitting against the nostrils. A two-step method of using the NNC system is also provided.

BACKGROUND OF THE INVENTION

Influenza viruses A, B and C; respiratory syncytial viruses A and B; parainfluenza viruses and the like are common causes for respiratory tract infections in humans. Presently, there are no effective drugs or vaccines to treat or prevent these viral infections. Human adults and school children are constantly exposed to these infectious agents at work and/or at school and may also be carriers of these infectious agents to and from the home. A practice of nasal and nasopharyngeal cleaning may reduce the microbial load of those tissues and reduce the chance of spreading these disease-causing microorganisms at home, school and at work.

Many disease-causing agents exist in the nasal and nasopharyngeal cavities. The shedding of communicable infectious microorganisms in the nasal and nasopharyngeal cavities causes spreading of the disease from the upper respiratory tract to the lower respiratory tract of the carrier. Shedding also causes the spreading these infectious agents to other people through sneezing and/or coughing (Hall, C. B., Douglas, R. J., in an article entitled: "Quantitative shedding patterns of respiratory syncytial virus in infants", *Journal of Infectious Diseases*, 132: 151–156, 1975; and Hall, C. B., Geiman, J. M., Breese, B. B., and Douglas, R. J., in an article entitled "Parainfluenza virus infections in children: Correlation of shedding with clinical manifestations", *Journal of Pediatrics*, 91: 194–198, 1977). For most viral infections, antibiotic prevention and/or treatment is generally ineffective. It would thus be beneficial to have a practical system and/or method to remove these disease-causing agents from the human body. In a manner similar to brushing one's teeth, nasal and nasopharyngeal cleaning in the general population will have a number of healthy benefits.

Nasal washes, nasopharyngeal swabbing and nasopharyngeal aspiration have previously been used to obtain specimens from patients for the determination of microbial pathogens (Hall, C. B., Douglas, R. J., in an article entitled: "Clinically useful method for the isolation of respiratory syncytial virus", *Journal of Infectious Diseases*, 131: 1–5, 1975). However, these procedures and devices were used only to obtain samples and are not effective in removing the infectious agents from the nasal and nasopharyngeal cavities of a human.

Ephedrine nasal washes have been used in the treatment of sinusitis and other nasal and paranasal symptoms and allergic rhinitis (Shaikh, W. A., in the *Journal of Allergy Clinical Immunology*, Vol. 96, No. 5, part 1: 597–600, 1995). The Shaikh procedure uses a 1% ephedrine hydrochloride solution in a normal saline solution and a Higginson's rubber syringe. After the rubber syringe was filled with the wash solution, the nozzle of the syringe was introduced into nostril and the bulb of the syringe was passed to push the fluid into the nasal cavity. As described by the author, most of the fluid exited from the same nostril, but some fluid exited through the other side of the nose after passing through the nasopharynx. This procedure was performed once every forty-eight (48) hours for a four (4) week period and caused a significant improvement in symptom scores and peak nasal inspiratory flow rates in patients with perennial allergic rhinitis as compared to those treated with a placebo wash (normal saline only). This procedure, however, has the following disadvantages:

(1) ephedrine was the key factor for the effectiveness of this procedure, but this chemical is not suitable for use by the general public on a daily basis;

(2) this procedure was performed only on patients with perennial allergic rhinitis;

(3) this procedure was mainly washing of the nasal cavity, the nasopharyngeal cavity was largely uncleaned;

(4) the apparatus used was clumsy and uncomfortable to use; and

(5) this procedure was performed once every forty-eight (48) hours which is not frequent enough to remove harmful materials from the nasal and nasopharyngeal cavities on a daily basis.

The Shaikh procedure would permit the infectious microorganisms to be brought into and spread around at home, office, school, or day care center. Therefore, there is a need to develop a generally acceptable and more effective nasal and nasopharyngeal cleaning system.

Nasal and nasopharyngeal cavities are common places for holding environmental allergens, such as pollen, fungal spores, animal body-originated dustings and volatile chemicals. These harmful agents cause allergic reactions and other ill consequences. Nasal and nasopharyngeal secretions combine with environmental particles to form big matters (solidified mucous) in the nasal cavity. These big matters narrow the airway and make the individual feel uncomfortable. Prior to the present invention, an aparatus and method to easily and effectively remove harmful agents from the nasal cavity and to prevent the formation of and remove the big matters in the nasal cavity has not been available to medical professionals and to the general public.

The human body is the only natural host for many kinds of pathogenic microorganisms. Nasopharyngeal mucous is one of the prominent places of viral shedding. These pathogens include, but are not limited to, influenza viruses, respiratory syncytial viruses and the like. The nasopharyngeal shedding of these pathogens is the major cause of person-to-person transmission. One skilled in the art will appreciate that those communicable pathogenic microorganisms present in the nasal and nasopharyngeal cavities will be decreased in quantity after the cavities have been cleaned. After nasal and nasopharyngeal cleaning, these infectious agents will be less likely to spread horizontally to non-carriers and/or vertically to the lower respiratory tract of the carrier.

Environmental pathogens may be encountered by inhalation. *Legionella pneumophila*, the causative agent of

Legionnaire's disease presents in aerosols. It is generated from air conditioning cooling towers, cold water taps, showers and other water systems. Depending upon wind speed, *Legionella pneumophila*, in these aerosols, may be carried up to 500 meters and infect a large number of individuals. Promptly removing these aerosols from the nasal and nasopharyngeal cavities will greatly reduce the incidence of infection.

Several methods have been reported to be useful in cleaning nasal and nasopharyngeal cavities. Grossan invented a nasal irrigation system (NASAL IRRIGATION SYSTEM, U.S. Pat. No. 3,047,145, issued Nov. 12, 1974) which provided for an isotonic saline solution under pressure flowing into one nostril, passing through the nasolacrimal duct, where the solution passes, sequentially, into the ostia of the frontal sinus, the ethnoids, the maxillary and the sphenoid. The solution then moves past the outlet of the eustachian tube and then through the nasopharynx to the upper posterior portion of the other nostril and outwardly therethrough, passing the same ducts and ostia, in reverse sequence, before being discharged from the second nostril. This system has numerous and serious shortcomings. First, the cleaning solution cannot be completely drained from the deep regions of certain sinuses due to their cavity structure. Second, certain infectious agents might be moved from one place to another and stay there to cause a new infection. Third, some dried or hard matters in the nasal cavity might be carried inward to the sinuses. Fourth, hard matters might cause a blockage when they are forced to flow into narrow spaces, such as the eustachian tube. Therefore, the reported nasal irrigation system of Grossan cannot be widely used by the general public for cleaning nasal and nasopharyngeal cavities.

A method of administrating a pharmacological solution into the nasal cavity of a patient was described by Löfstedt (METHOD FOR DRUG ADMINISTRATION, U.S. Pat. No. 5,116,311, issued May 26, 1992). Although the author mentioned that there was a possibility to use the reported method to irrigate the nasal cavity, the method and device of this patent were designed to administer pharmacological solutions into the nasal cavity, not to provide a flow of fresh cleaning solution continually into the nasal cavity, since the compressible container of Löfstedt not only forced the solution into the nasal cavity, but also aspirated the solution with nasal secretions and other contaminants back into the container. The effectiveness of the drug administration method was also heavily dependent on the patient's head bending angle. This method and device was designed to administer drugs into the nasal cavity for treating diseases over a short period of time. The Löfstedt device was not designed for and would not be useful to clean nasal and nasopharyngeal cavities by the general public on a daily basis.

Pena invented a device for treating infections of the nasal fossae (DEVICE FOR CIRCULATING TREATING FLUID THROUGH THE NASAL FOSSAE, U.S Pat. No. 4,029,095 issued Jun. 14, 1977). The Pena device was designed to be used by patients to treat diseases, not for the general public to clean nasal and nasopharyngeal cavities.

Babbitt et al. invented a portable device used to aspirate and remove fluids from nasal and sinus cavities (SINUS EVACUATOR APPARATUS, U.S. Pat. No. 4,403,611 issued Sep. 13, 1983). Since this device only aspirates the sinus fluids from the nasal and sinus cavities, the dirts and pathogenic microorganisms adhering to the surface of the nasal and nasopharyngeal cavities cannot be removed if they are not dissolved in a washing fluid.

The above systems and methods described in Grossan, Löfstedt and Babbitt et al. all utilize a conical nostril fitting. The conical nostril fitting creates a certain amount of "dead space" between the inserted part of the nostril fitting and the wall of the nasal cavity, which a cleaning solution cannot reach (if used in the Grossan et al. devices). To improve the efficiency of nasal cleaning, a new type of nostril fitting is needed. The prior art has failed to suggest a NNC system that is simple in construction and easy to use and that allows for the cleaning of the nasal and nasopharyngeal cavities in the separated steps. Since the nasal cavity: (1) is naturally in the lowest position as compared to the nasopharyngeal cavity and the other sinus cavities; (2) collects secretions from other sinus cavities; and (3) is the first place to meet and store the foreign matters, it is obvious that the first step of the nasal and nasopharyngeal cleaning method should be to initially clean the nasal cavity. Therefore, a new step-by-step cleaning method is disclosed in this invention.

Snoring is a major problem for many people. In fact, in the U.S. alone, about 90 million people suffer with snoring. This figure doesn't take into consideration the needless suffering of the loved ones living with them. Sleep deprived nights lead to irritation, tiredness, and a possible growing division or alienation between partners. Seeking a simple and effective solution honoring has been a major concern for a large number in our society. Snoring has become an everyday occurrence. It is much more common than many care to admit. Each nostril functions independently and synergistically in filtering, warming, moisturizing, dehumidifying, and smelling the air. The nostrils meet at the nasopharynx where mucous is accumulated. Although many factors cause snoring, the major reason may be that the nasal cavity is narrowed due to accumulated mixtures of mucous and environmental dusts. Habitual nasal cleaning will remove those accumulated dirty materials and help people to reduce snoring.

BRIEF DESCRIPTION OF THE DRAWINGS

These and other objects of the present invention will be apparent to those skilled in the art from the following description of the invention. The invention is described with reference to the following Figures:

FIG. **1** is a perspective view of a person using one embodiment of the NNC system of the present invention, shown leaning over a lavatory or washbasin, and holding the inventive device to the bottom of his nose;

FIG. **2** shows a frontal plan view of one embodiment of the flat-head nostril fitting, "Y" fitting (fluid division means) and handle;

FIG. **3** is a top plan view of one embodiment of the flat-head nostril fitting, the handle being shown in dotted lines;

FIG. **4** is a perspective view of one embodiment of the flat-head nostril fitting wherein the fluid division means (in this embodiment, a "T" fitting) is embedded in the flat-head nostril fitting; and

FIG. **5** is a perspective view of one embodiment of the flat-head nostril fitting with a valve means disposed between the "Y" fitting and the NNC solution container (not shown).

FIG. **6** is a perspective view of one embodiment of an assembled portable NNC system.

FIG. **7** is a perspective view of one embodiment of the type of valves that may be used with the present invention.

DETAILED DESCRIPTION OF THE DRAWINGS

In FIG. **1**, there is indicated generally at **10** a patient using one embodiment of the NNC system. It will be noted that the

patient's body is bent so that his head **12** is slightly bent over a conventional lavatory or washbasin indicated generally at **14** for receiving the discharge of the NNC solution from a nasal cavity. Adjacent to the washbasin **14**, and here shown as mounted on a wall **16**, is a container **18** of NNC solution. The solution is fed by gravity through a flexible hose **20** which is connected to a valve means **22** which is then connected to the fluid division means fitting **24** (here shown as a "Y" fitting). The "Y" fitting is in connective relationship to the flat-head nostril fitting **26**. FIG. **1** shows the patient's right hand holding the flat-head nostril fitting **26** to the underside of the patient's nostrils through holding the handle **42** shown in FIG. **2**.

FIG. **2** indicates generally at **30** one embodiment of the NNC system wherein the flat-head nostril fitting **26** has upper surface **32** and lower surface **34**. The flat-head nostril fitting is connectively engaged with the fluid division means shown here as a "Y" fitting **24**. The two arms of the "Y" fitting **36** extend through the flat-head nostril fitting **26** to create projections **38** above the flat-head nostril fitting upper surface **32**. The fluid transfer tubing **40** is in connective engagement with container **18** (not shown). Handle **42** extends from the lower surface **34** of the flat-head nostril fitting **26**.

FIG. **3** is a top plan preview of one embodiment of the flat head nostril fitting **26**. In this embodiment, the flat-head nostril fitting is generally semi-circular in shape. The straight edge **44** of the flat-head nostril fitting **26** is intended for engagement against the patient's upper lip. Projections **38** result from the extension of the arms of the fluid division means through the flat-head nostril fitting. The spacing of projections **38** relative to straight edge **44**, and to one another are such that most human beings upon placement of a device against their upper lip, will find projections **38** inserted into each nostril. While this embodiment is semi-circular in configuration, it should be understood that other shapes such as squares, rectangulars, triangles, hexagons and the like may also be used. The feature of the flat-head nostril fitting that is most critical is that straight edge **44** be of sufficient length and configuration so that proper sealing of the nostrils may be accomplished with top surface **32** of the flat-head nostril fitting **26** while projections **38** enter each nostril of the patient.

FIG. **4** is a perspective view in partial cross section of yet another embodiment of the invention wherein the fluid division means **24**, seen here as a "T" fitting, is embedded within the flat-head nostril fitting **26**. The nostril fitting in this embodiment possesses top surface **32** with projections **38** extending therefrom. Bottom surface **34** of the flat-head nostril fitting **26** may have a handle means adapted thereto (not shown). The tubing **40** is connected to a valve means (not shown).

FIG. **5** is a perspective view of another embodiment of the NNC system wherein the flat-head nostril fitting **26** possesses projections **38** through its top surface **32**. The fluid division means **24**, shown here as a "Y" fitting, is connectively engaged with a valve means **46**. This valve means may be any valve type known in the art and may be a squeeze type or push/pull type valve known to those in this field. Other valve means would include those associated with enteral nutrition feeding sets wherein a clamp flow regulator on the tubing permits easy, accurate flow rate adjustment. Preferably, the valve means **46** is configured such that it is closed in normal position and that only upon manual activation would the valve be open, allowing NNC solution to flow from the container **18** through tubing **20** into "Y" fitting **24** through projections **38** and into the nostrils of the patient.

FIG. **6** is a sectional view of one embodiment of the portable NNC system and FIG. **7** is a perspective view of one embodiment of the assembled portable NNC system. The solution container **47** is a soft bottle which may be hand-squeezed to produce pump-like pressure. The container has a unique cap **48**. The cap has two valves. One valve is a one-directional fluid-flow switch **49**. This liquid-flow switch only allows the cleaning fluid to flow out of the bottle and prevents the dirty washout from flowing into the bottle. The two ends of this fluid-flow valve connect to two different solution transfer tubes. Tube one is a short tube **50** contained within the bottle which transfers the cleaning solution to the nostril fitting leaving the bottle. Tube two connects to the "Y" shaped nostril fitting **54** through a sliding-connector **52**. The nostril fitting **53** is an oval object which is used to broaden or narrow the space between the two nostril fittings after moving then around the supporting stem **56**. The two supporting stems **56** are short and are in a fixed or movable position on the Y shaped nostril fitting. The nostril fitting has a "one-size-fits-all" adjustability. The second valve on the bottle's cap is a one-directional airflow switch **51**. This valve only allows air to flow into the bottle, which allows the bottle to always have positive pressure to make it easier to pump out the cleaning fluid from the container. The cap **58** is to prevent the nostril fittings and valves from gathering dust. The cleaning solution **57** flows through a short tube **50**, arrives to the one-directional fluid-flow valve, and fills the nostril fittings to irrigate the user's nasal and nasopharyngreal cavities.

SUMMARY OF THE INVENTION

The present invention provides a nasal and nasopharyngeal cleaning (NNC) system which is used to reduce the load of disease-causing agents; to reduce the concentration of infectious agents in the nasal and nasopharyngeal secretions; to prevent these infectious agents from presenting in aerosols/droplets; and to reduce the duration of environmental allergens and other harmful materials staying in nasal and nasopharyngeal cavities. The NNC system includes a washing solution and its container, a liquid transferring tube system and an all-purpose nostril fitting. The NNC system of the invention is portable and constructed of readily available and inexpensive materials. The NNC system is to be used in a method wherein the nasal cavity is cleaned first and then the nasopharyngeal cavity is cleaned thereafter. The method disclosed for using the NNC system may be applied by an individual to himself or herself as often as required or deemed convenient.

Thus, there is disclosed a nasal and nasopharyngeal-cleaning (NNC) system comprising a NNC solution, a container for said NNC solution, a tubing system, a valve means and a one-fits-all nostril fitting. The NNC system may additionally comprise a fluid division means between the valve means and the one-fits-all nostril fitting. The fluid division means may take the form of a "Y" fitting, a "T" fitting and the like. Numerous variations are possible. The fluid division means may be disposed within the flat-head nostril fitting. The portable NNC system has a unique mechanism which only allows cleaning fluid and air to flow in a designated direction.

There is further disclosed a nasal and nasopharyngeal cleaning (NNC) system for use by a patient comprising:

1) a container with a volume of at least 10 ml connected via tubing to a valve means;
2) said valve means being in the closed position nominally and open upon manual actuation;

3) said valve means connected via tubing to a fluid division means, wherein said fluid division means is selected from "Y" fittings and "T" fittings;

4) said fluid division means passing through a one-size-fits-all nostril fitting, said one-size-fits-all nostril fitting comprising a handle and two openings for passage of said fluid division means;

5) said flat-head nostril fitting comprising at least one curved edge for engagement with the upper lip of said patient and said two openings being positioned relative to said curved edge and to each other such that said fluid division means passing through said opening will insert into the nostrils of said patient.

DETAILED DESCRIPTION OF THE INVENTION

The present invention provides a new nasal and nasopharyngeal cleaning (NNC) system and a method of cleaning the nasal and nasopharyngeal cavities. In general, the NNC system comprises:

(1) a nasopharyngeal cleaning solution comprising at least 0.9 gms of NaCl per 100 ml of water;

(2) a container for said NNC solution, said container comprising a hanging means and a means for connection to tubing;

(3) a valve;

(4) a fluid division means; and

(5) a flat-head nostril fitting comprising a handle and one or two openings.

The NNC solution is supplied to the nostril fitting through the force of gravity, by a manual and/or mechanical pump, or provided manually through a squeezable soft bottle. In the embodiment where a pump is used, the pump may be a motor driven pump unit, preferably driven by way of a suitable micromotor. However, the pump means may also be a manually operable pump means in the form of an elastic bulb capable of being manually compressed, and capable of expanding when released by the operator; this particular pump means having at its suction inlet and pressure outlet, respectively, a pair of one way valves which permit the fluid to flow only from the suction tubular means into the plastic bulb when the latter expands and from the elastic bulb only into the pressure tubular means when the elastic bulb is compressed by the operator.

The NNC solution useful in the system and method according to the current invention may be water or an aqueous solution. The most common isotonic solution is a normal saline solution, which contains 9 g of sodium chloride in 1 liter of water (0.9% by weight). This solution may be used as a basal cleaning solution. It has been experienced that a phosphate buffered water solution (pH 7.4) containing sodium chloride at a concentration higher than 0.9% normal saline, resulted in a more comfortable nasal and nasopharyngeal cleaning. Thus, a phosphate buffered aqueous solution containing about 1 g of sodium chloride per 100 mL water is a preferred NNC solution. The NNC solution may also contain an appropriate amount of an anti-attachment agent. Representative anti-attachment agents include various carbohydrates or detergents which prevent or reduce the attachment of microbial pathogens to the nasal and nasopharyngeal cavities. The solution may also contain anti-allergy agents, or suitable detergents to improve the cleaning efficiency. The NNC solution may also contain corticosteroids, antibiotics, antihistamines, and/or mucolytic agents. The NNC solution may also contain a suitable decongestant such as phenylephrine hydrochloride. Pharmaceutically active agents should be employed in the NNC solution only under the direction of a physician. The temperature of the NNC solution, when administered, is typically about 20 to 40° C. and more preferably about 30 to 37° C.

The container for NNC solution may be made of any convenient material and may take almost any shape. The container may hold up to 50,000 mL of solution, preferably it may hold 10 to 10,000 mL of solution and more preferably, it may hold at least 50 mL of NNC solution. This container may be made from any kind of safe material which does not release any chemicals into the solution and does not absorb any chemicals from the solution. The common materials include, but are not limited to, plastic, rubber, glass, metals, china, etc. One end of the container preferably has a means to hang the container above the head of the patient and the other end is open with means to be connected to the tubing system. The container may be a soft bottle to produce fluid-flow force when manually squeezed.

A flexible tubing system is used to transfer the NNC solution to the flat-head nostril fitting and into the patient. The tubing may be from 30 cm to 2 meters in length. Preferably, it is between 0.5 to 1 meter in length. The inner diameter of the tubing is between 2 to 10 mm. Preferably, the inner diameter is between 3 and 7 mm. The material of the tubing may include, but is not limited to, plastic, rubber or any other suitable inert material. One end of the tubing is connected to the container of the NNC solution and the other end is connected to the valve means. If a portable NNC system is made, the tubing system will become a within-bottle short tube.

Disposed between the NNC container and the flat-head nostril fitting is a valve and a fluid division means. The valve allows the patient to control the flow of NNC solution from the container, through the nostril fitting and into his or her nasal cavity. In a preferred embodiment, the valve, which may be of any known and convenient design, is near to or incorporated into the flat-head nostril fitting as will be further discussed below.

The flexible tubing system may also comprise a fluid division means such as a "Y" fitting disposed between the valve means and the nostril fitting. The "Y" or "T" fitting takes the NNC solution and divides it so that each nostril is afforded simultaneous essentially equal irrigation. In one embodiment of the invention, the "Y" or "T" fitting is integrated into the flat-head nostril fitting.

The two arms of the fluid division means may have the same diameter enabling the smooth connection of the tubing system to the nostril fitting. The connection between the tubing, the valve and the nostril fitting may be formed by contraction force of the elastic tubing or by a plastic or metal screw connection. The combination of the NNC container, the tubing system, the valve and the connections are similar to the apparatus used in hospitals for intravenous infusion or the apparatus for gastric tube feeding. When a portable NNC system is made, the container, the tubing system, the valves and the connections are similar to a small liquid sprayer.

One important aspect of the NNC system according to this invention is the flat-head nostril fitting, or one-size-fits-all nostril fitting. The nasal fitting substantially prevents the NNC cleaning solution from leaking from the nostril during the irrigation step of the process. It has been observed that different people have different shaped nostrils and that not all people have round nostrils. Some people have an irregular opening, like a long narrow channel. Therefore, it is impossible to use the conical shaped nostril fitting of the prior art to prevent the liquid from leaking from the nostrils of these people. Additionally, the conical shaped nostril

fittings of the prior art always create a certain amount of dead space between the inserted part of the nasal fitting and the wall of the nasal cavity. The newly invented nostril fitting, as shown in FIGS. **2–5**, is called a "flat-head nostril fitting". The flat-head nostril fitting has the following characteristics in a preferred embodiment:

(1) It has a semi-circle head with a diameter of from 2.0 to 8.0 cm and a thickness of 0.1 to 0.5 cm. The function of the curved edge of the semi-circle (or any other shape) is for placement against the upper lip of the patient. The upper surface of the fitting is placed against the bottom of the nose so as to reduce liquid leakage from the nasal cavity during the cleaning process.

(2) The flat-head nostril fitting has 2 openings therethrough which allow passage of the tubing from the fluid division means. The openings have a diameter which is identical or slightly less than the outside diameter of the tubes penetrating through the head so as to provide for frictional engagement. The distance from the center of one opening to the center of the other opening is from 0.2 to 1.0 cm and is preferably about 0.5 cm so as to match the average distance between the center of each nostril of the patient.

(3) The length of the two tube-arms of the fluid division means is from 5 to 20 cm. A 10 cm or less length is preferred. In another embodiment of the nasal fitting, the fluid division means is embedded in the flat-head nasal fitting, as set forth in FIG. **4**. In this embodiment, the thickness of the head is increased to accommodate the fitting. The embedded "T" shaped configuration is preferred so as to keep the thickness of the head to a minimum. When a portable NNC system is made, the two tube-arms of the fluid division means is from 0.5 to 5 cm.

(4) The outside diameter of the tubes penetrating through the nostril fitting head is preferably from 0.2 to 0.5 cm.

(5) The length of the tubing projecting above the nostril fitting head, items **38** in FIGS. **2–5**, is from 0.0 to 0.5 cm, preferably 0.1–0.4 cm. The tube will preferably have a diameter smaller than the diameter of the patient's nostrils in a round shape. This is important so as to prevent the creation of any dead space, as discussed above, during the cleaning process.

(6) The nostril fitting may optionally comprise a handle means. While the NNC system is easily used by the patient without a handle means, it has been found convenient for the patient to have some feature attached to the nostril fitting to facilitate holding of the nostril fitting to the bottom of the nose, such as the solution container of a portable NNC system. In one embodiment, the handle means comprises a rod projecting form the bottom surface of the head. The handle may have a diameter of about 1.0 cm and a length of about 2.0 cm. This handle may also be square or rectangular in shape. This handle, no matter of what configuration, is to provide ease for the cleaner to hold the nostril fitting against the nostrils to introduce and to release the NNC solution during the cleaning process.

(7) Plastic, rubber, stainless metal materials or other safe materials may be used to make the flat-head nostril fitting. Soft, biocompatible silicons are preferred.

A driving force for the NNC solution flowing through the NNC system must be provided. Natural gravity force, manual pump, or a mechanical pump may be used to force the NNC solution into the nasal and nasopharyngeal cavities. Preferably, the force used to move the fluid through the tubing to the nostrils is produced by hanging the container of NNC solution at a position of at least 0.1 meter above the patient's forehead. The force to move the cleaning solution into the nostrils may be produced by a hand-squeezable bottle when a portable NNC system is made.

EXAMPLES

Example I

Cleaning of the Nasal and Nasopharyngeal Cavities

The method of using the NNC system is simple and readily accomplished by the patient. The NNC solution was made by dissolving 2.7 g of table salt into 200 ml of warm drinkable water. One minute before use, the solution was measured to be 37° C. 100 ml of this solution was charged to the NNC solution container. The container was suspended form a hook projecting from the wall of the bathroom at about 50 cm above the patient's forehead.

Cleaning was accomplished as follows:

Step 1:

The patient was in an upward position with the upper part of the body bending slightly forward to have the face above the washbasin, similar to a "teeth brushing" position. The patient used one hand to open the valve to allow the NNC solution to flow through the NNC system. The other hand held the flat-head nostril fitting against the bottom of the nose to allow the NNC solution to reach the nasal cavity. After the NNC solution filled the nasal cavity, the patient withdrew the nostril fitting from the bottom of his nose, after closing the valve, to allow the solution combined with the nasal cavity secretions to flow/fall into the washbasin. He repeated this liquid in-and-out process several times. The patient then closed the valve of the NNC system after his nasal cavity was filled with the NNC solution. While one hand held the nostril fitting in position, he used the other hand to gently rub his nose to allow the dried and hard matters to be released from the nasal cavity. Then the washing solution in the nasal cavity was released into the washbasin. He repeated this in-depth cleaning process several times. Through the mirror, he saw his nasal cavity was very clean. The cleaning result was verified by a medical examiner (physician).

Step 2:

Cleaning of the Nasopharyngeal Cavity

The same patient proceeded to the next step in the process; cleaning of his nasopharyngeal cavity. He was in an upward standing position. After his nasal cavity was cleaned, he placed the nostril fitting against his nose and let the NNC solution fill the nasal cavity without releasing it. When the nasal cavity was full of the NNC solution, he bent his head slightly backward to let the solution naturally flow through the nasopharyngeal cavity. The patient felt that there was some liquid in his mouth. When his mouth was filled with a comfortable amount of solution, he turned off the NNC solution supply (closed the valve) and returned his head to the teeth brushing position. The washing solution was then released from the mouth to the washbasin. This process was continued for two (2) minutes. The medical examiner/physician found that the patient's nasopharyngeal cavity was clean. During Steps 1 and 2, the patient did not get any pressure from any sinus cavity, because the liquid did not flow into any of the sinuses above his nose.

Example II

Cleaning the Nasal Cavity by an Adult

The NNC solution contained sodium chloride at a concentration of 1.35% by weight. One minute before use, the NNC solution was measured to be 37° C. The patient added this solution into the NNC solution container. This container was hung from the wall of the bathroom at about 60 cm above the patient's forehead. The patient placed the nasal fitting under his nose. After opening the valve, the NNC solution flowed through the tubing and the nostril fitting and filled the nasal cavities of the patient. The patient removed

the nostril fitting to let the solution flow out of his nasal cavities. By repeating this procedure, several big matters were removed from the nasal cavity. This procedure was repeated several times and the patient's nasal cavities were then examined. The medical examiner/physician could not see any dirty materials left in the patient's nasal cavities.

Example III

Cleaning the Nasopharyngeal Cavity by an Adult

The same patient as mentioned in Example II, continued with the method to clean his nasopharyngeal cavity. After cleaning his nasal cavity, he placed the nostril fitting against the nose and allowed the NNC solution to flow through the nasopharyngeal cavity until the solution reached the patient's oral cavity. The patient simply spit this solution into the washbasin. By repeating this procedure, his nasopharyngeal cavity was cleaned. He felt that the air he inhaled was much fresher than before he cleaned his nasopharyngeal cavity.

Example IV

Cleaning Nasal and Nasopharyngeal Cavities by a Child

The washing solution was made and used the same way as set forth in Example I. A nine (9) year old child performed the cleaning process. The procedure took 5 minutes to clean both the nasal and nasopharyngeal cavities. As seen by the medical examiner/physician, no dirty material was left in the child's nasal and nasopharyngeal cavities.

Example V

Cleaning Nasal and Nasopharyngeal Cavities to Prevent Snoring by an Adult and a Child

A male adult had been snoring for many years. After he learned how to use the nasal cleaning system, he practiced the nasal cleaning every day. Each night after nasal cleaning, no noise was produced.

A 14-year old boy had snored for several weeks. Before he learned to use the nasal cleaning system, the examiner observed that he had swollen mucous membranes on his turbinates in both left and right nasal cavities, and that made the airway narrow. Also, several pieces of dirty matter were on the surface of the turbinates. The boy used the nasal cleaning system washed out the dirty materials and felt immediately that he could breath much easier than before. For several nights after the cleaning he did not snore.

INDUSTRIAL APPLICABILITY

Through the use of the NNC system and process of this invention, the general population now has available to it a simple and inexpensive device that may be used to clean the nasal and nasopharyngeal cavities. As mentioned previously, this will reduce viral loads and thereby reduce the spread of infection and the opportunity for the disease to reach the lower respiratory tract. The medical community and the general population will greatly benefit from the device and method disclosed herein.

Those skilled in the art will appreciate that changes and modifications may be made to the device and the methods disclosed herein without departing from the spirit and scope of the present invention as set forth in the appended claims.

What is claimed is:

1. A modular nasal and nasopharyngeal-cleaning (NNC) kit, comprising:

a) a compressible bottle;

b) a cap for covering said compressible bottle, said cap having a uni-directional air-flow switch and a uni-directional fluid-flow switch passing there through, said fluid-flow switch adapted for connection above said cap to a nostril fitting and adapted for connection below said cap in said bottle to a NNC solution dispensing tube;

c) a nostril fitting adapted for releasable connection to said uni-directional fluid-flow switch;

d) a NNC solution dispensing tube adapted for releasable connection to said uni-directional fluid-flow switch, and;

e) a NCC cleaning solution for dispensing by said compressible bottle, wherein said NNC solution can be properly introduced to said nasal cavity by squeezing said compressible bottle.

2. A method of accomplishing nasal and nasopharyngeal-cleaning (NNC) comprising:

a) placing a NNC solution into a compressible bottle;

b) connecting a NNC solution dispensing tube to a bottom portion of a cap;

c) attaching said cap to a said compressible bottle, a top portion of said cap adapted for releasable connection to one or more interchangeable nostril fittings;

d) releasably attaching a nostril fitting to said cap;

e) inserting said nostril fitting at least partially into at least one nostril;

f) compressing said compressible bottle to dispense said NNC solution into said at least one nostril, and;

g) removing said nostril fitting from said at least one nostril.

3. The method of claim **2**, wherein the steps of NNC are performed as in the order the steps are written.

4. The method of claim **2**, wherein each of said nostril fittings is disposable.

5. The method of claim **2**, wherein each of said nostril fittings is re-useable.

6. The method of claim **2**, wherein said NNC solution, said compressible spray bottle, said NNC solution dispensing tube, and said nostril fitting, is sold together as a kit.

7. A modular nasal and nasopharyngeal-cleaning (NNC) kit, comprising:

a) a compressible bottle for containing and dispensing a NNC solution;

b) a NNC solution for placement in said bottle;

c) a cap adapted for attachment to said bottle, said cap having a uni-directional air-flow switch and a uni-directional fluid-flow switch passing there through;

d) a cleaning solution dispensing tube for attachment to a first end of said uni-directional fluid-flow switch, such that said cleaning solution dispensing tube is in communication with said cleaning solution when cap is installed to said bottle; and

e) a nostril fitting adapted for attachment to a second end of said uni-directional fluid-flow switch, such that said nostril fitting resides above said cap when said cap is installed to said bottle;

wherein, once assembled, compression of said bottle causes said NNC solution to pass from said bottle, through said cleaning solution dispensing tube and said uni-directional fluid-flow switch, and out of said nostril fitting; and wherein upon cessation of compression of said bottle, air re-enters and re-inflates said bottle through said uni-directional air-flow switch.

* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 6,736,792 B1
DATED : May 18, 2004
INVENTOR(S) : James Liu

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 2,
Line 9, please delete "passed" and insert -- pressed --.

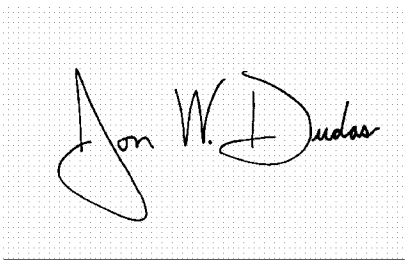
Column 4,
Line 25, please delete "honoring" and insert -- snoring --.

Column 5,
Line 25, please delete "preview" and insert -- view --.

Column 10,
Line 54, please delete "get any" and insert -- feel any --.

Signed and Sealed this

Twenty-seventh Day of July, 2004



JON W. DUDAS
Acting Director of the United States Patent and Trademark Office

Wharton
University of Pennsylvania

Could you please check if the two trademarks below are different or similar in commercial impression, Sound, Vision?

Sinupret and product **SinuPro and product**

		Signature	Date
Very different	Very similar		
X			4-19-09
	X		4-19-09
	X		4-19-09
X			4/19/09
X			4/19/09
X			4/19/09
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X			4-19-09

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Very different	Very similar	Signature	Date
	X		4/20/09
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X			4/20/09
X		Ashley Reinhardt	4/20/09
X			4/20/09
X			4/20/09
	X		4/20/09
X			4/20/09
X			4/20/09
X			4/20/09
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X			4-20-09
X			4/20/09

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Could you please check if the two trademarks below are different or similar in commercial impression, Sound, Vision?

Sinupret and product

SinuPro and product

		Signature	Date
Very different	Very similar		
✓		Dennis Kwiatkowski	4/19/09
✓		[illegible]	4/19/09
✓		John Armstrong	4/19/09
✓		[illegible]	4/19/09
	✓	[illegible]	4/19/09
	✓	[illegible]	4/19/09
✓		[illegible]	4/19/09
✓		[illegible]	4/19/09
✓		[illegible]	4/19/09
✓		[illegible]	4/19/09
✓		[illegible]	4/19/09