Lucile Packard Children's Hospital
STANFORD UNIVERSITY MEDICAL CENTER

Cystic Fibrosis Center NEWS

SUMMER 2003

Devon Wakefield has CF sinusitis and is a dedicated and enthusiastic soccer player. He receives monthly sinus flushes at LPCH.

Sinusitis and Cystic Fibrosis

Introduction

Respiratory disease in cystic fibrosis (CF) is usually associated with the lungs. However, acute and chronic sinusitis are common complications that can cause significant symptoms that sometimes adversely impact the lungs. Sinusitis is defined as inflammation of the nose and sinuses. Most persons with CF develop sinus symptoms, with onset typically between the ages of 5 and 14. Severity of symptoms and disease varies widely. Treatments include oral, systemic and inhaled medications as well as surgical and medical interventions. In this issue, we will discuss CF-related sinus symptoms, diagnoses and some treatment options that may minimize the discomfort caused by sinusitis.

The lungs, nose and sinuses comprise the respiratory tract, and all can be impacted by CF genetic mutations. Anatomically, the lungs comprise the "lower respiratory tract" while the nose and sinuses comprise the "upper respiratory tract." By evaluating the respiratory tract as one continuous structure, it is easier to understand the causes and treatment of sinus symptoms and disease in persons with CF.

Continued on Next Page

INSIDE

Sinusitis and Cystic Fibrosis

The Sinuses in Cystic Fibrosis

The sinuses consist of 4 pairs of air filled spaces: the ethmoid, maxillary, sphenoid and frontal sinuses, located behind the nose, cheeks and eyes. The sinuses warm and humidify the air you breathe. They also filter particles in the air, such as bacteria, spores and dust. The sinuses, like the lungs, are lined with epithelia cells that contain the defective CFTR that contributes to the inflammation and infection that causes CF complications. Most people with CF suffer from pansinusitis, inflammation and infection of all the sinuses.

The incidence of sinusitis in CF is not known, but the great majority develop sinus symptoms. Symptoms include:

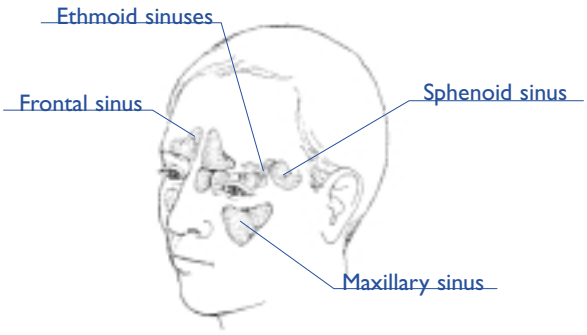
- nasal obstruction
- chronic congestion or discharge
- headaches
- post-nasal drip with morning cough
- cough that is aggravated by lying down
- severe bad breath
- constant need to "clear one's throat"

Adolescents and adults are more likely than children to report sinus-related headaches that often don't respond to typical headache remedies. Acute sinusitis is the term used when symptoms become severe. Many persons with CF have chronic, or recurring, sinusitis.

Nasal and sinus polyps, benign masses of tissue, occur in as many as 48% of persons with CF and increase in frequency with age. Polyps can grow over time, and often obstruct drainage of the nose and sinuses.

CF sinusitis is distinctive in imaging studies. Improper formation of the frontal sinuses, possibly a result of sinus obstruction early in life, is common and can be seen on x-rays. In CT and MRI scans, more than 75% opacification (cloudiness) of the maxillary and ethmoid sinuses is a hallmark of CF. Abnormal paranasal sinuses also are common.

CF-related sinus infections generally are distinct from non-CF bacterial sinus infections. Just as in CF lung infections, the most common sinusitis bacteria are *Staphylococcus aureus; Haemophilus influenza; Pseudomonas aeruginosa; Burkholderia cepacia; Achromobacter xylosoxidans* and *Stenotrophomonas maltophilia.* People with CF can have high bacterial loads in their sinuses without experiencing symptoms. Non-bacterial infectious agents are also found in CF sinusitis. Aspergillus molds colonize up to 40% of sinuses in adults with CF, although they often do not cause symptoms. Persons with CF are not more susceptible to common viral upper respiratory infections (the "common cold").



The incidence of "hay fever" or allergic rhinitis is the same as the general population. There is no known association of allergies causing nasal polyps or the development of asthma or more serious lung disease. However, since about 20% of persons with CF also have allergies, it is important to pay attention to known allergies or seasonal worsening of sinus symptoms so that they can be treated effectively.

Diagnosis

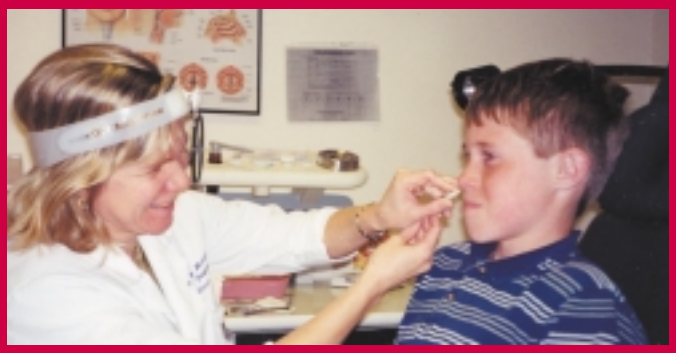
Diagnosis of CF-related sinusitis is based on symptoms. Imaging studies may help determine the extent of disease. Sinus endoscopy, placement of a small camera into the maxillary and sometimes ethmoid sinuses for direct viewing, is often used by an otolaryngologist (ear, nose and throat specialist) to visualize sinus polyps and obstructions.

Treatment

Treatment includes antibiotics, nasal steroids, clearance with saline or antibiotic flushes, antihistamines and decongestants and surgical interventions. Although there is no 'best' treatment for CF sinus disease, most people will benefit from a combination of therapies. Modalities are the same as those used for non-CF patients, although dosing and choice of drugs may be different, depending on the specific pathogens found in a culture.

Like the lungs, the sinuses benefit from "airway clearance." This includes anything to help remove mucus, such as nose blowing, saline flushes, saline nasal sprays to moisturize mucus so it can be "blown out" more easily and ENT-assisted interventions that remove mucus. More aggressive interventions are often recommended for people with frequent pulmonary exacerbations.

Antibiotic treatment for CF sinusitis is similar to that for lung exacerbations. Choice of antibiotic is based on the specific pathogens and their drug resistances. You should consult your CF physician before an antibiotic course is initiated for sinusitis to ensure the drugs, duration and dosing are appropriate. Combination antibiotic therapies are often



Anna Messner, MD, administers an antibiotic flush procedure on Devon Wakefield.

recommended and dosing can be significantly different than treatment of non-CF sinusitis. Nasal swabs and transantral aspirations for cultures are used, as well as sputum samples, since typically sinuses are infected with the same organisms as the lungs. Laboratories not associated with a CF Center often are not equipped to identify many CF pathogens and drug sensitivity levels that are important to optimum treatment. Treatment courses are usually 3–6 weeks due to the poor penetration of drugs into the sinuses, but there is no ideal length of therapy.

Antibiotics can be delivered systemically, via mouth or vein, or locally by inhalation or direct injection into the maxillary sinuses, a process referred to as antibiotic flushing. Systemic antibiotics are the standard of care, and sinus and pulmonary exacerbations are usually treated simultaneously. A recent study of non-CF patients using antibiotics nebulized directly into the sinuses found decreased nasal bacterial counts and inflammation. For users of inhaled TOBI™, sinus penetration of the drug occurs. Nebulizers adapted for inhalation through the nose coupled with an array of antibiotics are now available, and are reported to help some people with CF.

Flushing of the maxillary sinuses through catheters placed directly into the sinus is possible in people who undergo surgical antrostomies to enlarge the sinus openings. In two studies involving lung transplant patients, flushing with tobramycin through antrostomies resulted in absence or delay of contamination of the newly transplanted lungs with Pseudomonas. Another study of CF patients with chronic sinusitis showed that those who had monthly flushes with tobramycin had fewer surgeries over a two-year period of time. What remains unclear is how this treatment compares to other forms of "airway clearance" for the upper respiratory tract and the influence of monthly checks on the sinuses. Some patients have monthly appointments in the ENT clinic for flushes, whereas others do the flushes at home.

Some patients report relief of sinus symptoms by flushing with saline. Clearing mucus, infectious organisms and hydrating thick secretions may provide symptomatic improvement. Products include saline-filled squeeze atomizers, some of which contain the moisturizing agent glycerol. More economically, patients can flush with a homemade buffered saline solution. (Recipe: Add 1 teaspoon of salt and one pinch of baking soda to a pint of warm water.) The nostrils can be flushed with the saline using a bulb, catheter-tipped syringe or a specially designed nasal irrigation cup available from allergy supply sources.

Continued on Next Page

Sinusitis and Cystic Fibrosis

Continued from Page 3

Nasal steroids help some people with CF-related sinusitis. Regular use of nasal steroids may diminish the size and number of nasal polyps, and their use after polypectomy (removal of polyps) may decrease the rate at which polyps re-form.

The effectiveness of antihistamines and decongestants in CF is inconclusive. For some, they are too dehydrating. For others, especially those with allergies, antihistamines relieve stuffiness and runny nose and do not worsen lung congestion. Decongestants, such as pseudoephedrine (Sudafed™), sometimes relieve symptoms of sinus headache or fullness. Topical decongestants, such as oxymetazoline (Afrin™), may give temporary relief by promoting sinus drainage, but should not be used more than three consecutive days due to a rebound effect that can lead to increased nasal secretions. Mucolytics, such as guaifenesin, may also help sinus drainage.

Surgical treatment is an option for treatment of chronic symptoms such as headache, loss of taste or smell, severe post-nasal drip, frequent lung exacerbations and those awaiting transplant. Procedures include antrostomies (windows placed between the maxillary sinuses and the nasal passages that allow insertion of drainage tubes), clearing, ethmoidectomies (removal of tissue that separates the sinuses), and nasal polypectomy. Surgical intervention often relieves nasal obstruction, decreases purulent nasal discharge, increases energy levels, and improves the sense of smell.

Antrostomies and ethmoidectomies augment medical therapy by providing easier access to the sinuses via flexible catheters through which saline or antibiotics can be injected. In one study of CF subjects undergoing antrostomies followed by monthly flushing, all reported improvement. Polypectomy is the treatment of choice for obstructive polyps. With newer surgical techniques, recurrence is less frequent. Surgery done in childhood does not protect against the development of chronic sinusitis, and therefore should be reserved for symptomatic patients who fail less invasive interventions. Finally, surgery without meticulous follow-up care often is not successful. If routine flushing is not performed, the enlarged access to the sinuses and improved drainage may not be maintained.

Summary

Sinus disease is common in children and adults with CF. Symptoms vary in severity, though they are not life threatening. Many interventions improve symptoms and overall health. You should discuss your sinus symptoms with your CF physician to determine whether a consultation with an ENT physician, testing for allergies or other diagnostic work-ups are needed to determine the best course of treatment. Although sinusitis in CF is common, most people can achieve significant relief with proper treatment.

Sinus Care at Stanford and LPCH

Acute sinusitis in CF patients can be problematic, even after surgeries, due to chronic infections, sinus pressure, pain and drainage. The Stanford Sinus Center is a unique clinic founded by the ENT physicians at Stanford. These doctors use several newer tools to help with the diagnosis and treatment of sinus infections. Sinus Center physicians who routinely treat CF patients include Winston Vaughn, Director of the Sinus Center, Anna Messner, Chief of Pediatric Otolaryngology and Kay Chang, Assistant Professor of Pediatric Otolaryngology. New tools include video nasal endoscopy, sinus CT scans, sinus cultures, functional endoscopic sinus surgery (FESS) with computer guidance and nebulized anti-microbials. Some of these techniques and tools may offer new treatment options and symptom relief even for previously treated CF sinus patients.

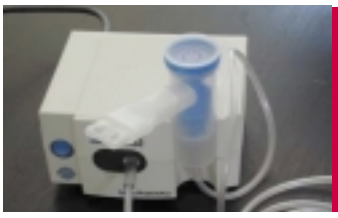
The Sinus Center, and the LPCH pediatric ENT clinic, focus on identifying the best medical or surgical treatment for problems of the nose and sinuses. Following an initial history and physical, patients are often examined with a video nasal endoscopy in which small cameras are placed through the nostrils to look at the sinus and drainage pathways.

Cultures and a CT scan are used to determine the cause and extent of disease. Functional Endoscopic Sinus Surgery (FESS) is sometimes used to open the sinus cavities, usually under general anesthesia.

During the surgery, computer guidance using the CT data is often helpful, especially for patients who have had previous surgery or who have severe disease or scarring (see www.surgicalnavigation.com for more information on this technology). After surgery, patients may go home the same day, depending on their lungs and recovery from anesthesia.

The various techniques described previously are helpful in the ongoing management of sinus disease. The physicians at the sinus and ENT clinics work closely with our CF patients and the CF Center physicians to identify the best treatment options for each patient.

The Stanford Sinus Center, located at Stanford Hospital and Clinics may be reached at 650-723-5281. Pediatric patients are seen at the Lucile Packard Children's Hospital ENT Clinic at 650-498-2565.



Nebulizer with nasal tip.
See: www.sinuspharmacy.com
for more information.

Frequently Asked Questions

LPCH Chief of Pediatric Otolaryngology Anna Messner and our CF Center physicians respond to questions about CF-related sinus disease:

Should I call my CF doctor or my primary care doctor for acute sinus symptoms?

It is important for all acute sinus infections to be evaluated. Since culture and sensitivity reports are a key element of treatment, we recommend calling your CF doctor.

When should a consultation for an ENT be considered?

An otolaryngologist (ENT or head-and-neck surgeon/physician) is helpful when there are problems with constant nasal obstruction (congestion), frequent nasal discharge, post-nasal drip, polyps or worsening cough or lung function thought to be related to the sinuses.

How do you evaluate a CF patient?

We start with a head and neck examination and, often, a CT of the sinuses. Nasal endoscopy, to look in the sinuses with small cameras, can also be done in the clinic, depending on the age of the child.

When is a CT scan of the sinuses requested and why?

A CT is critical to determining the status of the sinuses, particularly in someone who has not had sinus surgery and whose sinuses cannot be viewed with an endoscope. The scan can be used to determine anatomy, mucus and polyp build-up or how much air is in the sinuses. We look at whether there are bone changes as a result of the sinusitis and whether there are any mucoceles—mucus trapped in a sinus which can not escape. With the information on the symptoms and CT results we can determine whether surgery would be beneficial.

What is a nasal polyp?

A polyp is a swollen, thick portion of the lining of the nose or sinus. They are typically gray and look like little bags of water. Children with CF are particularly prone to developing polyps which can be a quite severe problem if they obstruct drainage.

What is bone remodeling?

Many people with CF have thick, boney walls in their sinuses due to chronic inflammation. When pressure from mucus builds to a high level over time, it can cause the boney wall to expand—this is called a mucocele.

When should sinus surgery be considered?

Every patient is evaluated individually. If a patient cannot breathe through his/her nose due to polyps or chronic sinusitis then surgery should be considered. If a mucocele is seen on a CT scan then sinus surgery is generally recommended. Chronic sinusitis seen on CT scan does **not** necessarily mean that sinus surgery is needed.

When is a child old enough for surgery?

There is no set age.

Is it an outpatient procedure?

Usually the patient spends one night in the hospital. An overnight stay is recommended, particularly for children, to make sure the patient is stable and that the lung function is good after undergoing anesthesia.

How long is the recovery? How painful?

Sinus surgery is a mildly painful procedure, requiring pain medications for an average of 2–3 days. It takes about 4 to 6 weeks for the sinus cavity to heal 90%.

What kind of therapy is recommended after surgery?

For the first 3–5 days after surgery we recommend irrigating the maxillary sinuses with topical tobramycin. My patients increasingly use inhaled antibiotics so that all the sinuses are exposed to the antibiotics—not just the maxillary sinuses. Some people benefit from coming to the clinic on a regular basis (up to one time per month) to have a topical antibiotic placed in the maxillary sinuses.

Are daily saline flushes beneficial?

Saline is helpful in the healing phase after sinus surgery by cleaning away mucus and old blood. A clean technique to wash the sinuses will be taught, and all apparatus should be cleaned carefully after use to decrease the chances of re-infection.

Is there a difference in CF sinusitis in children and adults?

Children are more likely to have problems with massive polyps compared to adults.

Do you recommend any nasal sprays, like Rhinocort™, etc.?

Frequently we recommend a steroid nasal spray such as Rhinocort®, Nasonex®, Flonase®, Nasocort®, Beconase® or Vancenase®, generally in consultation with your CF physician. These drugs are useful in people with environmental allergies and sometimes in people with polyps.

LPCH CF Education Day Highlights

The Stanford CF Education Day, on March 8, brought a large turnout of families, patients and center staff. The keynote speakers included noted disability attorney and advisor to the CFF, Beth Sufian, and Denise Angst, a national leader in research on treatment adherence. Other notable speakers included Stanford psychiatrist Jose Maldanado, MD, who spoke on coping with CF and depression and Gabriel Garcia, MD, Stanford GI-liver specialist, who spoke on CF-related GI issues (in particular DIOS and Reflux). CF Center speakers included dietitian Julie Matel, on encouraging good eating habits and nutrition in young children; Zoe Davies, research coordinator provided an update on gene therapy; Carol Conrad, MD spoke about azithromycin; and research coordinator Colleen Dunn, spoke about current and upcoming clinical trials at Stanford.

Nicole Eden, RN, pediatric nurse coordinator, and Kristin Shelton, RCP, CF respiratory therapist, with the day's youngest CF participant, two-week-old Marin Baugh, with parents Brad and Amy Baugh, and another parent, Katherine Cance

Parent Tib Hotson, left, and CF Center nurse educator Judy Kirby, RN, MS, right

CF Center physician, Laurie Witcoff, left, and speaker Denise Angst

Mary Helmers, RN, adult nurse coordinator, with sons Matthew (in Stanford sweatshirt) and John

Zoe Davies, PNP, research coordinator, and Rebecca Henig, daughter of CF physician Noreen Henig, enjoy a break between sessions.

CF Center social worker Joanne Asano and Diane Baxter, administrative assistant in CF research office, register parent Kathleen Flynn.

Active Research Recruitments

We are actively recruiting subjects for the following trials:

New Trials

- BIIL study to investigate the safety and efficacy of 24 weeks of oral medication that may reduce lung inflammatory response to infection (ages 6 and above)
- INS37217 Inhalation Solution (Inspire Pharmaceuticals) compared to placebo administered 3 times daily over 28 days (ages 10 to 50)
- Aerosolized tgAAVCF phase IIB gene therapy efficacy trial: placebo-controlled trial of 2 monthly doses, Must be ≥12 yrs old and have FEV1 ≥60% predicted

Ongoing Trials

- CF.Doc internet-based clinical care pilot project
- Infant and toddler pulmonary function testing
- Concentrated TOBI™: Comparison of safety and delivery time of a concentrated Tobramycin Solution for Inhalation in infants and children (6 months to 12 years)
- TheraCLEC™: Study of new oral enzyme (enrollment closed)
- Topical aminoglycosides: Study to activate CF genes in persons with a subgroup of CFTR mutations and controls (ages 6 and above)
- Duration of Pseudomonas Aeruginosa eradication by TOBI™ in children under age 6
- BIIL study of oral medication (enrollment closed)
- Once Daily Aminoglycoside Trial
- Standardization of Nasal Membrane Potential Difference
- Diabetes Therapy to Improve Body Mass Index and Pulmonary Function
- Hi-D FACS with CF blood and lung leukocytes of chronic oxidative stress in CF (cell samples needed)

Please consider participating in our research efforts. It is through the efforts of all of us that better treatments will become available.

Nutritionist Violet Hsieh Joins CF Team

Nutritionist Violet Hsieh has joined the CF team during Julie Matel's maternity absence. Violet spent three years at LA Children's Hospital prior to coming to Stanford. She earned degrees in Botany and Public Health with a focus on nutrition at Tulane University. She is enjoying getting to know the CF patients and their families.

Pulmonologist Harris to Join Adult CF Center Team

Pulmonologist Hugh Harris will join Noreen Henig in the adult CF clinic this summer. Dr. Harris completes a fellowship in pulmonology at Stanford in June. During his fellowship, he followed CF inpatients and outpatients. Dr. Harris attended medical school at Hahneman in Philadelphia and completed an internal medicine residency at University of Arizona. He looks forward to establishing clinical relationships with the adult CF clinic patients and becoming a part of the Stanford CF Team.

Stanford CF in the News

Terry Robinson, MD will speak on "Composite CT/PFT scoring and quantitative CT measurements—A shift in the paradigm of assessment of early CF lung disease" at the CFF Williamsburg meeting in June. **Rick Moss, MD** will be chairing a session on inflammation and will be speaking on the results of the tgAAV Phase II gene therapy trial at the CFF Williamsburg research conference and at the American Society of Gene Therapy in June. Dr. Moss also presented results of the inhaled interferon trial at the American Thoracic Society in May.

Phase IIB Gene Therapy Trial to Begin in June

The Phase IIB gene therapy study is scheduled to start in early June 2003. People with CF ages 12 and older with a FEV1 of greater than or equal to 60% are eligible to participate. The trial requires 8 clinic visits over a period of 3 1/2 months with 2 follow-up phone calls on Day 150 and Day 210. Two doses of gene therapy or placebo will be given via inhalation into the lungs on Day 0 and Day 30. Please contact a research coordinator if you have an interest in this or another trial.

New Cookbook—For The Whole Family!

Kids Crave the Darndest Things—and Grown-Ups Too!, the Center's new cookbook that includes recipes tailored for the calorie and nutrition needs of the whole family, is now available. To order your copy, send your name and address with the suggested donation of $10.00 made payable to Lucile Packard Children's Hospital (LPCH) to the following address:

CF Center Cookbook
c/o Judy Kirby
LPCH Stanford CF Center
701 Welch Rd. Suite 3328
Palo Alto, CA 94304

Ibuprofen Dosing Alert & Reminder

High dose ibuprofen therapy has been shown to reduce inflammation and slow the rate of decline in lung function in children and adolescents. Dosing levels are precisely determined by weight, and must be verified through peak and trough measurements of blood concentrations to ensure optimal therapeutic effect. Dosing must be adjusted when weight changes by more than 25% (increase or decrease). Recently, we have found that there is a significant variation in absorption and blood concentration among the brands of ibuprofen. Therefore, we are recommending that our patients who are on high dose ibuprofen therapy check the brand of ibuprofen tested and routinely used. You should first ask your pharmacist if it is possible to obtain the same brand, and if not, you should notify us so that dosing tests can be ordered.

Ross Mosier Classic July 28

The annual Ross Mosier Classic golf tournament and banquet will be held Monday, July 28 at the Stanford Golf Course. Two start times are scheduled at 7:15 am and 12:30 pm. Lunch will be served. At 5pm there is a wine tasting and silent auction, followed by dinner and a live auction. All proceeds benefit CF research at Stanford. The annual event, held in honor of Ross Mosier, has raised more than $1,250,000 to support CF research. To register, visit http://rossmosierclassic.org or call Clyde Mosier at 1-800-500-5598.

CYSTIC FIBROSIS CENTER AT STANFORD

Center Physicians: Richard Moss, Director; Noreen Henig, Adult Center Director: Carol Conrad, Terry Robinson, Lauren Witcoff, Hugh Harris

Clinic E Scheduling (Chandra McDuffie)	650-497-8841 Fax 650-497-8837
Nicole Eden, Pediatric Nurse Coordinator	650-736-1359
Mary Helmers, Adult Nurse Coordinator	650-636-1358
Kristin Shelton, Respiratory Coordinator	650-724-0206
Violet Hsieh, Nutritionist, Dietitian	650-736-2128
Joanne Asano, Social Work	650-736-1905
Zoe Davies, Research Coordinator	650-498-5315
Colleen Dunn, Research Coordinator	650-736-0388
Judy Kirby, Webmaster	650-724-3474
Penny Stroud, Newsletter	650-692-8884

For Urgent Issues:
Monday–Friday 8:30–5:00 pm contact RN Coordinator
All Other Times (ask for Pulmonary Physician On-Call)
650-498-8000

Medication Refills
Call pharmacy where medication was last filled
LPCH Pharmacy Refill Line 650-497-8289

See our Web site at http://cfcenter.stanford.edu for more information about our center, CF and current topics.

To subscribe to this newsletter please call or e-mail Judy Kirby at the numbers listed above.

We gratefully acknowledge the leadership of friend and parent Penny Stroud in producing this publication.

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