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Lucile Packard Children's Hospital AT STANFORD

CYSTIC FIBROSIS CENTER NEWS

CF Microbiology: Sticky Pests Need Special Tests

Ellen Jo Baron, PhD in lab

From the very youngest to the oldest person with CF, obtaining a respiratory culture is part of the clinic routine. Clinical research correlates frequency of cultures with improved health, most likely due to improved detection of new bacteria and treatment with the appropriate drugs. For the youngest persons with CF, early detection may allow eradication or prevention of chronic infection, factors associated with improved health and longevity. For the oldest, frequent cultures detect new and sometimes more virulent microbes that require aggressive treatment or infection control protocols to prevent transmission. Clinical laboratories at accredited CF centers take their detective work seriously, investing additional time and special procedures to ensure identification of the bacteria unique to CF.

The CFTR defect results in reduced water absorption in the lungs and overproduction of thick, sticky mucus. This facilitates colonization with a host of microbes: viruses, fungi and bacteria, that cause chronic inflammation, sinusitis, and bronchiectasis (lung scarring). In the normal lung, inhaled microbes are cleared by the innate defenses of the airway that include mucociliary clearance and lung defense cells, processes that are impaired in CF. Some microbes are unique to CF and require special attention to identify and determine the most effective treatment options. Failure to treat susceptible bacteria can result in selection for and persistence of multi-drug resistant organisms, or lead to infection with more exotic bugs such as *Achromobacter xylosoxidans*, *Stenotrophomonas maltophilia* and *Burkholderia cepacia* complex.

Certain microbes preferentially infect CF lungs. *Staphylococcus aureus* and Haemophilus *influenzae* are often among the first isolated from the cultures of young persons with CF. Although serious infections with these bugs are uncommon when treated aggressively with antibiotics, labs are now seeing atypical variants of *S. aureus* in CF. Because they do not look and act like typical strains, they are not detectable on the conventional agar plates used by most laboratories and require special media to grow. In fact, Ellen Jo Baron, Ph.D. Professor of Pathology and Director of the Stanford Microbiology laboratories, reports that a study last year resulted in use of a new medium (the term used for the plates on which they culture the sputum microbes) that detected bacteria in 10% more cultures than the medium used by most labs.

Asthma and Airway Reactivity in CF

We now know that *Pseudomonas aeruginosa* (PA) infects many people with CF far earlier than previously thought and eventually infects more than 80% of the CF population. Frequent cultures in young people help detect first infection, with CFF clinical guidelines recommending aggressive antibiotic treatment to attempt eradication and delay of chronic infection. Aggressive treatment and delayed infection are considered a major factor in longer life span and overall improved health. Certain strains of PA are over-represented in CF, though person-to-person transmission is rare when good infection control protocols are employed. Once infected, most people harbor the same PA strains for years. Over time, PA develops into mucoid variants that are more difficult to eradicate, hence the importance of early and aggressive identification and treatment. In 2003, the clinical lab at Stanford identified 966 strains of PA, 300 of which were derived from persons with CF. Of those 43% were mucoid varieties, of which 70% were sensitive to most of the antibiotics tested. Interestingly, when PA becomes mucoid, it requires lots of energy to maintain the biofilm structure (a filmy coating of the airways that is difficult to eliminate, like a slim-covered slippery rock in a stream), limiting its ability to retain antibiotic resistance factors. In one example, 47% of the non-mucoid strains of PA identified at Stanford in 2003 were resistant to tobramycin, compared to only 9% of the mucoid strains. In lab cultures, mucoid strains can overgrow other bacteria and fungi, preventing detection of significant other pathogens unless special media are used and cultures are incubated longer and examined more frequently than other types of cultures.

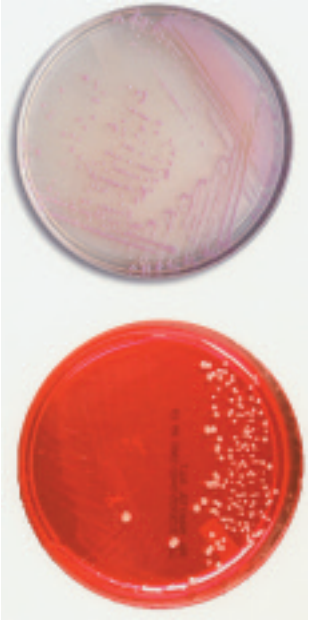
Burkholderia cepacia and *Stenotrophomonas maltophilia* often infect CF lungs later, though infection rates are much lower than for PA (fewer than 10% of the Stanford CF population). B. cepacia, feared for its particular virulence and multi-drug resistance, is actually several related microbes (classified into groups called genomovars) that have widely varying clinical impact. They are of particular concern due to known person-to-person transmission. There are now nine identified genomovars:

I. B. cepacia
II. B. multivorans
III. B. cenocepacia
IV. B. stabilis
V. B. vietnamiensis
VI. B. dolosa
VII. B. ambifana
VIII. B. anthina
IX. B. pyrrocinia

Genomovar III is the family that most often has strains causing "B. cepacia syndrome" which can lead to rapid clinical deterioration. In the lab, all genomovars are notoriously slow growing and hard to identify. No routine clinical laboratory in the U.S., including Stanford, currently identifies their isolates to a specific genomovar. However, even identification to the "cepacia complex" group is not easy. Dr. Baron notes, "Given the serious consequences of misidentification—either falsely positive or negative—it is imperative that laboratories adopt extraordinary practices for detection of this organism. Special selective agars, longer incubation times, heightened suspicion, and ample use of numerous biochemical and phenotypic tests are all required." In fact, Stanford microbiologists typically spend an average of 2.5 hours on each CF respiratory culture.

Fungal cultures are performed at least annually, or if there is a suspicion of allergy. These also require particular media and techniques. Dr. Moss, CF Center Director emphasizes the importance of frequent sputum cultures, "Changes in antibiotic susceptibilities, new bugs and atypical microbes won't be identified if we don't look for them—our laboratory and those at other accredited CF centers hold to higher standards to ensure CF-related infections are detected. The sooner treatment begins, the more effective we are at improving your health and limiting lung damage."

CF Patient Cultures



Using Acid-Blocking Medicines in Cystic Fibrosis: Is There a Downside?

Medicines to reduce stomach acid are commonly taken by people with CF to help with heartburn, reflux, stomachaches, or to make pancreatic enzymes work better. Many people take over the counter antacids such as Tums® or Mylanta®; others take stronger acid-blocking medicines called H2 blockers such as Cimetidine (Tagamet®), Ranitidine (Zantac®) or Famotidine (Pepcid®). The strongest class of acid-blocking medicines is the Proton Pump Inhibitors (PPI's) that include Omeprazole (Prilosec®), Lansoprazole (Prevacid®) and Rabeprazole (Aciphex®).

PPI's have been shown to be safe and to reduce stomach acid very effectively. Common side effects include diarrhea, headache and gastric bacterial overgrowth. However, are PPIs as safe for people with CF? The Stanford CF team is currently studying whether people with CF who use PPIs experience a side effect known as bacterial overgrowth.

Stomach acid normally kills any bacteria that we ingest within about 15 minutes. When stomach acid production is blocked by a medicine such as a PPI, those bacteria don't get killed. The bacteria can live in the stomach or pass on down to the small intestine. Abnormally high numbers of bacteria in the stomach and small intestine is called intestinal bacterial overgrowth. It can cause symptoms such as gas, bloating and diarrhea; all common symptoms for people with CF. Bacterial overgrowth can also worsen anemia and poor nutrition. People with CF may be at risk for bacterial overgrowth because many have low pancreatic fluid and poor gastrointestinal motility, conditions that favor the growth of bacteria.

Bacterial overgrowth has not been systemically studied in people with CF. Jackie Fridge, a Cystic Fibrosis Clinical Fellow in Pediatric Gastroenterology, Hepatology and Nutrition, is leading a team that includes Drs. Ken Cox (GI), Carol Conrad and Ricardo Castillo (GI) to determine the presence of intestinal bacterial overgrowth in persons with CF. The study will compare bacterial overgrowth in pancreatic insufficient persons who regularly take PPIs with those who don't. Subjects will take a breath hydrogen test, a routine diagnostic test often used in GI diagnostic work-ups, to check for bacterial overgrowth. If you or your CF physician suspects a problem with bacterial overgrowth, you may want to discuss a GI consult to determine whether taking the breath test is indicated. If bacterial overgrowth is a problem, then simple changes such as taking the PPI medicine only once a day rather than several times a day, or taking probiotics ("good" bacterial supplements such as Lactobacillus) sometimes corrects the problem. If you are interested in the study, talk to your CF physician.

Jackie Fridge

On the Road with CF

41-year-old Peter Judge has been an engineer, mastered the banjo, volunteered at the YMCA and Urban Ministry, but until last fall, he had never driven cross-country. 8500 miles, six weeks and one day later, he crossed that milestone off his list. Peter was diagnosed with CF at age 17, and has lived independently since going to college at age 18. He studied music and engineering, then worked at Hughes Electronics until age 26, when his health took a turn for the worse after acquiring Pseudomonas *aeruginosa*. As a young adult he didn't want to believe that he had to take care of himself differently than his peers.

Pete came to a realization a year after he retired on disability, "Although my life hasn't turned out the way I expected, at some point I realized that I had a choice of making the best of what I have or sitting around and being unhappy or mad at the world." In 1997, he began swimming 20-60 minutes each day, a habit he credits with stabilizing his lung function and health. He can now swim a mile without stopping. He also began an active volunteer life, working with the homeless. He's had good and bad years, averaging two to three hospitalizations a year. Using oxygen at night helps him sleep more comfortably. He does twice daily airway clearance, aerosolized antibiotics and a daily swim to keep in shape.

Last November Pete decided it was time to see the U.S. He took off in his Toyota 4 Runne—with a map of all the YMCAs with swimming pools between California and the North Carolina home of his best friend. He carried medications, an oxygen concentrator, a cooler and his swim trunks. The odyssey is chronicled on the website "Order Out of Chaos" (http://journals.aol.com/pjudge80/TheOdyssey/). Highlights of the trip included seeing old friends, meeting new ones and visiting Kitty Hawk. Here are a couple of his journal entries:

> *Pointing the car south from Port Townsend yesterday, the scenery down the Olympic Peninsula was lush and green. Following Hood Canal, there were many bays and coves. After many miles, the water finally ended, and soon I was passing through the city of Olympia. To the east were the Cascades, but Mt. Rainier was covered in clouds. I could see Mt. St. Helens, though, looking snowy and sinister. Crossing over the Columbia river for the second time-the first was between Spokane and Seattle; wider than either the Missouri or the Mississippi, with sheer cliffs extending down to the water, it had a primordial appearance; I could easily imagine huge marine reptiles breaking the water and pterodactyls drifting down the canyon on leathery wings-and crossed into Oregon.*

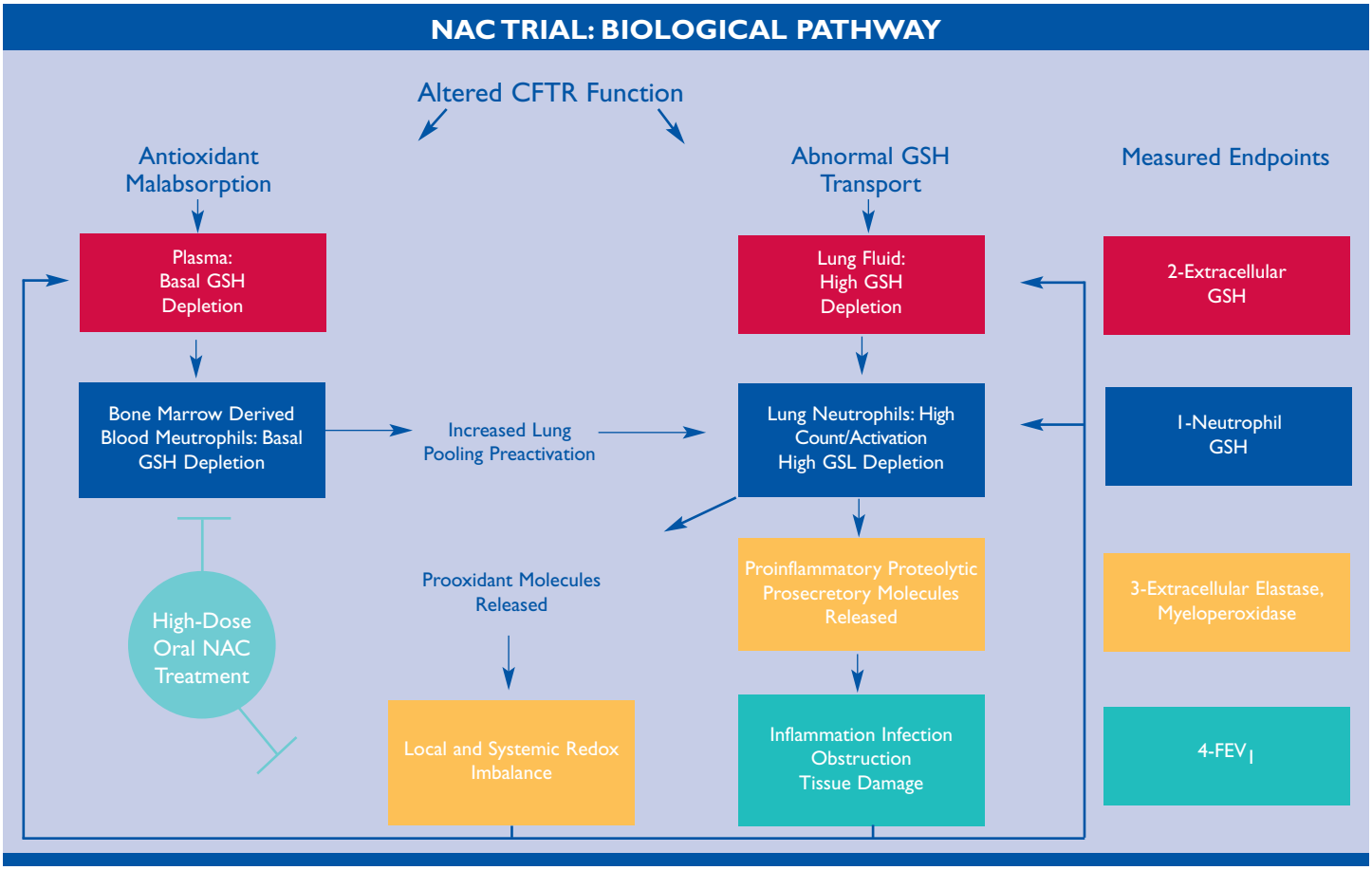
Pete reports that his health is the best it's been in many years, and that it's good to be back home.

Peter Judge

Tips for Traveling with CF

- Make sure you have enough medication to last the entire trip and carry copies of prescriptions with you.
- To avoid extra baggage or weight charges, call the airline to have them note the need for heavy medical equipment in your record.
- Some persons experience the need for extra oxygen when flying. Unless your lung function is normal or nearly so, check with your doctor to see if oxygen or other precautions are indicated.
- Drink plenty of fluids and consider wearing a mask when flying. Airplanes have notoriously poor air filtering systems and altitude causes dehydration.
- For extended stays, you can make arrangements to rent a Vest at your destination instead of having to take it with you. Vests (even the old ones!) fit into some of the larger suitcases with wheels and withstand baggage handling.

NAC→GLUTATHIONE AND CF



Glutathione (GSH) is a chemical the body uses to maintain a balance between fighting infection and healing. In CF, the neutrophils (white blood cells) are deficient in GSH, thereby limiting their effectiveness in controlling inflammation. Neutrophils are called to the lung, arriving in the blood, to fight bacteria such as *Pseudomonas* or *s. Aureus*. This causes inflammation through the release of proteins that work to destroy the bacteria. Dr. Carol Conrad likens the situation to a war: bacteria invade, the warrior neutrophils are called in to fight, and, in the normal lung, the body uses GSH to help stop the battle and mediate a truce. In CF, she says, the troops (neutrophils) are out of control: they keep fighting after the war has been won, causing over-inflammation and harming the host. In summary, there's not enough GSH in the neutrophils to control the inflammatory response, hence what was initially helpful begins to cause damage that includes scarring, dysfunction and bronchiectasis.

Dr. Conrad and the Stanford CF team are initiating a study to determine if GSH can be replenished in the CF airway by giving an oral nutritional supplement called N-acetylcysteine (NAC). NAC is a building block used by cells to make GSH. It is easily absorbed by the intestine and gets into the liver, which makes it into GSH. GSH is then delivered via the blood, to the bone marrow where neutrophils are made. In the bone marrow, GSH is "packaged" into the neutrophils, which are released into the blood which then flows to the lungs to fight an infection. NAC has been studied extensively in other diseases. Previous clinical trials with inhaled GSH have not shown any benefit in CF, however Dr. Conrad notes that inhaling may be an ineffective way of getting GSH into the lungs since there is already an overwhelming amount of inflammation and mucus present. GSH is unstable and may be compromised by the very act of nebulization.

The new study, which is funded by the CF Foundation, will determine if GSH levels can be increased in blood neutrophils. The first phase of the study will determine the safety and dosing levels over a four-week period. The second phase, which will be placebo-controlled, will determine efficacy over a twelve-week term. It is open to persons aged 10+, with higher than mild to moderate changes in pulmonary function. NAC will be taken orally three times a day in the form of a capsule. Blood and sputum samples, PFTs and clinic visits will be required. Contact a research coordinator at 736-0388 or ask your doctor if you are interested in participating.

CF EDUCATION DAY 2004

The 4th annual CF Education Day hosted 200+ guests who heard the Stanford CF team and an international panel speak about CF. The free event drew persons with CF, families, caregivers, and providers.

Hugh Harris presented an overview of lung transplantation, from evaluation and listing, the peri-operative experience, complications and prevention. Medical complications and psychosocial concerns are the principal reasons people aren't listed, though he noted that more than 80% of persons who are invited for an evaluation are accepted onto the transplant list.

Randah Whitley, RPT, a physical therapist at the University of North Carolina offered an enthusiastic program on exercise as an alternative to traditional airway clearance. The UNC program is modeled on the Swedish approach that she summarized as 1) Work to stay ahead rather than having to rehabilitate; 2) Aerobic activities such as bouncing, trampoline, jump rope, running, swimming and golf; and 3) Posture exercises such as wheelbarrows, push-ups, and abdominal strengthening. She stressed the importance of beginning in infancy to build and encourage life-long strength and habits. Her program involves a variety of activities that focus on upper body strengthening, aerobic training and mobility.

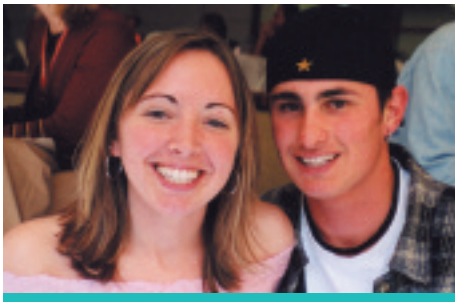
University of London psychiatrist Bryan Lask's talk focused on factors that help and deter adherence to therapies. He attributed poor adherence to inadequate knowledge; emotional distress; belief that the treatment is worse than the disease; or denial that treatment is needed. Dr. Lask, stated, "The family is in the strongest position to influence rates of adherence. It is import to listen, acknowledge, accept and understand motivational issues, and work as a team with consistency between each other and over time." He proposed negotiating "concordance" on treatment therapies between patients and caregivers. The lack of immediate results and complexity of treatments challenges consistent adherence. He suggested five "Musts" for good adherence:

- Taking a comprehensive approach
- Avoiding coercion
- Finding concordance
- Supporting the family
- Acknowledging and accepting feelings and enhancing motivation

Dr. Lask's book, *Psychosocial Aspects of Cystic Fibrosis*, is available from Oxford University Press.

Robin, patient, and Anna Modlin

Kristen Shelton, LPCH CF respiratory therapist, and Randah Whitley, physical therapist, University of North Carolina, speaker



Desiree Contreras, patient, and boyfriend Justin Liggett

Carley Rios, patient

Concordance

A model of prescribing, based on negotiating agreements that respect the patient's perspective, rather than telling the parent or patient what to do.

Ethicist Walter Robinson, MD, MPH from Harvard discussed understanding medical decision-making and reasoning in the context of a "story". He noted, "We reason in stories—not completely bottom up and not completely top down. Not every case is new, but every patient is. Not all rules are contingent, but every situation is." Dr. Robinson suggested thinking about a person with CF in the context of a story: how do our actions affect the "plot" of a patient's life; how does how we "tell" the story express our own character; and what are the responsibilities of caregivers as authors of a patient's story? The relative nature of each situation dictates a need for providers and caregivers to determine and understand what each person's story "depends" on, so that the ethical and appropriate choices are presented.

The day included presentations by Dr. Moss on disease progression and current CF research and Jackie Fridge, and a panel discussion with Joanne Asano and mother-daughter pairs, Carley and Miriam Rios and Robin and Anna Modlin who discussed strategies for managing life, school and CF.

Stanford in the News

A course entitled "Caring for the Adult Patient with CF" was held in May at the Stanford Center for Education and Professional Development. The program for health professionals was coordinated by Carole Nakamura, RN, Educator on the Adult CF Unit at Stanford. Faculty included team members Hugh Harris, MD, Kristin Shelton, RRT, Julie Matel, MS, RD, Mary Helmers, RN, BSN, and Joanne Asano, LCSW, and Lisa Levin, RN, MS Lung Transplant Coordinator, and Lawrence Witt, PharmD, Adult Medicine Clinical Pharmacist.

The adult CF inpatient service was highlighted during Stanford's recent Joint Commission on Accreditation of Healthcare Organizations (JCAHO) survey. The Adult CF Interdisciplinary Team participated and surveyors interviewed a CF patient who highly commended the care she received, impressing the surveyor with first-hand experience.

Carol Conrad has been appointed Medical Director of the Pediatric Lung and Heart-Lung Transplant Service. Center Director Rick Moss co-authored new Treatment Practice Guidelines for health insurance industry case managers to be published this summer. Dr. Moss talked about allergic bronchopulmonary aspergillosis at Texas Children's Hospital in Houston in February, and he gave a national web cast for CF caregivers in June "Rationale and Evidence for Early Antibiotic Treatment in Cystic Fibrosis." Hugh Harris will be leaving Stanford in July to take new position.

Current Research Studies

One CF drug can take 10 years, $600 million, and thousands of test subjects to reach the marketplace yet only a minority of people with CF participate. More participants result in higher throughput and faster results. To learn more about partipation, visit www.cfcenter.stanford.edu or contact our research coordinators.

- Phase IIB AAV-CFTR gene therapy 25E01
- CF.Doc internet-based clinical care (up to age 21)
- Infant and toddler pulmonary testing (4 months to 2 years)
- Concentrated TOBI (under the age of 6) IT004
- CF Diabetes
- Induced Sputum: evaluation of anti-inflammatory agents
- Altus TheraCLEC new pancreatic enzyme Phase II
- Oral glutathione precursor (NAC) study
- Studies recently completed: BIIL 284.45, Dry Tobi Powder, Aztreonam for inhalation
- Upcoming studies: Curcumin, human growth hormone, early Pseudomonas intervention, longitudinal chest CT scans, aztreonam for inhalation Phase III, parathormone for osteoporosis. Stay tuned!

Summer Hydration!!!

Remember to drink plenty of liquids during hot weather and physical exertion. Dehydration can be a problem that requires extra water and salt since people with CF lose excessive sodium and chloride when sweating. Most of the time, bodies self-regulate the use and loss of salt: most people want and consume salty foods, and the kidneys reduce the amount of salt lost in the urine. However, infants and young children may not be able to self-regulate, hence extra precautions are warranted. Electrolyte drinks such as Gatorade, or other drinks with salt such as sodas can help keep things in balance. Salt tablets with water may be helpful in some circumstances, though generally they are not needed. Drinking lots of fluids is always a good idea: most people underestimate their need for hydration during exercise and when it is hot.

New "Check First" Form Helps Phone Advice

We have a new form for you to use when calling the Center about illness and symptoms. Called "Check First", the form is designed to facilitate communication with the CF nurse coordinators. It is a checklist of information for you to know when you call coordinators Mary Helmers, Katherine Boyle or Nicole Eden to determine the need for further treatment. The form should expedite treatment and advice, reducing the need for callbacks and delays. Coordinator Boyle who designed the form conceived of the idea after noting that treatment is sometimes delayed when anxious callers leave inadequate information about their illness or current treatments. Having the form beside the phone will remind callers to know some basic information that will help us know what is needed. A grant from Digestive Care, Inc. is supporting production of the forms.

What to Know Before You Call

(Just SOME of the questions that help us!)

- Current temperature
- What medications are being taken, when were they taken and for how many days?
- What is the color, consistency and amount of sputum?
- Has frequency of cough changed and is it a productive cough?
- If there is abdominal pain, do you take enzymes and when was the last bowel movement?
- Is there a headache? Nasal congestion? Sinus pain?
- Has there been weight loss? Has energy level changed?

School/Sports Physicials

Please schedule appointments or request any health-related letters required by schools as soon as possible so we can best accommodate your needs! Last minute requests the week before school are sometimes difficult to fill, so take advantage of the rest of your summer and give us time to fill out forms and see you or your child well before school starts.

CYSTIC FIBROSIS CENTER AT STANFORD

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

Clinic E Scheduling	650-497-8841
Clinic Fax	650-497-8837
Katherine Boyle, RN Pediatric Coordinator	650-736-1359
Mary Helmers, RN Adult Coordinator	650-736-1358
Kristin Shelton, Respiratory Coordinator	650-724-0206
Julie Matel, Nutritionist, Dietitian	650-736-2128
Joanne Asano, Social Work	650-736-1905
Research Coordinators	650-736-0388

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

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

To subscribe to this newsletter please call or email Judy Kirby at 650-724-3474 or jkirby@stanford.edu

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