Sleep is vital to good health. Disrupted or inadequate sleep impairs alertness, which can jeopardize personal health, productivity, and public safety. It may also affect hormones that regulate height, weight, inflammation, metabolism, insulin sensitivity and immune function – all factors of major importance to persons with CF. Chronically disrupted sleep, whether from daytime sleepiness, inadequate sleep, insomnia, or sleep-disordered breathing, can lead to both psychological and physical issues including attention deficits, depression, anxiety, pain disorders, and disruptions at school, home and work.

CF and Sleep Disorders

There is increasing evidence of a higher incidence of sleep disorders and disruption among people with CF and their caregivers. A recent survey concluded that children and adolescents with CF have frequent sleep complaints, with the magnitude of sleep disruption associated with severity of lung disease. It found that:

- 74 percent reported daytime sleepiness
- 44 percent reported trouble falling asleep
- 39 percent reported trouble staying asleep
- 30 percent snored at night

CF-related sleep disorders can include respiratory-based sleep-disordered breathing (SDB) caused by obstructive sleep apnea due to enlarged tonsils or nasal polyps; cough; low blood oxygen; insufficient breaths; or pulmonary exacerbations. SDB may disrupt sleep quality, impair daytime functioning and worsen lung disease. One study reported significant correlation between sleep and FEV1 (Forced Expiratory Volume in the first second. This key pulmonary function test measures the volume of air that can be forced out in one second after taking a deep breath and is an important indicator of CF lung disease). In normal children, SDB is known to cause poor weight gain and decreased body mass index (BMI), factors strongly related to CF quality of life and survival.

The order and length of the different sleep cycles – called the “architecture” of sleep – may be different in people with CF. Sleep quality and...
architecture may be more variable in CF, making diagnosis and treatment of sleep disorders more complex. Non-lung disease-based causes of sleep problems include medication side effects (e.g. prednisone and certain antibiotics), as well as treatment schedules that cut into sleep time. A recent report also described a case of restless leg syndrome in a person with CF, resulting from iron deficiency which can result from chronic hemoptysis (coughing up blood).

Sleep and Caregivers

Caregivers of persons with chronic illnesses such as CF often report sleep disorders which can result from disrupted sleep caused by night wakings, poorer sleep quality or efficiency, and high levels of stress and worry. The result can be chronic partial sleep deprivation that negatively impacts mood, performance, energy levels and decision making that can lead to depression and fatigue.

Why is Sleep so Important?

Sleep is restorative. It helps the body recover from physical and mental work and stress. Sleep deprivation studies demonstrate negative physical and psychological impacts on overall health in normal as well as chronically ill people. The effects impact the individual with the problem as well as their family, caregivers, work, school and others who may come into contact with them. Higher health care utilization has also been documented in people with sleep problems.

Finding Solutions

Treatment of sleep disorders can have both physical and psychological benefits, improving health and quality of life in persons with and without CF. Treatment depends on the cause and extent of the problem and may include:

• Changing medications or timing of medications
• Sinus surgery or tonsillectomy
• Exercise
• Rehabilitation programs designed to improve cough or improve sleep patterns
• Night time oxygen
• Psychological or other counseling
• Stress management techniques
• Non-invasive positive pressure ventilation (NIPPV or Bipap) devices to assist with night time breathing. These devices are often used for obstructive sleep apnea or chronic obstructive pulmonary disease. A recent study in persons with late stage CF demonstrated that long-term NIPPV stabilized and improved ventilation, arterial blood gases and body mass index, and also improvement in symptoms such as sleep pattern, daily activity level, and morning headaches.

Diagnosing Sleep Problems

Physicians, persons with CF and caregivers should be alert to potential sleep problems, and determine causes and possible treatments. A physical examination may identify physical causes such as nasal polyps or enlarged tonsils.
Low oxygen levels (hypoxia) during sleep and exercise occurs in some people with CF. This may contribute to increased pulmonary artery pressure, reduced exercise ability and strength, and poor sleep quality. Animal research suggests disordered sleep in CF may even contribute to a decline in lung function by increasing lung inflammation and encouraging growth of *Pseudomonas aeruginosa*, though more research is needed to understand the frequency and impact in CF. If low oxygen is suspected, a physician may order overnight monitoring during hospitalization for a CF tune-up or lung exacerbation. This involves simply attaching a fingertip oxygen monitor and small monitor wires to track oxygen levels while sleeping. There are no Cystic Fibrosis Foundation guidelines for when to start oxygen therapy in CF, but supplemental oxygen can improve sleep quality for some people.

Using a “sleep diary” to record sleep patterns and times can be a helpful first step in determining if there is a problem that needs to be addressed. Depending on the severity, referral to a sleep specialist may be recommended. Stanford and Lucile Packard Children’s Hospitals have adult and pediatric sleep centers with experts in diagnosis and treatment. The Stanford Sleep Center, under the direction of Clete Kushida, MD, is renowned as the birthplace of the field of sleep medicine in 1970 and remains a leader in research and clinical care.

**Sleep Center Studies**

Pediatric pulmonologist Dr. Nanci Yuan is director of the pediatric sleep program at Packard Children’s. Following a consultation, Dr. Yuan typically orders a sleep study that requires spending a night in the specially monitored sleep lab that records brain, oxygen, movement and breathing patterns to help in the diagnosis of causes and treatments. The sleep center visit generally begins after 6 pm and starts with a sleep technician explaining the process to the patient and, if a child, a family member. The child is fitted with the non-invasive sleep equipment around 9 pm. Sometimes a blood test is ordered at the beginning and end of the study. The lights are turned off and the study begins whenever the child falls asleep. The study usually ends at 6 am when the child is assisted in removing the equipment and then goes home. The sleep study results are sent to the sleep physician for interpretation, which are then sent to the referring doctor within a week. The results, in combination with the consultation, are used to determine a treatment plan. Packard Children’s has sleep labs in the South Bay area and also works with the sleep lab at Community Hospital of the Monterey Peninsula.

**Summary**

The importance of sleep to physical and mental well-being is well-documented. Both adults and children with CF have lower sleep efficiency and more frequent nighttime awakenings than healthy non-CF individuals. Relationships between sleep quality and FEV1 and weight underscore the benefits of identifying and treating sleep disorders in persons with CF. Causes vary widely, from those that are relatively easy to diagnose and treat to causes that take the expertise of a sleep specialist and/or more complicated changes in lifestyle or medical interventions to correct. Parents, partners, persons with CF, physicians and others can work together as a team to identify and address sleep disorders. An effective treatment plan can yield immeasurable benefits and improved quality of life and health.
Frontiers of Cystic Fibrosis Drug Development

The landscape for CF therapy is undergoing a seismic shift. For the first time, drugs are in clinical trials that affect the basic cell dysfunction caused by mutations in the CFTR gene (cystic fibrosis transmembrane conductance regulator). There is early evidence from those trials of efficacy and potential clinical benefit. The Stanford CF Center is playing an active role in this research and is particularly excited about new drugs that directly treat distinct genetic categories of CF at their very root. One important aspect of this research is already clear: anyone with CF should know their genotype (the two CFTR mutations they carry).

VX-770 Works Around Blocked CFTR Regulation

One drug, VX-770, developed by Vertex Pharmaceuticals with support from the Cystic Fibrosis Foundation, is the first of the so-called “potentiators.” It was discovered by high-throughput screening, an automated drug discovery process that quickly tests thousands of compounds for a desired activity, such as getting CFTR to work, as evidenced by movement of chloride out of CF epithelial cells. VX-770 was identified and then tested extensively in the laboratory and animals for safety. The CFTR mutation G551D was selected for testing because it results in CFTR in the right location on the cell membrane of the airways and sweat ducts but it is not properly regulated (opened and closed). VX-770 overcomes this defect and potentiates (increases) the activity of CFTR by “opening the closed gate” of G551D. G551D is a Class III mutation that blocks proper functioning of the CFTR protein. The chart below illustrates the different CFTR classes and describes the type of malfunction in each class. G551D accounts for about 5 percent of CF mutations, but other mutations in Class III, as well as other CFTR classes (particularly Classes IV and V), may also be helped by VX-770.

“\textit{The current CF pipeline is finally realizing our long-held dream of new treatments that address CF at its roots rather than at its branches.}”

– Richard Moss, MD

A recent Phase II trial of VX-770 in adults with CF and the G551D mutation conducted at Stanford and other sites found that the oral pill was safe and showed early signs of effectiveness. Of the twenty participants, four received a placebo pill and 16 received VX-770. With careful attention to safety, evidence of effect was measured with nasal potential difference (NPD, a sensitive test of CFTR function in the nose), sweat test and lung function. Eight subjects receiving the highest dose of VX-770 showed a significant 10.1 percent increase in FEV1 compared to a slight decrease among patients receiving the placebo. The highest dose subjects also had improved NPD and decreased sweat chloride, from a mean baseline of 96 to 53 over the 14-day trial. Sweat chloride decreased to below 60 (the diagnostic cutoff for CF) in 6 of 8 patients in the high dose group. There was no notable change in sweat chloride in the placebo group. While the numbers are small and treatment period short, these astonishing results raise the possibility of a real control for at least some people with CF. Stanford is currently conducting a longer one month “Part 2” trial of VX-770.

VX-809: Possible CFTR “Corrector”

Vertex has identified another oral drug, VX-809, that is in a Phase I dosing and safety clinical trial in healthy non-CF volunteers. This drug is aimed at “correcting” the processing defect caused by the Delta F508 mutation, a Class II mutation that blocks processing of the CFTR protein. Delta F508 is found in about 85 percent of people with CF (50 percent have two copies of Delta F508 and another 35 percent have one
Delta F508 along with another CFTR mutation). This new line of corrector research could be of even greater importance than the VX-770 potentiator story. Stay tuned!

**PTC124 Bypasses Mutant CFTR**

PTC124, developed by PTC Corporation, addresses Class I “stop” mutations that affect 5-10 percent of persons with CF. These mutations generally end in X, such as G542X, W1282X, etc. PTC124 binds to ribosomes, the protein assembly apparatus inside cells, and allows the abnormal “stop” caused by the CFTR mutation to be bypassed.

A 2007 clinical trial conducted in the United States and Israel (where stop-mutation CF is very common), found PTC124 given as an oral suspension to adult subjects with stop mutations to be safe. It also improved nasal potential difference. Interestingly, elevated white blood cell counts (a measure of inflammation) decreased with use of PTC124, and there were trends toward improved weight and lung function. A more recent European trial confirmed the potential benefit of PTC124 in children with CF, and longer-term trials are underway in Israel. Currently PTC is working with the FDA to plan a definitive trial of PTC124 for CFTR stop mutations in the USA. The CF Foundation and Genzyme Corporation recently announced expanded investment in PTC124 due to the promising results in clinical trials in CF as well as other diseases caused by “stop” mutations, such as certain types of muscular dystrophy.

**Stanford’s Active Research Program**

The Stanford CF Center is one of a few US sites working on development of both VX-770 and PTC124. These trials, and others such as denuphusol and several drugs in the pipeline, are moving the potential treatment paradigm of CF from controlling disease effects and complications to treating the basic cause of CF, offering the prospect of long-term control and prevention of its serious consequences. The era we have all waited so long for – the definitive control of CF – is dawning. Stanford’s CF Center wants to encourage every person with CF and their family to participate in a clinical trial during the next few years. Robust participation of our community in these trials will bring us ever closer to this promising horizon.

---

**Current Research Studies**

- Development of new drugs and therapies requires people with CF to participate in clinical trials. Be a part of the cure! Volunteer for a study today. To learn more, visit http://cfcenter.stanford.edu, contact our research coordinators or talk to your physician.

- The following trials are currently underway:
  - Inspire Phase 3 “Tiger 2” drug for correction of salt and water abnormalities (enrolling)
  - NAC Phase Ib (enrolling September)
  - Pulmonary Exacerbation
  - Vertex potentiator
  - MPEX 204 inhaled levofloxacin (enrolling)
  - KaloBios anti-Pseudomonas antibody study (enrolling)
  - EPIC trial for early treatment of Pseudomonas
  - Sweat testing in newborns with CF
  - Chest CT and natural history of CF Lung disease
  - GlaxoSmithKline anti-inflammatory oral therapy

---

Ask your physician what type of CFTR mutations you have. If they don’t know, it’s time to consider getting tested! It’s simple, painless, and may be important as new therapies become tailored to specific types of mutation. Also, consider participation in one of our trials. The CFF needs to double the number of research participants to move new drugs form the bench to the public.
Vitamin E

Fat soluble Vitamin E exists in eight forms, called tocopherols. The name “tocopherols” comes from the Greek words tokos (childbirth) and pheros (to bring forth), which relate to the discovery of Vitamin E in 1922 when studies revealed its link to normal reproduction. The first supplement trials were conducted in infants in the 1940s when it was discovered that vitamin E prevented the destruction of red blood cells, a discovery that led to its addition to infant formulas.

Pancreatic insufficient persons with CF generally do not absorb enough vitamin E through food. Vitamin E is a powerful antioxidant that prevents oxygen from combining with compounds that can become destructive to cells and tissues, including red blood cells and the epithelial cells that line the lung and intestines. A recent study of antioxidant supplementation in people with CF comparing individuals receiving a high dose antioxidant supplement (298 IU of vitamin E) versus a low dose supplement (15 IU of vitamin E) found an improvement in oxidative defenses in the high supplement group.

Recommended Doses

The daily recommended dose of vitamin E for people without CF is 6 to 22 International Units (IU). Significantly higher doses are needed by people with CF, with doses increasing through early childhood.

### CFF Vitamin E Daily Recommended Doses by Age

<table>
<thead>
<tr>
<th>AGE</th>
<th>VITAMIN E (IU)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 to 12 months</td>
<td>40 - 50</td>
</tr>
<tr>
<td>1 to 3 years</td>
<td>80 - 150</td>
</tr>
<tr>
<td>4 to 8 years</td>
<td>100 - 200</td>
</tr>
<tr>
<td>8 years and older</td>
<td>200 - 400</td>
</tr>
</tbody>
</table>

Sources of Vitamin E

Diet alone will not provide sufficient Vitamin E for those with CF. Therefore vitamin supplements are needed. Nuts are good sources and also provide calories and protein.

<table>
<thead>
<tr>
<th>FOOD</th>
<th>VITAMIN E (IU)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Almonds (1 ounce)</td>
<td>11</td>
</tr>
<tr>
<td>Sunflower seeds, dry roasted (1 ounce)</td>
<td>9</td>
</tr>
<tr>
<td>Sunflower oil (1 Tbsp)</td>
<td>8</td>
</tr>
<tr>
<td>Safflower oil (1 Tbsp)</td>
<td>7</td>
</tr>
<tr>
<td>Wheat germ oil (1 Tbsp)</td>
<td>30</td>
</tr>
<tr>
<td>Peanut butter (vitamin fortified, 2 Tbsp)</td>
<td>2</td>
</tr>
<tr>
<td>Spinach, 1/2 cup cooked or 1 cup raw</td>
<td>2</td>
</tr>
<tr>
<td>Broccoli, 1/2 cup cooked</td>
<td>1</td>
</tr>
</tbody>
</table>

Vitamin E supplements are generally safe. Doses greater than the tolerable upper limit (TUL) of 1500 IU may interfere with blood coagulation and result in excess bleeding. Check with your CF team to determine the right dose.

Strategies to Optimize Vitamin E Levels

- Take vitamins and enzymes as prescribed
- Choose nuts and oils as part of a high-calorie, high-fat diet
- Check blood levels annually as part of recommended CFF clinical care guidelines

Pediatric Fellow Confirms Weight-Lung Function Links

Infants with CF who gain weight more quickly than their peers also have better lung function, new research by Packard Children’s fellow Christin Kuo, MD, and center team members Jacquelyn Zirbes, RN, Carol Conrad, MD, David Cornfield, MD, and Carlos Milla, MD. The findings, presented at the 2008 American Pediatric Society meeting, suggest parents should redouble efforts to keep very young children with CF well-nourished. It also reinforces previous research indicating that lung damage begins very early in life even in children with few or no visible symptoms.

“Freedom from respiratory symptoms and gaining weight steadily are important goals for infants with CF,” says Kuo. A link between nutrition and pulmonary function is well-established in adults with CF, but until now it had not been proven in infants. Exactly how nutrition affects lung function remains to be determined, but the findings underscore the benefits of newborn screening so that unique nutrition needs are addressed within weeks of birth.

Kuo analyzed data from infants with CF ranging in age from 2.5 to 40 months. When they compared daily weight gain every six months with lung function tests, they found that those who grew more rapidly retained less air in their lungs. Air retention, or “air trapping,” is an important measure of lung health. Abnormally high or low levels of trapping indicate lung problems. Retaining excess air in the lungs, perhaps due to inflammation in the tiniest airways of the lung, reduces the volume of fresh air that can be inhaled in the next breath and lowers breathing efficiency. Kuo’s research confirms an association between nutritional status and lung health even in young infants with CF and suggests a possible way to slow disease progression.

“We may need to intensify our nutritional rehabilitation of these children,” says Kuo.
Rabin Tirouvanziam, Ph.D. and others from the CF team published an article in *Proceedings of the National Academy of Sciences* describing unique differences in the neutrophils found in CF and normal sputum and blood. Katherine Boyle, RN, has accepted a position at George Mark Children’s House, a palliative care facility. She wishes the CF families and children she has worked with a fond farewell and best wishes for healthy lives. Jerome Booker, MD, the new pediatric pulmonary fellow, has joined Christin Kuo in the second year of the fellowship program.

**Nurse Practitioners Join Adult CF Inpatient Team**

Camille Washowich, MSN, ACNP, and Elika Derakshandeh, RN, MSN, NP, have joined the adult CF team to coordinate hospital admissions, inpatient care, discharge and follow-up. Their roles will be to provide a communication bridge and case management between inpatients, physicians, residents and fellows. When possible, they will also meet patients in clinic prior to hospitalization, a process particularly helpful for young adults transitioning to the adult hospital. Before coming to Stanford, Washowich worked for 17 years as a critical care nurse. A godson with CF drew her into the position. She enjoys the education and research aspects of her job and wants to work with patients and caregivers to “see CF as part of life, not their whole life.” Her goal is “to create a well-functioning team with smooth transitions from clinic to hospital to home.” Derakshandeh brings five years of ICU experience as well as pulmonology and immunology research. During her nurse practitioner training she received the California ALA Pulmonary Fellowship. Derakshandeh describes herself as passionate about advancing patient care. She is committed to education and growth through research as well as development of the nurse practitioner role within the CF team at Stanford.

**Research Team Expands**

Jacquelyn M. Zirbes, DNP, RN, CPNP, CCRC, has been named CF Newborn Screening Coordinator, pediatric pulmonarty nurse practitioner, research nurse coordinator and pediatric Lung and Heart-Lung Transplant Coordinator. Zirbes has 18 years of experience in CF and a doctorate in nursing. While working at the University of Minnesota with Drs. Carlos Milla and David Cornfield, she coordinated the thoracic and living lobar transplant programs, CF newborn screening program and managed a busy clinical practice as a pulmonary/critical care nurse practitioner and CF clinical research coordinator. She developed a comprehensive pediatric-to-adult CF transition program. At Stanford she will continue her research, with a focus on molecular predictors of airway inflammation, phenotype and disease progression, phenotype in CF newborns and infant pulmonary function. She is also charged with establishing a coordinating center for rare pediatric pulmonary diseases and lung transplant services at Stanford/Packard Children’s.

**CF Counseling Program Opens**

The Institute of Transpersonal Psychology of Palo Alto is offering counseling and psychotherapy services to the CF community. The new “Cystic Fibrosis Quality of Life Program: A Living Legacy of Peter Judge” is a collaborative effort of the Institute and Cystic Fibrosis Research, Inc. and The Center for Education in Family and Community Medicine at Stanford. The program is designed for people impacted by CF: patients, families, caregivers and clinical staff. It can help address stress, grief, anger, communication issues, time management and other psychological, social and spiritual aspects of living with CF. Fees are on a sliding scale. No one will be turned away due to inability to pay. For more information, visit their Web site, http://www.itp.edu/resources/counselingservices.cfm, or call (650) 493-5006 ext. 224.
CF Education Day, 2008 Highlights

CF Education Day Talks Available

The 2008 Stanford CF Education Day on March 15 featured research updates and practical advice. Robert Beall, CEO of the CF Foundation, discussed promising research, quality and access initiatives lead by the CFF, including precedent-setting clinical trials that are testing drugs that may address the fundamental defect in certain CF genetic mutations.

Other topics included:

- Lung Inflammation in Cystic Fibrosis: NAC by Carol Conrad, MD
- MPEX (Inhaled Levofloxacin/MP-376) by Zoe Davies, PNP
- Cleaning Your Respiratory Equipment by Colleen Dunn, RRT, CCRC
- Management of Pulmonary Exacerbation by Christopher Goss, MD MSC
- Salt: How Much, How Often, and Why? by Julie Matel, MS, RD, CDE
- Infection Control by Kathy Mathews, RN, CIC
- Research Progress by Richard B. Moss, MD
- Newborn Screening by Jacquelyn M. Zirbes, DNP, RN, CNP, CCRC

The presentations are posted at http://cfcenter.stanford.edu or videos can be purchased from CFRI at (650) 404-9445.

Robert Beall, President of the Cystic Fibrosis Foundation, delivered the keynote address at Education Day. His talk focused on CFF research, access and case management initiatives.

Visit our website at http://cfcenter.stanford.edu for more information about our center and CF.

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

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