Healthy people’s lungs are home to a diverse community of microbes that differs markedly from the bacteria found in the lungs of cystic fibrosis patients. That result comes from research from the Stanford University School of Medicine and Lucile Packard Children’s Hospital. The information has meaningful implications for treatment of CF and other lung diseases.

“The lung is not a sterile organ,” said David Cornfield, MD, an author of the study, which was published September 26, 2012, in Science Translational Medicine. Although decades of received scientific wisdom said healthy lungs lacked resident microbes, scientists had begun questioning that notion. “This research confirmed a long-held suspicion that a forest of microbes exists in both healthy and diseased lungs,” said Cornfield, a pulmonologist at Packard Children’s and a professor of pediatrics in pulmonary medicine at Stanford. “More surprising, our data presents a suggestion that the lung flora provides microbial homeostasis that might function to preserve health.”

Healthy lungs’ microbes have been overlooked in part because past research has focused heavily on lung diseases, Cornfield said. Another flaw in prior studies was a bias toward looking for microorganisms that could be grown in labs. Many of the types of microbes that the Stanford researchers found in healthy lungs have never been cultured in a laboratory.

In contrast, a large body of research had previously shown chronic microbial colonization in the lungs of people with cystic fibrosis, a genetic disease characterized by serious, progressive lung problems and death from respiratory failure. For instance, CF patients are vulnerable to chronic infection with the bacteria Pseudomonas aeruginosa, which can cause pneumonia.

The new study used sputum samples from 16 CF patients and nine healthy controls. The scientists also analyzed 90 lung tissue samples from CF patients’ explanted lungs, the organs removed when the patients received lung transplants. They extracted DNA from the sputum and tissue and selectively copied genes coding for the 16S ribosomal gene sequences, which are found only in bacteria. The resulting genetic material was measured to determine which phyla, or families, of bacteria it came from and the relative contributions of each bacterial phylum to the total bacterial population in the lungs.

Several differences emerged between CF patients and healthy people’s communi-
ties of lung bacteria. In general, healthy individuals had more diversity among their lung bacteria. Different bacterial phyla predominated in the two groups: members of the Bacteroidetes and Fusobacteria phyla were much more prominent in healthy individuals, whereas CF patients had a larger percentage of Actinobacteria. Also, healthy people had a larger proportion of bacteria that had never been grown in a lab.

“I think the tendency toward decreased diversity can be metaphorically viewed as the same phenomenon that might happen in a rainforest,” Cornfield said. “When the ecosystem of a rainforest is disturbed and one organism predominates, it undermines a carefully constructed balance and causes disturbances in overall ecosystem. I think it’s reasonable to assume something similar could happen in the lung microbiome, where pathogenic bacteria may out-compete organisms that may play a salutary, health-affirming role.”

The results open many questions for future research. No one has ever tested the idea that certain microbes benefit lung health, for instance. “We may need to consider strategies that allow favorable microbes to exist while eradicating disease-causing species,” Cornfield said. “That paradigm, if it’s true, would really turn the care of patients with pneumonia and other lower-airway diseases on its head.” Future research might test whether CF or pneumonia patients could benefit from doses of probiotic bacteria to their lungs, he said.

In addition, no one is sure how the antibiotics often given to CF patients change the microbes in their lungs.

“The marked differences in composition and diversity of microbial communities from adults with cystic fibrosis and normal controls are intriguing,” said Thomas Ferkol, MD, director of the Division of Allergy, Immunology and Pulmonary Medicine at the Washington University School of Medicine in St. Louis. Ferkol was not involved in the research. “The question that remains to be answered is whether these differences are directly related to the underlying lung disease or simply a consequence of frequent antibiotic use, which has been shown to change microbiota of the upper airways,” he said.

The question is a “chicken or egg” problem, Cornfield said, adding that his best guess is that antibiotic use is not the primary reason for the microbial differences, but that the notion deserves testing.

More questions arise from the fact that bacterial profiles varied within the group of CF patients. CF patients also differ widely in their disease progression, even when they have the same disease-causing gene mutations. It is possible that patients’ lung function may be linked to the bacteria present in their lungs. The research team now plans to study whether individual patients’ bacterial profiles can be used to predict their clinical condition. Cornfield collaborated with first author Paul Blainey, PhD, previously a postdoctoral scholar at Stanford and now a faculty member at the Massachusetts Institute of Technology; Carlos Milla, MD, an associate professor of pediatrics in pulmonary medicine at Stanford and a pulmonologist at Packard Children’s; and senior author Stephen Quake, PhD, professor of bioengineering and of applied physics at Stanford and an investigator at the Howard Hughes Medical Institute. The research was funded by grants from the National Institutes of Health, including an NIH Director’s Pioneer Award.

The research challenges the long held paradigm in CF that all bacteria are unfavorable. In caring for the lungs of CF patients it may be important to preserve bacterial diversity in the lung. Moreover, it may be the case that there are substantial differences in the diversity of species between CF patients with different genotypes. These phenomena may explain, to some degree, the divergent clinical manifestations of disease in people with similar genotypes. These studies are only just beginning but provide new and exciting opportunities to improve the care of patients with CF.

More information on the Department of Pediatrics, which also supported the research, is available at http://pediatrics.stanford.edu.

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The human gastrointestinal tract is an amazing group of organs and includes the mouth, pharynx, esophagus, stomach, pancreas, gallbladder, and intestines (small and large). These organs are able to change the food we eat into its molecular structures. Our body needs these molecular structures—including glucose, amino acids, and fatty acids, along with all of the vitamins and minerals—to function efficiently.

Digestion begins in the mouth when we chew our food. Saliva moistens our food and the beginnings of starch digestion occur by the enzyme, salivary amylase. Food bolus travels from the mouth down the pharynx and esophagus and into the stomach, where acid begins to churn the food bolus into chyme, a mainly liquid mixture. From here the chyme enters the small intestine, where it meets up with digestive enzymes that are made in the pancreas, an organ that sits behind the stomach. These enzymes are crucial in breaking down the fats into fatty acids, protein into amino acids, and carbohydrates into glucose so that these molecules can be absorbed into the blood stream. The blood stream carries these important nutrients to the cells of the body. Another important step in fat digestion is the mixture of fat from our food with bile. This step also occurs in the small intestine. Bile is made by the liver and stored in the gall bladder. Bile contains bicarbonate and bile salts that help to make fats water-soluble so that they can be absorbed through the intestinal wall. Food particles that are indigestible, such as fiber, pass through the small intestine and into the large intestine, where they are temporarily stored and concentrated. Finally, contractions of the rectum, the last part of the large intestine, send the feces through the anus.

About 85 to 90 percent of people with cystic fibrosis are pancreatic insufficient. This means that their pancreas is damaged by the thick sticky mucus that develops and prevents the enzymes from entering the small intestine to do their job. These individuals need to take pancreatic enzymes with every meal and snack in order to prevent signs of malabsorption, including loose, oily, malodorous stools, gas, and bloating. Because this system of enzyme delivery is not perfect, individuals with CF will experience mild forms of these symptoms from time to time, even if they are taking their enzymes as prescribed.

In order to get the most out of your enzyme therapy, keep in mind the following:

- Remember to store your enzymes at room temperature (do not store in the refrigerator, trunk or glove compartment of the car, or clothing pockets)
- Pay attention to expiration dates and do not use enzymes after they expire
- Remember to take enzymes with all meals and snacks that contain protein, fat, and complex carbohydrate. You do not need to take enzymes with foods that only contain simple sugars, including the following…
  - Fruits
  - Juice, juice drinks
  - Soft drinks or sports drinks
  - Tea, coffee (without cream)
  - Hard candy (like lollipops)
  - Fruit snacks
  - Jelly beans
  - Gum
  - Popsicles, freezer pops, flavored ice

Keep in mind that these foods and beverages are typically less nutrient- and calorie-dense. It is recommended to enjoy them only on occasion or as part of a high calorie meal or snack.

If you feel you are taking your enzymes as directed and are still experiencing symptoms of malabsorption as mentioned in this article, talk to your dietitian or medical provider about adjusting your dose or trying a different brand of enzymes.
Bronchodilators (Albuterol, Xopenex, Atrovent, Combivent)
• Usually, the first medication is a bronchodilator, which is given to open up the airways so that other medications can get into the airways more easily. This also helps with the expectoration of sputum.

Mucomyst
• This medication is a mucolytic which helps to thin the mucus so it can be coughed out more easily.

Hypertonic saline
• This medication is used to mobilize the secretions by drawing more water into the airways and making it easier to cough out the mucus.

Pulmozyme
• Extracellular DNA left behind by white blood cells contributes to thicker, stickier mucous. Pulmozyme cuts up that extracellular DNA and helps to thin the mucous making it easier to cough out.

Airway clearance: flutter, acapella, chest PT (manual), intrapulmonary percussive ventilator (IPV), vest
• When using the vest for airway clearance: bronchodilators, hypertonic saline and Pulmozyme can be administered during the vest treatment while aerosolized antibiotics and steroids should be administered after vest therapy.
• When using IPV for airway clearance, only bronchodilators and hypertonic saline can be nebulized via IPV. Other medications (Pulmozyme/inhaled antibiotics) need to be delivered via a sidestream nebulizer or PARI LC Plus nebulizer.

Antibiotics (Tobi, Colistin, Amikacin, Cayston)
• Antibiotics are used to fight infection-causing bacteria. Infections are common in the lungs of people with CF, so antibiotics are an important part of regular care.
• The antibiotic drug, the dosage, and the length of time to take the drug, all vary. Infection-causing bacteria can become resistant to some drugs.

Steroids (Flovent, Pulmicort, Advair, QVAR)
• Steroids contain anti-inflammatory properties that help contain the inflammation associated with CF airways.

PLEASE REMEMBER:
• Do not mix multiple medications in the same nebulizer cup with the exception of single dose bronchodilator + unit dose Atrovent, and single dose bronchodilator + Mucomyst.
• Use eflow only with: Colistin (dose adjustment by MD/NP)
• Use Altera only with: Cayston (dose 75 mg)
• Use Trio only with: TOBI (dose adjustment by MD/NP)

If you have any questions, please contact doctor or nurse.

Cystic Fibrosis Foundation Recommended Order of Nebulized Medications

According to the Cystic Fibrosis Foundation, the order in which medications are taken is critical to a positive therapeutic outcome. Inhaled drugs are commonly used in CF care because they reach the airways quickly and easily. Inhaled treatments can be given by aerosol (a mist made from liquid medicines). Some medications can also be given as metered dose inhalers (MDI), which deliver one dose of medicine at a time. The CFF has approved the following sequence of medications:
Non-Fractured Care: Managing Osteoporosis

BY CAMMIE WASHOWICH, MSN, ACNP

As cystic fibrosis patients age, they have an increasing risk of developing osteopenia (bone mineral density lower than normal) and/or osteoporosis (bone mineral density markedly reduced, "porous bones"). Rib fractures can require chest tube placements making airway clearance painful. Hip fractures often require surgery, are painful, and often need lengthy rehabilitation. Prevention begins with good nutrition and maintaining adequate calcium/vitamin D stores. This can be challenging in CF due to malnutrition and/or malabsorption. Adequate intake of both calcium and vitamin D is key, with vitamin D enhancing the intestinal absorption of calcium.

Cystic fibrosis patients have difficulty with absorption of both their foods and medications. One very helpful measure to evaluate bone health is the bone density score (BDS). In 1994, the World Health Organization (WHO) established a classification system of bone mineral density (BMD). Dual energy X-Ray absorptiometry (DXA) is the tool used to measure the bone mineral content and bone area, and then calculate the area to be measured. Typical measurements are done on areas at high risk for fracture like the spine, femur, and wrist. The value, a "T-score," is derived whereby -1 is normal; -1 to -2.5 is osteopenia; and greater than -2.5 is osteoporosis. This scan provides minimal radiation, establishes baseline values, and measures responsiveness to medical therapy. It takes only twenty minutes and is painless. Providers also encourage weight-bearing exercises (walking/running/sports) to facilitate bone growth.

Osteoporosis can develop when there is a lack of bone cell differentiation and decreased intestinal absorption of calcium and phosphorus limiting bone mineralization. This puts patients at higher risk for pathologic fractures. Furthermore, vitamin D stores decline with age as well as during the winter months, when many CF patients are admitted for CF exacerbations. Chest physiotherapy or airway clearance is increased, and unfortunately these aggressive treatments have been shown to cause rib fractures, especially in those already with osteoporosis. Those at higher risk of developing osteoporosis include institutionalized individuals, dark-skinned individuals, those with limited effective sun exposure, obese individuals (rare in CF patient) and pregnant women. Those with malabsorption, including inflammatory bowel and celiac disease, are also at higher risk.

The treatment for osteoporosis/osteopenia is threefold: good nutrition, appropriate medications, and exercise.

Nutrition: maintaining a healthy weight with a body mass index (BMI) of 22; healthy choices from all food groups.

Medications: Supplemental vitamin D: cholecalciferol (vitamin D3) and ergocalciferol (vitamin D2) are necessary. In malabsorptive states, vitamin D of 10,000 to 50,000 units daily is often required. Patients who remain deficient may also benefit from sunlamp therapy. Supplemental calcium requires an intake of 1000 mg/day in premenopausal women and 1500 mg/day in postmenopausal women. Fosamax given orally weekly or Arevia given intravenously every three months can also be effective in the treatment of osteoporosis.

Exercise: weight bearing activities daily for 30 minutes or longer. The Bone Density Score needs to be checked every 1 to 2 years, with medication adjustments as needed.
To become part of a research study requires that you be “eligible” to participate. This is a complex, multistep process. For each study, there are specific guidelines that are called the inclusion and exclusion criteria, which specify who can or cannot participate in a research study and are based upon different factors such as genotype, FEV1, age, etc. After receiving study details, the database coordinator will obtain a report from the Cystic Fibrosis Foundation’s patient database, which provides a list of the patients who may be eligible to participate. Once you have been identified, the team will then review your medical history and speak with your physician. When all of the details have been confirmed, a research coordinator will contact you to introduce the study, explain the study details, and what you can expect as a research participant. You may be contacted at your clinic appointment or with a phone call. You will receive a copy of the consent to read, discuss, and formulate any questions you may have. After you’ve had time to do this, a research coordinator will follow up to see if you are interested and answer any of your questions or concerns. If you agree to participate, the first visit will be scheduled. If you decline participation, we may inquire the reason in order to help us better understand the factors influencing your decision, and would then continue the same process with a different patient. We strive to make this as seamless a process as possible, because we appreciate research participation. Thank you to all of the patients and patients’ families who have contributed to research. We could not do this without you!

Pick me, Pick me!
BY CASSIE EVERSON, RC, RRT

The Parent Advisory Council is comprised of parents who work in partnership with members of the pediatric Cystic Fibrosis Clinic Care Team to provide the highest quality of care and service to patients and families. Council members are part of the Family Centered Care Department at Lucile Packard Children’s Hospital. Recent Council activities include providing and/or suggesting content for the CF Center at Stanford’s website and Facebook page, to better address the needs of patients and families. We continue to develop strategies to direct people to the website, which, in addition to providing information, has links to online surveys that help provide care teams with valuable patient and family perspectives. Please consider completing these surveys! The Council is also exploring strategies to meet the needs of the Center’s Spanish-speaking families, as well as the needs of families whose children are newly diagnosed.

The creation of transition materials to help teens, young adults and their families as they move from the pediatric to adult CF clinic has been the primary focus of the Council in recent months. With input from the pediatric and adult care teams, the Adult Advisory Council, as well as transitioning teens, the Parent Advisory Council has developed a concise but information-packed brochure to prepare patients and families for this important step. Stay tuned: we are also exploring ideas for a video tour of the adult center, led by a recently transitioned young adult.

We are seeking creative ways to increase participation and expand family input to the CF Center. Parents who have ideas related to any of the above issues are encouraged to email Siri Vaeth, Lead Parent for the Council, at svaeth@lpch.org.

Cystic Fibrosis Parent Advisory Council Update
BY SIRI VAETH, MSW

The Parent Advisory Council is comprised of parents who work in partnership with members of the pediatric Cystic Fibrosis Clinic Care Team to provide the highest quality of care and service to patients and families. Council members are part of the Family Centered Care Department at Lucile Packard Children’s Hospital. Recent Council activities include providing and/or suggesting content for the CF Center at Stanford’s website and Facebook page, to better address the needs of patients and families. We continue to develop strategies to direct people to the website, which, in addition to providing information, has links to online surveys that help provide care teams with valuable patient and family perspectives. Please consider completing these surveys! The Council is also exploring strategies to meet the needs of the Center’s Spanish-speaking families, as well as the needs of families whose children are newly diagnosed.

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Pediatric Cystic Fibrosis Center Update

BY MARY HELMERS, RN

The Cystic Fibrosis Foundation will soon release updated Infection Control Guidelines, which were discussed on the webcast held on March 27th. Any significant changes will be posted on the CF center website (cfcenter@stanford.edu) when available.

Our move to the new clinic is on hold for now. We will let you know when the new date is set.

FRIENDLY REMINDER:
We have new turquoise-colored masks that we ask all CF patients to wear. You may obtain one at the front desk. These masks have smaller filters that allow for more protection when walking outside during the hospital construction. We would like all patients to wear them to and from all clinic and hospital locations and when walking anywhere outside the Stanford University Medical Center. They should fit snug around the nose and mouth. If you have not received the new mask, ask the front desk staff or anyone from the CF Team.

Adult Cystic Fibrosis Center Update

BY KATHY GESLEY, RN

• The Adult CF clinic hours will change effective April 15th. New hours will be 12:30 pm to 3 pm, Wednesday and Friday. This change is made in conjunction with a Pulmonary Clinic Process Excellence Program to bring services closer to the patient and to improve the patient experience with team members. The Adult CF Clinic is the first clinic to pilot this change within the Advanced Lung Disease Program.

• The Stanford Hospital Respiratory Department now schedules two respiratory therapists to the Adult CF Clinic to improve clinic flow and to ensure patients receive ongoing respiratory education during regular clinic visits.

• The Adult CF team provides referral for family planning and reproductive care to specialists at Stanford Hospital: For female patients, Paula Hillard, MD, (650) 725-6079 Department of Obstetrics and Gynecology, and for male patients Michael Eisenberg, MD, (650) 723-3391 Department of Urology. Please speak with your Adult CF Team for further information or referral.

• The Adult CF Team utilizes psychiatrist Yelizaveta Sher, MD, for consultation for inpatient care, transplant evaluation, and follow up care after hospitalization. Consultations are determined by the Adult CF attending physician.

Be a part of the cure for cystic fibrosis!

Volunteer for a clinical trial today. To learn more, visit http://cfcenter.stanford.edu, contact our research coordinators, or talk to your physician. The following trials are currently underway:

• Sweat testing in newborns with CF
• Advanced Diagnostic Testing for Lung Disease
• Exercise study
• ABPA study
• EPIC trial for early treatment of Pseudomonas
• Lung Clearance Index

• E-ICE, study of Pulmonary Exacerbation utilizing home Fev1 monitoring
• Vertex 770-110/12 (for the R117H genotype only)
• Saliva Testing
• KaloBios (IV Anti Pseudomonas antibody study)

Upcoming protocols:
• Phase III study of VX-809 and VX-770, enrolling May–June 2013
• Electro-Flo study (airway clearance device) enrolling June 2013 – July 2013
Adult CF Advisory Council

Do you need help getting to your quarterly clinic appointments? The adult CF patients and community members of our Adult CF Advisory Council (ACFAC) are proud to announce the completion of a project, in partnership with the CF center, to support our fellow patients coming to clinic. We have raised funds to provide gas cards, hotel vouchers, taxi fares, and other transportation support. We’ve also researched detailed transit routes for patients coming from Monterey, Salinas, and Sacramento. Ask your adult CF social worker to share this information with you at clinic.

ACFAC is also piloting a Peer2Peer mentorship program, the very first of its kind at Stanford, co-developed with the heart transplant advisory council. In this program, adult CF patients support each other by phone on a confidential, one-to-one basis. The mentors received extensive training this fall. To be matched with a mentor, talk to your adult CF social worker.

For more info about ACFAC, go to http://cfcenter.stanford.edu/acfac/ or contact chairperson Laura Steuer at laurafs@juno.com

Research:
Colleen Dunn, Zoe Davies, Cassie Everson, Contact chairperson Laura Steuer at laurafs@juno.com