

Research Briefs

NEW DRUG FOR STOP CODON MUTATIONS

Drugs are being developed for CFTR stop codon mutations. These mutations ending in X (such as W1282X or G542X) lead to changes in the DNA code that stop the cell's protein production mechanism before it completes the entire CFTR protein. Certain drugs, including the antibiotic gentamicin, cause the cell to ignore the stop signal and continue producing the CFTR protein. PTC Therapeutics (Plainfield, NJ) has developed a drug called PTC124 which has the same effect. Initial studies demonstrated that this medication, which is taken by mouth three times daily, is safe. A Phase II trial is underway testing two doses of PTC124 for 28 days in adults with CF. Enrollment for this trial at Johns Hopkins will begin this spring.

CAN BETTER CONTROL OF DIABETES IMPROVE LUNG FUNCTION?

Diabetes is very common in CF patients, affecting up to 40 percent of adults. While it is well known that diabetes can be associated with a more rapid decline in lung function, an optimal therapy for CF-related diabetes has not yet been found. The National Institutes of Health is sponsoring a multi-center study coordinated by the University of Minnesota to determine if better diabetic control will improve nutrition and lung function. This one-year study will compare the outcome of patients who receive insulin injections, an oral medication or a placebo.

Many children and adults with CF have elevated blood sugars when they are sick or taking steroids. Recently, studies of other patient groups have shown that treating even mild elevation in blood sugar can improve outcome. The CF Foundation is sponsoring a study investigating whether in-

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Raising the Bar on CF Care



Pediatric pulmonary fellow **Brian McGinley** listens to a young patient's lungs.

Quality improvement sounds like a buzzword straight out of corporate America: how are we going to improve the quality of these widgets we're building? How can we improve the quality of our customer service?

To the CF team at Johns Hopkins, quality improvement means nothing short of saving lives – the productive, healthy, happy lives of their patients. It's also an internal buzzword for a major clinical initiative currently underway.

In 1964, the Cystic Fibrosis Foundation began tracking patient outcomes and other data from accredited CF centers to identify best practices and establish clinical practice guidelines. It's widely acknowledged that this important work – the Foundation's Quality Improvement Initiative (QII) – is the leading reason why people with CF who may have died young in the 1950s or 1960s live well into their thirties or beyond today. Inherent to the success of the QII is the Foundation's benchmarking of its accredited CF centers across the nation, which provides

a "ground level" view of best care practices, says CF Foundation Vice President Bruce C. Marshall (see Interview, page 2).

Constant re-examination of clinical practice is the key to improving patient care, according to Peter Mogayzel, M.D., Ph.D., Johns Hopkins CF Center director. "During the latter half of 2005, we took a hard look at every aspect of the way we care for patients to see where there was room for improvement. We don't want to provide just good care. We always want to do better."

With an eye toward the CF Foundation's recommendations, the Hopkins team launched its own Quality Improvement Initiative in June. Mogayzel, Michael Boyle, M.D., who directs the adult program, and their colleagues started with a systematic re-evaluation of all patients' nutritional status, a major concern in CF care. With this information, the team set nutritional goals for each patient, and developed individual plans for getting them there.

Clinicians have long known that lung growth is related to height. New information gleaned from the CF Foundation's QII

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NACFC Highlights

News from the North American Cystic Fibrosis Conference held October 20-23, 2005 in Baltimore.

MORE SALT AND WATER CAN HELP

The major problem in the CF lung is the presence of thick, sticky mucus, the result of excessive absorption of sodium from the airway. Drugs that restore salt and water into the airway may help thin the mucus, making it easier to clear. Several groups are taking different approaches to thinning mucus:

Parion Sciences (Durham, NC) has developed a drug called 552-02 that blocks the channel that transports sodium out of the airway and into cells (ENaC). In theory, the sodium remaining in the airway will attract water, hydrating the mucus and making it easier to clear. In Phase I trials of 80 people with and without CF, the drug quickly improved the clearance of mucus from the airway. The effect lasted for more than four hours. Phase II trials are planned for spring 2006.

Physicians in Australia observed that CF patients who surfed in the ocean had fewer lung problems, leading them to hypothesize that inhaling salt water may help lung function in people with CF. Australian investigators tested this hypothesis by treating 164 CF patients with inhaled hypertonic saline, a very concentrated salt solution, for one year. This therapy increased lung function (FEV1) by approximately five percent and decreased the number of exacerbations by one third. Additional studies are underway to determine which patients are most likely to benefit from this therapy. For the past year, selected patients have received this therapy at Johns Hopkins CF Center. While it's too early to tell what, if any, effect the saline has on lung function, overall it has been well-tolerated with minimal side effects, and seems to help prevent

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What is QI and why is it important?



This issue of *Partners in Discovery* highlights the Quality Improvement Initiative (QII) that has been started by the CF Foundation. We were fortunate to have Dr. Bruce Marshall

discuss this process at the Johns Hopkins Family Education Day in November, 2005. The goal of the QI Initiative is to improve the health of all CF patients by evaluation and improvement of current care practices.

My goal is to assure we provide the best possible care for the CF patients we treat at Johns Hopkins. To achieve this goal we must constantly re-examine our practices. Over the past six months the care team at the Johns Hopkins CF Center has engaged in a systematic review of the way that we care for CF patients to find areas that can be improved. Our first QI project has focused on developing a more aggressive approach to nutrition in CF Clinic.

Why focus on nutrition? Clinicians have known for some time that lung growth is related to height. However, a new analysis of data from the CF Foundation Patient Registry has shown that children and adults with a normal body mass index, or BMI, have strikingly better lung function. This data has changed the rules that we have used to guide our practice. "Good" nutrition is no longer good enough; we shoot for great. This is why our first QI project has focused on developing a plan so that every patient with CF can have the best possible nutrition.

For our QI effort to succeed patients, families and caregivers must act as a team. Therefore, we have created a Parent Advisory Board to help guide our QI efforts. We have also started a monthly parents' support group which had its inaugural meeting in December. Finally, the Hopkins CF website, www.hopkinscf.org, will debut this month. I anticipate that this website will not only be a portal to information about CF but will also enable patients, parents and caregivers to interact with one another in a new and exciting way.

Peter J. Mogayzel Jr., M.D., Ph.D.
Director, Cystic Fibrosis Center
at Johns Hopkins

Bruce C. Marshall, M.D. Vice President of Clinical Affairs, Cystic Fibrosis Foundation

What are the overall goals of the Cystic Fibrosis Foundation's Quality Improvement Initiative?

Our goal is exemplary care at all of our care centers in order to improve quality and extend life for people with cystic fibrosis.

From a national perspective, why is such a cohesive program necessary? Why not leave it up to individual care centers to set quality goals and implement their own programs?

We believe the stakes are too high to leave this entirely to individual care centers. The Foundation is the accrediting body for care centers nationally and we are proud of the care model that we have put in place for this disease. That said, we can't really mandate exemplary care. We have to appeal to the professionalism of our center staff. We can give voice to the vision of exemplary care, develop strategies and infrastructure to support that vision, and put forward worthy goals for our centers to consider as we recruit them to this effort. If we can focus the improvement activities on a handful of high leverage areas, then we can really make a difference.

Why is national benchmarking of CF care centers important?

Our benchmarking program is a way to fully understand how certain care centers achieve excellent outcomes. We identify these high performing centers from our patient registry data and send a multidisciplinary

team to visit and spend a day or two with the team. (Johns Hopkins dietician Amanda Leonard is part of this core team.) It's important to get a detailed "ground level" view of such centers to fully understand their delivery system in order to spread what they do and what they've learned to other centers for consideration. Our initial insights from this benchmarking suggest that excellent out-

comes are not the result of something as simple as the way a care center uses a particular therapy. It's much more subtle, and includes leadership, team dynamics, communication between people and families with CF and the care teams and consistency in practice patterns.

How will the CF Foundation measure success of the national QI Initiative?

In the near term we are tracking process measures like center involvement in quality improvement activities, centers with patient and family involvement, etc. In the long term, we're interested in moving the important metrics like pulmonary function, nutritional status and ultimately survival and quality of life.

Looking toward the future, where do you think the next breakthrough in CF research will be? What are the most promising avenues for discovery?

There are many promising therapies in the pipeline. We are excited that a number of these potential options are targeting the basic defect involved in CF. ■

Raising the Bar

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links normal body mass index (BMI) to improved lung function.

BMI is a relative measure of weight to height; children at the 50th percentile are of average, or normal, height for their weight. To maintain optimal lung function, the CF Foundation recommends that children strive for a BMI at or above the 50th percentile.

"We found that many patients who may have been considered to be getting adequate nutrition prior to the CF Foundation's new BMI guidelines now deserved stronger focus from the care team," Mogayzel says. "Good nutrition is no longer good enough; we must shoot for great."

Approximately 12 percent of the Center's patients fell into this category, he adds, or one in eight patients. They had either lost weight since their last visit, had poor weight gain in the preceding three months, or had dropped a height or weight percentile.

Why are these patients having trouble gaining weight, the clinicians ask. Are they taking in enough calories? If not, the team may prescribe supplements or recommend a surgically placed feeding tube. Are their bodies absorbing the calories they do consume? If not, more pancreatic enzymes might do the

trick. Is it possible the patient has cystic fibrosis-related diabetes? If so, it's time for a different treatment strategy.

"The way CF affects the digestive system, the 50th percentile BMI can be a hard goal for some kids," says Mogayzel. "It's not always easy to keep the weight on. But this new data shows strikingly better lung function at or above this level, so we need to get our patients there."

Taking a more aggressive, proactive approach to patient care has business implications in clinic, where exam rooms have to be scheduled, staffed and supplied and patients are looking for good care and customer service. As part of the QI project, Mogayzel and Boyle surveyed both staff and patients to identify ways to improve efficiency and the overall clinic experience.

"We thought the patient registration desk was going to be the obvious bottleneck in clinic operations," Mogayzel says. "We were surprised that, in reality, patients were spending more time back in the exam rooms. We realized we needed to schedule an additional clinic day to be able to spend more time with more patients."

The average patient visit prior to June was two
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Cystic Fibrosis Foundation's 7 Goals for Quality Improvement

1 People with CF and their families are full members of the care team. Communication will be open so everyone can be involved in decisions about care. Care will be respectful of patients' needs, preferences and values.

2 Children and teens will have normal growth and good nutrition. Adults' nutrition will be maintained as near to "normal" as possible.

3 Everyone with CF will receive the right therapies to keep lung function steady and to decrease the number of pulmonary exacerbations or respiratory infections. Exacerbations will be diagnosed early and treated appropriately.



People with CF and care teams will work together to eliminate the chances of patients getting respiratory pathogens or germs.



Children and teens will have normal growth and good nutrition.

4 People with CF and care teams will work together to eliminate the chances of patients getting respiratory pathogens or germs, particularly *Pseudomonas aeruginosa* and *Burkholderia cepacia*, in the hospital, clinic and home.

5 People with CF will be closely monitored for complications of CF, especially CF-related diabetes. For any complication, prevention and early treatment when possible should be the approach.

6 Everyone with CF will be able to receive appropriate therapies, treatments and support regardless of race, age, education or insurance coverage.

7 Everyone with CF will be supported by their CF team when making decisions about transplantation and end-of-life care.

Source: Cystic Fibrosis Foundation

Research Briefs

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tensive insulin therapy during hospitalization will improve weight gain, pulmonary function and decrease inflammation.

THE SEARCH FOR ACCURATE OUTCOME MEASURES

A major challenge in the search for new therapies is figuring out if they really work. The goal of new pulmonary medications is to preserve lung function and increase survival of CF patients, but we do not have the luxury of waiting decades to determine if they are effective. Therefore, research relies on so called "surrogate markers." The best known "surrogate marker" is lung function, typically the forced expiratory volume in one second or FEV1, since this value correlates with survival. Logically, better lung function and fewer infections should lead to better survival. However, changes in lung function are gradual. Also young children cannot perform routine lung function testing.

Recently, the presence of inflammatory compounds in the lungs or blood of CF patients has been proposed as another outcome measure of successful drug therapy. The Anti-Inflammatory Mediator (AIM) trial underway at Johns Hopkins will provide insight into whether measurement of the compounds is accurate and if such a marker will be useful in future studies. Newer CT scans which provide better pictures of the lungs with less radiation also offer a possible new outcome measure. Chest CT can detect very subtle changes in CF lungs even before pulmonary function abnormalities are noticeable. Several centers are developing standardized techniques to obtain and interpret these scans so that they can be part of future multi-center clinical trials. Future clinical trials at Johns Hopkins will likely assess these new scans. ■

Raising the Bar

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hours, 15 minutes. "If we're now asking patients to come in more frequently for more aggressive nutritional care, we owe it to them to keep those visits under one hour," Mogayzel says.

The team has gotten positive feedback from patients, but challenges lie ahead.

"Patients and parents agree in principle, but it's hard to actually do it," Mogayzel says. "It's hard to get your child to gain weight. It's hard to get into clinic more often than before." But it's important, he adds, and the CF center remains committed to the goals.

Over the next six months, Mogayzel and Boyle will focus on improving pulmonary care for all



patients. Their clinical data shows a clear decline in lung function as children age. The task ahead is to define care strategies early on to prevent dramatic decline.

The lessons learned will also make their way back to Marshall at the CF Foundation, where they'll complement best practice data from peer centers across the country.

"Hopkins is a superb center which is contributing at every level: basic science, clinical science and clinical care," Marshall says. "As we've come to expect, Hopkins has assumed a leadership position in the quality improvement work." ■

NACFC Highlights

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recurring lung infections in some patients.

The sugar mannitol also pulls salt and water into the CF airway. A dry powder form called Bronchitol has been tested in 39 patients with CF in a Phase II trial at eight sites in Australia. Two weeks of Bronchitol treatment led to a 120 ml increase in FEV1. A larger trial is planned in 2006.

NEW ANTIBIOTICS ARE ON THE WAY

Phase II trials have shown that inhaled aztreonam, an anti-pseudomonal antibiotic, can decrease the amount of *Pseudomonas aeruginosa* in the airway and increase lung function after 14 days. Three Phase III trials are ongoing to study inhaled aztreonam use alone for 28 days or alternating with TOBI®. Trial results should be available later this year.

Researchers at Transave (Monmouth Junction, NJ) have created a new form of the antibiotic amikacin that is embedded in lipid, or fat. In animal studies, inhalation of this novel drug, called SLIT™ amikacin, increased the concentration of the antibiotic in the lung and the duration of its effectiveness in killing *P. aeruginosa* more than fifty-fold as compared to TOBI.

This drug is not yet in clinical trials.

BLOCKING INFLAMMATION MAY BE CRITICAL

Much of CF lung disease is due to damage caused by inflammation. CF patients typically have low levels of glutathione, a substance which normally protects the lung from oxidative damage from inflammation. Carol Conrad, M.D., a pediatric pulmonologist at Stanford Medical School and Johns Hopkins alumna, studied the effect of oral N-acetylcysteine (NAC), which can replenish glutathione in CF patients. In a Phase I safety trial among 18 patients, she found that a three-dose regimen of NAC was well tolerated and led to a reduction in neutrophils and inflammatory compounds in the sputum of treated patients. A larger Phase II trial will begin this year. ■

Check this out...

Our new Web site
www.hopkinscf.org



JOHNS HOPKINS
MEDICINE

Cystic Fibrosis Center
600 N. Wolfe Street
Park 316
Baltimore, MD 21287
410-955-2795
www.hopkinscf.org

Adult CF Program
1830 East Monument Street
5th Floor
Baltimore, MD 21205
410-502-7044

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