The Transition

As the average life expectancy of patients with CF has risen dramatically over the past 20 years, more and more patients are living on their own, attending college and pursuing careers.

Celeste Dixon of Glen Burnie, Md., couldn’t have been more excited about graduating from high school and attending college. But as a 17-year-old with cystic fibrosis, she wanted to know if she could attend an out-of-state college. Could she have a roommate? Or would she, because of her vulnerability to lung infections, be limited to a single private room? Or was living on campus entirely out of the question?

Such concerns are not uncommon—and not without some anxiety—among patients with CF as they begin to leave adolescence for young adulthood, notes pediatric senior clinical nurse Donna Peeler of the Johns Hopkins Cystic Fibrosis Center.

“Concerns about moving from high school to college, leaving home, it’s a very normal thing,” says Peeler. “If we can ease that process and identify their fears and what they’re anxious about, we can help them build their confidence in living more independent lives.”

To help patients manage the myriad concerns that come with greater independence—from refilling prescriptions and dealing with insurance companies to making lifestyle choices—Peeler and her colleagues in the CF Center are utilizing a transition program for patients called “CF Rise.” The program provides a transition timetable, skills checklist and resources, among other aids, to facilitate the shift.

When this process begins depends on the patient, transition team members say, although they may begin transitioning as early as age 16. Considerations include their knowledge base, level of maturity and trust in adult providers.

“A lot of patients would be happy to hang on to pediatric care as long as they can,” says pediatric social worker Allison Pina. “They’re not eager to leave since they’ve been coming to us since they were born.”

Switching to adult care can be an emotional issue, too, says Pina, citing at least one 17-year-old girl who became tearful after being asked to make a transition appointment. “The patient might say of adult providers, ‘They may not like me, they may not get me—you guys get how I am,’” says Pina.

Also, Pina adds that some pediatric patients feel they need to know everything about their disease and how to manage it on their own before tran-
DIRECTOR’S COLUMN

CFTR is 25!

In 1989, mutations in the CFTR gene were identified as the cause of cystic fibrosis (CF). As I reflect back 25 years to that landmark date, it is clear that amazing advances have occurred in CF research, drug development and clinical care due to the discovery of CFTR. Incredibly, survival for people with CF has doubled in the past 25 years.

Unquestionably, the discovery of the CFTR gene ushered in an era of therapeutics development based on the understanding of the molecular defect in CF. Today there is a drug that treats the basic defect for 5 percent of the people with CF. And data released in 2014 demonstrates that a combination of drugs can improve lung function and decrease exacerbations for half of the people with CF who have two F508del CFTR mutations. We’ve come a long way.

As we also know, patient participation in clinical trials is essential to continued drug development. To facilitate the development of new therapies the CF Foundation in 1999 created the Therapeutics Development Network (TND), of which Johns Hopkins has been part of since the TND’s inception. Indeed, last year Johns Hopkins enrolled more patients with CF into clinical research trials than any other CF Center in the United States. One hundred and five children and adults with CF participated in a clinical trial, that’s more than 20 percent of the eligible patients at Johns Hopkins. This level of participation clearly illustrates the importance that our patients, families and clinical staff place on research.

Rest assured, Johns Hopkins and you, our partners in discovery, will continue to play an integral part in drug development in the coming year, when over 1,500 centers, patients were randomized into a Comprehensive Adherence Program (CAP) or standard care.

Putting CAP to the Test

I t’s a comprehensive behavioral and educational intervention a good approach to improve patients’ self-management of cystic fibrosis (CF)? In the ongoing iCARE trial at 18 cystic fibrosis centers, patients were randomized into a Comprehensive Adherence Program (CAP) or standard care. The preliminary findings? A focus on improving CF knowledge, increasing skills with devices, and problem-solving barriers to self-management may improve health outcomes. However, the intervention didn’t change medication adherence—an unexpected but still positive result, says Kristin Riekkert, co-director of the Johns Hopkins Adherence Research Center.

“We are seeing lower decline in lung function, better BMI percentiles and a trend for fewer exacerbations” says Riekkert. “It’s great news, it’s what we want most—to improve health.”

In the study, Riekkert explains, patients age 11 to 20 at half the centers received CAP care for 2 years, which includes a clinic-based problem-solving intervention that allowed teenagers to pick which aspect of the regimen they wanted to work on—nutrition, airway clearance, or medications. Patients at the other half of the centers received CAP in year 2 of the study.

Outcomes were determined by changes in prescription refills, lung-function, weight, exacerbation, and patient reported measures like quality of life and CF knowledge and skills.

For both parents and teens, knowledge scores were highest on lung health and lowest on nutrition, Riekkert notes. While most patients demonstrated good skills in taking enzymes, there were big gaps in airway clearance technique. Poor technique means that even when a person puts in the time to do the treatment, he or she might not get all the possible benefit.

Many parents and adolescents in the CAP group reported that the problem-solving sessions empowered the teen to be more engaged in their care. The clinical implications, says Riekkert, are that effective self-management programs can be delivered by healthcare providers in both outpatient clinics and hospitals.

Transitioning to Adult Care

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sioning to adult care: “We try to explain to them that that’s not what this is about.”

What it’s about, transition team members say, is education, preparation, and the thoughtful development of transition tools enabling a seamless switch. The CF Rise curriculum includes knowledge quizzes at ages 16 and 18 on topics like lung function and nutrition, and a checklist that evolves from what mom was doing to what the patient is doing today.

“The transition happens over multiple visits, it’s something we continually work on,” says adult CF nurse practitioner Meghan Ramsay. “It has to become routine for patients, where they want to learn about the disease for themselves.”

“Look, three months ago your mom was doing all these things,” adds Pina. “Look at your checklist now. Everything is moving toward you doing it yourself.”

But doing it right—and ensuring continuity of care during the transition—is the highest priority, say team members. Having both pediatric and adult providers under one roof at one CF Center, they add, helps immensely. Adult and pediatric physicians, nurses and social workers meet monthly to discuss transitioning patients and their psychosocial issues, and then meet with the patient at his or her final visit in the pediatric CF clinic.

“Our doctors specialize in adult care, and different issues come up as patients become adults,” says adult CF social worker Megan Langergren.

“We try to make it a natural experience, not a forced or negative change. It’s a milestone, you’re making it to the adult program.”

Kristin Riekkert, Ph.D.

Putting CAP to the Test

“We are seeing lower decline in lung function, better BMI percentiles and a trend for fewer exacerbations. It’s great news, it’s what we want most—to improve health.”

KRISTIN RIEKERT, PH.D.
The New CF Therapies—An Insider’s View

“Borderline revolution.” That’s how Michael Boyle sums what’s happening in cystic fibrosis (CF) therapy, beginning with the FDA’s 2012 approval of ivacaftor, the first drug to target an underlying CF cause. The pulmonologist holds genuine optimism about the new turn in therapy, tempered by an insider’s realism as research continues on ivacaftor and newer CF agents now surfacing.

Patients from three years of trials show ivacaftor works even though the therapy isn’t a cure. Its benefits are real for the 15 percent of patients with the G551D or other mutations that warp the key CFTR protein so it can’t channel normal chloride ion flow. Ivacaftor “activates” that flawed CFTR stationed in lung cells’ outer membranes, opening the way for the ions. “It’s like applying WD40 to a rusty gate,” one observer writes.

“Patients say they feel better,” says Boyle. “But hard data that we need are also there.” Chloride transport looks to be about 50 percent restored in lab-cultured respiratory cells. “That translates to about a 15 percent increase in patients’ lung function—a big change,” he adds.

Boyle and colleagues aren’t seeing children’s usual progressive decline. They are severely sick far less often, with hospital stays cut by half. Weight gain appears better and clearing infection seems easier, though those studies are ongoing.

“Ivacaftor can’t undo 20 years of lung damage,” Boyle says, “but it improves the lung that’s there.” Now studies are underway for children as young as age two, to try to prevent damage from taking hold.

“Knowing that having much less-than-100 percent correction at a cell level can make such a difference for patients is important—for all mutations,” he says.

But what of that majority of other CF patients whose CFTR mutations aren’t ivacaftor-targeted? By itself, the drug isn’t helpful for the roughly half of CF patients with the common F508del mutation, for example. Theirs is a “trafficking” problem where abnormal CFTR is quickly broken down in a cell’s cytoplasm before it reaches the outer membrane.

Fortunately, pairing ivacaftor with a second agent, lumacaftor, showed promise in Phase 2 studies several years ago, especially for patients with two copies of the F508del gene. Lumacaftor rescues enough CFTR molecules from certain destruction to travel to their cell membrane home. Together, Boyle says, the drugs likely give a one/two punch: “You get CFTR to the surface; you turn it on to maximum effect.”

Now, thanks to an FDA “breakthrough designation,” the streamlined, Phase 3 two-drug trial that Boyle heads—some 1,000 patients worldwide—has been completed. The combination of lumicaftor and ivacaftor led to a modest improvement in lung function and a significant decrease in exacerbations. These results have led the drug combination to be submitted to the FDA for approval.

“We are already looking to the future,” Boyle says.

Multiple pharma companies are readying new agents to boost the two drugs’ synergy. One, to go into trial late this fall, may up CFTR levels at the cell surface. “Just a 20 percent increase,” says Boyle, “could make such a difference.”

A Miraculous Serendipity

The push to clarify all CF-related mutations has placed geneticists, bench scientists and industry in each others’ pockets. It’s an arrangement likely to last as therapy’s potential begins to unfold.

In 2010, when this country finally snapped its mandate into place to screen newborns for CF, a small complicity settled briefly. “At first,” says geneticist Garry Cutting, “we were doing seemed good enough.” Work by Cutting and others had already uncovered 23 variants of the CFTR gene accounting for some 85 percent of U.S. cystic fibrosis. Inherit both F508del, the most common mutation, and one of the remaining 22, Cutting says, “and you could be sure of the CF diagnosis.”

Yet, as more screening added rarer genotypes to the list, that clouded diagnosis and treatment. When only a few people carry an uncharted change in their CFTR gene, predicting risk becomes difficult, he explains. “It’s harder to tell parents if that variant raises their newborn’s chances for CF and, if so, how intense the disease might be.”

So Cutting, the NIH and colleagues worldwide pushed for a way around the “disease liability” dilemma. Today, the resulting CFTR2 website and database (Clinical and Functional Translation of CFTR) is vital and expanding. And in what Cutting—who’s not given to drama—calls “a miraculous serendipity,” it has done more than raise awareness of less common variants. CFTR2’s database underlies more than a dozen therapies that appear poised for the clinic in two or three years.

CFTR2 started in 2011 as a project Johns Hopkins, the Cystic Fibrosis Centre in Verona, Italy, and the Hospital for Sick Children in Toronto shared, with the Cystic Fibrosis Foundation as underwriter. With a goal to sort harmless CFTR variants from riskier ones, it built on the Toronto group’s existing database. Today, from 40,000 patients’ records, the site reports close to 2,000 CFTR variants. Common ones tied to CF now number about 160. And starting a new worldwide phase, CFTR2 expects another

“Seeing CF patients on the hospital wards in the 1980s was tragic—everyone knew the kids were not going to live long. Pancreatic enzymes would improve nutrition but lung disease was rampant, parents were beyond exhaustion. Now we have insight into molecular-based therapy that is being translated to the bedside and clinic—the best development in the field in the 25 years since discovery of the gene responsible for CF.”

—GARRY CUTTING, M.D.
A Miraculous Serendipity  
(continued from page 3)

10,000 patients’ data, extending to China and the Pacific Rim, to India, the Middle East, Africa, Central and South America. And Cutting’s “serendipity?” That arose from desperation for tactics to clarify CF risks. His group turned to basic scientists at Johns Hopkins and elsewhere for the knottier variants. Working from CFTR2 data, molecular biologists could engineer patients’ specific CFTR proteins and then reveal their structural flaws. “But what caused everything to snowball,” Cutting says, “was adding industry to the mix.” With their initial CF drug, ivacaftor, biochemists with Vertex Pharmaceuticals found a way to compensate for molecular errors of specific CFTR variants.

Now the partnership is locked in: CFTR2 publishes its inventory of CFTR gene changes, basic scientists explain what the changes do and pharmaceutical companies scout for corrections. “Once you pry open the door for this disease, it’s far easier to push it the rest of the way,” Cutting explains. Already companies are tinkering with ivacaftor to expand its use for patients with similar CFTR errors. “Are there safety issues? Yes. It’s a problem ‘Big Pharma’ faces in broadening drug use. So they’re moving carefully,” he says. Signs also exist that the drugs don’t fix everything, like inflammation. “But we’re optimistic,” he adds. “What we’re seeing is nothing short of incredible when you realize where we were just 25 years ago.”

Ongoing Clinical Trials  
(continued from page 1)

Patients Experiencing Pulmonary Exacerbations Requiring Hospitalizations
The Pilot Observational Study to Determine Feasibility of a Standardized Treatment of Pulmonary Exacerbations in Patients with Cystic Fibrosis (STOP) is enrolling patients 18 and older who have CF and require hospitalization for intravenous antibiotics to treat a pulmonary exacerbation at Johns Hopkins Hospital. Participation in the study will last up to one month and requires up to 4 outpatient study visits.

Full information can be found at hopkinscf.org or email hopkinscf@jhmi.edu or call 410 955-1167

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Johns Hopkins Cystic Fibrosis Center
200 N. Wolfe Street
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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Gary Logan, Editor
Peter Mogayzel, M.D., Ph.D., Medical Editor
Marjorie Centofanti, Contributing Writer
Dave Dilworth, Design
Keith Weller, Photography

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Translating Theory into Therapy

Partners in Discovery
News from the Cystic Fibrosis Center at Johns Hopkins