



The Lung Life of a Cystic Fibrosis Patient: A Patient and Physician Perspective

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ABSTRACT

This article is co-authored by a patient living with cystic fibrosis, and her treating physician. The first section of this commentary article is authored by a patient, who describes their experience of living with cystic fibrosis. The following section is authored by the patient's physician, who discusses the management of cystic fibrosis in the context of the patient's experiences.

Keywords: Cystic fibrosis; Patient experience

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PATIENT PERSPECTIVE

Gabriella Balasa

The day I was born, the median life expectancy of someone living with cystic fibrosis (CF) was 31. I was shielded from this knowledge until about age 12, when I secretly read my mother's diary. The words "inevitable" and "death" still stick in my memory.

Today, I'm 28. CF is a genetic, progressive disease that causes thick, sticky mucus to build up primarily in the lungs, but also in the digestive tract and sinuses. Over time, this mucus breeds infections from bacteria, which I then inhale into my lungs; the cycle of infections and inflammation leads to lung damage, then eventually respiratory failure, and death. Lung transplantation is an option to prolong the life of someone who has severe lung disease, but it comes with its own set of challenges. I have come close to this reality, but have survived the last 10 years having around 30% FEV1 (a measure of lung function) and holding onto it as long as I can.

Growing up, I did everything most other kids my age did—playing soccer and scootering. But I also did many things they did not. Every day before lunchtime, I would go to the nurse's office and complete an inhaled breathing treatment, drink a weight gain supplement and take enzymes to digest my food properly. In the

third grade, I had four stints of hospital stays, each 2 to 3 weeks long, during which I received intravenous antibiotics.

I graduated college with a degree in biology and was offered my dream job, but I did not take it. Already having only 30% lung function, spending hours a day on breathing treatments, attending frequent doctors' appointments, taking antibiotics to treat the infections—not to mention maintaining a social life and community involvement—were not conducive to a full-time working schedule.

I also weighed the risks and benefits of losing Medicaid benefits and decided it was not a wise option, considering my disease would progress, and it would be only a matter of time before I would be forced to stop work and then have the uncertainty of how I would obtain health insurance. This has proved to be the right decision. The negative aspects are the inability to earn much money and maintain the resources limit, making me financially dependent on my parents—a difficult mental obstacle when living with a progressive chronic illness.

Choosing not to advance in my career made me feel left behind, and made my health the focus of my life. But I've made the most of it, through pursuing flexible, part-time work as a technician in a university microbiology lab and developing my skills as a writer and a patient advocate—something I never would have done otherwise.

As time has passed, some of the microbiology work in the lab has had intersection with CF, as common infections in CF lungs and antibiotic resistance they acquire are also commonly found and studied in water systems. Having this background knowledge has allowed me to explore and understand CF research and be involved in various research-related advisory committees tasked in providing patient perspectives on research questions and methods. I'm now able to provide a scientific voice to the CF community while having purpose and success in my life.

The only way I have been able to stay as stable in my lung function while having such advanced disease has been my adherence to treatment regimens, nutritious and caloric diet, exercise, enough rest, and the willpower to fight

my hardest through every health challenge that has come my way. In some ways, I feel like I've one-upped this disease. Thanks in part to a daily routine consisting of four 1-hour sessions of breathing treatments and airway clearance to move the mucus out of my lungs, someone meeting me for the first time probably would not recognize my condition. I use Albuterol (Nephron, Columbia, SC) to open the airways, hypertonic saline to break up mucus, Pulmozyme (Genentech, San Francisco, CA) to thin the mucus, and use a variety of devices to loosen the mucus from the lung walls including a high-frequency chest wall oscillator, also known as the Vest (Hillrom, Batesville, IN), and PEP (positive expiratory pressure) devices like the VibraPEP, the PEP mask, and the Flutter. I try to exercise 30 minutes to an hour each day, consisting of cardio and some strength training. Keeping the lungs moving as much air as they can is key to keeping the accumulation of mucus secretions at a minimum.

But over the past few years, infections have become more frequent, so much so that I have required oral antibiotics almost constantly. What's more, as my lung function has declined over the years, my physical limitations have increased. I have not been able to run for nearly 10 years. These days, taking a flight of stairs leaves me incredibly winded, and I use supplemental oxygen (about 4 L/m) through a nasal cannula when I sleep and when I exercise. My lungs have also endured four lung collapses, each requiring a separate surgery called pleurodesis to re-inflate the lung.

Last winter I became dangerously ill with the worst lung infection I have ever had. During the peak of my sickness, my body was a shell of an existence—at 18% lung capacity, supplemental oxygen was constantly filling my nostrils. I had been using intravenous antibiotics for over 5 weeks, with no relief in my symptoms, fevers, coughing, and mucus perpetually lining my airways. In the shower, reaching up over my head to wash my hair was exhausting. The antibiotics had stopped working. After years of chronic antibiotic use, the *Pseudomonas aeruginosa* bacteria in my lungs were resistant to every antibiotic. I desperately needed to try something different, and that is when I turned to a

non-FDA [Food and Drug Administration]-approved experimental treatment called phage therapy, which I received on a compassionate use basis [1].

Phage therapy is the use of a virus with a very specific host range that attacks bacteria. I traveled to Yale to receive this inhaled treatment once a day through a nebulizer. I inhaled a 10^9 concentration of phage mixed in normal saline. Phages work best when used in combination with antibiotics, because the bacteria that aren't immediately killed by the phage are then forced to give up their resistance to antibiotics, which makes them vulnerable again to the antibiotic attacking them. About a week after my treatment, I began expelling all of the dead bacteria from my lungs. I had never cleared an infection so quickly before, and I had used these antibiotics many times in the past, so I knew it could not have just been the antibiotics doing their job. Knowing the extent of infection I had—as well as the advanced lung disease and low lung function I suffer from—I definitely consider phage therapy to have been successful in clearing my infection [2].

With that said, phage therapy certainly is not a magic cure-all that will permanently rid a person with CF of infections. That's because there are multiple kinds of bacteria living in the lungs, and phages only have the ability to target a few. It can also be difficult to deposit phages deep into the smaller airways because they are often blocked by mucus, which prevents anything from passing through. It can be even more difficult in lungs that are severely damaged like mine. What's more, different bacterial strains can live in different lobes of the lungs, so treatment for a particular strain in one lobe may have no effect on those in another. For these reasons, many bacteria still survive in those smaller airways, and over time, they have the ability to take over the lungs again. Phages also did not help to improve my lung function, but I did not necessarily expect them to. After all, they are only used to kill specific bacteria and not for rebuilding damaged lung tissue—and for someone with the extent of lung damage that I have, even after infections are cleared, the lung damage remains.

Even though I recovered from this acute infection, my lungs remained very damaged and weak, and I was referred for lung transplant. I relocated down to Durham, North Carolina last spring to prepare to be listed at Duke University. I learned just about everything there is to know about what to expect after surgery, the medications, and longer-term care. I made friendships with fellow transplantees who were going through this at the same time, bonding over similar concerns as well as the excitement from a positive update from those who are on their way in recovery. After participating in cardiopulmonary therapy for 2 h a day, 5 days a week, my body was stronger, and I gained 2% lung function back, getting to 25% by the summer. Around that same time, I was notified that I would be eligible for a new drug that could halt the progression of my symptoms and perhaps even allow me to regain some lost function.

I was granted compassionate use for a modulator drug called Trikafta a few weeks before it was approved by the FDA. It's now the third approved drug to treat the most common genetic variation of the CF mutation, allowing properly formed transmembrane proteins to transfer chloride and water in and out of epithelial cells. This drug boasts the best results of the modulator therapies manufactured by Vertex Pharmaceuticals and expands potential use to nearly 90% of the CF population—including me.

My expectations of Trikafta, before starting it, were immense. I had been waiting years for the day to take a drug that would halt the thick, relentless mucus. I hoped that I might gain some lung function back and reduce my need for supplemental oxygen. To friends and family, I maintained an air of nonchalance. It was an attempt to minimize my inner anxiety through outward display.

My results have been gradual and moderate in comparison to other patients. Day to day, for example, mucus reduction has been slight, but over the course of a few months, I've found relief for a few more hours between breathing treatments. I have gained a few extra pounds, something I've struggled with my whole life despite always having a calorie-rich diet. During

exercise, I still require the use of about the same amount of supplemental oxygen, but I can push my body further and have started lifting weights. The volume of my breaths is now 30% FEV1, increased by 6%—as good as my highest lung function in the last three years, albeit a small overall change.

My life will be prolonged to some extent by this medication, and for now I have put lung transplant on pause. This may translate into 1 year or 5 before I will need a transplant, but with many new treatment options in the pipeline, I am optimistic for the possibilities of accessing some of these new therapies in the coming years.

Within the past few years, advancements in therapies targeting the CFTR proteins have increased exponentially. The latest treatments include inhaling messenger RNA (Translate Bio) and delivery of genetic therapies to the lungs through vectors. To treat the infections caused by bacteria harbored in the lungs, new therapies, such as inhaled nitric oxide and intravenous gallium, are being studied in clinical trials. They work differently from conventional antibiotics: nitric oxide promotes the immune system's defenses against bacteria, while gallium inhibits bacterial nutrient uptake—essentially starving them.

In addition to these new therapies, the Cystic Fibrosis Foundation recently committed \$100 million over the next 5 years to research addressing chronic infections. The project aims to improve infection-related outcomes using a comprehensive approach, involving enhanced detection, diagnosis, prevention, and treatment.

In addition to maintaining my strict daily treatment routine, over the years I have found that self-advocacy and good communication are vital to receiving optimal care. Through being open about sharing my needs and health experiences with my care teams and with others in the CF community, I have become much more informed about my own care. Receiving and providing valuable information that we can learn from each other is key to advancing the healthcare of those with CF and patient populations in general. I am on the patient advisory council at my CF clinic and serve as director of

the United States Adult CF Association (USACFA). My involvement in the CF community has expanded, and the friendships and relationships I have created have provided me much joy and fulfillment.

I do look forward to the day I'll be able to breathe deep with transplanted lungs. I sometimes daydream about being able to run in a park, ski down mountain slopes, or climb rock walls. But until then, I will make the most of what I am able to accomplish. Every day, I strive for more breaths, for more knowledge, for more personal connections that fulfill me. CF is my greatest of blessings but it's also my most awful curse. With it, I bear the hardship of health battles for a shortened lifetime, but without it, I wouldn't have this path through which I've learned many of life's lessons.

PHYSICIAN PERSPECTIVE

Nauman Chaudary

It is so exciting to write this article in 2020, the year which will be remembered in history as a life-changing year for all of humanity, but perhaps not so much for a patient with cystic fibrosis (CF). Why is that? What we see as a desperate response to contain the pandemic, making the entire world feel like one large hospital, is a normal, daily reality for patients with CF and has been for many decades. The most recent CF infection control guidelines were published in 2013 [3]. The guidelines recommended patients maintain a social distance of 6 feet, no more than one patient is to be seen inside a health facility or at social gatherings, patients should use hand sanitizer and wipe down after the use of patient care facilities, and should wear a surgical mask at all times when in a non-ventilated hospital area. Patients are not allowed to meet each other or interact in hallways. Considering this, it is not surprising that CF patients were already equipped to deal with changes as a result of the pandemic. CF providers and CF patients felt at ease transitioning to virtual clinics, as this is our theme and what we have been used to for more than a decade.

Ella's experience of CF life expectancy stems from a virtual reality—it was rare to see CF patient make it to high school in the early 1990s [5]. Since the discovery of the CF gene in 1989, no other genetic disease has seen as much progress as CF has in the past three decades. As a result, the Cystic Fibrosis Foundation (CFF) convened an adult care group in 1999 to discuss the status of care for individuals with CF who were aging beyond adolescence. It started small, and CFF quickly realized that there was an increasing need for centers and providers that could comprise team members who are experts in this field, and could primarily direct care to adults with CF [4]. In 2015, we saw for the first time that there were more adults than pediatric patients with CF [5].

One of the primary areas of focus in CF care has been to preserve lung function (measured as FEV1). This measure has been used to study the effectiveness of drugs in clinical development, and it is also used to primarily target strategies for preserving FEV1 as close as possible to a baseline value or a goal of 75% or more. CF patients can lose lung function at 1–2% per year due to frequent exacerbations as a result of inflammation and bacterial infections. If this goes unrecognized, it can lead to an exacerbation in 2 days, a week of exacerbation untreated can lead to a hospitalization, and a month of unrecognized or untreatable exacerbation can lead to death. There are numerous aerosols and airway clearance therapies that target preservation or restoration of FEV1. Patients may require hospitalization for intravenous (IV) antibiotics lasting up to 2 weeks. At times this becomes part of the life of a CF patient at home when IV therapy can be used via a percutaneous line several times a year. Exacerbations are very important, as only 75% of patients return to 90% of their baseline FEV1 with treatment [6].

Scientific advancements, better screening at birth, and CF care centers with dedicated registry input have been attributed to better health in the CF community (Fig. 1). Adults are leading successful lives with better careers, able to raise families and plan for their future and retirement, and in a truly evolving sense, we will need to prepare for CF geriatric care in the future. Healthcare providers are screening

patients for preventive care for cholesterol, blood pressure, diabetes, colon cancer, mammography, pap smears, eye exams, and hearing checkups, like a non-CF patient. Ella's experience also draws our attention to another aspect of CF care when choosing a job or career, and that is how accommodating the employer and work can be to their unique demands of care. A review conducted previously in CF patients showed that on average, a patient spends 108 minutes treating their CF on a daily basis [7]. This can vary especially if the patient develops advanced lung disease, which is FEV1 less than 40% with symptoms. On average, 40.5% of patients had one CF exacerbation reported in the 2018 registry [5]. Despite all of these advancements, CF remains a life-limiting illness, and patients continue to show decline in their lung function over time (Fig. 2).

As Ella reports, CF patients can progress to advanced lung disease from a vicious cycle of recurrent infections, inflammation, and multidrug-resistant pathogens, and require oxygen or noninvasive ventilation. Markers of prognostic significance include poor exercise capacity on the six-minute walk test with a distance of < 400 m, development of pulmonary artery hypertension on echocardiogram, chronic respiratory failure, multidrug-resistant infections, significant multi-organ comorbidities, pneumothorax, and hemoptysis [8].

As a CF provider, we can refer to CFF guidelines which are designed to help provide answers to questions that can arise during the management of a CF patient. These guidelines are rigorously reviewed, and treatment guidelines are based on evidence attesting to their efficacy and provide inner confidence to healthcare providers who use them in CF management decisions. Considering the rare nature of this illness, evidence for a certain treatment is on an individual basis, or based on a unique case report. Providers and patients must therefore make certain calls on non-FDA-approved treatments, as well as treatments that can be considered under expanded programs or compassionate use. Ella highlights her experience with phage treatment, which is considered non-FDA-approved, or experimental, in current CF care. As Ella points out, she was against a wall

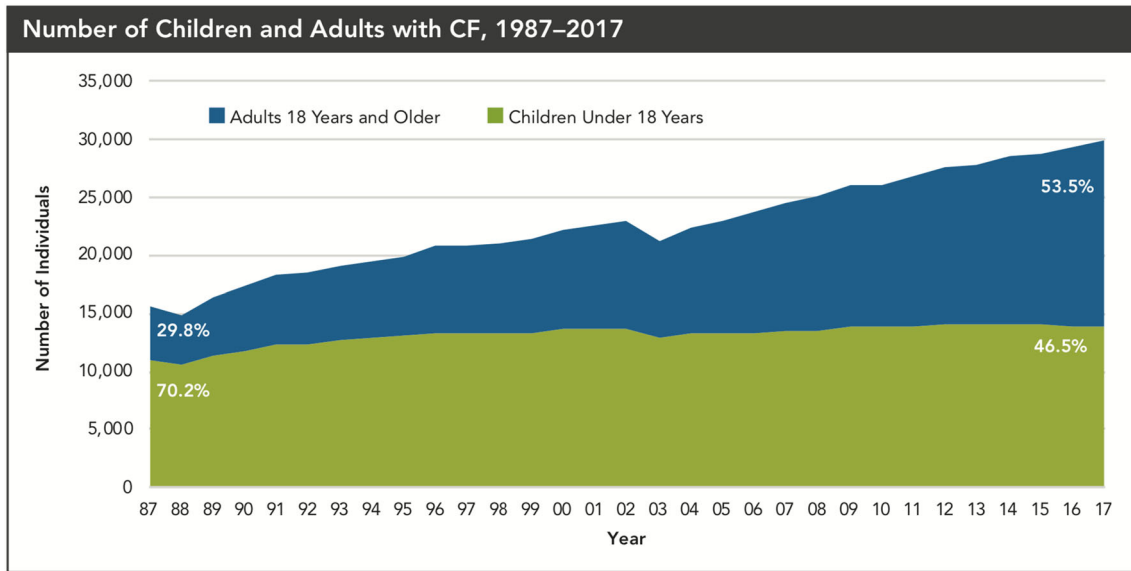


Fig. 1 Cystic Fibrosis Foundation Patient Registry, 2017 Annual Data Report, Bethesda, Maryland, ©2018 Cystic Fibrosis Foundation. Source of data: Cystic fibrosis

patients under care at CFF-accredited care centers in the United States who consented to have their data entered

Median FEV₁ Percent Predicted vs. Age, 1990 and 2009

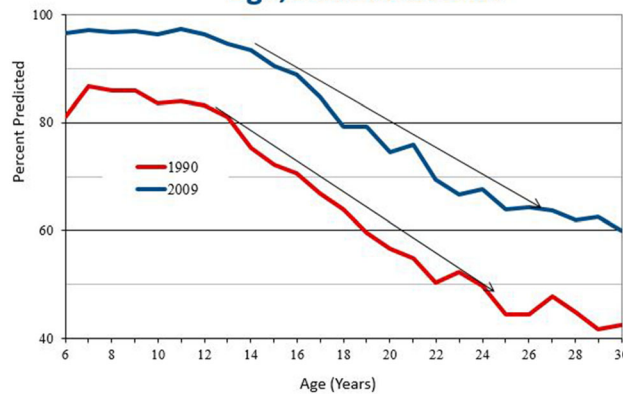


Fig. 2 Cystic Fibrosis Foundation Patient Registry, 2009 Annual Data Report, Bethesda, Maryland, ©2010 Cystic Fibrosis Foundation. Source of data: cystic fibrosis

patients under care at CFF-accredited care centers in the United States who consented to have their data entered

and had to make a choice regarding her future—lung transplant for prolonging her survival versus trying to take on potential experimental treatments that could possibly help her. With the advent of highly efficacious CFTR modulators, most recently Trikafta (registered trademark of Vertex Pharmaceuticals), the landscape of CF care has completely changed [8, 9]. The

world was made aware of its dramatic effects on heterozygous 508del patients, a mutation that Ella had as well. The CF community could not wait for its FDA approval. In fact, the results were so compelling that Vertex decided to provide the drug on an expanded access program about 4 months prior to its FDA approval in winter 2019. This proved to be a game changer

for many, and this was also true for Ella. In clinical trials, Trikafta showed an absolute FEV1 increase of 14% in people with one copy of 508del and 10% in those with two copies of 508del [9].

There may be a couple of possibilities why Ella did not notice the expected improvements from Trikafta. It may be that she had advanced lung disease and therefore advanced bronchiectasis, inflammation, and infectious burden, which is irreversible by restoring the CFTR modulator. It is also possible that meaningful subjective and objective improvements are hard to capture due to the development of pulmonary hypertension with advanced lung disease. Lastly, her expectations may be too high considering the severity of her lung disease, making it difficult to objectively consider the effectiveness of the therapy.

Clinical trials report promising results for both F508del homozygous and F508del heterozygous individuals, with minimal residual function mutations. It was originally thought that mutations that fit in a specific class would respond to all pharmacological CFTR compounds in a similar fashion. However, when these drugs were used in clinical trials as well as post-FDA approval, this was not seen to be true [10]. These CFTR compounds can then be tailored to individuals based on their cell culture response in in vitro lab testing to a specific CFTR compound using a process called theratyping. In the future, theratyping will also facilitate patient-specific treatments based on specific novel biomarkers [12–16].

Clinical trials are investigating whether these drugs can possibly allow patients to consider stopping some of the chronic aerosols that have been used in CF care for decades, such as hypertonic saline and dornase in a trial called SIMPLIFY. Future directions also include the expansion of triple combination therapy to gating and residual function mutations. Vertex is also developing a once-daily corrector and a super-corrector Vertex 121. Trials are ongoing for a PTI corrector/potentiator/amplifier. There will be ongoing testing of new potentiators by various drug companies [11].

Exploring different relationships within the CFF, Ella has gained a comprehensive view of

CF research. For her, the struggle does not end here—it drives her forward to gain more clinical research experience within the network. The CFF is one of the highest-ranking, focused foundations in the United States, perhaps in the world, exemplified by standards of quality, excellence, and innovation. With its sponsorship of cutting-edge research, the CFF has revolutionized CF clinical research. Acknowledging this unparalleled status of the CFF, clinicians and patients not associated with it wish to gain experience from it. These facts have driven Ella to stay very involved in their advisory council.

As Ella states, our partnership in CF care is the energy that drives us to excel in the field of CF, and one has to incorporate this level of good patient care and health care partnership as CF research progresses in the future. Clinicians and patients need not shy away from incorporating the latest discoveries to find a cure for CF. To help patients live longer and improve quality of life, clinicians and patients need to stay informed regarding every aspect of CF care and CF pathobiology. For many of us this has become a way of life in CF. We live with this motto: *For those who dare to dream, the world spreads out its arms; those who fulfill their dreams, conquer the world.*

Finding a cure for CF and taking care of complex patients is similar to solving a complex riddle. However, in CF, we know well, as Martin H. Fischer proclaimed: “the diagnosis is not the end, but the beginning of the practice.” The world is evolving, and so are medical practices and knowledge concerning CF pathobiology. Ella and I realize that research is the key to unlocking answers to critical CF questions. Finding a way out of the CF maze, solving the CF riddle inspires us to unlock this mystery. The CFF has laid the groundwork for the path to a cure, with a mission to complete this by 2025. Both Ella and I remain excited to see the day where we can make CF stand for “cure found.”

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