svb

LIVING WITH CYSTIC FIBROSIS

LIVING WITH CYSTIC FIBROSIS

COVER PAGE

Ann-Julie Desmeules, CF, bi-pulmonary transplant recipient since 2003, her partner and their four daughters.

Hello Ann-Julie, can you introduce yourself in a few words?

CF, 43 year-old photographer & graphic designer, mother of two beautiful sweeties aged 8 and 12, and step-mom to 2 year-old and 4 year-old cuties! I live in a remote region, so they say, in the Saguenay. I live a beautiful & eventful life with my wife. We also have two Sphynx cats, Simone & Everest. Our goal is to complete the family with a Cavalier King-Charles we would like to call « Adobe » in reference to my work.

How has been your life path?

When I was 19 years old, I decided on my own, without taking any advice from anyone, to move to Montreal. My mother told me repeatedly, «If you go far away, we won't be able to help you.» I did as I pleased and moved to the 629 as we call it. At that time, the owner, Laval, was renting rooms to people living with Cystic Fibrosis. It was there that I met my first spouse and we stayed together for 15 years and had 2 children. Shortly after my moving to Montreal, my condition deteriorated rapidly, and I had to undergo a bi-pulmonary transplant on January 7th, 2003.

Back then, it was still a rarity for local Saguenay CF folks to go as far as a transplant. At the time, I was the second CF patient in my clinic blessed with this second chance. Nowadays, transplants are more accessible for people living in remote areas. Procedures still remain complicated practices, but there is more support and help available with the whole process. I have become a bit of a living proof for CF people living in remote areas that transplants work. It's an upgrade allowing an entirely different quality of life.

How are you feeling today?

Happy and well! I'm aware that I'm not quite perfect health-wise, but I'm learning how to reconcile all of that. I've built a nice career for myself that allows me to work from home. My wife and I see life from the same perspective. The lockdown has been far from being a challenge for us, and we love cocooning with our 4 daughters. We've just purchased a house that will give us all the necessary space since it's been a bit of a challenge for my tween to be in constant contact with the babies, yet I love my family dynamic! Since my girlfriend has a Nursing bachelor's degree, she can help me more than effectively when I need help. In my view, I live a dream life surrounded by love.

Do you have any advice or message for our readers?

It's kind of crazy because if I hadn't followed my instincts, I probably would never have had my transplant. Everything happens for a reason! In my case, it was that my hard-headedness and perseverance that helped me pull through and discover my new life unfold.

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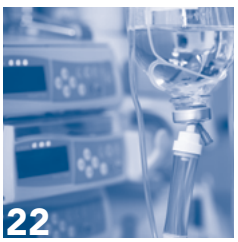


Keeping Hope

What a year 2020 was! It had many surprises in store for us. First off, here I am, vice-president, internal affairs, of your organization, writing to you. The lives of everyone were upended by the famous COVID-19 virus and the members of Living with Cystic Fibrosis didn't escape it. But since we need to know how to "reinvent" ourselves and show resilience in those challenging times, I'm lending a hand. Affected by cystic fibrosis and having had a double-lung transplant 11 years ago, I've been involved with the organization for two years as regional representative for the Montréal region, and vice-president for barely 6 months. It might not be the most "peaceful" moment to take office, but that's not what's going to stop me!

The global pandemic we are experiencing right now didn't spare anyone, but had a bigger impact on the vulnerable people of our society, such as the elderly, the chronically ill and the immunosupressed. For the fibrocystic community, the daily impacts have been visible in multiple ways: medical appointments, hospital stays and surgeries being post-poned, medical leave for people working in environments at risk for virus transmission, isolation related to lockdown periods, stress caused by the fear of contracting COVID-19, etc. This issue of SVB is timely, since we will try to shine a little more light on this virus and to share with you a bit of hope for what lies ahead.

I can't ignore a big event that went a bit under the radar this year, which is the 35th anniversary of Living with Cystic Fibrosis. Already 35 years! Thirty-five years fighting to promote and defend the rights and interests of the people affected by cystic fibrosis. And we have no intention of stopping there, since with the discovery of innovative drugs, like Trikafta, the next few years have the potential to be decisive for our community. The fight for accessibility to this drug for all corresponds exactly to the mission we are defending as an organization and we have the firm intention on seeing it to the end.

Despite the bad surprises and intense stress experienced in 2020, we continue to look to the future and hope that 2021 will bring its share of hope and good news. Know that Living with Cystic Fibrosis remains present for you, no matter the circumstances.

Viviane Crispin
Vice-President **Living with Cystic Fibrosis**

The Best Is Yet to Come...

It's been more than five months already since I've embarked on this wonderful adventure with **Living with Cystic Fibrosis**. Indeed, since mid-June 2020, and between two waves of the pandemic, I became the new executive director of the organization. It is with honour and humility that I gradually became aware of the scale of the work accomplished by my predecessor, but also by people with a good heart who contribute in their own way, against all odds, to the success of the organization's mission.

It goes without saying that the year 2020 will have seen its share of uncertainties and challenges, and will leave a forever mark on our collective conscience on a global scale. We often say that those situations push people to get closer together and help each other, as much as possible. However, those last months made me notice that our CF community was already very united and "closed-knit" before the pandemic: we could thus claim that we were forerunners of a way of living that is much more warm, open and humane.

So it will have taken a social and health crisis of this scale for the whole population to be more aware of issues we've always known and advocated for: those related to cross-contamination, the importance of physical distancing... Nonetheless, our CF community remains stronger and more united than ever in this challenging period.

This 2020 year also celebrates the 35 years of existence of the organization born under the QCFAC name, which became in 2015 **Living with Cystic Fibrosis**. We had planned on highlighting this important step with great fanfare, but the pandemic will have forced us to shift the festivities for the next year. It will happen another time, we will be in a festive mood and the party will only be more beautiful!

On another note, our organization also obtained funding from the OPHQ (Office des personnes handicapées du Québec), which allowed us to hire a new human resource in communications. Indeed, Living with Cystic Fibrosis will have its first communication and mobilization agent, Ms. Caroline Meyer. We are very happy to welcome her into our team, and to be able to lead with her the project The solidary CFs, united and healthy with help from technology [*Les FK solidaires, unis et en santé avec l'aide de la technologie*].

Also, I want to emphasize the vital contribution of all the volunteer members of the organization who invest unreservedly into our governance, our committees, our activities. Your welcome towards me was the most friendly and warm and I feel sincerely privileged to benefit from your precious and constant support. I'm very happy to be able to collaborate with all of you!

In closing, I must underscore the work of our coordinator, Sébastien Puli. Thanks to his perseverance and his devotion over the past three years, the organization was able to get through moments that could've put its survival at risk, and ultimately triumphed. From now on we can continue to imagine other dreams that will come true...

"Of course we can't defeat something over which we have no control. But to triumph doesn't necessarily mean to win against a disease; to triumph is also to dream our dreams, achieve them, live them. Our dreams are way stronger than illness, because they carry hope."

— Tomy-Richard Leboeuf-McGregor

Have a good read!

Josée Côté
Executive Director **Living with Cystic Fibrosis**

Looking ahead

2020, now that's a year we won't soon forget! While we were ending our midnight countdowns on December 31, 2019, we couldn't even imagine what this new year had in store for us. Indeed, less than three months later, we found ourselves in a lockdown, stressed, anxious, isolated from others, distanced and worried about the future. Information falls every day, we are presented daily with numbers on the situation, advices, expert results, predictions... and the worries that go with it. Almost a year later, we are still waiting, impatient to gain some calm back and to get out of this challenging period.

This situation, at once murky and anxiety-generating, pushed us, throughout this issue, to address different topics related to the situation, like anxiety, but also to turn our gaze to the future.

First of all, we suggest two study summaries on the effects of COVID-19 on cystic fibrosis patients.

Then, to bring a few solutions into the fight against anxiety, we are publishing the data of a meta-analysis on binaural sounds and their potentially beneficial effects on anxiety disorders, as well as an interview with Marine Miglianico, psychologist, who explains the positive psychology approach. Since we've been asked numerous questions about essential oils, we also present to you the results of a study on these.

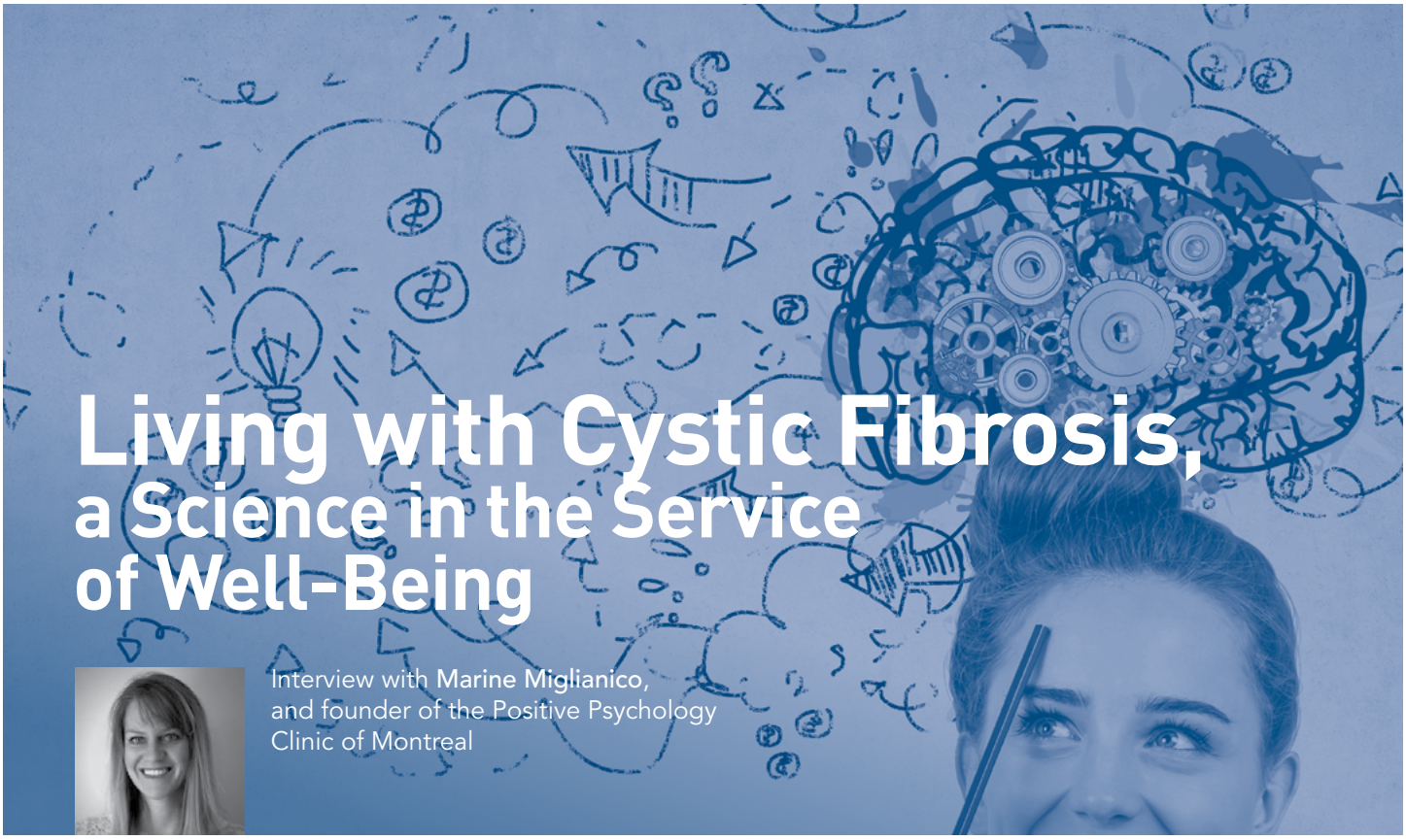
Despite the current situation, we need to keep an eye on the future. It's the case of the Lancet report on the future of cystic fibrosis care, as well as the one on the impact of a delay to access to Trikafta. Dr. Cantin has once again done us the honour to present the status of the research on the subject to date, talk about his challenges and, most of all, his hopes.

Finally, you will find three testimonies of three women from three different generations, who will tell you about their journey.

We all can't wait to travel again without fear, see our friends, hug our loved ones, look back on this year like a distant and bad memory. No doubt it will happen, but there is still a bit of a winding road to travel together. We will need to keep our spirits up and hope, celebrate all the small victories, allow ourselves moments of weakness, show compassion towards others, but mainly towards ourselves. It's by being human and closed-knit that we will get through all those hardships.

Sébastien Puli

Coordinator **Living with Cystic Fibrosis**



Living with Cystic Fibrosis, a Science in the Service of Well-Being

Interview with **Marine Miglianico**, and founder of the Positive Psychology Clinic of Montreal

Interviewed by **Sébastien Puli**

What is positive psychology?

Positive psychology is defined as the study of the conditions and processes that contribute to the flourishing or optimal functioning of people, groups, and institutions (Gable & Haidt, 2005). This science was born in 1998 at the APA (American Psychological Association) annual address. Martin Seligman, then president of the association and learned helplessness specialist, was studying depression (Seligman, 1972). Back then, the scientific literature was composed of a ratio of 21 studies on human dysfunction, for 1 study on good human function (Ben-Shahar, 2006). Yet, it isn't scientifically rigorous to only study half of a phenomenon. In 1998, Martin Seligman called for the development of studies focusing on positive aspects of the human being (Seligman, 1998). What are the factors of well-being, of motivation, of independence? What are the human strengths and virtues and how to develop them? What are the impacts of altruism on well-being? What role do positive emotions play on human function? Those are questions this science tries to answer. For over 20 years, thousands of studies have been done on the topic all over the globe (Compton & Hoffman, 2019; Snyder & Lopez, 2009).

Are positive psychology and positive thinking synonymous?

Positive psychology has often been blended —wrongly— with positive thinking. Positive thinking goes back to the idea that if we see the world in a positive way, if we have positive thoughts, we provoke the positive in our lives. However, reality proves way more complex (Norem & Chang, 2002). Indeed, a forced positive thought can in contrast reinforce the suffering state that is waiting to be listened to, heard and accepted. Carl Rogers, famed humanistic psychologist, worked for a long time on the notion of unconditional acceptation and supported in his work the importance to learn to love ourselves in all our states, good or bad, without rejecting any (Rogers, 1961). Positive psychology, on the other hand, is interested in the development of mental resources allowing to go beyond the difficulties of life (Sheldon & King, 2001).

How can positive psychology be useful?

Let's imagine a simple analogy: we could compare life to a boat trip.

At the bottom of the water are rocks, representing the difficulties we meet. The water level represents psychological resources available to us. When we experience difficult times, we need to draw on our water level to face it. However, if we only draw on our water level, at some point, our boat ends up on the rocks. And it's often at this moment that we go see a psychologist, who will help us identify the rocks, repair our boat and anticipate the rocks to come. And that work is essential. But what about our water level? It's also possible to add water under the boat, to develop psychological resources that will make us see the rocks at the bottom of the water with more serenity. Positive psychology studies and develops these tools.

What ware the main topics studied by positive psychology?

The PERMA acronym defines the pillars of well-being (Seligman, 2018). To develop our well-being, five elements are particularly significant:

1. Positive Emotions;
2. Engagement;
3. Positive Relationships;
4. Meaning;
5. Accomplishment.

Thus, those topics are largely studied. Regarding positive emotions, for example, psychology speculated that they were only a signal that everything is doing fine. However, the research of Barbara Fredrickson (2004) showed that they presented two major benefits. They allow us to develop our mental resources (adding water under the boat), all the while helping us take a step back from the situation. Laughter —through humour— can allow us to temper the emotions related to painful events, while keeping a positive attitude in front of adversity (Edwards & Martin, 2014).

Can you present us a positive psychology tool?

Recently, research focusing on self-compassion has expanded (Neff, 2003). Self-compassion is defined as being kind towards oneself in moments when we feel inadequate, in failure or in pain (Neff & Vonk, 2009). It's an important key in mental health development. Indeed, we often prevent ourselves from feeling or showing compassion towards ourselves, in fear of becoming complacent. Yet, research is showing us the opposite. By being gentler towards ourselves, we have more energy to get into action and thus overcome the difficulties quicker (Neff et al., 2007). Self-compassion includes three elements:

1. Self-kindness: in the face of sadness, loss or suffering, it's possible to act towards yourself as you would a loved one. If a friend would come and see you asking for support after a difficult event, you would never think about saying: "You can't do anything, you're useless!" Yet, that's what we tend to tell ourselves when things are difficult. Changing our internal dialogue and talking to ourselves as we'd talk to a friend are particularly efficient processes. If the exercise proved difficult nonetheless, it's possible to project our situation on a good friend, and to take note of what we'd say to reassure them. We can then read back those words while directing them towards us.

2. The recognition of our common humanity: when we suffer, we have a tendency to think we are alone in our suffering. However, every human being experiences suffering in their lives, at different levels. Knowing that we are not alone to experience failures or suffering removes the weight of mental ostracism.

3. Mindfulness: being fully aware of what we are going through means recognizing and accepting the current experience without judgment, without trying to change it. Multiple studies show its added value in pain management (Kabat-Zinn et al., 1985), in stress (Gotink, 2016), anxiety and depression (Goyal et al., 2014) reduction.

This way, positive psychology tools like self-compassion can contribute to improving everyday life by allowing us to have a more indulgent outlook on our experience. Creating mental resources allows to develop the necessary resilience for the development and conservation of mental health. The different resources attached can help you explore the subject further. ◂

Ressources

Akhtar, M. (2012). *Positive Psychology for Overcoming Depression: Self-Help Strategies for Happiness, Inner Strenght and Well-Being.* Watkins Media Limited.

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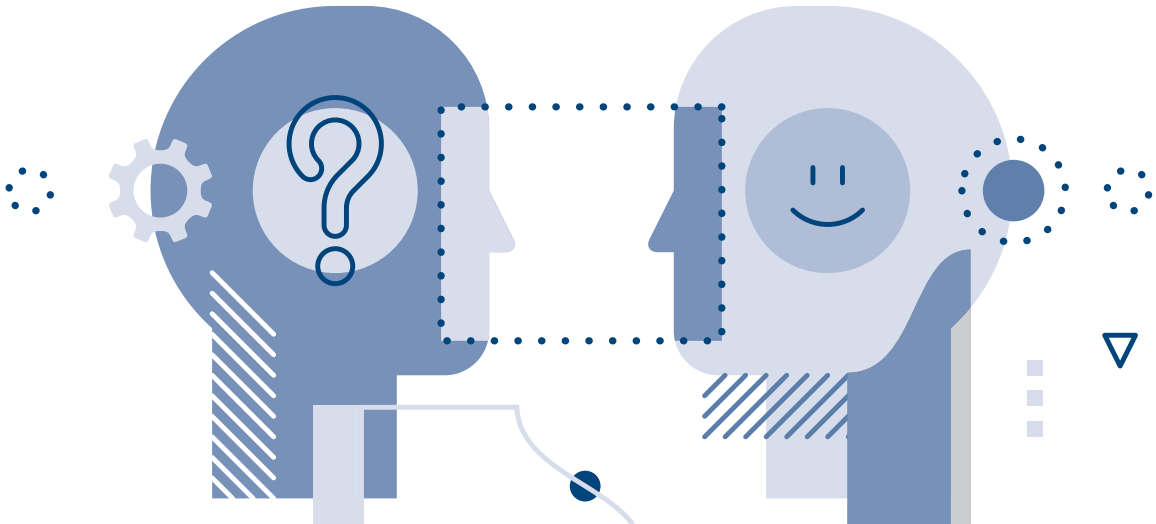
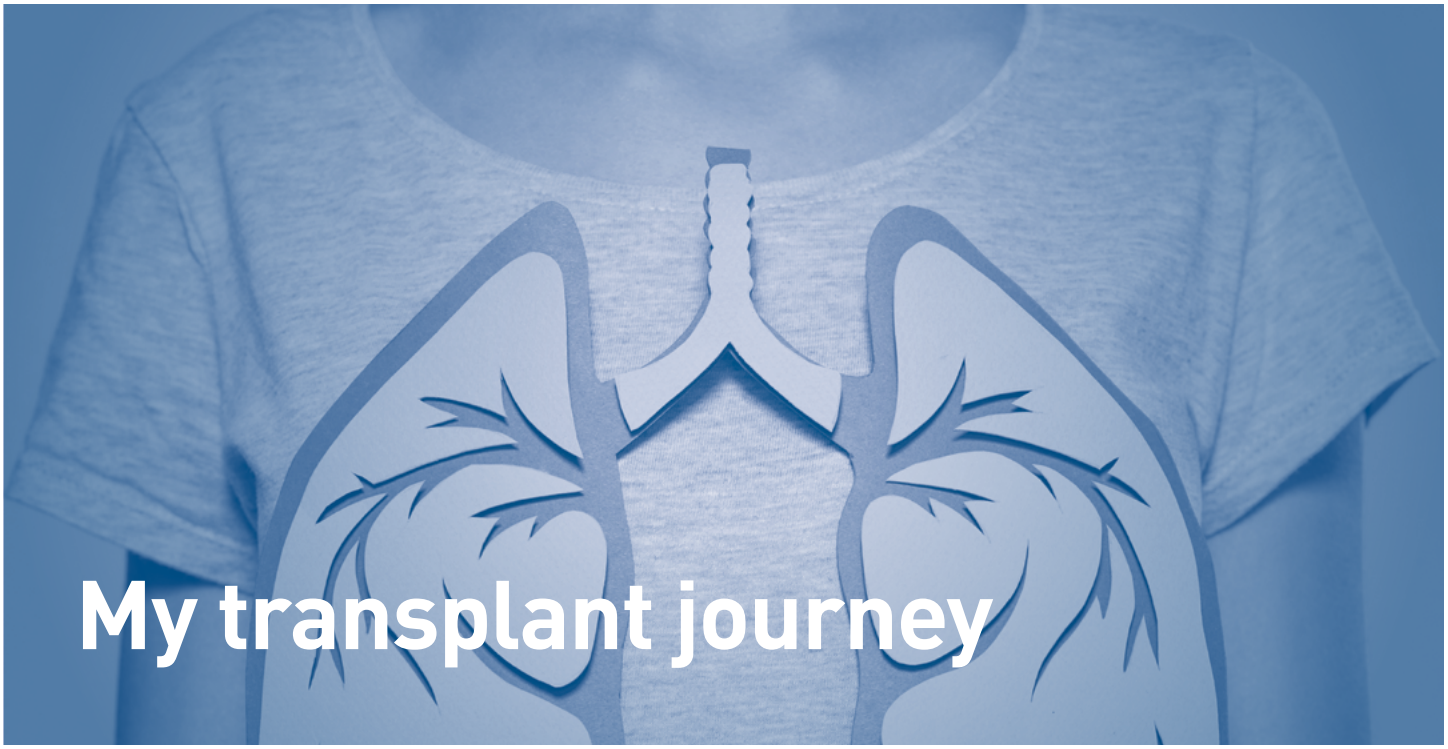




My transplant journey

Mélissa Doyon
Québec, Quebec
Canada

My name is Mélissa Doyon and I have cystic fibrosis. In January 2015, I was working 30 hours a week while my lung capacity was of barely 26%. In May 2015, I had to reduce to 12 hours a week, because the disease was evolving more and more. In August 2015, I completely stopped working. It was a difficult grieving process to do. Afterwards, we started the tests to see if I was a good candidate for the transplant.

I had a first meeting with the transplant team in Montréal in November 2015. Then, in January 2016, I stayed in Montréal for a week to do some tests I couldn't do in Québec City. In February 2016, the good news fell: I was a good transplant candidate. I was thus put on a waiting list by Transplant Québec and, in September 2016, I finally got the long-awaited call from Dr. Pasquale Ferraro.

That day, I was full of emotions. I climbed in the ambulance: and my second life would begin. I went into the operation room at about 4:45 p.m. and I got out around 11:30 p.m. I then was put in the ICU and the healing process started. I was first intubated, but the next morning, when I woke up, they were already removing the tube. I was also kept on life support for 24 hours to allow my new lungs to adapt. They then removed it so I could learn to breathe well on my own. The second day, I was able to walk in the corridor and as soon as the third day, I was leaving the ICU to go to my room on the eight floor of the Notre-Dame hospital. I was in the hospital for a month and stayed in Montréal until October afterwards, because I had weekly appointments for three weeks following my discharge from the hospital.

I went back home at the end of October 2016. Sadly, as soon as November 2016 and for the next two years, I was hospitalized numerous times at the IUCPQ in Québec City, because I suffer from gastroparesis. This was caused during surgery, when the surgeon accidentally nicked a bit of the stomach. Since that day, I must live with a gastrojejunostomy type stomach feeding tube. I've had to be tube-fed for a year and a half and now it's how we need to dispense my medication, including the anti-rejection drugs, because starting at the end of January 2017, my body decided to reject the transplant. We then increased my cortisone dosage, which is an anti-rejection drug, and everything fell into place.

It's now been four years since I received my transplant and I get better every day. I'm able to do little things, like my weekly housekeeping. This year, I was even able to do my complete spring cleaning.

If I can give you a tip, it's to be patient after a transplant. Time is a healer, and, even with the complications I've had, I don't regret my decision at all.

Thank you and have a good read. ◂

My anxiety management tools, special CF

Amélie Payment
Pincourt, Quebec
Canada

For my second testimony in the Living with Cystic Fibrosis magazine, I'd particularly like to try to help the numerous CF people suffering from anxiety by sharing my personal experience. My objectives are to inspire you with my experiences, to allow you to create psychological and emotional links between my life and yours and to give you tools to fight this nuisance that is anxiety. I will thus talk to you about the three main aspects that cause me the most daily anxiety and about my tips to reduce it.

Setting goals

Cystic fibrosis (CF) is a disease that takes time, structure, organization and independence. Which sometimes have the long-term effect of causing anxiety.

I'm now seventeen years old. The day of my birthday, the first thought that came into my head was: "Wow! I'm already celebrating my seventeenth birthday while I wasn't even supposed to experience a single one. That's what I call a beautiful miracle." It's proof that, sometimes, life plays crazy tricks on us and that no matter what we might think, it's not always negative.

Little, I was hospitalized for my whole first year of life. I received twelve blood transfusions, had surgery, a pulmonary hemorrhage, was in a coma for three months, had to live with a gastric tube for a few years and I could go on. Today, I go to the hospital every three months, I eat normally and I'm doing relatively well. See? There is always hope.

Having hope and goals is the first tool I can suggest to reduce your anxiety level. Keeping my mind busy by setting goals and working hard to achieve them distract my mind and prevent me from worrying and imagining things that haven't happened yet. What I also sometimes do, is writing down my objectives. That way, when I end up scratching them off my bucket list, it just increases my motivation for the next one to achieve.

Cystic fibrosis, an invisible disease

Cystic fibrosis (CF) is sadly an invisible disease. Often, when people learn I'm sick, they exclaim: "Oh! You are sick? But it doesn't show at all, you seem to be in great shape!" In my life, my goal isn't necessarily to be pitied. But even if I don't want to be pitied, this kind of reply makes me a bit sad and I feel misunderstood when I experience difficult times. I'm not in a wheelchair, I'm not "plugged" on machines and I am doing relatively well... according to the numbers evaluating my lung function. This doesn't mean, however, that I'm not a bit discouraged by my routine and by the fact that all my life was a string of hardships. Having to monitor everything I do ended up causing me anxiety. Also, the fact that some doctors or members of medical personnel sometimes say comments like "You know? You're not the worst!", it exhausts me. I then feel the need to justify myself when I'm tired, sad or anxious. This kind of comment makes me feel like I'm not being taken seriously, like I'm not "sick enough" to have the right to experience emotional lows. I think

medical personnel shouldn't, in any way, make comparisons between people living with CF. Every person experiences the situation differently and, sometimes, yes, we need to talk about it. Knowing we have an incurable and degenerative disease is hard. Nevertheless, we stand up and live our lives as if everything was normal. But yes, it happens that I need a day to rest when I take antibiotics or to do an activity I love to cling to life and not lose myself completely.

My second tool to manage my anxiety is thus to do things I enjoy, like writing, reading, watching a movie, walking, etc. To vary them so it's not repetitive. Why does it work? Because getting me out of my strict routine helps me be more positive and serene.

The stress of being transferred to an adult hospital

Being transferred to the adult hospital is very stressful for me. And I know it is for many of you. I often ask myself: "What does it look like? Will I find myself completely alone? Will I be able to organize all my appointments?" To leave the medical personnel I've known since birth at Sainte-Justine and change my habits to jump into a new world, it scares me. I feel like I'm leaving a family. I always had the same doctor, nurses, respiratory therapists, front desk receptionist, gastroenterologist, social worker, dietician and allergist. They know me and have seen me evolve.

I confided in these people about my fears because, yes, it's a difficult step to overcome. When I'll have passed it, I'll be able to explain to you what is the "adult hospital". For now, I ask myself many questions and prepare as best I can to become fully independent.

My third tool to reduce anxiety is thus to prepare. Make an appointment with your social worker so she can visit the new hospital with you. That way, the change won't be as brutal and you will be able to visualize this change to accept it. I sincerely think that when I'll have made the visit and accepted this radical change, my adaptation instinct as a child living with cystic fibrosis, which is already over-developed, will take over, and I am convinced that everything will play out like a charm.

To end on a positive note, cystic fibrosis, it's not easy, but it helped me a lot to be a young evolved woman and it allowed me to be very empathetic towards others. In my testimony, I talked about the three aspects that make me the most anxious in my daily life. I hope you were able to recognize yourself in it and feel a bit more understood.

#cysticfibrosiswarrior ◄

Being CF at sixty years of age

Manon Goulet
Dollard-des-Ormeaux
Quebec, Canada

It's not easy to share your journey.

There is the fear of being judged or of being accused of wanting to draw attention... But what is encouraging me to tell you my story, is the desire to give a bit of hope to those who, like me, have cystic fibrosis.

I'm in my sixties and I have cystic fibrosis.

I'm part of the dozen Canadian adults who, each year, receive a cystic fibrosis diagnosis. In fact, it's in 2016 that I received my diagnosis. It was a shock but also a relief. Everything became more logical. The multiple sinusitis and sinus surgeries since childhood, the cough, the pneumonias, the asthma, the secretions and the FATIGUE. It must be noted that in the sixties, life expectancy for children with cystic fibrosis didn't exceed kindergarten age. I believe that despite all those symptoms, which today would've undoubtedly be linked to cystic fibrosis, this diagnosis seemed less and less possible for the doctors I was consulting, since I was still alive.

Nevertheless, I had a fulfilling family and professional life. I have a spouse with whom I've shared my life for forty years and two children I adore. Not to mention two grandsons I love to death. When my pulmonologist announced my diagnosis, my first thought was for my kids. What a horrible feeling than to have unknowingly transmitted such a terrible gene!

Over time, the symptoms amplified, making my daily life more and more difficult. Then, suddenly, around the end of my fifties, I had to stop working. It was like I didn't have the strength anymore. That unsurmountable fatigue, associated with repetitive infections, gave me the impression that everything became a mountain I didn't have the strength to climb anymore. I had to mourn a demanding, but so rewarding, job.

I questioned myself on what my life was going to be, on what I would do. I had the feeling that I wouldn't be able to get over this fatigue.

With an FEV1 below 50%, I had the feeling that my life was reduced to doing wisely chosen activities according to the fatigue I was living with.

Then I started to knit. I must say the coming of a grandson was a nice incentive. It allowed me to concentrate on a project, to acquire new knowledge and to achieve something concrete. It was in complete harmony with what had become my three daily objectives:

- Learn something new;
- Do something for someone else;
- Laugh every day.

Laughter can do so much good. Particularly when everything seems grey. No need to laugh out loud for hours, just a small burst of laughter can be beneficial.

Having more time also allowed me to concentrate on physical activity to improve my lung capacity. In the past, my training was constantly interrupted because of respiratory infections and took a lot of my energy after a day of work. Now, I can take a nap after doing a physical effort, it helps me a lot.

I was even encouraged to start a running program, progressively, starting with one-minute intervals. My goal isn't to run a marathon, but to improve my cardio-respiratory function.

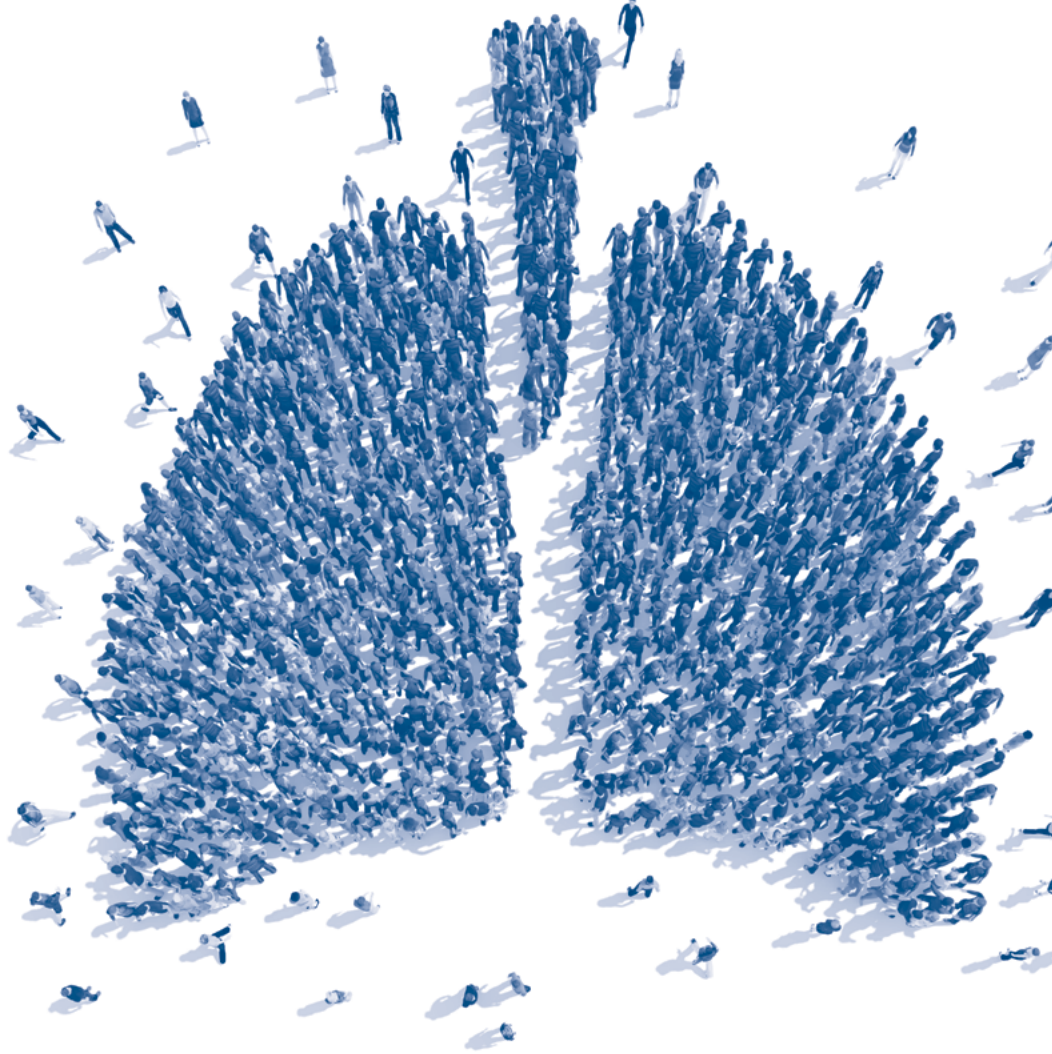
I must also mention that I receive a modulator therapy. I feel very positive effects, especially on my lung function, but also on my energy.

Even though it doesn't cure cystic fibrosis, and I need to continue the usual treatments and therapies, the positive impact on my health is important. I still need many hours of sleep and napping is part of my daily life, but I developed a routine that allows me to be diligent in my treatments, to include a bit of physical activity, rest, fun and, of course, knitting!

We must continue to hope that Canada will change the rules for the treatment of orphan diseases to allow pharmaceutical companies like Vertex to be able to submit to Health Canada new drugs like Trikafta. This one could allow 90% of Canadians living with cystic fibrosis to improve not only their condition, but also their quality of life, as well as extend it.

I know I am lucky and I hope that very soon we will all be able to enjoy new treatments and live with the hope of a full life and to all get, one day, to the age of retirement! ◂

The future of cystic fibrosis care : A GLOBAL PERSPECTIVE



Sources: The future of cystic fibrosis care: a global perspective
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Executive summary

The past six decades have seen remarkable improvements in health outcomes for people with cystic fibrosis, which was once a fatal disease of infants and young children. However, although life expectancy for people with cystic fibrosis has increased substantially, the disease continues to limit survival and quality of life, and results in a large burden of care for people with cystic fibrosis and their families. Furthermore, epidemiological studies in the past two decades have shown that cystic fibrosis occurs and is more frequent than was previously thought in populations of non-European descent, and the disease is now recognized in many regions of the world. The *Lancet Respiratory Medicine* Commission on the future of cystic fibrosis care was established at a time of great change in the clinical care of people with the disease, with a growing population of adult patients, widespread genetic testing supporting the diagnosis of cystic fibrosis, and the development of therapies targeting defects in the cystic fibrosis transmembrane conductance regulator (CFTR), which are likely to affect the natural trajectory of the disease. The aim of the Commission was to bring to the attention of patients, health-care professionals, researchers, funders, service providers, and policy makers the various challenges associated with the changing landscape of cystic fibrosis care and the opportunities available for progress, providing a blueprint for the future of cystic fibrosis care.

The discovery of the *CFTR* gene in the late 1980s triggered a surge of basic research that enhanced understanding of the pathophysiology and the genotype– phenotype relationships of this clinically variable disease. Until recently, available treatments could only control symptoms and restrict the complications of cystic fibrosis, but advances in CFTR modulator therapies to address the basic defect of cystic fibrosis has been remarkable and the field is evolving rapidly. However, CFTR modulators approved for use to date are highly expensive, which has prompted questions about the affordability of new treatments and served to emphasize the considerable gap in health outcomes for patients with cystic fibrosis between high-income countries, and low-income and middle-income countries (LMICs).

Advances in clinical care have been multifaceted and include earlier diagnosis through the implementation of newborn screening programs, formalized airway clearance therapy, and reduced malnutrition through the use of effective pancreatic enzyme replacement and a high-energy, high-protein diet. Centre-based care has become the norm in high-income countries, allowing patients to benefit from the skills of expert members of multidisciplinary teams. Pharmacological interventions to address respiratory manifestations now include drugs that target the airway mucus and airway surface liquid hydration, and antimicrobial therapies such as antibiotic eradication treatment in early-stage infections and protocols for maintenance therapy of chronic infections. Despite the recent breakthrough with CFTR modulators for cystic fibrosis, the development of novel mucolytic, anti-inflammatory, and anti-infective therapies is likely to remain important, especially for patients with more advanced

stages of lung disease.

As the median age of patients with cystic fibrosis increases, with a rapid increase in the population of adults living with the disease, complications of cystic fibrosis are becoming increasingly common. Steps need to be taken to ensure that enough highly qualified professionals are present in cystic fibrosis centres to meet the needs of ageing patients, and new technologies need to be adopted to support communication between patients and health-care providers.

In considering the future of cystic fibrosis care, the Commission focused on five key areas, which are discussed in this report: the changing epidemiology of cystic fibrosis (section 1); future challenges of clinical care and its delivery (section 2); the building of cystic fibrosis care globally (section 3); novel therapeutics (section 4); and patient engagement (section 5). In panel 1, we summarize key messages of the Commission. The challenges faced by all stakeholders in building and developing cystic fibrosis care globally are substantial, but many opportunities exist for improved care and health outcomes for patients in countries with established cystic fibrosis care programs, and in LMICs where integrated multidisciplinary care is not available and resources are lacking at present. A concerted effort is needed to ensure that all patients with cystic fibrosis have access to high-quality health care in the future.

Introduction

Since its original description in 1938, substantial progress in our understanding of the cause and underlying mechanisms of cystic fibrosis have seen it change from a uniformly fatal disease of infancy to one in which the median age of survival approaches (and in some populations exceeds) 50 years. Recognition of the increased salt content of sweat in people with cystic fibrosis by di Sant'Agnese and colleagues in the early 1950s led to the development of the stimulated sweat test, using pilocarpine iontophoresis, as a practical diagnostic method. In the 1980s, Quinton showed chloride impermeability in sweat glands to be the basis for the raised sweat electrolytes in patients with cystic fibrosis. These early works advanced understanding of the basic defect of membrane electrolyte transport. The gene responsible for cystic fibrosis, an autosomal recessive disorder, was discovered in 1989 through a concerted effort by teams led by Tsui, Riordan, and Collins, with the subsequent identification of its protein product, termed the cystic fibrosis transmembrane conductance regulator (CFTR). CFTR is responsible for chloride ions transport across apical membranes of epithelial cells in tissues of the airway, intestine, pancreas, kidney, sweat gland, and male reproductive tract. The protein is now known to have additional functions, such as bicarbonate secretion, which regulates the pH of the airway surface liquid, and inhibition of the epithelial sodium channel (ENaC), which has an important role in the hydration of secretions and mucins (figure 1).

More than 2000 variants in the *CFTR* gene have been described to date, although the functional consequences have not been defined for all of these variants. When the functional consequences are known, variants can be divided into different functional classes (figure 2). Class I, II, and III disease-causing variants (in legacy terminology, mutations) are associated with little or no CFTR function and are therefore linked to a more severe phenotype, including insufficiency of the exocrine pancreas; Class IV and V variants have residual CFTR function, which is often associated with preserved exocrine pancreatic function early in life. Overall, CFTR dysfunction causes a spectrum of disease, with a range in the number of organs involved and varying disease severity. For example, pancreas, liver, and lung diseases can be present from birth to the age of 5 years, whereas congenital bilateral absence of the vas deferens in the male reproductive tract10 can sometimes be the only notable feature of cystic fibrosis in an adult. In addition, phenotypic manifestations vary widely even among people with severe *CFTR* variants, underscoring the role of other factors, such as environmental triggers and modifier genes, in defining disease severity.

The cystic fibrosis phenotype is characterized by lung disease (bronchiectasis with persistent airway-based infection and inflammation), exocrine pancreatic insufficiency associated with nutrient malabsorption contributing to undernutrition, impaired growth, hepato-biliary manifestations, and male infertility (panel 2). Evidence-based care for people with cystic fibrosis is coordinated by multidisciplinary health-care teams, and therapies for cystic fibrosis have developed rapidly over the past three decades. The health of children with cystic fibrosis continues to improve, with increased lung function and growth by the time patients transition from pediatric to adult care, and reduced frequency of chronic infection, in particular *Pseudomonas aeruginosa*. The progressive improvement of survival in patients with cystic fibrosis over the past five decades has led to a dramatic increase in the number of adults surviving. Consequently, the number of cystic fibrosis care centres has rapidly expanded. Despite such improvements, morbidity associated with cystic fibrosis is still dominated by recurrent respiratory infections (frequently multidrug resistant), ultimately leading to lung destruction and respiratory failure. The emergence of complications of cystic fibrosis (panel 2), including cystic fibrosis-related diabetes, metabolic bone disease, gastrointestinal malignancy, and comorbidities including increased mental health conditions (depression and anxiety), have necessitated the development of specific expertise in the clinical care of patients with the disease. Although structured care in specialized centres and improved strategies to treat disease manifestations have been the main drivers of improved patient outcomes, over the past 15 years, a therapeutic pipeline has been established with the aim to develop safe and effective treatments that target the basic defect in cystic fibrosis (dysfunctional CFTR protein). The first successful drug—ivacaftor, a potentiator of CFTR function that increases the opening probability of the CFTR channel— was associated with remarkable clinical benefit in patients with residual expression of CFTR

on the cell surface but a reduced opening probability. Improvements in lung function, nutritional status, and health-related quality of life (HRQoL), and a lower frequency of respiratory exacerbations were reported than in participants receiving placebo. Subsequently, combinations of both CFTR potentiators and correctors that address the trafficking defect associated with the most common variant, p.Phe508del (also known as F508del), have been shown to have a positive effect on clinical outcomes, and the field is rapidly approaching a time when more than 90% of the current global cystic fibrosis population could benefit from these therapies. However, access to these drugs varies widely from country to country, which could further exacerbate the existing gap in outcomes for patients in different regions of the world.

At a time of very rapid therapeutic developments, advances in genetic diagnostic testing, and a huge increase in the population of adult patients with cystic fibrosis particularly in the developed world—with dramatic increases in the median survival of people with the disease—it seems fitting that we should review progress in the field, highlight the unmet needs of patients in developed and developing regions, and consider what cystic fibrosis care might look like in the future. This *Lancet Respiratory Medicine* Commission paper is intended to bring to the attention of patients, health-care professionals, researchers, funders, service providers, and policy makers the various challenges associated with the changing landscape of cystic fibrosis care and the opportunities available for progress. A concerted effort is needed to take full advantage of these opportunities, to improve health outcomes for people with cystic fibrosis across the globe.

Conclusion

Over the past few decades, we have seen major advances in the approaches to early diagnosis and treatment of people with cystic fibrosis. These include, but are not limited to, widespread adoption of NBS; increased understanding of the importance of highly skilled, multidisciplinary care teams; and improved definition of optimal treatment and management strategies for the main manifestations of cystic fibrosis. All of these aspects of health care have led to changes in the global population of people with cystic fibrosis and those with CFTR dysfunction.

With the changing spectrum of cystic fibrosis, new challenges have emerged. Many patients now have a milder phenotype than in previous decades, and striking the right balance between implementing necessary therapies and treatment burden has become a growing priority in clinical care. Advances in genetic technologies have facilitated the annotation of variants as potential disease causing, with the number of such variants rapidly increasing with time, but genetic testing has increased the identification of individuals with few phenotypic manifestations, for whom the risk of disease progression, and thus the benefit of a diagnosis, is not yet well defined. Despite the wide availability of genome sequencing technologies, functional tests to define the extent of CFTR dysfunction are yet to be widely applied in the clinical setting and require additional validation in this setting. How researchers use these different methodologies in the future is not only relevant to countries where cystic fibrosis has traditionally been diagnosed, but also to LMICs where access to facilities offering functional testing such as the sweat chloride test is restricted at present.

PANEL 1 : Key messages of the *Lancet Respiratory Medidne* commission on the future of cystic fibrosis care

Section 1: I he changing epidemiology of cystic fibrosis

1. Newborn screening has been implemented in a many parts of the world, supporting anearly diagnosis of cystic fibrosis.
2. Improved molecular genetic diagnostics have allowed the identification of cystic fibrosis in non-European populations and in individual with nonclassical presentations of cystic fibrosis and related disorders.
3. Cystic fibrosis transmembrane conductance regulator (CFTR)-related disease represents a spectrum ranging from single-organ manifestations to a multisystem disease. Defining the threshold of CFTR function associated with disease manifestations is a priority to guide disease monitoring and treatment decisions.

Section 2: Clinical care and its delivery

1. Children with cystic fibrosis are healthier than in previous decades and the vast majority are living well into adutthood in the developed world.
2. Diagnostics to allow enhanced monitoring and earlier detection of deterioration of organ function and detection of new airway infections are key priorities.
3. Models of care need to consider management approaches (including disease monitoring) to maintain health and delay lung transplantation, while minimising the burden of care for patients and their families.

Section 3: Cystic fibrosis care in developing nations

1. Informatiom about the genetic and clinical features of cystic fibrosis in non-European populations has improved understanding of the disease in low-income and middle-income countries (LMICs).
2. Partnerships between lay organisations, governments, and the pharmaceutical and industry are needed urgently to provide sustained, affordable access to cysfic fibrosis therapies for people with cystic fibrosis living in LMICs.
3. Clinical registries are being developed in countries where cystic fibrosis is now reconised. Data elements in new and established cystic fibrosis registries need to be harmonised to support understanding of health-care outcomes, especially in LMICs.

Section 4: Novel therapeutics

1. CFTR modulator therapies targeting the basic molecular defectin cystic fibrosis have been developed for specific *CFTR* mutations and are associated with improved health outcomes, including Improved respiratory function and nutritional status, and enhanced quality of life.
2. New CFTR modulator drungs are showing promise in up to 90% of pateints, including in patients with *CFTR* mutations for which earlier modulators were ineffective. Early commencement of CFTR-directed therapies might prevent the establishment of irreversible airway complications and slow disease progression in paediatric and adult patients.
3. Drug development requires substantial investment, which contributes to the current high cost or approved CFTR modulators and, in turn, to delays in funding for such therapies in many countries. Current drug prices make them unaffordable for many LMICs, and even in some developed countries, governments have not yet funded these therapies. These problems could be addresssed through increased transparency as to how prices are determinated, and opportunities to revise assessments in light of new information.

Section 5: Patient experience, engagement, and involvement.

1. The complexity of care has increased for people with cystic fibrosis in parallel with increased life expectancy, leading to a substantial burden or care and disease monitoring. Novel technologie has the potential to support self-monitoring and shared decision making between patients and heallh-care teams.
2. Mental health complications are more common in people with cystic fibrosis (and in the parents of children with cystic fibrosis) than in the general community, affecting quality of life for patients and their families. Adherence to complex therapeutic regimens is often suboptimal, which has a negative effect on clinical outcomes.
3. Patients are highly engaged in the approaches to delivery or clinical care and in providing their perspective on research priorities. Cystic fibrosis patient organisations have important roles as patient advocates for the delivery of clinical care, treatment access, and support and education for patients with cystic fibrosis and their families.

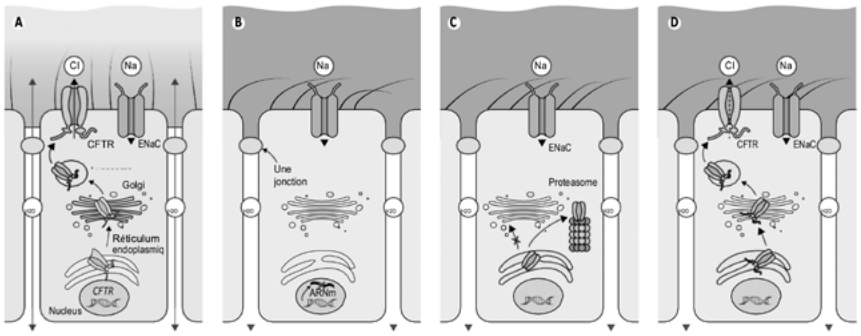


FIGURE 1 : Pathophysiology of cystic fibrosis

Role of CFTR in healthy airways and molecular mechanisms causing CFTR dysfunction in cystic fibrosis. (A) In healthy ainvays, CFTR is expressed at the apical surtace of airway epithelial cells together with ENaC. Coordinated regulation of CFTR and ENaC enables proper airway surface hydration and effective mucociliary clearance. (B-D) In cystic fibrosis, mutations in CFTR cause CFTR dysfunction via different molecular mechanisms. (B) CFTR nonsense or splicing mutations abrogate CFTR production. (C) Many missense mutations, incuding the common Phe508 del mutation, impair proper folding of CFTR and lead to its retention in the endoplasmicreticulum and subsequent degradation by the proteasome. (D) Some missense and splicing mutations produce CFTR chioride channels that reach the cel surface but are not fully functional.

Adapted trom Genizsch and Mall, by permission of Etsevier. CFTR=cystic fibrosis transmembrane conductance regutator. ENaC=epithelial sodium channel.

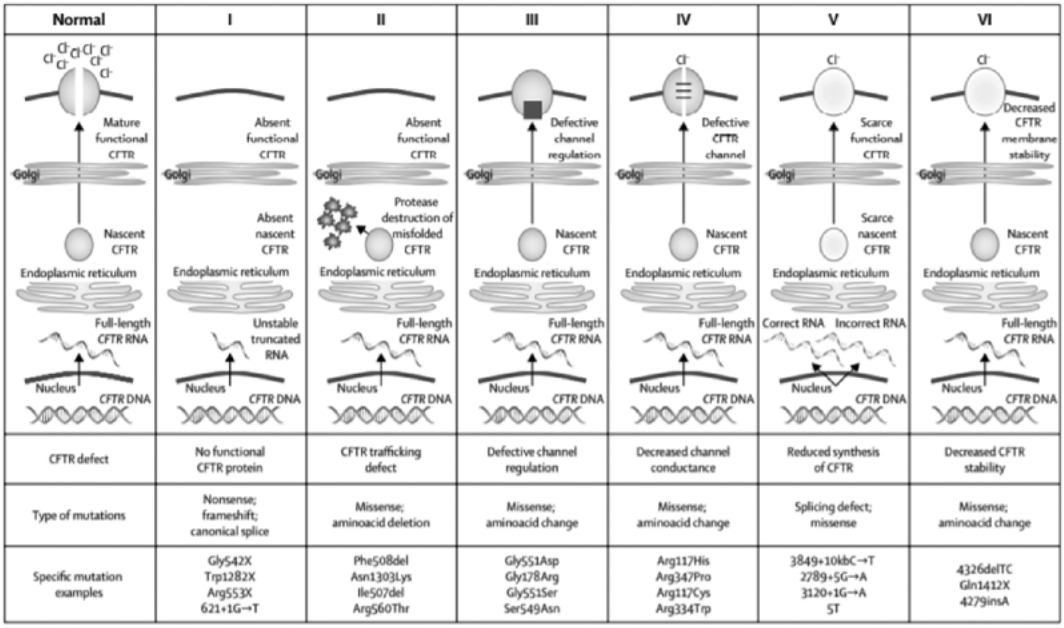


FIGURE 2: Classes of CFTR mutation

Mutations in the CFTR gene can be divided into six classes. Class I mutations result in no protein production. Class II mutations (induding the most prevalent, Phe508del) cause retention of a misfolded protein at the endoplasmicreticulum, and subsequent degradation in the proteasome. Class III mutations affect channel regulation, imparing channel opening (eg, Gly551Asp). Class IV mutants show reduced conduction (decreased flow of ions: eg, Arg117His). Class V mutations cause a substantial reduction in the mRNA of protein, or both. Class VI mutations cause substantial plasma membrane instability and include Phe508del when rescued by most therapeutic-correctors (rPhe508del).

Reproduced from Boyle and De Boeck by permission of Elsevier. CFTR=cystic fibrosis transmembrane conductance regulator. rPhe508del=rescued Phe508del.

PANEL 2: Phenotypic features of cystic fibrosis

Typical features of cystic fibrosis

Respiratory

- Bronchiectasis with chronic infection
- Pneumothorax
- Hasmentysis
- Respiratory failure
- Chronic rhinosinusitis and nasal polyposis

Gastrointestinal (luminal)

- Gastro-gesophageal reflux disease
- Distalintestinal obstruction syndrome
- Chronic constipation
- Rectal protapse
- Intussusception
- Colorectalcancer and colonic polyposis
- Other gastrointestinal malignancies

Gastrointestinal (hepatobiliary)

- Pancreatic insufficiency
- Recurrentacute pancreatitis (in patients with pancreatic sufficiency)
- Biliary sludge or cholelithiasis
- Biliary cirrhosis

Metabolic complications

- Cystic fibrosis-related diabetes: microvascular complications (210 years from diagnosis)
- Cystic fibrosis-related bone disease orosteoporosis: increased fracture risk
- Ureteric calculi
- Oligomenorrhoea

Male infertility

- Congenital bilateral absence ofthe vas deferens

Common issues complicating cystic fibrosis and its treatment

Mental health conditions

- Depression
- Anxiety

Vascular access complications

- Thrombosis risk with vascular access devices

Drug complications

- Antibiotic hypersensivity, reactions and intolerance
- Vestibulo-auditory disturbance including tinnitus
- Chronic kidney disease

Metabolic complications

- Overweight and obesity (especially in patients with residual exocrine pancreatic function)

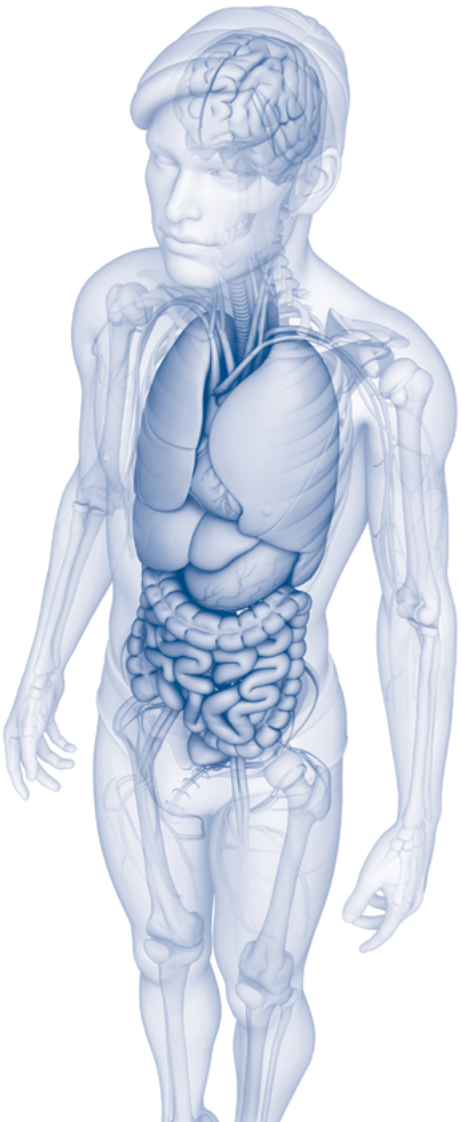
Post-transplant complications (relevant to cystic fibrosis)

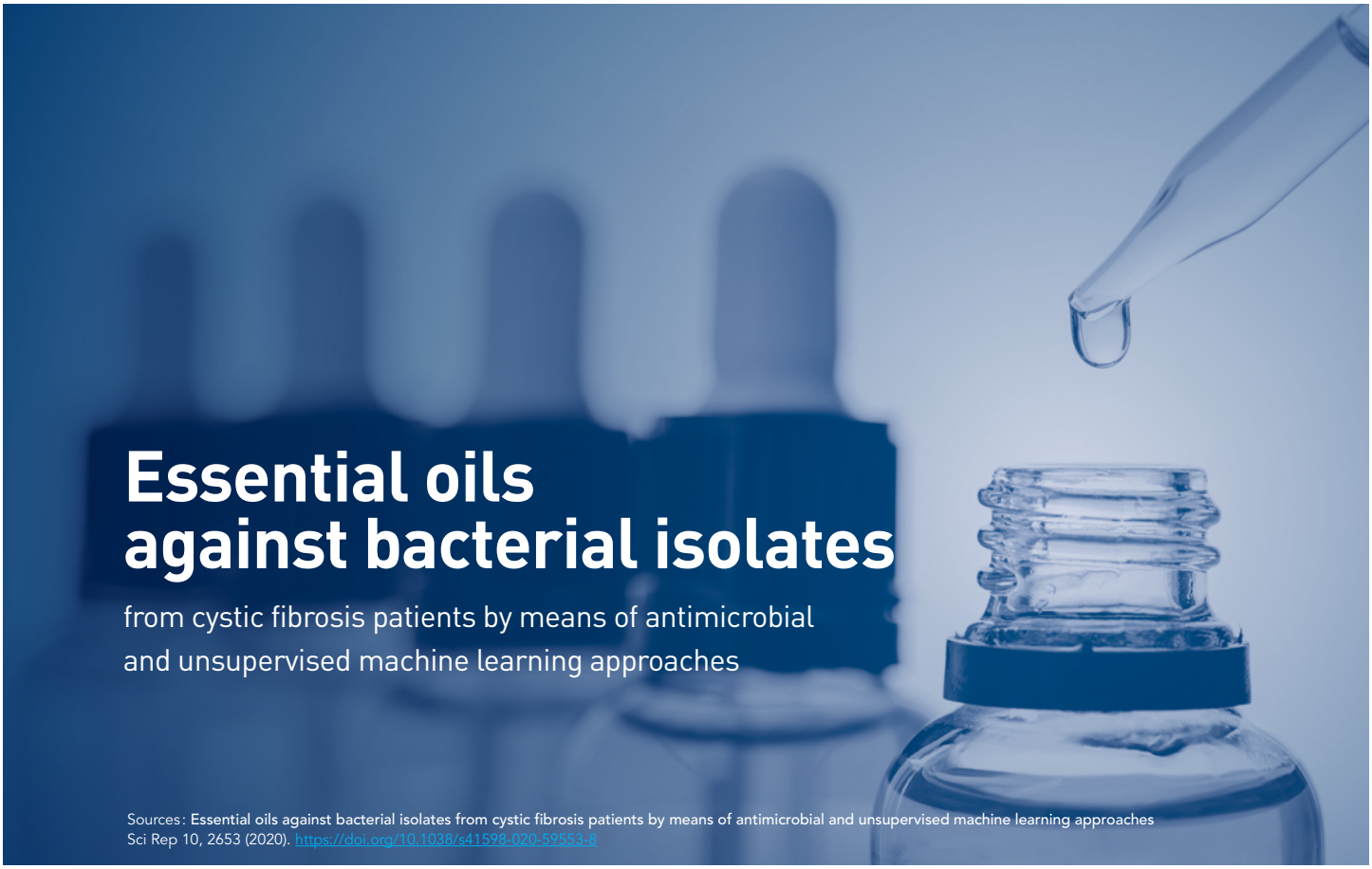
- Chronic kidney disease and renal failure (in people with or without pretransplant cystic fibrosis-related diabetes)
- Multiresistant organisms contributing to airway complications
- Cancer in long-term survivors (including gastrointestinal, skin, and urogenital cancers)

New drugs that target the basic defect in cystic fibrosis have provided hope for patients, and progress in drug development has been substantial over the past decade. However, these drugs come at a high economic cost, which is mainly driven by the costs associated with drug development rather than drug production costs. How people with cystic fibrosis and their advocates respond to the funding decisions of health-care systems—with the availability of current compounds already varying widely, even between developed countries—could have an impact on the availability of novel therapeutics in the future, not only for cystic fibrosis, but also for other rare disorders. New types of partnership between pharmaceutical companies and reimbursement bodies might be needed, and innovative solutions might be required for LMICs, to ensure that patients throughout the world have access to effective therapies and that the gap between those with therapy and those without does not widen even further.

With continuous progress, the shift of cystic fibrosis from a mainly pediatric disease to one in which many patients go through early adulthood maintaining a good level of health (albeit at the cost of requiring continuous ongoing and often intense treatments) will become increasingly pronounced. As early mortality becomes less common, care of ageing patients with cystic fibrosis will no longer be a rarity, and such care might require a new generation of health-care providers with specific training and broad skills to manage the emerging complications of cystic fibrosis in later life. The growing adult population might also require health-care providers to reconsider which components of care need to be delivered directly by the multidisciplinary team at cystic fibrosis centres and which can be undertaken remotely with new technologies to monitor the wellbeing of patients.

These are exciting times for cystic fibrosis, a disease that is often considered to be a model of care for other chronic diseases, and a model of progress in the development of targeted therapies for genetic disorders. With advances in health outcomes come new opportunities and challenges, and the cystic fibrosis community should now prepare for these so that health-care professionals, working in highly skilled, multidisciplinary teams, can continue to provide exceptional care to individuals with this multifaceted disease in the future. ◀





Essential oils against bacterial isolates

from cystic fibrosis patients by means of antimicrobial and unsupervised machine learning approaches

Sources: Essential oils against bacterial isolates from cystic fibrosis patients by means of antimicrobial and unsupervised machine learning approaches Sci Rep 10, 2653 (2020). https://doi.org/10.1038/s41598-020-59553-8

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Recurrent and chronic respiratory tract infections in cystic fibrosis (CF) patients result in progressive lung damage and represent the primary cause of morbidity and mortality. Staphylococcus aureus (S. aureus) is one of the earliest bacteria in CF infants and children. Starting from early adolescence, patients become chronically infected with Gram-negative non-fermenting bacteria, and Pseudomonas aeruginosa (P. aeruginosa) is the most relevant and recurring. Intensive use of antimicrobial drugs to fight lung infections inevitably leads to the onset of antibiotic resistant bacterial strains. New antimicrobial compounds should be identified to overcome antibiotic resistance in these patients. Recently interesting data were reported in literature on the use of natural derived compounds that inhibited in vitro S. aureus and P. aeruginosa bacterial growth. Essential oils, among these, seemed to be the most promising. In this work is reported an extensive study on 61 essential oils (EOs) against a panel of 40 clinical strains isolated from CF patients. To reduce the in vitro procedure and render the investigation as convergent as possible, machine learning clusterization algorithms were firstly applied to pick-up a fewer number of representative strains among the panel of 40. This approach allowed us to easily identify three EOs able to strongly inhibit bacterial growth of all bacterial strains. Interestingly, the EOs antibacterial activity is completely unrelated to the antibiotic resistance profile of each strain. Taking into account the results obtained, a clinical use of EOs could be suggested.

Cystic fibrosis (CF), one of the most common lethal genetic disorders in Caucasian population, is inherited as an autosomal recessive disease and affects 70.000 persons worldwide (Cystic Fibrosis Foundation, CFF). The defective gene, identified in 1989, is the Cystic Fibrosis Transmembrane Conductance Regulator (CFTR) that is carried by 4% of persons (among Caucasians). Since CFTR encodes for a chloride channel of the epithelial cell surface, CF patients manifest a variety of multi-organ problems due to the alteration of sodium and chloride secretion across cell membranes and the subsequent luminal dehydration. The impairment of mucociliary clearance, which should remove all microbes entering the airways, leads to the production of a thick and dehydrated mucus in the CF lung, which promotes the airway chronic bacterial colonization. The microbiology of CF respiratory tract is peculiar. In the early stage of life, it is characterized by the prevalence of the Gram-positive bacterium Staphylococcus aureus (S. aureus). Overall, in 2017 more than half of affected individuals had at least one culture positive for methicillin sensitive S. aureus (MSSA). The highest prevalence of methicillin resistant S. aureus (MRSA) occurs in individuals between the ages of 10 and 30, while MSSA reaches the peak among patients younger than 10 (Cystic Fibrosis Foundation. 2017. Patient Registry Annual Data Report. https://www.cf.org/Research/Researcher-Resources/Patient-Registry/2017-Patient-Registry-Annual-Data-Report.pdf). In early adolescence, CF patients' lung becomes chronically infected with Gram-negative non-fermenting bacteria. Among these, Pseudomonas aeruginosa (P. aeruginosa) is the most relevant and recurring, so that

30% of CF children and up to 80% of CF adults (25 years old and older) have lungs chronically colonized by this pathogen. P. aeruginosa isolated from respiratory secretions demonstrates great phenotypic diversity and develops genetic mutations over time to adapt and survive in the complex environment of the CF airway. P. aeruginosa mucoid phenotype, defined by the exopolysaccharide alginate overproduction within lungs of CF patients, is a hallmark of chronic infection and predictive of poor prognosis. Indeed, mucoid P. aeruginosa has also been associated with failure of eradication and, compared to non-mucoid counterpart, exhibits enhanced resistance to multiple antibiotics and host immune effectors. Due to current therapeutic treatments, life expectancy for CF patients has consistently grown, reaching a median life of 40 years. Assuming a positive trend of clinical care improvements at the actual rate, CF patients born in 2010 are expected to live up to 50 years of age. the intensive use of antimicrobial drugs to fight lung infections inevitably leads to the onset of antibiotic resistant bacterial strains. New antimicrobial compounds should be identified to overcome antibiotic resistance during the treatment of CF lung infections. Recent investigation has disclosed a few small molecules, such as peptides or mannosides, showing promising efficacy in prevention and treatment of both bacterial and fungal biofilm infection in vivo. Nevertheless, due to their mechanism of action based on a specific binding to a main target, the use of small molecules is known to select more and more resistant strains. Interestingly in the recent literature appeared some reports on the use of natural derived compounds that showed in vitro the potentiality to inhibit the development of CF associated infections. In particular essential oils seemed to be the most promising agents among tested natural compounds. In this study is reported an extensive study on 61 essential oils (EOs) against a panel of 40 bacterial strains isolated from CF patients. To reduce the in vitro procedure and to render the investigation as convergent as possible the following workflow was followed. Unsupervised machine learning algorithms and techniques, as implemented in python language, were firstly applied to pick-up a fewer number of representative strains (RS) among the panel of 40. To this aim, a number of categorical descriptors were collected and used to cluster the CF isolated strains. the clusters' centroids indicated the RS to be investigated for their susceptibility to a list of commercial EOs at fixed doses. Tree EOs showed a great efficacy to reduce the microorganism's growth and were therefore promptly assayed against all the available clinical isolates. The three EOs confirmed the initial assumption demonstrating their ability to inhibit bacterial growth. Gas chromatography coupled with mass spectrometry (GC/MS) was then performed on the three EOs to investigate on the likely chemical components mainly responsible for the antibacterial activity.

Discussion

Long-term administration of antibiotics to prevent and treat airway infections in CF patients has been shown to be associated with the emergence of multi-drug (MDR) antimicrobial resistant microorganisms. In particular, mecA/mecC genes acquisition in S. aureus and accumulation of resistance mechanisms after antibiotic exposure in P. aeruginosa, both key pathogens in CF lung, are a concern in this context19,20. Multidrug resistance significantly limits effective therapeutic options, affecting clinical outcome and prognosis of patients. For this reason, the identification and development of new antibacterial agents is fundamental to improve survival and quality of life of individuals with CF. Therefore the development of antimicrobial agents provided with novel molecular mechanisms that may allow to control bacterial infectious diseases without diffusing antibacterial resistance is desirable. Unsupervised Machine Learning algorithms applied to a panel of 40 strains of S. aureus and P. aeruginosa isolated from CF patients, led to select fewer representative strains using phenotypical and genotypical characteristics as categorical descriptors. Therefore, the antibacterial activity of all tested EOs was initially assessed on 9 selected bacterial strains: six representative strains for P. aeruginosa and 3 representative strains for S. aureus. The activity of all 61 EOs was also

assessed on reference strains. Antimicrobial assays led to identify 3 EOs (CEO, BEO and CCPEO) out of the tested 61, that exhibited the highest antibacterial activity on the previously selected bacterial strains and reference ones. The antibacterial activity of the 3 selected EOs was then extended to all strains of both species. Interestingly all three EOs showed an utmost antimicrobial potency on all studied strains. Nothing can be yet ruled out on the chemical compounds' role. Future studies involving machine learning application, will be devoted to investigate the importance of chemical constituent either on biofilm modulation or in antibacterial potencies. Several papers aimed at elucidating the antimicrobial mechanism of action of EOs. For example, cinnamaldehyde, the major component of cinnamon, is able to disrupt the transmembrane potential of P. aeruginosa. Furthermore, EOs of different origin (lavender, lemongrass, marjoram, peppermint, tea tree and rosewood) show antimicrobial activity against Burkholderia cepacia complex by inducing changes in membrane fatty acid composition, followed by membrane disruption. Also, EO from Alluaudia procera was active against S. aureus ATCC25923, a multi-resistant strain. Reported data confirmed the possibility to use EOs as therapeutic strategies in multi-resistant strains probably due to the heterogeneous composition of the oils themselves. Notably, in this work we found EOs antibacterial activity unrelated to the antibiotic resistance profile of each strain. This observation is of particular relevance as it suggests the EOs potential uses by topical administration without taking into account the complexity of drug resistance profile of the microbiota in each single patient. In conclusion the approach herein applied allowed to minimize the experimental steps and it was possible to identify the most promising EOs on the basis of probabilistic evaluations that confirmed their wide spectra of antibacterial potency with a reduced set of experiments. From a literature survey (www.scopus.com, accessed 2019 December 13, keywords: essential oil, antibacterial activity and resistance) no evidence of resistance to EOs antibacterial activity has yet been reported. Tis is a characteristic particularly relevant for antibacterial candidates to be administered for a chronic disease such as CF. Indeed, some papers report an increase of susceptibility to antibiotics after treatment with essential oils. Although a plethora of publications did not show development of resistance to EOs, a very recent publication suggested the induction of efflux pumps and multidrug resistance in P. aeruginosa by Cinnamaldehyde, the main component of cinnamon. Therefore, in light of the recent reports, much still needs to be clarified on the effect of essential oils on bacterial multi-drug resistance. ◄

Note to readers: we advise you to check with your health care professional before taking any action.

COVID-19
meets Cystic Fibrosis: for better or worse?

Sources: COVID-19 meets Cystic Fibrosis: for better or worse?. Genes Immun 21, 260–262 (2020). https://doi.org/10.1038/s41435-020-0104-y

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Abstract

Cystic fibrosis (CF) is one of the most common autosomal recessive life-limiting conditions affecting Caucasians. The resulting defect in the cystic fibrosis transmembrane conductance regulator protein (CFTR) results in defective chloride and bicarbonate secretion, as well as dysregulation of epithelial sodium channels (ENaC). These changes bring about defective mucociliary clearance, reduced airway surface liquid and an exaggerated proinflammatory response driven, in part, by infection. In this short article we explore the overlap in the pathophysiology of CF and COVID-19 infection and discuss how understanding the interaction between both diseases may shed light on future treatments.

COVID-19 (SARS-CoV-2) infection triggers a cytokine storm, sepsis, and life-threatening acute respiratory distress syndrome. Patients with cystic fibrosis (CF) also manifest cytokine dysfunction and hyper-inflammation that overlaps with the pathophysiology of COVID-19. Intuitively, it might be concluded that CF patients infected with COVID-19 would be at high risk of serious illness. As a result, health services have responded with shielding or cocooning policies. Thus, a Mendelian randomised experiment is effectively underway, in real time, whereby patients with two mutant copies of the CFTR gene are being exposed to a new virus. While respiratory viruses, such as rhinoviruses and influenza, are associated with increased pulmonary exacerbations, the morbidity and mortality from respiratory syncytial virus (RSV) infection is lower than expected in children with CF. In a past epidemic of RSV, it was noted that relatively few patients with CF became severely ill. For example, at a time when so many babies became ill that a regional intensive care unit exceeded its ventilator capacity for sick children, not a single CF affected child became ill (AM personal observations over two decades). This paucity of CF patients in the RSV cohort might be explained by the recent proposal that RSV may need an intact autophagic pathway for replication, allied to the finding that autophagy is dysregulated in CF cells. There is some speculation that inducing autophagy, which is increased in CF, may counteract COVID-19 infection, although data remain limited.

Conversely, there are sound theoretical reasons why CF might be expected to accentuate rather than mitigate the impact of COVID-19 infection. CFTR mutations disrupt cellular metabolism and exaggerate both lung and systemic inflammatory responses, with dysregulation of assembly of the multiprotein NLRP3 inflammasome complex that processes pro-inflammatory cytokines (Fig. 1). The SARS-CoV-2 virus enters host cells by using a spike protein to bind to the cell membrane protein, angiotensin converting enzyme 2 (ACE2). Cellular entry, via ACE2, is facilitated by the furin enzyme, making both critical players in infection. ACE2 has a site that is potentially activated by furin, which converts and activates viral surface glycoproteins and also regulates ENac. Activation of furin, which is increased in CF, together with the cellular damage induced by viroporins, might be expected to upregulate NLRP3 and cause inflammation. We, and others, have reported that NLRP3 inflammasome is abnormal in CF cells.

The role of furin in viral pathogenesis has recently been reviewed and the authors state that 'the pathogenesis of some CoVs has been previously related to the presence of a furin-like cleavage site in the S-protein sequence'. For example, the insertion of a similar cleavage site in the infectious bronchitis virus (IBV) S-protein results in higher pathogenicity, pronounced neural symptoms and neurotropism in infected chick-

ens. Thus, it is entirely plausible that furin activity may be a key factor in COVID-19 infections and the testing of furin inhibitors as therapeutic agents will be important in future studies. The SARS-CoV-2 virus is reported to mimic the proteolytic activation of ENaC, an ion channel which is significantly upregulated in CF, where it drives inflammation and is critical to airway surface liquid homeostasis.

As yet there are limited data on the response of CF patients to COVID-19 infection, although preliminary information suggests that the course of disease may be milder than expected. Globally, from a population of about 100,000 patients, there have been over a hundred cases of COVID-19 infection in people with CF, with around 90% exhibiting relatively few symptoms and complications. Although numbers and outcome may simply reflect effective shielding, it is highly likely that certain regions, such as New York State and Northern Italy, would have reported significant numbers of excess CF-COVID-19 deaths had patients been highly susceptible.

If further clinical experience indicates that the course of COVID-19 infection in CF patients is milder than anticipated, then it could be proposed that the relative protective effect associated with CF might accrue from CF-affected cellular processes linked to viral processing, including autophagy, mitophagy, endosomal function and cellular metabolism, which may all be co-opted by COVID-19 for viral replication.

We hypothesise that CFTR modulator therapy might also confer additional benefit to patients with severe respiratory problems due to COVID-19 infection. For example, CFTR modulator therapy given to people with CF helps to restore cellular function, increases airway hydration, reduces oxidative stress, and down-regulates activation of the NLRP3 inflammasome. The influence of CFTR in non-CF respiratory disease is intriguing and relatively poorly understood. Recent reports have demonstrated that acquired CFTR dysfunction occurs in smokers, and that the acute reduction in CFTR function due to cigarette smoke extract can be reversible by a CFTR potentiator in vitro. Carriers of the (commonest by far) Phe508del mutation found in over 70% of patients, have also been reported as having an increased risk of developing chronic bronchitis and bronchiectasis.

The role of CFTR in COVID-19 needs further elucidation in patients without CF. In an influenza model, the CFTR corrector, lumacaftor, was found to reverse in vitro down-regulation of CFTR and ENaC following viral infection and to restore airway surface liquid. Both CFTR and ENaC have been proposed as theoretical cleavage sites for the coronavirus proteinase 3CLpro enzyme, which controls viral replication. The transmembrane protease serine 2 (TMPRSS2), which can facilitate viral entry into the target host cell, also reduces ENaC activity in airway epithelium. The detailed analysis of clinical outcomes in CF affected people may provide clues as to how these factors interact in the real world of COVID-19 disease.

The clinical importance of characterising the effects of COVID-19 infection in CF patients, and understanding the possible underlying protective effects, could shed light on novel targets and new approaches to antiviral therapy. We suggest that clinical trials of modern CF drugs should be explored in those infected by this new virus. In practice, a pragmatic trial is already underway, the outcome of which will depend on the response to COVID-19 in patients who either receive or do not receive modern CF drug combinations, and we also urge all CF registries to collect such case control data to inform future studies. ◄

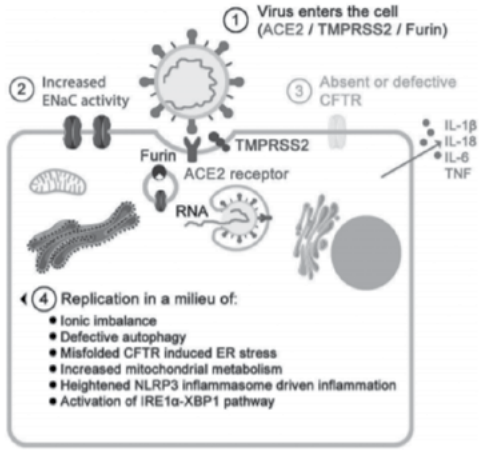
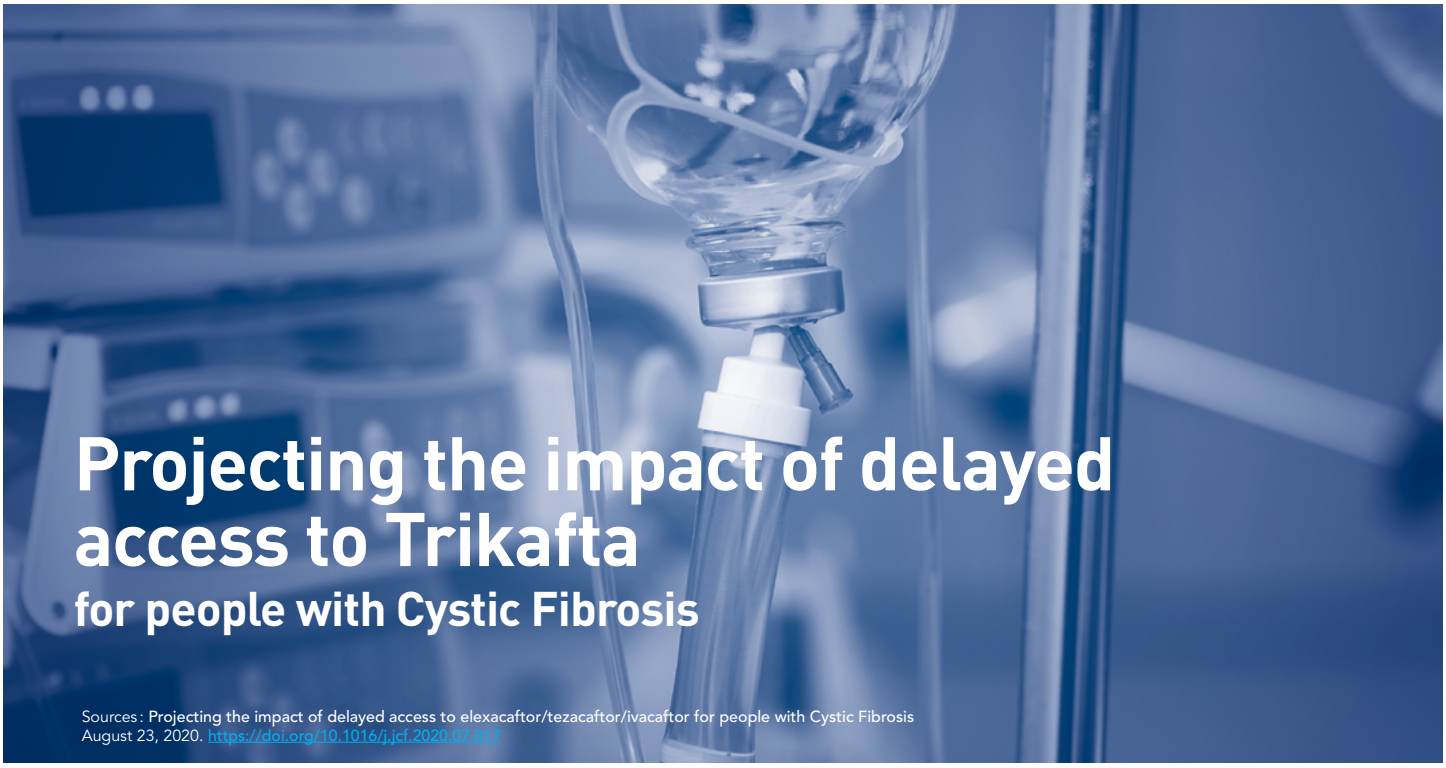


FIGURE 1: Fig. 1 SARS-CoV-2 and cystic fibrosis. The spike protein on the virion binds to the ACE2 cell membrane protein. Cellular entry is facilitated by the TMPRSS2 and furin enzymes, one or more of which may be altered in CF. Once inside the cell, viral processing, may be influenced either by overactive inflammation and/or CF-affected cellular processes including autophagy, mitophagy, endosomal function and cellular metabolism, which may all be co-opted by COVID-19 for viral replication.



Projecting the impact of delayed access to Trikafta

for people with Cystic Fibrosis

Sources: Projecting the impact of delayed access to elexacaftor/tezacaftor/ivacaftor for people with Cystic Fibrosis August 23, 2020. https://doi.org/10.1016/j.jcf.2020.07.012

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Background

Therapies that target the underlying defect in Cystic Fibrosis (CF) will likely impact the future characteristics of the CF population and healthcare utilization. The objectives of this study were to estimate the potential impact of elexacaftor/tezacaftor/ivacaftor on morbidity and mortality, and the impact of delayed access.

1. Introduction

Forecasting health outcomes can promote a better understanding of the long-term needs of a given population and anticipate the demand for future services and healthcare resources. The development of Cystic Fibrosis Transmembrane Conductance regular (CFTR) modulator therapies that address the underlying cause of Cystic Fibrosis (CF) for more than 90% of the CF popu-lation stand to significantly change the characteristics and health care utilization needs of the CF population. Phase III clinical trials of the most effective CFTR modulator combination, elexacaftor/tezacaftor/ivacaftor (TRIKAFTA®) have demonstrated improved lung function and reduced exacerbations in the short-term. CFTR modulator therapy may also change the trajectory of the disease and mortality rates in the long-term. As a result, it is expected that there will be an increasing number of adult CF patients living with this chronic illness which requires careful planning and anticipation of the future health care system needs. The triple combination drug, elexacaftor/tezacaftor/ivacaftor, was approved by the US Food Drug Administration in October 2019; however the expected approval process and timelines for other countries are not clear. Furthermore, national approval of a treatment does not necessarily translate into immediate availability of a therapy for all patients, especially for expensive treatments, where decisions about drug prices and coverage by national insurance plans can be prolonged. Disease modifying therapies have the potential to transform the lives of people living with CF and change the clinical trajectory of the disease. The impact of delayed access is not well understood. The objectives of this study were to estimate the potential impact of elexacaftor/tezacaftor/ivacaftor on morbidity and mortality of the CF population, as well as the impact of delayed access.

2. Méthode

A microsimulation transition model was applied to Canadian CF Registry data to forecast lung disease severity, pulmonary exacerbations, deaths and transplants to 2030 under three scenarios:

1) no availability of elexacaftor/tezacaftor/ivacaftor,
2) availability in 2021 ('early') or
3) availability in 2025 ('delayed'). Published Phase III data on treatment effects were used to estimate transition rates between disease severity states.

3. Results

The initial CF population is summarized in Table 3. A total of 4440 individuals had lung function values available in 2018 or values that could be assumed (either by carrying forward 2017 measurements (n = 393), or assuming a healthy state in children less than 6 years of age (n = 530)).

3.1. Projected outcomes based on microsimulation modeling

Table 3 summarizes the populations that were generated from the microsimulation model under the key assumptions regarding disease state and treatment effect.

3.1.1. Demographics and lung status

Under the baseline scenario where current transition rates continue and no new modulator therapies are introduced, the CF population was expected to increase from 4440 to 5415 (SD 15) individuals in 2030; consisting of approximately 35% children and 65% adults. Assuming elexacaftor/tezacaftor/ivacaftor was not available, we estimated there will be 3185 (SD 13) (~60%) individuals in the mild state, 1166 (SD 14) (~22%) in the moderate state and 447 (~8%) in the severe state by 2030. However, if all patients older than 12 years of age with at least one F508del mutation received elexacaftor/tezacaftor/ivacaftor in 2021 ('Early') and the treatment was effective in slowing the progression of lung disease, severe lung disease and an increase in those with mild lung disease, however, the changes to these states is considerably smaller compared to if the drug was introduced 'Early' (Table 3).

3.1.2. Pulmonary exacerbations

Applying the 2017 exacerbation rates of 0.09/year in the mild group, 0.9/year in moderate group and 2.2/year in the severe group to the baseline predictions, the estimated the number of pulmonary exacerbations requiring hospitalization or home IV antibiotics in 2030 increased from 1988 to 2311 (SD 36) (Table 3). Cumulatively, the model estimated 25,370 (SD 177) exacerbations requiring hospitalization between 2019 and 2030 if there was no availability to triple therapy. If the drug were available 'Early' and under the assumption that exacerbations were reduced by 63% (i.e. the exacerbation rates were 0.055/year in the mild group, 0.55/year in the moderate group and 1.35/year in the severe group) the predicted number of exacerbations would decrease, with approximately 4135 (95%CI 4042; 4226) fewer exacerbations between 2021 and 2030. Similarly, 'Delayed' introduction of the drug would still result in 2141 (95% CI 2043; 2239) fewer exacerbations between 2025 and 2030 but there would be significantly more exacerbations prevented if elexacaftor/tezacaftor/ivacaftor were introduced 'Early' (Fig. 3).

Table 3
Canadian CF population demographics and clinical characteristics based on baseline scenario and timing of introduction of elexacaftor/tezacaftor/ivacaftor using microsimulation model. Mean (SD) of 10 microsimulations presented unless otherwise indicated.

	Initial Population	Baseline(no new therapies)		Elexacaftor/tezacaftor/ivacaftor introduced in 2021 ('Early')		Elexacaftor/tezacaftor/ivacaftor introduced in 2025 ('Delayed')	
	2018	2025	2030	2025	2030	2025***	2030
Median age of survival*	57.6 **	59.1	58.4	62.5	67.5	59.0	63.1
(95% Confidence Interval)	(52.2–62.3)	(58.0; 60.2)	(56.9; 59.8)	(61.1; 63.8)	(66.7; 68.4)	(57.9; 60.3)	(62.4; 63.9)
Total Population	4440	4765 (10)	5415 (15)	4775 (14)	5497 (10)	4740 (16)	5450 (15)
Mild	2772	2799 (19)	3185 (12)	3113 (19)	3776 (15)	2869 (14)	3609 (20)
Moderate	1003	1064 (17)	1165 (14)	990 (11)	1071 (12)	1054 (16)	1084 (19)
Severe	380	404 (18)	443 (20)	232 (10)	232 (10)	341 (9)	340 (9)
Pulmonary Exacerbations	1988	2097 (40)	2310 (37)	1683 (19)	1700 (14)	1957 (25)	1957 (25)

* calculated in the 5-year window (i.e. 2030 represents the median age of survival between 2026 –2030).
** Does not match reported median age of survival for 2018 as the population included in this analysis are those with a reported lung function value. This value is included to be able to track the changes over time.
*** These values are not identical to baseline 2025 values because each model randomly simulations the rates and events in an individual subject.

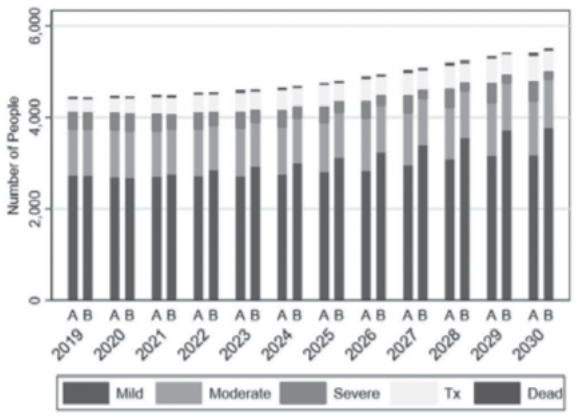

Fig. 2. Summary of disease state by year from a single simulation under baseline conditions (A) and elexacaftor/tezacaftor/ivacaftor introduction in 2021 (B).

3.1.3. Death or transplantation

Without elexacaftor/tezacaftor/ivacaftor the median age of survival remained stable between 2018 and 2030 (Table 3). Assuming all eligible patients started triple therapy 'Early', the total number of deaths would be reduced by 15% (95%CI 13.2; 18.4) by 2030. After 10 years of therapy, we would expect to see the estimated median age of survival increase an additional 9.2 (95% CI 7.5; 10.8) Fig. 4. Comparison of the projected median age of survival in 2030 from a single simulation in the baseline scenario (no new therapies or treatments, current transition rates), if elexacaftor/tezacaftor/ivacaftor are introduced in the CF population will be larger in 2030 and there will be fewer people living with severe lung disease compared to the estimates if the drug was not available (Table 3; Fig. 2). In 2030, the projections would result in 60% (95% CI 55.3; 63.9%) fewer individuals with severe lung disease, and 18% (95% CI 18.2; 19.0) more individuals with mild lung disease (Table 3). Delay of elexacaftor/tezacaftor/ivacaftor until 2025 ('Delayed') still resulted in fewer people with

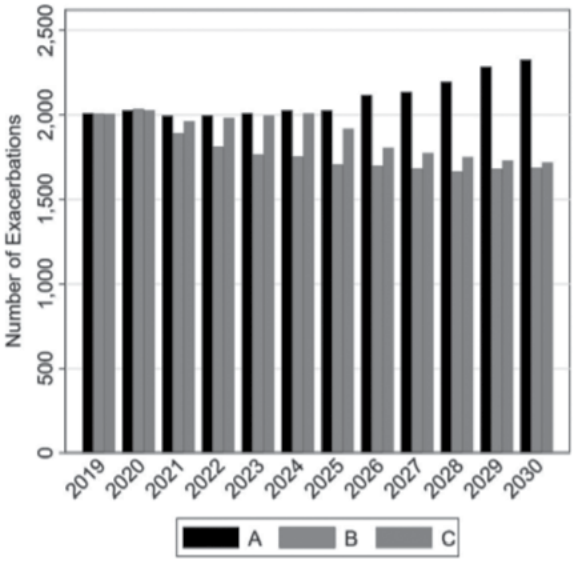

Fig. 3. Number of pulmonary exacerbations per year from a single simulation under the three scenarios: baseline (A), elexacaftor/tezacaftor/ivacaftor introduction in 2021 (B) and delayed introduction of elexacaftor/tezacaftor/ivacaftor in 2025 (C).

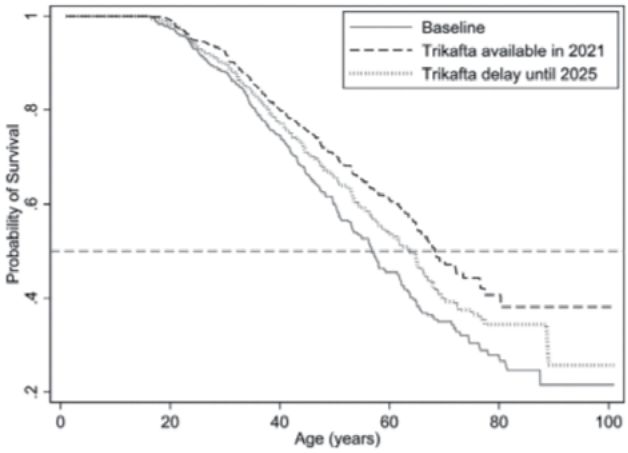

Fig. 4. Comparison of the projected median age of survival in 2030 from a single simulation in the baseline scenario (no new therapies or treatments, current transition rates), if elexacaftor/tezacaftor/ivacaftor are introduced in 2021 ('Early'), and if elexacaftor/tezacaftor/ivacaftor is delayed until 2025 ('Delayed').

2021 ('Early'), and if elexacaftor/tezacaftor/ivacaftor is delayed until 2025 ('Delayed'). years by 2030 compared to the baseline scenario and 74 (95% CI 62; 86) fewer deaths (Table 3; Fig. 4). If the drug is 'Delayed', the number of transplants and deaths will also be reduced but to a lesser extent than if the drug was introduced earlier. By 2030, 'Delayed' introduction of the drug will improve the median age of survival by 3.3 years (95% 1.7; 5.0), resulting in 31 (95%CI 19; 44) fewer deaths between 2021 and 2030 (Fig. 4). If the drug was available 'Early' we could expect 146 fewer transplants by 2030 which is driven by fewer individuals in the severe lung function category, compared with 98 fewer transplants if

Conclusions

Delayed access to elexacaftor/tezacaftor/ivacaftor will have a negative impact on lung health and survival in the CF population. ◄

The Research in Cystic Fibrosis: Hopes and Challenges

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A border is a complex structure. It must be defended all the while allowing for vital exchanges. The border between inhaled air and our body is located on the mucous surface of our bronchi. The air is constituted of nitrogen (80%) and oxygen (20%). It is vital that we have access to the oxygen in the air to ensure our survival, but that air is also the vehicle able to carry a myriad of dusts, bacteria, virus and other germs. The surface of our bronchi is exposed to toxic products like oxidants and white cell enzymes which can degrade tissues.

We all know the oxidation phenomenon. It's the fate awaiting our rusty cars and our grandmothers' tarnished silverware. A chemist defines oxidation as the substraction of an electron to a product. Oxygen is a powerful oxidant able to substract electrons to the lipids that are found in the membranes of our bronchial cells. There are oxidants that are way more toxic than oxygen. Cigarette and marijuana smoke contain over ten thousand billion oxidants in every inhaled puff. Moreover, our body's white cells, which are supposed to protect us against bacteria, generate powerful oxidants in the form of hydrogen peroxide and hypochlorite (bleach), as well as proteolytic enzymes allowing to kill undesirable microbes. Those powerful oxidants and enzymes have the potential to severely damage the cells lining our bronchi. Thankfully, we have defence mechanisms against those dangers at the border of the air and our bronchi. The most important defense mechanism is mucus.

Mucus is composed mainly of a family of proteins called the mucins. Mucins, for their part, are composed of amino acids and sugar chains. Sugar chains constitute more than 80% of mucins' weight. They have nothing to do with the sugar we consume. They are molecules added to mucus during mucins' synthesis. Mucins production in mucus increases each time we need to ensure the level of protection of our bronchi. Mucins are fond of water. In the contact of water, they unfold and form a fluid and slippery carpet. When there is less water, they become very viscous and sticky, like a maple syrup drop dried on a counter. Dehydrated mucus then forms a viscous layer that is very adherent to the bronchi walls. Our works and those of other researchers showed that abundant and viscous mucus can protect the bronchial cells against oxidants and enzymes coming from white cells. It is thus a natural protection barrier of our bronchi. In contrast, mucus can also protect the bacteria that end up in our respiratory secretions, which facilitate the colonization of the bronchi by pathogenic germs. This is why once the oxidative stress resolved (for example, after a bronchitis), it's very important that our bronchi can put water back into the mucus. That way the mucus will be fluid again and will be able to be evacuated by the synchronized beating of the cilia on the surface of the bronchi. How do our bronchi put water back into the mucus? By calling on the cystic fibrosis transmembrane conductance regulator or CFTR.

The CFTR plays a key role in the control of the mucus viscosity; sometimes the CFTR shuts down in the presence of oxidants to increase the protective barrier of mucus, sometimes it activates to chase away the mucus to which are stuck the pathogenic germs (bacteria, virus and mycosis). The CFTR allows mucus hydration by acting like a door that opens and lets salt pass into the mucus. Water always follows the salt and the mucus is thus liquefied.

When the CFTR is absent or doesn't work, there is an increase of bacteria and mycosis in the bronchi which leads to respiratory symptoms of cystic fibrosis. With time, the chronic infection of the bronchi leads to a loss in lung function. It is thus essential to do everything to counter the absence of CFTR by doing treatments to hydrate the mucus (nebulized hypertonic saline) and to evacuate the mucus (respiratory physiotherapy). Often, doctors add inhaled antibiotics to the treatment plan to decrease the bacterial charge in the mucus since it leads to inflammation and to an added production of mucus.

The ideal way to hydrate mucus remains the CFTR. Thankfully, there have been major pharmacological advances lately that allows us to hope for a functional correction of the CFTR defect in people living with cystic fibrosis whose genetic defect includes at least one F508del type allele (an allele is a specific variant of a gene). About 90% of CF people in Québec carry at least one F508del type allele. The triple therapy marketed for 1 year in the United States under the name Trikafta corrects the CFTR defect so well in the F508del carriers that the sweat test corrects itself, the lung function improves by 14% and the number of respiratory exacerbations decreases in a significant way. Patients also see their weight improve. Access to this medication is more than desirable, but for reasons that are difficult to explain, this product still isn't marketed in Canada.

There are several other approaches to correct CFTR function that being studied. Many researchers are using a classical pharmacological approach, while others aim to correct CFTR function by inserting an artificial chloride channel (for example the antifungal molecule amphotericin B) or by the delivery of vectors transporting molecular elements able to edit the defective gene. Those recent advances in molecular genetic engineering were made possible thanks to the works of professors Emmanuelle Charpentier of France and Jennifer A. Doudna of the United States who discovered the CRISPR/Cas9 technology. The Nobel committee incidentally attributed them the 2020 Nobel prize of chemistry for their discovery, which allows to edit or correct a specific allele defect like F508del. It is now possible to make this correction in vitro and even in vivo in animals. The arrival of this technology in CF clinics is expected within a few years. The advantage of a genetic correction is its permanence, which means a person with CF would no longer need to take CFTR correcting drugs.

While we wait for their arrival, it's important that we all can work together to maintain the health of CF people, accelerate the research and most of all, ensure access to drugs of which Canadians living with CF are currently deprived. The absence of treatment access is an unacceptable situation which needs to be corrected without delay. Let us show solidarity and work together for those research advances to transform into reality for all the Canadians living with cystic fibrosis.

Efficacy of binaural auditory beats in cognition, anxiety, and pain perception: a meta analysis

Sources: Efficacy of binaural auditory beats in cognition, anxiety, and pain perception: a meta-analysis. Psychological Research 83, 357–372 (2019). https://doi.org/10.1007/s00426-018-1066-8

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Abstract

Binaural auditory beats are a perceptual phenomenon that occurs when presenting separately to each ear two tones that slightly differ in their frequency. It has been suggested that binaural beats can influence cognition and mental states among others. The objective of this meta-analysis was to study the effect of binaural beats on memory, attention, anxiety, and analgesia. Twenty-two studies met our inclusion criteria for this meta-analysis. The results, based on 35 effect sizes, showed an overall medium, significant, consistent effect size (g = 0.45). Meta-regression results indicated that it does not seem to be necessary to mask binaural beats with white noise or pink noise in terms of effectiveness, obtaining similar effects with unmasked binaural beats. Moreover, the findings suggest that binaural-beat exposure before, and before and during the task produces superior results than exposure during the task. Time under exposure contributed significantly to the model indicating that longer periods are advisable to ensure maximum effectiveness. Our meta-analysis adds to the growing evidence that binaural-beat exposure is an effective way to affect cognition over and above reducing anxiety levels and the perception of pain without prior training, and that the direction and the magnitude of the effect depends upon the frequency used, time under exposure, and the moment in which the exposure takes place.

Discussion

The purpose of this meta-analysis was to provide an overall estimate of binaural auditory beats effectiveness on two cognitive functions (memory and attention), anxiety, and analgesia. We intended to answer two questions: (a) what was the overall magnitude of the effectiveness of binauralbeat exposure on the selected outcomes, and (b) were there any binaural-beat attributes that systematically moderated this efficacy? This meta-analysis provided robust evidence, although modest, regarding the efficacy of binaural beats on memory, attention, anxiety, and analgesia. Based on our results, we can observe that alpha (3 ESs), beta (10 ESs), gamma (1 ES), and theta (6 ESs) binaural-beat exposure affected the performance in memory tasks, and that the direction of this effect depended on the frequency used, being positive for the alpha, beta and gamma frequencies, and negative for the theta frequency (with the exception of studies 2 and 27). On the other hand, binaural beats consistently showed effectiveness in reducing the amount of intraoperative anesthesia. Both studies 10 and 21 applied multi-layered binaural beats, while study 25 did not report the frequency used. The efficacy of binaural beats in the reduction of anxiety scores after delta/theta exposure has also been confirmed in all included studies (k = 5), although study 29 did not report the frequency used. Finally, attention was also affected by

binaural-beat exposure. All studies (k = 7), excluding the study number 17, exhibited positive effects on attention utilizing alpha, beta, and gamma frequencies; based on our results, we can hypothesize that the reduced effectiveness observed in study 17 was caused by the moment of exposure—only during the task—and masking the binaural beat with music. With respect to these potential moderator variables, results provided supporting evidence for the hypothesis that the moment of exposure plays a pivotal part in the effectiveness of binaural beats, showing a greater effect when exposure occurs before, and before and during the performance of a task. Additionally, it appears that the time under exposure does not produce a habituation to binaural beats as it was initially hypothesized (Vernon, Peryer, Louch, & Shaw, 2014). On the contrary, our results indicate a positive relationship between time under exposure and effect sizes, which in turn reflects that not only it is advisable to undergo an induction phase to ensure that the desired frequency is entrained by the time that the event or task to be measured begins, but also that time under exposure should be long enough to obtain the maximum benefit. In line with this suggestion, recent studies manifested that to provoke changes in almost all cortical regions, binaural-beat exposure should last for 9–10 min (Jirakittayakorn & Wongsawat, 2017; Seifi Ala, Ahmadi-Pajouh, & Nasrabadi, 2018). In regard to binauralbeat masking, our findings indicated that unmasked beats were associated with larger effect sizes compared with binaural beats masked with music, but no differences were found in comparison to pink noise or white noise. We can hypothesize that the reduced effectiveness observed with binaural beats embedded in music might be due to some interference between the frequencies present in the music and the binaural beat, as musical rhythms, even when they are not strictly periodic, have been reported to entrain body movement (London, 2004; McAuley, 2010; Phillips-Silver & Keller, 2012). In relation to the binaural-beat frequency, our results denote that complex-frequency binaural beats (i.e., multilayered) produced the largest effect. Due to the limited number of studies that have studied multi-layered binaural beats (k = 3), it is plausible that these results are only valid for surgical procedures and may not be generalizable to a broader range of applications such as memory enhancement or anxiety reduction. Future studies should address this question and determine whether the reduction in analgesia can be extrapolated to all types of surgical procedures and other areas of cognitive enhancement, and whether multi-layered binaural beats offer a greater effect than simple binaural beats. Although most studies found significant differences between binaural-beat stimulation and the control conditions, it is necessary to identify why some studies could not find such differences. There are certain variables that could potentially explain interstudy differences in terms of effectiveness. For instance, one variable that might play a crucial role in binaural-beat effectiveness could be the carrier frequency, which should be investigated in future research to establish whether different frequency ranges produce different results. Other possible variables that might moderate the effectiveness of binaural beats, and that we have included in this meta-analysis, are the exposure time, the moment of exposure (i.e., before, during and before, and during the task), and the type of sound that was used to mask the binaural beat. Furthermore, we should not overlook the fact that there is a difference in the perception of binaural beats between males and females (Oster, 1973; Tobias, 1965) and that other inter-individual differences might be moderating the results. For instance, individual mesostriatal dopamine levels—indirectly measured by the spontaneous blink rate—have been found to determine the degree to which gamma binaural beats affect cognition (Reedijk et al., 2013; Reedijk et al., 2015). This could potentially be explained by a higher sensitivity and a more responsive mesostriatal dopaminergic system that initiates the neural processes more efficiently due to a hypodopaminergic state, which can be predicted by the spontaneous blink rate (Jongkees & Colzato, 2016). This higher sensitivity is prevalent in extraversion-related differences and implies an enhanced sensory reactivity such as lower auditory and noise thresholds (Smith, 1968; Stelmack & Campbell, 1974), and larger early visual event-related potential amplitudes like the N1 (Rammsayer & Stahl, 2004). In addition, introverts seem to be more responsive to induced changes in

dopaminergic activity, while extroverts display a more efficient compensatory mechanism whereby homeostasis in neurotransmission is maintained (Rammsayer, Netter, & Vogel, 1993). Therefore, it is of paramount importance to determine how these variables affect the effectiveness of binaural beats and which the optimal carrier frequency is to be able to use the most effective parameters and thus make the most of the binaural beats. For the afore mentioned reasons, the frequency of the binaural beats should be adjusted based on the sex of the listener to obtain similar and comparable results taking into account extraversion-related individual differences. Perhaps one way to reduce these extraversion-related differences might be to use carrier tones at higher frequencies where no significant differences in sensitivity between extroverts and introverts were observed (Stelmack & Campbell, 1974). A number of limitations may have influenced the results obtained in the present meta-analysis. For instance, with the exception of study 29, the rest of the included studies had a modest sample size ($n < 70$) that can compromise the statistical power and the estimations by overrating binaural beats effectiveness. Publication bias is always a concern in meta-analysis, although the statistical tests carried out did not suggest the presence of publication bias. We cannot rule out the possibility that if we had included all the non-significant studies and, therefore, not published, the estimation of the effect sizes would have been potentially smaller. Moreover, a greater number of studies are necessary since, at present, there are a very small number of studies that investigated the practical applications of binaural beats. In addition, notwithstanding the importance of the carrier frequency, we could not include it in our analysis, as many of the included studies (33%) did not report such information. Following reporting guidelines is crucial to further advance in this field. Finally, due to the limited number of included studies ($k = 22$) interaction effects could not be examined and it is possible that the statistical power was not sufficient for conducting a meta-regression. The associations obtained in the meta-regression should be considered with caution since they possess a weaker interpretation capacity than those made from randomized comparisons due to their observational and not causal nature (Thompson & Higgins, 2002). The results of this meta-analysis are encouraging and should be validated by larger sample size studies to ensure that the observed effectiveness can be replicated and applied to other areas such as implicit and episodic memory. On the other hand, the results obtained from the meta-regression should also be confirmed in future studies, as they are restricted insofar as the predictors were not theory driven. It is essential to validate the notion that exposure before, and before and throughout the task produces greater efficacy than just during the task. Taken together, these results suggest that binaural auditory beats affect memory, anxiety levels, attention, and perceived pain in a passive, automatic manner, and that the direction and the magnitude of the effect is determined by the binaural-beat frequency, moment and duration of exposure. The mechanisms behind how binaural beat stimulation translates into psychophysiological changes are still unknown. Hence, further work in this area is needed and may lead to the development of a better understanding of it and new practical applications where binaural beats may exhibit further efficacy. ◄

Note to readers: we advise you to check with your health care professional before taking any action.

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LIVING WITH CYSTIC FIBROSIS

LIVING WITH CYSTIC FIBROSIS

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Living with Cystic Fibrosis
mission is to promote quality of life
for people living with cystic fibrosis.

VISION

- Reach all people living with CF and their families.
- Be a leader in transmitting information on CF.
- Be a first hand support for people living with CF.

OBJECTIVES

- Promote and protect the rights and interests of those living with CF.
- Represent and support people living in Quebec with CF in their relations with government organisations.
- Transmit accurate information.
- Offer support to those living with CF.
- Promote a healthy lifestyle for those living with CF.