

Transcript Details

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ReachMD

www.reachmd.com
info@reachmd.com
(866) 423-7849

Catching Cystic Fibrosis: Key Diagnostic & Management Updates

Announcer:

You're listening to *Deep Breaths: Updates from CHEST* on ReachMD. This series is produced in partnership with the American College of CHEST physicians. The following episode was recorded live at the 2019 annual CHEST conference in New Orleans.

In this episode, we welcome our panelists: Dr. Kristina Montemayor – a fourth year pulmonary and critical care fellow at Johns Hopkins; Dr. Natalie West – assistant professor of medicine at Johns Hopkins, and Dr. Allison Lambert, an assistant professor at the University of Washington.

And, here is your host Dr. Kristina Montemayor

Dr. Montemayor:

Coming to you from the 2019 Annual CHEST Conference in New Orleans, I'm Dr. Kristina Montemayor, and joining me to discuss recent updates in the diagnosis and management of cystic fibrosis are Dr. Natalie West and Dr. Allison Lambert. Dr. West and Dr. Lambert, welcome to you both.

Dr. West:

Thank you so much for inviting us today. We are very excited to highlight the CF track at the American College of Chest Physicians Conference.

Dr. Montemayor:

So, why don't we start with you, Dr. West? In this year's cystic fibrosis education track at CHEST, what are some of the diagnostic and treatment advances that have been discussed?

Dr. West:

So, in terms of the diagnostic advances, it's important to review the sweat chloride test. So, as you know, this test measures the amount of chloride in sweat, and it helps to diagnose CF. Historically, a normal sweat chloride value was between 0 and 40 millimoles per liter, indeterminate between 41 and 59, with abnormal being greater than 60. The majority of individuals have sweat chloride around 100, and then two years ago the normal range was actually updated to be a smaller range between 0 and 29. That makes the indeterminate range being between 30 and 59 and abnormal range remaining greater than 60. A newborn screening is now mandated in all 50 states, so diagnosis has improved which has also helped to implement early treatment. It's important to know that 10 percent of patients, though, were diagnosed as adults because there was not newborn screening around when they were born, and, therefore, we really need to maintain a heightened awareness. So, it's really still important to consider CF as a diagnosis when you see clinical signs, which is bronchiectasis, repeated pulmonary infections, sinus infections, pancreatic insufficiency, and it's also important to note about 10 percent will have a normal sweat chloride, so in the appropriate clinical scenario, you really should proceed to genetic testing. And so I have a pearl here: Please ensure that you're ordering the correct genetic panel. There are genetic panels out there that test for only 20-30 of the most common genetic mutations, but we know there's over 2,000 mutations known to date, so you really want to make sure you're ordering a complete panel.

Dr. Montemayor:

I think those are really important points, and I would just add that it's also worth noting that states do modify the newborn screening process over time. For example, in Washington state, we recently modified our process, and these changes are only helpful if we can partner closely with our frontline clinicians receiving these test results. So, do reach out to your local or neighboring CF care team

during this work-up process. We anticipate referrals during the work-up process and are happy to consult by phone or accept referrals to assist you and support the complete the complete work-up.

Dr. West:

With regard to treatment advances, it's a really exciting time within the CF community. There's currently new medications out that started coming out over the past several years, and we call these CFTR modulators, and there's a session today just on this. It's really relevant to refresh our memory on how the CF protein works to understand how these medications work. So, when the CF channel doesn't work, there's an imbalance of sodium and chloride and therefore water, basically resulting in dehydration of the airway, which really makes it difficult to cough up any mucus or bacteria from the lungs. I really kind of picture cement in the lungs of CF individuals, and that leads to all the chronic infections, bronchiectasis, and the end stage lung disease that we see, but over the past seven years, for the first time we have medications that kind of correct the underlying genetic defect. So, in 2012, ivacaftor was initially approved for about 4 percent of our population with individuals that had G551D. It was the very first exciting breakthrough, and sweat chloride decreased by 40-50 millimoles per liter, so really going into that almost normal indeterminate range, and lung function increased by 13-15 percent. We also noted a 55 percent reduction in needing IV antibiotics. Several years later, in 2015, lumacaftor/ivacaftor was approved for those who had two copies of DeltaF508, which is the most common genetic mutation, so that means that almost 50 percent of our individuals had a drug that would be available to them. The thing here, though, is clinical outcomes were not as impressive. The sweat chloride dropped about 20 or so, so still in that abnormal range, and the lung function only increased by about 3 percent, but there was an impressive reduction in IV antibiotics by about 30 percent, and in 2017 tezacaftor/ivacaftor was approved for the same population and had similar benefits of lumacaftor/ivacaftor but was better tolerated and had less drug-drug interactions. So, now what's super exciting is now we have the triple therapy that hopefully will be approved by the FDA within the next six months. This is combining elxacaftor with tezacaftor and ivacaftor, and the exciting thing about this is that it should be available for about 90 percent of our patients with CF, and the clinical outcomes are very dramatic, lung function increasing 10-13 percent, and then from the bio marker standpoints, sweat chloride decreasing by about 45, which is really moving patients in the indeterminate range if not normal, and so really that means that our CF patients, instead of having cement in their lungs, are going to have much better hydrated airways, and there's also going to be a reduction of needing IV antibiotics by about 50-60 percent over six months.

Dr. Montemayor:

Thank you, Dr. West. The triple therapy definitely is an exciting time for both CF clinicians as well as patients. Specifically, I've noticed in the Johns Hopkins Adult CF Center that nearly every clinic visit patients are inquiring about the upcoming approval timeline for the triple modulator therapy that Dr. West just described. However, at the same time, I know the CF Foundation is committed to finding therapies for those patients, those 10 percent of patients with genetic mutations that do not respond to this triple therapy. The CF Foundation will not rest until CF stands for Cure Found, and with those developments in mind, Dr. Lambert, what challenges are you seeing as these patients begin to live longer with advanced treatment?

Dr. Lambert:

Yeah, I would say before I comment on the challenges, I just think it's worth noting that with these advances in the CFTR modulator therapy and the critical clinical trials that are underway and being discussed at the CHEST conference this week, how we each care for our patients with cystic fibrosis is continuing to evolve and improve, and really we hope these advances will continue to extend the lifespan of our patients with CF. So, in 2017, a patient born with CF has a median predicted survival age of 46 years, and so it's a really exciting time to be taking care of adults with CF, in particular, in my case, and I think these advances in survival can be in part attributed to the Cystic Fibrosis Foundation and their model of care delivery, which involves accrediting care centers, developing a patient registry, and sharing de-identified center-specific outcomes with participating care centers to really motivate us to self-reflect on how we can improve and change the care that we're providing. So, with this continuous quality improvement and the trials underway, we continue to anticipate extension in our patients' life, and we're excited to see how the change affects our care delivery model.

So, I guess to answer your question regarding challenges, I would say there are several key opportunities for improvement in our care delivery. Specifically, in partnership with the CF Foundation, we are looking to better characterize patients with advanced lung disease caused by cystic fibrosis and to really identify or understand the optimal approach to evaluating and referring this subpopulation of patients with CF for lung transplant. Additionally, as with any aging population, we are increasingly aware of the need to screen, diagnose, and treat comorbidities. So, specifically, our adult patients with cystic fibrosis require evaluation for premature colon cancer risk, they need to be worked up for osteoporosis and diabetes and mental health, and as this population ages and grows over time, we are really focused on engaging our internal medicine, our family medicine, and our subspecialty partners to engage in the delivery of primary and subspecialty care to our patients and to deliver healthcare with the mindset of an extended lifespan in cystic fibrosis. And lastly, I would just say that there is still so much to learn and improve, and we're excited about the trials underway, and we realize that not all patients with cystic fibrosis are the same, and so we are dedicated to understanding what drives risk for poor outcomes in our

sickest patients.

Alright, so to answer your question regarding challenges, I would say there are several key opportunities for improvement in our care delivery. Specifically, in partnership with the Cystic Fibrosis Foundation, we are looking to better characterize patients with advanced lung disease caused by CF and to understand the optimal approach to evaluating and referring this subpopulation of patients with CF for lung transplant. Additionally, as with any aging population, we are increasingly aware of the need to screen, diagnose, and treat comorbidities. Specifically, our adult patients with cystic fibrosis require evaluation for premature colon cancer risk, osteoporosis, diabetes, and mental health, and so we're really focused on engaging our internal medicine, our family medicine, and our subspecialty providers to engage in delivery of primary and subspecialty care to our patients and to deliver this healthcare with the mindset of an extended lifespan in CF. And lastly, there's much to learn and improve, and we're excited about the trials that are underway that are being discussed at the CHEST conference this week, but we also realize that not all patients with CF are the same, and so we're dedicated to understanding what drives risk for poor outcomes in our sickest patients.

And so in line with other fields of chronic pulmonary disease now recognizing gender-based disparities, multiple researchers in the field, including Dr. Montemayor and her colleagues, have identified that women suffer increased morbidity and mortality in CF, and so I just wondered if you wanted to comment on some of those findings?

Dr. Montemayor:

Sure, thank you, Dr. Lambert, and we'll be highlighting this during our session today as well, but briefly, prior researchers in the field of CF have shown that women have decreased mortality, more frequent pulmonary exacerbations, and women are less likely to recover after treatment for a pulmonary exacerbation, and most recently, our research group just found that women receive more days of IV antibiotics for a pulmonary exacerbation.

And for those of you just tuning in, you're listening to ReachMD. I'm Dr. Kristina Montemayor coming to you from the 2019 Annual CHEST Conference in New Orleans, and I'm speaking with Drs. Natalie West and Allison Lambert about recent advances in cystic fibrosis. So, Dr. West, continuing our discussion on how we can better treat this disease, what effective approaches are you seeing for the management of pulmonary exacerbations?

Dr. West:

Yeah, so we will be talking about this in our session today, and really pulmonary exacerbations are a sentinel event in the lives of individuals with CF, and we usually characterize these by increased symptoms, drop in lung function, and physician decision to treat with antibiotics. There is a wide variability in how clinicians treat patients with exacerbations but very little evidence to help guide us, so we don't really have evidence on choice of antibiotics, route, dosing, duration, or whether some time in the hospital is better than doing IV antibiotics at home. So, in 2009, the CF Foundation convened a working group to really help develop clinical trials to help answer these questions. I'm a part of this group, and the first trial that was designed was an observational trial, Standardized Treatment of Pulmonary Exacerbations. We call it STOP. So, there was about 220 patients at 11 centers that were observed over the course of an exacerbation. We collected lung function data, symptom scores, treatment practices, and outcomes. Then, we used this to design STOP2, which is currently ongoing, and this is a clinical trial that is randomizing patients to different duration of IV antibiotics based on clinical response. So, we check pulmonary function tests and symptom scores in the beginning, and then we repeat it approximately 7-10 days after starting IVs, and then based on your response, we will randomize you, if you've responded to 10-14 days, or if you haven't responded, 14-21 days.

We used this to design STOP2, which is currently ongoing. STOP2 is a clinical trial randomizing patients to different durations of IV antibiotics based on the clinical response at approximately 7-10 days after starting IVs. If FEV1 has increased by 8 percent or more and the symptom score is improved, then patients are called early robust responders, and they are randomized to either 10 days or 14 days. If this threshold has not been reached, then we characterize those patients as non-early robust responders, and we randomize them to either 14 days or 21 days. We anticipate the clinical trial to end in the first quarter of 2020, and we will have results next summer, and the STOP program is ongoing to design further clinical trials to answer further questions.

Dr. Montemayor:

Thank you. And just to help bring all of this together, Dr. Lambert, if you can give one call to action to your colleagues who are diagnosing and treating patients with cystic fibrosis, what would that be?

Dr. Lambert:

Well, first I would just like to thank the CHEST Foundation and ReachMD for the opportunity to really highlight the evolving and exciting field of CF. I think this gives us a platform to share our findings. I would say my one call to action would be to join us in the care for adults with cystic fibrosis. As our population ages, we need to engage our internists and non-pulmonary subspecialists to support in the screening, diagnosis, and treating of comorbidities that we are observing in our aging population.

Dr. Montemayor:

And how about you, Dr. West? What's your one main call to action?

Dr. West:

I think with the dramatic improvement in therapies with CFTR modulator therapy, I really want to have everyone think about how we can deescalate our patients' drug regimen. Patients take two to three hours to do all of their therapies, and with the dramatic improvement in the CFTR modulators, we probably don't need everything that they're taking, so really thinking about what we can take off, and the CF Foundation is already ahead of the curve. They're proceeding with the Simplify trial, which will actually look at this question.

Dr. Montemayor:

Thank you. Those are two great calls to action, and I would like to end with just incorporating one more call to action that I have, and I know briefly we just talked, there are the sex and gender differences in CF, and I hope that people can be mindful of that, and I just do want to highlight that the CF has supported the foundation of the Women's Health Consortium who consists of five steering committees right now and are going to be putting out a lot of work geared towards this, so there will be a lot more work done on sex-based and gender disparities in CF outcomes.

So, I just want to thank my guests for joining me to discuss the latest updates in diagnosis and management of cystic fibrosis. Dr. West, Dr. Lambert, it was great having you both on the program. I'm Dr. Kristina Montemayor, and thank you for listening today.

Dr. West:

Thank you so much for having us.

Dr. Lambert:

Yes, we've had a great time discussing the updates in CF.

Announcer:

This was *Deep Breaths: Updates from CHEST* produced in partnership with the American College of Chest Physicians. To access other episodes of this series, visit reachmd.com/CHEST, where you can be part of the knowledge.