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Bronchiectasis Update: Diagnostic Innovations and Therapeutic Frontiers

Announcer:
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Dr. Richards:
Hello, I'm Christopher Richards. I'm a pulmonologist at the Massachusetts General Hospital in Boston. I run the bronchiectasis program and the pulmonary genetics program in our division.

Dr. Losier:
I'm Ashley Losier. I am one of the Assistant Professors at Yale University in Pulmonary and Critical Care. And today I'm going to be speaking on the section looking at the natural history, risk factors, exacerbations, and disease progression of bronchiectasis.

Dr. Richards:
Today's talk is going to be *Bronchiectasis Update,* with a focus on diagnostic innovations and therapeutic frontiers.

So our learning objectives today are that, by the end of the activity, we'll be able to describe the role of neutrophilic inflammation as well as neutrophil serine proteases in the pathophysiology of bronchiectasis, summarize the natural history of bronchiectasis, including associated patient risk factors and the impact of pulmonary exacerbations on disease progression. We hope that you'll be able to differentiate bronchiectasis from other respiratory conditions such as asthma and COPD to help achieve an early and accurate diagnosis, and assess the latest clinical trial results for emerging therapies in the treatment of bronchiectasis.

Our agenda for today is going to be to review the pathophysiology of bronchiectasis, address the natural history, risk factors, exacerbations, and disease progression, discuss emerging treatments, and have a review of a patient case about the pathophysiology of bronchiectasis.

First, we have to start with the definition. What is bronchiectasis? Bronchiectasis is a condition, the final end pathway of many possible causes, that all result in the dilation of the proximal as well as the distal airways. During that process of dilation, the tissue of the lungs becomes much more heterogeneous. There tend to be cystic forms in the airways that are prone to accumulate excessive mucus production, and the symptoms that result from this are not terribly specific and may mimic other conditions like asthma or COPD.

The distortions that develop in the airways lead to this impaired mucus clearance, either from anatomic changes on a macro scale or on the microscopic changes wherein cells that line the airways lose their ciliary function. There becomes an overaccumulation of mucus-secreting cells, as well as a loss of ion channels that usually hydrate and thin the mucus—all of which allow mucus to pool and become static in different regions of the lungs.

The region of the lung that is affected can, but not always, be informative of the underlying cause. There's cystic fibrosis, for instance, tend to have upper-lobe predominant disease. Tuberculosis bronchiectasis resulting from prior tuberculosis infection can be in the upper lobes, whereas we think of maybe in the lower lobes issues like recurrent aspirations or the effects of long-term immune deficiency.

Bronchiectasis can be found in the lung in many different patterns. You can think of it as a focal as well as a diffuse disease. Focal disease we tend to associate with post-infectious causes, whether that's prior tuberculosis, prior nontuberculous pulmonary infections, or there's some sort of airway obstruction—a foreign body, a bronchial stricture like we see in the right middle lobe syndrome, or the development of an endobronchial mass or tumor.

More diffuse disease is caused by more diffuse conditions and syndromes. Infections may not necessarily occur in one part of the lung, so you can get post-NTM or TB diffuse disease. Congenital syndromes like cystic fibrosis, the alpha-1 antitrypsin deficiency, or primary ciliary dyskinesias affect multiple parts of the lung. Immune deficiencies, whether acquired or innate, also tend to have diffuse disease in the lungs. And other conditions like rheumatoid arthritis, Sjögren's, and inflammatory bowel diseases often present with multiple areas of bronchiectasis.

The standard model for thinking about bronchiectasis is this idea of a constant cycle, or maybe a vicious vortex of etiologies, where, in some way, abnormal mucus clearance develops, leading to mucus stasis. This leads to some degree of bacterial infection and colonization. That chronic infection then attracts immune cells, specifically neutrophils, which then cause a chronic inflammatory state in the lung with excessive amounts of elastases and serine proteases, which then leads to airway destruction and distortion.

The thing is, is that this is not a simple cycle; it's more of a vortex, wherein there is no one part of the cycle that is the beginning nor the end. They all interact with each other in very complex ways, which make the disease hard to manage but also allow for opportunities for different therapeutics.

We also know from data from the U.S. Bronchiectasis Registry that about 1/3 of patients with bronchiectasis are chronically infected with Pseudomonas aeruginosa, about 12 to 15%, Staph aureus, Haemophilus influenzae is the third most common chronic infection, with Stenotrophomonas maltophilia and Streptococcus pneumoniae rounding out the top five chronic infections.

In bronchiectasis, there's a way to think of this in terms of different inflammatory states. There is a neutrophilic and eosinophilic inflammatory state, or endotype, that we often see when we're managing bronchiectasis.

In the neutrophilic subtype of the disease, this tends to be more severe. Patients will have lower fractional exhalations of nitric oxide if that testing is performed. They often have a weak or at least a weaker bronchodilatory response. And if their sputums are tested, they can have high levels of IL-8.

But eosinophils, on eosinophilic inflammation on the other hand, tends to be less severe, with higher FeNO levels. There tends to be a strong bronchodilatory response and higher levels of IL-13. All these features of the eosinophilic endotype of the condition is what can lead to challenges in distinguishing bronchiectasis with eosinophilia from common asthma.

As we saw in the last slide, about 85% of all cases of bronchiectasis have a neutrophilic-predominant form of inflammation. Looking at the lavage fluid of patients with neutrophilic bronchiectasis, we see that they tend to have a twofold increase in the amount of neutrophils in their lavage fluid, and three times as much overexpression of neutrophil elastase in the lavage fluid. This means that the neutrophils are both present and overly active in the lungs of individuals living with bronchiectasis.

So the role of neutrophil elastase in airways disease is that once the neutrophil migrates to the tissue of the lung, these neutrophil elastases go on to increase mucin expression, so you get longer and more polymerized mucus. There tends to be less, or at least a developing impairment in ciliary motility. The expression of the elastases and other serine proteases disrupt the epithelium and lead to scarring. Scarring and degradation of the epithelium leads to further recruitment of neutrophils. And there's also loss of the activity—the innate immune function of the lung.

So one of the actively studied targets for management of bronchiectasis is to inhibit this neutrophil-mediated inflammatory pathway at the level of the enzymes expressed in the lung. So one of the targets is cathepsin C. And cathepsins are a large family of proteases that are involved in protein degradation and normal cell turnover. In mammals, the CTSC gene is most often expressed in the lungs, spleen, kidney, liver, and is produced and found in neutrophils, mast cells, monocytes, and in macrophages.

Now, cathepsin C, in particular, plays a key role in the activation of other serine proteases in the cytotoxic T cells, natural killer cells, mast cells, as well as neutrophils. And this is through the activation of cathepsin G, neutrophil elastase, and proteinase 3.

Neutrophil serine proteases don't just degrade foreign cells and bacteria, but they also self-regulate the recruitment of additional neutrophils to the target tissue by silencing the inducers of neutrophil accumulation, which are CXCL8 and MIP-alpha.

A bacterial colonization in the lung often is happening when there is insufficient bacterial killing to begin with. Pathogens that are able to evade this NSP-mediated degradation are often able to do that because they don't cause immediate damage to the lung tissue, and instead they evade by not causing a robust and immediate inflammatory response. The bacteria are able to colonize, and then the

damage to the organ is triggered not by the bacteria themselves, but indirectly through the mediation of neutrophil dysfunction.

It's this constant recruitment and overexpression of cytokines that lead to increasing numbers of neutrophils in the tissues, lead to an excess of reactive oxygen species, production of even more proinflammatory cytokines, which recruit cell types beyond the neutrophil. And from all this, the connective tissue destruction.

So there are a couple of different illustratory syndromes for this concept. So in a loss-of-function condition, like the Papillon–Lefèvre syndrome, where you lack neutrophil serine proteases, people living with that condition will have some keratoderma—a thickened skin on the hands and soles of the feet—very obvious and aggressive periodontitis. And this is all stemming from the NSP impairment.

In conditions with high or overactivity of NSP—this would be something like COPD, cystic fibrosis, COVID infection, ANCA-mediated vasculitides—it's through this enhancement of protease activity that you get tissue destruction and airways damage. And the goal is to target this, and this is the target of the DPP-1 inhibitors we'll talk about in a moment.

So key takeaways: non-CF bronchiectasis is a pulmonary disease that's characterized by chronic cough, purulent sputum production, inflammation, airways dilation. Or sputum clearance typically leads to a cycle of bacterial infection or colonization, neutrophilic inflammation, and airway destruction and distortion. Neutrophil serine proteases are hypothesized to play a central role in this cycle.

Dr. Losier:
I'm Ashley Losier. I am one of the Assistant Professors at Yale University in Pulmonary and Critical Care, and today I'm going to be speaking on the section looking at the natural history, risk factors, exacerbations, and disease progression of bronchiectasis.

So when we look at the epidemiology of bronchiectasis, a U.S. estimate based on healthcare claims data suggests that non-CF bronchiectasis is becoming increasingly prevalent, with about 340,000 to 522,000 U.S. adults being diagnosed with bronchiectasis. The majority of these are women, with approximately 67%, and it increases amongst those greater than age 65 years, with about 76% of those with a diagnosis of bronchiectasis being greater than 65.

There is a higher prevalence among Asian Americans, where we see that there's about a 2.5- to 3.9-fold higher prevalence than those who are White or Black. And notably, the prevalence is increasing, where we see that the annual prevalence growth rate is about 8% over the past handful of years as we're looking at the diagnosis of bronchiectasis.

And some of this is thought to be perhaps related to just our detection modalities. With the increased recommendations for low-dose CT screening among asymptomatic smokers, we are catching bronchiectasis perhaps earlier than we had initially. And so that leads us to think that perhaps there is still an underlying underdiagnosis of bronchiectasis, just given that we are catching a lot of this incidentally on some of the scans.

Something to take away is that there is about 1 patient with bronchiectasis for every 20 patients with COPD amongst Western countries, and there's only about 40,000 people in the U.S. who have CF-related bronchiectasis within the United States. So overall, this prevalence is expected to continue to rise.

When we look at the healthcare resource burden of bronchiectasis, we see that it does have tremendous impacts on countries throughout the world in terms of the healthcare burden. This is looking at a study in CHEST that was relatively recent as a systematic review looking at the economic burden of healthcare utilization in adults and children with bronchiectasis over a period from 2001 to 2022. And it said ultimately what they looked at was about 53 studies and they saw that there were significant related healthcare costs, along with indirect costs related to lost income due to illness or perhaps missed school days in the pediatric populations.

And we can see that what the aggregate annual healthcare costs are is quite staggering amongst all of the countries that were studied. They looked at Australia, Singapore, Germany, South Korea, Spain, the UK, and the United States. And it ranged from anywhere from $17.7 million per year to about $14.68 billion per year in the United States of aggregate healthcare costs. So really a substantial economic burden throughout the world in those who are diagnosed with bronchiectasis.

So knowing what we know about the increasing prevalence and the significant burdens and impacts of quality of life that we will get to, the diagnosis becomes quite important. And really, to confirm a diagnosis of bronchiectasis, it does require radiographic imaging to confirm. And this is typically done through the use of high-resolution CT chest and also using pulmonary function testing.

There is a core set of assessments that's recommended to determine the etiology of bronchiectasis, and this generally involves laboratory analysis to look for specific treatment approaches. So generally, that includes things like a complete blood count and a differential, which will help us see if there's any potential elevations in neutrophilia or eosinophilia. Also, we generally check immunoglobulins, which includes IgG with its subclasses, along with IgM, IgA, and IgE. Sputum cultures are recommended in the basic workup, and that typically does include a bacterial culture, mycobacterial culture, and fungal cultures. And then a basic genetic workup,

looking at Alpha-1 antitrypsin levels and phenotyping.

Then, as we start getting towards some of the targeted testing—again, this is largely completed to help proceed with specific treatments—but we do tend to screen for allergic bronchopulmonary aspergillosis as a common cause of bronchiectasis. Again, additional genetic testing can be considered to include cystic fibrosis testing. And this often entails both a sweat chloride test or CFTR genetics. Then we have primary ciliary dyskinesia testing, which may entail nasal nitric oxide or ciliary biopsy or genetic analysis as well. Autoimmune panels, along with a gastrointestinal evaluation if there are any concerns for reflux or aspiration that might be suspected.

And different centers may utilize different tests or panels, but this is the generic recommendation of things to consider when looking for potential targeted testing for specific treatments.

So for the radiographic features of bronchiectasis, there are some common radiographic features that are associated, including things like cystic changes or airway thickening. As I previously mentioned, to obtain a diagnosis of bronchiectasis, you do need to have the radiographic features to include dilated airways, which typically looks at the airway diameter in comparison to the corresponding blood vessels and that the airway is enlarged. And that is generally where we rely on the help of our radiologists when they are performing these reads to make sure that we are able to have that included in our reports as we are looking to give these patients the diagnosis.

Some of the common features that might be associated include things like cystic changes. So this is a really nice chest x-ray on this slide looking at some cystic changes up in the upper lobes. And then has a really nice picture of the tram-track airways, as we see at the basilar portions on this chest x-ray. We are not always as fortunate to have the chest x-ray show us some of these abnormalities and do require more of a CT chest to be able to fully distinguish some of these features.

And on this CT that's corresponding, you can see the cystic changes located here, along with some of the airway thickening and some of the tram-track type description, which is the cylindrical bronchiectasis located at these arrow locations.

As we move into some of the other features that are associated with bronchiectasis, one of the most common ones that we will see on our reports include mucus plugging along with these cylindrical lesions. But as you can see here in this portion on the left-hand side of the screen, we have areas of mucus plugging also kind of scattered throughout the posterior portions of the lungs.

And then we have some of the tree-in-bud nodules or nodularity that are present. Then again some of the cylindrical bronchiectasis that is present at the arrowheads here, or perhaps some of the signet ring sign, which is present here where you can see the airways corresponding with the corresponding blood vessel, and how the airway is actually larger than the blood vessel that's beside it.

But something that we should note is that not all bronchiectasis is related to airway disease. So there is traction bronchiectasis, which is a common description in disease conditions such as interstitial lung disease, where the airways are essentially pulled or distorted towards some of the fibrotic changes in the lungs.

So when we look at bronchiectasis comorbidities, it's important to realize that the relationship between bronchiectasis and multiple comorbidities is not always clear. Some of them may be causal, but some of them may also contribute to poor outcomes or potentially progression as well.

A lot of what we're looking at when we're looking at treatments or management is trying to manage some of the corresponding comorbidities to see if we might be able to improve the prognosis of bronchiectasis patients.

There's many, many different types of comorbidities that have been associated with increased mortality risk in bronchiectasis. This is just a list of some of them, but we do see that there's infectious processes, so things like chronic airways infections, such as NTM infections, but also other post-infectious changes from pneumonia or TB. There's anatomic focal bronchiectasis. There's post-inflammatory pneumonitis, so from things like GERD or chronic sinusitis. There's genetic conditions that can contribute to bronchiectasis development, along with some of the connective tissue diseases or autoimmune conditions that have sustained inflammation that may also impact the lungs.

Then, as we get into some of the corresponding airways diseases such as COPD and asthma, we can see that some of those with long-standing inflammation can contribute to bronchiectasis development as well. And then altered immune responses or immunodeficiencies can contribute to the underlying inflammation. And otherwise, there's inflammatory bowel disease listed under other or congenital causes, and then just idiopathic bronchiectasis as one of the other buckets for bronchiectasis development.

And when we look at the etiologies of bronchiectasis, there is a scoring system called the Bronchiectasis Aetiology and Comorbidity Index, which is BACI. And this was a tool that was developed to assess the mortality risk that's associated with comorbidities. So it can be helpful to determine the mortality risk, and really a score greater than 5 is considered to be high risk.

So as we understand all the comorbidities that can contribute to the development of bronchiectasis, it is really highlighting how

heterogeneous this condition is. As we try to understand some of this heterogeneity of bronchiectasis, we can see that there is this new precision-based medicine focus on endotypes. And so endotypes are really defined as subtypes of disease that are defined by biological mechanisms. So this can include comorbidities and underlying causes, infective agents, and inflammatory profiles, and genetics as well.

And so this kind of highlights a little bit on the comorbidities and underlying causes, such as COPD and bronchiectasis overlap, where the two can coexist and worsen each other's course, with often more severe exacerbations and microbial colonization.

And as it does highlight amongst all this heterogeneity, that there is really no one-size-fits-all management approach to this. And perhaps that concept is outdated, and we really need to start focusing on some of the precision-based techniques or personalized medicine to really create a tailored approach as we are trying to decrease morbidity and mortality in the treatment of this condition.

So our current understanding of bronchiectasis pathophysiology has really morphed into this concept of the vicious vortex, where each process contributes to the others, leading to this persistent and progressive pathophysiology of airway inflammation. With that being said, interventions at one point on this vortex may only have modest effects, so we often will have to treat things with a multi-tiered approach.

And with the treatment goals of bronchiectasis, a lot of it is surrounding the prevention of exacerbations. And so we have to define or understand what is an exacerbation in bronchiectasis. So the patient-focused definition, or when a patient comes with symptoms, they are generally going to be reporting a change in respiratory symptoms significant enough for them to seek care. And there's some research going on right now looking at patient-focused diaries so that they're able to track their symptoms more effectively to know what is a change from their baseline.

But for the purpose of clinical trials, or often in the clinical care settings, exacerbations are defined by a deterioration of three or more of key symptoms for a duration of 48 hours. And generally, in bronchiectasis, that means a change in the cough, which may occur with a change in sputum volume or consistency, or a change in the color or purulence of that sputum. Symptoms of breathlessness or exercise intolerance, fatigue, malaise, or hemoptysis. So it can be any three of those. And then amongst that, an exacerbation generally involves a physician agreement that these symptoms put together require a treatment change at that time point.

And so why are exacerbations so important? We do know that exacerbations are common in patients with bronchiectasis. And this is looking at an insurance claims database analysis from a recent study in 2023 that had about 15,000 patients identified in this study. And what it did show was that over a 1-year follow-up period, 67.4% of the patients—so in the blue, the light yellow, and the dark yellow—had more than one exacerbation in the first year of follow-up. And then subsequently, in the second year of follow-up, we saw even higher numbers, so about 76.5% of patients had more than one exacerbation in the 2 years of follow-up.

Why is this so important? We do know that as people who have more than two exacerbations during their baseline period are again more likely to have increased exacerbations on their years of follow-up. So as it get more exacerbations typically do progress to even an increased number of exacerbations in the future as well.

With that, and the frequency of exacerbations and the symptoms of bronchiectasis, we do know that there is a negative impact of exacerbations on patient quality of life. So the more frequent the exacerbation typically correlates with higher scores on the SGRQ—or the St. George's Respiratory Questionnaire—and higher scores typically correlate with poorer outcomes. Even from baseline, when a patient has an exacerbation, we can see that score changes are even higher with exacerbations. And typically, the more frequent the exacerbations, the poorer the quality of life associated with the patient and their bronchiectasis.

Additionally, more frequent exacerbations are associated with poorer healthcare outcomes. So this is a study that was completed in 2018 that looked up the follow-up hospitalization rate and survival in patients with bronchiectasis exacerbations. And then you can see here, as most strikingly is in the red plot were those who had greater than three exacerbations per year at baseline. And what we saw was that percent survival had a correlative decrease in those who had more frequent exacerbations. So overall, the more frequent the exacerbations, the worse quality of life that is reported, and also the percent survival is decreased with the higher number of exacerbations.

So key takeaways in the natural history of bronchiectasis is that it is increasing in its incidence and prevalence. We should really take note on exacerbations and how their diagnosis is surrounding a change in respiratory symptoms that prompts a change in treatment, and generally will require a clinical encounter and sometimes increased hospitalizations with those who have more frequent exacerbations. And lastly, these exacerbations are associated with decreased quality of life, along with the increased risk of hospitalization and subsequent exacerbation frequency as well.

Dr. Richards:

Emerging treatments. Many of the emerging therapeutics and future treatments for bronchiectasis are focusing on modulating the uninhibited inflammatory state of the lung that is caused by overexpression and accumulation of neutrophil serine proteases in the pulmonary tissue. At the heart of that is an enzyme called dipeptidyl peptidase 1, or DPP-1. This enzyme, present in mature neutrophils, activates other serine proteases such as Cat G, PR3, and neutrophil elastase by cleaving the N-terminus of the dipeptide into its active form. DPP-1 inhibitors are a focus of active research.

One of the early studies of DPP-1 inhibition was in a phase 2 study, where a DPP-1 inhibitor was shown to, over the course of 24 weeks of therapy, lead to marked reductions and significant reductions in the sputum neutrophil elastase, the sputum proteinase 3 concentrations, as well as sputum cathepsin G concentrations, suggesting that targeting DPP-1 would reduce not one, but multiple enzymes known to be involved in the destruction of the lung and the damage to the lung in bronchiectasis.

It wasn't just that, and by taking systemic therapy, you saw that inhibiting DPP-1 also led to not just reductions in the concentrations of neutrophil elastase in the target tissue of the lung, was also seen to be reduced in the peripheral white blood cells. This drug, which would later be called brensocatib, was then tested again in a pivotal phase 3 trial called ASPEN. ASPEN recruited about 1,700 patients, all of whom were over the age of 12 that had no history of cystic fibrosis but did have a history of non-CF bronchiectasis. And those people needed to have had two or more exacerbations in the prior month that required an increase in their treatment, either from some change in baseline therapy or the prescription of antibiotics, as deemed by their physician.

The study followed patients for 52 weeks with a primary endpoint of the annualized rate of a pulmonary exacerbation. Other endpoints that were assessed were time to first exacerbation, proportion of patients who were exacerbation-free, the change in the FEV1 at week 52, the annualized rate of severe exacerbations, so exacerbations requiring hospitalization, and a change in respiratory symptoms.

The study did meet its primary endpoint with a significant reduction in the annualized rate of pulmonary exacerbations over 52 weeks. That was seen in both of the test doses—10 mg and 25 mg of brensocatib. This pivotal phase 3 trial for a first-in-class drug in the treatment of an orphan disease led to it being approved by the FDA just on August 12, 2025.

The current indications for brensocatib are for the treatment of adults with non-cystic fibrosis bronchiectasis. And there are two different once-daily dosings, either 10 mg or 25 mg. In the study, 10 and 25 mg achieved all endpoints, except with a notable difference that for those patients taking 25 mg rather than 10, there was both 10 and 25-mg dosings improved the rate of decline of FEV1 after 52 weeks.

That finding was more significant in the 25-mg group. Safety: The drug was well tolerated. Most common adverse reactions were an upper respiratory infection, headache, rash, dry skin, some hyperkeratosis, and hypertension. The drug is now packaged with additional warnings and precautions for dermatologic adverse events. And patients and providers are asked to watch for new rashes on the skin, and specifically the hands and soles of the feet. There is also concern for gingival disease and periodontal disease. We are advising patients to see their dentist regularly and to perform just regular routine dental hygiene.

Another drug in development, BI 1291583, also targets an upstream regulator of the neutrophil serine proteases called Cat C. Inhibition of Cat C is analogous to inhibition of DPP-1, with resulting decreases in the concentrations of neutrophil elastase, protease3, and Cat G, all of which is occurring at the drug's target in the bone marrow during the maturation and differentiation of the neutrophil.

This drug was tested in a phase 2 trial called AIRLEAF, in which the outcomes were assessed by a dose-response curve, as you can see in the top left. This graph is essentially a series of hazard ratios plotted upon themselves at different timepoints at the different doses to estimate what the net effect of the drug would be amongst a larger population. The bottom graph is a much more conventional Kaplan-Meier plot of the time to first pulmonary exacerbation, with higher doses of the study drug leading to more time to first exacerbation as compared to placebo or the 1-mg dosing. This data is the basis for an actively recruiting phase 3 trial in adults with bronchiectasis, and notably also with a small arm within the trial of patients with cystic fibrosis.

An additional target of inflammatory inhibition comes from the use of inhaled phosphodiesterase 3 and 4 inhibitors. An FDA-approved drug called ensifentrine is currently. So ensifentrine is currently approved for the use of COPD to treat GOLD 2 and above disease. It is a nebulized medication a patient takes twice a day. In COPD, it notably has a pretty good bronchodilatory and increased ciliary clearance response. And so extrapolating from that experience trying to be used in non-CF bronchiectasis.

By using PD3 inhibition, you tend to give more bronchial relaxation or that bronchial dilation. And for the PD4 inhibition, this tends to cause increased amounts of CFTR activity as well as increased ciliary function. And the two drugs overlap in their effect to decrease neutrophil and eosinophilic migration to the lung, and also decreases the proliferation and survival of these immune cells in this chronically infected, low-grade inflammatory state.

And the effect of ensifentrine in COPD was proven in the ENHANCE-1 trial and the ENHANCE-2 trial. In both cases, patients who were taking the medication had a fairly rapid—within 30 to one hour—peak effect in the FEV1, with an improvement in the FEV1 that lasted

for 6 to 8 hours after drug administration.

Our key takeaways: There are new approaches in development for treating bronchiectasis, including DPP-1 inhibitors, also known as Cat C, to reduce neutrophil serine protease activity and associated neutrophilic inflammation. Those drugs would be brensocatib and the newly approved brensocatib and the drug in testing, BI 1291583 as well as clinical trials looking at the efficacy of phosphodiesterase inhibitors, specifically PD3 and PD4, with the drug, ensifentrine FDA-approved for COPD management.

Patient case.

Dr. Losier:
I'm sure many providers will have seen similar cases before. This is a 75-year-old female with a history of bronchiectasis that she has noted that she's had a diagnosis for at least 15 years. On note, she does report that she's had a prior treatment for NTM, or nontuberculous mycobacterial infection with MAC and this was treated with 2.5 years of IV amikacin, ethambutol, azithromycin, and rifampin. And she reports that she had culture conversion to negative sputum cultures more than 10 years ago. Additionally, she has had chronic pseudomonas with frequent exacerbations noted at about two to three times per year, and generally she has increased sputum or fevers during these exacerbations.

Throughout her treatment courses, she reports that she's been maintained on airway clearance, which generally has included twice-daily albuterol and saline nebulizers, along with her airway clearance that includes percussive vest and oscillatory PEP and huff cough.

So she returns to clinic and she is reporting that she has chronic cough, shortness of breath or dyspnea, and fatigue, and she continues to follow up due to her frequent bronchiectasis exacerbations.

So on review of her case history, she has a past medical history that's notable for a very remote smoking history. She quit over 35 years ago with a 5-pack-year history. She does report recurrent respiratory infections, largely since her adulthood, around the age of 30, where they began, bronchiectasis, which she has the former diagnosis prior to coming to clinic, and osteopenia. There's no significant social history apart from what we've reviewed, and no known drug allergies. Her family history is noncontributory, without any pulmonary history noted in the family. And then her medications are really only notable for the nebulized albuterol and sodium chloride 3% and a calcium and vitamin D supplement.

On her physical exam at your initial clinic visit, you note that she has a slightly tachycardic heart rate at 104. Her saturations are normal on room air, and her BMI is normal, but on the lower end of normal at 19.9. She's thin. She's in no acute distress, and predominantly her exam is normal, apart from bilateral rhonchi that are present with the right being worse than the left.

Her initial labs following the first referral were really notable for a slight leukocytosis with a white blood cell count of 13.6. Of note, on the differential, she did not have any profound eosinophilia, and she had a slightly neutrophilic predominance. The microbiology at the time of her referral was notable for Pseudomonas aeruginosa, with a 2+ burden on her cultures, and AFB cultures were negative for MAC. And per the referral packet, they had not been positive for over 10 years.

She had additional bronchiectasis testing, as we had reviewed previously in this talk of potential diagnostics that might be indicated, including immunoglobulins with subclasses, all within normal limits. She had had an Alpha-1 antitrypsin and Z phenotype, but she had a normal level at 182. Cystic fibrosis testing was completed with a 32-gene screen panel, and along with sweat chloride testing that was normal. Respiratory allergy testing was within normal limits, and allergic bronchopulmonary aspergillosis assessment was normal as well.

So looking at initial imaging, as I mentioned on her physical exam, she had had worse rhonchi on her right than her left, and this corresponds to some of the bronchiectatic changes that we can see here, predominantly noting some of these cylindrical into varicoid bronchiectatic changes, predominantly at the right base and the right middle areas with some thickened airways present as well.

And this is just some of the additional sections on her CT chest imaging that show some of the cylindrical changes mixed with some of the airway thickening and varicose changes that we can see scattered throughout her lungs. The right side is definitely worse than the left, but we can see that she does have some left-sided disease as well, with some of the airway thickening scattered throughout the left as well.

So one of the things when we first go through part of our clinical assessment of bronchiectasis patients and looking at their imaging and underlying comorbidities and perhaps their airway colonization status, is to consider risk stratification. So when we think about risk stratification, there's multiple different scores that we can use. The most common or most recognized is perhaps the Bronchiectasis Severity Index, or the BSI. And this is a scoring system that helps predict the risk of future mortality, hospitalization, exacerbations, and quality of life. It requires the input of metrics, including age, FEV1, the status of plus or minus pseudomonas infection, the extent of the lobes that are involved in the airways, the BMI, along with prior hospitalizations reported. There's also the FACED score, which is similar

to the BSI. And largely, these risk stratification scores are helpful to predict mortality in bronchiectasis.

There are online calculators that are available, and it's more of an informative risk stratification to help in guiding patients in clinical practice to help them understand their risk of progression or risk of exacerbations, just as you're starting to consider different treatment options that might be available to help them in preventing progression of disease.

So back to our case. She did have pulmonary function testing completed, and as we previously noted on the Bronchiectasis Severity Index, generally a positive score would be in those who have a low FEV1. This patient actually had relatively normal pulmonary function testing, apart from some borderline restriction, with a lung TLC, or total lung capacity, at 73%, and a moderately reduced diffusing capacity when corrected for hemoglobin at 50%.

And in our patient, who had presented to clinic, she had multiple culture data in her referral packet. She had initially, as I'd mentioned, had Mycobacterium avium prior to her evaluation that was treated successfully and has been culture negative for many years. But then on her most recent cultures, she had started first with pseudomonas that was largely sensitive to most antibiotics, including fluoroquinolones such as ciprofloxacin, and things like piperacillin-tazobactam and tobramycin.

But over time, as she progressed through her treatment, she was noted to have additional subclasses of her pseudomonas that were isolated, and her culture data was starting to show different strains with different sensitivities present on her antibiotic susceptibilities. And we started to see that she was developing resistance over time to common medications, including fluoroquinolones like ciprofloxacin and also variable resistance patterns to medications like to tobramycin.

So in our patient, as I mentioned, she had had multiple exacerbations that were commonly treated as an outpatient, about two to three, with as many as four exacerbations per year, requiring outpatient treatment, generally with an oral fluoroquinolone. She had had one admission where she was treated as an inpatient with piperacillin-tazobactam. And over time, she did continue to have these frequent exacerbations.

So when we're considering azithromycin as a maintenance therapy versus inhaled antibiotics, one of the things to consider is looking at azithromycin and its potential utility to decrease the exacerbation frequency. There was a study called the EMBRACE trial in *The Lancet*, published about 10 plus years ago, looking at the use of azithromycin as a potential to decrease exacerbation frequency. And as you can see here, in patients who received azithromycin, we have the time to exacerbation was reduced in those who were taking azithromycin in comparison to placebo in bronchiectasis patients.

This was a really promising study, and generally azithromycin is a really well-tolerated antibiotic, but this is not being used as for antibiotic purposes in these patients; it's being used more for the immunomodulatory or anti-inflammatory purposes to help decrease the frequency of exacerbations. So this can be a really nice option for patients to help when they may have frequent exacerbations, but we

must pay careful attention to their history of nontuberculous mycobacterial infections. So sometimes in patients who have had a history where they're at risk for recurrence or have had variable cultures with positive nontuberculous mycobacteria present, this may be an option that you may want to possibly consider something different rather than using azithromycin.

And now do have options with inhaled antibiotics largely for pseudomonas to potentially help with decreasing the risk of exacerbations. Perhaps the most commonly used in the United States is tobramycin. The use of tobramycin can help with reducing sputum quantity of pseudomonas, along with decreasing the risk of exacerbations. And oftentimes, tobramycin is used in an alternating 28 days on and 28 days off. But there are also recent studies looking at the use of colistin to help reduce exacerbations from pseudomonas.

So in this case, she was started on nebulized tobramycin as an alternating 28 days on and 28 days off. Azithromycin was avoided because she had isolated a one-time positive Mycobacterium avium, along with her history of MAC about 10 years ago. And ultimately, with her results following about 6 to 12 months of tobramycin, she had a slightly decreased exacerbation frequency from about two to four times a year down to one to two times per year, but ultimately was still producing copious amounts of sputum and as a reported significant quality of life burden from treatment fatigue with her airway clearance along with her chronic daily productive cough and sputum.

So key takeaway points and clinical practice tips in the management of bronchiectasis in this case is that patients with pseudomonas can have increased exacerbation frequencies, and we need to be aware that with these increased exacerbation frequencies and chronic pseudomonas, there might be a progressive decline in FEV1. The use of the Bronchiectasis Severity Score can be helpful to predict severity of illness and in counseling patients in the clinical setting. And then the use of nebulized antibiotics are an option to help in reducing symptom burden and exacerbation frequency.

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