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Bridging the Bronchiectasis Gap: The Latest Emerging Multimodal Treatment Approaches

Announcer:
Welcome to CME on ReachMD. This activity, titled "Bridging the Bronchiectasis Gap: The Latest Emerging Multimodal Treatment Approaches," is provided by the France Foundation. Prior to beginning the activity, please be sure to review the faculty and commercial support disclosure statements as well as the learning objectives.

Welcome to Bridging the Bronchiectasis Gap: The Latest Emerging Multimodal Treatment Approaches. Bronchiectasis is a growing yet underrecognized airway disease, and diagnostic delays continue to cost patients lung function and quality of life. This activity gives you the tools to change that. In this module, you will learn how to recognize the cardinal symptoms and red flags that set bronchiectasis apart from asthma and COPD, so you can diagnose it earlier and more accurately; understand the neutrophilic inflammation that drives disease progression and pulmonary exacerbations; translate the latest clinical trial data on novel therapeutic agents into practical multimodal treatment plans; and put it into practice through an interactive patient case and "What Do You Know?" knowledge checks led by expert pulmonary faculty.

Dr. Brenner:
The planning committee and faculty for today's lecture include Dr. Ashley Losier from Yale Medical School, Dr. Ari Ciment from Mount Sinai Medical Center in Miami, Florida, and myself, Dr. Laura Brenner from Mass General Brigham in Boston.

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So let's start with our learning objectives. The objectives are to summarize the epidemiology, patient risk factors, and disease progression of bronchiectasis; identify key symptoms to allow an early and accurate diagnosis of bronchiectasis; and describe the roles of neutrophilic inflammation and neutrophil serine proteases in the pathophysiology of bronchiectasis, and thus we'll apply evidence-based emerging therapies within a multimodal approach to bronchiectasis management.

Throughout this presentation, you'll see these brain icons. This is a knowledge check. Look for the symbol in the top right corner of the screen to find the answers to the "What Do You Know?" questions.

Here's our agenda for today. One, we're going to work on minimizing diagnostic delays, focus on cardinal symptoms, and other red flags. We'll do a bronchiectasis overview and the role of neutrophilic inflammation in the impact on pulmonary exacerbations. We'll examine clinical trial data with novel therapeutic agents, and then we'll do a patient case review, implementing a multimodal treatment approach to improve outcomes.

So first, let's talk about minimizing diagnostic delays, a focus on cardinal symptoms and other red flags. So, how do we define bronchiectasis? It's defined mostly by imaging, specifically high-res CT with the airway-to-artery diameter ratio of greater than 1,

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meaning the airway is larger than the artery. Some people consider this a ring sign, the lack of airway tapering and airway visible in the periphery. It's also defined by clinical features with cough, with sputum production most days of the week, frequent pulmonary infections or exacerbations, hemoptysis, and purulence. Or FEV1 may decline with frequent exacerbations as well.

These are important bronchiectasis features. First is airway distortion and impaired mucus clearance are consequences of bronchiectasis pathobiology. So you can see in this picture on the left, you can see the normal airway versus the airway of bronchiectasis. And then we also look at the pulmonary distribution may suggest etiology but overlap between causes is really substantial. So in the upper airway, you can often see with cystic fibrosis and tuberculosis, the central parts of the lung, cystic fibrosis, ABPA, and then lower lobe is childhood infection and aspiration.

There are many symptoms indicative of bronchiectasis. Some are productive cough, hemoptysis with recurrent infections, exacerbations, and frequent antibiotics, and persistent bacterial infections. There's also overlap with other pulmonary diseases, including COPD and asthma. And they may be part of other systemic diseases, including congenital and genetic causes, autoimmune, immunodeficiencies, and gastrointestinal, including inflammatory bowel disease and reflux, also persistent cough despite treatment.

The epidemiology of bronchiectasis, recent estimate was 340,000 to 522,000 of US adults, with 67% being women and 76% greater than 65 years old. There's been increasing incidence and prevalence from 2001 to 2013 with an 8% annual increase. As you get older, this prevalence increases throughout life, with 65 to 74 and 75 having the greatest number of people with bronchiectasis in the US.

Bronchiectasis is very heterogeneous with many different endotypes. So let's describe what an endotype versus a phenotype is. A phenotype are observable characteristics related to clinically meaningful outcomes. Endotypes are biological classifications based on specific pathophysiologic processes or biomarkers.

Bronchiectasis has a broad constellation of phenotypes and endotypes, and endotypes can drive treatment decisions.

There are a neutrophilic endotype, which we see with neutrophilic inflammation. There are endotypes derived from different types of infections, including Haemophilus and proteolytic endotypes. There's an eosinophilic endotype with eosinophilic inflammation. There's our protective endotype with a higher microbiome diversity and healthy airways, and there's an epithelial responsive endotype with reduced microbiome diversity but increased mucins.

So let's talk about the genetic diseases in bronchiectasis. There are three main known genetic diseases that are associated with bronchiectasis, including cystic fibrosis, which involves extrapulmonary involvement as well as pulmonary involvement. This is confirmed with sweat testing as well as genetic genotyping and can be treated with CFTR modulator therapy.

There's primary ciliary dyskinesia, which also has extrapulmonary involvement and is evaluated with ciliary ultrastructure and exhaled nasal nitric oxide. It's also confirmed with genetic testing, and there are new therapeutics for PCD.

Alpha-1 antitrypsin deficiency is associated with COPD, emphysema, bronchiectasis, and liver disease. Clinical liver disease develops in about 10% of patients, and plasma-derived alpha-1 antitrypsin has demonstrated benefit in emphysema. Currently, there are new therapeutics under development for alpha-1 antitrypsin deficiency.

The diagnostic evaluation for bronchiectasis. So you confirm diagnosis with a high-res CT. The basic workup includes pulmonary function tests, or PFTs, laboratory testing including CBC differential, neutrophilic versus eosinophilic inflammation, immunoglobulins, IgG, IgM, IgA, IgE, IgG subclasses, sputum culture, bacterial, mycobacterial, and fungal. Alpha-1 antitrypsin is another test.

There's also targeted testing, including ABPA testing, IgE, Aspergillus eosinophils, cystic fibrosis, including sweat test or CFTR genetics, PCD, nasal nitric oxide, ciliary biopsy and genetics, an autoimmune panel, including ANA, rheumatoid factor, and ANCA, a gastrointestinal evaluation if aspiration or reflux is suspected, and induced sputum collection for those who do not produce, or for looking for mycobacterial infection.

The targeted assessment for patients with bronchiectasis really depends on how they're presenting. So, if you have upper-lobe predominant bronchiectasis or early-onset disease with chronic sinusitis and Pseudomonas and Staphylococcus aureus infection, you can test for cystic fibrosis or CFTR-related disease.

If you tend to have middle-lobe predominant bronchiectasis or history of neonatal respiratory distress, chronic rhinosinusitis, or situs inversus or wet coughs in childhood, along with male infertility. That would be for testing for PCD.

If you have localized bronchiectasis with a high-resolution CT suggesting NTM or obstructive bronchiectasis, you can test for NTM-related disease with like a bronchoscopy or induced sputums.

But if you have systemic symptoms such as skin changes or fatigue, coexisting autoimmune disease, or signs of systemic vasculitis,

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that would be testing for autoimmune diseases, including ANA, rheumatoid factor, ANCA, anti-CCP antibodies, ENA, and referral to a rheumatologist.

If you have coexisting basal-predominant emphysema, or early-onset COPD, and/or unexplained liver disease, and a family history of COPD or liver disease at a young age, that would be a good sign to test for alpha-1 antitrypsin deficiency with an alpha-1 antitrypsin level, and potentially phenotyping and genotyping of the alpha-1 antitrypsin.

If you recur in severe respiratory and/or extrapulmonary infections, an onset in childhood or early adulthood, diffuse bilateral bronchiectasis, especially in the lower lobes, use of immunosuppressant medications or hematologic malignancies, that'd be a good time to test for immunodeficiency, like specific antibody responses to pneumococcal tetanus vaccines or IgG subclasses and referral to an immunologist.

These are some features seen on bronchiectasis on imaging on chest x-ray. You can see some cystic changes or tram-track opacities. In these high-resolution CTs, you can see cystic areas, areas of airway thickening, some tree-in-bud nodularity and mucus plugging, and some cylindrical bronchiectasis.

Key tips and strategies for diagnosis: Consider bronchiectasis when treatment for other obstructive diseases fail, for example, with asthma, or a diagnosis doesn't fit, like COPD without smoking. Chest x-ray is insufficient for diagnosis, and high-resolution CT is always needed. Think of bronchiectasis as the third obstructive disease. Always review primary imaging; reports may miss the finding, and a history of recurrent cough and bronchitis should trigger a CT scan. Recurrent cough requires frequent empiric antibiotics prescribing for bronchiectasis or sinusitis would be something to trigger.

There are multiple tools for risk stratification for bronchiectasis, including the Bronchiectasis Severity Index and the FACED scale. The BSI predicts the risk of future mortality, hospitalization, exacerbations, and quality of life, with the scoring from 0 to over 8, with 0 to 4 being mild, 5 to 8 being moderate, and greater than 8 being severe. The FACED scale predicts a 5-year mortality, with scoring of 0 to 2 being mild, 3 to 4 being moderate, and 5 to 7 severe.

Now, if you look at the chart, you can see that these are based on different scoring metrics, with age being part of it, the FEV1, the dyspnea score, the radiological severity, and the FACED variable you can look at chronic colonization by Pseudomonas. It gives you different point values that we've put into this score.

Here are the section takeaways. Key symptoms of bronchiectasis include chronic cough and recurrent chronic airway infections. Bronchiectasis is diagnosed by high-res CT. Lab assessments for bronchiectasis often include routine and expanded testing, and testing is focused on identifying underlying endotypes to help provide targeted treatments.

And now I'd like to pass it along to my colleague, Dr. Losier, who will tell us more about the role of neutrophilic inflammation and the impact of pulmonary exacerbations.

Dr. Losier:
When we think about the role of inflammation in bronchiectasis, we have to think about different inflammatory cell mediators. In bronchiectasis, the neutrophil is one of the key components of inflammatory processes, and in neutrophilic inflammation, it is typically associated with more severe disease, lower FeNO, or fractional exhalation of nitric oxide, weaker bronchodilator responses, and higher levels of IL-8. In eosinophilic inflammation, which is typically less common, it has been associated with less severe disease, higher FeNO, stronger bronchodilator response, and higher levels of IL-13. When we think about the interleukins, typically IL-8 levels are correlated with exacerbation frequency, and IL-13 levels are correlated with bronchodilator response.

When we look at neutrophils and bronchiectasis, we know that the predominant inflammatory mediator of bronchiectatic airways is driven by neutrophils. Neutrophil numbers and markers of activation correlate with bacterial load, and higher neutrophil levels tend to correlate with higher rates of exacerbations. In this table here that we're looking at, neutrophilic inflammation was compared in a control group and a group with bronchiectasis, where they looked at the bronchoalveolar lavage fluid. And when we see the total percentages of neutrophils, we can see that in the bronchiectatic patients there were higher levels of neutrophils in the BAL fluid and higher levels of elastase as well when they compare it back to the control group.

So when we think about neutrophilic inflammation, we have to wonder what particular in this cascade is a potential target that might be driving some of the inflammation. So DPP-1, or dipeptidyl peptidase 1, activates neutrophil serine proteases, or NSPs, and NSPs that get activated are typically neutrophil elastase, proteinase 3, or cathepsin G. And these neutrophil serine proteases help in degrading extracellular matrix components and disrupting epithelial barrier integrity, leading to some of the progression of bronchiectasis or bronchiectatic airways.

So neutrophil serine proteases and their products contribute to the vicious vortex, which is commonly referred to as one of the main

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pathophysiology models of bronchiectasis and its progression. NSPs tend to contribute to mucus hypersecretion, which ultimately results in impaired mucociliary clearance within the vortex. They contribute to the structural lung destruction caused by the cleavage of SLPI and elafin and degradation of elastin and collagen through the activation of MMPs, or matrix metalloproteases. They also contribute to the elevated release of pro-inflammatory cytokines that contribute towards chronic infection and chronic inflammation within the airways.

Within bronchiectasis, one of the key findings that we need to focus on is defining a bronchiectasis exacerbation, as many of our treatment goals are surrounding prevention of exacerbations. So first, we must define what is the definition of a bronchiectasis exacerbation. From a patient-focused definition, this typically is from a change in respiratory symptoms that are significant enough for them to seek care either at their primary provider, their pulmonary provider, or urgent care. They may be following with novel, patient-focused exacerbation diaries; can be subjective, but largely the symptom changes can be subtle and hard to recognize.

The clinical trial definition for bronchiectasis exacerbation is considered to be a deterioration of three or more of these key symptoms for at least 48 hours, and that's typically including cough, sputum volume or consistency, sputum purulence or color, breathlessness and/or exercise intolerance, fatigue and malaise, hemoptysis, and largely this requires a physician agreement that constitute an exacerbation such that a treatment change is needed, and this is most often with antibiotics. And typically, frequent exacerbations are associated with poorer quality of life scores.

So I already mentioned that bronchiectasis exacerbations are a frequent area of focus. Frequent exacerbations are associated with poorer outcomes in bronchiectasis patients. So, in a 5-year follow-up of hospitalization and survival rates, stratified by number of exacerbations per year at baseline, we can see that those with more frequent exacerbations have a higher percentage of hospitalization during follow-up, such that those who had greater than or equal to three exacerbations had about greater than 40% risk of hospitalization during the year of follow-up. Additionally, those with frequent exacerbations tend to have a lower percentage of survival on follow-up. And then when we look at 5-year follow-up, those with three or more exacerbations had a survival rate around 80% when they were compared back to those with zero or one being greater than 90%.

So, a model of the bronchiectasis pathophysiology is really focused on the vicious vortex, and our management strategies really are centered around trying to treat or disrupt this vicious vortex. So this is from one of our recent guidelines that were updated in the ERS. So when we think about the vicious vortex, we try to treat at different levels, including the inflammation, the chronic infection, the impairment of mucociliary clearance, and lung damage. So, particularly when we think about inflammation, we often will focus in on potential anti-inflammatory modalities that are available. If we think about chronic infection, then we're often looking to see if there's any role for potential long-term antibiotic therapy. When we think about impaired mucociliary clearance, we're looking to see about potential mucoactive drugs or airway clearance, and then for lung damage or shortness of breath related to the lung damage, we're looking to consider things like pulmonary rehabilitation.

And over time, our treatment strategies have evolved, knowing that we really do need to disrupt multiple areas of the vicious vortex, and trying to really focus in on what are the potential driving factors for inflammation. And treatment strategies have really started to become more personalized or targeted by the bronchiectatic endotype. So in this part, we consider treatment of the underlying endotypes, such as neutrophilic inflammation, and targeting the neutrophil. Whereas the levels can be aberrantly high in bronchiectatic patients, and so ultimately we're trying to minimize the effects or the impacts that neutrophilic inflammation can have, and trying to try some of the targeted treatments at inhibiting some of the neutrophil function, such as NETosis or the neutrophil serine proteases that we already reviewed.

Then, when we look at mucosal abnormalities, areas where we have ciliary dysfunction or mucus hypersecretion, a lot of our treatment is really focused on trying to help with mucociliary clearance, which is where some of the mucolytic agents or mucoactive agents come into play in airway clearance.

When we think about chronic infection, we are trying to disrupt some of the bacterial burden that might be present, and that can come from kind of multiple modalities, whether it's through mucus clearance or potentially bacterial, killing the actual pathogens that are in the airway with antimicrobials. For autoimmune endotypes, we're trying to focus at the level of the inflammation to prevent tissue damage. Treatment is largely going to be dependent on treating the underlying disorder at hand, and then for eosinophilic endotypes, we have T-helper cells that are the predominant immune reaction, and from that is like we often have kind of an allergic component or eosinophilic component, and treatment is really based at trying to control the T-helper cell-mediated inflammation.

The cornerstone of treatment for all bronchiectasis patients is largely centered around airway clearance. When we think about trouble in mucociliary clearance, we can see that mucus plugging leads to local tissue hypoxia, decreased ion channel function, and bacterial infection and overgrowth. So, airway clearance strategies promote mucus clearance via mechanical stress and hydration, and these strategies reduce cough, they improve quality of life, and reduce exacerbations.

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Although we must be aware that there is no data currently that exists for the optimum frequency or duration or the ideal modality that each bronchiectasis patient should use, and for that, it really comes down to each patient and developing an individualized type of airway clearance routine that they are able to adhere to.

Potential strategies for airway clearance include device-mediated strategies such as positive expiratory pressure devices, or oscillating positive expiratory pressure devices, or PEP devices, or high-frequency chest wall oscillation, which is commonly referred to as the vest. There are also modalities that do not require any devices, such as active cycle breathing techniques, forced expiratory techniques, manual percussion or vibration, autogenic drainage, and postural drainage is another modality as well.

As an overview of the pharmacologic treatment strategies, we should know that there is no one treatment for bronchiectasis, but there are several that we rely on, including several pharmacologic and non-pharmacologic treatments. So, first, if we think of the different modalities or mechanisms of action of potential therapies that we use, we think about bronchodilators, as oftentimes, these tend to be quite responsive in patients with bronchiectasis overlap syndromes, and we can see that a bronchodilator may actually help increase FEV1.

If we think about mucoactive drugs, these can include isotonic saline or humidification that can help with sputum clearance. If we think about hypertonic saline, this can help improve quality of life and also augment sputum clearance. There's inhaled dry powder mannitol, which can help with sputum clearance, potentially decreasing antibiotic use, improving quality of life, and improving the time or increasing the time to next exacerbation. And then, if we think about NAC, or N-acetylcysteine, the exacerbation risk has been suggested to be decreased as well.

For inhaled antibiotics—and these are commonly nebulized antibiotics, but can also be in an inhaler form as well—there is some evidence to suggest a reduction in bacterial load, improvements in quality of life and exercise capacity, and decreased exacerbation frequency.

And then for our anti-inflammatory agents, we have inhalers or inhaled corticosteroids, which have particular benefits in eosinophilic bronchiectasis. We have long-term macrolides, which can improve quality of life and increase time to next exacerbation. We have brensocatib as a dipeptidyl peptidase 1 inhibitor, and then there's additional therapies that are ongoing in clinical trials.

And the route of administration of these agents is important to consider when guiding patients who are on multimodal therapy. Common sequences that are suggested in the airway clearance regimens include first using a short-acting bronchodilator, followed by a mucolytic or mucoactive agent, and then third in the sequence would be to start using their airway clearance techniques to help them with the mechanical or shearing forces of the mucus, then followed by the inhaled antibiotics and then the inhaled corticosteroids.

So when we're thinking about some of the pharmacologic strategies for management of bronchiectasis, we have to look through and consider some of the adverse effects that might be associated with these medications. So first, when we're considering bronchodilator agents such as short-acting beta agonists, some of the common adverse effects that can occur with them typically include tremor or palpitations or jitteriness that can occur with the beta agonist component of the medication. The serious adverse events that can occur with this largely are related to arrhythmias, given the potential increased risk of tachycardia or tachyarrhythmias with these agents, and they really should be used with caution in patients who have potential for cardiac arrhythmias as well.

Next, when we consider mucoactive agents such as nebulized hypertonic saline, some of the potential common adverse effects that can happen are bronchospasm, cough, throat irritation, or dysphonia. The serious adverse events with these can be related to bronchospasm and potentially having trouble tolerating them. And then, as for important safety considerations, these are generally considered relatively safe in most of our patient populations, but in those who have significant airway hyperreactivity, we may need to consider additional caution in these patient populations.

For inhaled antibiotics, common side effects that can occur with them are additionally cough, chest tightness, and bronchospasm, and then sometimes dysphonia, depending on the antibiotic type. The serious adverse events can come from potential ototoxicity or nephrotoxicity that might be associated with them, or potentially the development of resistant organisms through long-term exposure to antibiotics. So, for important safety considerations, largely we have to consider whether or not the patient has underlying comorbidities such as kidney insufficiency or potential hearing insufficiency as well before starting patients on these long-term antibiotic regimens, and also as a review with the patients the potential risk for antibiotic resistance and what implications this might have.

So then, for our anti-inflammatory agents, we discussed how there's the use of inhaled corticosteroids, long-term macrolides, and brensocatib. For the common adverse events in inhaled corticosteroids, this is often including thrush, hoarseness of the voice, or potentially throat irritation. The serious adverse events that are associated with inhaled corticosteroids tend to be an increase in pneumonia risk or as other chronic infections, and then the potential systemic steroid effects with higher exposures. Particular safety

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concerns in bronchiectasis patients is really to use this selectively. You're really trying to balance benefit against infection risk and try to find the appropriate patient population.

For long-term macrolides, the common adverse events include GI upset and potentially some taste disturbances. The serious adverse events really are surrounding QT prolongation, which could potentially cause arrhythmias, hearing loss, rash, and antibiotic resistance as well. Special considerations for chronic macrolide include monitoring QTc intervals and considering EKG monitoring, and also monitoring for ototoxicity and doing intermittent hearing testing. And then, of particular note, in bronchiectasis patients, checking for drug-drug interactions and watching for antimicrobial resistance, particularly NTM, and monitoring for presence of NTM.

And then the last anti-inflammatory agent for approved therapies and pharmacologic adverse side effects to watch for is brensocatib. And so, side effects that are commonly reported in brensocatib include rash or dry skin, hyperkeratosis, gingival or dental concerns, headache, and upper respiratory tract infection symptoms. The serious adverse events are largely related to dental or gingival complications, elevated liver enzymes, possible skin cancer signals, and severe infection events reported in trials. And then, for important safety considerations, monitoring the skin, oral, and dental health with routine dental visits, and monitoring laboratory abnormalities.

When we are optimizing management of bronchiectasis patients, we must consider the frequency of their exacerbations to help determine their next steps in treatment strategies. So, typically, a 12-month re-evaluation is suggested. However, earlier reassessment is considered if needed, and this is specifically in the case of adverse events or clinical deterioration. So, patients who are at risk of future exacerbations include those who have experienced greater than two exacerbations per year, or one exacerbation per year plus severe symptoms, or those who have had greater than one severe exacerbation requiring hospitalization in the prior year.

When we consider the algorithm of what agents to use for those who have frequent exacerbations, we must first look at their underlying bronchiectasis management and trying to optimize all different strategies, particularly optimizing airway clearance, treating underlying etiologies or comorbidities, and making sure that they are staying up to date with vaccinations so that they can help prevent them from future infections.

Once that is done, if we identify the patient is still at increased risk of future exacerbation, we start to look to see if they have any signs of chronic Pseudomonas aeruginosa airway infection. If yes, then we might be considering potential long-term macrolides or long-term inhaled antibiotics. If we start one of these agents, then we should be looking to see if the patient has responded to treatment in the following year. If they are continuing to have frequent exacerbations, then we should be looking to see if we need to switch their treatment.

If we go back to the algorithm, thinking if a patient has had chronic Pseudomonas airway infection, if they do not have airway infection with Pseudomonas, then we might consider potentially using long-term macrolides as a first line, given that many of our long-term inhaled antibiotics are targeted at Pseudomonas. If we start a long-term macrolide, then again we should be reassessing by at least 12 months to see if a patient has had clinical response. If they have had response, then we should continue with treatment. If not, then we need to consider alternative agents.

It should be noted that many of our current guidelines have come out prior to the approval of brensocatib, which is another potential therapeutic agent for frequent exacerbator phenotypes, and we will review that later in today's slides.

So, section takeaways include neutrophilic inflammation is known for playing a key role in bronchiectasis. Neutrophil serine proteases have been identified as a therapeutic target for treating bronchiectasis. Bronchiectasis treatments are centered around preventing exacerbations, which are associated with disease progression. And targeted treatments require a multimodal approach to interrupt the vicious vortex.

And now I will hand it back to Dr. Brenner to talk about exciting clinical trial data.

Dr. Brenner:
So next, we're going to examine clinical trial data with novel therapeutic agents. Recently, there's been approved therapy for bronchiectasis, brensocatib. Brensocatib is a small molecule inhibitor of DPP-1. DPP-1 activates NSPs during neutrophil maturation, and brensocatib reduces neutrophil-driven inflammation, leading to lower levels of neutrophil elastase and other proteases. This leads to lung function improvement measured by FEV1, reduction in pulmonary exacerbations, and improved respiratory symptoms.

This new drug was approved in August of 2025 to treat non-CF bronchiectasis in patients over 12 years old. Brensocatib was approved using the ASPEN clinical trial. The clinical trial was a phase 3 international, double-blind, randomized, and placebo-controlled trial for adults and adolescents with bronchiectasis to evaluate the efficacy and safety of once-daily 10 mg or 25 mg of brensocatib added to existing clinical management. The inclusion/exclusion criteria included non-CF bronchiectasis, included patients with greater than two

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pulmonary exacerbations that required antibiotics, and excluded those with COPD, asthma, CF, or those being treated for NTM.

The key result was that treatment with brensocatib led to lower annualized rate of exacerbations than placebo in patients with bronchiectasis, and the lung function decline was less in the 25-mg dose than the placebo. So the mean FEV1 decline was 50 in the 10-mg dose, 24 in the 25-mg dose, and 62 in the placebo doses, and this is all in milliliters. Overall, this drug was generally well tolerated, and the safety profile was comparable to the placebo.

The FEV1 endpoints for ASPEN trials were exacerbations over 52 weeks, as you can see in the graphs here. The brensocatib 10- and 25-mg doses decreased exacerbations, as well as looking at the change in post-bronchodilator FEV1 from baseline. The brensocatib 25-mg dose in the dark blue had a lower decrease in FEV1 than the 10-mg dose and placebo.

The safety summary is shown here. I would like to draw your attention to the adverse events resulting in death. In the 10-mg dose, which had three, aspergillus infection, acute respiratory failure, and bronchiectasis were the causes of death. In 25-mg dose, there were four deaths from pneumonia, myocardial infarction, general physical health deterioration, and road traffic accident. And in the placebo, there were seven deaths with pneumonia, acute respiratory failure, bronchiectasis, hemoptysis, cardiac arrest, and cardiorespiratory arrest, and cerebrovascular fracture. Additionally, there were some side effects, including hyperkeratosis, periodontitis, or gingivitis, that were increased in the brensocatib groups versus placebo.

There are multiple bronchiectasis therapies that are currently undergoing investigation, including anti-interleukin-33 monoclonal antibody, a PDE3 and PDE4 inhibitor, which has been approved for COPD, and then a few more DPP-1 inhibitors are also being currently investigated. And these work on multiple different pathways, including chemotaxis inhibition, direct neutrophil elastase inhibition, like the DPP-1s, and the Cat C inhibition.

The mechanism of action of itepekimab inhibits IL-33 from activating the downstream inflammatory cascade through its receptor ST2, IL1RL1, and reduces inflammation from the immune cell recruitment to the damaged tissues. It's currently in phase 2 clinical trials for non-CF bronchiectasis, and you can see how it acts through this pathway in the diagram to the right, which leads to decreased airway inflammation, remodeling, and lung damage.

The mechanism of action for ensifentrine is for PDE3 and PDE4 inhibition. In bronchial epithelia, it combines enhanced effects on the inflammation, bronchodilation, mucociliary clearance, and it's approved already for maintenance treatment of COPD in adults. It's currently in phase 2 clinical trials for non-CF bronchiectasis, and thus by inhibiting PDE3 and PDE4, it acts upon the airway smooth muscle, leading to increased bronchial relaxation; on inflammatory cells, leading to decreased cell activation, migration, and proliferation and survival; and bronchial epithelial cells by increasing CFTR activation and ciliary function. Thus, it leads to bronchodilation, anti-inflammatory effects, and mucociliary clearance.

The overview of verducatib, a DPP-1 inhibitor. It's a clinical trial with a phase 3, which is called the AIRIVITY study. It's an international, randomized, double-blind, placebo-controlled study to assess the efficacy, safety, and tolerability of the drug. The study design is participants will be randomized to receive either 2.5 mg of drug or placebo administered once daily for up to 76 weeks. And key inclusion, which is notable for this, is that the CF or non-CF bronchiectasis, and you have to have pulmonary exacerbations requiring antibiotic treatments. And the primary outcome measure was annualized rate of pulmonary exacerbations.

Another trial that's undergoing evaluation is for HSK 31858, another DPP-1 inhibitor. It's a phase 3, it’s international, randomized, and double-blind, placebo-controlled multicenter study to assess the efficacy and safety in non-CF bronchiectasis. The participants were randomized to receive either drug or placebo for 52 weeks, and the primary outcome measure is frequency of pulmonary exacerbations.

The section takeaway is brensocatib is the first FDA-approved medication for bronchiectasis. It reduces neutrophil-driven inflammation by inhibiting DPP-1. Additional therapeutics targeting neutrophilic inflammation are in development, and endotypes may help guide anti-inflammatory therapy with other treatment modalities in developing targeting alternative pathways.

So I'll pass it on back to Dr. Losier for the final part of this presentation.

Dr. Losier:
Okay. So now we're going to switch gears and try to consolidate some of the knowledge points that we just touched upon and apply it to a patient case review and implementing a multimodal treatment approach to improve patient outcomes.

So let's begin with this case. Meet Darlene. She is a patient who has a high-resolution CT chest confirming bronchiectasis. She is a 59-year-old woman who presents with chronic productive cough greater than 12 months, frequent bronchitis episodes requiring antibiotic treatment, intermittent hemoptysis, and exertional dyspnea. Her BMI is 21.5. On examination, her physical exam is notable for inspiratory wheezes. She has sputum cultures that grew Pseudomonas aeruginosa, and she's had one positive culture for NTM. Her high-resolution CT chest showed dilated, thick-walled bronchi, and she had spirometry that was demonstrating an FEV1 of 62%

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predicted.

So often, when we see these patients, some of our first treatment questions is: Has she been started on airway clearance? And whether or not, if she has, has it been optimized? And has she potentially had any instruction from respiratory therapy for formal teaching?

When we see Darlene in clinic, one of the first questions that we have that comes to mind is: How severe is Darlene's case? So part of this workup to try to help determine the severity of her illness might include what additional tests we need to confirm the bronchiectasis and identify its etiology. So, some of the initial panel for evaluation might include a CBC with differential, blood testing to measure total levels of IgG, IgA, IgM, and IgE, and potentially including the subclasses of IgG, to repeat or review sputum cultures for bacteria, mycobacteria, and fungi, as we already noted, she had Pseudomonas and she had one positive culture for NTM, and then to screen for comorbidities, including connective tissue disorders, inflammatory bowel disease, immunodeficiencies, and other potential airways conditions such as asthma or COPD.

When determining how severe Darlene's case is, we start looking at the scoring indices, including the BSI, or Bronchiectasis Severity Index, or the E-FACED score. So for Darlene, we saw that she had an FEV1 of 62% predicted. Her age was 59. She has daily symptoms. She has chronic Pseudomonas and frequent exacerbations, which places her by the BSI at moderate to severe risk, likely a score of 5 to 8, which kind of places her in that moderate to severe range. And with that, we start stratifying her risk and prognostication into high risk for future exacerbations and mortality, which warrants intensive multidisciplinary and multimodal treatment.

So, how to manage Darlene? So, first off, if we're thinking about airway clearance as one of the main cornerstones for bronchiectasis management, we must look to try to figure out what is the best approach for airway clearance for this individual. So, airway clearance is considered the standard of care for bronchiectasis, and all patients should be taught techniques by a trained respiratory therapist and individuals who are very familiar with all the airway clearance techniques.

As we have previously mentioned, there are many different options for airway clearance. So there's device-dependent and non-device-dependent, including active cycle breathing techniques, oscillatory PEP devices, or high-frequency chest wall oscillation. And what we see in having this formal education session is that supervised instruction improves efficacy and adherence, and re-education should be documented and reviewed after every exacerbation.

What is the expected trajectory of lung function, and how often should spirometry and imaging be repeated in a patient such as Darlene? So, where Darlene has underlying lung dysfunction and bronchiectasis, typically annual spirometry is recommended. The frequency of which should be increased if you have more symptoms, frequent exacerbations, or accelerated decline. For sputum surveillance, repeat sputum cultures are typically recommended every 3 to 6 months, and at each exacerbation. Though it should be noted that official guidelines do not set official frequencies on these surveillance. And then a repeat high-resolution CT chest should be considered if clinical deterioration or substantial changes in symptoms are noticed.

In patients who have exacerbations and in bronchiectasis patients in general, we might consider creating an action plan for them. And so, what might be included in Darlene's action plan? So, airway clearance typically a minimum of once or twice daily, and the technique should be individualized and confirmed by a trained physiotherapist. For an action plan, patients should be educated on the symptoms so that prompt antibiotics may be tailored and provided for the exacerbation and really guided by the sputum cultures that are available, long-term macrolide or inhaled antibiotic therapy for chronic Pseudomonas and frequent exacerbations should be considered if they are following routinely in clinic to be able to be assessed for these therapies, and then inhaled bronchodilators as needed for airway obstruction.

Given her moderate disease severity, chronic Pseudomonas infection, and frequent exacerbations, Darlene may be an appropriate candidate for brensocatib. Enhancing Darlene's quality of life—some of the additional support that may enhance Darlene's quality of life could include individualized care, such as a referral to a respiratory physiotherapist, mental health providers, including psychologists or counselors, dietitian, social work, respiratory nursing, and patient support groups. Many of these strategies can help support mental health and facilitate self-management strategies as well.

So as we mentioned, Darlene may be an appropriate candidate for brensocatib, and to initiate the treatment for her, her airway clearance remains a standard of care. So she should continue with that regardless. And in her, brensocatib 25 mg orally once daily was added to her treatment regimen.

Over the next 6 to 12 months, Darlene reported fewer bronchiectasis exacerbations and a reduced need for antibiotic courses. She did develop mild, dry skin and an intermittent rash early in treatment, which were managed conservatively and without discontinuation of the medicine. No serious adverse events occurred, and she did not develop clinically significant gingival complications or hypertension. Her FEV1 remained stable at 63% of predicted, and she had no clinically meaningful decline in her spirometry.

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So, important domains to consider in the treatment of Darlene are focusing on her exacerbations, her FEV1 decline, her symptoms, and safety profiles when we're considering the dosing of brensocatib. Current doses that are available for brensocatib include the 10-mg dose and the 25-mg dose. And when we review the differences between the doses, the main factor came at the FEV1 decline, where the 25-mg dose had better lung function preservation. Additionally, under the symptom domain, the 25-mg dose had better symptom relief, and then under the safety domain, the 10-mg dose may be used if toxicity or if there's side effects that are limited at the 25-mg dose.

Key takeaways: Early diagnosis is important, and clinicians should consider bronchiectasis in patients with chronic cough and recurrent chest infections. Airway clearance is key and foundational. Airway clearance comes in many shapes and sizes, and consistency is key. Airway clearance needs to be discussed with patients, revisited at each encounter, and possibly logged or tracked for adherence. Early identification of exacerbations can lead to better patient outcomes.

Thank you, everyone, for listening to this session today on bronchiectasis.

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