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Cole's Vicious Cycle & Vortex: Key Mechanisms of Bronchiectasis

### Announcer:

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### Dr. Basavaraj:

Welcome to *Deep Breaths: Updates From CHEST* on ReachMD. I'm Dr. Ashwin Basavaraj, Assistant Professor of Medicine at NYU Grossman School of Medicine and Associate Director of our Bronchiectasis and NTM Program here. Joining me today is Dr. Christopher Lippincott, an Assistant Professor of Medicine at the Johns Hopkins University School of Medicine and Clinical Director for Nontuberculous Mycobacterial and Bronchiectasis Care. Today, we'll be exploring the pathophysiology and diagnostic evaluation of bronchiectasis.

Dr. Lippincott, welcome to the program.

### Dr. Lippincott:

Thanks so much, Dr. Basavaraj. It's a pleasure to be here with you today.

### Dr. Basavaraj:

Great. So, start us off, Dr. Lippincott, can you give us some background on the pathophysiology of bronchiectasis?

### Dr. Lippincott:

Sure. So, bronchiectasis is a syndrome where you have an interconnected cascade of airway dysfunction, dysregulated airway inflammation, infection, and structural damage to the lungs.<sup>1,2</sup> It's a heterogeneous disorder, and it's still not fully understood, but a wide range of conditions can cause bronchiectasis,<sup>1,3</sup> including hereditary or congenital diseases like cystic fibrosis, autoimmune diseases such as rheumatoid arthritis or lupus, and infections, which may or may not be related to an underlying immunodeficiency, such as common variable immunodeficiency disorder.<sup>1-3</sup> The end result of this process is irreversible lung injury, which manifests in patients as a variety of chronic symptoms, including a productive cough, as well as recurrent exacerbations and worsening of their chronic symptoms.<sup>4</sup>

### Dr. Basavaraj:

So, Dr. Lippincott, how has our understanding of this evolved with the Cole's vicious cycle hypothesis? You mentioned the four components of the vicious cycle, but how has that thought process evolved into other models that we may think about clinically?

### Dr. Lippincott:

Sure. So, well, first, why don't I sort of go into a little bit more detail on Cole's vicious cycle. So, the hypothesis proposes that it's an environmental insult, and this could be in the background of some genetic susceptibility or a host defense deficiency that causes some progressive bronchial wall destruction or dilatation.<sup>2</sup> This then leads to the impairment of mucociliary clearance and leads to a buildup of secretions in the lungs, which is essentially a breeding ground for bacterial infections.<sup>2</sup> This then leads to susceptibility to chronic infections or just colonization, and it's that chronic infection or colonization that can then lead to a dysregulated inflammatory response of both neutrophils and cytokines among other pathways.<sup>2</sup> So, once this all starts happening, it continues to perpetuate itself.<sup>2</sup> So, the inflammatory response leads to further bronchial wall destruction, and then it rinses and repeats.<sup>2</sup> So, interrupting this cycle is really critical to the management of patients with bronchiectasis, and it can occur in a variety of ways throughout this cascade.<sup>2</sup> So, for example, that may include improving airway clearance of sputum. So, if increased secretions in the lungs are leading to worsening infections, then getting that out of your lungs will start the process of interrupting this. We obviously give antibiotics for infection, which can be important, and then there's evolving ways of downregulating that inflammatory response.<sup>3</sup> So, you target three of these sort of

four components there, and then by doing that, you interrupt the fourth component, which is progressive lung injury.<sup>4</sup>

**Dr. Basavaraj:**

Exactly, and you mentioned inflammation as a key component of the vicious cycle and the vicious vortex.<sup>1</sup> What kinds of roles does inflammation have? And what are the different types of inflammation that may be present in patients with bronchiectasis?

**Dr. Lippincott:**

Sure. So, there are a lot of different types of inflammation in general, probably too long for this podcast, so I'll just briefly touch on a few types that are specific to bronchiectasis and related lung diseases. So, a critical component of most inflammatory responses are white blood cells, and there's obviously a few important white blood cells that we think about here, specifically neutrophils and eosinophils, and different white blood cells lead to different types of inflammation.<sup>1</sup> So, for example, bronchiectasis is classically thought of as a neutrophilic inflammatory disorder, though as with most things in medicine, there's some overlap.<sup>1</sup> Neutrophils are some of the first immune cells that become activated in response to an infection, and in bronchiectasis, it's thought that colonization with bacteria rather than overt infection is often the trigger for neutrophils migrating to the lungs, which further worsens the inflammatory response and can lead to further lung destruction.<sup>1</sup> Additionally in bronchiectasis, there's some data that suggest that neutrophils may have reduced functional properties, like defective phagocytosis or consumption of pathogens, and there's also lower numbers of macrophages present in the lungs, which are critical in clearing neutrophils.<sup>1</sup> Taken together, this dysregulated inflammatory response likely further perpetuates neutrophilic inflammation in the setting of bacterial colonization that would otherwise only be expected in somebody who has infection.

Eosinophilic inflammation, by comparison, is a more common inflammatory pathway in patients with asthma as well as COPD.<sup>1</sup> With that said, there are a subset of patients with bronchiectasis who have a component of eosinophilic inflammation,<sup>1</sup> and we sometimes diagnose this either through an increase in eosinophils from a bronchoalveolar lavage specimen or an increase in peripheral eosinophils on a CBC, usually greater than about three to four percent.<sup>1,5</sup> In terms of, you know, what that looks like in a patient who's having a bronchiectasis exacerbation—so that's basically the clinical outcome of this inflammatory cycle that we've been discussing.<sup>4</sup> It's commonly defined as a deterioration in three or more symptoms within a 48-hour window, and those symptoms can include, for example, cough, sputum volume or consistency, sputum purulence, breathlessness or exercise intolerance, fatigue, and malaise, as well as hemoptysis.<sup>4</sup>

**Dr. Basavaraj:**

So, for those just tuning in, you're listening to *Deep Breaths: Updates From CHEST*. I'm Dr. Ashwin Basavaraj, and I'm speaking with Dr. Christopher Lippincott about the clinical mechanisms behind bronchiectasis.

Dr. Lippincott, let's switch gears and focus on diagnosis of bronchiectasis for a bit. Are there any specific symptoms or clues that you look out for to identify if the patient has bronchiectasis?

**Dr. Lippincott:**

Absolutely. So, I guess we can start with the obvious clue, which is diagnosing bronchiectasis on imaging. We can see bronchiectasis on a chest x-ray. Most commonly, though, we diagnose it on a CT scan.<sup>6</sup> While patients are often diagnosed or suspected to have bronchiectasis based on a symptom or historic clue, it's not uncommon that a patient is asymptomatic and has imaging for unrelated reasons.<sup>2</sup> They have a CT of the abdomen and pelvis where we might find an abnormal finding at the lung bases that later prompts a chest CT, or they may be getting a cardiac CT calcium score, and that picks up bronchiectasis. So, we do often diagnose bronchiectasis the easy way, but there are a variety of symptoms that we watch out for. So, as we previously discussed, patients with bronchiectasis can have a wide range of symptoms, and they include chronic cough with or without sputum production, with or without hemoptysis.<sup>4,7</sup> They can have fatigue.<sup>4,7</sup> They can have shortness of breath, as well as other symptoms, like unintentional weight loss.<sup>4,7</sup> The historical clues that we look for in these patients are wide-ranging, and that can include a history that might suggest an underlying immunodeficiency, such as skin, lung, or sinus infections from a very early age. It may include gastrointestinal symptoms, such as dysphagia or gastroesophageal reflux, with the thought that this is leading to progressive lung injury that can set them up for future infections and set off the cascade that we were discussing earlier.<sup>8</sup> Other patients have not necessarily sinus infections, but sinus symptoms or postnasal drip that can subsequently predispose to infections and bronchiectasis.<sup>9</sup> So, there's a lot of symptomatic, historical, and radiographic clues that ultimately lead to the diagnosis.

**Dr. Basavaraj:**

So, after a patient is diagnosed with bronchiectasis, where can you refer them to learn more about it?

**Dr. Lippincott:**

Yes, that's a great question. So, it's important to talk about who manages patients with bronchiectasis. As we're talking here, I think it's worth noting you're a pulmonologist by training. I'm an infectious diseases specialist. But we both manage these patients. So, historically, pulmonologists have been the backbone of managing patients with bronchiectasis, and I think that's probably still the case. However, increasingly we see providers adopting a multidisciplinary approach where a patient with bronchiectasis may be co-managed by a pulmonologist and an infectious diseases specialist, either within the same multidisciplinary practice or in separate practices, and in part, this is due to the significant overlap between bronchiectasis and the various infections that are commonly encountered in these patients.<sup>10</sup> Increasingly, we're seeing larger medical centers develop programs that specifically focus on the care and management of

patients with bronchiectasis and nontuberculous mycobacterial infections due to the overlap seen with these conditions.<sup>10</sup> In my experience, one of the advantages of such programs is that they commonly engage with other subspecialties that, as we noted earlier, are important in the care of patients with bronchiectasis, including chest radiologists; physical and respiratory therapists; gastroenterologists; ear, nose, and throat providers; as well as allergy and immunology specialists.<sup>10,11</sup>

**Dr. Basavaraj:**

Dr. Lippincott, what are a few of those resources that we can refer our patients to?

**Dr. Lippincott:**

Sure, that's a great question. So, in addition to finding a provider to manage bronchiectasis, there's several organizations involved in advocacy and outreach for patients with bronchiectasis. Some of these include the American Lung Association, the COPD Foundation, and NTMIR, which stands for NTM Information Research. These organizations commonly sponsor outreach activities and they provide patient resources for anybody who's interested in learning more about bronchiectasis, which includes both patients and providers, and they are also helpful resources in connecting a patient with a provider in their area.

**Dr. Basavaraj:**

Right. Yes, those are some great resources. You know, I have patients sometimes that come, you know, reading on the internet not knowing what to believe, so we want to direct them to some trusted resources. So, the ones that you mentioned are some great resources. I would also include the chestnet.org. That has some great information. I think also patients learn from their providers as well. You know, in terms of who's managing the bronchiectasis. It's an interdisciplinary approach in the management of these patients. You know, you're from infectious disease, I'm a pulmonologist, but we know that it involves potentially care from a gastroenterologist, from an ENT doctor, or a speech pathologist, you know, sometimes thoracic surgery if patients with localized bronchiectasis are not improving and they need a resection.<sup>6</sup> So, patients can definitely learn from all of these great resources but also from their providers as well.

Before we close, Dr. Lippincott, do you have any final thoughts that you'd like to share with our audience?

**Dr. Lippincott:**

Thanks so much, Ashwin. Well, it's just been a pleasure speaking with you today. There's a lot of important work to be done in bronchiectasis, but a lot of exciting things that are happening and progress that's being made.

**Dr. Basavaraj:**

Yes, it's great. So, with those considerations in mind, I want to thank my guest, Dr. Christopher Lippincott, for joining me to share insights on bronchiectasis. Dr. Lippincott, it was great speaking with you today. Thank you.

**Dr. Lippincott:**

Thank you very much.

**Announcer:**

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