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Managing Refractory Chronic Cough: Strategies for Accurate Diagnosis and Effective Care

Announcer:
You're listening to *Deep Breaths: Updates from CHEST* on ReachMD. This series is produced in partnership with the American College of Chest Physicians, and this episode is a non-promotional, non-CME educational program brought to you by CHEST in collaboration with GSK. And now, here's your host, Dr. Michael Ghobrial.

Dr. Ghobrial:
Welcome to *Deep Breaths: Updates from CHEST* on ReachMD. I'm Dr. Michael Ghobrial, Director of the Chronic Cough Clinic at Cleveland Clinic in Ohio. Here with me today to discuss the differential diagnosis and differentiation of refractory chronic cough, also known as RCC, are Drs. Anju Peters and Michael Blaiss.

Dr. Peters is part of the Division of Allergy and Immunology at Northwestern Medicine in Chicago, where she's a Professor of Medicine and the Associate Chief of Clinical Research and Practice Innovation. Dr. Peters, it's great to have you with us.

Dr. Peters:
Thank you very much, Michael. I'm delighted to be here.

Dr. Ghobrial:
Thank you. Also joining us is Dr. Blaiss, who is a Clinical Professor of Pediatrics at the Medical College of Georgia and an allergist at Good Samaritan Health Center of Gwinnett in Georgia. Dr. Blaiss, thanks for being here.

Dr. Blaiss:
Thank you. I appreciate being here and the opportunity to participate.

Dr. Ghobrial:
Starting off with you, Dr. Peters, what distinguishes a normal cough from chronic cough, and even more specifically, refractory chronic cough?

Dr. Peters:
Sure, Michael. So when we think of cough, often we think cough from an infection or cough from something like asthma—that's a symptom, and usually, cough is not the etiology. And when we think of refractory chronic cough, or what we often call RCC, it's a subset of chronic cough—chronic cough being defined as cough lasting greater than eight weeks. But in terms of refractory chronic cough, it's a cough that persists despite us using guideline-directed therapy. And there are different guidelines from Europe, the US, or the CHEST guidelines, and also from Britain.

Here, you treat all the underlying causes, you do a thorough investigation, and you do adequate treatment for known cough-related etiologies, and the cough persists. And this is a type of cough called refractory chronic cough, which we think has more a neuronal dysregulation, and it involves both the peripheral and central nervous system.

So that is what I think of as refractory chronic cough. And it sets apart from unexplained chronic cough, which I feel like suggests that there's no identifiable cause at all.

Dr. Ghobrial:
Iit's quite common in our practice How common do you see this as a problem that patients are dealing with?

Dr. Peters:
Unfortunately, a lot of healthcare practitioners and even the general public are not aware of it yet. We need to inform them.

Chronic cough is one of the most common reasons patients see their primary care doctors. Of this chronic cough, what percentage is refractory chronic cough is not exactly clear. And Michael, I'm not sure if you can suggest what percent; some people say 5 to 10 percent, some people say even higher. But our goal is people to be aware of this condition.

Dr. Ghobrial:
Yeah, 5 to 10 percent is exactly what most studies have shown to be the case. Thank you so much, Anju.

Turning to you now, Dr. Blaiss, what's the typical patient's journey like before reaching an RCC diagnosis? And how does it impact their quality of life?

Dr. Blaiss:
So Michael, what we know unfortunately is that patients that turn up with refractory chronic cough have an extremely long journey before they get diagnosed.

There's a very interesting study out of Kaiser Permanente in Southern California that was published in the *Journal of Allergy and Clinical Immunology: In Practice* a few years ago that looked at 565 adults who were diagnosed with chronic cough by either a pulmonologist or a gastroenterologist, allergist, or ENT. And they found that the average duration of the cough at the time, again, by the time they got diagnosed, was 8.6 years. So a very long journey. And what happens here is these patients go through multiple referrals and diagnostic delays.

So if we look at these patients, we can see that they really suffer physically, socially, and psychologically. So we see physical symptoms like dizziness and headaches, in women, stress urinary incontinence, sleep disturbance, and just exhaustion from the severe bouts of cough that they can have. And when we go further, we find how this is really affecting these patients socially. It interferes with their normal lifestyles. They can't go to social gatherings. They're concerned about going to the theater or movies because of having these bouts of cough. They have these speech interruptions, which makes it very difficult, especially for patients that have to use their voice for a living, like teachers. It makes it very hard for them to do their job.

And then we get into the real psychological problems that we see in these patients. They're extremely frustrated. They're embarrassed by their condition. They have great anxiety because they don't know what is leading to their underlying condition, and this then leads to depression.

So it really matters that we really do an extensive workup early in these patients—getting a detailed history and understanding what medications they've been on. And are they on something like an ACE inhibitor that could cause chronic cough? And again, in this evaluation, if we don't find anything acutely to begin with, we need to look at some of the more common things that can lead to cough in this patient population, like upper airway cough syndrome, asthma, non-asthmatic eosinophilic bronchitis, and gastroesophageal reflux disease.

So we really need to do an extensive workup and quickly so that these patients don't have this long journey as far as getting to a diagnosis of their condition.

Dr. Ghobrial:
Great. Yes, that's absolutely correct.

For those just joining us, this is *Deep Breaths: Updates from CHEST* on ReachMD. I'm Dr. Michael Ghobrial, and I'm speaking with Drs. Anju Peters and Michael Blaiss about how we can differentiate and diagnose refractory chronic cough.

So, Dr. Peters, if we zero in on strategies for diagnosing refractory chronic cough, can you tell us about some of the tools that clinicians often use to quantify patients' cough severity or its impact on them?

Dr. Peters:
Sure. So, Michael, there are actually quite a few tools available for us for diagnosing refractory chronic cough, or RCC. One of the biggest things, just as in any other medical condition, is getting a good history and figuring out what's been done. Many of these patients have seen multiple physicians and healthcare practitioners and have tried many different things. They often will describe their cough as a tickle in their throat, and even innocuous stimuli—change in temperature, talking, or laughing—can trigger their cough. And other things that I think are important are to exclude what we call red flag symptoms—for example, hemoptysis, fevers, or dyspnea with minimal exertion. So history is one of the biggest tools we have.

But in addition to history, there are other tools that are validated. There are questionnaires. There's one called LCQ, which is the

Leicester Cough Questionnaire, that helps guide you as to severity and different parts of someone's cough. The other thing that I often use in my clinic are Visual Analog Scales, where you could say on a scale of 0 to 10 or 0 to 100, how severe is the cough? That gives you a severity of how severe someone's cough is and how much, as Michael mentioned, it's impacting their quality of life. In terms of research tools, there are even cough counters you can use.

And then finally, most of us rely on guidelines. CHEST guidelines are used extensively. There are European guidelines. UpToDate is something that I often use. There are many different strategies we can use for diagnosing refractory chronic cough.

Dr. Ghobrial:
That's great. Yes. Thank you so much. I can't emphasize enough the idea of getting adequate and comprehensive history. These patients oftentimes need to feel validated and listened to, and oftentimes, they will tell you what their cough is like.

And Dr. Blaiss, once we suspect refractory chronic cough, how should we approach the differential diagnosis?

Dr. Blaiss:
So what's important to understand here is that the diagnosis of refractory chronic cough is really by exclusion. In other words, as Anju mentioned, we need to do a very detailed history to begin on the patient, looking for possible causes for their cough. She mentioned red flags, which, again, are conditions that can lead to severe underlying disease that could be causing the patient to have the cough.

And then we need to make sure that we rule out the most common causes of cough that we see in the immunocompetent person who has a normal chest x-ray. So things like upper airway cough syndrome—running the tests there, looking for sinus conditions, looking for either allergic or non-allergic rhinitis problems, and doing a full evaluation to make sure the patient doesn't have any evidence of asthma or non-asthmatic eosinophilic bronchitis.

Then, very importantly, is workup—and in many cases, empiric treatment—related to gastroesophageal reflux disease, which can definitely be a trigger of chronic cough in the patient.

So once we go through all of this extensive evaluation, and again, no etiology is found, or let's say we find some clues that the patient may have asthma, but we treat the asthma and the patient is still coughing, then we're talking about a patient where the symptoms are still there. So again, this is another example of refractory chronic cough.

And what we're starting to understand more is that these patients have evidence of a hypersensitivity cough reflex. So we're starting to understand more and more what may be going on there; it seems to be similar to what we see as far as neuropathic pain pathways. And there are many theories behind exactly what's going on here—whether whatever disease state started the cough, now the patient is left with some underlying chronic inflammation, which is triggering the cough; or there's some neuronal dysregulation, either peripherally related to receptors on the vagal afferents; or it could be central, as far as cortical, where we do not have the normal cough suppression areas of the cortex working normally.

And very importantly, as Dr. Peters mentioned, many times, we can get from the history that the patient is having symptoms of cough hypersensitivity. So we get those patients that have that urge to cough. They notice that tickle or irritation or a globus sensation in their throat.

She mentioned allotussia—or cough triggered by non-tussive stimuli—things like just talking, eating, or singing. And then we even may have hypertussia, where things that don't normally trigger a cough in a low level, like dust, smoke, or odors, trigger cough in these patients.

So again, to get to that diagnosis, it does take an extensive workup in this patient population.

Dr. Ghobrial:
Thank you. Yes, agreed. Extensive workup, extensive experience, and sensitive listening—and it's not just one visit that could take care of this.

Now, Dr. Peters, once we diagnose a patient with RCC, what are the available and emerging management options?

Dr. Peters:
So, Michael, I think this is actually very exciting because we have new treatment options in development. It's important to know that in the US, there are no FDA-approved agents specifically for refractory chronic cough.

One that's being studied is something called P2X3 antagonists, which inhibit the P2X3 receptor on the vagal afferent nerves. Other emerging therapies include drugs that modulate the TRP. There's one opioid agonist-antagonist that acts both centrally and peripherally as a kappa agonist and mu antagonist, or KAMA.

These are all emerging treatment options. What we currently have available, we use off-label. So we'll often use neuromodulators like gabapentin or even sometimes low-dose morphine, although we have to remember the side effects.

In addition, I also use behavioral therapy or speech-language interventions. These are all different things we try off-label to help this, unfortunately, chronic, vexing problem.

Dr. Ghobrial:
Great. Thank you. As we approach the end of our program today, I would like to ask each of you to share one key takeaway for clinicians who may encounter refractory chronic cough in their practice. Dr. Peters, I'll start with you.

Dr. Peters:
Sure. So, Michael, For many of us who are healthcare practitioners who take care of refractory chronic cough and chronic cough in general, there's a significant unmet need in both understanding and managing refractory chronic cough. There's a need for recognition of RCC as a disease by both healthcare providers as well as the general public, and that's a very important step. And once that happens and we have better treatment options, I'm hoping that we can treat this chronic, often very troublesome, really affecting quality of life, chronic medical problem.

Dr. Ghobrial:
Thanks, Dr. Peters. And how about you, Dr. Blaiss, what's your one takeaway?

Dr. Blaiss:
So I think it's extremely important that we're empathetic with all of these patients. When you see them for the first time, they come in and they're very frustrated. They're very agitated because many times they've already been to other physicians. They've had numerous tests done, and no one can help them or find the cause of their problem.

So we have to become their partner. We have to work with them and make sure that all the testing is done, and then work with them as far as the types of management we now have available, as far as helping these patients with refractory chronic cough.

Dr. Ghobrial:
As those key takeaways bring us to the end of today's program. I want to thank my guests, Dr. Anju Peters and Michael Blaiss, for joining me to break down the diagnosis of refractory chronic cough. Dr. Peters, Dr. Blaiss, it was great having you both on the program today.

Dr. Peters:
Thank you, Michael.

Dr. Ghobrial:
Thank you, Michael.

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