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Patient Case Studies on the Emerging Treatment Strategies for the Management of Chronic Cough

Announcer:
Welcome to CME on ReachMD. This activity, entitled Emerging Treatment Strategies for the Management of Patients with Chronic Cough - Cases is provided by The American Thoracic Society and AKH and is Supported by an educational grant from Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc.

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Dr. Garrison:
Hello, happy Saturday afternoon to everybody. Thank you for coming to this webinar on the management of patients with chronic cough. My name is Garth Garrison. I'm an Associate Professor of Medicine here at the Robert Larner College of Medicine at the University of Vermont. I'm a pulmonologist and the program director of our fellowship training program, and love participating in education. I have no relevant financial disclosures pertinent to this talk.

In terms of the goals and objectives for today, we will discuss the unmet clinical need and the impact of chronic cough in patients who don't find relief from recommended management strategies, analyze the clinical trial data and mechanisms of action as emerging therapies for patients with chronic refractory cough, and to summarize the current guidelines with emerging treatment strategies for the management of patients with chronic cough.

This is a second part of our webinar series. And in this - in today's webinar, we'll be looking at the guidelines in a little bit more detail compared to the first presentation.

I wanted to take a minute to review some of the definitions that pertain to this presentation. So the terminology around chronic cough can be a bit confusing. There are some definitions that are proposed and are fairly consistent. Acute cough is defined as a cough that's lasting three weeks or less. Subacute cough would be a cough that's lasting between three and eight weeks. And chronic cough would be a cough that's greater than eight weeks in duration. There is a term, chronic refractory cough or refractory chronic cough, that to cough greater than eight weeks that persists despite a thorough evaluation and therapeutic trials. And I think that when most of us think about chronic cough, that's really the group of people that we often think about. Over-the-counter cough from pharmacotherapies generally have limited efficacy for chronic cough and this is a significant burden globally.

Now it's thought that an inciting pathology of chronic cough can be often identified following a thorough evaluation. If we can identify the cause, the strategy is generally to optimize the therapy for the underlying diagnosis. And the most common etiologies of chronic cough are thought to be asthma, non-asthmatic eosinophilic bronchitis, gastroesophageal reflux, upper airway cough syndrome, COPD, upper airway, and ACE inhibitor induced cough

So today we're going to take two cases and walkthrough using the two most commonly used guidelines on chronic cough, that from CHEST and that - and the next from the European Respiratory Society. These guidelines are fairly similar, but do have some subtle differences in terms of how cases are worked out.

So for case study one, we'll have Angelo, who is a 62-year-old male, a lifelong nonsmoker presenting with a six-month history of cough following a brief hospitalization for a new diagnosis of congestive heart failure. In terms of his past medical history, he has heart failure with reduced ejection fraction, type 2 diabetes mellitus, dyslipidemia, and hypertension. His current medications include atorvastatin, metoprolol, lisinopril, and metformin. So a pretty common patient to see in clinic. The cough is described as being non-productive. Triggers included talking and laughing. This cough occurs at rest and with exertion, and often occurs after waking in the morning. There are no associated symptoms including reflux, chest pain, upper airway symptoms, including rhinitis or sinusitis. There is some shortness of breath as cough worsens, but generally not in between cough periods. There's no hemoptysis and no improvement with over-the-counter cough medications, as is typical in cases like this.

So in the CHEST guidelines, initial evaluation is focused on obtaining a thorough history and physical, obtaining a chest x-ray, and identifying red flags. This patient is in no acute distress, is conversing in complete sentences, has a fairly normal physical exam with no adventitial breath sounds, their symmetric air entry throughout, the PMI is nondisplaced, and cardiac auscultation is normal. There is no lower extremity edema, no digital clubbing, and chest x-ray is without abnormality.

So, again, in the CHEST guidelines, we obtained a thorough history and physical. Again, they place a lot of emphasis on identifying red flags.

So in this patient, there is no hemoptysis. This patient does not have a significant smoking history. The patient does not have prominent dyspnea, hoarseness, fever, weight loss, peripheral edema, trouble swallowing, vomiting, recurring pneumonia, or an abnormal respiratory exam.

When present, these red flags should take you off of the chronic cough pathway and prompt evaluation for a more urgent diagnosis. After that diagnosis is evaluated and treated, if cough persists, you should return to the algorithm.

In this patient with no red flags, we should be considering medication-related cough. And when considering medication related cough, we should stop offending medications which are most commonly ACE inhibitors and reevaluate in four to six weeks. Remember that cough is reported about 15% of ACE inhibitor users. The timing and onset of the cough can be variable. It's typically a dry cough. Mechanisms include accumulation of bradykinin, which increases cough sensitivity, and drug withdrawal is the most effective therapy. Other drugs that possibly cause cough could include sitagliptin, interferon gamma, ribavirin, leflunomide, and there can be idiosyncratic reactions to many other medications. So it's important to think of the timing of the cough and recognize if any other new medications have been started prior to the cough onset.

So this ACE inhibitor was stopped, and we reevaluated in four to six weeks. In a six-week follow-up, the cough was still present, but the shortness of breath seems much worse. We obtained pulmonary function testing and see that the FEV1 is 88% of predicted FVC is 92% predicted, and the ratio is normal. There was no reversibility on bronchodilator. The methacholine challenge was negative for hyperreactivity, and the exhale - but the exhaled nitric oxide was significantly elevated at 55 parts per billion.

In this patient, a diagnosis of non-asthmatic eosinophilic bronchitis was made, and we initiated fluticasone 220 micrograms twice daily. In follow-up at six weeks, the cough had notably improved, there was no notable dyspnea. The patient was revaluated three months, and we were unable to withdraw the medication and the patient remains on the inhaled corticosteroid.

The use of inhaled corticosteroids is one of the places where the CHEST and the ERS guidelines differ slightly. Airway inflammation is commonly seen in asthma and nonasthmatic eosinophilic bronchitis and this is typically eosinophilic. These are both also very common causes of chronic cough. Because of the frequency of these as an underlying diagnosis, the European Respiratory Society does suggest that empiric therapy with inhaled corticosteroids could be considered. In CHEST, the use of inhaled corticosteroids is favored in patients who have strong suspicion of asthma or eosinophilic bronchitis.

There is one study from 2004 where we have 120 patients with cough for over a year randomized to inhaled fluticasone for 14 days versus placebo. In the primary outcome, there was a significant improvement in cough, and the cough Visual Analogue Scale in the fluticasone group. The exhaled nitric oxide, sputum eosinophils, and total IgE levels were predictors of a successful trial. Patients without those tended not to respond to the therapy.

Okay, how about a little bit more complicated case using the ERS pathway. So Juliana is a 55-year-old woman with a history of progressive cough over the last year. Past medical history includes hypothyroidism and hypertension. Current medications include levothyroxine 125 micrograms daily, and hydrochlorothiazide 12.5 milligrams per day. Physical exam is normal.

Here's a graph of the initial assessment and management strategy from the European Respiratory Society. Again, the first priority is to obtain a good history and physical examination. The European Respiratory Society does place more effort around the assessment of cough using a validated tool like the Visual Analogue Scale.

The Visual Analogue Scale is a easy to use tool for assessing the impact of cough. It's basically a straight line with a mark at - a straight line that measure about 100 millimeters, and the patient places their finger at where they think their cough severity is. The mark for where their finger is can be measured, and that can be used to follow the patient over time. The minimum clinically important difference is undefined for chronic cough, but it's around 17 millimeters in acute cough. And so it's thought to be likely similar for chronic cough. But this gives you a pretty easy way to objectively measure the patient's cough severity or at least their perception of cough severity.

There are certainly more involved ways of assessing cough, including the Leicester Cough Questionnaire, or LCQ. This is a 19-item survey with a 7-point scale. This is intended to assess the impact of cough over the preceding two weeks. This has total physical, psychological, and social domain scores. The minimal clinically important difference on this is 1.5 to 2 points. So this is certainly a well validated scale. It is a bit more cumbersome to apply in clinical practice, but can give very useful information.

So for Juliana, further history taking revealed that this patient did have triggers that included spicy foods. The cough occurred at night and during the day. There was associated reflux symptoms and minimal sputum production. We did ask about red flags. There was no hemoptysis. This patient did have a prior minor history of smoking. Has tried lozenges with no improvement in symptoms. The Visual Analogue Scale is 60 millimeters.

Routines spirometric testing showed it FEV1 that was 92% of predicted and FVC that was 90% of predicted and FEV1 to FVC ratio that was 0.76. There is no reversibility seen on bronchodilator. Chest x-ray was normal.

One question that often comes up when dealing with chronic cough is should a CT scan be performed in patients with chronic cough if there is a normal chest x-ray and physical exam. And the European Respiratory Society specifically addresses this by saying CT chest is not recommended routinely when chest x-ray and physical exam are normal. Now in a patient with a smoking history like this, you certainly could consider a CT chest for unexplained cough. I think that would be justifiable but in general practice, if there's no other reason to suspect lung cancer, or another diagnosis that you can diagnose more reliably by CT, that shouldn't be part of the routine evaluation.

Alright, so back to the graph here. So again, the initial part on the - from ERS, just like with CHEST is to obtain a thorough history and physical examination, to formally assess the cough severity using something like the Visual Analogue Score or the LCQ, to assess for associated symptoms that could suggest an underlying diagnosis, to obtain routine evaluation that includes chest radiography or pulmonary function - and pulmonary function testing, with the possibility of obtaining exhaled nitric oxide, sputum or blood eosinophils.

Those are questionable evaluations. The exhaled nitric oxide is not routinely available in all labs, and rigorous data on the use of exhaled nitric oxide to screen patients for airway disease related to chronic cough is lacking.

The initial management suggested by ERS is to stop any risk factors, to initiate corticosteroids, either oral or exhale - or inhaled corticosteroids for two to four weeks. Now, this is particularly suggested when there's evidence of eosinophilic airway inflammation. However, as I just said, some of this testing is not always available to practitioners. And so an empiric therapy challenge for two to four weeks is certainly reasonable, given the frequency of this as the diagnosis. They suggest only initiating PPI therapy when there are peptic symptoms or evidence of acid reflux.

Then follow-up should occur with a validated assessment to see if there's any improvement and to assess if there's any associated symptoms. If there is improvement, you would continue for three months and attempt withdrawal. If there's no improvement, we move to a different part on the algorithm with neuromodulatory agents.

Other evaluations that could be considered include esophageal manometry, induced sputum for eosinophils, sputum AFB, laryngoscopy, methacholine challenge, CT chest for cases where there may be risk factors for that disease, and bronchoscopy.

So this patient does have a history of reflux symptoms, and it's certainly reasonable to place this patient on PPI therapy. Unfortunately, in four weeks reflux symptoms were improved, but cough remained bothersome. Now, many people think that empiric therapy with PPI should be considered in patients with chronic cough, but in patients without peptic symptoms, empiric therapy with PPI is not something that should be routinely done.

There are several studies which describe lack of efficacy when using acid suppression therapy. This study from 2011 took 50 patients with chronic cough, randomized to esomeprazole versus placebo. And there was no change in cough score at eight weeks. There was a trend towards improvement in patients with dyspepsia. This was a fairly small study though.

Another study from 2011 took 40 patients with chronic cough and no symptoms of reflux specifically, and randomized them to high-dose esomeprazole 40 milligrams twice daily versus placebo. And there was really no change in measures of cough severity at 12 weeks.

So you know, this patient, Juliana, had reflux symptoms, and I think that should definitely be treated. But if there are no symptoms of

reflux, PPI administration really should not be should not be done.

This patient then was initiated on a trial of fluticasone 220 micrograms twice daily. And at four weeks, there was no improvement in cough severity.

So I think a lot of us have been in this kind of in this kind of place where there is a cough that doesn't seem to respond to therapies, and there may be suggestive symptoms that get treated and the cough isn't improving. And sometimes this can lead to a lot of other workup like impedance monitoring, occasionally an EGD, especially in a patient with reflux symptoms, barium swallow to screen for esophageal dysfunction or aspiration, bronchoscopy to look for eosinophilic airway inflammation, and some sinus evaluation which could include just a clinical evaluation and occasionally involves imaging of the sinuses.

Additional pulmonary testing can certainly be considered. That could include a methacholine challenge and exhaled nitric oxide in this case. Here, both of these were negative. So this is a patient where there's really no clues as to what's causing the cough. We don't have eosinophilic airway inflammation, and we may need to look at different strategies. So again, the ERS guidelines are to mitigate risk factors and avoid triggers, treat potential causes. Then, if you find something as successful, to treat it for three months and attempt a taper. If you're unsuccessful, you can consider other things like speech therapy interventions, low-dose opiates, promotility agents, and - or pregabalin or gabapentin.

Speech pathology can be a particularly effective intervention for people with chronic cough. This utilizes central control of cough to mitigate cough symptoms. There's four components that can be delivered over three to four sessions. So this is not necessarily a really long intensive intervention. They work with education, helping patients to understand their condition and the rationale for therapies. They provide psychoeducational support, discussing adherence and emotional barriers to treatment. They discuss cough suppression strategies, including breathing and laryngeal reposturing, and responding to urge to cough with other behaviors, and reducing laryngeal irritation. So looking with lifestyle interventions to reduce potential exposures which could be contributing, which include minimizing exposure to alcohol, working on reflux mitigation, and reducing phonotraumatic behaviors. This has been shown in multiple studies to improve cough-related quality of life, cough severity, cough frequency, and urge to cough. So it's really something that is worth considering in these patients with refractory chronic cough who are failing therapy. And, you know, we may see over time that this intervention gets moved higher in the priority list for use.

So unfortunately with this patient speech pathology intervention led to only a minor improvement in cough with a VAS of 55 millimeters, started at 60 was a bit worse at 65 and improved to 55. So some improvement but still having a bothersome cough. So what should we consider next?

So, at this point, we really should be considering neuromodulatory therapies. Now neuromodulatory therapies can include things like gabapentin, can include other therapies like opiates. Gabapentin has been described in chronic cough for a number of years. So in 2012, there was a study from Ryan and colleagues with 62 patients with chronic cough randomized to gabapentin or placebo, and gabapentin starting at 300 milligrams a day escalating to 1,800 milligrams a day divided – b.i.d. led to significant improvements in cough severity as measured by the LCQ. There was a 74% improvement with the intervention and 40 - 46% in placebo. Now, this was interesting because there was no change in cough reflex sensitivity or urge to cough frequency or laryngeal dysfunction scores, but certainly improves the cough severity. So this is certainly one worth considering.

Morphine is also something that has been suggested from ERS for use in refractory cough. So in this patient, gabapentin was initiated with a slow titration up to 300 milligrams twice daily. The patient returns in six weeks, and the Visual Analogue Scale is now down to 45. So we've improved significantly from the worst cough. And we continue titration up to 600 milligrams twice daily. And our follow-up has the Visual Analogue Scale at 24 millimeters. So now a significant improvement in cost severity.

And, you know, this patient can be treated then for three months with an attempt to taper. And often at that three-month timeframe, you can taper off these medications and the cough remains improved.

So this is a good time to talk about some of the differences between the CHEST and the ERS guidelines. So like I said, they are fairly similar. They do have some slight differences. I think if you're approaching a patient with chronic cough, look at both of these guidelines and see which ones kind of makes sense to you to use. Subtle differences, but they do get to the - they do tend to get to the same place. Speech pathology is certainly recommended in both guidelines as intervention for sort of refractory cough. They do differ in in terms of empiric use of inhaled corticosteroids with the ERS guidelines do suggesting that you can use inhaled corticosteroids empirically because of the lack of access to sputum eosinophil testing and exhaled nitric oxide testing. The CHEST guidelines favor using corticosteroids when we have strong suspicion of asthma or non-asthmatic eosinophilic bronchitis. Gabapentin or neuromodulatory therapies is recommended in both guidelines. So the CHEST guidelines, really this is for the refractory chronic cough guideline but in ERS it is also recommended. Empiric anti-reflux therapy is not recommended in both guidelines. It's recommended against actually in

both guidelines. Morphine is one place that where we also have a little bit of difference. So in the ERS guidelines, morphine is suggested as a neuromodulatory therapy to consider but the CHEST guidelines which this was addressed more in the 2016 CHEST guideline on chronic refractory cough, morphine was not recommended. The morphine was considered but given the efficacy data around morphine, ultimately didn't make it to recommendation.

So at this point, we've sort of walked through a couple of patients who would have fairly typical chronic cough and had a little bit of time to compare how these guidelines might be a little bit different. The title of the talk is Emerging Therapies for Patients with Chronic Cough. And so we do want to take a few minutes here to discuss the - some of the newer medications that may be on the way to help us manage this significant problem. And we should have plenty of time for additional questions here after this.

So really at this point, the most promising category of novel medications to treat chronic cough are the P2X3 antagonists. These plain - these receptors are purinergic receptors that respond to extracellular ATP. These receptors play an important role in the activation of C fibers, so vagal afferent that are integral to the cough reflex. There are multiple that are under development right now. Now, again, these medications have not been approved for use in the United States and so are not part of the guidelines at this point.

So the medication that is most far along in the approval process is gefapixant. So this is again an antagonist of P2X3. The early Phase 1 and Phase 2 clinical trials did show positive results for decreasing cough and 24 [26:16] cough frequency. Higher doses of these lead to taste disturbances which were dose limiting. In dose-finding studies, the optimal dose is somewhere - appears to be somewhere between 30 and 50 milligrams, and there are no safety concerns. Again, the most common adverse event was dose-dependent taste alterations, and those taste alterations subside when treatment is discontinued.

The two larger trials, COUGH-1 and COUGH-2 have been completed. These were parallel, double-blind, randomized, placebo-controlled trials that are assessing the efficacy and safety of gefapixant at different doses in patients with chronic cough. So in terms of these outcomes, we're looking at 24-hour cough frequency, percentage of people with adverse event, and percentage of participants who discontinued due to an adverse event. So this was - these were initially 24-week and extended to 52 weeks. There was a statistically significant reduction in the 24-hour cough frequency with gefapixant at 40 milligrams twice daily versus placebo. And this is seen in both COUGH-1 and COUGH-2. The lower dose of gefapixant did not meet the primary efficacy. And so, it does look like the 45-milligram dose is going to be needed. And the adverse events with this in these studies are consistent with the prior studies with taste alterations that are dose dependent, so more frequent in the gefapixant group - in the in the 45-milligram dose. So, this medication has been - is being reviewed at the FDA. An application was submitted in March, and we may see later this year, this medication be approved.

There are other P2X3 antagonists that may be coming as well. So ___ 28:26 is a another P2X3 antagonist that is undergone Phase 1 and Phase 2 trials, which do show that higher doses again lead to decreased cough frequency. These patients do have again taste - dose-dependent taste alterations, which improve with drug removal.

BLU-5937 is a third agent that is undergoing Phase 2 trials. So this is the RELIEF trial. In this trial, individuals are on 16-day treatment periods with escalating doses. This trial was a bit limited because it occurred during the COVID pandemic. And so we're a little bit behind on getting data from this. There was some reductions in cough frequency, but in the intent-to-treat population, there was not clinically - there was not a statistically significant difference, other than in those patients who had significantly high cough frequency. This did not have study discontinuations due to alterations in taste.

Sivopixant is a another selective P2X3 antagonist, again undergoing Phase 2 trials with a number of different doses. There is a 406-patient trial that shows changing baseline cough frequency, an improvement in cough frequency. But these results are currently being evaluated. A Phase 2A study that was conducted in Japan showed a 30% reduction in objective frequency of daytime cough after two weeks and a 30% reduction in frequency over 24 hours. There were much fewer taste-related adverse events compared to some of the other P2X3 antagonists.

So, in conclusion, chronic cough is very common. This is a significant impact for our patients. There are multiple assessment tools including the LCQ and the Visual Analogue Scale that are available to objectively follow patients. The guidelines from CHEST and/or ERS can be used to guide management. These guidelines are similar, they do approach things slightly differently. And I think it's important to pick a clinical guideline and use this to guide you through these patients with chronic cough.

It's that felt that many, if not most cases, can ultimately be attributed to an underlying diagnosis which is most commonly asthma or nonasthmatic eosinophilic bronchitis after a thorough evaluation. However, in those patients with refractory chronic cough, additional therapy with speech pathology interventions or neuromodulatory therapy should be considered. And neuromodulator therapies can include gabapentin, amitriptyline, and morphine.

There are other new targeted agents that are under investigation that could provide greater efficacy with it appears good safety and

tolerability profile. And you know in - with gefapixant, we see significant improvements in cough and also patient-reported outcomes, cough-related quality of life. And so this may be a really important tool in the future for these patients with chronic refractory cough.

I want to thank the American Thoracic Society for sponsoring these two webinars. I would like to thank AKH and Trish, Lynn, and Steve for helping put together this really beautiful slide deck.

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