Transcript Details
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Clinical Exchanges®: Optimizing Management of Nontuberculous Mycobacteria Lung Disease

Dr. O'Donnell:
Hello. I'm Dr. Anne O'Donnell, Professor of Medicine at Georgetown University Hospital in Washington, D.C. In this interactive clinical exchange CME activity I will be discussing the ongoing management of nontuberculous mycobacterial lung disease with one of my patients, Brinkley. The management of Brinkley's lung disease will highlight the use and benefit of share decision making during the necessary long-term treatment of NTM lung disease. Brinkley's case will help to illustrate the growing prevalence of NTM lung disease in both men and women. A recent study using U.S. Medicare beneficiary data estimated that more than 86,000 patients in the United States are infected with NTM. Most of these cases result in lung disease. Approximately 70% of the cases arise in the coastline and Gulf states. The MAC species is the most common cause of NTM lung disease worldwide, and is responsible for the great majority of NTM lung disease cases in the U.S. Among Americans, the prevalence of NTM lung disease increased 8.2% per year over a recent 10-year period from 1997 to 2007.

And individuals burdened with NTM lung disease is potentially high. When compared with healthy persons, people with NTM lung disease experience worse physical functioning, worse general health, worse social functioning, more pain, and poor energy due to limited pulmonary function. This is regardless of whether they are receiving treatment or not. When compared with controls, individuals who develop NTM lung disease have a 4.3-fold higher chance of developing respiratory failure. People with MAC lung disease live an average of 16 years after diagnosis, and sometimes have a poor prognosis. A recentreview showed a five-year all-cause mortality exceeding 25%.

The burden of treatment is also high. Treatment should continue for 12 months past conversion of sputum samples from positive to negative. Additionally, there is a high risk of adverse drug reactions because of the number of drugs used and the length of the treatment. Likewise, treatment failure rates can be high. Only about 50% of people with NTM lung disease achieve a long-term response with the antituberculous medications.

At the time of Brinkley's initial presentation to a pulmonologist, he was a 59-year-old man with a one-year history of recurrent cough and sputum production. Except for a history of hypothyroidism, Brinkley was healthy and had no history of pulmonary disease. Brinkley was initially diagnosed with bronchitis and treated with oral azithromycin, as well as an inhaled corticosteroid and a long-acting beta-agonist for his respiratory symptoms. On physical exam at that time, Brinkley was a thin, otherwise well-appearing man with an active productive cough. His physical examination was significant for mild bilateral wheezes heard on chest auscultation. A high-resolution CT scan of the chest at that time revealed nodular bronchiectasis. Bronchoscopy with bronchoalveolar lavage revealed Mycobacterium avium-intracellulare, or MAC; hence, Brinkley was diagnosed with nontuberculous mycobacterial lung disease and was prescribed a three-times-per-week regimen of azithromycin, ethambutol, and rifampin, which he continued for 18 months.

According to guidelines, when should sputum cultures have been obtained during Brinkely's extended treatment for NTM lung disease due to MAC? Every one to three months? Once every six months? At 12 and 18 months? Or at the 18-month end of treatment? The best answer is A: Every one to three months. During Brinkley's treatment for NTM lung disease, AFB smears and cultures of sputum should have been obtained every one to three months according to therapeutic guidelines. The goal of therapy is the conversion of sputum cultures from positive to negative. Sputum cultures should convert to negative within 12 months of receiving a macrolide-containing regimen, and therapy should be considered – continued for another 12 months after conversion. In Brinkley's case, disease monitoring with both surveillance sputum cultures and periodic CT imaging would have been appropriate for assessing the success of his pharmacologic regimen. Unfortunately, this did not occur.

The recommended initial treatment for nodular bronchiectatic disease, as in the case of Brinkley, is a three-drug regimen containing a macrolide such as azithromycin, along with ethambutol and rifamycin. This regimen is given three times weekly. For fibrocavitary disease, and aminoglycoside is added to the three-drug regimen, which is given daily. Surgery may also be considered in cases of fibrocavitary disease.

In the management of a chronic disease such as NTM lung disease, shared decision making with the patient is useful for selecting a regimen that will maximize adherence throughout the necessarily long course of treatment. To better illustrate the process of shared decision making, Elwin and colleagues have created and refined a fluid interactive three-talk model. In this model, the clinician sets up a collaborative or team approach, and with the patients, make therapeutic decisions. The patient is provided with all of the reasonable diagnostic or treatment options available to them at any stage of the management process. After the patient gains comfort with the available options, detailed explanations of the possible management steps are discussed. Efficacy and safety of all treatment options are clearly relayed to the patient. And once the patient is armed with the benefits and disadvantages of each option, the patient can then engage in “decision talk” with the healthcare provider who guides the patient to express his or her goals and preferences about the next steps in management. The guidelines for the management of NTM lung disease address the use of shared decision making for optimal management. Notably, the choice of a therapeutic regimen for a specific person depends on the goals of therapy for that person. For instance, less aggressive therapy may be appropriate for patients with indolent disease in whom there might be a high likelihood of drug intolerance or drug interactions. It’s important to remember that many patients with nontuberculous mycobacterial lung disease are often older or have underlying conditions, which must be considered when prescribing pharmacologic therapy.

I’d like to introduce Brinkley, who’s our patient with nontuberculous mycobacterial lung infection, and talk a little bit about the treatment regimen that you undertook for this infection. So why don’t you tell us a little bit about the three-drug regimen that you took.

Brinkley:
Initially, I had a wheezing in my throat that I thought I should do something about, so I went to a doctor, and they did prescribe prescribe a three-drug regimen for me for 18 months. I took it as prescribed and my – I thought that I would, after that 18 months, be cured. I didn’t see any real improvement after three months, after six months, 12, 18 months. I was still – the symptoms were – I was still coughing. I was still wheezing. And I thought my end goal obviously was to be cured.

Dr. O’Donnell:
So you were told you had this infection, this nontuberculous mycobacterial infection, and when the plan of treatment was laid out to you, what was your goal?

Brinkley:
Well, my goal ultimately obviously is to be cured of whatever this – I was explained to me that it was sort of a tuberculosis, and I thought that this, after 18 months, that I’d be cured and walk away a healthy man.

Dr. O’Donnell:
And in terms of just dealing with the antibiotic, you took it as prescribed, and what kind of side effects did you have?

Brinkley:
No side effects really. I took it as prescribed and, I just thought that again at the end of this that I would be fully cured.

Dr. O’Donnell:
And what kind of monitoring was done while you were on the treatment? Do you recall having sputum cultures?

Brinkley:
I recall having an initial sputum culture. But beyond that I don’t recall having any sputum cultures throughout the 18 months.

Dr. O’Donnell:
So in terms of you were still feeling poorly, still coughing, still short of breath – or not short of breath, but still having –

Brinkley:
Tired.

Dr. O'Donnell:
Still having wheezing, tiredness.

Brinkley:
Yeah, I was tired.

Dr. O'Donnell:
Right.

Brinkley:
And still wheezing, and it was, I didn't think that the – the three course – courses were doing the job I guess.

Dr. O'Donnell:
But you stuck with it.

Brinkley:
I stuck with it.

Dr. O'Donnell:
Right. You took it religiously.

Brinkley:
Yes, I did.

Dr. O'Donnell:
Yeah. So at the end of treatment, it was just sort of arbitrarily stopped at 18 months I guess, right?

Brinkley:
Right, correct.

Dr. O'Donnell:
And then it was – you needed to be followed up or have more sputums. Was anything done along those lines?

Brinkley:
No. Not really. It just sort of waned off.

Dr. O'Donnell:
So, let me tell you a little bit about how I approach patients when I first meet them with the initial diagnosis of nontuberculous lung disease. We do talk about, you know, the goals of the antibiotic treatment to alleviate the patient's symptoms and to – and to hopefully get a cure of the infection, meaning that the bacteria has gone away. But it can be pretty daunting and – and I think a lot of education for the patient can be helpful. One thing I really focus on is monitoring – monitoring the patient while they're on the treatment so that we get routine sputum cultures as surveillance while the patient is taking the antibiotics with the idea that will tell us, you know, how the patient is responding to the treatment.

Brinkley:
Yeah, that's, you know, that seems to be – that would probably have been a lot more – it would have given me something to hang my hat on, whether I'm improving or not improving is important for the patient I think.

Dr. O'Donnell:
Right. To see the – number one, you feel better, but number two that there's some microbiologic improvement, either the cultures –

Brinkley:
You know, it's important for the patient to have the knowledge of whether it's progressing or going the other direction.

Dr. O'Donnell:
Right. And the – one of the things about checking sputums, it does help us determine how long the patient needs to be on the antibiotics because we – the guidelines suggest that the antibiotics should be continued for 12 months after the sputum converts negative. So it is one of those things that really helps the physician treating the patient, but also I think the patient themselves for understanding where – how things are going.

Brinkley:
Right.

Dr. O'Donnell:
Alright. So six months after Brinkley completed his 18-month regimen, he again began experiencing recurrent cough and sinus infections, and ultimately required surgery and repeated antibiotic therapy. Sinus cultures were significant for Pseudomonas, Trichosporon, and other fungi. Over the next three years, Brinkley also sustained an eardrum rupture due to Pseudomonas infection. In addition, he was diagnosed with squamous cell carcinoma of the left parotid gland, and was treated with surgery, radiation, and chemotherapy. He continued to use an inhaled corticosteroid. Notably, recent sputum cultures were negative for acid-fast bacilli, but positive for Pseudomonas species. So, Brinkley, you experienced some significant medical issues after you concluded the three-drug treatment for the nontuberculous mycobacterial lung infection. Could you tell us a little bit about the problems that you've had and some of the issues surrounding your subsequent health?

Brinkley:
Well, I got head and neck cancer. I then had some sinus infections that were pretty – pretty bad, and I had multiple surgeries. The radiation and the chemo affected my health. So overall my health was – I was in poor shape for a long time. And I was just concerned about my overall health. And then concerned about the antibiotics for the sinus infections. I would take an antibiotic and it seemed – the Pseudomonas would seem to clear up, and then I would go off, and it would flare up again. But then it – I had concerns about building up immunities to the various antibiotics I was on because what my concern was, as the patient, what's going to happen long-term if we really need high-test antibiotic, and there's nothing left in the grab-bag for us to use to combat this very bad infection that I might get. That was – that's a major concern of mine.

Dr. O'Donnell:
Right. So multiple rounds of antibiotic and the potential for side effects, but that worry about some long-term issues and resistance developing, right? To the bacteria.

Brinkley:
Absolutely.

Dr. O'Donnell:
To the antibiotic that the bacteria was being targeted.

Brinkley:
Yes.

Dr. O'Donnell:
Or. Yeah.

Brinkley:
Exactly.

Dr. O'Donnell:
Yeah, so I'm sure that weighed on your mind and, you know, you wanted to think about what perhaps alternative options there were. You know, and one of the important things I think is you were having recurrent cultures at that time to try to target the antibiotics but it's still a concern.

Brinkley:
Right.

Dr. O'Donnell:
So let me talk a little bit about what I often consider in patients who have your set of problems. We think about adding some nonpharmacologic treatments, particularly what we call airway clearance. And airway clearance involves a number of different techniques. It can be really simple, little devices to help mobilize the sputum. It can be nebulizer treatments to help reduce the – the thickness of the sputum. And it includes things like exercise and sometimes pulmonary rehabilitation. Would that make sense to you to add some non-drug treatments like that?

Brinkley:
Sure. I would – that would be – as a patient, that would be terrific actually. That way, we're not so reliant – I'd like to, if at all possible, wean myself from so many antibiotics. And if this is an effective way of doing that, absolutely I'd be on board all the way.

Dr. O'Donnell:
Yeah, so this involves time commitment on the patient's part to do these kind of treatments. But there is a whole spectrum, like I said, of different ways to help mobilize the secretions, and even to clear the sinuses with some rinsing and things like that. And so, it is an attractive alternative because it means less antibiotic burden, less risk of getting side effects or resistance to those antibiotics. So again, some of the – some of the techniques I've mentioned, we often do really recommend exercise as a good way to help with the – for patients who are in less good shape, they might go to a pulmonary rehabilitation program. We – we really emphasize keeping the patient's weight up, ensuring good nutrition, and just sort of ensuring good health in general in order to try to minimize the antibiotic burden.

Brinkley:
I think that's very important. And I can't imagine any patient not getting on board with that.

Dr. O'Donnell:
So we still want to emphasize while on these treatments we want to monitor the sputum cultures, the sinus cultures in order to see the trajectory of the infections in the future.

Brinkley:
That would be great from a patient perspective. I mean, I'd like to be educated on where I am, if I'm progressing, not progressing, whatever. I think it's important for the doctor-patient relationship.

Dr. O'Donnell:
Right. And you're a partner in the, you know, in terms of your commitment to do it. We're partners in treating this.

Brinkley:
Right.

Dr. O'Donnell:
So thank you very much, Brinkley, for being part of this program and really shedding light on the – from the patient's perspective dealing with these infections. Thank you.

So, given Brinkley's interim medical history and concerns, which of the following is best next step? Prescribe azithromycin, ethambutol, and rifampin with ciprofloxacin if a repeat CT scan shows fibrocavitary disease? Recommend repeat bronchoscopy with bronchoalveolar lavage for AFB culture? Add a long-acting beta agonist to the inhaled corticosteroid? Or conduct a workup for underlying immunodeficiency and prescribe airway clearance? The best answer is D: Conduct a workup for underlying immunodeficiency and prescribe airway clearance. A number of important recommendations were missed in the management of Brinkley's lung disease, which has been complicated more recently by his recurrent sinus infections and his parotid cancer. His initial antimicrobial regimen was appropriate; however, important adjunctive therapies such as airway clearance techniques were never prescribed. Brinkley also did not receive adequate education about his disease, which could have improved his initial understanding of his illness and promoted necessary adherence to his long-term treatment. His use of an inhaled corticosteroid, in hindsight, should have also been avoided. Brinkley should have been evaluated for underlying structural or genetic risk for an immunodeficiency, given his history of NTM lung

disease and recurrent sinus infections.

General therapeutic principles in the management of NTM lung disease include the search for a treatable underlying disorder such as cystic fibrosis or an immune disorder. During therapy, sputum smears for acid-fast bacilli and cultures should be obtained monthly during treatment to determine the efficacy of therapy. The goal of therapy is the conversion of sputum cultures from positive to negative. Cultures should convert to negative within 12 months of receiving a macrolide-containing regimen. The ultimate duration of the treatment is 12 months after the conversion of sputum cultures. So, for instance, if sputum cultures convert to negative at 6 months, a total of 18 months of therapy should be completed. Finally, adjunctive therapies are urged, particularly in cases of bronchiectasis. During the management of NTM lung disease, the benefits of adjunctive airway clearance should be stressed. Guidelines emphasize the use of newer methods for the clearance of mucus in cases of bronchiectasis. These include autogenic drainage, the use of oscillating positive expiratory pressure devices, or high-frequency chest wall oscillating devices. These techniques should be considered, especially in patients with significant mucus production and mucus clearance problems. If the patient smokes, he or she should be urged to quit. In addition, good nutrition and weight gain, if necessary, should be urged, as well as regular exercise and cardiovascular fitness to promote overall respiratory and good health.

When pharmaceutical therapy is recommended in cases of NTM lung disease, specific safety and tolerance issues should be conveyed to manage patient expectations, encourage patient feedback about ongoing therapy, and to promote patient adherence. For instance, patients who receive rifampin should be advised of the harmless discoloration of urine and secretions. The major adverse effects of standard treatments for NTM lung disease are tabulated here, along with the recommended monitoring procedures.

For refractory disease, liposomal amikacin in an inhaled suspension was approved in 2018 as an adjunctive treatment to a standard background regimen. This approval was based on a randomized trial of several hundred people with refractory NTM lung disease. The most common adverse effects of liposomal amikacin are listed here, including dysphonia and respiratory symptoms.

Because an educated patient is more likely to actively and productively engage in the management of his or her disease, it is important to recommend authoritative and patient-friendly educational resources. A number of high-quality online resources for NTM lung disease are provided here, including web pages from the American Lung Association, the American Thoracic Society, and the CHEST foundation.

Given Brinkley's desire to avoid further pharmacologic therapy, if possible, considerations should be made about his anticipated tolerance and adherence to future antibiotic regimens. He has continued to experience recurrent sinus problems, requiring both antibiotics and surgical debridement. In Brinkley's case, however, because there has been no recent evidence of active NTM lung disease, less aggressive therapy in the form of regular airway clearance is appropriate. This is recommended in conjunction with regular exercise to which he has been adherent.

This concludes this CME activity. Please be sure to complete the post-test and evaluation. Thank you.