

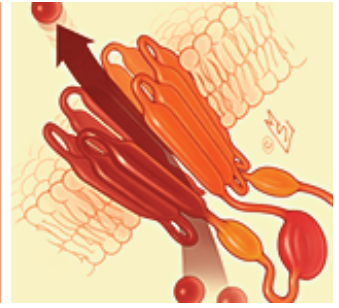


eLITERATURE
REVIEW

eCysticFibrosis Review
Podcast Issue

Presented by the Johns Hopkins
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Institute for Johns Hopkins Nursing

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VOLUME 3 – ISSUE 12: TRANSCRIPT

Featured Cases: Emerging Pathogens in Cystic Fibrosis

After participating in this activity the participant will demonstrate the ability to:

- Discuss the evidence for potential treatment options in patients with CF, with new and/or persistent MRSA infection,
- Describe the evidence for potential treatments options in CF patients with *Mycobacterium abscessus* and *Burkholderia cenocepacia* infection and,
- Discuss ongoing studies to address the current knowledge gap in treatment of MRSA infection in patients with CF.

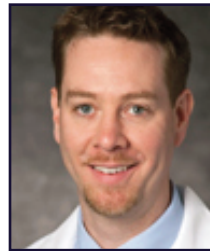
This audio activity has been developed for clinicians caring for patients with issues related to cystic fibrosis. You can also read the [companion newsletter](#). In this edition Dr. Dasenbrook will discuss treatment strategies to address the recent increased prevalence of potentially pathogenic microorganisms in the respiratory tracts of individuals with CF.

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Unlabeled/Unapproved Uses

The author indicates that there will be a reference to unlabeled/unapproved uses of vancomycin, amikacin and inhaled meropenem in the presentation.

MEET THE AUTHOR



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Elliott C Dasenbrook, MD, MHS has indicated that he is an advisor to Savara Pharmaceuticals.

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MR. BOB BUSKER: Welcome to this eCysticFibrosis Review podcast. eCysticFibrosis Review is presented by the Johns Hopkins University School of Medicine and the Institute for Johns Hopkins Nursing. This program is supported by an educational grant from Abbott Laboratories, Gilead Sciences Medical Affairs, and Vertex Pharmaceuticals.

Today's program is a companion activity to our June 2012 eCysticFibrosis Review newsletter: *Emerging Pathogens in Cystic Fibrosis*. Our guest today is Dr. Elliott Dasenbrook, from the Case Western Reserve University School of Medicine in Cleveland.

This activity has been developed for physicians, nurses, respiratory therapists, dietitians, and physical therapists caring for patients with cystic fibrosis. There are no fees or prerequisites for this activity. The Accreditation and Credit Designation Statements can be found at the end of this podcast.

For additional information about accreditation, Hopkins policies, expiration dates, and to take the post-test to receive credit on-line, please go to our website newsletter archive, www.eCysticFibrosisReview.org, and click the July 2012 podcast link.

Learning objectives for this audio program are that after participating in this activity the participant will demonstrate the ability to:

- Describe the evidence for potential treatment options in patients with cystic fibrosis, with new and/or persistent MRSA infection,
- Describe the evidence for potential treatment options in patients with cystic fibrosis, with *Mycobacterium abscessus* infection, and,
- Describe the evidence for potential treatment options in patients with cystic fibrosis, with *Burkholderia cenocepacia* complex and cepacia syndrome.

The Johns Hopkins University School of Medicine takes responsibility for the content, quality, and scientific integrity of this CME activity.

I'm **BOB BUSKER**, managing editor of eCysticFibrosis Review. On the line we have with us Dr. Elliott Dasenbrook, Assistant Professor of Medicine and

Pediatrics and Associate Director of the Adult Cystic Fibrosis Program at Case Western Reserve University School of Medicine in Cleveland.

Dr. Dasenbrook has disclosed that he is an advisor to Savara Pharmaceuticals. He has also indicated that his presentation today will include references to vancomycin and amikacin, agents that are unlabeled or unapproved for treating infection in patients with cystic fibrosis.

Dr. Dasenbrook, welcome to this eCystic Fibrosis Review podcast.

DR. ELLIOTT DASENBROOK: Thank you very much, Bob, I'm happy to be here and excited to do the podcast today.

MR. BUSKER: Your newsletter issue reviewed recent data on the prevalence and virulence of particular respiratory pathogens in people with cystic fibrosis. Today I'd like to focus on the clinical implications of that data. So please start us out with a patient.

DR. DASENBROOK: Case number one is an 11-year-old girl with cystic fibrosis who presents for a quarterly cystic fibrosis clinic visit. She is asymptomatic, with no signs of a pulmonary exacerbation. Physical exam is unchanged from previously and her lungs are clear. Her FEV₁ is at her baseline of 85%. Her previous throat cultures include methicillin sensitive *S. aureus* and *P. aeruginosa*. Her respiratory medications include hypertonic saline, DNase, albuterol, azithromycin, ibuprofen, and every other month, inhaled tobramycin. The lab calls to say her throat swab from clinic grows MRSA.

MR. BUSKER: All right, so this patient is now growing MRSA. Key question: watchful waiting versus treatment? What's the evidence about a patient with a new MRSA infection?

DR. DASENBROOK: A key point is to distinguish between new infection and persistent infection. Clearly in the case here, we have a patient with a new MRSA infection. When you're making a decision about treatment versus watchful waiting, there is actually good evidence for both approaches.

In favor of watchful waiting, our patient is asymptomatic and her FEV₁ is at her baseline.

Second, there is some evidence that MRSA infections, when they are new, may clear on their own. Three studies using three different patient populations have estimated that anywhere from a quarter to a third of new MRSA infections may clear on their own.

Furthermore, studies show that MRSA that clears on its own does not subsequently affect lung function or survival. Therefore, watching patients to see if they develop symptoms or end up persistently culturing MRSA is a very reasonable approach.

In favor of treatment, however, several facts would also allow treatment. As we will talk about further, most of the epidemiologic evidence for the impact of MRSA is from persistent MRSA infections. Obviously, all persistent MRSA must start out as a new MRSA infection. From our experience with *Pseudomonas*, we know that the easiest time to eradicate an infection is when it is initially cultured. Therefore, treatment of a new, asymptomatic infection may provide benefit if a chronic infection can therefore be prevented.

I think it's pretty clear that in terms of a new MRSA infection, there are good arguments for watchful waiting, and you can also make equally strong arguments in favor of treatment

MR. BUSKER: Let me ask you then, if she were your patient — watchful waiting or initiating treatment? Which would you choose?

DR. DASENBROOK: First, there are no guidelines in the United States for treating MRSA infections or even how to approach eradication. And so I would favor treating a patients since the clinical impact of a new MRSA infection is unclear, I would opt for a low-risk treatment regimen with oral and topical antibiotics to attempt MRSA eradication and potentially prevent a chronic infection.

I would choose approximately a two to three-week length of treatment with oral antibiotics that the patient tolerates and are sensitive on the MRSA antibiogram. Antibiotics that I usually choose are either trimethoprim sulfamethoxazole or doxycycline, and I'll use that in combination with rifampin. It's been shown that rifampin, in combination with another antibiotic, has eradicated MRSA in multiple previous CF studies, and we'll talk about some of these studies later.

In addition to treating with oral antibiotics, to help with MRSA colonization at other sites of the body, I also recommend that patients use chlorhexidine body washes that they can get over the counter, and I also prescribe mupirocin nasal cream. Cystic fibrosis patients are known to have a significantly higher rate of *S. aureus* in their anterior nasal carriage compared to non-CF controls.

Finally, I also talk to the patients about environmental decontamination, which basically is having them wipe down high-touch areas in their houses with over-the-counter Clorox or Lysol wipes.

MR. BUSKER: The potential risks associated with the agents you've chosen — explain those to us, please.

DR. DASENBROOK: Trimethoprim sulfamethoxazole and doxycycline are very well tolerated but can be associated with allergic reactions, gastrointestinal side effects, skin rashes, and sun sensitivity. I definitely warn patients that if they develop a rash, they should immediately stop the antibiotics. In addition, even though we're in Cleveland we only have a couple of months with sun, I tell patients to avoid extended time in the sun; if you're in a different part of the United States or the world this can definitely play a significant role, as well. I also tell patients they should not use tanning booths while taking these antibiotics.

MR. BUSKER: And what about the rifampin?

DR. DASENBROOK: Rifampin is another antibiotic that has good activity against MRSA, but rifampin is known for causing a significant amount of heartburn. So again, I actively warn patients about this potential side effect and ask them to contact us if they notice that they are having increasing heartburn symptoms, and then we will treat it at that time.

In addition, rifampin causes reddish secretions, so tears and urine can turn orange-ish/red colors, so I make sure that patients are aware of that, as that can be quite alarming if you are not expecting it. Rifampin is also known to decrease the effectiveness of oral contraceptive pills. When I prescribe this to females taking oral contraceptive pills I also recommend another form of birth control.

Finally, occasionally patients will also be prescribed linezolid. And I've been increasingly concerned about linezolid resistance as it is becoming a bigger

problem. A recent study from the Cleveland Cystic Fibrosis Center reported that 15% of their patients treated with linezolid developed linezolid-resistant MRSA.

The biggest risk factors for linezolid resistance were long, repeated courses of linezolid. A one-time course is not associated with linezolid resistance, but that definitely becomes a concern as patients have repeated courses with linezolid.

MR. BUSKER: I want to note to our listeners that links to many of the studies Dr. Dasenbrook refers to our discussion can be found in the transcript version of this podcast.

Now, as you said, there's no guidance regarding MRSA treatment. That's an area under current investigation, isn't it?

DR. DASENBROOK: Definitely. I think it is pretty clear from what we've talked about so far that there is definitely clinical equipoise in this question of do we treat a new MRSA infection or do we watch it? Investigators at the University of North Carolina and Seattle designed the STAR-2 study to look at this exact question.

This is a randomized, open-label, multicenter study in children who will be four years or older and adults, comparing a two-week eradication treatment protocol to an observational group that will get antibiotics only if MRSA continues to cause respiratory symptoms.

They plan to enroll a total of 90 patients with new MRSA infections and treat patients with oral rifampin and trimethoprim sulfamethoxazole or minocycline if they're intolerant to the trimethoprim sulfamethoxazole. Patients will also receive topical chlorhexidine and nasal mupirocin.

The primary outcome for this study will be a negative respiratory culture for MRSA at day 28. The study is currently ongoing and we look forward to the results, as they will definitely help in the clinical management of our patients with a new MRSA infection.

MR. BUSKER: Thank you, Dr. Dasenbrook. Move us on now to another patient, please.

DR. DASENBROOK: This patient is a 25-year-old male who presents to a routine quarterly clinic visit

complaining of continued increase in his cough and sputum production. It has not responded to treatment with fluoroquinolones. His physical exam is unchanged from previously and his lungs are clear. His FEV1 is at his baseline of 75%. His previous cultures include a pan-sensitive *P. aeruginosa* and he has cultured MRSA at his last two clinic visits.

His respiratory medications include hypertonic saline, DNase, albuterol, and azithromycin, and inhaled aztreonam every other month. His throat swab from clinic grows MRSA and *P. aeruginosa*. This is his third MRSA culture in the last 12 months.

MR. BUSKER: One of the key differences between this CF patient and the first one you presented is that here we're seeing persistent MRSA infection. What does the evidence say about treating it?

DR. DASENBROOK: Several epidemiologic studies suggest that persistent MRSA is associated with worse outcomes, and thus treatment may benefit these patients. The three main studies all used the United States CF patient registry.

We published an analysis of the US Cystic Fibrosis Foundation patient registry and found a more rapid rate of decline in lung function in patients with MRSA compared to those without MRSA even after adjusting for severity of illness. This study suggests that if we were able to treat or eradicate a persistent MRSA, we might be able to slow lung function decline in our patients with cystic fibrosis and persistent MRSA infections.

The second study was done by DB Sanders and Chris Goss and colleagues at the University of Washington. They also used the USCF patient registry and studied over 8,500 cystic fibrosis exacerbations. Their study had two interesting findings. First, even after treatment with IV antibiotics, a quarter of CF patients still did not achieve at least 90% of their pre-exacerbation lung function. Therefore, prevention of exacerbations is a key goal in maintaining the long-term respiratory health of our patients with cystic fibrosis.

Next, the authors explored risk factors for failure to reach this baseline lung function. One of those risk factors turned out to be respiratory tract MRSA. They found that CF patients with MRSA, compared to patients who never had MRSA, were at a higher risk

of not responding to treatment; therefore, again it appears that treating MRSA may be associated with a decreased risk of exacerbations.

Now, exacerbations and loss of lung function are very important and clinically relevant outcome measures. However, the most important outcome measure is survival. And that brings us to our third study, which we talk about in the associated newsletter. Again we used the United States CF patient registry to look at the impact of respiratory tract MRSA infection on survival. The study showed that patients with MRSA had worse survival compared to patients who did not culture MRSA.

In conclusion, these three studies lead us to believe that MRSA is, in fact, associated with worse outcome and provides impetus to treat MRSA in these patients.

MR. BUSKER: Again, I want to note to our listeners that links to many of the studies Dr. Dasenbrook refers to are available in the transcript version of this podcast.

Those studies you mentioned were primarily epidemiologic. What about studies that directly focus on treating MRSA infection in CF patients?

DR. DASENBROOK: Unfortunately, the published studies are small and have been limited by a lack of control groups, a single center, retrospective design, variable follow-up, and failure to distinguish new versus persistent MRSA infection.

A small study by L.A. Garske and coworkers focused on treatment of adults with cystic fibrosis who had persistent MRSA. Patients had an average FEV₁ of 36% of predicted, and all of them had chronic *Pseudomonas*. Five out of the seven patients, or 71%, were MRSA-culture-negative six months after completing a six-month treatment regimen of oral fusidic acid and rifampin.

So again, we see another regimen where rifampin is added with success in eradicating MRSA. Oral fusidic acid is not available in the United States.

A second study by SJ Doe and colleagues evaluated their experience with eradication of MRSA at the Manchester Adult CF Center in the UK. In this study they looked at 37 patients, and their general strategy was to segregate patients who were infected and

provide aggressive antibiotic treatment to facilitate MRSA eradication.

They used many different eradication regimens to try to eradicate MRSA, but the general theme was that they used combinations of two oral antibiotics such as rifampin, fusidic acid, and/or trimethoprim sulfamethoxazole. In addition, they used nebulized vancomycin for many of the study patients.

They reported that eradication of MRSA was achieved in 81% of the participants at six months. Again, in this study, no distinction was made between patients with new or persistent MRSA infections; however, the authors did report that approximately 38% of the patients included had multiple positive MRSA cultures, and thus we can guess that approximately that many patients may have had persistent MRSA infections.

In conclusion, we have two studies with successful eradication measures; however, we must keep in mind the limitations stated previously.

MR. BUSKER: You just brought up the use of inhaled vancomycin. What safety issues should clinicians be aware of when using this agent?

DR. DASENBROOK: There have been numerous reports of the clinical use of nebulized vancomycin in both CF and non-CF populations, all of which have suggested that it is well tolerated and may be efficacious. Doses of inhaled vancomycin have ranged from 125 mg to 500 mg and anywhere from twice a day to four times a day.

In the largest study to date, 51 non-cystic fibrosis patients received 125 mg of nebulized vancomycin twice a day for an average of 14 days in an attempt to eradicate respiratory tract MRSA.

The authors reported that there were no adverse events associated with inhaling vancomycin in these 51 participants. They also checked whether vancomycin was detectable in the blood two hours after inhaling the vancomycin, and they were unable to detect any vancomycin in the blood.

In another case report, Mayes and colleagues also reported their experience with a 10-year-old patient with CF treated with nebulized vancomycin, 250 mg twice a day for 17 continuous months. The patient had

no adverse events and did not develop antibiotic resistance. They checked for VRE on fecal cultures and looked for the development of vancomycin-intermediate *S. aureus*. The authors did not report any antibiotic resistance.

In another study, Hayes and colleagues reported treating a posttransplant patient with cystic fibrosis and refractory MRSA with inhaled vancomycin twice a day, 250 mg, for six months. The patient had undetectable serum vancomycin levels at two hours, as in the previous case report, and despite taking numerous other nephrotoxic medications, the patient did not have a change in creatinine levels.

In my clinical experience, especially when patients pretreat with albuterol, inhaled vancomycin is very well tolerated.

MR. BUSKER: Please tell us about the PMAP trial — the persistent MRSA eradication protocol.

DR. DASENBROOK: This study is a two-center, randomized, double-blind comparator-controlled study in patients with CF aged 20 to 60 years. The study will compare the safety of an aggressive 28-day inhaled and oral antibiotic combination protocol in 40 patients with CF and persistent MRSA infection. Twenty patients will be randomly assigned to vancomycin for inhalation, 250 mg twice a day in 5 cc of sterile water, and 20 patients will be randomized to taste- and volume-matched placebo. In addition, both groups will receive oral rifampin, a second oral antibiotic, mupirocin intranasal cream, and chlorhexidine body washes and will be given instructions on how to decontaminate high-touch areas in the household.

The primary outcome measure will be the percentage of patients that are MRSA free at one month after completion of the four-month eradication protocol. This study will provide some much-needed guidance on the treatment of persistent MRSA in patients with cystic fibrosis.

MR. BUSKER: We'll return, with Dr. Elliott Dasenbrook from Case Western Reserve in just a moment.

<<COMMERCIAL>>

MR. BUSKER: Welcome back to this eCysticFibrosis Review podcast. I'm Bob Busker, managing editor of the program. Our guest is Dr. Elliott Dasenbrook, Assistant Professor of Medicine and Pediatrics, and Associate Director of the Adult Cystic Fibrosis Program at Case Western Reserve University School of Medicine in Cleveland. And our topic is "Emerging Pathogens in Cystic Fibrosis."

We've been looking at cases that illustrate the evidence basis for treating specific respiratory pathogens in CF. So let's continue with another patient profile.

DR. DASENBROOK: The patient is a 32-year-old female with cystic fibrosis who presents for a sick visit to the CF clinic. She states that her cough has increased in frequency and it is waking her up at night. She usually has a dry cough, but lately has been bringing up sputum. She is also concerned because she is having fevers, which was not a typical symptom with her previous CF exacerbations. She just finished a course of oral antibiotics and there was no change in her symptoms.

On review of systems she states that she has also been more tired than usual and has a decreased appetite. Physical exam is unchanged from previously and her lungs are clear.

Spirometry revealed that her FEV₁ has dropped 8 percentage points below her baseline. Her culture from clinic grows methicillin-sensitive *S. aureus*. The patient was admitted to the hospital and started on IV antibiotics targeting MSSA. On hospital day number two, the microbiology lab called to state that 2+ acid fast bacilli were observed on the AFB smear. Subsequently, the mycobacterium species was identified as a rapid grower.

MR. BUSKER: How would that AFB positive culture change your approach to treatment in this patient?

DR. DASENBROOK: I find the American Thoracic Society and the Infectious Disease Society of America joint statement about the diagnosis and treatment of nontuberculosis Mycobacterial disease to be very helpful in this situation.

First, I maximally treat other non-NTM pathogens. Second, while treatment for, in our patient's case, the MSSA, is ongoing, I also obtain a CT scan of the chest

and additional Mycobacterial cultures. It is important to note that a single positive culture is generally not sufficient to make the diagnosis of NTM lung disease. Both of our patient's cultures were also AFB smear- positive.

In addition, the chest CT of our patient did have some nodular findings that could be consistent with either NTM or CF lung disease. Normally, NTM is a slow and progressive disease process similar to tuberculosis; however, the one exception is *Mycobacterium abscessus*. *Abscessus* can cause a rapidly progressive course; therefore, patients whose AFB culture is initially identified as a rapid grower should be followed closely to make sure that rapid deterioration is not occurring while the workup for NTM is under way.

In our patient's case, despite our treating the methicillin-sensitive *S. aureus* with intravenous antibiotics, her symptoms and lung function did not return to baseline.

MR. BUSKER: What would your next step be?

DR. DASENBROOK: It is a very important point that the diagnosis of NTM requires both clinical and microbiologic criteria. Our patient met both criteria. She met the clinical criteria, because her pulmonary symptoms did not respond to treatment of other organisms that she was culturing, she continued to have fever, sputum production and increased cough, and she had CT scan findings of the chest that could be consistent with NTM. She met the microbiologic criteria because she had two additional AFB-positive expectorated sputum samples.

Therefore, the next step is to consider therapy. Again, I find the guidelines to be very helpful here as they explicitly state that the diagnosis of NTM lung disease does not automatically imply treatment. Clinicians should weigh the risks of the side effects from the treatment of NTM against the potential benefits of treatment in each individual patient.

MR. BUSKER: Is the prevalence of NTM increasing?

DR. DASENBROOK: Absolutely. The prevalence of NTM is increasing. In a recent, prospective, multicenter study in the United States of patients with cystic fibrosis, the overall prevalence of NTM was 13%. The most common isolate was

Mycobacterium avium complex, or MAC, and there was a higher than expected prevalence of *Mycobacterium abscessus* in the CF community.

Data from this study reinforces the point that treatment should not be initiated after just one positive culture. Only 20% of patients with positive NTM cultures went on to meet the ATS microbiologic criteria for disease. Therefore, treating after a single positive culture may expose patients who would not meet diagnostic criteria to potential morbidity from the side effects of the treatment regimen.

In addition to the increasing prevalence, older CF patients are more likely to culture NTM than younger patients. I am concerned about the impact of chronic NTM infection, especially *Mycobacterium abscessus*, on lung function.

In a recent paper by CR Esther and colleagues, which was discussed in the newsletter, NTM was found to be associated with an increased rate of lung function decline. While the authors group all NTM together, the primary driver of the lung function decline was the patients who cultured *Mycobacterium abscessus*. Therefore, I have used the results from the Esther and colleagues study when discussing treatment options with my patients. That study presents yet another argument for the potential benefits of therapy, because treatment may slow the rate of lung function decline.

MR. BUSKER: What are the treatment options for patients with NTM?

DR. DASENBROOK: The first thing I would like to say is that strong consideration should be given to consultation with an infectious disease or pulmonary expert in the treatment of pulmonary NTM. Since our patient had *Mycobacterium abscessus*, let me talk a little bit about the treatment of this infection.

And important point to recognize is that it is very difficult to successfully eradicate *Mycobacterium abscessus*. Since eradication may not be achieved, clinicians must turn to other measures to determine whether the therapy is successful. Examples include improvement in a patient's symptoms, improvement in lung function, and improvement in CT scan of the chest. Therefore, I find obtaining a baseline CT scan very helpful.

To achieve eradication, symptom relief and/or improvement in the CT scan, treatment with IV, oral, and inhaled antibiotics should be considered. The first one to two months of therapy consist of treatment with multiple IV antibiotics, one of which is amikacin, followed by oral antibiotics for at least a year. My personal practice is to occasionally have patients nebulize amikacin twice a day every other month as suppressive therapy for *Mycobacterium abscessus*. Anecdotally, I've found that it seems to control symptoms and decrease the need for toxic intravenous antibiotics. Case reports in the literature have also noted the same.

Fortunately, a trial about to be started looking at inhaled antibiotics for the treatment of NTM lung disease should provide more data about the risks and benefits of inhaled therapy.

MR. BUSKER: Thank you for that case, Doctor. Let's look at one more patient now, please.

DR. DASENBROOK: Our next case is a 55-year-old male patient with cystic fibrosis who chronically cultures *Burkholderia cenocepacia* and presents with a complaint of progressive dyspnea over two weeks and is currently short of breath at rest. His cough is significantly greater than baseline and his sputum is dark green and thick, which is unusual for him. He has also noted subjective fevers associated with sweating and chills.

He inhales meropenem every other month, and these symptoms started during his off month. He saw his primary care physician, who started him on a fluoroquinolone and high-dose corticosteroids.

His physical exam was notable in that he appeared pale, tachypneic, tachycardic, and febrile. His oxygen saturation was 82% on room air. He had diffuse bilateral rales and had an increased work of breathing.

Spirometry revealed that his FEV₁ was 37% of predicted, which was significantly decreased from his baseline of 50%. Chest x-ray revealed bilateral diffuse necrotizing pneumonias. He was started on intravenous meropenem, intravenous tobramycin, and inhaled meropenem. His blood and sputum cultures revealed *Burkholderia cenocepacia*.

MR. BUSKER: What are the criteria for the diagnosis of cepacia syndrome?

DR. DASENBROOK: The presentation of cepacia syndrome is much different from that of a CF pulmonary exacerbation. Suspicion that the patient has cepacia syndrome should occur when patients have high fevers and have a greater degree of tachypnea and respiratory distress compared to their previous pulmonary exacerbations. In addition, the patients may appear toxic.

Imaging will frequently show necrotizing pneumonias, and again, this is not commonly seen with the CF pulmonary exacerbation. Finally, blood cultures will be positive for *Burkholderia cepacia* complex.

MR. BUSKER: This is a patient who, as you presented him, has chronically cultured cepacia for quite a while. What would cause him to develop cepacia syndrome now? What are your thoughts on that?

DR. DASENBROOK: That is a great question. Interestingly, the patient had a history of cancer and had received multiple rounds of chemotherapy, which was associated with neutropenia, and he never had so much as an exacerbation. We still have his original infecting strain from 20 years ago, and the strain from his blood was similar, so we were able to rule out that he had acquired a new strain of cepacia.

A recent paper by JEA Zlosnick and colleagues, which is discussed in the newsletter, may shed some light on the etiology. The authors found a relationship between nonmucoïd status and increased rate of lung function decline. Furthermore, ceftazidime and ciprofloxacin may induce a nonmucoïd phenotype and therefore increase the virulence of the cepacia. Interestingly, meropenem was not associated with the change in the phenotype, so perhaps there was a change in our patient's mucoïd status of his *Burkholderia cenocepacia*, and that led to the enhance virulence.

Based on the results of this paper, with all other things being equal, if I am deciding between treatment with either ceftazidime or meropenem in a patient with a history of cepacia, I would choose meropenem.

MR. BUSKER: Do corticosteroids have a place in the treatment of cepacia syndrome?

DR. DASENBROOK: That is another great question. Surviving cepacia syndrome is extremely rare; in fact, it is case-reportable. Our patient survived his episode and has done quite well without any recurrences.

There is a case report of a young girl who also survived the cepacia syndrome. The patient was deteriorating after a week of treatment with IV antibiotics, and therefore she was started on high-dose IV steroids. She improved over the next 24 hours. Then the steroids were weaned and she worsened again. The steroid dose was then increased and again her symptoms improved immediately. Ultimately the steroids were weaned over five weeks and the patient did quite well.

In our case, the patient went to his primary care physician at the onset of his symptoms. His physician prescribed an oral antibiotic and high-dose corticosteroids. We continued them in the hospital. Given that the mortality of cepacia syndrome approaches 100% and the downsides to corticosteroids are outweighed by potential for survival, a trial of corticosteroids in patients with cepacia syndrome is warranted, in my opinion.

MR. BUSKER: Which antibiotics would you suggest to treat cepacia syndrome?

DR. DASENBROOK: I would suggest the same antibiotics that are used to treat a CF pulmonary exacerbation associated with the patient's particular strain of *Burkholderia cepacia* complex. The only difference is that I am much more aggressive about adding more early in the course in case there is an issue with resistance to one of the antibiotics initially chosen.

Since patients are septic, which is a risk factor for renal failure, I pay very close attention to the development of nephrotoxicity. The antibiotic options are based on the antibiogram and include intravenous meropenem and other intravenous antibiotics such as trimethoprim sulfamethoxazole, aztreonam, fluoroquinolones, and chloramphenicol. I will add inhaled antibiotics to treat the necrotizing pneumonias that are frequently associated with cepacia syndrome.

Another point to mention is that it's also important to look for any collections of infection that may not respond to IV antibiotic therapy. Cepacia syndrome

is also associated with the development of mediastinitis and empyema. If you do have these in your patients, surgical consultation is warranted for immediate drainage.

MR. BUSKER: Thank you, Dr. Dasenbrook, for all those interesting cases. Now I'd like to summarize the key points we talked about today. Let's begin with the evidence for potential treatment options in patients with CF patients who have new and persistent MRSA infections.

DR. DASENBROOK: The current state of research consists of epidemiologic studies suggesting that these infections, new and persistent MRSA, are associated with worse outcomes. Furthermore, we have uncontrolled studies that suggest various therapeutic options that may be useful. Fortunately, right now we have two ongoing controlled studies to determine the optimal treatment regimens, if any, for new and persistent MRSA infection.

MR. BUSKER: What is the evidence for potential treatment options in CF patients with *Mycobacterium abscessus* infection?

DR. DASENBROOK: For *Mycobacterium abscessus*, I think it's important to first make sure that the patient meets the ATS and IDSA criteria for the diagnosis of *M. abscessus* lung infection. Once they do meet those criteria, it is important to remember that just because patients meet diagnostic criteria does not automatically imply that they should undergo treatment. A conversation with the patient discussing the risks and benefits of these potential toxic therapies in their individual case is key.

MR. BUSKER: Finally, what is the the evidence for potential treatment options in CF patients with *Burkholderia cenocepacia* complex and cepacia syndrome?

DR. DASENBROOK: For *Burkholderia cepacia* complex and the associated cepacia syndrome, consideration should be given to high-dose corticosteroids in patients presenting with the cepacia syndrome. There are downsides to treatment with corticosteroids, but given the high mortality of the cepacia syndrome, the potential benefits outweigh the risks.

MR. BUSKER: Dr. Elliot Dasenbrook from the Case Western Reserve University School of Medicine, thank you for participating in this eCystic Fibrosis Review podcast.

DR. DASENBROOK: Thank you, Bob. I really enjoyed it.

MR. BUSKER: This podcast is presented in conjunction with eCysticFibrosis Review, a peer-reviewed CME and CNE-accredited literature review emailed monthly to clinicians treating patients with cystic fibrosis. This activity has been planned and implemented in accordance with the Essential Areas and policies of the Accreditation Council for Continuing Medical Education through the joint sponsorship of The Johns Hopkins University School of Medicine and The Institute for Johns Hopkins Nursing.

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