Pseudomonas aeruginosa Eradication and Outcomes: Key Questions

Our guest author is Christopher Oermann, MD, Director, Division of Pulmonary and Sleep Medicine at Children's Mercy Kansas City.

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

- Discuss potential antibiotic eradication treatment strategies for early Pseudomonas aeruginosa infection.
- Evaluate a proposed therapeutic approach to failed Pseudomonas eradication.
- Summarize a management plan for patients who have recurrent Pseudomonas aeruginosa-positive respiratory cultures following failed eradication.

This discussion, offered as a downloadable audio file and companion transcript, covers the important topic of Pseudomonas aeruginosa Eradication. This program is a follow up to the Volume 6, Issue 9 eCysticFibrosis Review newsletter—Pseudomonas Eradication and Outcomes: Key Questions.

Unlabeled/Unapproved Uses

Dr. Oermann has indicated that his presentation will reference the unlabeled or unapproved use of inhaled colistin, as well as the use of inhaled antibiotics specifically labeled for use in eradication protocols but not labeled for use in children less than 6 years of age.
BOB BUSKER: Hello and welcome to this eCysticFibrosis Review podcast. I'm Bob Busker, managing editor of eCysticFibrosis Review. Our discussion today follows up on our recent newsletter issue on Unanswered Questions about Pseudomonas Eradication. Our guest is that issue's author, Dr. Christopher Oermann, Director of the Division of Pulmonary and Sleep Medicine, in the Department of Pediatrics at Children's Mercy Kansas City.

eCysticFibrosis Review is jointly presented by the Johns Hopkins University School of Medicine and the Institute for Johns Hopkins Nursing. This program is supported by educational grants from Chiesi USA Inc, Vertex Pharmaceuticals Incorporated, and Gilead Sciences.

Learning objectives for this audio program include:

- Discuss potential antibiotic eradication treatment strategies for early Pseudomonas aeruginosa infection.
- Evaluate a proposed therapeutic approach to failed Pseudomonas eradication.
- Summarize a management plan for patients who have recurrent Pseudomonas aeruginosa-positive respiratory cultures following failed eradication.

Dr. Oermann has disclosed that he has received royalties for written material from UpToDate® Pediatrics.

He has also indicated that his presentation today will reference the unlabeled or unapproved use of inhaled colistin, as well as the use of inhaled antibiotics specifically labeled for use in eradication protocols but not labeled for use in children less than 6 years of age.

Dr. Oermann, thank you for joining us today.

DR. OERMANN: Hi, Bob, it's a pleasure to talk with you and your listeners today.

MR. BUSKER: In your newsletter issue, doctor, you reviewed the current Cystic Fibrosis Foundation guidance and compared it to a contemporaneous Cochrane review, and you described how new research is working toward answering the key question of why some patients fail eradication.

Today I'd like to focus on how this information can impact clinical practice. So start us off, if you would please doctor, with a patient scenario.

DR. OERMANN: You provide care for a 6 year old boy with pancreatic-insufficient cystic fibrosis. He has minimal respiratory symptoms with normal spirometry. His nutrition is good and he maintains a normal BMI. He does not expectorate sputum and has not previously grown Pseudomonas aeruginosa from throat swab cultures. Respiratory care includes a bronchodilator followed by hypertonic saline and airway clearance twice daily. Dornase alfa is used once daily. Nutrition and GI care includes pancreatic enzyme replacement therapy and fat soluble vitamin supplementation. His respiratory culture from a routine clinic visit grows Pseudomonas aeruginosa for the first time.
MR. BUSKER: This child is asymptomatic, but with his first *Pseudomonas*-positive culture. So AET — antibiotic eradication therapy — do you think it’s necessary for this child? And if so, what would you consider the most appropriate treatment plan?

DR. OERMANN: Chronic *Pseudomonas* infection is very clearly associated with increased morbidity and mortality among CF patients; therefore, I think antibiotic eradication therapy has become an international standard of care that is clearly indicated for this child and any other patient with new emergence of *Pseudomonas* from a respiratory culture.

The EPIC and ELITE trials which were reviewed in the newsletter provide the most compelling data for AET and support the safety and efficacy of 300 mg of inhaled tobramycin twice daily for 28 days. This approach has been adopted by the Cystic Fibrosis Foundation, which strongly recommends inhaled antibiotic therapy for the treatment of initial or new growth of *Pseudomonas* favoring inhaled tobramycin 300 mg twice a day for 28 days.

The European Cystic Fibrosis Society, in its consensus statement from the Artimino Conference, also states that antibiotic eradication therapy is recommended in CF: 28 days of tobramycin, 300 mg twice daily, is their recommended treatment strategy. They add that other treatment protocols have been shown to be of similar effectiveness and that an optimal regimen isn’t known.

MR. BUSKER: I want to follow up on the last part of what you just said. Other treatment protocols: what are the alternatives to the tobramycin regimen, and when would you consider using them?

DR. OERMANN: Several antibiotic eradication therapy treatment plans have been investigated. The ALPINE study evaluated 75 mg of inhaled aztreonam three times daily for 28 days. This trial wasn’t included in the CF Foundation or Cochrane Reviews discussed in the newsletter for two reasons. First, only abstract data was available at the time of these analyses; and second, it was an open label rather than randomized trial. However, the data from the trial indicates an eradication success rate similar to those reported for inhaled tobramycin, making this a viable treatment option.

Several European trials have evaluated inhaled colistin and oral ciprofloxacin independently, as well as compared to inhaled tobramycin with and without oral ciprofloxacin. These studies have shown that a combination of inhaled colistin and oral ciprofloxacin are effective in *Pseudomonas* eradication and are not inferior to 28 days of inhaled tobramycin. Thus, the use of inhaled colistin with oral ciprofloxacin is another reasonable treatment approach. The concern is that colistin is not FDA approved for inhaled use in the United States, and an inhaled preparation isn’t available.

When to use the treatment plans is a somewhat more challenging question. In the US we certainly have more experience with inhaled tobramycin than with other treatments, as well as more cumulative data. An alternate treatment plan is clearly appropriate for any patient with a history of an adverse reaction to tobramycin.

As pointed out in the Vidya paper reviewed in the newsletter, elevated tobramycin minimum inhibitory concentration (MIC) is associated with an increased risk of eradication failure. Thus, an alternative plan may be appropriate if microbiology laboratory results suggest and increased minimal inhibitory concentration (MIC). Other considerations might include drug availability, cost, and patient preference.

MR. BUSKER: So in the child you described: he’s got a first time *Pseudomonas*-positive culture, but he’s asymptomatic. The guidance says you should attempt eradication, so you’re going to use inhaled tobramycin, 300 mg twice a day, as the guidance recommends. My question is, are there any benefits you might want to consider in using cycled inhaled antibiotic therapy, adding oral antipseudomonal agents, or even providing a longer course of treatment? Your thoughts, please.

DR. OERMANN: The EPIC trial addressed two of these questions. The study found no benefit from cycled vs cultured therapy. Exploring this a little further, Mayer-Hamblett reported that although more patients on cycled therapy achieve sustained eradication than do those on culture-based therapy, those receiving culture-based therapy responded to subsequent therapy and the prevalence of *Pseudomonas* positivity was the same in both groups at the end of the trial.

Additionally, the use of cycled therapy was associated with an increased risk of developing chronic *Pseudomonas* infection
during follow-up. So there is no evidence supporting a benefit associated with cycled therapy vs culture-based therapy, and there is a potential for adverse effects.

Similarly, oral ciprofloxacin didn’t provide additional benefit in the eradication rate, and the cohort treated with inhaled tobramycin plus oral ciprofloxacin had results similar to those of the cohort treated with inhaled tobramycin alone.

As reviewed in the newsletter, the ELITE trial compared 28 day vs 56 day treatment courses. No benefit was seen in the 56 day vs 28 day cohorts. Thus, 28 days of inhaled tobramycin, 300 mg twice daily, is the gold standard for eradication therapy, and there is no benefit to cycled therapy, added oral antibiotics, or prolonged treatment.

MR. BUSKER: Thank you, doctor. And we’ll return with Dr. Christopher Oermann from Children’s Mercy Kansas City, in just a moment.

MR. BUSKER: This is Bob Busker; I’m the managing editor of eCysticFibrosis Review.

eCysticFibrosis Review is a combination newsletter and podcast program delivered via email to subscribers. Newsletters are published every other month. Each issue reviews the current literature in areas of importance to pulmonologists, gastroenterologists, infectious disease specialists, pediatricians, respiratory therapists, dietitians, nutritionists, nurses, and physical therapists.

Bimonthly podcasts are also available as downloadable transcripts, providing case-based scenarios to help bring that new information into practice in the clinic.

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MR. BUSKER: Welcome back to this eCysticFibrosis Review podcast. I’m Bob Busker, managing editor of the program. We’re with Dr. Christopher Oermann from Children’s Mercy Kansas City, discussing how the New Insights into Pseudomonas Eradication he presented in his newsletter issue can be applied in the clinic.

So let’s continue, if you would please doctor, with another patient scenario.

DR. OERMANN: So let’s talk about a 14 year old girl that you care for. She has pancreatic-insufficient cystic fibrosis and mild respiratory symptoms with some daily cough. Her baseline FEV₁ is in the upper 80s, her nutrition is good, and she maintains a normal BMI. She doesn’t typically expectorate sputum but does have a productive cough during pulmonary exacerbations.

She typically grows MSSA and has recently grown Pseudomonas from an expectorated sputum. In an attempt at eradication therapy, she was treated with inhaled tobramycin, 300 mg twice daily for 28 days. Her routine respiratory care includes a bronchodilator followed by hypertonic saline and airway clearance twice daily, and then dornase alfa once daily. Nutrition and GI care includes pancreatic enzyme replacement therapy and fat soluble vitamin supplementation.

Her repeat sputum specimen following eradication therapy has shown continued growth of Pseudomonas.
MR. BUSKER: Her sputum still shows *Pseudomonas* and this patient has failed antibiotic eradication therapy. What are the next steps in treating her?

DR. OERMANN: Failed eradication therapy is a relatively common scenario. We know from the trials reviewed in the newsletter that eradication failure occurs in up to 40% of patients. The greatest challenge in this situation is that we don’t have any data on which to base therapeutic decisions and very little guidance from existing medical literature.

Failed eradication wasn’t addressed in the CF Foundation Guidelines. It was discussed in the European Consensus Guidelines referenced previously, but only in very generic terms. The Artimino recommendation is repeated first line eradication therapy if the patient fails the first attempt, but specific regimens are not included, and there is no statement regarding changing regimens or duration of therapy.

Similarly, the recommendation for continued failure to eradicate after a second course of therapy is “aggressive third line clearance,” but this isn’t defined. As I said, there is no evidence on which to base treatment decisions and very little guidance.

MR. BUSKER: So without evidence-based guidance, what to do next — that next step — has to be based on expert opinion and clinical experience. So let me ask you: based on your clinical experience, what would you do in this situation?

DR. OERMANN: I usually provide a second 28 day course of therapy with 300 mg of inhaled tobramycin twice daily. I don’t typically add an oral antibiotic, but it’s certainly a consideration. If you think about the airways being obstructed distal to mucus impaction, it’s certainly possible that inhaled antibiotics aren’t reaching those distal areas and that systemic therapy might be beneficial.

Changing antibiotics is also a consideration. If the laboratory reports suggest elevated MIC for tobramycin, I’d consider using inhaled aztreonam 75 mg three times daily for 28 days.

It’s worth mentioning that often patients have not received significant inhaled or systemic antibiotic therapy, but usually they don’t have elevated MICs for tobramycin. I would consider inhaled aztreonam mostly as a matter of family preference. Many families would prefer to do three short treatments a day vs two longer treatments per day. Both are equally effective, so there is no reason not to comply with family preferences in this situation.

MR. BUSKER: Let’s take things a step further. Let’s say your patient has a second course of eradication therapy but continues to be positive for *Pseudomonas*. Is this a point where you would consider hospitalization for IV antibiotic therapy?

DR. OERMANN: As we’ve already learned, there is not a great deal of guidance in this situation. I think hospitalization for intravenous antibiotic therapy is certainly a reasonable thing to do. Although it’s disruptive to families and extremely burdensome, hospitalization for aggressive therapy allows us to do several things. The morbidity associated with chronic *Pseudomonas* infections warrants exhausting all approaches to eradication.

Additionally, intravenous therapy may allow antibiotics to reach distal portions of the respiratory tract that are obstructed by mucus. Lastly, hospitalization ensures that all therapies, including eradication therapy and airway clearance and others, are appropriately delivered.

MR. BUSKER: And would you continue the inhaled antibiotic?

DR. OERMANN: I typically include an alternate inhaled antibiotic if I find I may need to admit patients because of failed eradication therapy. If I’ve used two cycles of inhaled tobramycin, I would generally use inhaled aztreonam.

MR. BUSKER: Thank you for that case and discussion, Dr. Oermann. We’ve got time to look at one more patient scenario — so if you would please.
DR. OERMANN: You provide care for a 17 year old adolescent who has a daily productive cough with a baseline FEV₁ in the low 80s. He has marginal nutrition, with a BMI at the 25th percentile. He typically grows MRSA from sputum specimens. Routine respiratory care includes a bronchodilator followed by hypertonic saline and airway clearance twice daily. Dornase alfa is used once daily. Nutrition and GI care includes pancreatic enzyme replacement therapy and fat-soluble vitamin supplementation.

He has grown *Pseudomonas* from multiple sputum cultures in the past year and has undergone three courses of eradication therapy. Two of his most recent respiratory cultures have grown *Pseudomonas*, despite hospitalization for *Pseudomonas* eradication.

MR. BUSKER: Three courses of eradication therapy, two of them in the hospital. And he's still continuing to grow *Pseudomonas*. At what point do you consider a patient to be chronically infected, as opposed to having early or intermittent *Pseudomonas* infection?

DR. OERMANN: A number of different classification systems are used when discussing *Pseudomonas* infection, but we have no universally accepted definition of chronic infection. However, one of the more frequently referenced classification systems is the one used in Leeds and described by Lee and colleagues in 2003. They classify patients as “never infected,” which means patients have never had a sputum culture or throat swab positive for *Pseudomonas*. Patients are “free of infection” if they have had no growth of *Pseudomonas* during the past 12 months but have had a previous positive *Pseudomonas* culture. Patients have “intermittent infection” if *Pseudomonas* cultures are positive in 50% or fewer of the previous 12 months. They define “chronic infection” as *Pseudomonas* positive cultures in more than 50% of the previous 12 months.

MR. BUSKER: So by that classification system, this patient would be considered chronically infected. What's your approach to treatment?

DR. OERMANN: If our approach to failed eradication therapy suffers from lack of evidence on which to base therapeutic decisions, our approach to managing chronic *Pseudomonas* infection suffers from even greater lack of evidence. The CF Foundation consensus guidelines for managing lung health includes an “A” rating, indicating a high degree of certainty of substantial benefit of using inhaled tobramycin in patients with moderate to severe lung disease. They also provide an “A” rating indicating a high degree of certainty of substantial benefit with inhaled aztreonam in patients with moderate to severe lung disease. Lastly, they recognize that an optimum treatment approach has yet to be identified and there are key unanswered questions.

The European Consensus Conference recommends intermittent one month on/one month off treatment with an inhaled aminoglycoside or continuous administration of inhaled colistin, which is not approved in the United States. Changing antibiotic regimens should be considered in patients with frequent exacerbations or rapid lung function deterioration. Lastly, they recommend considering continuous alternating antibiotic therapy for patients with unstable disease.

My personal approach in CF patients with chronic *Pseudomonas* is inhaled antibiotics continuous alternating antibiotic therapy. The choice of specific antibiotics is based on individual patient microbiology results. I want to stress that this is based on my own philosophy of care and personal experience, not on evidence, as there is none addressing this particular question. A complete discussion of the issues is beyond the scope of what we can do here today, but as pointed out by the CF Foundation Consensus Statement, it is a key unanswered question.

As we’ve discussed, there isn’t any guidance for optimum use of inhaled antibiotic in CF care. Again, I believe that continuous alternating antibiotic therapy is appropriate. If we look at diabetes or hypertension or other disease processes that are always there, most of these diseases are treated every day, not alternating days or months. And so my feeling is that for patients who have *Pseudomonas* in their lower respiratory tract all the time, it’s most appropriate to treat them every day as opposed to alternating months.

Another consideration is, in the patients that I’ve treated with continuous alternating therapy, I have seen gradual improvement in lung function over time, suggesting there may be some benefit to this type of therapy.

MR. BUSKER: A moment ago you said the CF Foundation recognizes that there are key unanswered questions about
the optimum treatment approach to *Pseudomonas* infections. Before we wrap things up, I'd like to get your thoughts on that. To your mind, what are the most important unanswered questions about *Pseudomonas* eradication therapy?

DR. OERMANN: I think there are a couple of critical unanswered questions that we desperately need answers to. The first one is that although none of the clinical trials reported to date has identified patient-specific factors that are associated with failed eradication, continued efforts to identify patient characteristics that increase the risk of failure are important.

Another important research question is the identification of *Pseudomonas*-specific predictors of eradication failure. Mayer-Hamblett and Vidya, as noted in the newsletter issue, have both indicated that some *Pseudomonas* characteristics can be identified by microbiology laboratories and may predict failed eradication therapy. Collaboration with microbiology laboratories may allow more individualized AET regimens.

Additional research may yield information regarding *Pseudomonas* markers that place patients at increased risk for eradication failure.

Finally, much more research is necessary on our approach to failed eradication. A much more rigorous and evidence-based approach is desperately needed.

I do want to add that the debate over a “best regimen” is somewhat irrelevant to me. There are three well-described effective approaches to antibiotic eradication therapy, none of which has been shown to be superior to the others.

MR. BUSKER: Thank you for sharing your thoughts, doctor. Let’s wrap things up now by reviewing today’s discussion in light of our learning objectives. So to begin: potential eradication treatment strategies for early *Pseudomonas* infection.

DR. OERMANN: We reviewed three potential eradication regimens today. These include inhaled tobramycin 300 mg twice daily for 28 days; inhaled aztreonam 75 mg three times a day for 28 days; and inhaled colistin combined with oral ciprofloxacin. All have been proved effective and none has been shown to be superior to another, so any of these regimens would be appropriate.

The CF Foundation and European Consensus documents do state that tobramycin is a preferred therapy. I want to add that although colistin is widely used in European countries, an inhaled form of colistin is currently not available in the United States.

MR. BUSKER: And our second learning objective: the proposed therapeutic approaches to *Pseudomonas* eradication failures.

DR. OERMANN: As we’ve discussed, there isn’t any compelling data to guide clinicians in treating patients who have failed a first attempt at eradication. The European Consensus Conference suggested a second course of first line therapy, which is likely the approach most North American clinicians would take. This could be any of the three regimens previously reviewed, but it is often inhaled tobramycin, which has been recommended by the CF Foundation and the European Consensus Conference. Using different inhaled antibiotics, oral antibiotics, and intravenous antibiotic have all been considered to be reasonable by the CFF.

MR. BUSKER: And finally: developing a management plan for patients who have recurrent *Pseudomonas*-positive respiratory cultures following failed eradication.

DR. OERMANN: Again, there is very little evidence regarding the optimum approach to chronic suppressive antibiotic therapy for CF patients who have chronic *Pseudomonas* infection. Good evidence exists for the independent use of multiple inhaled antibiotics and was reviewed today. The real question is how to best use existing medications in combination, as well as those medications that will undoubtedly be developed in the future.

MR. BUSKER: Dr. Christopher Oermann from Children’s Mercy in Kansas City, thank you for participating in this eCysticFibrosis Review Podcast.
DR. OERMANN: Bob, you’re welcome. I really appreciate the opportunity to talk with you and your listeners today.

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