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Podcast Issue

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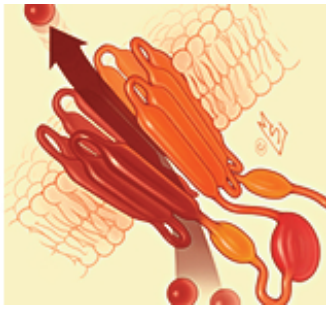

VOLUME 5 — ISSUE 4: TRANSCRIPT

Featured Cases: *P. aeruginosa* Eradication and Reinfection

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

- Explain the available options to treat early *Pseudomonas aeruginosa* infection.
- Discuss whether treatment should be repeated in patients who develop recurrence of infection.
- Describe potential treatment options for patients failing eradication therapy.

This discussion, offered as a downloadable audio file and companion transcript, covers the important issues related to *P. aeruginosa* eradication in the format of case-study scenarios for the clinical practice. This program is a follow up to Volume 5, Issue 3 *eCysticFibrosis Review Newsletter* – *P. aeruginosa* eradication and reinfection.

MEET THE AUTHOR

Felix Ratjen, MD
Division Chief,
Respiratory Medicine
Hospital for SickKids
Professor of Pediatrics
University of Toronto
Toronto, Canada

Guest Faculty Disclosure
Dr. Felix Ratjen has disclosed that he has served as a consultant for Gilead Sciences and received grant funding from Novartis Pharmaceuticals.

Unlabeled/Unapproved Uses
Dr. Felix Ratjen will not discuss any off-label or unapproved uses of any drugs or products.

Release Date
February 26, 2015

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February 25, 2017

PROGRAM DIRECTORS

CME/CE INFORMATION

⇩ PROGRAM BEGINS BELOW

ACCREDITATION STATEMENTS

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LAUNCH DATE

This program launched on November 12, 2014, and is published monthly; activities expire two years from the date of publication.

INTENDED AUDIENCE

This activity has been developed for pulmonologists, pediatric pulmonologists, gastroenterologists, pediatricians, infectious disease specialists, respiratory therapists, dieticians, nutritionists, nurses, and physical therapists.

STATEMENT OF NEED

Based on a review of the current literature, including national and regional measures, detailed conversations with expert educators at Johns Hopkins, and a survey of potential program participants, this program will address the following core patient care gaps:

Disease-Modifying Therapies

- Clinicians may be unfamiliar with recently introduced disease-modifying therapies and how they are altering the therapeutic landscape for patients with cystic fibrosis.
- Clinicians may be uncertain how to integrate genotyping into therapeutic decisions and how to communicate with patients and families about the relationship between genotype and therapy

Nutrition

- Many clinicians lack strategies to persuade patients to adhere to CF nutritional requirements, resulting in low body weight and nutritional failure in patients with cystic fibrosis.
- Many clinicians remain uncertain how to optimize pancreatic function in patients with cystic fibrosis.

Treating CF Patients with Inhaled Antibiotics

- Clinicians lack knowledge about the use of existing and emerging inhaled ABX to treat chronic pulmonary infections.
- Clinicians need more information to make informed decisions about the use of inhaled ABX in combination.
- Clinicians lack information about best practices for scheduling ABX therapy to suppress chronic airway infections.
- Common clinician assumptions about treating pulmonary exacerbations lack supporting evidence.
- CF clinicians are not aware of and/or are not actively advocating inhaled ABX patient-adherence strategies.

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Johns Hopkins University School of Medicine
Office of Continuing Medical Education
Turner 20/720 Rutland Avenue
Baltimore, Maryland 21205-2195

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HARDWARE & SOFTWARE REQUIREMENTS

PC: Internet Explorer (v6 or greater), or Firefox
MAC: Safari

MR. BOB BUSKER: Welcome to this *e*CysticFibrosis Review podcast. Today's discussion is a follow-up to our newsletter topic: *Pseudomonas eradication and reinfection*. Joining us today is that issue's author, Dr. Patrick Ratjen, Division Chief of Respiratory Medicine at the Hospital for SickKids and Professor of Pediatrics at the University of Toronto, in Toronto, Ontario, Canada.

*e*CysticFibrosis Review is presented jointly by the Johns Hopkins University School of Medicine and the Institute for Johns Hopkins Nursing. This program is supported by educational grants from AbbVie, Gilead Sciences Inc., and Vertex Pharmaceuticals.

Learning objectives for this audio program include:

- Explain the available options to treat early *Pseudomonas aeruginosa* infection.
- Discuss whether treatment should be repeated in patients who develop recurrence of infection.
- Describe potential treatment options for patients failing eradication therapy.

Dr. Ratjen has indicated that he has received grant funding from Novartis and served as a consultant for Gilead Sciences. He has indicated that there will be no reference to unlabeled or unapproved uses of drugs or products in today's discussion.

I'm Bob Busker, managing editor of *e*CysticFibrosis And I want to thank you, Dr. Ratjen, for joining us today.

DR. RATJEN: Thank you for having me.

MR. BUSKER: In your newsletter issue you reviewed recent publications describing protocol-based *Pseudomonas* eradication strategies, the efficacy of both inhaled tobramycin and aztreonam lysine and new ways to evaluate *pseudomonas* infection and eradication success. Today I'd like to discuss how that new information might impact practice in the clinic. So please start by describing a patient.

DR. RATJEN: The first patient we will discuss is a four year old female CF patient with her first positive *Pseudomonas aeruginosa* culture detected at a routine clinic visit.

MR. BUSKER: Four years old, first *pseudomonas* infection. How was her infection detected? Was it done by throat swab?

DR. RATJEN: Yes, it was done by throat swab, as is commonly the case in this age group because patients at this age rarely produce any sputum.

MR. BUSKER: How should this infection be treated?

DR. RATJEN: We have learned over the years that treatment for first *pseudomonas* infection is beneficial. Therefore, a patient who has a positive culture should be treated, even in the absence of clinical symptoms. So we should not base our decisions to treat on whether symptoms are present, but whether *pseudomonas* is present. So if we have a positive culture, treatment should be initiated.

MR. BUSKER: There are a number of treatment options. Based on your knowledge and experience, which treatment should be used and for how long?

DR. RATJEN: A number of studies have been done in the field, and based on those studies, inhaled tobramycin inhalation solution is the best studied option. And based on the knowledge that we have, 28 days of treatment is sufficient. We also have studies that have looked at whether adding ciprofloxacin to the treatment will have any added benefit, and that is not the case. So in essence, 28 days of inhaled tobramycin inhalation solution would be the first treatment of choice.

MR. BUSKER: After 28 days of inhaled tobramycin, at what point should this patient be seen for follow-up?

DR. RATJEN: We recommend follow-up after cessation of treatment, ideally one week after therapy has been stopped. If patients are still on therapy, the cultures might be negative even though *pseudomonas* is still present in the lower airways. So we recommend following up one week after treatment cessation. At that point cultures should be repeated, and if negative, further follow-up should be planned.

MR. BUSKER: I want to ask you about the reliability of throat swabs to define infection. I know there is some controversy there. What are your thoughts on that?

DR. RATJEN: Throat swabs are not ideal for predicting lower airway infection. We have learned this from comparative studies where throat swabs have been compared to bronchoalveolar lavage, which is kind of our gold standard to define infection; or by comparing them to sputum in patients who are able to produce sputum. The bronchoalveolar lavage studies have shown us that while the positive predicted value of throat swabs is not ideal, the negative predicted value is relatively high.

That means, if a patient has a negative culture based on throat swab it is unlikely that *pseudomonas* is present in the lower airways. On the other hand, a positive culture doesn't necessarily mean that *pseudomonas* is always present in the lower airways. But if we want to follow our patients after eradication therapy, then having a negative culture has a relatively high predictive value that lower airway cultures will actually be negative. But because it's just a single culture, we try to rely on more than one culture by performing multiple cultures rather than relying on one time point alone.

MR. BUSKER: Thank you for that case and that information, doctor. And we'll return, to discuss *pseudomonas* eradication with Dr. Ratjen from the University of Toronto in just a moment.

MS. MEGAN RAMSEY: Hello, my name is Meghan Ramsay, nurse practitioner and adult clinical coordinator for the Johns Hopkins Cystic Fibrosis Program at the Johns Hopkins University School of Medicine. I am one of the Program Directors of *e*CysticFibrosis Review. These podcast programs will be provided on a regular basis to enable you to receive additional current, concise, peer-reviewed information through podcasting, a medium that is gaining wide acceptance throughout the medical community. In fact, today there are over 5,000 medical podcasts. To receive credit for this educational activity and to review Hopkins policies please go to our website at www.ecysticfibrosisreview.org.

This podcast is part of eCysticFibrosis Review, a bimonthly, email-delivered program available by subscribing. Each issue reviews a current literature on focus topics important to clinicians caring for patients with cystic fibrosis. Continuing education credit for each newsletter and each podcast is provided by the Johns Hopkins University School of Medicine for physicians and by The Institute for Johns Hopkins Nursing for nurses.

Subscription to *e*CysticFibrosis Review is provided without charge, and nearly a thousand of our colleagues have already become subscribers. The topic-focused literature reviews help keep them up to date on issues critical to maintaining the quality of care for their patients.

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MR. BUSKER: Welcome back to this *e*Cystic Fibrosis podcast. I'm Bob Busker, managing editor of the program. Our topic is *Pseudomonas aeruginosa* eradication and reinfection. Our guest is Dr. Felix Ratjen from the Hospital for Sick Kids and the University of Toronto.

We've been discussing how some of the new information Dr. Ratjen presented in his newsletter issue can inform clinical practice. So please bring us another patient.

DR. RATJEN: This case is a six year old male patient with cystic fibrosis who had a past infection with *pseudomonas* at age five, and now at a routine clinic visit with clinical symptoms, he has another positive culture for *pseudomonas*.

MR. BUSKER: So he had a successful eradication, and now a year later he has no symptoms but the culture is positive for *pseudomonas* again. Should treatment be initiated now, despite the absence of symptoms?

DR. RATJEN: Yes is the short answer. From what we learned about first *pseudomonas* and early *pseudomonas* infection, the second infection does not necessarily differ in impact, but also in the success rate of eradication therapy. Having said that, it's important to clarify whether in the meantime the patient had negative cultures, because if you have cultures for less than a period of a year, it is difficult to say that the patient ever became negative for *pseudomonas*. That relates to the previous issue we discussed, that relying on one or two cultures alone to define the status of *pseudomonas* infection is not necessarily enough.

But let's assume he had multiple negative cultures and this is likely a new infection: treatment should be initiated again.

MR. BUSKER: What do we know about why this patient became reinfected with *pseudomonas*?

DR. RATJEN: Overall, all patients with CF have a risk of developing *pseudomonas* infection, and even if you treat it successfully, that doesn't mean that the overall risk of getting *pseudomonas* will go away. In this case, since there was about a year between the first infection and the subsequent infection, the question will always come up whether he has ever cleared the *pseudomonas*. For that it's important to rely on multiple cultures ,as I mentioned before. In addition, there are some risk factors that we know make it more likely that a patient will get *pseudomonas* infection. Those involve issues such as severe genotypes and more significant lung disease. But overall, every patient with CF has the risk of developing *pseudomonas* infection, so it can always happen again.

MR. BUSKER: Are environmental factors involved in *pseudomonas* reacquisition?

DR. RATJEN: Yes, there are multiple sources in the environment where patients can acquire *pseudomonas*, and in a given patient it is always difficult to find out where this actually happened. We know that standing water or wells are potential sources of *pseudomonas*, but other sources such as nebulizers can be contaminated with bacteria such as *Pseudomonas*. Sometimes family members with airway disease could have *pseudomonas*; that's less likely but can happen in individual cases.

Overall what we tell patients is that *pseudomonas* is basically everywhere in the environment, so completely avoiding any contact to *pseudomonas* is virtually impossible.

MR. BUSKER: Before you attempt eradication again, how important is to know whether this is the same subspecies of *pseudomonas* or a variant?

DR. RATJEN: Scientifically it's an interesting question, but for clinical purposes you don't necessarily need to know that.

It's always difficult to completely define whether an infection that we have in a patient with cystic fibrosis is a new infection or an infection that has been there before. In clinical studies what we have used is to say that a patient has to be free of *Pseudomonas* for at least a year to consider it a new or early infection with *pseudomonas*. But in the studies we have also implemented the rules that we need at least two cultures per year, ideally more than that to make that case. If that's not the case we have to use longer time intervals, up to two years, to clarify whether a patient actually has a new infection.

A number of studies done in the past have shown that in the majority of cases, it's actually a new genotype of *pseudomonas* that you find in this setting, which would support the idea that it's a new acquisition rather than persistence of the *pseudomonas* over time. But in managing a given patient, knowing that doesn't necessarily help.

MR. BUSKER: Following either an initial or reattempt at eradication, how do you determine success?

DR. RATJEN: In clinical practice we like to see multiple cultures over a period of a year, ideally four or more, to clarify whether a patient is free of *pseudomonas*. And as I mentioned before, with a recent infection we always encourage patients to bring in multiple samples over the first six months after the infection to give us a better feeling for whether *pseudomonas* has actually been cleared.

MR. BUSKER: Is there evidence that a *pseudomonas* reinfection is any more or less severe than the initial infection?

DR. RATJEN: For *pseudomonas* infection, our treatment is based on culture positivity. That can be a situation where actually *pseudomonas* only colonizes the airways and doesn't necessarily cause symptoms of an infection. That is usually the situation for the second positive culture after first initial therapy, very similar to the situation that you find the first time around.

The short answer for that is no: no evidence suggests that the second time is any different from the first time, either in severity or in success rate of therapy.

MR. BUSKER: Thank you. We have time for one more patient.

DR. RATJEN: This patient is seven years of age and let's say it's a female patient. In this case there have been two courses of tobramycin inhalation solution, and despite these two courses the patient is still positive for *pseudomonas* infection.

MR. BUSKER: After failing two attempts at eradication, many clinicians would just throw up their hands and say: "I give up on eradication. This is a chronic infection." What are your thoughts on that?

DR. RATJEN: I think that at this time it's still too early to say this is chronic infection. It may just be that our current treatment regimens have failed, because so far we have used the same therapy twice, but we haven't tried any other forms of therapy. But I also need to say that the transition between initial or early infection and chronic infection is not entirely clear, especially as we intervene with therapy.

MR. BUSKER: What other forms of therapy are you considering? What does the evidence say?

DR. RATJEN: At this stage of infection, we have relatively little evidence for the efficacy of different treatment strategies. What I mean by that is, we have little comparative data to suggest that one treatment strategy is necessarily better than another. However, our own data suggest there is still a chance that you can clear *pseudomonas* at this point in time. I think in the future it will be a challenge to define the best strategy we can use at this stage of infection. So far the data we have is based on relatively small numbers because, overall, eradication therapy is highly successful. So the rates of failure become smaller and smaller in a patient like this who has failed two courses of therapy.

MR. BUSKER: And your experience with different eradication regimens?

DR. RATJEN: In our center, our regimen is to use intravenous antibiotics at this stage in combination with inhaled therapy, but other forms of therapies could also be used, such as another inhaled antibiotic. Data came out recently showing that inhaled aztreonam is efficacious as a therapy for *pseudomonas* eradication, but I have to say it has not been studied in this setting.

MR. BUSKER: What about oral antibiotics like the quinolones?

DR. RATJEN: We don't have a lot of evidence that all quinolones add anything to the success rate of inhaled antibiotics alone in eradication therapy. But most of that evidence comes from treatment of the first infection or a recurrence after a period of being infection-free, which we call early infection.

In a situation like that some people would use oral quinolones as an option for therapy. We would not because we want to maximize therapy, which is why we become relatively aggressive and use IV antibiotics. No data that I'm aware of suggest that using a quinolone in association with inhaled antibiotics or a quinolone alone would be of any benefit. At least with the regimen we use with intravenous antibiotics, we have some data that in about a third of the patients we can still clear *pseudomonas*.

MR. BUSKER: What would be your agents IV antibiotics of choice?

DR. RATJEN: In a situation like this, we are usually dealing with a highly sensitive strain of *pseudomonas*, and our first treatment choice would be the combination of ceftazidime and tobramycin intravenously for 14 days. We would then add an inhaled antibiotic for another 28 days after completing the IV therapy and then reassess the patient about a week after the inhaled therapy course has stopped.

MR. BUSKER: Is there any evidence describing the use of inhaled antibiotics at the same time as IV antibiotics?

DR. RATJEN: There's no evidence, either in chronic infection or early infection with *pseudomonas*, that adding on inhaled antibiotics at the same time as intravenous antibiotics increases the benefit or the success rate of therapy. So we don't use them at the same time. The other issue is that currently our regimen is to use tobramycin inhalation solution as an inhaled antibiotic for first-line therapy, and also in patients who have failed previous courses of therapy. Using IV antibiotics with tobramycin on one hand, and inhaled tobramycin on the other hand at the same time, increases the risk of side effects. So since we don't have any evidence of increased benefit and there's a higher risk of side effects, we would not use this in our regimen.

MR. BUSKER: Thank you, Dr. Ratjen, for today's cases and discussion. I want to ask you to look into the future for us: what are the next steps to improve early *pseudomonas* eradication?

DR. RATJEN: I think what we've seen so far is that we learned that being more aggressive initially does not seem to make a lot of sense, because if we use longer courses of therapy it does not necessarily increase the success rate. So I feel that we have to learn from what oncology has learned from their protocols: once you are at the point where your initial therapy is highly successful then you have to deescalate this therapy and make it as simple and short as possible. And I think we are already at this point in using inhalation therapy alone for eradication and relatively short courses of 28 days for this initial therapy.

I think in the future we need to focus on stratifying patients according to risk, and that's very similar to oncology where patients are not necessarily all treated the same. As we learn more about patient groups that have a higher risk of failure, we would treat them differently and would use protocols to see if that will increase the success rate of therapy.

The other thing that we need to focus on is to study rescue therapy as we talked about a couple of minutes ago. That is, protocols for patients who have failed initial or repeated courses of eradication therapy. This requires a more challenging study design but it's also very important because we have to be clear what we should do to maximize the chances that we clear *pseudomonas*, even at a later time and again when we have multiple courses that have already been attempted.

MR. BUSKER: Which current studies do you find most interesting?

DR. RATJEN: Two larger studies are currently ongoing, one in Europe and one in the United States. Let's start with the study in the US, the OPTIMIZE trial, which is currently enrolling. The OPTIMIZE trial asks whether adding azithromycin to inhaled tobramycin alone increases the success rate of eradication and also reduces clinically relevant endpoints such as the rate of pulmonary exacerbations.

The other study is being done in Europe or more specifically in the United Kingdom, the TORPEDO study. The TORPEDO study will compare using intravenous antibiotic therapy as a first-line therapy for patients with first or early infection, versus using the combination of ciprofloxacin and colistin, which is commonly used in Europe and is an off-label application of colistin. In this study they will try to see whether using IV as a first-line therapy will increase the success rate of treatment.

Ideally, we would like to see a comparison of IV therapy to inhaled tobramycin, which is the first-line therapy in most countries around the world. So there will be some open questions, even when this study has been completed.

MR. BUSKER: Thank you for sharing your insights, doctor. Let's wrap things up by reviewing what we talked about today in light of our learning objections. So to begin: the available options to treat early *pseudomonas* infection.

DR. RATJEN: We have different options to treat for *pseudomonas* or early *pseudomonas* infection, and they include inhaled antibiotics alone, which is inhaled tobramycin, or as a newer option inhaled aztreonam; as well as adding ciprofloxacin as an oral agent, or using intravenous antibiotics. As I explained, the best currently available evidence is for inhaled tobramycin, and there is no added benefit that we know of from adding any other therapy to that.

MR. BUSKER: And our second objective: deciding whether treatment should be repeated in patients who develop recurrence of infection.

DR. RATJEN: Based on the evidence that we have, the answer is absolutely yes: patients who have repeated infection with *pseudomonas* should be treated again. So far the evidence suggests that the success rate is very similar because it's likely a new infection with *pseudomonas* rather than recurrence of the same organism.

MR. BUSKER: And finally: potential treatment options for patients failing eradication therapy.

DR. RATJEN: For patients failing eradication therapy, we suggest not giving up after two courses of the same regimen, which usually is inhaled tobramycin, but try a different regimen. In our center we use intravenous

antibiotics at that point, followed by a course of inhaled antibiotics, but are other options could potentially be useful such as using another inhaled antibiotic such as aztreonam.

MR. BUSKER: Dr. Felix Ratjen from the University of Toronto, thank you for participating in this eCystic Fibrosis Review Podcast.

DR. RATJEN: Thank you for the opportunity.

MR. BUSKER: To receive CME credit for this activity, please take the post-test at www.ecysticfibrosisreview.org/test.

This podcast is presented in conjunction with *e*CysticFibrosis Review, a peer-reviewed CME/CE credit, emailed monthly to clinicians treating patients with Cystic Fibrosis.

This activity has been developed for the CF Care Team, including pulmonologists, pediatric pulmonologists, gastroenterologists, pediatricians, infectious disease specialists, respiratory therapists, dietitians, nutritionists, pharmacists, nurses and nurse practitioners, physical therapists, and others involved in the care of patients with cystic fibrosis.

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