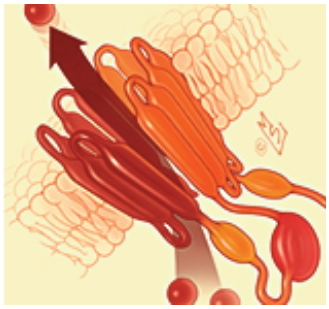
JOHNS HOPKINS MEDICINE
eLITERATURE REVIEW
eCysticFibrosis Review
Podcast Issue
Jointly presented by the Johns Hopkins University School of Medicine and the Institute for Johns Hopkins Nursing
Vol 5: Supported by an educational grants from AbbVie, Gilead Sciences Inc., and Vertex Pharmaceuticals Incorporated



VOLUME 5 — ISSUE 14: TRANSCRIPT

Featured Cases: Agents for the Management of *Pseudomonas aeruginosa* Infection

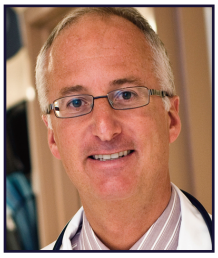
Our guest author is Shawn Aaron, MD from the University of Ottawa, in Ottawa, Ontario.

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

- Discuss optimal therapy of chronic *Pseudomonas aeruginosa* infection in patients with cystic fibrosis.
- Describe the pathophysiology of pulmonary exacerbations associated with *Pseudomonas* infection in patients with cystic fibrosis.
- Evaluate the optimal choice of antibiotics to treat *Pseudomonas*-associated pulmonary exacerbations in patients with cystic fibrosis.

This discussion, offered as a downloadable audio file and companion transcript, covers the important issues related to the effects of CFTR modification targets in the format of case-study scenarios for the clinical practice. This program is a follow up to Volume 5, Issue 13 *eCysticFibrosis Review Newsletter* — Agents for the management of *Pseudomonas aeruginosa* infection.

MEET THE AUTHOR



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Guest Faculty Disclosure
Dr. Aaron has disclosed that he has no relationships with a commercial entity.

Unlabeled/Unapproved Uses
Dr. Aaron will include references to the off-label or unapproved uses of drug or products, including inhaled colistin, inhaled levofloxacin, inhaled ciprofloxacin, liposomal amikacin, doripenem, and sitafloxacin.

Release Date
November 19, 2015

Expiration Date
November 18, 2017

CME/CE INFORMATION

⇩ PROGRAM BEGINS BELOW

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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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Guest Author Disclosure

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PC: Internet Explorer (v6 or greater), or Firefox
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MR. BOB BUSKER: Welcome to this *e*CysticFibrosis Review podcast.

Today's program is a follow-up to our newsletter topic "Agents for the management of *Pseudomonas aeruginosa* infection." Our guest today is that issue's author, Dr. Shawn Aaron, Senior Scientist for the Clinical Epidemiology Program at Ottawa Hospital Research Institute, as well as Professor and Division Director of the Respirology Department at the University of Ottawa, in Ottawa, Ontario.

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

- Discuss optimal therapy of chronic *Pseudomonas aeruginosa* infection in patients with cystic fibrosis
- Describe the pathophysiology of pulmonary exacerbations associated with *Pseudomonas* infection in patients with cystic fibrosis
- Evaluate the optimal choice of antibiotics to treat *Pseudomonas*-associated pulmonary exacerbations in patients with cystic fibrosis

Dr. Aaron has disclosed that he has no relationships with a commercial entity. His presentation today will include references to the off-label or unapproved uses of drug or products, including inhaled colistin, inhaled levofloxacin, inhaled ciprofloxacin, liposomal amikacin, doripenem, and sitafloxacin.

Dr. Aaron, welcome to this *e*CysticFibrosis Review Podcast.

DR. SHAWN AARON: Thank you, I'm glad to be here.

MR. BUSKER: Your newsletter issue reviewed some of the newer research in managing *Pseudomonas* infections in patients with cystic fibrosis, including efficacy comparisons between inhaled antibiotic agents and new insights into this pathogen's role in pulmonary exacerbations. Our focus today is on how some of that information can affect clinical practice. So please start us off with a patient scenario.

DR. AARON: Last week in the clinic I saw a 21 year old female with cystic fibrosis that's delta-F508 homozygous. She's a new referral to the clinic, a transfer student from another city. The referring notes revealed that her sputum cultures are growing chronic mucoid *P. aeruginosa*, which she's had for a number of years now. Her lung function is 60% of predicted and appears to be stable.

MR. BUSKER: Chronic mucoid Pseudomonas and a stable FEV_1 of 60%. What are your overall impression and thoughts about treating this patient?

DR. AARON: She appears to be relatively stable now and has a chronic endobronchial infection. We want to try to keep her in good health and with stable lung function. The mainstays of treatment we reinforce at every clinic visit are a good optimal approach to overall health care for patients with cystic fibrosis. That would involve, most importantly, regular chest physiotherapy to ensure secretion clearance.

We also recommend to all of our patients that they maintain regular exercise therapy. Aerobic exercise at least 30 minutes two to three times a week will improve chest secretion clearance and will augment and supplement regular chest physiotherapy.

In addition, the beneficial effects of exercise are numerous for our CF patients and include better cardiovascular fitness and better muscle strength and better overall health status. So chest physiotherapy and exercise are two of the mainstays we don't want to forget for our patients with CF, whether or not they have chronic infection with *Pseudomonas*.

The other obvious mainstays of treatment to keep this patient healthy involve good nutrition and regular use of pancreatic enzymes to ensure absorption of fat-soluble nutrients.

It's important to recognize that this patient has a chronic infection with a mucoid strain of *Pseudomonas* growing in her sputum, and the mucoidy implies chronic infection and probable conversion of some of the infection into a biofilm phenotype. This means that this Pseudomonas infection is unlikely to be eradicable. In other words, giving her antibiotics, whether oral or inhaled or intravenous, may control the infection but it's

unlikely to eradicate it and unlikely to render her sputum sterile.

So the issues here are chronic treatment and control of her *Pseudomonas* infection to try to keep her status optimized and her lung function as ideal as possible.

MR. BUSKER: And your thoughts about anti-Pseudomonal therapies?

DR. AARON: We could consider a number of therapies for this patient to chronically treat her Pseudomonas, and one of the mainstays of therapy, as we reviewed in this newsletter issue, is inhaled tobramycin. Inhaled tobramycin given twice a day in 28 day cycles — that is 28 days on and 28 days off — has proved in several very well done randomized, controlled trials to improve lung function and also to somewhat prevent exacerbations in patients who are chronically infected with *P. aeruginosa*. So inhaled tobramycin would clearly be a therapy that we would want to consider for this patient, especially since her lung function is about 60% of predicted, which would place her well within the range for this therapy.

Certainly other options could be considered specific to her Pseudomonas; one of them is inhaled aztreonam. We reviewed a paper that clearly showed that inhaled aztreonam given in three 28-day cycles was potentially as good or superior to tobramycin for improvement in lung function in patients with chronic *Pseudomonas* infection. Inhaled aztreonam would be another option. Aztreonam is generally given three times daily, as opposed to tobramycin, which is given twice daily.

Finally, another anti-Pseudomonal inhaled antibiotic that is not actually used as much in North America but is used frequently by our colleagues in Europe, is inhaled colistin. This can also be given twice daily. For patients who have relatively severe infections and decline in lung function in our clinic, we'll sometimes use inhaled tobramycin in the 28 day cycle, and in the off months we'll use a second antibiotic, either aztreonam or colistin. Therefore the patient is getting alternate inhaled antibiotics on alternate months. We've had some success with this regimen, but I have to stress that this regimen has not been approved or proved yet in clinical trials.

It is important to note that the makers of aztreonam are conducting a clinical trial alternating inhaled tobramycin in 28-day cycles with inhaled aztreonam in 28-day cycles over six months to see if that alternate therapy is superior to inhaled tobramycin alone with no therapy in the second alternate month. So we will have an answer to whether we should be alternating inhaled anti-Pseudomonal antibiotics, but we don't have it yet.

We should also consider other therapies for patients with chronic Pseudomonas. The most important one would be oral azithromycin, which can usually be given as 500 mg every Monday, Wednesday, and Friday. Clinical trials have clearly shown that in patients with chronic Pseudomonas infection, oral azithromycin will also improve lung function relative to placebo and to some extent will prevent exacerbations as well.

Another therapy we use a lot in our clinic which is not specific against Pseudomonas but will certainly improve lung function, is hypertonic saline which can be given twice daily. Hypertonic saline doesn't have any particular anti-Pseudomonal or other antibacterial effects; however, it is very good treatment to improve secretion clearance, and studies have shown, as well, that it improves lung function in patients with chronic cystic fibrosis and *Pseudomonas* infection.

The major issue is not whether we should start a therapy, but how many therapies we should start and whether we should use therapies concurrently. In our practice we often use multiple modes of therapy to treat patients, so we might use an inhaled antibiotic as well as a mucolytic such as hypertonic saline or potentially DNase. Sometimes we'll combine inhaled antibiotics in patients who are doing poorly along with azithromycin. So we certainly can use a multitude of treatments to try to improve this patient and treat her chronic infection.

MR. BUSKER: When you use azithromycin, do you continue the inhaled antibiotic? Do you have any concerns about drug-drug interactions or any particular side effects clinicians need to be aware of?

DR. AARON: Yes, we'll often use an inhaled antibiotic such as tobramycin, along with azithromycin at the same time. Azithromycin is generally safe in cystic fibrosis, although in patients without CF there are reports of potential hearing loss and also a potential for long QT syndrome and QT prolongation on the

ECG with azithromycin. However, this treatment has been used for over a decade now in cystic fibrosis and thus far we haven't seen much in the way of side effects. So, yes, we will use treatments together and we don't generally worry about drug-drug interactions with these classes of medicine.

MR. BUSKER: What do the data on CFTR modulation therapies show about their potential effect on her chronic infection?

DR. AARON: We don't know for sure yet that CFTR-specific modulating therapy will help to treat chronic *Pseudomonas* infection. But there is some interesting data that we present from an article in the newsletter, a clinical paper of a cohort study of patients with G551D cystic fibrosis who were treated with ivacaftor. When the patients who were G551D mutation status with an intermittent infection with *P. aeruginosa* — that is, those in whom fewer than 50% of cultures were positive for *Pseudomonas* in the preceding year — were followed over time after starting ivacaftor, up to 70% had cultures negative for Pseudomonas over the next year. So some interesting information suggests that CFTR modulators may have an impact on culture status and infection status in patients with cystic fibrosis.

Although we don't know this for sure yet, it will be important in future trials of CFTR specific therapy to assess infection status as a secondary outcome. The bottom line is that patients whose mutation status is G551D should be considered for ivacaftor therapy because the clinical trials clearly show that ivacaftor improves lung function. In addition, the cohort study we've reviewed suggests that ivacaftor may also potentially render sputum culture negative, ie, may have some antibacterial effects against *P. aeruginosa*, either directly or indirectly by improving the CFTR function.

The other specific therapy that has just been approved for cystic fibrosis is ivacaftor/lumacaftor combination therapy for patients who are homozygous for delta-F508. We do not know at this point if this therapy would have any impact on infection status, and obviously we will need studies to see if there is potential clearing of *Pseudomonas* with this therapy in patients who are homozygous for delta-F508. So the future will tell us whether this is also a promising therapy to treat chronic *Pseudomonas* infection.

MR. BUSKER: Thank you, doctor. And we'll return, with Dr. Shawn Aaron from the University of Ottawa, 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.

MR. BUSKER: Welcome back to this *e*CysticFibrosis Review podcast. I'm Bob Busker, managing editor of the program. Our guest is Dr. Shawn Aaron, Division Director of the Respirology Department at the University of Ottawa. And we're talking about "Agents for the management of *Pseudomonas aeruginosa* infection."

To continue, please give us a follow-up on the patient we've been discussing.

DR. AARON: You might remember that she was chronically infected with Pseudomonas, and when we first saw her she was quite stable and her lung function was 60% of predicted and had been at that level for over a year. So at the point when she transferred to our clinic, we decided to continue her chronic therapy which was oral azithromycin 500 mg every Monday/Wednesday/Friday, as well as inhaled tobramycin 300 mg twice daily, which she was using in 28 day on/28 day off cycles. We didn't add any new

therapies at that time because she seemed to be stable and doing quite well.

However, the same lady came back several weeks later reporting worsening respiratory symptoms. Specifically, over the last several weeks she had been having increasing cough, increasing sputum production, and increasing sputum purulence such that her sputum had now turned dark green. She also noted increased shortness of breath for the last three days.

Her sputum cultures were still growing mucoid Pseudomonas, but her lung function had deteriorated significantly and was now down to 45% of predicted.

MR. BUSKER: What do you think is going on here?

DR. AARON: I think this patient is having an exacerbation of her cystic fibrosis lung disease. She meets most of the classic criteria for a CF pulmonary exacerbation; that is, she's complaining of increasing cough, sputum production, sputum purulence, and dyspnea, and her lung function has fallen by 15% from her baseline. So she meets all the classic criteria for a CF pulmonary exacerbation at this point.

MR. BUSKER: What's known about the pathophysiology of pulmonary exacerbations?

DR. AARON: We know that pulmonary exacerbations are clearly associated with neutrophilic inflammation, and we believe that bacteria within the airways are for some reason triggering an increased neutrophilic inflammatory response, which then leads to further compromise of the airway with further loss of lung function. The inflammatory response in the airway seems to be correlated with bacteria, as well as with neutrophils, and the neutrophils seem to be activated and releasing inflammatory cytokines. The cytokines that have specifically been documented to increase during exacerbations include interleukin-8, which has a signaling cytokine that calls neutrophils into the airway, as well as interleukin-6, interleukin-1-beta, and tumor necrosis factor.

When these neutrophils come into the airway, they're activated and release degradative enzymes such as proteases and neutrophil elastases, which mediate further damage within the airway. It's clear that at least part of the pathogenesis of CF pulmonary exacerbations are caused by the increased proteolytic enzymes that are released from the neutrophils and damage the airways and cause increased airway inflammation and increased airway edema.

MR. BUSKER: And the role of *Pseudomonas* in pulmonary exacerbations?

DR. AARON: We used to think that CF pulmonary exacerbations were associated with proliferation of *Pseudomonas* within the airway, but it seems that this is actually not the case. Several recent articles, including the study we've reviewed in our newsletter, suggest that quantitative cultures in patients with stable cystic fibrosis, or do quantitative PCR from airway secretions when patients are stable, and compare these values to those when the patients are having a pulmonary exacerbation, we don't actually see greater density of *Pseudomonas* within the airway. So even though the dogma has held that CF pulmonary exacerbations were associated with proliferation and greater density of *Pseudomonas* within the airway, at least three studies now suggest this is not the case. Other studies that we haven't reviewed in the newsletter suggest that CF pulmonary exacerbations are not associated with isolation of new strains of *Pseudomonas* at the time of exacerbation; ie, the strains that we isolate during exacerbation have been exactly same strains we've seen when the patient is clinically stable.

New work that suggests that some of these CF pulmonary exacerbations are associated with viral infection, and viruses can clearly trigger neutrophilic inflammation in the airways and potentially make patients worse without potentially having much of an effect on the bacteria within the airways.

Other studies suggest that anaerobic bacteria and some strep species may also be responsible for exacerbations. I expect we may get a better handle on bacterial causes of exacerbation as we examine the airway microbiome with molecular techniques to try to pick up new species of bacteria that may have previously not been culturable on our typical bacteriologic studies. I think we'll learn more about the potential microbial triggers or exacerbation with these new airway microbiome techniques, and hopefully in about a year or two we'll have a lot more knowledge of what is causing CF pulmonary exacerbations.

MR. BUSKER: Antibiotic treatment is clearly indicted for this patient. What can you tell us about the best way to choose an agent?

DR. AARON: We had previously thought we could do better than our usual methods, and I'll just quickly go over our usual methodology for choosing antibiotics. Basically, we culture the sputum aerobically, and any species of bacteria that grow are isolated from the culture. Then we generally test these species of bacteria to determine susceptibility to anti-Pseudomonal antibiotics. So we would test the bacteria against a panel of antibiotics in vitro to decide which antibiotics might be most effective for treating the patient.

This is our standard approach to sputum culture and sensitivity, and we've been using it in clinical medicine for probably 50 years or so. We clearly thought we could do better, and perhaps we could try to choose antibiotics in a better fashion. One of the first ideas was that since we generally treat *Pseudomonal* infection with two anti-Pseudomonal antibiotics in patients who are ill and need IV antibiotics. One theory was that using antibiotic synergy testing to look at combinations of antibiotics that might be most effective would be a better way to direct therapy. Our group did in a study, published in 2005, that actually tested antibiotic synergy testing against usual culture techniques. Basically, we found that antibiotics chosen based on synergy tests did not result in better clinical outcomes than antibiotics chosen based on usual culture and sensitivity techniques. So unfortunately, synergy testing has been abandoned as a method to choose antibiotics in patients with CF exacerbations. And the synergy labs that were operating in the early part of 2000 have basically all now been closed.

The other question was whether we should do biofilm susceptibility testing to better choose our antibiotics. There is certainly a biologic rationale for this because we know that *P. aeruginosa*, especially mucoid *P. aeruginosa*, grows as a biofilm within the CF airway, meaning this is a colony of bacteria that encases itself in a mucopolysaccharide coating where they are generally relatively inactive, and metabolically some of them go into an anaerobic state.

We know that when we examine these biofilm phenotype *Pseudomonas* bacteria in vitro, they exhibit significantly less susceptibility to conventional anti-Pseudomonal antibiotics than when they are grown in a free-floating planktonic state. Therefore, the idea was posed that perhaps if we grow the bacteria in vitro as biofilms and test their susceptibility to antibiotics, we might get a better sense of which antibiotics will kill the biofilm and therefore which antibiotics will be most effective clinically in patients with CF exacerbation.

Dr. Yao and colleagues from the University of Toronto completed a trial, which we summarized in our newsletter. Dr. Yao's study unfortunately showed that treating patients according to the results of their biofilm susceptibility test did not improve outcomes compared to whether we treated patients according to their conventional culture and microbiology test.

So the bottom line is, the way we've been choosing antibiotics for the last 50 years seems to be the best we have and we should continue to choose antibiotics using the regular culture and antimicrobial sensitivity testing that we do in the everyday clinical laboratory.

Generally, in patients who are severely ill with a CF exacerbation, we will choose two anti-Pseudomonal antibiotics, based on the antibiogram generated from the usual culture and sensitivity tests.

MR. BUSKER: So how would you treat the patient we've been discussing?

DR. AARON: I would admit this patient to the hospital. She's clearly short of breath, she's having symptoms of a cystic fibrosis pulmonary exacerbation, and her lung function has deteriorated significantly. The optimal treatment would involve admission to hospital and provision of twice-daily chest physiotherapy to try to improve her secretion clearance.

We would also want to treat her with *P. aeruginosa* infection. Generally in patients who are admitted to hospital we choose two intravenous anti-Pseudomonal antibiotics. The choice of antibiotics would be predicated on the standard culture and sensitivity tests with the antibiogram that comes back from this testing. Generally most of us, if possible, will try to use two anti-Pseudomonal antibiotics from different antibiotic classes.

For instance, we might try to use a beta lactam drug that has anti-Pseudomonal properties such as

piperacillin tazobactam, or potentially ceftazidime, and combine that with another antibiotic class, perhaps an aminoglycoside such as tobramycin, or potentially a fluoroquinolone like ciprofloxacin. So typical treatment for this patient might include intravenous antibiotics with ceftazidime and tobramycin, or piperacillin and tobramycin, or some combination thereof.

MR. BUSKER: Would you continue her inhaled antibiotic therapy during this treatment?

DR. AARON: There is no clinical trial evidence to say one way or another what we should do, but generally we will continue the inhaled antibiotic in the usual regimen while the patient is concomitantly receiving intravenous antibiotics. But that is really a bit of a personal decision from the treating physician. I suspect that half my colleagues would continue the inhaled antibiotics and half would probably put the inhaled antibiotics on hold while the patient is on intravenous antibiotics. There is really no consensus on the right approach there.

MR. BUSKER: Thank you for today's discussion, Dr. Aaron. Let me ask you to turn your thoughts to the future for us: what might clinicians expect to see in the way of new and/or improved therapies to manage Pseudomonas infections?

DR. AARON: We're clearly getting new evidence that suggests that aztreonam is a very good option to treat chronic *Pseudomonas* infection. So I think aztreonam is moving up the ladder as one of our go-to inhaled antibiotics for *Pseudomonas*.

Other newer inhaled antibiotics are being developed which are not yet marketed or FDA approved, but might be in the future, which include inhaled levofloxacin, inhaled ciprofloxacin, as well as liposomal amikacin. If any of these drugs come to market, they're going to give us a further useful armamentarium of anti-Pseudomonal antibiotics that we can use to treat patients chronically to try to improve their chronic infection.

Other newer antibiotics also in development might be useful to treat cystic fibrosis exacerbations. So, for instance, there is a new carbapenem under development called doripenem, which seems to be useful for treating multidrug resistant *Pseudomonas*. If this drug becomes available, we might use it to treat relatively severe CF exacerbations associated with multidrug resistant *Pseudomonas*.

A new fluoroquinolone is being developed that has better antigyrase activity against multidrug-resistant *Pseudomonas*. This drug is called sitafloxacin, and may also be, if it comes on market, a useful addition to the only fluoroquinolone we have now to treat Pseudomonas which is, of course, ciprofloxacin. So we definitely do need new antibiotics to treat *Pseudomonas*, and it sounds like some are in the pipeline that hopefully will be available in the next few years.

The next future therapy that might hold some promise, as we've already discussed, is CFTRdirected therapy. There is some evidence suggesting that improving CFTR function may help clear chronic Pseudomonal infections in some patients. So if we can improve the basic defect of CF and restore airway surface liquid, we could certainly help improve chronic infection status in our patients.

MR. BUSKER: Thank you for sharing your thoughts, Doctor. Let's wrap things up by reviewing today's discussion in light of our learning objectives. So to begin: the optimal therapy for managing chronic Pseudomonas infection in patients with CF.

DR. AARON: I think there's no real optimal therapy. Patients need to be managed on a case by case basis, but the broad-stroke objectives here are to control chronic *Pseudomonas* infection in the long term with inhaled antibiotics such as aztreonam or tobramycin, as well as potentially with mucolytic therapies such as hypertonic saline or DNase and also with azithromycin as needed for patients with more severe chronic infections and worse lung function.

The second point, of course, is that patients with chronic *Pseudomonas* infection can have acute exacerbations of their underlying lung disease, and when this happens we treat with specific anti-Pseudomonal therapy to treat their CF exacerbations. The most common therapies we would use as outpatients in patients who have moderate exacerbations might be ciprofloxacin. In patients who have more severe exacerbations and require IV antibiotics, we generally choose two anti-Pseudomonal antibiotics from different classes such as ceftazidime and tobramycin or some similar combination.

MR. BUSKER: And our second learning objective: the pathophysiology of CF pulmonary exacerbations.

DR. AARON: The pathophysiology of CF pulmonary exacerbation relates to neutrophilic activation and migration to the airway with release of proteolytic enzymes that cause damage and inflammation in the airway which then result in pulmonary exacerbations. It does not appear that proliferation of *P. aeruginosa* within the airway is a major feature that provokes pulmonary exacerbation.

MR. BUSKER: Finally: the optimal choice of antibiotics to treat pulmonary exacerbations.

DR. AARON: As clinicians we choose our antibiotics based on the usual culture and sensitivity results. We will generally choose antibiotics that *Pseudomonas* species growing within the sputum culture are sensitive to, and the optimal choice of antibiotics depends to some extent on the severity of the exacerbation. For patients with mild or moderate exacerbations associated with *Pseudomonas*, we'll usually use oral ciprofloxacin as a first choice. For patients with more severe exacerbations who require IV antibiotics, we'll choose two antibiotics from different classes that the organisms are sensitive to from the most recent sputum culture.

MR. BUSKER: Dr. Shawn Aaron from the University of Ottawa — thank you for participating in this *e*Cystic Fibrosis Review Podcast.

DR. AARON: Thank you very much for having me. This was a great opportunity, and I hope everybody learned something.

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

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*e*CysticFibrosis Review is supported by educational grants from AbbVie, Gilead Sciences Inc., and Vertex Pharmaceuticals.