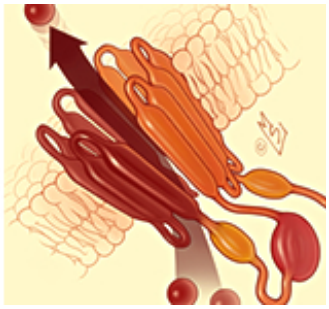
JOHNS HOPKINS MEDICINE
eLITERATURE REVIEW
eCysticFibrosis Review
Podcast Issue

Presented by the Johns Hopkins University School of Medicine and the Institute for Johns Hopkins Nursing

Supported by Educational Grants from Genentech, Inc., Eurand Pharmaceuticals, Inc., Vertex Pharmaceuticals, Incorporated, Axcan Pharma, Inc. and Gilead Sciences Medical Affairs



VOLUME 2 — ISSUE 12: TRANSCRIPT

Featured Cases: Guidelines: New Inhalation Therapies

At the conclusion of this activity, participants will demonstrate the ability to:

- Discuss the potential benefits and risks of inhaled antibiotics at various stages of CF lung disease,
- Describe the similarities between hydrator, therapies and therapeutic expectations based upon clinical trial data, and
- Summarize the potential use of therapies currently in development for young children with mild CF lung disease.

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. Donaldson will help expand our understanding of the use of new inhalation therapies for the treatment of cystic fibrosis, with the discussion some typical case scenarios.

Unlabeled/Unapproved Uses
The author has indicated that there will be a reference to unlabeled or unapproved uses of denufosol and mannitol for treatment of CF in the presentation.

MEET THE AUTHORS

Scott H. Donaldson, MD
Associate Professor of Medicine
Associate Director,
Adult CF Center
Division of Pulmonary and Critical Care Medicine University of North Carolina at Chapel Hill
Chapel Hill, North Carolina

Guest Faculty Disclosure
Scott H. Donaldson, MD discloses that he receives grants and research support from Gilead Sciences, Inspire Pharmaceuticals and Vertex Pharmaceuticals. Dr. Donaldson also works as a consultant to Parion Sciences, Inspire Pharmaceuticals, Pulmatrix and Novartis.

Release Date	Expiration Date	Next Issue
December 2, 2010	December 1, 2012	TBA

PROGRAM DIRECTORS

Michael P. Boyle, MD, FCCP
Associate Professor of Medicine
Director, Adult Cystic Fibrosis Program
The Johns Hopkins University
Baltimore, MD

Peter J. Mogayzel, Jr., MD, PhD
Associate Professor of Pediatrics
Director, Cystic Fibrosis Center
The Johns Hopkins University
Baltimore, MD

Donna W. Peeler, RN, BSN
Pediatric Clinical Coordinator
Cystic Fibrosis Center
The Johns Hopkins University
Baltimore, MD

Meghan Ramsay, MS, CRNP
Pediatric Clinical Coordinator
Adult Clinical Coordinator
Cystic Fibrosis Center
The Johns Hopkins University
Baltimore, MD

ACCREDITATION STATEMENTS

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. The Johns Hopkins University School of Medicine is accredited by the ACCME to provide continuing medical education for physicians.

The Institute for Johns Hopkins Nursing is accredited as a provider of continuing nursing education by the American Nurses Credentialing Center's Commission on Accreditation.

The Institute for Johns Hopkins Nursing and the American Nurses Credentialing Center do not endorse the use of any commercial products discussed or displayed in conjunction with this educational activity.

CREDIT DESIGNATIONS

Physicians

Podcast: The Johns Hopkins University School of Medicine designates this educational activity for a maximum of 0.75 *AMA PRA Category 1 Credit(s)*™. Physicians should only claim credit commensurate with the extent of their participation in the activity.

Nurses

Podcast: 0.50 contact hour Educational Activity is provided by the Institute for Johns Hopkins Nursing. Each podcast carries a maximum of 0.50 contact hours or a total of 3.0 contact hours for the six podcasts in this program.

To obtain contact hours, you must complete this Education Activity and post-test before December 1, 2012.

Allied Health

Podcast: the Johns Hopkins University has approved this activity for 0.75 contact hours for non-physicians.

Respiratory Therapists

For United States: Visit this page to confirm that your state will accept the CE Credits gained through this program.

For Canada: Visit this page to confirm that your province will accept the CE Credits gained through this program.

There are no prerequisites to participate in the activity.

INTENDED AUDIENCE

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

LAUNCH DATE

This program launched on March 9, 2010, and is published monthly; activities expire two years from the date of broadcast, ending in March 8, 2012.

SUCCESSFUL COMPLETION

To take the post-test for eCysticFibrosis Review you will need to visit the Johns Hopkins University School of Medicine's CME website and the Institute for Johns Hopkins Nursing. If you have already registered for other Hopkins CE programs at these sites, simply enter the requested information when prompted. Otherwise, complete the registration form to begin the testing process. A passing grade of 70% or higher on the post-test/evaluation is required to receive CE credit.

STATEMENT OF RESPONSIBILITY

The Johns Hopkins University School of Medicine and the Institute for Johns Hopkins Nursing take responsibility for the content, quality and scientific integrity of this CME/CE activity.

INTERNET CME/CE POLICY

The Office of Continuing Medical Education (CME) at the Johns Hopkins University School of Medicine and the Institute for Johns Hopkins Nursing are committed to protect the privacy of its members and customers. The Johns Hopkins University maintains its Internet site as an information resource and service for physicians, other health professionals and the public.

Continuing Medical Education at the Johns Hopkins University School of Medicine and the Institute for Johns Hopkins Nursing will keep your personal and credit information confidential when you participate in a CE Internet-based program. Your information will never be given to anyone outside the Johns Hopkins University program. CE collects only the information necessary to provide you with the service you request.

FACULTY DISCLOSURE

As a provider accredited by the Accreditation Council for Continuing Medical Education (ACCME), it is the policy of Johns Hopkins University School of Medicine to require the disclosure of the existence of any relevant financial interest or any other relationship a faculty member or a provider has with the manufacturer(s) of any commercial product(s) discussed in an educational presentation. The presenting faculty reported the following:

- **Michael P. Boyle, MD, FCCPD** discloses that he has received grant/research support Vertex Pharmaceuticals, Inc.
- **Peter J. Mogayzel, Jr, MD, PhD** discloses that he has no financial relationship with commercial supporters.
- **Meghan Ramsay, MS, CRNP** discloses that she has no financial relationship with commercial supporters.
- **Donna W. Peeler, RN** discloses that she has no financial relationship with commercial supporters.

DISCLAIMER STATEMENT

The opinions and recommendations expressed by faculty and other experts whose input is included in this program are their own. This enduring material is produced for educational purposes only. Use of Johns Hopkins University name implies review of educational format design and approach. Please review the complete prescribing information of specific drugs or combination of drugs, including indications, contraindications, warnings, and adverse effects before administering pharmacologic therapy to patients.

HARDWARE & SOFTWARE REQUIREMENTS

Pentium 800 processor or greater, Windows 98/NT/2000/XP or Mac OS 9/X, Microsoft Internet Explorer 5.5 or later, 56K Modem or better, Windows Media Player 9.0 or later, 128 MB of RAM, monitor settings: high color at 800 x 600 pixels, sound card and speakers, Adobe Acrobat Reader.

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 Genentech, Eurand Pharmaceuticals, Vertex Pharmaceuticals, Axcan Pharma, and Gilead Sciences Medical Affairs.

Today's program is a companion activity to our October 2010 eCystic Fibrosis Review newsletter topic: Guidelines: New Inhalation Therapies. Our guest is Doctor Scott Donaldson, from the University of North Carolina at Chapel Hill.

This activity has been developed for physicians, nurses, respiratory therapists, dieticians, 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 on the November 2010 podcast link.

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

- Discuss the potential benefits and risks of inhaled antibiotics at various stages of CF lung disease,
- Describe the similarities between hydrator, therapies and therapeutic expectations based upon clinical trial data, and
- Summarize the potential use of therapies currently in development for young children with mild CF lung disease.

I'm **BOB BUSKER,** managing editor of eCysticFibrosis Review. On the line we have with us our August newsletter issue's author, Doctor Scott Donaldson is an Associate Professor of Medicine and Associate Director of the Adult CF Center, Division of Pulmonary and Critical Care Medicine University of North Carolina at Chapel Hill. Doctor Donaldson has disclosed that that he receives grants and research support from Gilead Sciences, Inspire Pharmaceuticals and Vertex Pharmaceuticals. Dr. Donaldson also works as a consultant to Parion Sciences, Inspire Pharmaceuticals, Pulmatrix and Novartis.

His presentation today will include reference to unlabeled or unapproved uses of denufosol and mannitol for treatment of CF.

Doctor Donldson — welcome to this e-cystic fibrosis review Podcast.

DR. DONALDSON: Thank you very much for having me.

MR. BUSKER: To help increase our understanding of the use of new inhalation therapies, we've asked Dr. Donaldson to discuss some typical case scenarios. So if you would, doctor, bring us our first case, please.

DR. DONALDSON: The first patient we're going to discussion is an 18-year-old male with cystic fibrosis who is transitioning to the adult cystic fibrosis clinic. His lung function has been stable, with a FEV1 of 78 percent of predicted. He has had 3 pulmonary exacerbations that required intravenous antibiotics during the last 7 years. He chronically grows *Pseudomonas aeruginosa,* which is pan-sensitive to all tested antibiotics in his sputum.

His current maintenance regimen includes hypertonic saline and recombinant human DNA. This patient performs airway clearance twice every day, and he exercises regularly. On physical exam, he was noted to have a normal nutritional status, and his chest and abdominal exams were normal as well. The patient wants our advice on his condition and his overall treatment regimen.

MR. BUSKER: Doctor, please characterize his current status and regimen, and let's start with talking about his lung function.

DR. DONALDSON: DONALDSON: This young man has a fairly good FEV1 at 78 percent of predicted and has had relatively few exacerbations, requiring only 3 IV courses over the last 7 years. In this patient I'd want to know the history of rate of decline of lung function, so I'd look back at serial levels and whether this has been a recent change or been very steady.

MR. BUSKER: And your characterization of his antibiotic use?

DR. DONALDSON: Again, this young man has required only a few courses of IV antibiotics over the last few years, but when looking at his chronic regimen, we see that he's not using a chronic oral macrolide. He's not using any inhaled antibiotics as a prophylactic measure, either.

MR. BUSKER: Would this patient be a candidate for an inhaled antibiotic? How would you determine that?

DR. DONALDSON: I think this patient would be a candidate, and this is based largely upon his microbiologic status and his lung function. When we're making individual decisions for patients, we have the best evidence and the most comfort when our individual patient matches up with similar groups of patients who have been studied in trials of antibiotics.

This patient does have chronic Pseudomonas infection, so he is very much like patients who have been studies in trials of either inhaled Tobramycin or inhaled aztreonam, and his lung function is similar to those who have been studied with an FEV1 near that 25% to 75% range in clinical trials.

But getting to the issue of whether this specific person should be on a chronically inhaled antibiotic is still a point of debate. Clearly, there are short-term, meaning months to a couple of years, of benefit that have been demonstrated in trials. However, there are certainly longer-term risks over the course of many years and decades that are potentially applicable to each patient we treat. And this longer-term benefit is truly unknown. So ultimately, we would really like to find a way to personalize this patient's and every patient's regimen to maximize the benefit they get over the long run, but how we do that really is not agreed upon.

In my practice, I like to look at the rate of lung function decline over the last few years and the frequency of pulmonary exacerbations that require antibiotics of any sort. I think patients who show evidence of declining lung function or episodic exacerbations are the best candidates for this intervention and have more to gain and less to lose.

MR. BUSKER: If you were to prescribe chronic cycling, inhaled antibiotics for this patient, how would you chose which one?

DR. DONALDSON: The currently available therapies are either inhaled tobramycin solution or inhaled aztreonam. Those two agents are approved and have proved beneficial in patients with CF. Other therapies include inhaled colistin, or colimycin, which has a fairly large experience in Europe and some in the U.S., but doesn't have the same basis of clinical trial evidence for efficacy.

Choosing something with the best evidence base makes the most sense to me. For this patient, I would look at his sensitivity patterns and sputum cultures, and if there was a differentiating factor of sensitivity or resistance to one of the available options, that would guide me. However, in the absence of culture data that would direct me toward one therapy or another, often it boils down to preferences of the patient and preferences of the prescriber because we don't have great data of head-to-head comparisons of efficacy between two different antibiotic interventions.

Here we start to consider more the time it takes to do a therapy, how often that therapy must be administered. We worry about long-term toxicities related to repeated exposures that might be associated with one therapy or another, and certainly delivery device preferences come to play as well.

MR. BUSKER: Doctor, let me ask you to go a bit deeper into the differences between the two major inhaled antibiotics and differentiate between them.

DR. DONALDSON: I'd be glad to. The antibiotic that's been approved and available to us traditionally has been inhaled tobramycin. Tobramycin solution is delivered with a conventional jet nebulizer. Typically, the time required to deliver one treatment is approximately 15 minutes, and the usual dosage of this medication is twice daily. More recently, inhaled aztreonam is becoming available to us. Aztreonam is delivered with a different type of delivery device, the eFlow nebulizer. This is a very different technology that can deliver the solution over just a couple of minutes, 2 to 3 minutes on average.

The downside of this is that this drug is delivered 3 times a day rather than twice a day, so there is some

tradeoff there, as well. Another tradeoff is that some patients perceive cleaning the eFlow nebulizer might be a bit more cumbersome than taking care of a conventional jet nebulizer. So clearly, there are differences between these two therapies in terms of time that required to deliver them but also some tradeoffs in terms of number of times the therapy has to be delivered and perhaps some differences in taking care of the devices that do the delivery for the patient.

MR. BUSKER: Let me ask you another follow-up. In your practice and from your clinical experience with your patients, which form of therapy do they prefer?

DR. DONALDSON: That's a good question too, and I think in my practice I have patients who fall on both sides. But I think clearly more and more patients, as they're introduced to the newer delivery technologies based on the eFlow technology, they really do appreciate the shorter delivery time delivery. In general, that advantage has outweighed the disadvantages that might come with more frequent delivery of a drug or the additional steps required for cleaning and maintaining the device.

So I think this has been a nice addition to our options available to patients, and patients do appreciate this new technology.

MR. BUSKER: Thank you for that additional clarification and information, doctor. Let's go to another case now.

DR. DONALDSON: The next patient I'd like to present is a 26-year-old woman with CF who has moderately severe lung disease. In clinic, the measured FEV1 was about 50% of predicted. She has chronic infection with Pseudomonas and has required 5 courses of oral antibiotics for episodes of increased chest congestion in the past year alone. She uses recombinant human DNase and azithromycin, and she performs airway clearance regularly.

On physical exam, it's apparent that she has a reduced body mass index at 18, suggesting malnutrition. There are crackles over the upper lobes when listening to her chest. She also has digital clubbing. In clinic she's seeking our input on her treatment regimen.

MR. BUSKER: My first question would be, is there reason to change her current treatment regimen? And if there is, what would you suggest be done?

DR. DONALDSON: I think there is. When we think about this woman's condition, I think it's fair to say that she has relatively advanced lung disease, as marked by having an FEV1 that's only 50% of predicted. But also, the fact that she's having very frequent flares of her pulmonary symptoms that have required antibiotic interventions. So in thinking about what else might be done, we have to look at all the available therapies that might be pertinent to her condition.

We know that she's already using DNase and azithromycin, and she does airway clearance. So when thinking about what else might be available, it would certainly include hypertonic saline, which has been shown to reduce exacerbations, as well as inhaled antibiotics.

I think in this case, the decision is relatively straightforward: to use more aggressive therapy to try to improve her lung function and reduce the frequency of her flares of lung disease. The options would be, in my mind, to either institute hypertonic saline or introduce inhaled cycline antibiotics.

MR. BUSKER: How does her microbiology status affect decisions? And let me ask, what if she did not have *Pseudomonas*?

DR. DONALDSON: Regarding her microbiologic status, that primarily relates to the use of inhaled antibiotics. As we mentioned earlier in this conversation, most of the studies that have looked at the use of inhaled antibiotics and CF have focused on patients with *Pseudomonas aeruginosa*. So if this patient did not have *Pseudomonas*, we're immediately moving to less firm ground in terms of the evidence basis for using any therapy.

That said, clearly many patients have organisms other than *Pseudomonas* that we as clinicians would like to treat. Usually, these decisions are based on clinical grounds that the isolated bacteria are, indeed, pathogenic and that there is at least a good likelihood that the organism will be sensitive to the antibiotic that's being used. Typically, we're in a situation where our patient grows another typical CF pathogen other than *Pseudomonas*, such as *Stenotrophomonas, Alcaligenes,* or other Gram-negative bacteria.

Another specific infection that we deal with frequently in CF is patients who have *Burkholderia* infections. This is another Gram-negative infection that can have

particularly problematic outcomes with regard to lung transplantation, but that may also be more difficult to treat because of resistance patterns.

While we don't have the evidence that we would like in terms of treating organisms other than *Pseudomonas*, fortunately, progress is being made in the form of studies that are looking at inhaled antibiotics for these other infections. Specifically, trials are currently going on for inhaled aztreonam for *Burkholderia* infection. So we're hopeful that we will learn more in the near future regarding the use of inhaled antibiotics for these other infections, as well.

MR. BUSKER: Dr. Donaldson, other considerations that clinicians should be aware of in this patient because she does seem to be having some difficulties.

DR. DONALDSON: You're absolutely right. In this setting, where you have a patient who is struggling a bit, I think one of the key thoughts that needs to come to our mind is how can we maximize her therapy? While inhaled antibiotics may be one of the options, this patient is also not on hypertonic saline, and that is an additional therapy and one of the small handful of currently available therapies we certainly would want to consider using in that patient.

After we've worked through each of the available therapies that might be beneficial, I think we have to take the next step and look very closely at how compliant or adherent the patient is to their therapy, their technique with therapies that require coordination or specific maneuvers, such as airway clearance, and then also begin to look for other drivers of more severe disease, such as cystic fibrosis-related diabetes, her poor nutritional status, and other complications, such as allergic bronchopulmonary aspergillosis, or even atypical infection, such as with nontuberculous mycobacteria.

I think taking a more comprehensive look at all of these factors is important when you have a patient who's not doing as well as we hope they would be.

Perhaps a final consideration in this patient is that perhaps there may be a preference for using oral or inhaled antibiotics in a patient quite frequently, when perhaps switching to more aggressive use of intravenous antibiotics to combat the symptoms and decline in lung function that's occurring makes sense as well.

MR. BUSKER: We've been looking at case scenarios that illustrate the challenges of managing *Pseudomonas* in adults. How does that compare to caring for pediatric patients with CF? Would you give us a case to illustrate that, please?

DR. DONALDSON: I'd be happy to. Our third case is a 5-year-old with cystic fibrosis. She was diagnosed by newborn screening and has never been hospitalized or treated with IV antibiotics in her life. She successfully completed her first set of pulmonary function tests, and happily they're normal. She had a chest X-ray performed as well that reveals minimal hyperinflation, and the physical examination was normal too.

Her parents administer albuterol befoe performing chest physiotherapy once a day, and she does not produce sputum on most days. In physical exam, she's a young, energetic girl with normal growth parameters, she has clear lungs on auscultation, and she has a benign abdominal exam and no clubbing. An oropharyngeal swab was obtained and cultured, and it grew only normal oropharyngeal flora and no pathogens.

MR. BUSKER: Dr. Donaldson, is it likely that this little girl has any lung disease to speak of? I mean, she has great lung function tests and she has a great physical exam. Do you think she has any lung disease?

DR. DONALDSON: Unfortunately, likely she does. One of the key considerations to think of in this very young population is, the tools we have available to us to detect and measure lung disease are rather insensitive in detecting mild lung disease. This includes spirometry, chest X-rays, and certainly our physical exam as well. What we really need to avoid is lulling ourselves into a sense of complacency when patients aren't complaining of symptoms and are doing generally well.

We know from studies that have recently beeb done that if we use CAT scans, for example, to evaluate lung disease, we know that bronchiectasis, which is really a severe form of airway damage, is present in up to about 50% of children like this one by the age of 3 or years old. And even more patients have less dramatic manifestations of disease, like mucus plugging, airway thickening, and air trapping.

So I think while we can be very happy that this young girl is doing well clinically and has not required a lot

of therapies, I think we have to keep in mind that almost certainly she has some lung disease that may be inapparent to our eyes and ears, unless we use more advanced methods to detect lung disease, and that's something we're learning about now and which may be part of our clinical routine in the future.

MR. BUSKER: We have a young, mildly affected girl. Are there any proven therapies that might improve pulmonary outcomes in a patient like this?

DR. DONALDSON: In fact, I think the only proven therapy for a young child like this with very mild lung disease is oral ibuprofen. We know that this therapy was shown quite some time ago to reduce the rate of lung function decline in similarly young children. Unfortunately, we don't have a lot of other proven therapies. However, a lot of the new therapies we've been talking about today and in our review certainly have potential relevance and potential benefit in patients like this, and we're just on the cusp of being able to adequately evaluate these therapies and determine whether they're going to be helpful in preventing lung disease in these most mildly affected young patients.

One study that's currently being done is looking at the role of inhaled hypertonic saline in infants and toddlers with CF. In this study, hypertonic saline is being compared to a control therapy through a year of treatment. And this is called the ISIS study, or the Infant Study of Inhaled Saline. So this study and others that likely are to follow soon thereafter will for the first time give us information about the use of these therapies directed at the underlying problem of CF and whether we can make a big difference in children in preventing progression of disease.

MR. BUSKER: Tell us about other therapies that are in late stage development that, if they're approved, might be appropriate for a young child with mild disease.

DR. DONALDSON: I think the greatest promise of therapies appropriate for these young kids really are those that are directed at what we believe to be the pertinent pathogenesis of lung disease. Briefly, we think CF lung disease evolves because airway secretions become dehydrated. Secretions become essentially stuck in the chest and don't clear out of the lung well. That sets up a nidus for infection and development of inflammatory lung disease that ultimately destroys the airways.

What we would like to do is use therapies that prevent that first dehydration step and maintain normal hydration of secretions and normal clearance of secretions, which theoretically would prevent that whole vicious cycle of infection, inflammation, and poor clearance. There's a handful of therapies under development currently. One of them I've already mentioned, hypertonic saline, is an approved therapy available to us today but is currently under trials that will hopefully determine that it is or is not effective in these young children.

Another therapy that has a similar mechanism of action to hypertonic saline is dry powder mannitol. Dry powder mannitol, like hypertonic saline, is an osmotic agent that draws water out into the airway, helps hydrate secretions, and therefore accelerates mucus clearance out of the chest. This would be another potentially appropriate therapy for young children with CF.

A third agent that could be found to be useful in CF is a drug called denufosol. Denufosol's mechanism of action is different from either hypertonic saline or mannitol in that it binds to a specific receptor in the airway and, in turn, switches on ion channels that improve the secretion of chloride and water out into the airway surface liquid and therefore achieve hydration of airway secretions via a different mechanism. So denufosol, because it also hydrates the airway surface liquid and accelerates mucus clearance, is another attractive, rational therapy for treating children with CF lung disease.

Going forward, we're fortunate that the CF pipeline is filled with other potentially beneficial agents as well. Certainly, among the most exciting are agents that are specifically directed against the CFTR molecule itself. In development are oral medications, such as VX8 or 9, VX770, PTC124, all of which are aimed at achieving better functioning of the CFTR molecular that's mutated in CF. If that can be achieved, that too may restore the hydration of the airway surface liquid and prevent development of disease over time.

I think all of these agents have potential benefit in the youngest patients as a potential way of preventing disease down the road.

MR. BUSKER: From your knowledge of these agents that you talked about, those that are in development, those that are being tested, has anything been shown

to have a negative impact specifically on children? I guess I'd say as opposed to adults.

DR. DONALDSON: I think that's a good question. Unfortunately, we're in a situation where we just don't have a lot of information on how these experimental medications affect children. What is critically important is conducting the clinical trials so we can learn more about the safety of these medications and whether they are indeed beneficial, as we propose they may be.

That said, we do have some short-term trials suggesting that hypertonic saline is safe and well-tolerated in young children, but certainly more information will come from the longer-term ISIS study that's currently underway.

Mannitol is a little different from the other agents that I mentioned in that it's delivered as a dry powder rather than a nebulizer. So mannitol might be more difficult to administer with current technologies to young children who aren't coordinated enough to activate a dry powder inhaler. That's one therapy that might be less applicable with current technologies to that very young population.

I would finally say that denufosol is more specifically being developed for a younger population with milder lung disease. Denufosol has been studied only in patients with CF who have very mild disease, so it is specifically being targeted toward this population. But, again, we do need to see clinical trial data in the youngest patients to show that it's both safe and effective.

MR. BUSKER: Dr. Donaldson, I think we have time for one more case, so let's talk about a patient who has severe lung disease.

DR. DONALDSON: Our next case is a 30-year-old man with CF who has severe lung disease and an FEV1 of 40% of predicted. Unfortunately, he's had frequent exacerbations and is now being seen for follow-up after a hospitalization. He's back to his previous level of health at this time, and he's currently using recombinant human DNase and azithromycin daily. Recently, he began using inhaled tobramycin and inhaled aztreonam in alternate months. Now, he's read about studies of hypertonic saline, mannitol, and denufosol in CF patients, and he wonders which of these would be most appropriate for him.

MR. BUSKER: Let me echo that patient's question: would any of these therapies be especially appropriate or inappropriate for this patient?

DR. DONALDSON: I think much likely, just discussed in the young patient with CF, these therapies are all aimed at improving the hydration of secretions and improving mucous clearance. We think that's important, both at the beginning of life to try to prevent disease and also, perhaps equally important in patients with severe disease, to prevent the development of pulmonary exacerbations and the further decline in lung function. In fact, I think all of these have a similar mechanism of action.

That said, we know that denufosol has been primarily tested in patients with very mild disease, so while it is logical that it could have a role in this patient, it would be a larger extrapolation of study results to this clinical situation than with some of the other therapies. I think for denufosol we're on less firm ground that it might be beneficial in somebody with severe disease. That said, I think that's an open question for study.

With regard to the other agents he's inquiring about, hypertonic saline and mannitol, we know that hypertonic saline has been shown to have a substantial effect on exacerbation frequency, which is certainly a desirable outcome in this patient who is troubled with that problem. For mannitol, we're still waiting for further data to see if it will have similar impact on reducing exacerbation frequency in patients with more severe disease.

We're hopeful that both hypertonic saline and mannitol would be helpful, but I think currently the best available data is for hypertonic saline, and we anxiously await the final study results for mannitol, as we've covered in our review.

MR. BUSKER: To follow up on what you just said, this patient is already on a large number of therapies. What concerns should there be over adding a therapy, especially looking at potential interactions.

DR. DONALDSON: I think every time we're adding new therapies, especially when the patient is already on a number of other therapies, we have to have some concern, both from a safety standpoint and from an efficacy standpoint. While we're aware of particular safety problems with usual CF therapies, we don't

know how these therapies interact from an efficacy standpoint. That's probably our larger concern in the area where we don't have enough data. That said, some data is available from late-stage studies or phrase III studies that answer some of the questions, though others certainly remain.

We know from the study from Mark Elkins and colleagues and the *New England Journal* where they examine the use of hypertonic saline over a year-long period, that patients taking recombinant human DNase seem to benefit as much as those who did not take DNase. And so that gives us some comfort that these two agents, both of which are aimed at improving mucus clearance, don't cancel each other out and that there may be additional benefit from combining them.

We also know that patients in this study were using inhaled antibiotics to some degree, but really, azithromycin use is rare. So we don't have any information how, for example, hypertonic saline and azithromycin might interact.

With regard to the studies of mannitol, we really have some conflicting conclusions about combining mannitol with other drugs, and specifically, DNase.

In the study by Manasian, et al. that we reviewed in the newsletter, a negative interaction was observed; that is, there was less improvement with the combination therapy than with either agent alone, either mannitol or DNase. That's certainly a concern, and it raised a lot of questions about why this might be the case.

However, in early presentations of phase III data of studies with mannitol, the same phenomenon of a negative interaction between DNase and mannitol was not observed. And this, I think, provides significant reassurance that combination therapy with mannitol and DNase likely does not contraindicate it. The reason why I might place more emphasis on the second set of studies is that they were much larger and had a much more straightforward study design, which I think provides a lot of reassurance that we don't have a peculiar drug-drug interaction to worry about with mannitol and DNase. But certainly, future studies would be beneficial.

Now, of note, hypertonic saline has been specifically excluded in studies of mannitol and denufosol because it has a very similar mechanism of action. Going forward, we have to consider, once we have multiple agents available that have similar mechanisms of action, are we likely to benefit by using more than one at a time? This probably does need to be studied but there is no data available to date. Personally, I think there probably won't be a role for dual therapy with, say, mannitol and hypertonic saline or denufosol and a second hydrator agent, but it's an open question that we'll have to face some day.

MR. BUSKER: Just a note to our listeners that a link to the Elkin study in the *New England Journal* that Dr. Donaldson mentioned will be - is available in the transcript of this podcast.

Dr. Donaldson, now talk about any potential additional benefits that we might find from these agents in existing clinical trials if you would. Okay, so I think my question there really becomes something like let's apply what we know from the existing clinical trials to this specific patient, what potential benefits might there be?

DR. DONALDSON: Yeah, to this patient with severe disease, something like that. Well, for this specific patient who has severe disease, we know from trials of hypertonic saline that on average we would predict that he would have fewer pulmonary exacerbations and, again, on average, might have a small increase in lung function. If we were to choose Mannitol as the additional therapy to use in him, we know from existing clinical trials that on average he would be predicted to have an improved FEV-1. But we're waiting to see if clinical trail data would predict an improvement in exacerbation frequency as well.

With regard to Denufosol, we really don't have any relevant clinical trials to predict whether this patient with severe disease would benefit or not. End.

MR. BUSKER: Okay, Dr. Donaldson, take the final word for us, if you would, please. Take the final word on the development of these inhalation therapies or whatever we're going to talk about.

DR. DONALDSON: I think in general, when we think about the development of new inhaled therapies for CF, this is really an incredibly exciting time. More and more agents that target different aspects of CF lung disease are becoming available to us, whether those aspects are infection, defective mucus clearance, hydration of secretions, and even antiinflammatory aspects of the disease. We're developing more and

more tools. Not only are we getting individual therapies in each of these classes, we're developing multiple therapies that use slightly different mechanisms of action to accomplish some of the same things. In the future, we'll have more and more tools in our toolbox to try to benefit patients.

That said, a lot of key questions in key areas I think will be the focus of research going forward. Probably the most important, because it has the potential for the largest impact on this disease, is learning how to assess therapies very early in life. We believe as a community that an effective therapy aimed at correcting the pathogenesis of disease applied very, very early in life has the most potential benefit. The difficulty is showing that benefit in a patient who has very little disease, no symptoms, and no abnormalities of pulmonary function.

Our community is working hard to develop better outcome measures and better trial designs to answer that question. I think the rewards are going to be huge, however.

Another really important topic that I'd like to mention is, because we're developing so many different therapies that hopefully will be available to us clinically, we're going to have to learn as a community how to mix and match these therapies together to get the optimal benefit. Some therapies could have very long-term benefits, but others may provide more short-term and less long-term benefit. It's possible that some therapies may work synergistically or additively together, whereas others could potentially not provide any additional benefit when added to an existing therapy.

This is an area that's difficult to address and get a handle on, but I think our community is certainly up to that challenge, and we're going to work hard to figure out just how best to optimize and personalize each of these therapies in individual patients. So it's certainly an exciting time, and it's great to have these challenges of having to learn how to use multiple, different, available therapies for patients with CF.

MR. BUSKER: Dr. Scott Donaldson —— from the University of North Carolina at Chapel Hill — thank you for participating in this e-Cystic Fibrosis Review Podcast.

DR. DONALDSON: Thank you very much for having me. It's been a pleasure to be with you.

MR. BUSKER: This podcast is presented in conjunction with eCysticFibrosis Review, a peer-reviewed CE-accredited literature review e-mailed 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, with a joint sponsorship of the Johns Hopkins University School of Medicine, and the Institute for Johns Hopkins Nursing.

The Johns Hopkins University School of Medicine is accredited by the Accreditation Council for Continuing Medical Education, to provide continuing medical education to physicians. For physicians, the Johns Hopkins University School of Medicine designates this educational activity for a maximum of 0.75 *AMA PRA Category 1 Credits*™. Physicians should only claim credit commensurate with the extent of their participation in the activity.

For nurses, this 0.50 contact hour educational activity is provided by the Institute for Johns Hopkins Nursing. Each podcast carries a maximum of 0.50 contact hours.

This educational resource is provided without charge, but registration is required. To register to receive eCysticFibrosis Review via e-mail, please go to our website, www.ecysticfibrosisreview.org.

The opinions and recommendations expressed by faculty and other experts whose input is included in this program are their own. This enduring material is produced for educational purposes only.

Use of The Johns Hopkins University School of Medicine name implies review of educational format, design, and approach. Please review the complete prescribing information of specific drugs, combination of drugs, or use of medical equipment – including indications, contraindications, warnings and adverse effects — before administering therapy to patients. Thank you for listening.

Thank you for listening, eCystic Fibrosis Review is supported by an educational grant from Genentech,

Eurand Pharmaceuticals, Vertex Pharmaceuticals, Axcan Pharma, and Gilead Sciences Medical Affairs.

REFERENCES

Mark R. Elkins, M.H.Sc., Michael Robinson, Ph.D., Barbara R. Rose, Ph.D., Colin Harbour, Ph.D., Carmel P. Moriarty, R.N., Guy B. Marks, Ph.D., Elena G. Belousova, M.Appl.Sc., Wei Xuan, Ph.D., and Peter T.P. Bye, Ph.D. for the National Hypertonic Saline in Cystic Fibrosis (NHSCF) Study Group. A Controlled Trial of Long-Term Inhaled Hypertonic Saline in Patients with Cystic Fibrosis. N Engl J Med 2006; 354:229-240.