Featured Cases: Allergic Bronchopulmonary Aspergillosis (ABPA)

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

- Evaluate the possibility of ABPA as a cause of cystic fibrosis pulmonary exacerbations and describe how to initiate treatment
- Discuss the circumstances meriting initiation of antifungal therapy
- Describe how to optimize the use of antifungals and explain how Aspergillosis respiratory infection without ABPA may lead to decline in lung function.

His 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. Moss will help expand our understanding of ABPA with the discussion some typical case scenarios.

Unlabeled/Unapproved Uses: The author has indicated that none of the agents discussed are approved for ABPA.

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Richard Moss, MD has disclosed:

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MR. BOB BUSKER: Welcome to this eCystic Fibrosis Review podcast. eCystic FibrosisReview 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 and Axcan Pharma, and Gilead Sciences. Today’s program is a companion piece to our February, 2010, eCysticFibrosisReview Newsletter, “Allergic Bronchopulmonary Aspergillosis” or ABPA.

Our guest is Dr. Rick Moss from Stanford University. This activity has been developed for physicians, nurses, respiratory therapists, clinicians, and physical therapists caring for patients with issues related to cystic fibrosis. There are no fees of prerequisites for this activity.

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The learning objectives are that at the conclusion of this audio activity, participants should be able to evaluate the possibility of ABPA as a cause of cystic fibrosis pulmonary exacerbations and describe how to initiate treatment, discuss the circumstances meriting initiation of antifungal therapy, and describe how to optimize the use of antifungals and explain how Aspergillosis respiratory infection without ABPA may lead to decline in lung function in cystic fibrosis patients.

I’m BOB BUSKER, managing editor of eCysticFibrosis Review. On the line we have with us the newsletter issue’s author. Dr. Richard Moss is a Professor of Pediatrics and Pulmonary Medicine and Allergy and Immunology, as well as the Co-Director of Cystic Fibrosis Center at the Lucille Packard Children’s Hospital at Stanford University Medical Center in California. He has disclosed the following relationships with commercial supporters. He is or has been a principal investigator for Gilead, GlaxoSmithKline, Inspire Pharmaceuticals, PTC Therapeutics, and Vertex Pharmaceuticals. He works or has worked as a consultant to Aritis (phonetic) Pharmaceuticals, Arriva Pharmaceuticals, Genentech, Inspire, Johnson & Johnson, Lantibio, OAP Orphan Pharmaceuticals AG, Empex Pharmaceuticals, Novartis Pharmaceuticals, PTC Therapeutics, and Vertex Pharmaceuticals. Dr. Moss is a shareholder of Gilead stock, and his speaker bureau affiliations include Novartis Pharmaceuticals and Genentech. His presentation today will include discussion of off label product uses, as none of the agents discussed are approved for ABPA.

Dr. Moss, welcome to this eCysticFibrosis Review podcast.

DR. RICHARD MOSS: Thank you, it’s nice to be with you.

MR. BUSKER: To help expand our understanding of ABPA, we have asked Dr. Moss to discuss some typical case scenarios. So if you would, Dr. Moss, please present our first case.

DR. MOSS: Our first case is a 14 year old female with CF who is admitted to the hospital for treatment of pulmonary exacerbation, after a phone call and clinic visit. She was diagnosed at age four months after hospitalization for RSV bronchiolitis and failure to gain weight. Her diagnostic sweat test was 98, and her genotype is homozygous delta-F-508. Sputum cultures show chronic mucoid Pseudomonas aeruginosa, for which she has been treated with alternate month inhaled tobramycin for the last two years.

There is no previous history of any pulmonary complication. She now reports exercise intolerance, fatigue, anorexia, markedly increased cough and some chest tightness over the last week. On admission, she is noted to have a 1-1/2 kilogram weight loss, low grade fever, but otherwise normal vital signs, including pulse oximetry on room air. Increase cough and sputum, crackles in the right base and mid lung zones, and occasional bilateral wheezing without retractions or respiratory distress.

Initial CBC shows a white count of 12,300, with 82 percent polys, 2 percent bands, 10 percent monos, 4 percent EOs and 2 percent BASOs. Her CRP is mildly elevated. A chest radiograph shows a new density in the right lower lobe. Pulmonary function tests show a
12 percent drop in percent predicted FEV1 from previous stable clinic baseline two months earlier.

Based on our prior sputum sensitivities, therapy is begun with intravenous ceftazidime and daily tobramycin, along with four times daily airway clearance, bronchodilators, and nutritional supplementation.

After one week of treatment she feels better, crackles are diminished and the wheezing is gone, but FEV1 is not changed. A laboratory test was performed?

MR. BUSKER: Well, which lab test, and by that I mean which laboratory test would be most likely to yield data that would effect a change in the treatment plan?

DR. MOSS: Well a number of tests might be useful in this situation. One thing you could consider would be a chest CT. A chest CT might show new consolidation, mucous plugging, air trapping, atelectasis, increased interstitial markings, but these are all findings that one can see in cystic fibrosis nonspecifically, that is without ABPA as a necessary cause for those changes.

There is one CT finding that is more specific for ABPA, and that’s what’s called hyperattenuating mucoid impactions, which are basically large airways filled with mucous that show up as very dense on a CT. The density is higher than the adjacent soft tissue, and that has been linked to ABPA due to the presence of some cations that can build up in the mucous in ABPA.

Unfortunately, though, it is not a finding that is found in the majority of cases of acute ABPA changes. So unless you see it, you really are left with more nonspecific findings from a CT.

A second option would be to look at the sputum culture. Now the sputum culture might show the presence of *Aspergillus fumigatus*, or it might not. The problem is that this finding is not specific for ABPA, so that if it’s present it doesn’t indicate that ABPA is the problem, and if it’s absent it doesn’t really indicate that ABPA is not the cause. It’s not considered one of the major diagnostic criteria.

A third option, which I think would be the most helpful, would be a total IgE level in the blood. If it’s over at least 500 international units per milliliter, and oftentimes it’s over 1,000, that would be a fairly specific sign of ABPA unless you knew that the patient had very high baseline levels.

Another way to look at IgE levels is to look at it in comparison to a stale baseline. If there is at least a two to four-fold increase over the baseline level, it might indicate ABPA even if that level doesn’t exceed 500.

So, for example, if the patient had a baseline level from an annual screen that was 50 and now comes in with 250 or 350, that might, in fact, indicate and ABPA flare. Those are fairly rare cases, in most instances, the elevation is very striking.

MR. BUSKER: So what treatment would you recommend this patient receive?

DR. MOSS: This is a patient that has no prior history of ABPA. Once you’re fairly certain that that is the diagnosis, and that would be established from looking at the elevation in the total IgE level, looking at an imaging, whether it’s a chest x-ray or a CT examination, and doing some specific serologies that show the presence of both specific IgE and IgG antibodies to *Aspergillus*, then you could conclude that this patient has presented with ABPA as a form of pulmonary exacerbation, and that the treatment should be initiated.

The mainstay of initial treatment is prednisone, and usually that is started at a dose of at least .5 milligram per kilogram per day, and that would be continued for roughly a week, and then at that point might be followed by a switch to an alternate day regime at the same dosage for about another week, followed by a slow taper over several more weeks, so that a total course would be somewhere in the neighborhood of 2 to perhaps 3 months. Now many people would also start a patient on some kind of acid suppressor to reduce gastrointestinal intolerance of steroids at that time.

Now there would be some consideration to the addition of antifungal treatment, usually itraconazole is the agent that would be considered. But according to consensus recommendations, an initial treatment of ABPA does not need to include an antifungal agent such as itraconazole. Itraconazole would be added to the regime if the patient relapsed after trying to taper her off, either during or after that taper period, or if she had some underlying complication that made her
especially intolerant to steroids, such as diabetes or already severe osteoporosis, or if she developed steroid intolerance during treatment for one reason or another. Any of those situations would then trigger the use of itraconazole, but it is not necessarily recommended as a first line treatment, it would be steroids initially.

Then the monitoring for the response would obviously include close follow-up of the patient with clinical examination and also some objective tests. You would obviously like to see the exacerbation resolved, lung function improved, and then very importantly, measurement of a follow-up IgE level which can be done as soon as 10 to 14 days after the initial one.

In the majority of cases with acute ABPA, the total IgE level have a pretty dramatic reduction, often in the range of 50 to 70 percent from its highest value. And that is a really good indicator that the patient is having an immunologic as well as a clinical response and can be used to follow the patient. After that value, continued IgE surveillance would be recommended on some regular basis, perhaps quarterly for the next year.

MR. BUSKER: For this patient, what was her original response to treatment?

DR. MOSS: She had a good initial response in the hospital and was discharged and it was decided to see her again one month after discharge in clinic. So at the one-month clinical follow-up after the discharge, she had now been tapered down to 5 milligrams every other day of prednisone and was feeling pretty good. However, when we repeated her spirometry, her lung function tests had declined from her discharge value and we did notice that she was coughing more than on discharge.

MR. BUSKER: What would you recommend a clinician do in this situation?

DR. MOSS: So at this point, there are a number of options. First of all, you might want to check another IgE level to corroborate that the ABPA has perhaps relapsed. Now IgE levels are usually sent out, the turnaround time can be a few days to a week or more. So part of the consideration is how quickly you can get your IgE level back at your own institution, but it can be a guide if you have that information in fairly short order.

In most cases, if the patient is having deteriorating lung function and is starting to have symptoms again, you would classify this as a relapse and there are really two things at this point that get triggered by that decision. One would be another course of prednisone similar to the first one. So you would have to go back to daily therapy at a higher dose and then work it down again.

Now the difference this time to try and prevent future relapses would be to initiate antifungal therapy. The drug that is recommended at this point is itraconazole, Triazole antifungal agent with very good activity against Aspergillus, and the starting dose is 5 milligrams per kilogram per day. In the case of most teenagers and adults that will translate to a usual dose of 200 milligrams twice a day.

No remember that we put her on omeprazole when she started her steroids and that does present a problem for the use of itraconazole. Itraconazole requires an acidic environment for better absorption. So there are two possibilities here. One would be to stop her omeprazole; however, you don't want to do that. Another would be to simply have a discussion with her about taking her itraconazole with something like cola, which is an acidic solution to help improve absorption and then ask her to make sure to take her itraconazole an hour before she takes her dose of omeprazole in the morning, and that would allow her to hopefully absorb her itraconazole before she gets her next dose of omeprazole.

So the management of acid suppression and itraconazole is something that is very important and should be taken into account whenever you are using this kind of therapy.

MR. BUSKER: Thank you, Dr. Moss. And now if you would, please, bring us another case scenario.

DR. MOSS: Okay, for our next case we have a 23 year old male with CF. His genotype is heterozygous delta-F-508-W12-82X, and he was diagnosed with ABPA three years ago. He is atopic, he has positive skin test to grass pollen, house dust mite and cat dander, as well as several molds including Aspergillus. And he takes seasonal medications for allergic rhinitis, cetirizine and intranasal flunisolide, and he also has an asthmatic component and is on chronic inhaled fluticasone/salmeterol combination therapy for asthma.
He has been unable to come off of prednisone. In fact, he has relapsed whenever his regime is reduced below about 10 milligrams every other day of prednisone. And he has become mild to moderately Cushingoid in appearance. And has been on itraconazole for 18 months, no evidence of intolerance or toxicity. His IgE levels have remained elevated at about 1,600, which is far lower than his initial ABPA presenting value of 4750, but they are higher than his pre-ABPA level of 350, which was 4 years ago.

So the problem now is that recently he’s had increasing difficulty maintaining his nutritional status, his BMI greater than 22. And at the same time, his last screening oral glucose tolerance test 10 months earlier showed impaired glucose tolerance without fasting hyperglycemia for the first time. A bone densitometry six months prior to this visit showed moderate osteoporosis.

The main complaint he has at this visit is the result of a recent eye exam that revealed that he has earlier bilateral cataract formation and he had complained of mild intermittent blurry vision.

So the discussion at this visit is that this young man wants to stop taking prednisone, but he is very worried about an ABPA flare and he doesn’t want to, as he puts it, “roll the rock up the hill again.” So a laboratory test was performed.

MR. BUSKER: What test and what test results might change your treatment approach?

DR. MOSS: At this point, there are a number of things that might be useful. Firstly, an itraconazole level may show inadequate steady state blood levels and there are a whole host of reasons for this. It could be due to drug interaction, it could be due to the use of acid suppressing medication, like an antacid over the counter that he might be taking. It could be due to the fact that the bioavailability of the capsule is not very good and he is taking the capsule formulation.

So we could address this by increasing his dose if his blood level is inadequate. Another thing we could do would be to change his itraconazole formulation from the capsule to the suspension. There is a suspension of itraconazole and cyclodextrin, which is a lipophilic carrier, which markedly enhances the bioavailability to 20 to 50 percent higher than the capsule.

So there are a number of these options. A recent study, in fact, showed that adults with CF might require dosing as high as 500 milligrams twice a day to get effective blood levels without toxicity.

The second possibility would be to get another glucose tolerance test. This might show that he’s progressed to diabetes. In addition to initiating insulin therapy, there is a lot of worry about our inducing or worsening his diabetes as well as his cataracts and osteoporosis, and your thinking at this time might be that the steroid toxicity has become unacceptable so you start to think about some alternatives.

A third test that might be helpful is another IgE level. If it shows continued chronic elevation, along with his multiple aeroallergen sensitivities and his history of clinical respiratory allergies and asthma, that all suggests that he may be a good candidate for a trial of immunotherapy with omalizumab, which is an anti-IgE monoclonal antibody.

MR. BUSKER: Are there alternative treatments that should be considered?

DR. MOSS: There are a number of further alternative options that probably would be considered in a case such as this. First of all, you could try switching from itraconazole to another triazole agent with activity against Aspergillus.

Now there are two of those available, voriconazole and posaconazole. And they both have markedly improved bioavailability in comparison to itraconazole. However, there is very little experience at this point with posaconazole in ABPA, there is some more with voriconazole, but it needs to be kept in mind that voriconazole has a much greater interpatient variability than itraconazole. And that is because voriconazole is metabolized by several hepatic cytochrome oxidases, and there is a lot of variation in the population in these enzyme activities. So that it is very hard to predict what that patient’s steady state level is going to be on a given dose. So I would say if using voriconazole it is very important to do blood monitoring.

Another alternative would be instead to use inhaled amphotericin B. Now, amphotericin B, of course, is very toxic when given systemically and the indication is really restricted to more invasive forms of Aspergillosis. However, when it’s inhaled it is usually
very well tolerated, and the blood levels are very low and you don’t run into problems of renal toxicity.

We can usually give it in dose regimes that are likely to reduce or eliminate Aspergillus in the airway. With our current nebulizer systems, if you give a dose of 20 milligrams you can get enough into the BAL to exceed the MIC of most Aspergillus species. So that is something that can be done and commonly it’s given at a dose of 20 milligrams twice a day, sometimes that can be tapered rather than just discontinued as the patient responds.

I would also mention a third possibility, and that is switching from chronic alternate day prednisone to a monthly IV pulse therapy with methylprednisolone. There have been several reports of this approach which indicate that this is a way, perhaps, to reduce steroid toxicity, and in most patients who have gotten this form of treatment that has been the main indication.

Finally, I would also mention the fact that inhaled corticosteroids are really not something you would consider as the best way to go in this situation. For one thing, inhaled corticosteroids, particularly budesonide, can result in enhanced steroid toxicity if you are giving the patient itraconazole because of interference with the hepatic metabolism of budesonide.

So there are a number of options that exist in patients who have run into this kind of problem.

MR. BUSKER: And we will return in a moment with Dr. Rick Moss from the Stanford University Medical Center.

MS. MEGAN RAMSEY: Hello, I’m Megan Ramsey, nurse practitioner and clinical coordinator for adults at the Johns Hopkins Cystic Fibrosis Program at The Johns Hopkins University School of Medicine. I am one of the program directors of eCysticFibrosis. 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.

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MR. BUSKER: Welcome back to our March, 2010, eCysticFibrosis Review Podcast. Our topic is allergic bronchopulmonary Aspergillosis or ABPA. I’m Bob Busker, Managing Editor of eCystic Fibrosis Review. Our guest is Dr. Richard Moss, Professor of Pediatrics and Pulmonary Medicine, and Allergy and Immunology, and Co-Director of the Cystic Fibrosis Center at the Lucille Packard Children’s Hospital at Stanford University Medical Center in California. We have been bringing the data presented in our February newsletter into clinical practice via case study scenarios.

So, Dr. Moss, let’s continue now with a peds case.

DR. MOSS: Okay, this is something a little bit different but related, I think you’ll see. Here we have a 12 year old male with CF, he is homozygous for delta-F-508, and this boy has been in good health and adheres to quarterly clinic visits, staying on his multimodal treatment program for CF.

Now over the last 9 months his percent predicted FEV1 has declined from 103 to 88 percent predicted, but he has not really been complaining of any significant clinical changes.

On clinical exam his chest auscultation is clear, his respiratory cultures consistent grow methicillin Staph aureus and Aspergillus fumigatus. So since he has had a decline in lung function you are concerned about ABPA and you check his IgE level, and it comes back at 183. And you look back to his annual evaluation which occurred 10 or 11 months ago and it was 144 at that time.

A chest CT is ordered and this shows some mild multifocal bronchiectasis, but doesn’t show any major infiltrates, mucoid impaction or atelectasis. You also do an induced sputum for acid fast bacillus stain and culture and those are negative. So you decide to give him a two-week course of cephalexin for his Staph aureus and ask him to augment his airway clearance. And he then returns to clinic and you recheck his lung function, but it has not improved.

MR. BUSKER: Well, Dr. Moss, what interventions would you consider trying in this patient?

DR. MOSS: At this point is not really clear what is behind the decline in his lung function, so one of the things that you might consider is more intensive treatment of his S. aureus. You might have him hospitalized and treated with intravenous methicillin, for example. You might even consider doing fiber optic bronchoscopy and bronchoalveolar lavage because you might be concerned about a pathogen that is not being detected in the upper airway cultures that you are monitoring him with.

A second possibility is that he has mild bronchiectasis consistent with CF, but could this be ABPA? Well, his IgE level really hasn’t changed at all, so that would make it difficult to see how that would be the cause of his deterioration, but just to be sure you might follow that up by looking at specific IgE and IgG antibodies against Aspergillus to see if those are elevated and that might increase your level of suspicion and inclination, perhaps, to initiate treatment for ABPA.

The third thing that you need to think about is the possibility that his chronic positive Aspergillus fumigatus cultures might indicate an underlying Aspergillus infection. Some people have called this Aspergillus bronchitis, and that would underlie his decline in lung function.

There have been a number of epidemiologic studies recently which have suggested that chronically positive cultures for Aspergillus are associated with more rapid decline in lung function. If that’s the case, and given his deterioration, you might consider a therapeutic trial of an antifungal triazole like itraconazole, and follow him carefully, but to see that he is tolerating the drug, that it is being used optimally, and, of course, that he has an improvement in his pulmonary function.

MR. BUSKER: And which option was tried in this patient?

DR. MOSS: Well it was decided to start this patient on itraconazole in the hopes that this represented an
infection with *Aspergillus* rather than ABPA and that antifungal therapy might improve his lung function.

The problem was that baseline liver functions at the time of initiation of therapy, which were checked as a baseline, were normal, but after two weeks they were rechecked and at that time his liver enzymes had elevated. So his ALT was up to 184 and his AST was 304. And concerns about that and the possibility of significant liver toxicity, at that point you stopped the itraconazole.

**MR. BUSKER:** So now what would the next therapeutic move be?

**DR. MOSS:** So at this point you have a number of options. Obviously you could just not pursue it, but you are concerned about the decline in lung function. Since there is no really strong evidence that ABPA is the problem, probably the use of steroids or omalizumab would not be indicated.

Another alternative that you might consider is switching from itraconazole to voriconazole, or posaconazole, but again, these are in the same class so liver function abnormalities could also be seen with either of these two drugs, and that might be risky also.

A third option here would be to use inhaled amphotericin B. That would avoid the problem of liver toxicity and might be effective in eradicating the *Aspergillus* in his sputum cultures. Now if you are going to use inhaled amphotericin B, it’s important to pretreat with albuterol to lessen the irritative reactions which some people have and also to talk about the fact that it may have an unpleasant taste. Otherwise the tolerability seems pretty good and we do know that it can clear the sputum.

**MR. BUSKER:** From what you just described it sounds like ampho B might be the best therapy for this patient; is that what happened?

**DR. MOSS:** That’s right. This patient was started on amphotericin B nebulization 20 milligrams twice a day. Amphotericin B is a lyophilized preparation that has to be reconstituted in sterile water and he tolerated it well, and was seen back in clinic two months later. And at that time his FEV1 had improved back to 101 percent predicted and his fungal respirator culture was negative. However, he was complaining of intermittent tightness with the administration of the amphotericin despite the albuterol pretreatment, and he also is complaining about the taste.

**MR. BUSKER:** So what would be the best option now?

**DR. MOSS:** Well at this time there are a number of options. It is important to note that there have not been any controlled trials, randomized or otherwise, double-blind or open, looking at any of these antifungal therapies for this entity of putative *Aspergillus* bronchitis without ABPA. So you really don’t have any guidance from evidence. So I think that it would be reasonable to just discontinue therapy and follow this patient closely.

Another possibility that is often not considered is the environmental side of the picture. It may be worthwhile to investigate environmental exposure as part of the picture and when you do that with this patient, it’s interesting, you find out that he lives in a rural area, the family owns a horse, and he is the person that takes care of the horse and turns the hay pile at the stable himself.

So learning this, you can advise him to change his potential exposure to *Aspergillus* by not doing that job. *Aspergillus* can grow in areas like hay piles or compost, and when they are turned, huge spore clouds can be released. And there have been case reports of illness due to this kind of massive exposure to *Aspergillus* spores in the environment. So it is always worth thinking about the environment as part of the picture in this situation of *Aspergillus*, whether it’s *Aspergillus* bronchitis or ABPA, or other forms of disease.

If he then gets sick again then it is possible to consider the use of posaconazole that so far looks to be very effective and may have a lower toxicity profile than itraconazole or voriconazole. However, I would caution that there are really no published reports on the use of posaconazole for respiratory *Aspergillus* disease of this type.

**MR. BUSKER:** One final question, Dr. Moss, what do you see as the top research considerations in ABPA?

**DR. MOSS:** There is a lot of interest now in ABPA because it’s becoming more widely recognized, not only in CF, but in asthma. There are some studies that indicate its prevalence in asthma is much higher than
had previously been thought. So I think there is a great deal of interest in it as a serious allergic lung disease.

I would say the top priority for the future really has got to focus on controlled trials of some of these agents. There really is an awful paucity of literature and evidence that can guide rational therapy. Most of the things I've talked about are really based on mechanistic rationale rather than solid data.

So I would just point out that several controlled trials are now underway looking at some of these options. For example, there is a double-blind, placebo-controlled trial of Omalizumab for treatment of ABPA in cystic fibrosis underway internationally now, and there is also a multicenter trial in Canada of the use of itraconazole in a randomized controlled trial for Aspergillus in the sputum.

So trials such as this are going to be helpful in telling us what really is effective and also developing more information about toxicity. Down the road we’re going to need better diagnostic tools and some of these have been developed or are in the state of being developed and we hope to have a single lab assay that can clearly distinguish patients with ABPA from those who are merely allergic to the mold without having the full blown disease.

There are some indications of some possible tests that can do this. One is a chemokine called TARC, another possibility is some combination of IgE to a number of Aspergillus allergens that have been cloned and are available as pure recombinant reagents for testing.

So these are some of the things that I think will be very helpful as we go forward.

MR. BUSKER: Dr. Rick Moss from the Lucille Packard Children’s Hospital at Stanford University Medical Center, thank you for participating in this eCysticFibrosis Review Podcast.

DR. MOSS: Thank you for having me, it’s been a pleasure.

MR. BUSKER: This podcast is presented in conjunction with eCysticFibrosis Review, a peer reviewed CME and CNE 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.

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