JOHNS HOPKINS MEDICINE
eLITERATURE REVIEW
eCysticFibrosis Review

Jointly presented by
the Johns Hopkins University School of Medicine
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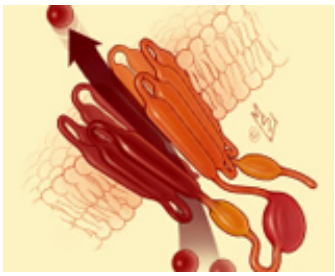

eCysticFibrosis Review Special Edition

In this Issue...

The use of inhaled antibiotics to combat pulmonary infections (primarily *Pseudomonas aeruginosa*) in patients with cystic fibrosis is nearly universal and until recently has been primarily scheduled as intermittent (28 days on, 28 days off) dosing. But how did this scheduling regimen come about? Is it the most effective use of inhaled antibiotics for all patients? What evidence describes the potential benefits and detriments of other dosing schedules, either continuous monotherapy dosing or two different inhaled antibiotics on an alternating schedule?

In this eCystic Fibrosis Special Edition, guest author Dr. Patrick Flume of the Medical University of South Carolina:

• provides background and insight on scheduling inhaled antibiotics
• discusses the recently released results from the Continuous Alternating Therapy (CAT) trial presented at the 2015 NACFC meeting in San Francisco with eCystic Fibrosis Review Program Director Dr. Peter Mogayzel of the Johns Hopkins School of Medicine [audio link and transcript available from within this newsletter]
• discusses current inhaled antibiotic scheduling protocols with: [audio link and transcript available from within this newsletter]

- o Dr. Scott Bell from the Prince Charles Hospital in Queensland, Australia
- o Dr. JP Clancy from Cincinnati Children's hospital in Cincinnati, Ohio
- o Dr. Stuart Elborn from Queens University in Belfast, Northern Ireland

LEARNING OBJECTIVES

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

- Review the history of the current approved regimen for inhaled antibiotics for the treatment of airways infection in patients with cystic fibrosis.
- Identify the perceived inadequacies of inhaled antibiotics and current practice patterns in patients with cystic fibrosis.
- Evaluate the findings of the recently completed trial investigating continuous alternating inhaled antibiotic therapy for patients with cystic fibrosis.

The Johns Hopkins University School of Medicine takes responsibility for the content, quality, and scientific integrity of this CME activity.

Program Information
CME/CE Info
Accreditation
Credit Designations
Intended Audience
Learning Objectives
Internet CME/CE Policy
Faculty Disclosures
Disclaimer Statement

Length of Activity
1 hour Physicians
1 contact hour Nurses

Release Date
December 22, 2015

Expiration Date
December 21, 2017

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Suzanne Sullivan has received honorarium from Vertex Pharmaceuticals Incorporated.

No other planners have indicated that they have any financial interests or relationships with a commercial entity.

IMPORTANT CME/CE INFORMATION

IN THIS ISSUE

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Guest Faculty Disclosures

Dr. Patrick Flume reports that he served as a consultant for Novartis, Vertex Pharmaceuticals, Inc, and Pharmaxis Limited. In addition he has received grant and research support from Novartis, Vertex Pharmaceuticals, Inc, Pharmaxis Limited, Boehringer Ingelheim Pharmaceuticals, Savara Pharma, and KaloBios.

Dr. Scott Bell reports that he has served as a consultant for Vertex, Rempex, Gilead, and Novartis.

Dr. Stuart Elborn has disclosed that he has served as a consultant for Novartis, Raplor and Vertex. He has received research support from Vertex, Bayer, and Novartis.

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Dr. Clancy reports that he has received grants and research funding from Vertex Pharmaceuticals, Incorporated, Nivalis, ProQR, Gilead, Parion, and Bayer. He also serves on a speakers bureau for Genentech.

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Unlabeled/Unapproved Uses

Dr. Patrick Flume reports there will be discussions of off-label or unapproved uses of colistin.

Planning Committee Disclosures

COMMENTARY

Inhaled antibiotics are considered standard of care for patients with cystic fibrosis (CF) who have chronic infection of the airways by Pseudomonas aeruginosa (Pa).[1-3] Antibiotic formulations have approved for inhalation by regulatory agencies, but this has not always been the case. Ad hoc use of antibiotics by inhalation were reported as early as the 1940s,[4] but the first controlled study of inhaled antibiotics in CF patients did not appear in the literature until 1981,[5] followed by a series of small studies.

The path to approved products started with the novel, off-label use of nebulized IV formulations, but it was the investment of the Cystic Fibrosis Foundation that spurred meaningful commercial investment in new CF drugs. The early industry approach was to repurpose existing drugs (eg, tobramycin) and to work with regulatory agencies on what would be required for marketing authorization.

Tobramycin was the first drug to undergo development as an inhaled formulation. In 1989 Dr. Arnold Smith et al[6] observed that the pharmacokinetics of tobramycin clearance were unusual in patients with CF compared to that of other patients, primarily because CF sputum acted a reservoir for tobramycin. It was important that the drug was in the sputum, at the site of infection, but the sputum itself rendered the drug inactive. This observation led to the hypothesis that larger quantities of tobramycin, which could only be delivered by the inhaled route, could improve outcomes. Subsequent clinical trials demonstrated an increase in lung function (ie, forced expiratory volume in 1 second, FEV_1) during prolonged exposure to inhaled tobramycin, as long as three months. The further observation and cause for concern, however, was that the treatment selected for tobramycin-resistant Pa at the end of three months reverted to tobramycin susceptibility after follow up. The fact that the peak FEV_1 response at two weeks was sustained at four weeks but was somewhat less at eight weeks led to the decision for a shorter course of therapy, based on studies comparing four to eight weeks of treatment.[7] There seemed to be little efficacy advantage for the longer treatment duration, which led to the intermittent (ie, 28 days on-28 days off) regimen for the pivotal phase 3 clinical trials[8], under the belief that chronic intermittent use might reduce emergence of tobramycin resistance while retaining the improved pulmonary function for a longer period.

RECOMMEND TO A COLLEAGUE

NEWSLETTER ARCHIVE

The development of inhaled tobramycin was contingent upon accepted clinical endpoints. Microbiological endpoints (ie, a reduction in bacterial density) were not considered acceptable surrogate endpoints, as they did not correlate well with how a patient feels, functions, or survives. Although there was skepticism about an improvement in FEV_1, that measure became the accepted primary endpoint. Pulmonary exacerbations, frequent events in the lives of CF patients yet requiring many more patients to power a study, initially became the secondary endpoint but were later seen to be of critical importance.

Since the approval of tobramycin solution for inhalation, there has been approval of additional inhaled antibiotics in the US, including aztreonam lysine and a powder formulation of tobramycin. The approval of these products was based upon a similar regimen used for tobramycin solution (ie, month on-month off). Since the approval of these inhaled antibiotics, a key question has arisen: Is the intermittent regimen the most effective, or would a chronic, daily regimen prove more effective?

The question is becoming of greater importance as the reported use of inhaled antibiotics has evolved over the last few years. Since the approval of inhaled aztreonam in 2009, there has been considerable change in the prevalence of patients receiving multiple antibiotic classes,[9] suggesting more clinicians are adopting and prescribing a new, continuous treatment regimen, but one with alternating antibiotics. In 2009 nearly 13,000 patients were reported to be using inhaled antibiotics, of which approximately 86% were on monotherapy (ie, only one inhaled antibiotic), presumably following the indicated intermittent regimen. Just three years later, in 2012, nearly 14,000 patients on inhaled antibiotics, approximately 30%, were reportedly prescribed more than one antibiotic.

One might consider a continuous regimen of antibiotic therapy on clinical worsening of the patient despite regular use of the intermittent regimen. It has been known since the original trials that lung function declined during the period off inhaled antibiotics, and some patients may continue to suffer pulmonary exacerbations. Thus, keeping antibiotic pressure on the infected airways has become an accepted approach to treatment. A regimen of continuous inhaled antibiotics can take several forms. One could use continuous monotherapy — ie, no time off drug — or there could be a rotation of antibiotics, ie, continuous alternating therapy (CAT). Studies have provided some evidence that changing to a new antibiotic may yield further improvements in FEV_1.[10] Further, as more inhaled agents become available, one could conceive of even more complex rotational regimens. The investigation of whether a CAT regimen is superior to the approved intermittent regimen presents potential challenges. The dosing of medications can be simplified into open label use of an approved product (every other month), while the between months would be a comparison of a second drug (approved or investigational) to placebo. Pragmatically, this may require use of more than one device, as the approved products are not administered through the same inhalation mechanisms. One might question whether every 28 days is the best duration for a rotating antibiotic schedule, but since the current approved duration is 28 days, it is most practical for the first test of regimens to follow that course.

The clinical endpoint of interest is also challenging. The motivation to change from the approved intermittent regimen to a CAT regimen is driven by perceived adverse outcomes, such as a drop in lung function or the occurrence of pulmonary exacerbations. The precedent for approval of an inhaled antibiotic has been a change in lung function, but given the early discomfort of regulatory agencies with this endpoint and the likelihood that there may be limited ability to further improve lung function on treatment with an alternate antibiotic, this is not a good choice. Thus a reduction in pulmonary exacerbations becomes an attractive primary endpoint that is relevant to patients as well as to regulatory agencies. This is the logic that led to the design of the CAT trial (NCT01641822), a study to investigate whether using a continuous, alternating therapy regimen of two antibiotics of different classes may reduce acute pulmonary exacerbations, maintain lung function, and control respiratory symptoms for patients with CF.

References

1. Döring G, et al. Treatment of lung infection in patients with cystic fibrosis: Current and future strategies. *J Cyst Fibr*. 2012;11:461-479.
2. Mogayzel et al. Cystic Fibrosis Pulmonary Guidelines: Chronic Medications for Maintenance of Lung Health. *Am J Respir Crit Care Med*. 2013;187:680-689.
3. Smyth AR, et al. European Cystic Fibrosis Society Standards of Care: Best Practice guidelines. *J Cyst Fibr* 2014; S23-S42.
4. Hodson et al. Aerosol carbenicillin and gentamicin treatment of Pseudomonas aeruginosa infection in patients with cystic fibrosis. *Lancet*. 1981 Nov 21;2(8256):1137-1139.

5. Mendelman et al. Aminoglycoside Penetration, Inactivation, and Efficacy in Cystic Fibrosis Sputum. *Am Rev Respir Dis*.1985;132:761-765.
6. AL Smith, BW Ramsey, DL Hedges, et al. Safety of aerosol tobramycin administration for 3 months to patients with cystic fibrosis. *Pediatr Pulmonol*. 1989;7:265–271.
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9. Dasenbrook EC., Konstan MW., VanDevanter DR. Association between the introduction of a new cystic fibrosis inhaled antibiotic class and change in prevalence of patients receiving multiple inhaled antibiotic classes. *J Cyst Fibr*. 2015;14:370-371.
10. McCoy et al. Inhaled aztreonam lysine for chronic airway Pseudomonas aeruginosa in cystic fibrosis. *Am J Respir Crit Care Med*. 2008;178:921-928.

CLICK HERE to listen to eCysticFibrosis Review Program Director Dr. Peter Mogayzel discuss the design, findings and impact of the CAT trial with Dr. Patrick Flume of the Medical University of South Carolina.

Read transcript here

CLICK HERE to listen to Guest Author Dr. Patrick Flume of the Medical University of South Carolina discuss current inhaled antibiotic protocols at the Prince Charles Hospital in Queensland, Australia with Dr. Scott Bell.

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Click here to listen to Guest Author Dr. Patrick Flume of the Medical University of South Carolina discuss the CAT trial and its impact on antibiotic scheduling at Cincinnati Children's Hospital in Cincinnati Ohio with Dr. JP Clancy.

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Click here to listen to Guest Author Dr. Patrick Flume of the Medical University of South Carolina discuss the CAT trial and its impact on antibiotic scheduling at the Queens University Adult Cystic Fibrosis Center in Belfast Northern Ireland with Dr. Stuart Elborn.

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back to top

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INTENDED AUDIENCE

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

There are no fees or prerequisites for this activity.

LAUNCH DATE

This program launched on December 18, 2015; this activity will expire two years from the date of publication.

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, 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.

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Suzanne Sullivan has received honorarium from Vertex Pharmaceuticals Incorporated.

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Guest Author's Disclosures

This activity is supported by educational grants from Chiesi USA,Inc, Gilead Sciences, Inc, and Vertex Pharmaceuticals Incorporated.

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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

- Although ivacaftor is approved for treating patients with specific CFTR mutations (eg, G551D, R117H), clinicians remain uncertain about its use in young children, the risk for possible drug interactions, and recent data describing its use in other mutations.
- Clinicians may be unfamiliar with emerging data describing novel and in-development agents, including correctors and potentiators, to manage patients with CFTR class II mutations, such as F508del.
- Clinicians may be unaware of recent studies of novel agents, including correctors and potentiators, targeting class I CFTR mutations and the potential role of these agents in clinical care..

Nutrition

- Clinicians who manage patients with chronic HCV infection may be unclear about how new/emerging drugs target different points in the viral life cycle.
- Clinicians may be unaware of emerging clinical trial data for current and emerging HCV therapies.

Pseudomonas Aeruginosa

- Clinicians lack information to most appropriately determine the optimal choice of inhaled antibiotics to manage chronic Pa infection.
- Clinician scheduling of inhaled antibiotic maintenance therapy lacks adequate evidence-based guidance.
- The most effective use of inhaled antibiotics for the treatment of pulmonary exacerbations remains unknown.
- The evidence-basis describing inhaled antibiotic protocols for Pa early eradication remains confusing.

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back to top

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