



Special Edition: Highlights of the 36th European Cystic Fibrosis Conference

Welcome to Part 1 of this eCysticFibrosis Review Special Edition, our two-part series reporting on some of the key information presented at the 36th European Cystic Fibrosis Conference (ECFS) in Lisbon, Portugal June 12 – 15, 2013.



As a special feature, many of these reports include links to streaming video of eCysticFibrosis Review Program Director Peter Mogayzel, MD, discussing the new data with the presenters.

Look for the to link to this feature.

In this Issue...

The 36th ECFS convened in Lisbon, Portugal, providing a forum for scientific and clinical teams from around the world to discuss the newest high-quality investigations from all areas of cystic fibrosis (CF) research. While identifying therapies to address the basic defect of CF remains a central part of CF research, clinicians need new and better ways to treat the symptoms of CF in individuals with CF. Improving the management and quality of life of individuals with CF remains a firm priority, as was reflected in the multitude of studies presented on these and related topics at the ECFS Conference.

In this issue we report the presentations focusing on:

- **Acute Pulmonary Exacerbations:** Hypertonic saline shows statistically relevant improvements in the rate and magnitude of exacerbation resolution, with patients regaining their pre-exacerbation lung function.
- **Exacerbation Biomarkers:** Sputum biomarkers show promise in accurately predicting acute pulmonary exacerbations to within six months (HMGB-1) and show a strong causal relationship to exacerbations in sick CF patients (GM-CSF).
- **Inhaled Antibiotics:** Development of new types of aerosolized antibiotics is under way, and clinicians are optimizing drug regimens to improve their effects.
- **Targeting the basic defect:** A combined corrector and potentiator approach, VX-661 and ivacaftor, for the treatment of the F508del-CFTR mutation-type increases the trafficking of CFTR to the apical membrane and simultaneously increases CFTR activity.
- **Nontuberculous mycobacteria (NTM):** Investigators outline the diagnosis and treatment of NTM, a rapidly emerging and highly resistant pathogen.

Program Information

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Length of Activity

- 1 hour Physicians
- 1 contact hour Nurses

Launch Date

August 29, 2013

Expiration Date

August 28, 2015

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- Step 1.** Please read the newsletter.
- Step 2.** See the post-test link at the end of the newsletter.
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LEARNING OBJECTIVES

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

- Describe the use of hypertonic saline in reducing the time to exacerbation resolution and lung function improvement
- Identify sputum biomarkers of acute pulmonary exacerbation and understand how they are helpful
- Discuss new inhaled aerosolized antibiotics and the patients most likely to profit from them
- Explain the impact of VX-661/ivacaftor combination therapy for F508del homozygotes
- Implement ECFS/CFF Guidelines for nontuberculous mycobacteria infections

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▼ Program Begins Below

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LAUNCH DATE

This program launched on August 29, 2013 and is published monthly; activities expire two years from the date of publication.

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Michael P. Boyle, MD, FCCP discloses that he has served as a consultant for Vertex, Novartis, and Genentech.

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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

- Clinicians remain uncertain how CFTR genotypes relate to phenotypes in patients with CF.
- Clinicians may not understand how CFTR genotype affects CFTR processing and function in CF.
- Clinicians may be unfamiliar with recently introduced and emerging disease-modifying therapies for CF and their appropriate use for individual patients.

Treating CF Patients with Inhaled Antibiotics

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

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Updated 4/09

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

Unlabeled/Unapproved Uses

Dr. Donaldson has indicated that there will be reference to the following unlabeled or unapproved uses of drugs: VX-661 and VX-770 (ivacaftor).

Dr. Olivier has indicated that there will be reference to the following unlabeled or unapproved uses of drugs: azithromycin, amikacin, tigecycline, imipenem, ceftazidime, cefepime, ceftriaxone, cefazolin, cefuroxime, cefepime, cefepime, cefepime, cefepime, rifampin, and ethambutol.

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HYPERTONIC SALINE FOR EXACERBATIONS

Workshop 19: Clinical Perspectives

Presentation Abstract WS19.4: A randomized controlled trial of the effect of hypertonic saline (HS) inhalation on exacerbation resolution, hospital length of stay and time to relapse in adults with CF; R. Dentice, M. Elkins, P. Middleton, J. Bishop, P. Wark, D. Dorahy, C. Harmer, P. Bye, HSHS Study Group. Abstract from the 36th European Cystic Fibrosis Congress; June 12-15, 2013; Lisbon, Portugal

Hypertonic saline (HS) had a significant impact on both the rate and magnitude of resolution of cystic fibrosis (CF) pulmonary exacerbations and helped reduce the length of hospital stay, according to the outcome of an Australian study that explored the effects of



HS during hospitalization for a CF exacerbation and secondarily determined the day of exacerbation resolution, improvement in lung function, symptom severity, quality of life (QoL), exercise tolerance, bacteria, and HS tolerance.

According to Ruth Dentice, MD, of Royal Prince Alfred Hospital, Sydney, and the University of Sydney, Australia, who presented the study as part of a workshop titled *Clinical Perspectives* at the 36th European Cystic Fibrosis Congress, "The summed effects of HS in this investigation is likely to make the inexpensive addition of HS management of a CF exacerbation worthwhile in clinical practice."

The multicenter, randomized, controlled trial included 132 CF patients (mean age was 28±9 years, forced expiratory volume in 1 second (FEV₁) 48±20 percent predicted, mean exacerbation score: 7±1) recruited from three adult CF centers in New South Wales, who had a confirmed diagnosis of CF and planned management of a pulmonary exacerbation in the hospital for a minimum of at least seven days.

Sixty-seven of the study participants received nebulized HS (7% saline) and 65 controls received placebo (0.12% saline) in doses of 4.0 ml inhaled three times/day. Sixty-six of 67 patients receiving HS and 62 of 65 patients receiving placebo, remained in hospital for the duration of the therapy and were included in the study results. The study was blinded using a taste-masking agent (quinine sulfate).

Exacerbations (defined by the Fuchs exacerbation score) resolved on day 10 in the HS group and on day 11 in the control group (mean difference: 1 day; 0 to 2). Participants were significantly more likely to return to their baseline FEV₁ at discharge in the HS group (75%) than the control group (57%), yielding a number needed to treat ((NNT) of 6 (3 to 65).

HS resulted in a greater improvement in FEV₁ during admission. The mean difference in FEV₁ during admission to day 10 was 172 ml (95% confidence interval [(CI): 42 to 301). A benefit in forced vital capacity (FVC) was apparent at discharge in individuals treated with HS, and a greater proportion returned to baseline FEV₁.

On a 100 mm visual analogue scale recorded daily, the HS group had significantly greater improvement than the control group in sleep disturbance by 15 mm (95% CI: 6 to 23), chest congestion (9 mm, 4 to 14), and dyspnea (6 mm, 1 to 12). There was borderline significance for fatigue (8 mm: 0 to 15), and cough (6 mm, 0 to 11).

At discharge, the HS group had significantly less severe sleep disturbance by 13 mm (95% CI: 4 to 23), chest congestion (10 mm, 3 to 18), and dyspnea (8 mm, 1 to 16). Furthermore, after 12 months' follow up, no significant difference in the time to next exacerbation requiring hospitalization was detected between groups (P = 0.3).

The mean difference between the two groups for length of stay was one day (95% CI: 0 to 2), 12 days HS vs 13 days control. Similarly, the mean difference in exacerbation resolution was one day (95% CI: 0 to 2), 10days HS vs 11 days control.

Twenty- five percent of the HS group and 43% of the control group failed to regain their previous FEV₁ levels, NNT 6. This failure rate has been considered a very important part of this treatment, Dr. Dentice noted.

All of the patients passed the initial tolerance test: a pass was a fall in FEV₁ ≤ 15% and SaO₂ ≥ 90%, and there was no significant difference in QoL, exercise tolerance, or sputum microbiology.

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CAUSAL CF BIOMARKERS FROM SPUTUM

Symposium 27: Biomarkers of Exacerbation and Lung Function Decline

Sputum biomarkers for the prediction of acute pulmonary exacerbation;
Theodore Liou MD

Talk held at the 36th European Cystic Fibrosis Congress; June 12-15, 2013;
Lisbon, Portugal



Assessing early inflammation based on biomarkers – the AREST study; Peter Sly, MD

Identifying causal cystic fibrosis (CF) biomarkers would give physicians the unique chance to intervene at a specific point in the disease process and provide clinical monitoring tools. Causal biomarkers could also provide predictive value, which is very important for clinicians with patients who need to understand both their short- and long-term health expectations.

According to Theodore Liou, MD, the Director of the Intermountain Adult CF Center, Salt Lake City, Utah, USA, changes in biomarker levels at healthy, and exacerbation disease states may indicate causality. During a discussion he held on *Sputum biomarkers for the prediction of acute pulmonary exacerbation*, Dr. Liou shared his insights on two particular markers, HMGB-1 (high mobility group box 1) and GM-CSF, which had highly significant relationships to acute pulmonary exacerbations (APE).

HMGB-1 emerged as an important molecule for its predictive value. Dr. Liou's research showed that changes in the level of this molecule could predict APE to within six months of the last APE, within a reasonably narrow confidence interval.

HMGB-1 functions as a DNA shepherd and a multiple use molecule. All of its extracellular forms are pro-inflammatory, and it is abundant in both sputum and the CF airway.

Using multivariate analyses, Dr. Liou found that HMGB-1 levels reliably predicted the number of APEs over five years, by taking the natural log of HMGB-1 measured in an individual with CF in a stable state and multiplying that value by 0.33. Each additional log unit of HMGB-1 predicted another third of an APE. Interestingly, neither FEV₁ percent predicted nor any other of the tested biomarkers were significant in this analysis.

Dr. Liou could predict which patients would have an APE within six months with 88% accuracy in a group of 26 individuals with CF. Furthermore, dividing individuals into high or low HMGB-1-level groups showed that half of the people with high HMGB-1 levels had an APE within three months, and the remainder had an APE by six months (except one). By contrast, individuals with low HMGB-1 values took twice as long for their next APE, with one individual with a low-level HMGB-1 going four years before his next APE. "These results revealed that we may have identified a molecule with the potential to be causal in CF," Dr. Liou said.

Although in practice, proper clinical care during an APE seems to be the factor that most strongly affects the time to the next APE, Dr. Liou's observations seem to advocate the sputum HMGB-1 level as a strong predictor of future events. He observed no response to treatment in the levels of HMGB-1 and has theorized that the molecule may reflect long-term inflammatory trends, which he hopes to confirm.

Another potentially causal biomarker, GM-CSF (granulocyte-macrophage colony-stimulating factor), showed a strong causal relationship to APEs in sick patients and a weak correlation in those who were stable. At APE onset, this sputum marker was significantly associated with APE-associated declines in lung function (-10.8 FEV₁, P < 0.001).

"These data were intriguing. The GM-CSF data need to be verified. However, identifying patients with large acute declines in FEV₁ would make GM-CFS a reliable support tool for determining an APE diagnosis. These data give us a better clue as to what happens to the patient on his way to the APE state."



[Dr. Peter Sly – YouTube video link](#)

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INHALED ANTIBIOTICS

Symposium 13: New Inhaled Therapies

Inhaled Antibiotics; Patrick Flume, MD

Talk from the 36th European Cystic Fibrosis Congress; June 12-15, 2013; Lisbon, Portugal



Aerosolized antibiotics (AB) are employed as standard practice in individuals with cystic fibrosis (CF) to eradicate early infections and in chronic suppressive therapy, mostly for *Pseudomonas aeruginosa* (PA). New aerosolized AB options are in development for individuals with an intolerance to existing medications, have an excessive treatment burden, and perceive treatment that is not effective. In his discussion on *Inhaled Antibiotics*, Patrick Flume, MD, from the University of South Carolina in Charleston, SC, USA, offered his insights on where the CF community is making progress and some of the difficulties encountered in treating individuals with CF with inhaled AB.

The goal of eradication is essentially to delay the time at which chronic infection becomes established, resulting in an improvement in overall health and longevity. The ECFS recommends rigorous AB treatment to eradicate early PA colonization and infection.

The ELITE trial resulted in a high PA eradication rate after TIS therapy, in which TIS 300 mg was given twice daily for either for 28 or 56 days, in two treatment groups. The eradication rate — patients who were PA-free — was 92% at one month. The median time to recurrence of PA was 26.12 months in the first group and 25.82 months in the second group.

Other aerosolized AB trials for PA eradication involve aztreonam and colistin. The ALPINE trial (Aztreonam Lysine for *Pseudomonas* Infection Eradication Study), an open-label study in individuals with CF aged 3 months to 18 years with newly detected PA uses a 28-day course of aztreonam lysine for inhalation (AZLI) 75mg, three times daily, with 196 days' follow up to test for safety and PA recurrence. Also, nebulized colistin for three months is being given alongside either oral ciprofloxacin or IV ceftazidime/tobramycin to establish the potential advantages of these drug combinations and the effects of different drug administration routes.

P. aeruginosa is not the only pathogen threatening the CF lung that requires urgent attention and new therapy options. Studies that look at the effects of inhaled AB on methicillin resistant *Staphylococcus aureus*, an organism in the CF lung that is associated with a more rapid decline in lung function and increased mortality, are now in phase 2 trials and actively enrolling, using vancomycin powder as a chronic suppressive therapy. Inhaled AB for *Stenotrophomonas maltophilia*, which is far more pathogenic than previously thought, *Burkholderia cepacia*, which is especially worrisome in patients needing transplants, and nontuberculous mycobacteria, which are becoming increasingly threatening, are urgently needed.

The ECFS states that inhaled AB have been proved successful as a treatment for chronic airway infection in maintaining lung health and are therefore the therapy standard. In spite of this, the very real problem remains that lung function continues to decline in individuals with CF, regardless of the AB choice, administration route, and patient adherence.

Part of the problem is finding the right treatment pattern. Regimens involving the cyclic use of AB in a one month on/one month off fashion may not be optimal and require adaptation, as even adherent patients suffer progression. The study of different regimens is desirable and Dr. Flume believes a more continuous choice would be better, using either a monotherapeutic approach or continuous combination therapy rotation. The CAT trial is currently testing TIS in continuous rotation with placebo or AZLI for three rotations.

Some CF providers suggested that two-week drug rotations could improve therapeutic benefits because in their experience, drug effects plateau after the initial two weeks. Ultimately, however, a therapy must make sense pragmatically and financially, and physicians must continue to urge their patients to adhere to the prescribed drug regimens.

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VX-661/IVACAFTOR COMBINATION THERAPY OUTCOMES

Workshop 7: Novel Therapies

Abstract: WS7.3: VX-661, an investigational CFTR corrector, in combination with ivacaftor, a CFTR potentiator, in patients with CF and homozygous for the F508del *CFTR* mutation: interim analysis; S. Donaldson, J. Pilewski, M. Griese, Q. Dong, P-S. Lee, for the VXII-661-101 Study Group. Abstract from the 36th European Cystic Fibrosis Congress; June 12-15, 2013; Lisbon, Portugal



First patient experience with the drug combination VX-661/ivacaftor revealed a more-than-additive effect in cystic fibrosis transmembrane conductance regulator (CFTR) transport for patients with the F508del *CFTR* mutation, according to Study 661-101, which was recently presented at the 2013 ECFS Congress. The results showed a clear dose-related response to combination VX-661/ivacaftor therapy, with improvements in pulmonary function (FEV₁) observed in all patients taking the combined drugs; the best effects were seen at dosages of 100 mg and 150 mg.

Scott Donaldson, MD, from the University of North Carolina at Chapel Hill, North Carolina, USA, who presented the study results during a conference workshop entitled *Novel Therapies*, reported that Study #661-101, evaluated the safety and efficacy of VX-661, an investigational CFTR corrector, alone and in combination with ivacaftor, a CFTR potentiator, in 128 adults with cystic fibrosis (CF)(forced expiratory volume in 1 second (FEV₁) >40% to 90%, inclusive) who were homozygous for the F508del-*CFTR* mutation. The analysis assessed four escalating dose levels of VX-661 (10 mg, 30 mg, 100 mg, 150 mg), given once daily for 28 days for both monotherapy and combination therapy. Approximately twice as many subjects were in the combination arm than in the monotherapy arm. Randomization between active and placebo was about 4:1. The change in sweat chloride and in FEV₁ was also evaluated.

The mean absolute change from baseline in sweat chloride at day 28 was small, for patients taking VX-661 monotherapy at the two lowest doses but was significantly reduced in the 100 mg and 150 mg groups, with a similar response at those two higher doses. Individuals receiving combination the drug combination therapy had a significant reduction in sweat chloride on the order of 5-6 mEq/L.

The relative change in FEV₁ percent predicted on day 28 from baseline was improved at 10 mg and 30 mg doses of combination therapy, which reverted to baseline on cessation of therapy. At the two higher doses of combination therapy, an even greater response was noted, shown by a rapid improvement in lung function during active therapy, followed by lung function reverting to baseline on cessation. Therapy caused very little change in patients receiving placebo.

VX-661 monotherapy caused increases in predicted FEV₁ at day 28, but did not reach statistical significance. No decrease in FEV₁ was observed in the monotherapy arm.

The relative change in FEV₁ percent predicted combination therapy reveals a very encouraging improvement in lung function: 60% of the patients had at least a 5% improvement.

The relative and absolute changes from baseline in lung function show that at its highest effective dose of 100 mg, combination therapy led to a 9% (P = 0.01) relative improvement in FEV₁, which translated into a 4.8% (P = 0.01) absolute improvement. At 150 mg, combination therapy led to a 7.5% (P = 0.02) relative improvement in FEV₁ and 4.5% (P = 0.01) absolute improvement.

The frequency of serious adverse events was similar in the treatment and placebo groups, with adverse events occurring in ≥ 15% of patients in any active drug arm. VX-661 alone and in combination with ivacaftor was generally well tolerated; the most common adverse events were respiratory.

The study outcomes were consistent with earlier data from in vitro studies, in which F508del-mutated cells reached about 25% wild-type CFTR transport when exposed to a VX-661/ivacaftor combination.

“The data supports the concept of a combined corrector and potentiator approach for treatment of patients who are homozygous for the F508del *CFTR* mutation. These compounds are effective for this mutation type by increasing the trafficking of CFTR to the apical membrane and simultaneously increasing CFTR activity,” Dr. Donaldson noted.



[Dr. Scott H. Donaldson – YouTube video link](#)

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NTM GUIDELINES: SCREENING AND TREATMENT

Special Symposium: ECFS/CFF Guidelines for the Management of NTM in CF

Treatment of Mycobacterium; Ken Olivier MD

Talk from the 36th European Cystic Fibrosis Congress; June 12-15, 2013;
Lisbon, Portugal

Dangerous emerging pathogens like nontuberculous mycobacteria (NTM) have magnified the relevance of careful screening in individuals with cystic fibrosis (CF). Identifying asymptomatic those who are positive for NTM gives clinicians the chance to segregate them appropriately and intervene early. Two discussions from the *Special Symposium on ECFS/CFF Guidelines for the Management of NTM in CF* focused on the pressing issues of diagnosis and treatment of NTM in CF.

According to Charles Haworth, MD, Director of the Cambridge Centre for Lung Infection at Papworth Hospital, Cambridge, UK, in his presentation on *Diagnosing NTM*, it is vital to screen all patients for NTM, especially when concerns arise about patient-to-patient transmission. Screening involves performing cultures and smears for acid-fast bacilli from sputum. Induced sputum or bronchoalveolar lavage (BAL) samples; oropharyngeal swabs are not recommended on three separate days and processing the samples within 24 hours to optimize detection. The United States Cystic Fibrosis Foundation recommends yearly cultures in spontaneously expectorating patients with stable clinical courses.

The American Thoracic Society/ Infectious Diseases Society of America (ATS/IDSA) definition of NTM pulmonary disease includes characteristic symptoms: two or more positive sputum samples of the same NTM or one positive lavage, radiology studies consistent with NTM infections and appropriate exclusion of other diagnoses. Shared characteristics of NTM and *P. aeruginosa* (PA) infection, such as cough, sputum, fever, and malaise, may obscure diagnosis, along with nonspecific radiology. Bacterial overgrowth with PA, inhibitory effects of antibiotics such as azithromycin, mixed cultures with *M. abscessus* and *M. avium* complex, and distinguishing treatment failure from reinfection, can also make microbiologic findings confusing.

Should clinical suspicion of NTM pulmonary disease arise, clinicians are urged to first withhold azithromycin for > 2 weeks, as monotherapy can cause resistance. If a patient meets the ATS criteria, the clinician must decide whether to start treatment or observe the patient. A symptomatic patient may require immediate treatment, and if the treatment aim is to eradicate the organism, it should be started early. To prevent progression, however, in patients with a small chance of clearing the organism (eradication), a watch and wait policy would be warranted. Furthermore, finding the balance between under- and overtreatment can be challenging, Dr. Haworth said.

In his *Treatment of Mycobacterium* presentation, Ken Olivier, MD, of the Laboratory of Clinical Infectious Diseases, NIAID, Bethesda, Maryland, USA, noted that *M. abscessus* infections require a treatment regimen consisting of an intensive phase followed by a continuation phase. The intensive phase should include a daily oral macrolide, preferably azithromycin, with 3-12 weeks of IV amikacin, plus one or more of the following intravenous drugs, guided but not dictated by susceptibility tests: tigecycline, imipenem, or ceftazidime. The duration of the intensive phase should be determined by the severity of infection, response to treatment, and tolerability of regimen.

The continuation phase should include a daily oral macrolide (azithromycin) and inhaled amikacin, with the primary goal of limiting the toxicity of IV amikacin. This phase should also include two or three of the following oral antibiotics guided but not dictated by susceptibility tests: minocycline, clofazimine, moxifloxacin, linezolid.

M. avium complex may be easier to treat, using daily oral macrolide (preferably azithromycin), rifampin, and ethambutol, for clarithromycin-sensitive *M. avium* complex. For milder disease, the clinician may choose an intermittent regimen (three times a week). The treatment regimen for cavitary *M. avium* complex pulmonary disease includes an initial course of IV amikacin.

Monitoring NTM treatment for a therapeutic response and toxicity is as follows: expectorated or induced sputum samples should be sent for NTM culture every 4-8 weeks to assess the microbiologic response. Sputum conversion is expected to occur between 3-6 months for the majority of patients. A schedule for detecting drug toxicity based on the specific drugs

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Step 3.
Complete the post-test and course evaluation.

prescribed should be in place at the time of NTM treatment initiation and continued throughout treatment.

Antibiotic therapy for NTM should be prescribed for 12 months beyond culture conversion, which is defined as three consecutive negative cultures with the time of conversion set at the date of the first of the three negative cultures, and no positive cultures during the 12-month period. Patients who fail to culture convert despite optimal NTM therapy may benefit from long-term suppressive antibiotic treatment.

A CT scan of the lungs should be performed shortly before starting NTM treatment and at the end of NTM treatment to assess the radiologic response.

All individuals with CF being considered for lung transplantation should be evaluated for NTM pulmonary disease. Current or previous NTM positive respiratory cultures should not necessarily preclude evaluation for lung transplantation.

 [Dr. Ken Olivier – YouTube video link](#)

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Step 4.
Print out your certificate.

PHYSICIAN
POST-TEST

NURSE
POST-TEST

* (The post-test for the newsletter is 1 credit hour.)

Respiratory Therapists
Visit [this page](#) to confirm that your state will accept the CE Credits gained through this program or click on the link below to go directly to the post-test.

RESPIRATORY
THERAPIST
POST-TEST

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