

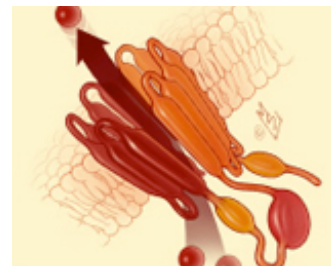


eLITERATURE
REVIEW

eCysticFibrosis Review

Presented by the Johns Hopkins
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eCystic Fibrosis Review Volume 3 Issue 2 Special Edition: Highlights of the 34th European Cystic Fibrosis Conference



Welcome back to eCystic Fibrosis Review and the second installment of our two-part special series reporting on some of the key information presented at the European Cystic Fibrosis Society (ECFS) Congress in Hamburg, Germany June 8-11 2011. As in the previous issue, some reports include links to streaming video of eCystic Fibrosis Review Program Director Dr. Peter Mogayzel discussing the data with the presenters. Look for the  to link to this feature.

In this Issue...

One of the key points made at this year's ECFS Congress was that to achieve better clinical outcomes, both researchers and practicing clinicians must change their approach to managing CF. For investigators, as patients with CF become healthier, study designs will have to include larger patient samples over longer times to demonstrate effects. Further, newly approved therapies will have to be tested for drug-drug interactions, currently approved agents will have to develop Phase IV studies to provide long term safety and efficacy assessments, and placebo testing will become much more difficult to institute.

To best help their patients, clinicians will have to increase the integration of nutrition and vitamin supplementation into their practices. Although bacterial infections in non-CF patients generally respond to antibiotic treatment, the unpredictability of the effects of antibiotic resistance in the bacteria colonizing of the CF airway means they must question whether prescribed agents will actually affect the organisms they're targeting. They must prepare for the potential introduction of gene-modifying therapies. As shown at the Hamburg Congress, the increasing pace of new CF knowledge challenges every current treatment paradigm and portends a future with increased therapeutic options as well as vastly more effective ones.

In this issue, we report on:

- **Nutrition:** investigations reconfirm that low vitamin D levels are associated with pancreatic insufficiency, diabetes mellitus and more severe lung disease in patients with CF.
- **Infections:** What we do and what we don't know about the action of antibiotics, the methicillin resistant *Staphylococcus aureus* (MRSA) HA strain's strong association with decreased FEV₁ lung function.
- **Gene Modulation:** The latest research into the investigational compound VX-770.
- **Therapies:** The encouraging results from an *in vitro* fosfomycin:tobramycin combination trial.

Program Information

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Length of Activity

Physicians
1 hour
Nurses
1 contact hour

Release Date

September 7, 2011

Expiration Date

September 6, 2013

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October 4, 2011

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LEARNING OBJECTIVES

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

- Describe the nosocomial origin of MRSA infections and the related health risks
- Identify the pitfalls and advantages of susceptibility testing
- Discuss the advantages and disadvantages of treating by observed clinical outcomes as opposed to targeting specific pathogens
- Explain the role of vitamin D in CF disease and the importance of vitamin D supplementation
- Describe the efficacy of a fosfomycin: tobramycin combination for combating *Pseudomonas aeruginosa* under aerobic and anaerobic conditions
- Assess the new trial evidence supporting the safety and efficacy of VX-770 therapy in patients with a G551D *CFTR* mutation.

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LAUNCH DATE

This program launched on July 25, 2011, and is published monthly; activities expire two years from the date of publication.

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The authors have indicated that there will be reference to the following unlabeled or unapproved uses of drugs: Ataluren/PTC-124, Denufosol, Mannitol, Tobramycin, VX-770, VX-809.

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NUTRITION: Vitamin D

Workshop 13- New Challenges in Nutrition

Hjelte, L. What Is Known About Vitamin D and CF?

Abstract 301- Brodli., M. Is the Bar too High? Vitamin D Status of Children with Cystic Fibrosis at a Regional Centre in the North East of England [Abstract from the 34th European Cystic Fibrosis Congress: June 8-11, 2011; Hamburg, Germany.](#)

Abstract 306: Pincikova T, Mared L, Hjelte L. Interaction of fat-soluble vitamins with immunosuppressant drugs in lungs transplanted cystic fibrosis patients. [Poster exhibited at 34th European Cystic Fibrosis Congress: June 8-11, 2011; Hamburg, Germany.](#)

Abstract 299: Orchard W, Brodli M, Thomas MF, Reeks GA, McCabe H, O'Brien C, and Spencer DA. Vitamin D status in pancreatic insufficient children with cystic fibrosis - are we doing enough? [Poster exhibited at 34th European Cystic Fibrosis Congress: June 8-11, 2011; Hamburg, Germany.](#)

Chronic vitamin D insufficiency in patients with cystic fibrosis (CF) has been implicated in modulating severe inflammatory lung conditions (asthma, chronic obstructive pulmonary disease) and may contribute to CF lung inflammation (associated with high IgG levels, low IL-10 levels, and poor lung function); a high incidence of CF-related diabetes and low bone mineral density (BMD).

Professor Lena Hjelte of the Stockholm CF Center, Sweden conducted an investigation that studied the vitamin D status of 133 patients with CF, reporting a correlation between serum levels of 25-hydroxy vitamin D (25-OHD) and IgG levels, but none with serum IL-10. She noted a seasonal variation of 9% in 25-OHD, with a slightly better vitamin D status in summer. She could attribute only 7% of the variation in vitamin D insufficiency to seasonal variations. The majority of Stockholm patients with CF have suboptimal serum 25-OHD levels in both winter and summer. In her previous work with vitamin D, Prof Hjelte found a correlation between CF and low serum 25-OHD levels of under 30 nmol/L. "Studies consistently show strong associations between vitamin D status and chronic inflammation and diabetes mellitus in CF," she said.



In a poster she and her team presented at the ECFS meeting, entitled *Interaction of fat-soluble vitamins with immunosuppressant drugs in lung transplanted patients with CF*, Prof Hjelte showed that the observed changes in vitamin A and E metabolism and the interference of vitamin D with immunosuppressant drugs may have an impact on immune modulation and bone health in patients with CF following lung transplantation. She observed that with high levels of vitamin D, there was no accumulation of cyclosporine A. She speculated that by acting like an immune modulator, vitamin D reduces cyclosporine levels.

Achieving adequate levels of serum 25-OHD (75 nmol/L) in patients with CF is difficult to achieve, but Malcolm Brodrie, MD of the Paediatric CF Unit of Great North Children's Hospital in Newcastle-upon-Tyne, believes that part of the problem may be that the target is set too high. Dr Brodrie and his team sampled 97 children with CF at Great North Children's Hospital, Newcastle, UK, over a 12-month period from 2007 to 2008 and found that only 7% had greater than 75 nmol/L serum 25-OHD. This finding caused dietitians and physicians to become proactive, raising vitamin D3 supplementation for children older than 1 year from 800 IU/day to 3000 IU/day and for children younger than 1 year from 400 IU/day to 1900 IU/day. In 2010, Dr. Brodrie sampled all pancreatic-insufficient children receiving supplements and found that they had a significant increase in median 25-OHD levels, no adverse effects, and no cases of hypercalcemia. In 2008 the median 25-OHD level was 49 nmol/L, and in 2010 it was 72 nmol/L. Nevertheless, 55% of the children were still under 75 nmol/L despite increased supplementation, raising the question, is 75 nmol/L a realistic target?

Dr Brodrie and his team took a close look at 25-OHD supplementation in a poster shown at the ECFC, *Vitamin D status in pancreatic insufficient children with CF. Are we doing enough?* He gave 7/16 pancreatic sufficient children at his hospital 25-OHD supplements and 9/16 none (median age was 3.5 years). Three of seven children receiving supplements fell below the benchmark 75 nmol/L serum 25-OHD, while 5/9 children receiving no supplements were above the benchmark.

Take home message: *Most pancreatic insufficient children with CF require significant supplementation with vitamin D, although the optimal approach to achieving an adequate level of vitamin D requires additional study.*

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GENE MODULATION: VX-770 in CF patients with G551D-CFTR mutations

Workshop 17- Late Breaking Science

Elborn, S. Efficacy and safety of VX-770 in Subjects with CF and the G551D Mutation

In his Late Breaking Science presentation, Stuart Elborn, MD on behalf of the CF & Airways Microbiology Research group, Belfast, UK, reported that lung function improvements in cystic fibrosis (CF) patients with the G551D mutation receiving the CF transmembrane conductance regulator (*CFTR*) potentiator VX-770 were rapid in onset and sustained through 48 weeks of treatment. The pattern of improvement in *CFTR* function mirrored the improvements in lung function, he said.

CF lung disease is caused by defective or missing *CFTR* proteins of the lung epithelial cells, which make up the ion transport gate that allows chloride ions to pass through the channel and hydrate mucous secretions. Dysfunctional *CFTR* proteins cause poor ion flow across the cell membranes, resulting in highly viscous mucus secretions, a predisposition to chronic lung infections, and progressive lung damage.

"The archetype mutation of a type III gating dysfunction involves the G551D gene mutation. The *CFTR* potentiator, VX-770, aims to increase the function of defective *CFTR* proteins by increasing the gating activity, or ability to transport ions across the cell membrane, and thereby make a significant impact on CF disease," Dr. Elborn explained.

The double blind study included 167 patients with CF with at least one G551D mutation in at least one *CFTR* allele and a forced expiratory volume (FEV1) of between 40 to 90% predicted. Subjects were randomized for placebo (83) or VX-770 (84) therapy at 150 mg twice daily.



Gender, mean age (25 years), mean weight (61.5 kg), and mean sweat chloride concentration (100 mmol/L) were well balanced among the placebo and active drug groups. The majority of the patients had the G551D/F508del genotype combination. The mean FEV₁ was 64% predicted in the two groups.

The study results revealed a rapid change from baseline within two weeks in the VX-770 group for all primary and secondary outcome measures. FEV₁ (primary endpoint) changed from baseline by a mean 10.5% (p=0.0001), which was sustained over the entire 48-week duration of the trial. The change from baseline in sweat chloride concentrations (secondary outcome measure) was -48.1 mmol/L (P = 0.001), and sustained for 48 weeks. Quality of life questionnaire (CFQ-R) respiratory domain exceeded the minimal clinical important difference (4) in the active drug group, achieving 8.6 (p =0.001) at 48 weeks. VX-770 patients showed a mean sustained weight gain of 2.7 kg (P = 0.0001) by week-16, which was the largest weight gain seen in a clinical trial for the treatment of lung disease. Dr. Elborn noted that most lung exacerbations within the first 24 weeks of the study with a very significant reduction of the hazard ratio of 0.46 (P = 0.0001). Overall, pulmonary exacerbations and their duration, hospitalizations and their duration, need for IV antibiotics, and treatment duration were all significantly reduced in the VX-770 group.

Headache, upper respiratory tract infection, nasal congestion, rash, and dizziness were the adverse events seen most frequently in the VX-770 group. Adverse events that were more prevalent in the placebo group included pulmonary exacerbation (physician-determined), cough, hemoptysis, and decreased pulmonary function test. Markus Mall, MD of the Division of Pediatric Pulmonology and Allergy and Cystic Fibrosis Center of Heidelberg University, Germany, who co-moderated the ECFC Workshop of Late Breaking Science, asked if there was any evidence of reduced inflammatory markers associated with the improved clinical findings, which would herald the beginning of the cessation of lung damage. Dr. Elborn replied he and his group monitored peripheral blood inflammatory markers, which were trending toward a reduction in inflammation, although it was difficult to get a reliable blood or lung signal.

Take home messages: *Patients with CF with the G551D 'gating' CFTR mutation benefit from treatment with the potentiating agent VX-770, achieving a substantial, rapid, and sustained increase in FEV₁ as well as improvements in secondary outcome measures.*



VIDEO: Dr. Peter Mogayzel and Dr. Stuart Elborn discuss VX-770.

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INFECTIONS: Targeting Microorganisms

Symposium 12- Pipeline Update

Flume, P. Targeting microorganisms

Physicians treating patients with CF are often at a loss to interpret and explain antibiotic treatment results. While diagnosis, treatment, and outcomes work one way according to the medical books, the actual way they work—or don't work—in CF are baffling and seem to suggest that physicians are either choosing to use the wrong antibiotics or, conversely, targeting the wrong organisms.

As part of the Pipeline Update Symposium, Patrick Flume, MD of the Medical University of South Carolina in Charleston, SC, USA discussed a new perspective in the CF physician's approach to antibiotics in CF. "When a patient comes in with an exacerbation, I do not take antibiotic susceptibilities into account. I treat with an antibiotic that was proven successful in the past, until I no longer get the outcome I hope for. When treating a chronic infection, I use the drug the patient can best tolerate, not the one that targets the organism he is most susceptible to. In fact I have reduced the frequency of susceptibility testing to once per year. There is so much we still need to understand about the pathogens in CF lung disease," Dr. Flume reported.

While his approach seems to break the rules, Dr. Flume's experience shows him that treating CF with antibiotics follows no logical progression. A patient's symptoms sometimes improve despite antibiotic treatment with the continued presence of bacteria resistant to that therapy,

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while at other times, a patient's health deteriorates in spite of treatment with the "right" antibiotic agent. Furthermore, antibiotics chosen by *in vitro* combination testing are not more effective than those chosen by clinicians with respect to treatment failure rate, change in clinical signs and symptoms, change in pulmonary function, or time to next exacerbation, he noted.

Dr. Flume suspects, moreover, that sputum cultures may not tell physicians all they need to know. What may in fact be affecting the patients with CF lies deep within the lungs, unseen in sputum. Although standard microbiological techniques indicate that a majority of U.S. patients with CF exacerbations carry multiple species of bacteria, what molecular diagnostics now show us is that there are even more organisms in the airway than we thought.

In fact, studies have shown that there is a different distribution of organisms in an individual at different times of his chronological life, during times of stability/exacerbations, during a patient's particular treatment phase, or in recovery.

"So if *Pseudomonas aeruginosa* is the most numerous organism, is it also the most virulent? Any number of organisms could be harmful, and it is hard to tell which is causing symptoms. Furthermore, a seemingly harmless organism might inadvertently cause or contribute to the patient's pathogenesis," he observed.

The lack of a correlation between the changes achieved in bacterial density with antibiotics and lung function poses the question, are we targeting other pathogens? "Should physicians reevaluate *Pseudomonas aeruginosa* as more of a marker of those patients who will benefit from antibiotic therapy than a culprit?" Dr. Flume challenged.

Take home message: *As physicians cannot always know which bacteria are being targeted with antibiotics, it is important to recognize that physicians treat a community of pathogens when treating chronic CF lung disease and should target symptoms and clinical outcomes.*



VIDEO: Dr. Peter Mogayzel and Dr. Patrick Flume discuss a different approach to antibiotics.

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INFECTIONS: Microbiological Endpoints

Symposium 20 - Clinical Trials of Inhaled Therapy: What Microbiological Endpoints Tell You

Højby, N. Quantitative Microbiology - Is It relevant?
Smith, A. Antimicrobial Resistance – Does It Matter?

When asked if it made sense to continue assessing microbiological endpoints such as colony forming units (CFU) and susceptibility testing in patients with CF, specialists' approaches diverged. Niels Højby, MD of Copenhagen University and Arnold Smith, MD of the Seattle Children's Hospital shared their views on quantitative microbiology and susceptibility testing at the ECFS.

There is, at times, no correlation between *P. aeruginosa* density and patient well being, so why measure it? The answer is, because many times, there can be a strong correlation that provides the treating physician with positive feedback that therapy is successful.

"The *P. aeruginosa* count says a lot about the patient's well being. Knowing the diversity of organisms we deal with in CF does not change the way we deal with it. We should continue using quantitative CFU to assess bacterial number," said Niels Højby, MD in his presentation at a symposium on *Clinical Trials of Inhaled Therapy: What Microbiological Endpoints Tell You*. He explained that many relevant studies associated improved health of patients with CF, with reduced bacterial number. For instance, the reduction of sputum *P. aeruginosa* density by antibiotics improved lung function in CF more than did bronchodilators and chest physiotherapy, a U.S. study showed. Also, an improvement of inflammatory parameters was shown to result in decreased bacterial number and improved symptoms. Furthermore, the mean change in the density of *P. aeruginosa* in samples of expectorate with inhaled tobramycin one month on/one month off therapy showed a decrease in the number of bacteria during the "on month," with concomitant improved health. Evidence from still another trial

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validated that decreased bacterial density was indicative of treatment efficacy, showing how the use of aztreonam lysine resulted in decreased sputum *P. aeruginosa* during the 28 days of therapy compared to placebo, which correlated with better lung function and patient well being.

Susceptibility testing is often put in question, because of contradictory evidence of resistant organisms responding to a certain antibiotic while targeted 'susceptible' ones do not. According to Arnold Smith, MD, susceptibility testing need not be done. "Clinicians ignored antimicrobial susceptibility tests for treatment of pulmonary exacerbations, years ago, saying that a patient's response to the antibiotic was more important than the *P. aeruginosa* susceptibility. Clinical improvement was and is a better test of the antibiotic therapy," Dr. Smith maintained. The literature tells us that antibiotic therapy improves the response in management of acute exacerbations in CF. Although *in vitro* *P. aeruginosa* antibiotic resistance commonly emerges as a result of treatment, *in vivo*, resistance at the initiation of antibiotic therapy does not appear to impact the probability of observing a clinical response to therapy," he explained.

Dr. Smith recommended sticking with those antibiotics that were proven successful in a given patient, plus any other agent that might improve pulmonary function, such as hypertonic saline. If the patient stops responding, the physician must collect the organism and test it with nonroutinely used antibiotics, such as rifampin, with which Dr. Smith had very good results against *P. aeruginosa*.

From the audience, John Moore, PhD of the Northern Ireland Public Health Laboratory, UK, commented that he was not convinced that susceptibility testing was completely useless. He observed that there was a much higher than predicted resistance to antibiotics in very early isolates and recommended, therefore, to be cautionary and continue doing susceptibility testing for early infections, as it would be predictive at that stage of the infection.

Take-home message: *Clinical evidence supports the bacterial burden as measured by CFU as indicative of the patients' with CF, well being, while susceptibility testing is not always indicative of the patient's response.*



VIDEO: Dr. Peter Mogayzel and Dr. Niels Høiby discuss quantitative CFUs and susceptibility testing.



VIDEO: Dr. Peter Mogayzel and Dr. Arnold Smith discuss quantitative CFUs and susceptibility testing.

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INFECTIONS: MRSA

Workshop 7 - Infection Control: Challenges from Transmissible Organisms

Abstract 160 - De Meirleir, L. Acquisition of methicillin-resistant *Staphylococcus aureus* (MRSA) by patients with CF: risk factors and impact on outcome [Abstract from the 34th European Cystic Fibrosis Congress: June 8-11, 2011; Hamburg, Germany.](#)

Abstract 133 - Muhlenbach, M. Characteristics and Susceptibilities of MRSA in Pediatric patients with CF in USA [Abstract from the 34th European Cystic Fibrosis Congress: June 8-11, 2011; Hamburg, Germany.](#)

Studies verify that MRSA infections in patients with CF result in more rapid lung destruction, thus accentuating the importance of identifying the risk factors associated with MRSA acquisition. At an ECFS Workshop dedicated to *Infection Control: Challenges from Transmissible Organisms*, Belgian and U.S. investigators compared observations on MRSA prevalence, clinical manifestations, and methods for control.

Reporting on a retrospective case-control study carried out at the CF Center of the Vrije Universiteit, Brussels, Linda de Meirleir MD and her team used data from the CF clinic's registry from 2002 to 2010 and found a 15% prevalence of MRSA in patients with CF, of which 12.6% of infections were chronic (n=19). When contrasting variables with an equivalent

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number of patients with CF with chronic MSSA, matched for gender and age, there was a statistically significant difference ($p < 0.05$) between the patients for pancreatic insufficiency (PI), bronchiectasis, severe lung disease, delF508 genotype, and hospitalizations, but no correlation for CF lung disease or *P. aeruginosa*.

Dr De Meirleir noted no statistically significant difference in FEV₁ from the time of diagnosis of MRSA to one year before diagnosis. FEV₁ declined with statistical significance ($P < 0.05$), however, within the first year after diagnosis. The MRSA group also showed a stronger decline in FEV₁ one year after diagnosis than the MSSA group. Within the year before MRSA diagnosis, Dr De Meirleir observed that the patients were hospitalized frequently, which seems to suggest a nosocomial association. The two-year and six-year follow-up analyses confirm a significant continued FEV₁ decline in the MRSA group compared to the MSSA group. "MRSA is associated with a more rapid lung destruction. Nonetheless, we see an increased survival of CF in our patients due to improvements in care, which may have something to do with the use of antibiotic therapy. This, of course, has the added disadvantage of increased resistance of organisms," Dr De Meirleir said.

Marianne Muhlenbach, MD of the University of North Carolina at Chapel Hill noted a 24% prevalence of MRSA in the patients with CF she studied as part of the STAR-CF investigation, which analyzed the prevalence of community associated (CA) versus hospital associated (HA)-MRSA in patients with CF, based on SCCmec typing, at seven U.S. CF centers. In the presentation she gave on the study's results, Dr. Muhlenbach revealed that of the 296 isolates (chronic patients that had at least two MRSA-positive cultures over one year), 205 (69%) were SCCmecII (HA), of which all were pvl-, 52 (17.6%) were SCCmecIV pvl+ (CA), and 39 (13.2%) were SCCmecIV pvl- (CA).

Dr Muhlenbach observed that none of the isolates was resistant to vancomycin, although there was an overall high resistance to ciprofloxacin, levofloxacin and clindamycin. HA strains were predictably resistant to clindamycin, levofloxacin, and erythromycin, while CA strains were mostly resistant to erythromycin. A low rate of resistance was observed against trimethoprim/sulfamethoxazole, fusidic acid, and tetracycline, making these viable candidates as first line agents, she maintained. She noted that infections with SCCmec IV pvl+ were significantly shorter (mean duration: 30+/- 21months) than infections caused by SCCmec IV pvl- (mean duration: 49+/- 37months), and SCCmecII pvl- (mean duration: 56 +/- 35 months) ($P < 0.001$).

Take-home message: MRSA is common in patients with CF and it is associated with an increased prevalence of PI, bronchiectasis, decline in FEV₁, delF508 genotype, and hospitalizations.

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TREATMENT: Fosfomycin/Tobramycin Combination Antibiotic

Oral Poster Session 3 - CF Microbiology: Identification, Pathogenesis and Treatment

Abstract 100 - McCaughey, G. Synergistic Effects of a fosfomycin: tobramycin combination on CF pathogens grown aerobically and anaerobically - [Abstract from the 34th European Cystic Fibrosis Congress; June 8-11, 2011; Hamburg, Germany.](#)

The number of patients with CF with both *P. aeruginosa* and MRSA infections is universally rising, most notably in the U.S., where MRSA prevalence is up to 24% by some estimates, presenting physicians with a difficult treatment challenge. Combined therapies must be explored and may hold more promise than single antibiotics to combat *P. aeruginosa* and MRSA, which are becoming increasingly resistant to conventional antipseudomonal and antistaphylococcal antibiotics.

In an oral poster session on the synergistic effects of a fosfomycin:tobramycin (F:T) combination, Gerard McCaughey, MD of the CF & Airways Microbiology Research Group showed that F:T was rapidly bactericidal under both aerobic and anaerobic conditions and maintained bactericidal killing at 24 hours. He observed that synergistic activity was more pronounced under anaerobic conditions. The results suggest that F:T may prove promising as a treatment option for anaerobic and aerobic infections caused by bacterial respiratory pathogens.

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He applied F:T in a ratio of 4:1 and used time-kill studies of fosfomycin, tobramycin, F:T, and controls under aerobic and anaerobic conditions on 15 *P. aeruginosa* and 5 MRSA isolates for a 24-hour period. The F:T concentration was twice the aerobic MIC (eg, 20 mg/L), and both antibiotics alone were applied at the concentration used in the F:T combination (eg, FOS 16 mg/L, TOB 4 mg/L).

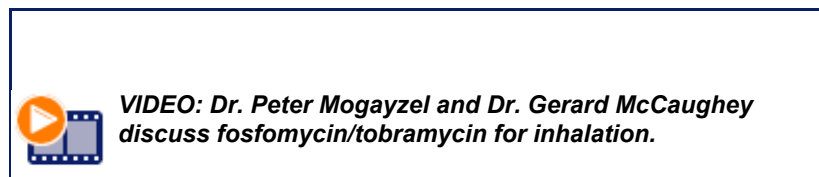
Under both anaerobic and aerobic conditions, controls continued to show growth over 24 hours. Under aerobic conditions, fosfomycin was bacteriostatic for all 15 *P. aeruginosa* isolates, while tobramycin and F:T were both rapidly bactericidal. Under anaerobic conditions, fosfomycin was mostly bacteriostatic. F:T was rapidly bactericidal, but tobramycin, although bactericidal at first (within four hours), showed bacterial re-growth from hours 6 to 24 in three *P. aeruginosa* isolates under anaerobic conditions. F:T and tobramycin had a bactericidal effect on the MRSA isolates under aerobic conditions. Under anaerobic conditions, however, there was strong regrowth after 24 hours of 3/5 of the MRSA organisms treated with tobramycin. Fosfomycin was bactericidal against 2/5 of the MRSA isolates, and F:T was bactericidal in all cases.

Synergy was increased under anaerobic conditions (7/15 *P. aeruginosa* isolates) compared to aerobic conditions (3/15 *P. aeruginosa* isolates). Similarly, synergy improved among the MRSA isolates under anaerobic conditions (2/5 isolates) compared to aerobic conditions (1/5 isolates). F:T showed no antagonism when tested against any of the isolates under either growth condition.

Michael Tunney, MD, who moderated the CF Microbiology, Identification, Pathogenesis, and Treatment session, expressed concern about resistance to fosfomycin. He said that the very high level of spontaneous mutations seen among bacterial strains treated with fosfomycin could pose a problem to therapy. Dr McCaughey responded that although the spontaneous mutation rate for fosfomycin was very high *in vitro*, it was cause-associated and likely to be absent *in vivo*. He noted that the F:T combination might delay the onset of resistance.

Fosfomycin/tobramycin for inhalation (FTI) in a 4:1 combination is currently in clinical development.

Take home message: *F:T showed rapid bactericidal action against P. aeruginosa and MRSA isolates under both aerobic and anaerobic conditions, and worked better than either fosfomycin or tobramycin individually.*



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