ANTIMICROBIAL NEW THERAPIES

Marilù Furnari
Centro Fibrosi Cistica di Palermo
Gruppo di Lavoro della SIFC "Nuove Terapie"
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Background
Patients with cystic fibrosis (CF) can be chronically infected with several pathogens, including *S.aureus*, *P. aeruginosa*, *B. cepacia* and others. By 18 years of age; 80% of patients are infected with *P. aeruginosa* (P.a.). With time, it converts to a mucoid phenotype which often heralds deterioration in respiratory status. Approximately 4% of patients in the U.S.A. become infected with *B. cepacia complex*, it can be particularly virulent and is associated with increased mortality.
The pathogenetic nature of many infectious bacteria is enhanced by their ability to form surface-associated, protected communities known as biofilm. Due to various factors, bacteria in biofilm communities display significantly greater resistance to traditional antimicrobial therapies.
So new therapies can be separate into:
1) Treatment of first colonisation with P.a.
2) Treatment of chronic infection P.a. and treatment of multidrug resistant bacteria.

1) The first step of our description is the treatment of **first colonization from P.a.** The time before chronic colonization with P.a. represents a window of opportunity to eradicate bacteria and delay persistent infection. Increasing evidence suggests that early eradication can slow progression of lung disease. The question now facing the clinician is how to best manage these mostly asymptomatic younger patients with cystic fibrosis who have evidence of lower airway bacterial infection or inflammation (1).

The following drugs are being studied for their effectiveness in fighting lung infections for people with CF in the last years (2).

- **TOBI** (Novartis Pharmaceuticals) – This aerosolized form of the antibiotic tobramycin is commonly used by older children and adults with CF (3,4). A Phase 4 study of TOBI is underway to help determine the most effective use of TOBI in very young children with CF (5).

- **Azithromycin** (Pfizer, Inc.) – An extensive trial showed improved lung function and decreased hospital stays by people with CF who used azithromycin, which is an antibiotic and an anti-inflammatory (6). Two follow-up studies will help ensure the safety of long-term use and determine the most effective use of this drug (7,8).

- **Aztreonam Lysine for Inhalation** (Gilead Sciences) – An aerosolized form of the intravenous antibiotic aztreonam is now being tested in people with Pseudomonas lung infections.

- **TIP** (TOBI Inhaled Powder) (Novartis Pharmaceuticals) – A dry powder form of tobramycin is being tested to make inhaled tobramycin treatments faster and more convenient.

- **MP-610.205** (MPEX Pharmaceuticals, Inc.) – An aerosolized drug that may help reverse or prevent antibiotic resistance of bacteria infecting CF lungs. It is a bacterial efflux pump inhibitor that may increase the effectiveness of antibiotics in the treatment of chronic and acute bacterial respiratory infections in CF.

- **Pseudomonas Vaccines** (Berna Biotech) – Vaccination against Pseudomonas bacteria may prevent or delay this infection in the lungs of people with CF. Vaccines are now being evaluated in Europe and studies in the United States are being planned (9,10,11).

- **SLIT-amikacin** (Transave, Inc.) – It is a lipososomial formulation of the antibiotic amikacin. This new inhaled formulation of the antibiotic amikacin contains lipids, or fatty particles, that help the drug attach and kill Pseudomonas bacteria better, thus reducing the amount of infection in the lungs of people with CF. Animal model studies have shown it to decrease the Pseudomonas aeruginosa burden in the lung.

About this first step we show the main results and the authors conclusions of Cochrane review (12):

MAIN RESULTS: The search identified 15 trials. Three trials (69 participants) were eligible for inclusion. There is evidence from two randomised controlled trials, of questionable methodological quality, that treatment of early P. aeruginosa infection with inhaled tobramycin results in microbiological eradication of the organism from respiratory secretions more often than placebo and that this effect may persist for up to 12 months, however incomplete data from one of the trials precludes an accurate analysis.One randomised controlled trial of oral ciprofloxacin and nebulised colisitin versus usual treatment was identified. This trial was of poor methodological quality.
The results suggested treatment of early infection results in microbiological eradication of P. aeruginosa more often than usual treatment, after two years,RR 0.24 (95% CI 0.06 to 0.96). There is insufficient evidence to determine whether antibiotic strategies for the eradication of early P. aeruginosa decrease mortality or morbidity, improve quality of life, or are associated with adverse effects compared to placebo or standard treatment.
AUTHORS' CONCLUSIONS: From the three trials included in this review, there is some evidence that antibiotic treatment of early P. aeruginosa results in short-term eradication but it remains uncertain whether there is clinical benefit to people with cystic fibrosis.

2) Chronic *Pseudomonas aeruginosa* lung infection is a major problem for patients with CF. The biofilm mode of growth of the pathogen makes it higly resistant to antibiotic treatment, and this is especially pronounced with mucoid strains. Then in past two decades, intrinsically antibiotic resistant, gram-negative organisms such as *Burkholderia cepacia, Stenotrophomonas maltophilia* and *Achromobacter*

xylosoxidans are newly emerging microrganisms isolated with increased frequencies from CF patient's lung. The lack of effective antibiotic led the clinician to consider non conventional drug and there is a strong need to develop new anti-bacteria drug.

Now we report recent studies on this topic:

a. The antimicrobial cationic peptides are ubiquitous in nature. They are a key component of the innate immune system acting as the first line of defence against infectious agents. Not only are the fast acting, bactericidal, and active against multidrug-resistant bacteria, but certain peptides exhibit anti-inflammatory and wound healing activities in addition to antimicrobial activity. In a recent Canadian study have tested 155 peptides for their antimicrobial activity against bacteria and yeast. 5 of them showed a selective activity against gram-negative bacteria. In another study, novispirin G10, a synthetic antimicrobial peptide patterned loosely on sheep myeloid antimicrobial peptide 29, was tested in a rat model of mucoid P.aeruginosa lung infection. The average bacterial loads remaining in the lungs of treated rats on days 3 and 5 were more than -170 and -330-fold lower than in the control groups. In accordance, the macroscopic and microscopic lung pathology was also significantly milder in the treated group compared to the control group. Lung cytokine responses in the treated group were significantly lower than in the control group. The results suggest that novispirin G10 might be useful in treating antibiotic-resistant P. aeruginosa lung infection. (13,14,15).

b. Mucoid, *mucA* mutant *Pseudomonas aeruginosa* cause chronic lung infections in cystic fibrosis (CF) patients and are refractory to phagocytosis and antibiotics. In this study, the authors believe that have discovered the Achilles' heel of the formidable mucoid form of *P. aeruginosa*, which could lead to improved treatment for CF airway disease. Under conditions that mimicked the CF airway mucus, HNO_2 was transformed into toxic species that specifically and negatively affected viability of mucous *P. aerations*. More importantly, HNO_2 killed mucous bacteria (a) in anaerobic bio films; (b) in vitro in ultra supernatants of airway secretions derived from explanted CF patient lungs; and (c) in mouse lungs in vivo in a pH-dependent fashion, with no organisms remaining after daily exposure to HNO_2 for 16 days. HNO_2 at these levels of acidity and NO_2^- also had no adverse effects on cultured human airway epithelia in vitro. In summary, selective killing by HNO_2 may provide novel insights into the important clinical goal of eradicating mucous *P. aerations* from the CF airways. Still, despite these known pitfalls, mucous *P. aerations* organisms were previously considered impossible to eradicate from the airways of patients with chronic CF lung disease. The authors believe that their data offer hope that effective treatment strategies can be designed with the ultimate goal of eradicating this formidable foe in CF lung disease (16).
c. New approach to treat Burkholderia cepacia complex in suggested by Middleton PG et al in this report in which it is described a new approach to treat B. cepacia that is associated with significant morbidity and mortality, yet no definitive treatment is currently available. This paper describes a new

approach to treat B. cepacia infection in CF patients, using a combination of amiloride and tobramycin aerosols. Aerosols of amiloride and tobramycin were given three times daily for 1-6 months, and repeated sputum cultures were collected to assess efficacy. Amiloride could be increased the effect of tobramycin because it rules the salt concentration. Three of the four patients treated with the combined therapy eradicated B. cepacia from their sputum cultures for at least 2 yrs, and there were no adverse events. This novel combination may provide a new therapeutic option for Burkholderia cepacia infections. Furthermore, the strategy of combining antibiotics with ion transport agents may have ramifications for the treatment of other multi-resistant organisms (17).

OTHER THERAPIES: Hypertonic saline solution.

The effect of nebulized hypertonic saline on lung function for people with cystic fibrosis was first studied in 1996. The recent findings supports the hypothesis that the liquid layer lining the airways is depleted in CF. Moreover hypertonic saline improves the rheological properties of the mucus and stimulates cough. The final result is accelerated mucus clearance (18, 19). In addition it improves, after short period, the lung function. Finally hypertonic saline preceded by a bronchodilator is an inexpensive, safe and effective therapy for a patients with cystic fibrosis (20).

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