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Review

Cystic fibrosis microbiology: Advances in antimicrobial therapy

Valerie Waters [a,*], Alan Smyth [b]

[a] Division of Infectious Diseases, Department of Pediatrics, Hospital for Sick Children, University of Toronto, Toronto, Canada
[b] Division of Child Health, Obstetrics & Gynaecology, University of Nottingham, Department of Paediatrics, Nottingham Children's Hospital, Nottingham, UK

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Abstract

Much of the improvement in the survival of individuals with cystic fibrosis (CF) is due to advancements in antimicrobial treatments. New aerosolized antibiotic formulations have recently been introduced (such as inhaled aztreonam), and others are in development (inhaled levofloxacin and liposomal amikacin). Licensed dry powder formulations include tobramycin inhalation powder and dry powder colistimethate (available in Europe). Although inhaled antibiotics have the advantage of being able to deliver high intrapulmonary concentrations of drug, antimicrobial resistance can still develop and is a concern in CF. Antimicrobial resistance might be mitigated by using non-antibiotic treatments, antibiotic adjuvants, which have activity against bacteria. Examples include agents such as gallium, antimicrobial peptides and anti-biofilm compounds such as alginate oligosaccharides (OligoG) and garlic. Vaccination strategies and antibody therapy (IgY) against *Pseudomonas aeruginosa* have also been attempted to prevent initial infection with this organism in CF. Although aggressive and long-term use of antibiotics has been crucial in slowing lung function decline and improving survival in people with CF, it has added a significant burden of care and associated toxicities in these individuals. Careful surveillance and the use of preventative strategies for antibiotic related toxicity (such as nephrotoxicity and ototoxicity) are essential. Continued development of effective antimicrobial agents that can function in the conditions encountered in the CF lung, such as against bacterial biofilm growth and under anaerobic conditions, is needed.

Keywords: Cystic fibrosis; Antimicrobials

Contents

* Corresponding author at: Department of Pediatrics, Division of Infectious Diseases, The Hospital for Sick Children, 555 University Avenue, Toronto, Ontario M5G 1X8, Canada. Tel.: +1 416 813 7654x204541.
E-mail addresses: Valerie.Waters@sickkids.ca (V. Waters), Alan.Smyth@nottingham.ac.uk (A. Smyth).

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1. Introduction

There has been a significant improvement in the survival of individuals with cystic fibrosis (CF) over the last half century, from a median age of survival of 5 years in the 1970s to approximately 40 years of age as of 2011. The reasons for the improvement in clinical outcomes are multifactorial but include the intense use of antibiotic therapy in this patient population. Despite these improvements, however, the majority of CF deaths still occur in young adulthood, typically between the ages of 21 and 30 years [1]. Continued development and optimal usage of new antimicrobial compounds (including antibiotic combinations) are essential to improve the quality and survival of people with CF.

In the last several years, there have been an increasing number of available antibiotics, of different classes and formulations, for the treatment of pulmonary infections in CF patients. This review will discuss some of the new antibiotics including novel methods of delivery, the implications of the development of antimicrobial resistance, potential non-antibiotic treatments of CF lung infections and the lifetime burden and toxicity of repeated courses of antibiotic therapy.

2. New antimicrobials and methods of delivery

Several new inhalational antibiotics have recently become available for the treatment of *Pseudomonas aeruginosa* pulmonary infections in CF patients (Table 1). Antibiotics delivered via aerosolization have the advantage of being able to achieve very high intrapulmonary concentrations with few associated systemic side effects.

2.1. Inhaled aztreonam

Inhaled aztreonam, commercially known as AZLI or Cayston, is currently on the market for the treatment of *P. aeruginosa* infections in CF patients. It is an aerosolized formulation of the monobactam antibiotic aztreonam and lysine. In contrast, the intravenous formulation of aztreonam contains arginine which can cause airway inflammation. The initial randomized controlled trial of inhaled aztreonam was performed in 211 individuals with CF 6 years of age or older with *P. aeruginosa* infection [2]. After a 28 day course of tobramycin inhalation solution (TIS), patients were randomized to receive either 75 mg of inhaled aztreonam three times daily or placebo for 28 days. Inhaled aztreonam treatment increased the median time to requiring additional anti-pseudomonal antibiotics for symptoms of pulmonary exacerbation by 21 days, compared with placebo ($p = 0.007$). In addition, inhaled aztreonam improved mean symptom scores ($p = 0.02$), forced expiratory volume in 1 s (FEV_1) (6.3%, $p = 0.001$) and sputum *P. aeruginosa* bacterial density (-0.66 $\log_{10}$ CFU/g, $p = 0.006$) compared with placebo. The drug was well tolerated and the in vitro susceptibilities of *P. aeruginosa* isolates to aztreonam from baseline to end of therapy were comparable. Similar improvements in respiratory symptoms, lung function and microbiological outcomes were also observed in another Phase II trial of inhaled aztreonam in CF patients with moderate to severe lung disease and no recent use of anti-pseudomonal antibiotics or azithromycin [3]. In CF individuals greater than 6 years of age and mild lung disease ($FEV_1 > 75\%$ predicted), however, the effects of inhaled aztreonam treatment were more modest with no statistically significant improvement in respiratory symptoms and only a 2.7% improvement in relative FEV_1% predicted ($p = 0.021$) compared to placebo treatment [4]. When compared to TIS in an open-label, parallel-group international trial in 273 patients with CF, after 3 cycles of inhaled aztreonam (28 day on; 28 days off), the mean change in FEV_1 was 2.05% for aztreonam compared to -0.66% for TIS ($p = 0.002$) [5]. Patients in the aztreonam arm also had fewer respiratory hospitalizations and additional anti-pseudomonal antibiotics compared to the TIS arm. However, it is important to note that over 85% of subjects had already

Table 1
Aerosolized antibiotics for the treatment of *P. aeruginosa* infection in CF patients.

Antibiotic	Formulation	Trade name	Dosage	Frequency
Tobramycin	Solution	TOBI	300 mg/5 mL	Twice daily
	Inhalation powder	TIP	112 mg	Twice daily
Aztreonam	Solution	Cayston	75 mg	Three times daily
Levofloxacin	Solution	Aeroquin	240 mg	Twice daily
Colistimethate sodium	Inhalation powder	Colobreathe	1 662 500 IU	Twice daily
Amikacin	Liposomal	Arikace	590 mg	Once daily