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Clinical applications of pulmonary delivery of antibiotics ☆

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ABSTRACT

The treatment of infection typically involves administration of antibiotics by a systemic route, such as intravenous or oral. However, pulmonary infections can also be approached by inhalation of antibiotics as the infection is more directly accessible via the airways, making inhalation delivery essentially topical administration. This approach offers deposition of high antimicrobial concentrations directly at the site of infection but with a potentially reduced systemic exposure. This review covers the evidence for aerosolized antibiotics for the treatment of a number of conditions such as cystic fibrosis (CF), where it has become the standard of care for chronic infection, as well as non-CF bronchiectasis, non-tuberculous mycobacteria, and ventilator-associated infection where such therapy does not have an approved indication but has been used with increasing frequency.

Contents

1. Introduction

Inhaled antibiotics have long been used to treat patients with cystic fibrosis (CF); their chronic infection of the airways is associated with considerable morbidity and an early mortality, and clinicians have used inhaled antibiotics to suppress the infection in order to improve health and long-term survival. The success of aerosol antibiotics in CF has led to consideration of similar therapy in other patients with chronic airways infection. Here we will review the use of inhaled antibiotics in CF patients as well as other conditions where such therapy might be considered.

2. Why deliver antimicrobials by inhalation?

Microbial infections targeted by inhalation have the common attribute of a nidus of infection that is more directly accessible via the

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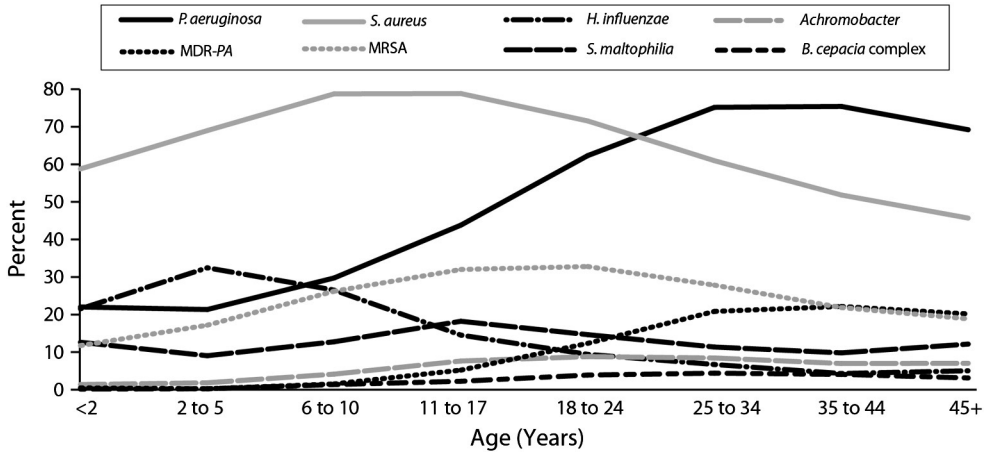

Fig. 1. Pathogens identified in a CF population. Prevalence of bacterial species cultured from respiratory specimens in CF patients [7]. These data are derived from the US CF Patient Registry and represent a cross-sectional analysis of the respiratory culture results which include 27,804 unique patients in 2012. MDR-PA: multi-drug resistant *P. aeruginosa*.

respiratory tract than the circulatory system, making inhalation delivery essentially topical administration. Direct access via the airway allows for deposition of high antimicrobial concentrations directly at the site of infection but without the systemic exposures that would be necessary to achieve similar airway levels by oral or intravenous (IV) delivery [1]. Advantages include reduced potential for the dose-limiting systemic toxicities associated with many antimicrobials and an ability to overwhelm acquired microbial resistance mechanisms by elevated local drug exposure [2].

There are, of course, shortcomings with inhalation delivery that warrant attention. Perhaps most importantly, inhalation can only deliver drug to ventilated areas of the airway, and so cannot deliver drugs past airway obstruction [3]. Further, ventilation inhomogeneity can result in variable deposition within different ventilated regions [4]. These effects can result in localized airway regions with sub-optimal antibiotic exposure which may contribute to selection for less antibiotic-susceptible bacteria. Effective doses of antimicrobials may be tens to hundreds of milligrams of drug per dose, requiring extended administration times and relatively elaborate administration devices. As aerosol delivery devices become more efficient (e.g., dry powder inhalers) the burden associated with treatment can be reduced and, potentially, patient adherence improved [5]. Inhalation can be accompanied by local adverse events, including but not limited to, cough, bronchospasm, hoarseness, dysphagia, and dysgeusia. These tend to be reversible events and there is evidence that their incidence and severity can decrease with exposure, but they can be serious barriers to patient adherence. Finally, inhaled antimicrobials reach the systemic circulation to varying degrees as a function of deposited dose in the lung and the extent of drug absorption across the lung epithelia [6]Gibson, 2006 #1818;Geller, 2011 #639}, and thus treated patients are at some risk for systemic toxicity, particularly with extended exposure. Importantly, there are no preclinical animal models to predict risks associated with *very* long term (e.g., decades), low level chronic systemic exposure to these agents.

3. Airways infection in cystic fibrosis

Chronic bacterial infection of the airways is one of the key complications of patients with CF and we have our greatest knowledge about inhaled antibiotic therapy for *Pseudomonas aeruginosa*. Epidemiological data (Fig. 1) [7] demonstrate that *P. aeruginosa* can be isolated by selective culture from patient airway secretions early in life, and is the most common bacterial opportunist in adult patients. In this setting *P. aeruginosa* is associated with worse symptoms, more pulmonary exacerbations, and earlier death [8–19]. This is why there has been great interest in treating *P. aeruginosa*; however, more recently there is growing interest in the other pathogens, such as methicillin resistant *Staphylococcus aureus* (MRSA) [20].

Our current understanding of the development of chronic *P. aeruginosa* infection in the CF airways is as follows. It is thought that *P. aeruginosa* is not present in the CF airways at birth, but the CF defect in mucociliary clearance is associated with eventual isolation of *P. aeruginosa* from the airways. It is now common practice at CF centers to perform periodic surveillance cultures of respiratory secretions, whether by oropharyngeal swab, sputum, or lower airway samples obtained by bronchoscopy. The first observation of a culture positive for *P. aeruginosa* is defined as first infection, although it is more accurately named first positive culture. Repeated subsequent cultures may be intermittently positive for *P. aeruginosa* [21]; although it is conceivable that patients are able to clear an initial infection spontaneously, it is equally likely that the infection persists but is intermittently below the level of detection using standard culture techniques. Ultimately, repeated airway cultures will become mostly, or always, positive for *P. aeruginosa*; when >50% of airway cultures are positive for *P. aeruginosa* over the course of a year, a patient is considered to be chronically infected [22]. Experience has demonstrated that chronic infection is impossible to eradicate; recent approaches to treatment have tested this observation by treating first infection with the hopes of delaying the time to chronic infection.

4. Aerosol antibiotic treatment options for *P. aeruginosa* in cystic fibrosis

4.1. Suppression

As stated earlier, chronic infection by *P. aeruginosa* is associated with excessive inflammation, progression of injury to the airways, and considerable morbidity and early mortality [9–14,17,18]. The use of inhaled antibiotics to suppress the infection has become standard of care [23, 24]. The history of inhaled antibiotics dates back to the 1940s, when there was *ad hoc* use of penicillins and polymyxins [25]. A crossover study design compared IV preparations of carbenicillin and gentamicin to placebo resulting in improved lung function and fewer IV antibiotics courses when on inhaled antibiotics [26]. Empiric use of aerosolization of IV formulations became increasingly common at CF care centers [27]. The first aerosol antibiotic specifically developed and approved for use in CF patients with *P. aeruginosa* airway infection was tobramycin inhalation solution (TIS) (http://www.pharma.us.novartis.com/product/pi/pdf/tobi.pdf). The decision to study an aminoglycoside was based on their chemical stability, data to suggest a prolonged post-antibiotic effect and an acceptable taste; tobramycin was selected based on its low systemic toxicity as well as other pragmatic factors

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