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Original Article

Effectiveness of inhaled tobramycin in eradicating *Pseudomonas aeruginosa* in children with cystic fibrosis

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Abstract

Background: Inhaled tobramycin therapy has been shown to be efficacious in clinical trials for the eradication of initial *Pseudomonas aeruginosa* infection in children with cystic fibrosis (CF). However, the effectiveness of different regimens in eradicating *P. aeruginosa* and preventing the development of chronic infection in actual clinical settings has yet to be determined.
Methods: This was an observational study of children (<18 years of age) with CF with incident *P. aeruginosa* infection from 2005–2012 based on data collected from the Toronto CF Database and medical charts. Patients who received inhaled tobramycin (80 mg/2 ml twice daily for 365 days) were compared to those who received tobramycin inhalation solution (TIS) (300 mg/5 ml twice daily for 28 days) with respect to eradication and development of chronic infection. We also examined the risk factors for recurrence of infection.
Results: During the study period, 65 patients were identified with incident *P. aeruginosa*, of which 7 (11%) failed eradication therapy. Eradication failure was similar between the two treatment groups. A total of 4 patients (6%) developed chronic *P. aeruginosa* infection in the 12 months following the end of therapy with no differences between treatment groups. Female gender, older age, pancreatic insufficiency, lower lung function and worse nutritional status were identified as risk factors for recurrence of *P. aeruginosa* infection.
Conclusions: Both regimens of inhaled tobramycin have similar effectiveness in eradicating *P. aeruginosa* and preventing chronic *P. aeruginosa* infection in CF patients in clinical practice. Further work is needed, however, to identify patient characteristics and bacterial factors that play a role in eradication failure, in order to develop more effective antimicrobial rescue treatment strategies.

Keywords: *Pseudomonas aeruginosa*; Tobramycin; Eradication; Pediatrics

1. Introduction

Children with cystic fibrosis (CF) typically develop pulmonary infection with *Pseudomonas aeruginosa* early in life and without treatment go on to develop chronic infection, typically within a year of the first infection [1,2]. Chronic pulmonary infection with mucoid *P. aeruginosa* is associated with accelerated decline in lung function and earlier mortality in CF [3–5]. As a result, much effort has been made to prevent the development of chronic *P. aeruginosa* through various antibiotic regimens [6]. Since the early 1980s, eradication programs for *P. aeruginosa* have been attempted in younger patients with CF, with the goals to eliminate the organism, prevent the establishment of persistent infection and prolong the time to subsequent infection [7,8]. In addition, although the risk factors for initial *P. aeruginosa* infection have been defined, factors affecting the risk of re-infection have yet to be determined [9–11]. Failure to eradicate *P. aeruginosa* has been shown to be associated with an increased risk of subsequent pulmonary exacerbations [12], which can affect the rate of lung function decline [13].

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While multiple antibiotic strategies have been studied for the eradication of *P. aeruginosa*, many protocols include inhaled tobramycin as the backbone of the regimen. Randomized control trials of inhaled tobramycin have shown both tobramycin 80 mg twice daily and tobramycin 300 mg twice daily to be more effective than placebo for eradicating *P. aeruginosa* from the airways of children with CF [14,15]. However, there have not been any studies evaluating the effectiveness of these eradication protocols within the clinical setting. This is particularly important because not all antimicrobial agents are equally available to all patients due to costs and health insurance coverage, and not all patients fully comply with the protocol, resulting in varying treatment durations.

The objectives of this study were thus to compare the effectiveness of two inhaled tobramycin regimens (inhaled tobramycin (80 mg/2 ml twice daily, typically for 365 days) or tobramycin inhalation solution (TIS) (300 mg/5 ml twice daily, typically for 28 days) with respect to 1) *P. aeruginosa* eradication and 2) development of chronic infection. In addition, we sought to identify risk factors for recurrence of *P. aeruginosa* following eradication therapy.

2. Materials and methods

2.1. Subject population and data collection

This was a retrospective observational study based on data collected from the Toronto Cystic Fibrosis Database as previously described [16]. Pediatric patients (<18 years of age) followed at the Hospital for Sick Children Cystic Fibrosis clinic from 2005–2012 were eligible for this analysis (n = 453). A detailed description of the inclusion/exclusion criteria is presented in Fig. 1. We focused on incident *P. aeruginosa* cases during the study period, thus patients were excluded if they had a positive *P. aeruginosa* culture prior to 2005, if they did not have a positive *P. aeruginosa* culture before 2012, or had a lung transplant. All microbiology data were based on culture results from sputum, bronchoalveolar lavage samples or throat swabs. To be included in these analyses, patients had to have at least 3 negative cultures documented in the previous 12 months, have received inhaled antibiotics within 180 days of the incident positive *P. aeruginosa* culture, and had at least one culture after the end of treatment. Patients with incomplete exposure and outcome data in the database were excluded from the study. This study was approved by the Research Ethics Board at the Hospital for Sick Children (REB# 1000013759).

2.2. Definitions of variables

Height and weight measurements from all clinic visits were used to calculate body mass index (BMI), which were then converted to age-standardized z-scores using the WHO 2006 growth charts for children <2 years of age, and the CDC 2000 growth charts for children ≥2 years of age [17,18]. Children older than 5 years of age routinely performed spirometry at our clinic. Absolute values of forced expiratory volume in 1 s (FEV_1) were corrected for height, age and sex and analyzed as percent predicted and z-scores [19]. Thereafter FEV_1 was summarized as 1) FEV_1 at the time of first *P. aeruginosa* infection and 2) the rate of FEV_1 change in the year preceding the first *P. aeruginosa* infection, calculated using all available observations for each patient separately. A pulmonary exacerbation was defined as a hospitalization for respiratory symptoms requiring intravenous antibiotics [20]. *Burkholderia cepacia* complex, *Haemophilus influenzae*, *Staphylococcus aureus* and *Stenotrophomonas maltophilia* infections were classified as any positive sputum or throat swab culture in the year preceding first *P. aeruginosa* infection. MRSA infection was not included due to its low prevalence in the CF population in Canada and in this center [21].

2.3. Treatment categorization

Patients were categorized according to treatment received: inhaled tobramycin (80 mg/2 ml twice daily, typically for 365 days) or tobramycin inhalation solution (TIS) (300 mg/5 ml twice daily, typically for 28 days). TIS was introduced in this CF clinic in 2007 and the 1 month TIS regimen was thus preferentially used from 2007 onwards when medical insurance was available to cover the costs; prior to 2007, inhaled tobramycin (80 mg/2 ml) was used. The treatment received was verified in the patient medical records. Inhaled antibiotics had to be given within 180 days of the incident *P. aeruginosa* positive culture to be considered as treatment associated with the first positive culture.

2.4. Outcomes

We compared the two tobramycin regimes with respect to two outcomes 1) *P. aeruginosa* eradication based on the microbiological results of the first culture after the patient stopped treatment and 2) development of chronic infection defined as >50% of cultures were positive for *P. aeruginosa* [22] in the year after the patient stopped initial treatment.

We also investigated risk factors for *P. aeruginosa* recurrence, both for 1) time to next *P. aeruginosa* infection and 2) *P. aeruginosa* recurrence in the 12 months following antimicrobial treatment.

2.5. Statistical analysis

The proportion of eradication failures and the proportion of patients that developed chronic *P. aeruginosa* infection (>50% of cultures positive in the year after treatment ended) were compared using Fisher's Exact test. The risk factors for time to subsequent *P. aeruginosa* after the end of treatment were assessed using univariable Cox proportional hazard analysis, whereas the risk factors for becoming *P. aeruginosa* positive in the year following the end of treatment were assessed using univariable logistic regression analysis.