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Original Article

Eradication failure of newly acquired *Pseudomonas aeruginosa* isolates in cystic fibrosis

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Abstract

Eradication of *Pseudomonas aeruginosa* (PA) is critical in cystic fibrosis (CF) patients.
Objectives: To determine eradication success rate of newly acquired PA and to identify characteristics associated with eradication failure.
Methods: In an observational study, data from patients with newly acquired PA infection from 2007 to 2013 were collected. Clinical variables were compared in patients with and without successful eradication for ≥ 1 year.
Results: Of 183 patients out of 740 (25%) from 7 CF Centers that had newly acquired PA, eradication succeeded in 72%. Patients with the highest risk of failure had multi-resistant PA, fewer sputum cultures taken, were older, and were diagnosed at a later age. The risk of eradication failure increased by 1.3% with each year of delayed CF diagnosis; successful eradication increased by 17% with each additional sputum culture taken.
Conclusions: Delayed detection of PA infection leading to delayed treatment and growth of multi-resistant organisms is associated with eradication failure.

Keywords: Cystic fibrosis; Pseudomonas infection; Eradication failure

1. Introduction

Respiratory infection with *Pseudomonas aeruginosa* (PA) is a leading cause of morbidity and mortality in patients with CF [1–5]. The presence of PA in the lower airways is associated with a more rapid decline in pulmonary function, worsening of nutritional status, more hospital admissions, and a shorter life expectancy [2,6]. Once chronic infection with PA is established, it is almost impossible to eradicate it [7]. The rate of PA infection increases with age, and by 25 years, over 60% of the patients are already infected [5].

Since colonization and chronic infection with PA are associated with poor prognosis, therapies that can prevent chronic infection are expected to significantly improve the length and quality of life

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of patients with CF. Furthermore, these therapies are cost-effective compared with conventional antibiotic therapy for chronically infected CF patients [8].

Eradication protocols for newly acquired PA were shown to eradicate PA in about 80% of the cases in both different randomized trials and in real-life studies [8–14]. However, in about 20% of the cases, PA cannot be eradicated and infection becomes chronic.

The aim of the current study was to analyze the rate of eradication failure of newly acquired PA in a non-clinical trial setting, and to identify clinical and laboratory factors associated with eradication failure.

2. Patients and methods

Patients with CF treated during the years 2007–2013 in 6 Israeli CF Centers (Hadassah-Hebrew University Medical Center, Jerusalem; Schneider Children's Medical Center, Petach Tikva; Carmel Medical Center, Haifa; Rambam Medical Center, Haifa; Soroka Medical Center, Beer-Sheva; and Shaare- Zedek Medical Center, Jerusalem) and in the CF Center at the Hospital Universitari Vall d' Hebron, Barcelona, Spain, were included in the study. The study was approved by the Committee of Research Involving Human Subjects of each hospital, and written informed consent for participation in a center-based study and in a national data registry was obtained from all patients or parents/caretakers.

3. Inclusion criteria

All CF patients for whom *P. aeruginosa* (PA) was either isolated for the first time or newly isolated after successful eradication prior to 2007 were included in the study as defined by at least 1 year prior to enrollment with no PA-positive result in at least 4 consecutive sputum cultures or at least 6 consecutive PA-negative cultures taken over 24 months and with no ongoing anti-PA antibiotic therapy.

4. Data collection

The database of each participating CF center was used to obtain clinical data including demographics (e.g., age, sex), pancreatic status (CF with pancreatic insufficiency [CF-PI] and CF with pancreatic sufficiency [CF-PS]), and CF-related diabetes (CFRD). In addition, for all patients, every detection of PA prior to the study period was recorded. Results of all sputum samples provided by the patients, by nasolaryngeal suction, or by bronchoalveolar lavage were analyzed and divided according to the number of antibiotics that the bacteria was sensitive to: *sensitive*, resistant to ≤ 3 antibiotics; *multi-resistant*, resistant to 4–5 antibiotics; and *pan-resistant*, resistant to ≥ 6 antibiotics. Sensitivity to the following antibiotics was analyzed in each laboratory: amikacin, ceftazidime, ciprofloxacin, colistin, cotrimoxazole, gentamicin, imipenem, piperacillin, piperacillin + tazobactam, ticarcillin-clavulanic acid, and tobramycin. Sensitivity was determined using the standard microbiology lab methods. Concomitant infections with other microorganisms were also recorded. Clinical data from the year prior and at the time of PA isolation were obtained, including age, body mass index (BMI),[2] lung function measured by forced expiratory volume in 1 seconds (FEV_1) [15,16], and the number of sputum cultures taken during that year. Furthermore, data regarding the type of antibiotic eradication therapy and the success of eradication were analyzed.

5. Infection and eradication status definitions

5.1. Successful eradication

PA-negative respiratory samples in at least 4 cultures obtained over 12 months or at least 6 cultures taken over 24 months. *Chronic infection*: > 50% PA-positive airway samples taken during 12–24 months. *Intermittent infection*: $\leq 50\%$ PA-positive airway samples taken during 12–24 months. *Failure of eradication* was defined as subsequent chronic or intermittent infection. All definitions were based on the Leeds criteria [17]. Since the policy in some centers was to treat patients with long-term inhaled antibiotics after achieving eradication, successful eradication was further analyzed according to "eradication and no inhaled antibiotics" (ENIA) and "eradication and continuous inhaled antibiotics" (ECIA), i.e., successful eradication with continuing inhaled therapy with anti-PA inhalations (tobramycin or colistin).

6. Statistical analysis

In order to compare quantitative (continuous) variables between two independent groups, the two-sample *t*-test and the non-parametric Mann–Whitney test were applied. When comparison of quantitative (continuous) variables adjustments between 3 or more groups was carried out using the ANOVA procedure, the Scheffe or the Bonferroni post hoc tests were applied to correct the significance level for multiple pairwise comparisons. In addition, the non-parametric Kruskal–Wallis test was applied. The non-parametric tests were carried out for variables that had a skewed, non-normal distribution. The association between two categorical variables was assessed using either the chi-square test or the Fisher exact test. The Pearson correlation coefficients were calculated in order to assess the association between two quantitative (continuous) variables. The stepwise logistic regression model was applied in order to test the simultaneous effect of several independent variables on a qualitative, dichotomous dependent variable. We collected all the information data from the patients' files, and the statistical analysis was done for each variable only for the available data, with no intent to complete by statistical methods missing data. For the multivariate analysis, we included only variables for whom all the data were available. The missing data were added in the tables. The variables that were chosen for the multiple logistic regression model were the ones found to be statistically significantly associated with the outcome variable (eradication

[2] BMI was calculated only for patients ≤ 20 years of age and is presented as percentile for age (16 patients ≥ 20 years were excluded) from this analysis. BMI at the time of a new PA isolation was the BMI on the same date or, if not available, on the date closest to a positive PA culture.