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Short Communication

Randomized controlled trial of biofilm antimicrobial susceptibility testing in cystic fibrosis patients☆

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Abstract

This study aimed to determine whether antimicrobial susceptibility testing of *Pseudomonas aeruginosa* grown as a biofilm, rather than planktonically, improves efficacy of antibiotic treatment for pulmonary exacerbations. This was a multicenter randomized, double-blind controlled trial of 14 days of intravenous antibiotic treatment for pulmonary exacerbations chosen based on conventional vs. biofilm antimicrobial susceptibility results in CF patients with chronic *P. aeruginosa* infection. There were 74 exacerbations in 39 patients. A total of 46% (12/26) exacerbations in the conventional group compared to 40% (19/48) exacerbations in the biofilm group achieved a ≥3 log drop in *P. aeruginosa* sputum density (difference −0.03, 95% CI −0.5 to 0.4, p = 0.9). Lung function improvements were similar in both groups. Biofilm antimicrobial

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susceptibility testing did not lead to improved microbiological or clinical outcomes compared to conventional methods in the treatment of pulmonary exacerbations in CF patients with chronic *P. aeruginosa*.
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Keywords: Pulmonary exacerbation; Antibiotics; *Pseudomonas aeruginosa*; Biofilm

1. Introduction

Although pulmonary exacerbations are responsible for significant morbidity in cystic fibrosis (CF) [1], there are currently no in vitro methods that can predict which specific antibiotics a patient will respond to as treatment for a pulmonary exacerbation [2–4]. Conventional antimicrobial susceptibility testing is performed on bacteria grown in a planktonic or "free-floating" state. However, in the CF lung, bacteria such as *Pseudomonas aeruginosa*, are known to exist in a biofilm, or polymicrobial community [5]. This randomized controlled trial aimed to determine whether antibiotics chosen based on biofilm antimicrobial susceptibility testing would result in a better microbiologic and clinical response compared to antibiotic chosen based on conventional, planktonic susceptibility testing in the treatment of pulmonary exacerbations in CF patients with chronic *P. aeruginosa* infection.

2. Study methods

This was a randomized, double-blind study conducted at 5 CF centers in Canada from January 2009 to December 2013 in CF patients with chronic *P. aeruginosa* infection [6]. Subjects were randomized at the time of a pulmonary exacerbation to two intravenous antibiotics chosen based on conventional or biofilm antimicrobial susceptibility testing. The predominant morphotype of *P. aeruginosa* from sputum cultures was chosen for conventional susceptibility testing using broth microdilution or biofilm susceptibility testing. The primary outcome was the change in sputum *P. aeruginosa* density from day 0 to day 14 of antibiotic treatment. Secondary outcomes included pulmonary function tests, CFQ-R respiratory symptom scores [7], blood and sputum inflammatory markers measured at day 0, day 14 of antibiotic therapy and at the 1 month follow-up visit. The change in each of the outcomes was then compared between the conventional and biofilm groups using generalized estimating equations to account for the inclusion of more than one exacerbation per patient. Time to subsequent pulmonary exacerbation was compared between the groups using a Mantel–Cox test. See Supplementary materials for more details.

3. Results

During the 5 year study period, there were 74 exacerbations in 39 patients (Fig. 1). The biofilm group had older patients with a higher body mass index (BMI) compared to the conventional group (Supplementary Table 1). Intravenous tobramycin and ceftazidime were the most common antibiotic choices (Supplementary Table 2). Significantly fewer *P. aeruginosa* isolates were susceptible by biofilm compared to conventional susceptibility testing for all antibiotics tested (Supplementary Fig. 1).

A ≥ 3 $\log_{10}$ drop in *P. aeruginosa* sputum density at day 14 was achieved in 12 of the 26 (46%) exacerbations in the conventional group compared to 19 of 48 (40%) exacerbations in the biofilm group (difference −0.03, 95% CI −0.5 to 0.4, p = 0.9). When the change in sputum *P. aeruginosa* density was compared between the two groups, there was no statistically significant difference from day 0 to day 14 (difference 0.1, 95% CI −1.1 to 1.3, p = 0.9) or from day 0 to the 1 month follow-up (difference 0.4, 95% CI −0.2 to 1.0, p = 0.2) between the biofilm group compared to the conventional group (Fig. 2).

With respect to pulmonary function tests, there was no statistically significant difference in the change of FEV_1 (L) from day 0 to day 7 (difference −0.01, 95% CI −0.1 to 0.1, p = 0.9), from day 0 to day 14 (difference 0.1, 95% CI −0.1 to 0.2, p = 0.3) or from day 0 to 1 month (difference 0.004, 95% CI −0.2 to 0.2, p = 1.0) between the biofilm and conventional groups (Fig. 3A). A similar trend was observed with FVC (Fig. 3B). At day 14, FEV_1 returned to $\geq$90% of baseline in 19 of 26 (73%) exacerbations in the conventional group compared to 33 of 48 (69%) exacerbations in the biofilm group (p = 0.3).

There was a statistically significant difference in the CFQ-R score response from day 0 to day 14 (difference −8.8, 95% CI −17.6 to −0.08, p = 0.048) and from day 0 to 1 month (difference −15.1, 95% CI −27.9 to −2.4, p = 0.02), favoring the conventional group (Supplementary Fig. 2). With respect to the minimal clinically important difference in respiratory score [8], 20 of the 26 (77%) exacerbations had an increase of 8.5 points or more from day 0 to day 14 of antibiotics in the conventional group, compared to 33/48 (69%) of exacerbations in the biofilm group (p = 0.3).

Changes in blood inflammatory markers from day 0 to day 14 were not significantly different between the biofilm and conventional arms for WBC count, CRP or ESR. For both sputum IL-8 and neutrophil elastase measurements, there was no significant difference in the change from day 0 to day 14 or from day 0 to 1 month follow-up between the biofilm and conventional groups (Supplementary Fig. 3).

Antibiotics were changed at day 7 in 4 of the 26 (15%) exacerbations randomized to the conventional arm and in 4 of the 48 (8%) exacerbations in the biofilm arm (p = 0.3). Antibiotic treatment was prolonged beyond 14 days in 8 (31%) exacerbations in the conventional group and in 17 (35%) exacerbations in the biofilm group (p = 0.8). The time to

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