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Effective strategies for managing new *Pseudomonas* cultures in adults with cystic fibrosis



To the Editor:

Pseudomonas aeruginosa is a common chronic pulmonary infection in cystic fibrosis (CF). It is associated with poor outcomes and new detection should prompt an early eradication attempt [1–3].

Strict segregation and eradication policies have led to a declining prevalence of chronic *P. aeruginosa* infection, with only 30% of CF adolescents having chronic infection when they transition to adult services [4]. Adult CF physicians increasingly manage new *P. aeruginosa* cultures in adults without robust evidence to guide decision-making. We evaluated the success of our eradication and suppression strategies for adults

with a new or re-emergent *P. aeruginosa* culture in the clinical setting of a large European adult CF centre (Adult Cystic Fibrosis Centre, Royal Brompton Hospital, London, UK).

We undertook a retrospective cohort study of consecutive adult CF patients who were treated with intent to render sputum *P. aeruginosa*-negative after a new *P. aeruginosa* culture in either sputum samples or cough swabs between 2008 and 2012. All patients were diagnosed with CF according to standard published criteria [5]. Patients were included if they had a minimum of three *P. aeruginosa*-negative respiratory samples in the 12 months preceding the treatment period. Patients were categorised into the following groups. Group A: first-ever *P. aeruginosa* culture; group B: new *P. aeruginosa* culture and prior history of *P. aeruginosa*-positivity on inhaled antibiotics; and group C: new *P. aeruginosa* culture and prior history of *P. aeruginosa*-positivity but not on chronic inhaled antibiotics. The primary analysis was *P. aeruginosa* culture-negativity success based on sputum taken within 1 month of completing treatment. Subsequent sputum results were recorded from clinic appointments (every 2–12 weeks) up to a minimum of 24 months after the treatment period. At the time of this study, our first-line therapy comprised 3 months of nebulised colomycin 2 MU twice a day and 3 weeks of oral ciprofloxacin 750 mg twice a day; second-line regimens were alternative nebulised (usually tobramycin solution for inhalation (TSI))/oral antibiotic combinations. Second-line regimens were used if the patient was intolerant to, or had previously failed, first-line drugs. For patients already on nebulised colomycin, their first-line regimen was the addition of ciprofloxacin for 3 weeks, and second-line was a switch to an alternative nebulised (TSI)/oral antibiotic combination. In situations where there was evidence of a pulmonary exacerbation, intravenous antibiotics were the preferred option.

New *P. aeruginosa* isolates were identified using our CF departmental database and verified by electronic patient records (EPR). Baseline clinical characteristics and demographics were taken from the UK CF registry, which is collected yearly with informed written consent. Relevant co-existing conditions and medications were recorded from the EPR. Data were analysed using SPSS v22 (IBM, New York, NY, USA). Intergroup variability was tested using an independent samples t-test, ANOVA or a Chi-squared test. We used a 95% CI and a p-value of <0.05 was considered significant.

53 new *P. aeruginosa* cultures (13 in group A, 25 in group B and 15 in group C) from 48 patients (25 (47%) from female subjects, 45 (85%) from pancreatic insufficient subjects, 25 (47%) from patients homozygous for *F508del*, 13 (25%) from patients with CF-related diabetes (CFRD)) were included in the analysis. A new *P. aeruginosa* culture was preceded by a median of 6 (range 3–20) *P. aeruginosa*-negative respiratory samples in the prior 12 months. Baseline characteristics were similar between groups (median \pm SD forced expiratory volume in 1 s (FEV₁) 65 \pm 21.2% predicted and body mass index (BMI) 22 \pm 3.2 kg·m⁻²) although patients in group B were younger (28 (16–54) years in group A, 20 (16–49) years in group B, 29 (17–66) years in group C; p=0.017). Patients in group B were most commonly maintained on continuous inhaled colomycin (16 cases) or a monthly alternating inhaled regimen including colomycin and a second agent (TSI) (eight cases).

28 (53%) patients received our first-line regimen of ciprofloxacin and colomycin, 16 (30%) patients received *i.v.* antibiotics, five (9%) patients received TSI with ciprofloxacin and the remaining four (8%) received tailored regimens.

Overall, eight (61.5%) patients in group A had *P. aeruginosa* successfully eradicated after the treatment period. Eight (61.5%) patients in the group received first-line treatment, with six (75%) achieving successful eradication. By 24 months, only two (25%) patients remained free of *P. aeruginosa* (fig. 1).

P. aeruginosa culture negativity was achieved in 18 (72.0%) and 11 (73.3%) patients in groups B and C, respectively (nonsignificant). 15 (60.0%) patients in group B and five (33.3%) patients in group C received first-line treatment, with similar proportions achieving culture negativity at 1 month (73.3% in group B, 60.0% in group C; nonsignificant). Of the patients in group B who did not receive first-line treatment, seven (28.0%) received *i.v.* antibiotics and the remaining three (12.0%) received TSI/ciprofloxacin.

Comparable proportions of patients who received first-line treatment remained culture negative at 24 months (26.7% in group B, 20.0% in group C; nonsignificant) (fig. 1). We found no association between the success in achieving *P. aeruginosa*-negative cultures and age, sex, BMI, baseline FEV₁, pancreatic status, co-infection status, CFRD, allergic bronchopulmonary aspergillosis (ABPA) status and mutation class.

Overall patients who had their sputum rendered *P. aeruginosa* negative at 1 month had a median time to re-culturing *P. aeruginosa* of 19.0 months (range 8.3–29.6). There was no significant difference in the time to reacquisition between groups A, B and C (log rank p=0.66), or first- and second-line regimens (log rank p=0.81).

We have shown that sputum can be successfully rendered *P. aeruginosa*-negative in adult patients. Treatment is effective irrespective of first-ever detection *versus* re-emergence, although the majority of patients re-cultured *P. aeruginosa* within 2 years.

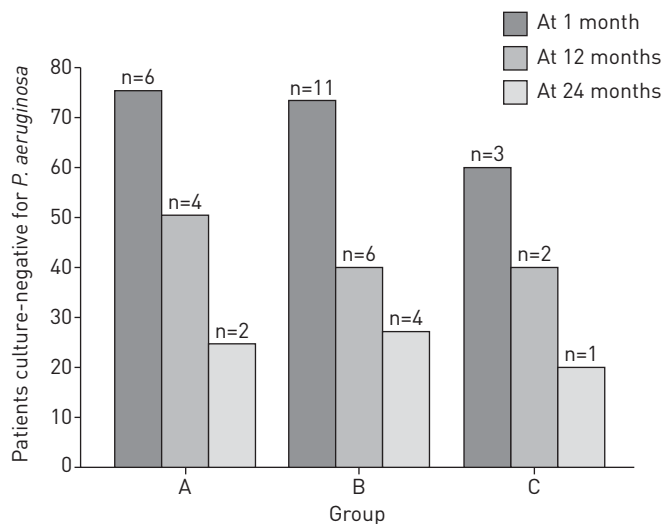


FIGURE 1 *Pseudomonas aeruginosa* status in patients receiving first-line therapy according to *P. aeruginosa* culture group. Group A: first-ever; group B: re-emergence on inhaled antibiotics; group C: re-emergence off inhaled antibiotics. There was no significant difference in the proportion of patients who were *P. aeruginosa*-free at 1 and 24 months ($p=0.81$).

Data reporting the success of *P. aeruginosa* eradication and suppression strategies in adult CF patients are lacking. The only study exclusively of adult patients was retrospective and small ($n=20$) with a reported eradication success of 79% [6]. Previous study populations have had milder lung disease, where preserved airway function might facilitate microbial clearance. Our population is older with lower baseline lung function and higher rates of non-*P. aeruginosa* chronic infection (75% had bacterial co-infection), factors which may influence treatment success.

Patients in groups B and C represent an increasingly common scenario in adult CF clinics. These are patients who have cultured *P. aeruginosa* in childhood/adolescence but achieve eradication or sustained subclinical suppression into adulthood. It could be argued that group B may represent chronic (but suppressed) infection justifying exclusion from this analysis. Local practice of the paediatric CF unit at our hospital at the time of this study was to have a high threshold for discontinuing inhaled antibiotics in patients with a history of at least two re-emergent *P. aeruginosa* cultures, particularly if they could only provide cough swabs after “eradication” treatment. We believe that including group B, although controversial, adds important information to this debate by demonstrating equivalent rates of sputum negativity regardless of whether this represents true eradication or suppression. A more aggressive approach to a “new” growth in this cohort may be appropriate but longitudinal follow-up is important to determine whether this affects prognostic indices. Measuring *P. aeruginosa* antibodies may have helped assess whether they had truly eradicated *P. aeruginosa* in the past [7]. We also acknowledge that measuring time to chronic infection using *P. aeruginosa* antibodies may be a more clinically useful parameter than categorising recurrence as a single *P. aeruginosa* culture. Our patients with *P. aeruginosa*-negative sputum re-acquired *P. aeruginosa* at a median of 19 months, which is similar to paediatric populations [8–10].

Although small, this study provides insight into the effectiveness of our treatments. As CF care advances, more patients will transition to adult services with preserved lung function, free of *P. aeruginosa* cultures. Consequently, eradication and suppression studies in adults are becoming ever more relevant.



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Sputum can be rendered *P. aeruginosa* culture-negative in adults with CF, although recurrence within 2 years is high <http://ow.ly/KPBsY>

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Tuberculosis outbreak in East Greenland: groups at risk in an isolated arctic setting

To the Editor:

In 2009, an unusually high number of tuberculosis (TB) cases were reported from a settlement (Settlement X) in East Greenland. 4 years earlier, screening among schoolchildren had documented all children in this settlement to be free of *Mycobacterium tuberculosis* infection (MTI), whereas similar screenings had shown an MTI prevalence of 8% among schoolchildren in the rest of East Greenland [1]. The average TB incidence rate in East Greenland 5 years prior to the outbreak was ~300 per 100 000 populations (fig. 1) [2, 3].

The documentation of areas with differences in *M. tuberculosis* transmission prior to a TB outbreak provided a special opportunity to study the risk of TB in these settings that have an otherwise comparable population. The objective of the study was to estimate the risk of TB and MTI during an outbreak, and to evaluate whether individuals from a previously *M. tuberculosis* transmission-free environment exhibited particular risk.

We conducted a cohort study including all inhabitants living in East Greenland on January 1, 2008 (n=3541). Participants were followed until TB notification, death, emigration or December 31, 2012. A personal Civil Registration System (CRS) identifier given to Greenlandic citizens at birth combined data across public registries. The cohort was stratified by residency (Settlement X or the rest of East Greenland) at study entry.

Notification of TB to the National Board of Health is mandatory and the Greenlandic TB case definition follows that of the World Health Organization (WHO) [4, 5]. A positive interferon- γ release assay (IGRA) (QuantiFERON-TB Gold; Cellestis, Venlo, the Netherlands) defined an MTI case. IGRA results among the cohort participants were obtained from routine diagnostics, contact tracing or previously conducted population screening and projects [1, 6]. Information on covariates was obtained from the CRS, TB notifications and medical records. A Greenlandic birthplace of both parents defined Greenlandic heritage.

Since 1955, all newborns have been offered bacille Calmette–Guérin (BCG) vaccination with national coverage rates of 90–99%. However, the BCG vaccination programme was temporarily discontinued between 1991 and 1996, and children born in these years were considered unvaccinated [2, 6, 7].

Crude TB incidence rates (IR) were estimated as TB cases per 100 000 person-years. Incidence rate ratios were estimated with Cox proportional hazard models with age as the underlying time axis and baseline hazard rate stratified by sex [8].