

# Eradication of *Pseudomonas aeruginosa* in adults with cystic fibrosis

S L Kenny,<sup>1,2</sup> T D Shaw,<sup>1,2</sup> D G Downey,<sup>2</sup> J E Moore,<sup>3</sup> J C Rendall,<sup>2</sup> J S Elborn<sup>1</sup>

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SLK and TDS are joint first authors and contributed equally to this study.

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## ABSTRACT

**Background:** Eradication of new infection of *Pseudomonas aeruginosa* is an important intervention in managing cystic fibrosis (CF). Previous trials, studying predominantly under 18-year-olds, indicate that antibiotic eradication therapy (AET) has success rates of 62.8–93.0%. In this retrospective cohort study, we report the outcomes of AET in an adult population.

**Methods:** Adults with a confirmed diagnosis of CF and a first isolation of *P aeruginosa* were studied between 1999 and 2012. Choice of therapy, time to eradication and reinfection, and lung function (forced expiratory volume in 1 s (FEV<sub>1</sub>)) were determined.

**Results:** 20 patients (median age 27 years) isolated *P aeruginosa* during the study period. 10 patients were treated with oral ciprofloxacin (median duration 6 weeks) and nebulised colomycin (median duration 3 months). 7 patients were treated with intravenous antipseudomonal antibiotics (median duration 14 days). 2 patients received other combinations of oral and inhaled antipseudomonal therapy and one patient received no therapy. AET was successful in 15 cases who received antipseudomonal therapy (79%). The median time to eradication was 1 month. The median time to reinfection with *P aeruginosa* was 43 months. There was no significant change in FEV<sub>1</sub> after 12 months.

**Conclusions:** Aggressive AET of new infection of *P aeruginosa* in adults is successful in the majority of patients and has similar efficacy to the reported efficacy in paediatric populations.

## INTRODUCTION

Chronic infection with *Pseudomonas aeruginosa* is associated with an adverse prognosis in adults with cystic fibrosis (CF).<sup>1</sup> *P aeruginosa* induces a prolonged inflammatory response which leads to progressive pulmonary tissue destruction. In patients with CF, this manifests as a more rapid loss of lung function, frequent pulmonary exacerbations and a shorter median survival.<sup>2</sup>

Once chronic infection with *P aeruginosa* is established, it is rarely possible to eradicate.<sup>3</sup> However, the early and intensive use of antibiotic eradication therapy (AET) following a new isolation of *P aeruginosa* has been shown

## KEY MESSAGES

- ▶ More patients with cystic fibrosis are being transferred from paediatric to adult CF services without a history of chronic *P aeruginosa* infection.
- ▶ Aggressive antibiotic eradication therapy of new isolation *P aeruginosa* has similar efficacy in adults and children with cystic fibrosis.
- ▶ More evidence is needed to determine the most efficacious regime of antibiotic eradication therapy for new isolation *P aeruginosa*.

to eradicate the pathogen from the respiratory tract, thus preventing or delaying the establishment of chronic infection.<sup>4</sup> Therefore, the eradication of new *P aeruginosa* infection is important in managing patients with CF.

Most studies of *P aeruginosa* eradication report median ages in the paediatric range.<sup>2</sup> It is not known whether adult patients with CF who isolate *P aeruginosa* for the first time have outcomes similar to children. CF centres are transferring more children to adult services without chronic *P aeruginosa* infection.<sup>5</sup> Our aim was to study the efficacy of AET for first *P aeruginosa* isolation in adults in order to determine the optimum management and prognosis of this growing patient group.

Previous trials report a variety of antipseudomonal regimes in predominantly under 18-year-olds with eradication success of 62.8–93.0%.<sup>6–8</sup> We hypothesised that AET for first isolate *P aeruginosa* would be less effective in adults compared with children on account of cumulative pulmonary tissue destruction and other CF-related disease processes.

## METHODS

### Study design

This was a retrospective cohort study conducted at the Northern Ireland Regional Adult Cystic Fibrosis Centre. The study period was 1 January 1999 until 31 December 2012.



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<sup>1</sup>Centre for Infection and Immunity, Queen's University Belfast, Belfast, UK

<sup>2</sup>Adult CF Centre, BHSCT, Belfast, UK

<sup>3</sup>Department of Bacteriology, Belfast City Hospital, Belfast, UK

### Correspondence to

Dr Timothy D Shaw;  
tdshaw@doctors.org.uk

### Population demographics

There were 279 patients attending the Northern Ireland Regional Adult Cystic Fibrosis Centre who were registered with the UK Cystic Fibrosis Registry database during the study period. All registered patients met the current criteria for the diagnosis of CF.<sup>9</sup> The median age of these patients was 30 years. Forty-four per cent were women and 56% were men. Thirty-six per cent of patients were homozygous F508del. This was the most predominant single genetic mutation in this population.

### Inclusion/exclusion criteria

Adult patients with CF attending the Northern Ireland Regional Adult Cystic Fibrosis Centre who isolated *P aeruginosa* for the first time during the period 1999–2012 were included in the study. All patients had a diagnosis of CF, confirmed by sweat test and genetics. Patients who died during the study period were included. Patients who received *P aeruginosa* eradication at another centre were not included.

### Data collection

The Cystic Fibrosis Registry database was used to obtain background demographics and results of genetic testing of the patients with CF registered to this centre. A chart review was performed including all bacteriology results from the respiratory cultures (including sputum and throat swabs) of the cases studied. Paediatric bacteriology records were used to confirm that *P aeruginosa* had not been isolated prior to transfer to adult services. Data were collected and analysed on the choice and duration of therapy, the success of eradication, the time until *P aeruginosa* was eradicated and the duration until a new isolation of *P aeruginosa* was identified. The forced expiratory volume in 1 s (FEV<sub>1</sub>) of patients at baseline, before the first *P aeruginosa* infection, at the time of isolation and following the completion of AET was also studied.

### Bacteriological examination of sputum

The technique of sputum bacteriological examination remained unaltered throughout the duration of the study. Briefly, freshly expectorated sputum specimens from patients with CF were mixed (1:1) with Sputasol (Oxoid, UK) and plated onto Columbia blood agar (Oxoid CM331), supplemented with 5% defibrinated horse blood, as well as *Pseudomonas* isolation agar (Oxoid 559) and incubated prior to examining for *Paeruginosa*. All presumptive *P aeruginosa* isolates were confirmed phenotypically, at which a *Pseudomonas* positive report was issued.<sup>10</sup>

Patients had sputum examination at median intervals of 2 months (range 1–6 months) in the 6 months preceding first isolation *P aeruginosa*. Following first isolation, sputum was serially re-examined at median intervals of 24 days (range 4–154 days) until eradication. In patients who later reisolated *P aeruginosa*, sputum was examined at median intervals of 1 month (range 1–11 months) from eradication until reinfection. In patients

who remained free from *P aeruginosa* from first eradication, sputum was examined at median intervals of 1 month (range 1–15 months) until the end of the study period.

### Defining successful eradication and new isolation

Eradication was considered to be successful when the patient did not culture *P aeruginosa* for at least 12 months, determined as at least three sputum cultures were performed, each separated by at least 1 month.<sup>11</sup> The time to achieve successful eradication of *P aeruginosa* was taken to be the time from the start of therapy until the first negative sputum culture was recorded, after which cultures remained negative for at least 12 months. The duration until reinfection with *P aeruginosa* was determined as the number of months from the date of successful eradication until the date of a subsequent *P aeruginosa* positive respiratory culture.

### Lung function

Baseline lung function was taken to be the best FEV<sub>1</sub> (%) recorded in the 6 months preceding the first *P aeruginosa* isolation. FEV<sub>1</sub> at the time of culture of *P aeruginosa* was taken to be the FEV<sub>1</sub> on the date of the positive sample if recorded and, where not available, the date closest to the date of positive culture. The best FEV<sub>1</sub> values between 6 and 12 months following the start of treatment were collected.

### Statistical analysis

Comparison between the FEV<sub>1</sub> of patients at baseline, before the first *P aeruginosa* infection, at the time of isolation and following the completion of AET was made using the paired Student t test. Mean (SD) was used for data which were normally distributed, and median was used for data which were not normally distributed. A p value  $\leq 0.05$  was considered to be significant.

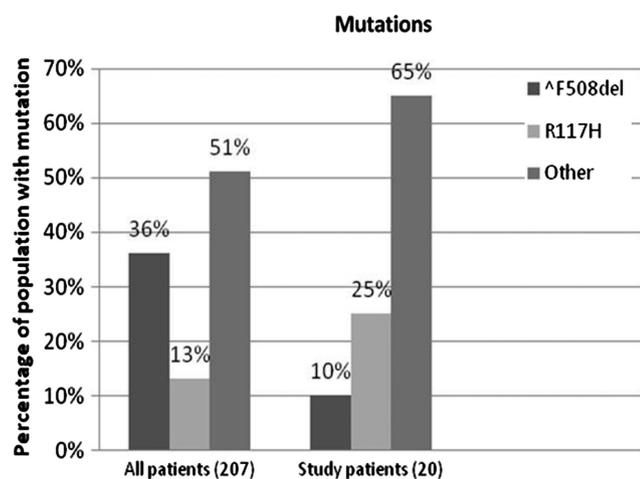
## RESULTS

Twenty patients who met the inclusion criteria were identified as isolating *P aeruginosa* in a respiratory culture for the first time during the study period. One patient isolated *P aeruginosa* for the first time but was treated at another centre.

### Patient demographics

Figure 1 compares the genetic mutations between the study group and the total population recorded on the CF registry. Of the total population on the CF registry, 71% of F508del homozygotes were infected with *P aeruginosa*. Of all patients who were infected with *P aeruginosa*, almost half had a F508del homozygous mutation (49.5%).

The median age of the study group was 27 years (range 18–81 years), compared with 30 years in the adult CF population. Two of the 20 patients were F508del homozygous. There were fewer F508del homozygous patients in the study group (10%), compared



**Figure 1** Comparison breakdown of genetic mutations between the study patients and all adult patients with cystic fibrosis on the registry.

with the adult CF population (36%). There was a greater proportion of R117H heterozygous patients within the study group (35%) than in the adult CF population (15%). The mean baseline FEV<sub>1</sub> before first isolate *P aeruginosa* was 83.34% predicted (95% CI 73.32% to 94.36%).

### Eradication therapy

**Box 1** outlines AET for each patient during this study. Ten patients were treated with oral ciprofloxacin (10–20 mg/kg twice daily to a maximum 1000 mg twice daily) and nebulised colomycin (1 million units twice daily) for a median duration of 6 weeks (range 2–8 weeks) and 3 months (range 2–3 months), respectively.<sup>12</sup> Seven patients received intravenous antipseudomonal antibiotics (median duration 14 days, range 9–14 days). Three of these patients continued on nebulised therapy after finishing intravenous antibiotics as their sputum was persistently positive for *P aeruginosa*. One patient was treated

#### Box 1 Choice of antipseudomonal eradication therapy

Eradication therapy (median duration)

- Oral ciprofloxacin (6 weeks) and nebulised colomycin (3 months)—10 cases
- Intravenous antibiotic therapy (14 days)—7 cases
  - Ceftazidime and tobramycin (3 cases)
  - Ceftazidime and amikacin plus nebulised colomycin
  - Ceftazidime, gentamicin and meropenem plus nebulised colomycin
  - Aztreonam and tobramycin
  - Piperacillin–tazobactam and tobramycin
- Other therapy—2 cases
  - Nebulised tobramycin and oral ciprofloxacin
  - Oral ciprofloxacin alone.
- No therapy—1 case

with inhaled tobramycin and oral ciprofloxacin. One patient received oral ciprofloxacin only.

One patient was not started on antipseudomonal therapy as she was receiving long-term therapy for *Mycobacterium chelonae* (clarithromycin, ethambutol and rifampicin).

### Success of eradication therapy

**Figure 2** illustrates the patient outcomes of AET. Successful eradication with first-line therapy was achieved in 15 of 19 treated cases with a negative sputum culture within 6 weeks of starting treatment, followed by at least three negative sputum cultures in the following 12 months. Six patients continued to isolate *P aeruginosa* in sputum samples, following the completion of the first choice therapy. These six patients were started on further therapies which resulted in successful eradication in two patients. Therefore, 15 out of 19 treated patients (79%) had successful *P aeruginosa* eradication. The median time to eradicate *P aeruginosa* from respiratory cultures was 1 month (range 1–6 months).

### Chronic infection and *P aeruginosa* reinfection

Four patients (21%) continued to culture *P aeruginosa* and became chronically infected (defined as  $\geq 50\%$  cultures positive in 12 months) despite early treatment and repeated courses of AET. Ten patients who had been successfully cleared of *P aeruginosa* infection following the first isolation later cultured a new isolation within the study period. The median time from successful eradication to reinfection with *P aeruginosa* was 43 months (range 9–68 months). The eradication of subsequent isolations of *P aeruginosa* was successful in eight of these patients but two became chronically infected during the study period. The patient on long-term AET for *M chelonae* became chronically infected with *P aeruginosa* 11 months after first isolation.

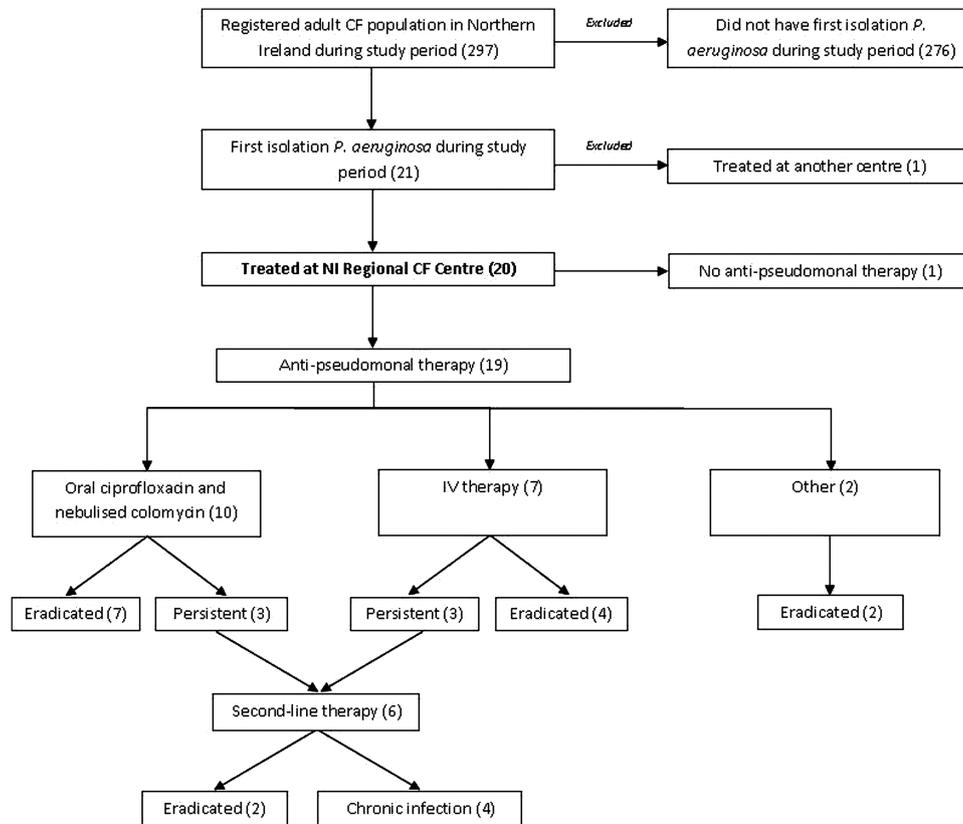
By the end of the study period, the patients who did not reisolate *P aeruginosa* after eradication had been free from *P aeruginosa* for a median of 99 months (range 13–120 months).

### Chronic *P aeruginosa* infection and associated mortality

Three of 20 patients died within the study period (mortality 15%). One patient died from traumatic injuries in a road traffic accident 97 months after first isolating *P aeruginosa*. One patient became chronically infected with *P aeruginosa* after first isolation and died 84 months later from complications of the lower respiratory tract infection. The third patient died from respiratory and hepatic failure 65 months after first isolation but was not chronically infected with *P aeruginosa*.

### Lung function

At the time patients isolated *P aeruginosa*, there was a mean (SD) fall from baseline FEV<sub>1</sub> 82.4 (24.0)% to 77.3 (26.3)% predicted ( $p=0.002$ ). After completion of AET, there was improvement in mean FEV<sub>1</sub> to 81.2 (23.9)%



**Figure 2** Chart showing outcomes of antipseudomonal therapy of study population. CF, cystic fibrosis; NI, Northern Ireland.

predicted ( $p=0.02$ ). After 12 months, there was no significant deterioration in lung function compared with baseline (from 82.4% to 82.3%,  $p=0.91$ ). Additionally, there was no significant difference between patients who developed chronic *P aeruginosa* infection (mean FEV<sub>1</sub>% predicted at: baseline 83.1%; after AET 83.9%) compared with those successfully eradicated (mean FEV<sub>1</sub>% predicted at: baseline 82.0%; after AET 81.5%) after 12 months ( $p=0.63$ ).

The use of intravenous antipseudomonal therapy as the first-line AET was consistent with these patients being more clinically unwell at the time of *P aeruginosa* infection, as evidenced by the greater fall in the mean FEV<sub>1</sub> from baseline. The patients treated with intravenous therapies had a fall in mean FEV<sub>1</sub>% predicted of 7.9% (from 80.9% to 73.0%) compared with 3.3% for those treated with nebulised plus oral therapy (83.3–80.0%), although this was not significant ( $p=0.16$ ).

### Impact of mutations

Patients with the F508del homozygous mutation displayed a greater fall in FEV<sub>1</sub>% predicted (from 81.2% to 65.3%) compared with those who were non-F508del homozygous (from 82.5% to 78.6%) after isolating *P aeruginosa* for the first time ( $p=0.007$ ). Both F508del homozygous patients failed to eradicate first isolate *P aeruginosa* and became chronically infected.

Patients with the R117H mutation displayed a smaller fall in FEV<sub>1</sub>% predicted (from 96.2% to 93.2%)

compared with those without the R117H mutation (from 78.9% to 73.3%), although this was not significant ( $p=0.46$ ). All four patients with the R117H mutation had successful eradication of the first isolate of *Paeruginosa* and did not become chronically infected.

## DISCUSSION

### Comparing *P aeruginosa* eradication in adults and children

The recognition of chronic *P aeruginosa* infection as a poor prognostic factor for patients with CF has prompted a number of clinical trials into determining the optimum AET.<sup>2</sup> Most of these trials report median ages in the paediatric range, which is consistent with first-time *P aeruginosa* isolation occurring most often in childhood. This study was a review of first isolate *P aeruginosa* eradication in adults (median age 27 years) which sought to compare eradication rates with children.

The success of eradication in this study (79%) is comparable to the range found in the published literature among younger populations (68–93%).<sup>6–8</sup> The median time to eradicate was 1 month (range 1–6 months), which is similar to that reported in paediatric studies. The median time until reinfection with *P aeruginosa* (median 43 months) also compares favourably with the previous studies in children (5–26 months). Therefore, this study suggests that AET of first isolate *P aeruginosa* is equally effective in adults and children.<sup>13</sup>

Patients who are F508del homozygous are less likely to reach adulthood without *P aeruginosa* infection than those with other mutations.<sup>14</sup> This is the most likely explanation for the notable difference in the proportion of patients who were F508del homozygous in our study population (10%) compared with the total population on the CF registry (36%). It is also possible that AET is more effective in patients with mutations associated with residual chloride function. This is consistent with the successful rates of eradication in patients with the R117H mutation seen in this study.

### Comparing choice of antipseudomonal therapy

Previous trials into AET of *P aeruginosa* have varied greatly in the study design and the choice of the eradication regime. In 2010, the Cochrane Collaboration produced a review of antibiotic strategies for *P aeruginosa* eradication in patients with CF.<sup>13</sup> It found that most studies had focused on inhaled tobramycin versus placebo, with one study comparing inhaled tobramycin with inhaled colistin and oral ciprofloxacin. It concluded that, although both antibiotic regimes were better than placebo, there was insufficient evidence to determine which was superior. Later studies by Taccetti *et al*<sup>15</sup> and Proesmans *et al*<sup>8</sup> found that eradication success was very similar between the two regimes.

The value of intravenous antibiotics in *P aeruginosa* eradication is still under investigation. Some trials have reported economic benefits and reduced lung inflammation in the use of systemic antibiotics.<sup>16 17</sup> The TORPEDO-CF trial is currently underway to establish its comparative eradication efficacy.<sup>18</sup> In our study, intravenous therapy was generally reserved for patients who were more unwell, as demonstrated by a greater reduction in FEV<sub>1</sub> from baseline. However, there was no standardised method to determine what degree of reduction warranted systemic antibiotics over other regimes. This may be a useful research focus for future studies.

There are two main explanations for the wide variety of AETs reported in this study. The first is the frequency of patients being switched to alternative agents following the failure or adverse reactions on first-line treatments. The second and more significant reason is the developing evidence base for different first-line regimes during the 13-year study period (1999–2012). Nebulised tobramycin has the best reported eradication success,<sup>6</sup> but since this was established late in the study period only a few patients received it.

Decisions over AET can be further complicated by coinfection, as demonstrated by the patient who isolated *P aeruginosa* while on long-term therapy for *M chelonae*. The complex microbial community found in airways of patients with CF is a current focus of research as the clinical significance of many pathogens is not well understood.<sup>19</sup> *P aeruginosa* and non-tuberculous mycobacterium are established as pathogenic in CF,<sup>2</sup> although little data are available to compare their associated morbidity. In this case, no change was made to the patient's

therapy as it was determined that the risks of interfering with non-tuberculosis mycobacterium AET outweighed the benefits of attempting *P aeruginosa* eradication.

### Comparing efficacy of antipseudomonal therapy

It is difficult to compare efficacy with previous studies as there are significant variations in patient demographics, choice and duration of therapy and measures of success. We observed an eradication success of first *P aeruginosa* isolate of 79%. This compares well to Taccetti *et al*<sup>7</sup> who achieved 81% eradication with oral ciprofloxacin and nebulised colomycin (mean age 8.9 years). However, the ELITE trial found that tobramycin inhaled for 28 days resulted in 93% eradication after 1 month, with 66% remaining free of *P aeruginosa* after 27 months (mean age 8.7 years).<sup>6</sup> There were too few patients on inhaled tobramycin in this study to compare efficacy.

Studies by Hansen *et al*<sup>12</sup> and Schelstraete *et al*<sup>20</sup> found that a short *P aeruginosa* free interval following AET may predict chronic infection. We observed a 66% reinfection rate of *P aeruginosa* in successfully eradicated patients. The median time to reinfection was 43 months. Taccetti *et al*<sup>7</sup> reported 51% (24 patients) becoming reinfected with a median recurrence interval of 18 months over a 9-year period. The increased *P aeruginosa* free period and incidence of reinfection in our study may be attributable to the longer study period of 13 years.

### Study limitations

The study is limited by the small number of adult patients isolating *P aeruginosa* for the first time during the period of study (20). In addition, there was a significant variety in choice and duration of antipseudomonal therapies. This study was a chart review which depends largely on comprehensive and accurate documentation of therapies and outcomes over a 13-year period. Therefore, it is difficult to reliably establish the efficacy of varying treatments retrospectively in a small patient population.

### CONCLUSION

Even with its limitations, this study demonstrates that aggressive AET of first-time *P aeruginosa* infection in adults at this centre is successful in the majority of patients and is of similar efficacy to the reported success in younger, mainly paediatric populations. Similar to previous studies, there is evidence that despite successful eradication of the first isolation, the reinfection of *P aeruginosa* is common. However, the eradication of recurrent *P aeruginosa* can still be successful among the adult CF population and can prevent chronic infection in the majority of adult patients.

The number of patients with CF entering adult care with no history of *P aeruginosa* infection is increasing and the need for AET in adults will become more frequent.<sup>5</sup> The results of the TORPEDO trial are awaited to determine the role and efficacy of intravenous antipseudomonal

therapy. Further research should include a multicentre prospective study to establish optimum AET in first-time *P aeruginosa* isolation in adult patients with CF.

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**Competing interests** None.

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