

# Eradication regimens for early or recurrent *Pseudomonas aeruginosa* infection

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## Introduction

Although in the early stages of cystic fibrosis (CF) there may be few or no clinical abnormalities, bronchoscopy studies have documented respiratory infection and inflammation in well infants (Armstrong *et al*, 1995; Khan *et al*, 1995; Armstrong *et al*, 1996; Rosenfeld *et al*, 2001).

Viral and bacterial infections with *Staphylococcus aureus* and *Haemophilus influenzae* predominate in younger patients. Chronic infection with *P. aeruginosa* used to be common in most patients by their late teens. This is no longer true. Less than 20% of our paediatric (Lee *et al*, 2003) and about 55% of our adult population have chronic *P. aeruginosa* infection. The impact of this epidemiological change can be seen in the outpatient clinics where one to two sessions each month are reserved for patients free of *P. aeruginosa* infection in the adult clinic, and only two clinics a month are designated for children with chronic *P. aeruginosa* infection. Chronic infection can be prevented, or at least be substantially delayed by intensive treatment of the first *P. aeruginosa* isolate, using an 'eradication regimen' of antibiotics, often combinations of nebulised, oral and/or intravenous antibiotics (Vazquez *et al*, 1993; Frederiksen *et al*, 1997; Ratjen *et al*, 2001; Taccetti *et al*, 2005; Lebecque *et al*, 2006). The most effective regimen is still uncertain (Conway *et al*, 2003). It is critically important to offer this treatment to all patients because chronic *P. aeruginosa* infection results in worse clinical status, lower respiratory function, lower weight, height and BMI, more hospital admissions and increased treatment costs (Konstan *et al*, 1999; Emerson *et al*, 2002; Taccetti *et al*, 2005). In the majority of patients chronic *P. aeruginosa* infection is with the mucoid form of the bacteria. This defends itself against ingestion and destruction by the blood's white cells by producing large amounts of a protective film/mucus called alginate (Lyczak *et al*, 2002). Alginate also protects *P. aeruginosa* against the activity of antibiotics (Aaron *et al*, 2002). The huge numbers of peripheral white blood cells which congregate in the lung in an attempt to kill these bacteria release powerful enzymes, directed at the bacteria but also damaging to the lung itself. These fuel a continuing inflammatory process in the lungs, the end result of which is destruction of lung tissue (Venaille *et al*, 1998). Following repeated respiratory tract infections it is the body's response to *P. aeruginosa* infection which is largely responsible for causing lung damage (Heeckeren *et al*, 1997; Konstan & Berger, 1997).

## Eradication regimens for early or recurrent *P. aeruginosa* infection

### Leeds criteria for *P. aeruginosa* infection:

Chronic infection: *P. aeruginosa* isolated in more than 50% of months when sputum, cough or throat swab taken in previous 12 month period

Intermittent infection: *P. aeruginosa* isolated in 50% or less months when sputum, cough swab or throat swab sample taken in previous 12 month period

Free of infection: *P. aeruginosa* isolated previously but not for 12 months or more

Never infected: *P. aeruginosa* never isolated

## Background

Chronic *P. aeruginosa* infection is associated with the mucoid phenotype of *P. aeruginosa* (Lyczak *et al*, 2002), a worse prognosis and a more rapid decline in lung function. Strategies aimed at preventing or delaying progression from initial acquisition of *P. aeruginosa* to chronic infection are an essential part of CF management and have proved highly effective. Recent data suggest that the window of opportunity for such strategies may be quite large (Li *et al*, 2005). Whilst acquisition of *P. aeruginosa* may occur quite early in life, the transition from the non-mucoid to the mucoid phenotype may take several years.

Evidence from several studies has shown that early administration of antibiotics, once colonisation with *P. aeruginosa* has been identified, significantly reduces the risk of chronic infection (Littlewood *et al*, 1985; Valerius *et al*, 1991; Frederiksen *et al*, 1997; Ratjen *et al*, 2001; Gibson *et al*, 2003; Taccetti *et al*, 2005; Lebecque *et al*, 2006). A common feature of these trials is the use of aerosolised antibiotics. Conversely trials using intravenous antibiotics as early eradication therapy have been disappointing (Steinkamp *et al*, 1989).

In the study conducted by Valerius *et al*, 26 patients received oral ciprofloxacin plus aerosolised colistin twice daily for three weeks or no treatment, in response to an initial isolation of *P. aeruginosa*. After 27 months of the trial significantly fewer patients who had received treatment were positive for *P. aeruginosa* (14% vs. 58%,  $p < 0.05$ ), (Valerius *et al*, 1991). This protocol was further refined by the Copenhagen group to increase the duration of treatment with oral ciprofloxacin and aerosolised colistin to three months. Further follow-up after three and a half years revealed that only 16% of treated patients developed chronic *P. aeruginosa* infection in comparison to 72% of untreated historical controls ( $p < 0.005$ ), (Frederiksen *et al*, 1997). Ratjen *et al* gave 15 patients aerosolised tobramycin 80mg twice daily for 12 months in response to initial colonisation with *P. aeruginosa* (Ratjen *et al*, 2001). After one year of follow-up, 14 of 15 patients remained negative for *P. aeruginosa*. Gibson *et al* randomised 21 children under the age of six years who became positive for *P. aeruginosa* to receive 300mg Tobramycin Solution for Inhalation (TOBI®) or placebo twice daily for 28 days (Gibson *et al*, 2003). At the end of treatment all eight children who received TOBI® vs. one of 13 who received placebo ( $p < 0.0001$ ) were negative for *P. aeruginosa*.

Early eradication therapy is believed to be a major reason for the increased survival of patients with CF, mainly as a result of reduction in the prevalence of chronic *P. aeruginosa* infection (Johansen *et al*, 2004; Lee *et al*, 2004).

The Leeds eradication regimen

There have been no studies comparing colistin with TOBI® for early eradication of new isolates of *P. aeruginosa*. While there is evidence for the efficacy of TOBI®, the cheaper alternative colistin has been extensively used and has proved highly effective when combined with oral ciprofloxacin in preventing, or at least substantially delaying, the first *P. aeruginosa* isolate (Valerius *et al*, 1991; Frederiksen *et al*, 1997). In our centre we use three months of nebulised colistin (2MU bd) in combination with oral ciprofloxacin (35-50mg/kg/day in two divided doses) on first isolation of *P. aeruginosa* (Figure 1). For the first month we also prescribe azithromycin to hopefully increase the success rate by decreasing both *P. aeruginosa* adherence to the respiratory epithelium and biofilm growth. We prescribe 500mg or 250mg azithromycin daily on Monday, Wednesday and Friday depending on whether the patient's weight is greater or less than 40kg. For children less than eight years old we prescribe 10mg/kg once daily on Monday, Wednesday and Friday. We are presently auditing the effectiveness of this additional treatment. TOBI® is substituted for patients intolerant of nebulised colistin.

If the above first line treatment fails or there is an early pseudomonas recurrence we prescribe two weeks of intravenous anti-pseudomonal antibiotics followed by a further three months of nebulised TOBI® and oral ciprofloxacin, and a further nine months of on/off TOBI®.

Patients whose new pseudomonas isolate is associated with a respiratory exacerbation, however mild, are treated with two weeks of intravenous anti-pseudomonal antibiotics before starting one month of oral azithromycin and three months of nebulised colistin and oral ciprofloxacin.

We treat an acute rise in *P. aeruginosa* antibodies in a patient from whom pseudomonas has not been isolated for more than a year with the above protocol even in the absence of a new pseudomonas growth.

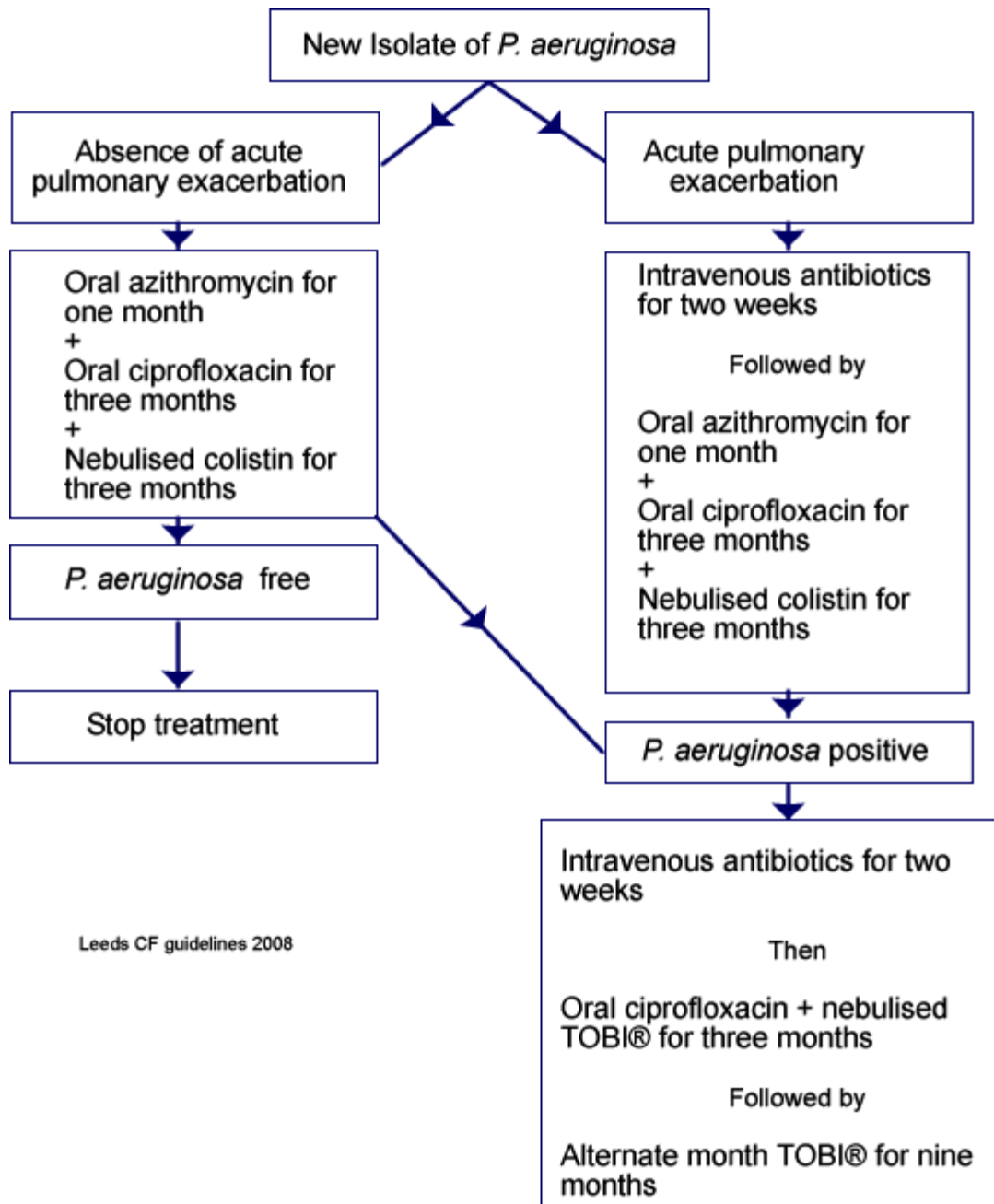


Figure 1. The protocol for *P. aeruginosa* eradication followed in the Leeds CF Unit

### Safety concerns

Eradication therapy is usually well-tolerated. Absorption of aerosolised tobramycin does not reach sufficient levels in the majority of patients to affect renal function. A retrospective review of children with CF receiving inhaled gentamicin showed significantly raised urinary N-acetyl-b-D-glucosaminidase (NAG) activity indicating renal tubular damage compared to control children who had never received inhaled gentamicin or who had discontinued the drug at least three months previously (Ring *et al*, 1998). The long term clinical implication of these findings remained uncertain as urinary NAG activity returned to normal at the end of treatment.

There has been no evidence to suggest significant increases in antimicrobial resistance during eradication therapy, even after multiple repeat courses (Ho *et al*, 2004). Aerosolised antibiotics and oral ciprofloxacin have been associated with an increased risk of colonisation with *S. maltophilia* (Denton *et al*, 1996), *Aspergillus* species (Bargon *et al*, 1999) and MRSA (Nadesalingam *et al*, 2005).

### Monitoring

We recommend that all patients who are free of *P. aeruginosa* or intermittent growers should be regularly monitored using pseudomonas antibody titres (three monthly) and regular sputum or cough swab specimens (one to two monthly). Eradication therapy will only be effective if appropriate microbiological surveillance is undertaken.

#### Key points

- Chronic *P. aeruginosa* infection can be significantly delayed or prevented
- Chronic *P. aeruginosa* infection is associated with a worse prognosis and a more rapid decline in lung function
- Early eradication therapy is a major reason for increased patient survival, mainly as a result of a reduction in the prevalence of chronic *P. aeruginosa* infection

#### Recommendations

- First line therapy should be based on a regimen including three months of nebulised colistin in combination with oral ciprofloxacin
- If first line treatment fails we recommend two weeks of intravenous anti-pseudomonal antibiotics followed by three months of nebulised TOBI® and oral ciprofloxacin, and nine months of on/off TOBI®
- Patients presenting with a new growth of *P. aeruginosa* and a respiratory exacerbation should receive two weeks of intravenous anti-pseudomonal antibiotics before the three month regimen
- TOBI® should be substituted for colistin for patients intolerant of nebulised colistin

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