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Pseudomonas aeruginosa infection in cystic fibrosis: prevent, eradicate or both?

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Lung disease in cystic fibrosis (CF) starts early in life. Infection, inflammation, reduced lung function and abnormal chest CT findings are present in a significant proportion of infants with CF at a time when many of these children have no clinically apparent lung disease.^{1–6} Infection and inflammation are intimately linked early in the course of CF lung disease.^{2 7–9} The detection of airway inflammation in the absence of apparent infection led to the speculation that CF is associated with an intrinsic abnormality of immune regulation.¹⁰ However, more recent data argue against a primary CF-associated dysregulation of local immune function where inflammation might precede infection; they rather support the central role of bacterial pathogens in initiating and sustaining the neutrophil-mediated airway inflammation characteristic of CF lung disease, with a higher inflammatory burden in children infected with *Pseudomonas aeruginosa* (PA) than in those infected with organisms other than PA or uninfected.^{6 11 12} Chronic respiratory infection is one of the main characteristics of CF and significantly contributes to morbidity and mortality.^{12 13} In young children *Staphylococcus aureus*, *Haemophilus influenzae* and PA are the major lower airway pathogens.^{12 13} Chronic infection with PA is known to be associated with a worse prog-

nosis in children, adolescents and adults, and patients with mucoid PA strains do worse than those with non-mucoid strains.^{14–18} Thus, prevention or early detection and treatment of infection, in particular with PA, may prevent or delay irreversible lung damage from inflammation and consequently may improve prognosis. In order to prevent acquisition of PA, hygienic measures to decontaminate environmental reservoirs of this organism including medical equipment have been stressed, and CF centres have adopted meticulous microbiological surveillance and effective segregation policies to limit cross-infection between patients. Furthermore, several trials have been undertaken to assess the value of vaccination as a preventive strategy for PA infection but, with the variable outcomes of these trials, vaccines against PA cannot be recommended.¹⁹ At present, early treatment of initial infection—that is, an attempt to eradicate PA—is the agreed standard.²⁰ Literature on antibiotic prophylaxis of PA infection has so far remained scarce.^{21 22}

In this issue of *Thorax*, Tramper-Stranders *et al* report on a randomised controlled trial investigating the effectiveness of cycled antibiotic prophylaxis in children with CF (*see page 915*).²³ Children between 0 and 18 years of age received 3-monthly 3-week treatments with oral ciprofloxacin and inhaled colistin or placebo for 3 years. The authors apparently chose this regimen because many CF centres across Europe have used the combination of oral ciprofloxacin and inhaled colistin as eradication therapy for PA, going back to the first randomised controlled trial of an eradication regimen almost 20 years ago.²⁴ Patients were

followed at 3-monthly intervals in between treatment cycles and respiratory specimens collected for microbiology studies were either oropharyngeal cough swabs or sputum samples (notably, the vast majority of patients did not produce sputum). In addition, serum samples were collected every 6 months for measurement of anti-*Pseudomonas* antibodies. Infection with PA (the primary end point) was defined as either two positive cultures taken >1 week apart or one positive culture and a 'severe pulmonary exacerbation'. Nineteen out of 65 patients (29%) reached the primary end point (in only 4 of them was PA detected in sputum); information on how many strains were mucoid or non-mucoid is not given. Fourteen patients had positive antibody titres during the study period once or more often; 10 of them were culture-positive before they were serology-positive. This study once more shows that detection of infection in children with CF is difficult. In general, young children are not able to expectorate sputum, and oropharyngeal cultures do not reliably predict the presence of bacterial pathogens in the lower airways of young children with CF.^{13 25} Thus, cultures from bronchoalveolar lavage (BAL) fluid are usually taken as the gold standard for detection of infection in the lower airways. However, owing to sampling problems, even a negative BAL fluid culture or the absence of a particular organism on culture does not guarantee that the organism is not present in the lungs of the patient.²⁶ For this reason, additional markers of infection are desirable and the use of specific serum antibodies against PA may be helpful in defining the status of PA infection. However, the majority of patients are antibody-negative at the time of first infection so specific antibodies against PA alone are not recommended to diagnose early infection.²⁷ With oropharyngeal cough swabs being the prevailing respiratory specimens, one might speculate that at least some patients with positive upper airway cultures might have had negative

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cultures from lower airway specimens (and vice versa in a probably smaller number) in the present study. Thus, the reported results such as incidence rates of PA infection, mean duration to acquiring PA infection and median age at PA infection have to be interpreted with some caution.

In the study by Tramper-Stranders *et al*, patients with PA infection did not receive further study intervention but received 'standard anti-*Pseudomonas* treatment'. This treatment resulted in eradication of PA in 60% of the control group and 67% of the treatment group after one or more eradication cycles. Finally, chronic infection (defined as >50% of evaluable months PA culture-positive) was reported for 10 of 65 patients (15%)—that is, half of the patients with initial PA infection—at the end of the study period.²³ Today there is consensus that early treatment of PA infection with the aim of eradicating the organism (and thereby achieving a reduction in airway inflammation) is worthwhile, although insufficient evidence exists to determine whether antibiotic strategies for the eradication of PA decrease mortality or morbidity, improve quality of life or are associated with adverse effects compared with placebo or standard treatment.^{20–28} Numerous strategies for eradication of PA have been proposed, but many questions pertaining to the selection of antibiotics, dosages, modes of delivery and duration of therapy still remain unanswered.^{28–30} The eradication success rate with 'standard anti-*Pseudomonas* treatment', as reported by Tramper-Stranders *et al*, appears to be relatively low when compared with the success rates in recent publications which have been reported to be around 90%.^{12–30–32} With one exception, the latter studies employed cultures from BAL fluid and, in the study by Gibson *et al*, there was a less pronounced effect of inhaled tobramycin on the eradication of PA defined on the basis of oropharyngeal cultures compared with BAL fluid cultures.³¹ This further corroborates the abovementioned doubts regarding the validity of oropharyngeal cough swabs in detecting initial PA infection. As an alternative explanation, the relatively low eradication rate might partially be due to the presence of PA of the mucoid phenotype which is less amenable to treatment.³¹ As a side note, the rate of decline in forced expiratory volume in 1 s (FEV₁) expressed as percentage predicted—approximately 2.8% per year for the control group and 3.5% per year for the treatment group (no difference between the groups)—appears to be quite high compared with recent publications from Europe and the

USA, especially for the age group investigated.^{33–34} High baseline FEV₁, which has been recognised as a significant risk factor for lung function decline, may partly explain these surprising numbers; alternatively, the patients with chronic PA infection (the latter being well known as an independent risk factor for decline in FEV₁) may have contributed excessively to this result.

A significant weakness of the present study is that mannitol was used for placebo inhalation. Mannitol, a naturally occurring sugar alcohol, has been used as an osmotic agent and has been reported to increase mucociliary clearance since the late 1990s.³⁵ Inhaled mannitol was recently shown to improve hydration and surface properties of sputum and lung function in patients with CF and to be at least as effective as recombinant human deoxyribonuclease (rhDNase), although with marked individual variation in both tolerance and response to treatment.^{36–38} Aerosolised rhDNase in patients with CF was reported to result in less positive airway cultures and a reduced demand for antibiotics.³⁹ On the basis of the above studies, it may be speculated that inhaled mannitol acts in a similar way to rhDNase and, by improving mucociliary clearance, has some impact on PA infection. Thus, although these studies used higher dosages of mannitol than the present one and compliance in the control group might have been suboptimal due to adverse events to mannitol such as bronchoconstriction and cough, it cannot be ruled out that one active treatment has been compared with another one and not with a true placebo.

With no significant and/or clinically relevant differences found between the treatment and control groups, Tramper-Stranders *et al* conclude that '3-monthly cycled anti-*P aeruginosa* prophylaxis does not reduce the risk of initial and chronic infection in *P aeruginosa*-negative children with CF of all ages'.²³ As discussed by Tramper-Stranders *et al*, continuous prophylaxis may be more effective in the prevention of PA infection than cycled prophylaxis. Two observational retrospective studies that used such continuous prophylaxis have been published. In the CF centre in St Luc, Belgium, 95% of paediatric patients with CF receive intermittent or continuous inhaled antibiotic therapy (mainly tobramycin or amikacin) and this centre reports a very low rate of chronic colonisation with PA.²² In a retrospective evaluation of our practice to give prophylactic nebulised gentamicin continuously to patients with CF with defined risk situ-

ations for acquisition of PA, we showed that such long-term prophylaxis can effectively delay PA infection.²¹ The discrepancy between these findings and the results of Tramper-Stranders *et al* may be interpreted as showing that any attempt at preventing or delaying PA infection in CF will be more successful when using continuous prophylaxis. Clearly, there are downsides to the long-term use of antibiotics including the emergence of other and (multi)resistant microorganisms and, particularly for aminoglycosides, side effects such as cumulative nephrotoxicity and cochleotoxicity.^{40–42} Over the last decade important changes have occurred in the patterns of CF airway microbiology, including increased aminoglycoside resistance and the emergence of other (multi)resistant organisms.⁴² Tramper-Stranders *et al* also describe shifts in bacterial colonisation in their treatment group.²³

The authors should be applauded for undertaking the first prospective study on antibiotic prophylaxis of PA infection in children with CF. With a cycled antibiotic prophylaxis, however, this study more likely involved a mixture of prevention and early treatment of intermittent PA infection than just prevention alone. In this context, the results of the large EPIC clinical trial, which are expected to be published in the next year, will be of interest. The EPIC study compares cycled antibiotic therapy (regardless of findings from respiratory cultures) and culture-based antibiotic intervention (treatment based on recovery of PA from respiratory cultures) throughout an 18-month study period.⁴³ With PA being the most common and significant pathogen for patients with CF, further large-scale studies on the prevention or delay of PA infection are essential before any definite judgement can be made on the clinical value of anti-*Pseudomonas* prophylaxis.

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Relearning an old lesson: stopping trials early

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A well designed and delivered clinical trial is the main tool to define whether medical interventions ‘work’, and how well. As such, they are potent weapons in the armoury of medical progress—and like all potent weapons need to be used with care.

In this month’s Thorax, Koegelenberg *et al* (*see page 857*) report the findings of a trial comparing the diagnostic accuracy of closed pleural biopsy (Abrams needle) and cutting needle pleural biopsy after thoracic ultrasound, for the diagnosis of pleural tuberculosis (TB).¹ This question is clearly important given the global significance of TB, and the key role of pleural biopsy in the diagnosis and microbiological assessment of its pleural presentations. To date, there are no published studies assessing ultrasound-guided pleural biopsy for the diagnosis of