Eur Respir J 2005; 26: 373–375
DOI: 10.1183/09031936.05.00069705

EDITORIAL

Eradication therapy for early *Pseudomonas aeruginosa* infection in CF: many questions still unanswered

A.M. Jones

Pseudomonas aeruginosa remains the most common and significant pathogen for people with cystic fibrosis (CF). Strategies to prevent or delay the onset of chronic *P. aeruginosa* infection should be an essential component of the clinical care from CF centres, as the development of chronic *P. aeruginosa* infection is associated with a progression in the decline of lung function [1, 2] and chest radiograph scores [2], increased treatment requirements [3] and a decrease in survival for patients with CF [3–6]. In this issue of the *European Respiratory Journal*, TACCETTI *et al*. [6] report the experience of a large CF centre in Florence (Italy), which involved early eradication treatment for *P. aeruginosa* infection using a protocol first developed at the Copenhagen CF Centre (Denmark) [5]. Their study is a reminder of the potential long-term benefits of early eradication therapy for *P. aeruginosa* infection in people with CF.

The study by TACCETTI *et al*. [6], however, is not original and adds to, rather than increases, the current literature of eradication therapy for early *P. aeruginosa* infection in CF. It, like many of the previous studies, is limited by problems in methodology. Principally, it is a retrospective evaluation of the policy of the Florence CF Centre (Italy) since 1992 for treating early *P. aeruginosa* infection and (due to ethical limitations) lacks a suitable control group.

Previous studies of eradication therapy for early *P. aeruginosa* infection have examined the use of nebulised antibiotics alone [7–10], or in combination with oral [5, 11] or intravenous anti-pseudomonal antibiotics [12]. The duration of therapy has varied from a minimum of 3 weeks [5, 11] to 12 months [8, 9]. Only three previous prospective trials have included a control group [8, 10, 11], of which only two were placebo controlled [8, 10]. All three trials contained only small numbers of patients, with between 21–26 patients in each study. No large, prospective, multicentre trial of eradication therapy has been published. Still, a consensus statement from the committee of the European Cystic Fibrosis Society accepts that antibiotic therapy for early *P. aeruginosa* infection can prevent persistent infection [13]. The findings of TACCETTI *et al*. [6] support the previously published experience of the Danish CF centre team (Denmark) in highlighting the potential clinical benefits of eradication therapy for patients with CF [5, 6]. In addition, TACCETTI *et al*. [6] are the first to report the economic benefits and cost-effectiveness of such a policy.

Many questions, however, remain unanswered. The optimal antibiotic combination, dosages, modes of delivery and duration of therapy all remain unresolved. Whether the same regimen should be applied again or another antibiotic combination substituted if *P. aeruginosa* is grown from the respiratory secretions of a patient who has previously received eradication therapy is unknown. Similarly, how often should cultures be obtained during eradication treatment to evaluate its success? If cultures remain positive, should the same regimen be continued for a longer period or should it be changed to a different antibiotic combination? If cultures become negative, when should the antibiotic treatment be discontinued? Should it be stopped at all? Of the 47 patients studied by TACCETTI *et al*. [6] who cleared *P. aeruginosa*, 24 (51%) eventually became re-infected during the 9-yr follow-up period, with a mean (SD) of 25.2 (21.7) months between isolated episodes of infection. The Vienna paediatric CF centre team (Austria) has published the results of a retrospective evaluation of their practice to give prophylactic nebulised gentamicin continuously to CF patients deemed as high risk for acquisition of *P. aeruginosa* infection [14]. They reported that 12 patients who had taken prophylactic gentamicin for 3 yrs had avoided *P. aeruginosa* infection, whilst seven out of 16 patients who had stopped their treatment for a variety of reasons had developed *P. aeruginosa* infection.

Currently, other prospective studies of eradication regimens are being conducted, including a European study of the efficacy of 28 days or 56 days continuous treatment with preservative-free high dose nebulised tobramycin solution (Chiron Corporation, Emeryville, CA, USA). Other strategies to prevent *P. aeruginosa* infection are also being evaluated, principally the use of *Pseudomonas* vaccines.

It can be questioned whether aggressive antibiotic therapy merely suppresses rather than eliminates early *P. aeruginosa* infection in CF. By the inclusion of molecular fingerprinting of individual bacterial isolates, TACCETTI *et al*. [6] and a previous study by MUNCK *et al*. [12] have demonstrated if re-infection occurs that it is usually by a different strain, providing evidence that in the majority of cases treatment truly eradicated the initial infection [6, 12].

During early infection in CF lungs, the *P. aeruginosa* phenotype resembles that of environmental isolates, demonstrating a nonmucoid phenotype, smooth lipopoysacharide and sensitivity to usual anti-pseudomonal antibiotics. The

CORRESPONDENCE: A.M. Jones, Manchester Adult Cystic Fibrosis Centre, South Manchester University Hospitals NHS Trust, Southmoor Road, Manchester, M23 9LT, UK. Fax: 44 1612912080. E-mail: andrew.jones@smtr.nhs.uk

change from a nonmucoid to a mucoid exopolysaccharide alginate-producing phenotype is associated with an increased inflammatory response and clinical deterioration [4]. At this stage, *P. aeruginosa* adopts a biofilm mode of growth with microcolonies embedded in an exopolysaccharide matrix that provides a formidable barrier to antibiotics, such that it becomes impossible to eradicate the infection. It is estimated that the conversion from a nonmucoid to a mucoid phenotype can occur as early as 3 months from initial onset of infection [15]. Prompt eradication treatment at the very onset of infection intuitively would seem advantageous, since success is only likely prior to the transition to a mucoid variant. All CF centres should practice pro-active surveillance for early infection in *P. aeruginosa*-negative patients, with sputum or throat swab samples screened for growth of *P. aeruginosa* at a minimum frequency of every 3 months. CF centres should create an alternative way for their patients who attend at intervals >3 months to deliver specimens, such as using appropriate kits for postal delivery of microbiological specimens.

The success in the prevention or delay in chronic *P. aeruginosa* infection for patients with CF is dependent on a number of factors, including good hygienic practice and infection control. Previously, it was thought that *P. aeruginosa* cross-infection was rare among CF patients, except siblings. A number of recent studies from the UK and Australia have provided evidence that this is no longer the case [16–21]. In the absence of appropriate infection control measures, transmissible strains of *P. aeruginosa* pose a threat to *P. aeruginosa*-negative CF patients through exposure to an increased risk of acquisition of infection. Clinical experience also suggests that early infection with transmissible multiresistant strains may be more difficult to eradicate than sporadic strains of *P. aeruginosa* [17]. Implementation of infection control measures, screening and aggressive eradication of early *P. aeruginosa* infection has reduced the prevalence of chronic *P. aeruginosa* infection from 24.5% in 1990 to 4.3% in 2000 for children <11 yrs of age at the Leeds Regional Paediatric Cystic Fibrosis Centre (UK) [22]. With an increasing number of CF patients who have remained free of chronic *P. aeruginosa* infection at transition from paediatric to adult centres, it is crucial that paediatric and adult CF teams alike receive the importance of this message.

The successes of eradication regimens for early *P. aeruginosa* infection have varied from 81–93% in most studies with follow-up for over 1 yr [5, 6, 9]. Given the apparent success of eradication treatment for *P. aeruginosa*, should the same ethos of aggressive antibiotic therapy for eradication of early infection also be applied to other known pathogens for patients with CF, such as organisms of the *Burkholderia cepacia* complex?

In summary, *Pseudomonas aeruginosa* remains the most common and significant pathogen for people with cystic fibrosis. The study by TACCETTI *et al*. [6] emphasises that eradication regimens remain an important and cost-effective part of the armamentaria of the cystic fibrosis multidisciplinary team against this pathogen [6, 13], although the optimal antibiotic combination, dosages, modes of delivery and duration of therapy remains unresolved.

REFERENCES

1 Pamukcu A, Bush A, Buchdahl R. Effects of *Pseudomonas aeruginosa* colonization on lung function and anthrometric variables in children with cystic fibrosis. *Pediatr Pulmonol* 1995; 19: 10–15.
2 Kosorok MR, Zeng L, West SE, *et al.* Acceleration of lung disease in children with cystic fibrosis after *Pseudomonas aeruginosa* acquisition. *Pediatr Pulmonol* 2001; 32: 277–287.
3 Nixon GM, Armstrong DS, Carzino R, *et al.* Clinical outcome after early *Pseudomonas aeruginosa* infection in cystic fibrosis. *J Pediatr* 2001; 138: 659–704.
4 Henry RL, Mellis CM, Petrovic L. Mucoid *Pseudomonas aeruginosa* is a marker of poor survival in cystic fibrosis. *Pediatr Pulmonol* 1992; 12: 158–161.
5 Frederiksen B, Koch C, Hoiby N. Antibiotic treatment of initial colonization with *Pseudomonas aeruginosa* postpones chronic infection and prevents deterioration of pulmonary function in cystic fibrosis. *Pediatr Pulmonol* 1997; 23: 330–335.
6 Taccetti G, Campana S, Festini F, Mascherini M, Doring G. Early eradication therapy against *Pseudomonas aeruginosa* in cystic fibrosis patients. *Eur Respir J* 2005; 26: 458–461.
7 Littlewood JM, Miller MG, Ghonheim AT, Ramden CH. Nebulised colomycin for early *Pseudomonas* colonisation in cystic fibrosis. *Lancet* 1985; 1: 865.
8 Wiesemann HG, Steinkamp G, Ratjen F, Bauernfeind A, Przyklenk B, Doring G. Placebo-controlled double blind randomized study of aerosolized tobramycin for early treatment of *Pseudomonas aeruginosa* colonisation in cystic fibrosis. *Pediatr Pulmonol* 1998; 25: 88–92.
9 Ratjen F, Doring G, Nikolaizik WH. Effect of inhaled tobramycin on early *Pseudomonas aeruginosa* colonisation in patients with cystic fibrosis. *Lancet* 2001; 358: 983–984.
10 Gibson RL, Emerson J, McNamara S, *et al.* Significant microbiological effect of inhaled tobramycin in young children with cystic fibrosis. *Am J Respir Crit Care Med* 2003; 167: 841–849.
11 Valerius NH, Koch C, Hoiby N. Prevention of chronic *Pseudomonas aeruginosa* infection in cystic fibrosis by early treatment. *Lancet* 1991; 338: 725–726.
12 Munck A, Bonacorsi S, Mariani-Kurkdijan P, *et al.* Genotypic characterization of *Pseudomonas aeruginosa* strains recovered from patients with cystic fibrosis after initial and subsequent colonization. *Pediatr Pulmonol* 2001; 32: 288–292.
13 Doring G, Conway SP, Heijerman HGM, *et al.* Antibiotic therapy against *Pseudomonas aeruginosa* in cystic fibrosis: a European consensus. *Eur Respir J* 2000; 16: 749–767.
14 Heinzl B, Eber E, Oberwaldenr B, Haas G, Zach MS. Effects of inhaled gentamicin prophylaxis on acquisition of *Pseudomonas aeruginosa* in children with cystic fibrosis: a pilot study. *Pediatr Pulmonol* 2002; 33: 32–37.
15 Govan JRW, Deretic V. Microbial pathogenesis in cystic fibrosis: mucoid *Pseudomonas aeruginosa* and *Burkholderia cepacia*. *Microbiol Rev* 1996; 60: 539–574.
16 Cheng K, Smyth RL, Govan JR, *et al.* Spread of beta-lactam-resistant *Pseudomonas aeruginosa* in a cystic fibrosis clinic. *Lancet* 1996; 348: 639–642.
17 Jones AM, Govan JR, Doherty CJ, *et al.* Spread of a multiresistant strain of *Pseudomonas aeruginosa* in an adult cystic fibrosis clinic. *Lancet* 2001; 358: 557–558.

18 McCallum SJ, Corkill J, Gallagher M, Ledson MJ, Hart CA, Walshaw MJ. Superinfection with a transmissible strain of *Pseudomonas aeruginosa* in adults with cystic fibrosis chronically colonised by *P aeruginosa*. *Lancet* 2001; 358: 558–560.

19 Armstrong DS, Nixon GM, Carzino R, *et al*. Detection of a widespread clone of *Pseudomonas aeruginosa* in a paediatric cystic fibrosis clinic. *Am J Respir Crit Care Med* 2002; 166: 983–987.

20 O'Carroll MR, Syrmis MW, Wainwright CE, *et al*. Clonal strains of *Pseudomonas aeruginosa* in paediatric and adult cystic fibrosis units. *Eur Respir J* 2004; 24: 101–106.

21 Scott FW, Pitt TL. Identification and characterisation of transmissible *Pseudomonas aeruginosa* strains in cystic fibrosis patients in England and Wales. *J Med Microbiol* 2004; 53: 609–615.

22 Lee TWR, Brownlee KG, Denton M, Littlewood JM, Conway SP. Reduction in prevalence of chronic *Pseudomonas aeruginosa* infection at a regional paediatric cystic fibrosis center. *Pediatr Pulmonol* 2004; 37: 104–110.