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Eradication of early *Pseudomonas aeruginosa* infection

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Abstract

Chronic pulmonary infection with *Pseudomonas aeruginosa* is responsible for most of the morbidity and mortality in cystic fibrosis (CF). Once established as a biofilm, chronic *P. aeruginosa* infection caused by the mucoid phenotype cannot be eradicated. However, a period of intermittent colonization with *P. aeruginosa* precedes the establishment of the chronic infection. This window of opportunity can be utilized to eradicate *P. aeruginosa* from the respiratory tract of CF patients by means of oral ciprofloxacin in combination with nebulized colistin for 3 weeks or, even better, for 3 months or by means of inhaled tobramycin as monotherapy for 4 weeks or longer. This early, aggressive eradication therapy has now been used for 15 years without giving rise to resistance to the antibiotics and without serious side effects. The therapeutic results have been very successful and have completely changed the epidemiology in the Danish Cystic Fibrosis Center and a few other centers which have used this strategy for several years. The chronic *P. aeruginosa* lung infection is not seen in CF infants and children anymore due to the aggressive therapy, and no other bacteria have replaced *P. aeruginosa* in these young patients. The aggressive therapy has been shown to very cost-effective, and a European Consensus report recommends this approach.

1. Introduction

Chronic *Pseudomonas aeruginosa* lung infection is the most prevalent infection of cystic fibrosis (CF) patients [1]. This infection is responsible for most of the morbidity and mortality of CF patients [2,3]. Once acquired, chronic *P. aeruginosa* infection cannot be eradicated, and the current strategy is therefore to maintain the lung function of the patients by giving chronic suppressive antibiotic therapy (maintenance therapy) for decades [1,2]. This is, however, a costly therapy [4] with many side-effects such as allergy and resistance to the antibiotics [5,6]. Fortunately, the old medical dogma 'prevention is better than cure' also applies for *P. aeruginosa* infection in CF patients, since a combination of prevention of cross-infection and early aggressive antibiotic therapy of intermittent *P. aeruginosa* colonization can prevent chronic *P. aeruginosa* infection in most CF patients [2,7–9].

2. Diagnostic use of the antibody response

Although some centers such as the Danish CF Center in Copenhagen follow their patients by monthly control in the out-patient clinic, most patients are only examined every 4 months unless otherwise indicated, e.g., by the clinical condition [8]. That means that distinction between intermittent colonization and chronic infection becomes difficult, since a respiratory culture positive for *P. aeruginosa* may reflect either continuous colonization for nearly 4 months or acquisition of the bacteria the day before the examination. An epidemiological study was carried out in the Danish CF Center which showed that the continuous presence of *P. aeruginosa* in the lower respiratory tract for 6 months indicated that the bacteria would never disappear [10]. Subsequently, based on early work of Burns and May [11], an antibody method was developed [12,13] which could distinguish between intermittent colonization and chronic infection with a predictive value of a positive and a negative test of 93% and 89%, respectively [14]. The antibody method for diagnosing chronic *P. aeruginosa* infection was further developed in subsequent publications which showed that a similar diagnostic performance could be obtained with

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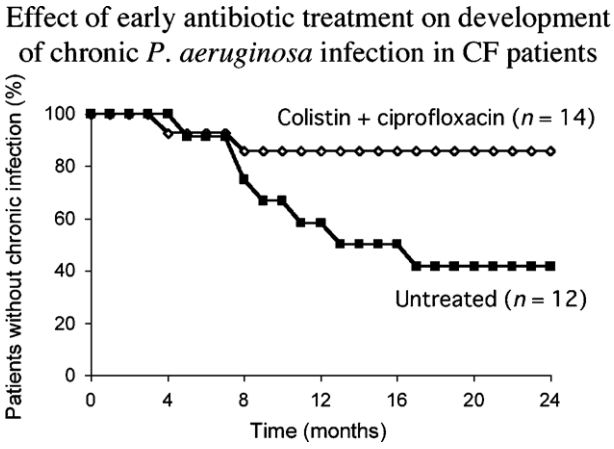

Fig. 1. Bacteriological results of treatment of cystic fibrosis patients with intermittent *P. aeruginosa* colonization with either oral ciprofloxacin and nebulized colistin or with no treatment for 3 weeks. Two years follow-up [37].

many different serological methods employing many different *P. aeruginosa* antigens [15–26]. In most patients, an average period of 12 months of intermittent colonization precedes chronic infection, but the individual variation is large, and approximately 10% of the patients will continue as chronically infected directly after the first positive culture and these patients harbour mucoid strains [27,28]. The current definition of chronic *P. aeruginosa* infection (continuous presence of *P. aeruginosa* in the lower respiratory secretions for 6 months and/or 2 precipitating antibodies against *P. aeruginosa*) is therefore based on the published results summarized above and has been in use in the Danish CF Center for the last 30 years. Similar definitions have now been adopted by others [1,8,29]. Intermittent *P. aeruginosa* colonization is therefore the presence of *P. aeruginosa* in lower respiratory tract secretions for <6 months continuously and normal level of antibodies against *P. aeruginosa* [2]. It should, however, be realized, that many patients will experience repeated intermittent colonization of *P. aeruginosa* throughout their entire life, e.g., the 1-year period prevalence of intermittent *P. aeruginosa* colonization is 15–20% in the Danish CF Center [30].

3. Colistin and ciprofloxacin as eradication therapy

The principles of antibiotic therapy in the Danish CF Center have always been to keep bacteria away from the lower respiratory tract of CF patients using early aggressive antibiotic therapy based upon the monthly examination of lower respiratory tract secretions whether there are clinical symptoms or not [31]. This bacteriological approach was successfully used to treat, e.g., *S. aureus*, *H. influenzae* and *S. pneumoniae*, but it could not be used for *P. aeruginosa* in the out-patient clinic until ciprofloxacin was marketed 20 years ago as the first oral antibiotic active against *P. aeruginosa*. However, ciprofloxacin was restricted to adult patients at that time although subsequent investigations showed that the use in children could be justified without any risk [32]. Since penetration of antibiotics to CF respiratory secretions was low [33], it was thought that a combination of oral and nebulized antibiotics would be preferable. Since Littlewood et al. [34] had shown that colistin inhalation reduced the number of lower respiratory samples containing *P. aeruginosa* in CF patients with early colonization and since development of resistance to that drug was rare [35] and colistin inhalation was already used for maintenance therapy of chronic infection [36], it was decided to combine nebulized colistin with oral ciprofloxacin in a randomized, controlled study compared to no treatment of CF patients with intermittent *P. aeruginosa* colonization [37]. The outcome was very encouraging, since it was possible to prevent chronic *P. aeruginosa* infection in 85% of the treated patients compared to only 42% in the non-treated patients ($p < 0.05$) (Fig. 1) [37]. Furthermore, a

Table 1
Improved prevention of chronic *P. aeruginosa* infection by early treatment of intermittent colonization [38]

- Introduction of "early treatment" according to a fixed treatment protocol
  - 1st isolate: 3 weeks inhaled colistin (1 mio. units b.i.d.)+oral ciprofloxacin (10–20 mg/kg b.i.d.)
  - 2nd isolate: 3 weeks inhaled colistin (2 mio. units t.i.d.)+oral ciprofloxacin (10–20 mg/kg b.i.d.)
  - 3rd and subsequent isolates: 3 months inhaled colistin (2 mio. units t.i.d.)+oral ciprofloxacin (10–20 mg/kg b.i.d.)

Table 2
Off-label use of colistin for inhalation and use of Tobi® in the Danish CF Center, Copenhagen

- R-60 high-flow®+Sidestream®, Ventstream®, Mediaid nebulisation chamber®, 8 L/min
- 10-min inhalation of bronchodilatory drug
- PEP mask for 10 min
- Off-label use of colistin 1–2 mio. units dissolved in 2–4 mL isotonic sterile saline is inhaled for 10–15 min t.i.d.
- Tobi® 300 mg b.i.d. for 1 month, Pari LC Plus® nebulizor for 15 min
- Cleaning of the inhalation equipment with 70% ethanol, or heating to 80 °C for 10 min, or boiling for 1 min

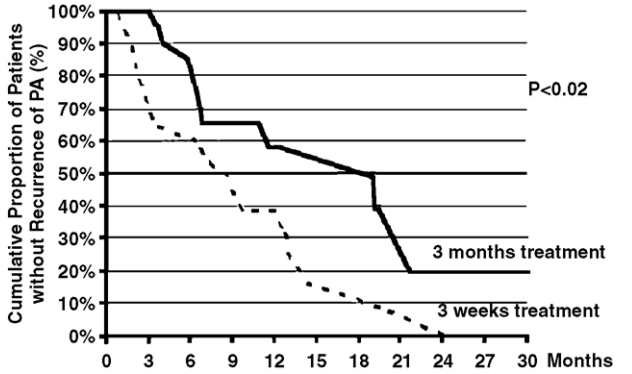

Fig. 2. Bacteriological results of treatment of intermittent *P. aeruginosa* colonization in CF patients with either 3 weeks or 3 months of oral ciprofloxacin and nebulized colistin. Forty-two patients were included in the study.

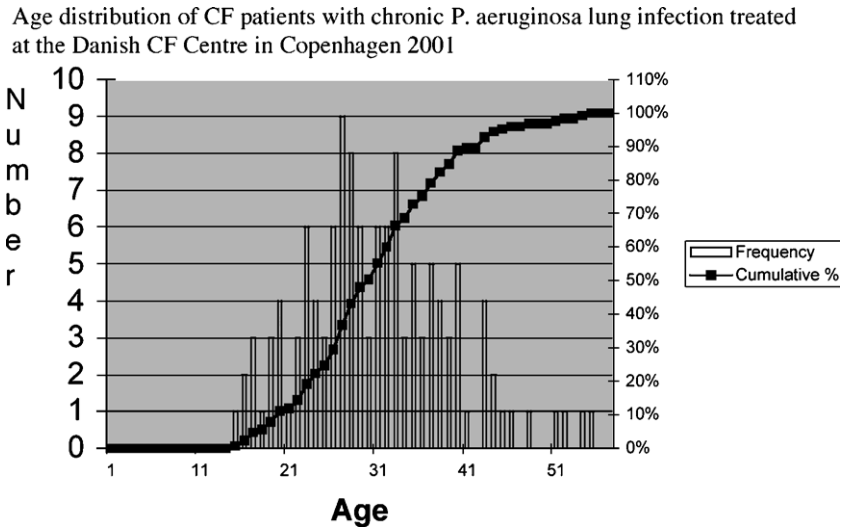

Fig. 3. Age distribution of CF patients with chronic *P. aeruginosa* lung infection treated at the Danish CF Center in Copenhagen 2001. The youngest patient with chronic *P. aeruginosa* infection was 14 years.

follow-up study from the Danish CF Center using historical controls showed that the results were consistent and correlated to improved lung function in the treated patients [38]. Since not all CF patients got rid of *P. aeruginosa* colonization, an intensified treatment protocol was developed (Tables 1–2) [38] which subsequently was shown to give a longer period free from *P. aeruginosa* until the next positive culture occurred (Fig. 2).

4. Changing epidemiology of chronic *P. aeruginosa* infection

The early aggressive therapy against intermittent *P. aeruginosa* colonization has been used since 1989 in the Danish CF Center and the results have completely changed the epidemiology of chronic *P. aeruginosa* lung infection in the Danish CF patients [30]. No CF infant or child has contracted chronic *P. aeruginosa* infection since 1990, and this infection is now only a problem in CF patients >14 years old (Fig. 3), and *P. aeruginosa* has not been replaced by chronic infections caused by other bacteria in CF children. The long-term results have now been confirmed by others [39,40].

5. Management of individual CF patients

Since CF patients may experience repeated intermittent *P. aeruginosa* colonization, they will be subject to repeated courses of anti-pseudomonal therapy, and measurements of the antibody response in such cases can be helpful in the management of the infection as illustrated in Figs. 4–5. Fig. 4 shows a patient who presented five *Pseudomonas*-positive cultures during 88 months and who was treated successfully with 3 weeks and 3 months courses of ciprofloxacin combined with colistin. The antibody response to *P.*

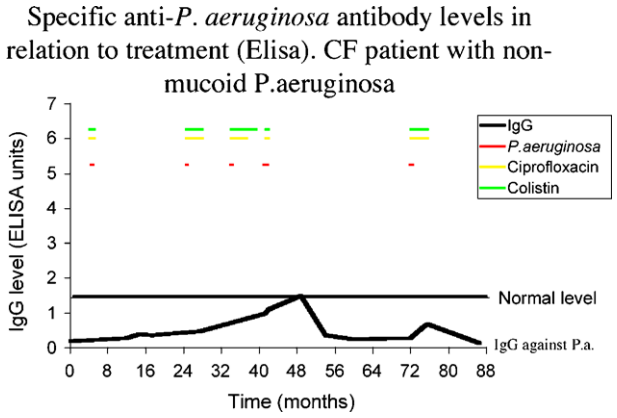

Fig. 4. Specific anti-*P. aeruginosa* antibody levels (ELISA) in relation to treatment of a CF patient with intermittent non-mucoid *P. aeruginosa* colonization.

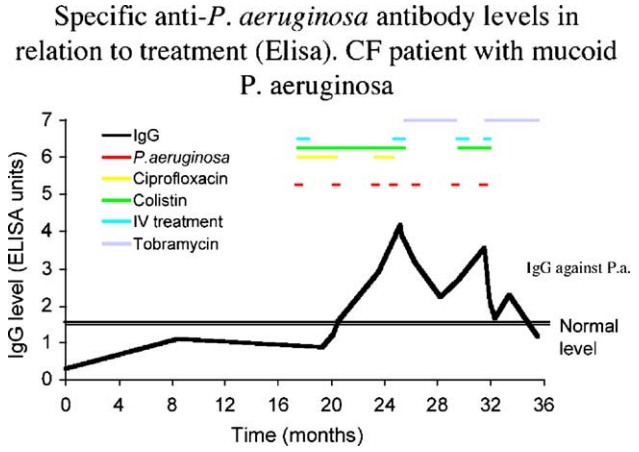

Fig. 5. Specific anti-*P. aeruginosa* antibody levels (ELISA) in relation to treatment of a CF patient with early chronic mucoid *P. aeruginosa* infection.

Table 3
Prevention of chronic *P. aeruginosa* infection by aggressive eradication of intermittent colonization is cost-effective in CF patients [4]

- Average cost for a CF pediatric patient in Germany: 24,000 Euro per year
- The annual cost for a CF paediatric patient with chronic *P. aeruginosa* infection is more than 3 times higher (36,400 Euro) than the cost for a CF paediatric patient without infection (10,900 Euro) and 2 times higher than intermittently colonized patients (17,500 Euro), based on the results in the CF Center in Hannover, Germany ($n=138$, 49% with chronic *P. aeruginosa* infection)
- Delaying onset of chronic *P. aeruginosa* infection with 1 year would save >25,000
  – 18,000 Euro per patient per year

aeruginosa as measured by ELISA [41] increased but never became significantly elevated and, eventually, the antibodies decreased. The second patient (Fig. 5) was more difficult since he initially was colonized with a mucoid *P. aeruginosa* strain and produced seven positive cultures within 18 months. He was therefore treated intravenously with tobramycin and anti-pseudomonal β-lactam antibiotics in addition to ciprofloxacin orally and colistin inhalation. In spite of the therapy, his antibody response became significantly elevated indicating chronic infection. After additional therapy including tobramycin inhalation (Table 2), he eventually got rid of *P. aeruginosa* and the antibody response decreased.

6. Lack of side-effects

In spite of the use of colistin and ciprofloxacin for early aggressive therapy against intermittent *P. aeruginosa* colonization for 15 years, there have been no antibiotic resistance problems in contrast to the situation in chronically infected CF patients [6,42]. The reason is most likely that the number of *P. aeruginosa* bacteria is lower during intermittent colonization and the probability of mutations therefore also lower. The patients have tolerated the therapy without major side-effects [36,37].

7. Use of other antibiotics for early eradication therapy

In addition to ciprofloxacin and colistin treatment of intermittent *P. aeruginosa* colonization, other antibiotics and protocols have also been used and proven to be effective, e.g., inhalation of tobramycin 80 mg b.i.d. for 1 year or 300 mg b.i.d for 28 days [8,43–49]. Subsequent typing of re-occurring *P. aeruginosa* strains showed that, in approximately 75%, it was a new strain [45].

8. Summary—the window of opportunity

The reason why the early aggressive eradication therapy of intermittent *P. aeruginosa* infection has been so successful is probably that it focuses on the only window of opportunity which exists before the chronic, mucoid biofilm-growing *P. aeruginosa* prevents successful eradication therapy of the lung infection in CF patients [48]. Furthermore, the successful therapy has drawn the attention of clinicians on the idea that CF bronchopulmonary disease is initiated by infection in the lower airways and is accompanied by airways obstruction as a later and presumably secondary feature [50,51]. It is therefore important that clinicians should focus more on early childhood prevention and treatment of lower respiratory tract infection and inflammation in CF, and in this respect, eradication of *P. aeruginosa* colonization has been proven to be very successful and cost-effective (Table 3) [4]. The early aggressive eradication therapy is therefore expected to contribute to the continuing improvement of the survival of CF patients [8,50,52]. A European Consensus Report has now recommended this approach [8].

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