

Cystic fibrosis in Copenhagen

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The past 30 years have witnessed a dramatic improvement in life expectancy and quality of life for patients with cystic fibrosis. This can be ascribed to improved management of bronchopulmonary infections, which cause premature loss of pulmonary function. The basis of management is a high level of clinical and microbiological surveillance coupled with aggressive antimicrobial treatment. In this article we summarise the key features of the current approach at the cystic fibrosis centre in Copenhagen, which manages 239 of the 291 Danish patients with cystic fibrosis and all five of the patients from the Faroe Islands.

All patients are seen regularly at monthly intervals, and nearly all admissions for treatment of pseudomonas infection are to our department. To avoid cross colonisation within the centre we categorise the condition of patients according to whether their sputum contains no *Pseudomonas aeruginosa* or contains sensitive *P aeruginosa*, multiresistant *P aeruginosa*, or *P cepacia*.¹ Each visit includes a clinical assessment, lung function determination, and culture of lower respiratory tract secretions. Chest radiography; assessment of mineral bone age in growing children; routine haematological tests; blood and urine chemical tests for evaluation of liver and kidney function; measurement of serum albumin concentration; immunoglobulin (IgG, IgM, IgA, and IgE) titres; acute phase reactants; titres of specific antibodies against common pathogens including fungi; and an oral glucose tolerance test (WHO standard criteria) are carried out at least once a year. All data are presented graphically on flow charts, including details of treatment.²

Specific antimicrobial treatment is instituted whenever pathogens are isolated, regardless of the clinical condition of the patient, usually for two weeks and at a high dosage.³ *Streptococcus pneumoniae* is treated with penicillin and *Haemophilus influenzae* with ampicillin. Erythromycin and other drugs are used in cases of resistance or drug hypersensitivity. Routine treatment of *Staphylococcus aureus* is two weeks of dicloxacillin and fucidic acid, and rifampicin with fucidic acid is given in cases of penicillin allergy or in the presence of rare isolates of dicloxacillin resistant *S aureus*.⁴ The overall eradication rate is 74%, regardless of the number of previous courses.⁴ In the event of failure prolonged treatment with these drugs or with clindamycin is used and sometimes methicillin by inhalation is tried.⁴ Less than 10% of patients will harbour *S aureus* for six months, and less than 1% for longer periods.⁴ We found that 41% of the 224 patients treated under our regimen had normal serum titres of specific *S aureus* antibodies and that the titres remained stable over many years, with no correlation between antibody values and long term prognosis.⁴

In older patients chronic infection with *P aeruginosa* is the main problem.¹ In 1975–6 we changed from “on demand” antibiotic treatment to regular two week courses every three months for all patients with chronic *P aeruginosa* infection,⁵ giving a combination of intravenous tobramycin and a suitable β lactam or oral fluoroquinolone. The rationale for this was based on studies of the immune mechanisms leading to tissue damage in patients with chronic infections.^{6,7} This change was followed by an improved prognosis from a five year survival rate of 54% after the onset of chronic *P aeruginosa* infection before regular treatment to a 10 year survival of 90%.⁸ Pulmonary function can now be maintained in most patients.⁸ In patients whose condition is unstable prolonged courses, shortened intervals, and oral fluoroquinolone treatment between courses are used,⁹ and most patients receive continuous inhalations with colomycin (1–2 MU twice daily).¹⁰ It should be emphasised that this intensive treatment has inherent problems. These are mainly bacterial resistance and hypersensitivity reactions.¹¹ Tobramycin toxicity has not yet become a major problem despite some patients’ having received more than 50 courses.¹²

Once established chronic *P aeruginosa* infection cannot be eradicated though efforts have been made to prevent its occurrence. Regular colistin inhalation in the early phase of colonisation decreases the number of isolates of *P aeruginosa*.¹³ We recently completed a trial of very early treatment with colistin inhalation and oral ciprofloxacin, which showed that the establishment of chronic infection can at least be postponed (unpublished data). If postponement or even prevention could indeed be achieved it would have far reaching implications for patients with cystic fibrosis.

Other pathogens may threaten the patient. Atypical mycobacteria sometimes cause pulmonary disease, although the infection rate does not seem to be higher than that in Danish children without cystic fibrosis (unpublished data). *Aspergillus fumigatus* commonly colonises the lungs in patients with cystic fibrosis and leads to a host immune response.¹⁴ Specific IgE and IgA antibodies seem to offer protection against colonisation,¹⁴ but a few patients react with a dual IgE and IgG response and suffer from clinical allergic bronchopulmonary aspergillosis.¹⁵

Positive expiratory pressure mask physiotherapy is standard in our patients, and the technique is checked at each outpatient visit. It seems to improve ventilation and reduce the volume of trapped gas¹⁶ by mobilisation of secretions.¹⁷

Obviously, adequate nutrition must be ensured. Whether active hyperalimentation leads to improved long term prognosis is, however, uncertain.¹⁸ We believe that weight loss most often reflects poor control of bronchopulmonary infection, as substantiated by the recent finding of raised concentrations of tumour necrosis factor α in patients with cystic fibrosis.¹⁹ Diabetes mellitus becomes an increasing problem as patients grow older, and

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impaired carbohydrate tolerance may be associated with progressive clinical deterioration.²⁰ A recent survey in our clinic showed that as many as 5% of patients above the age of 15 years will develop impaired glucose tolerance or insulin dependent diabetes each year.²¹

The spectacular recent advances in molecular genetics will lead, it is hoped, to improved and more direct corrective treatment of cystic fibrosis.²² The future also holds the hope of gene replacement therapy, but for thousands of current and prospective patients extension and improvement of our current management already offers hope of a normal lifespan and a full and rewarding life. It is important to acknowledge the support of the well organised and highly effective Danish lay organisation, which together with a highly developed social security system is of major importance in bringing about a high degree of parent and patient compliance.

- 1 Høiby N, Pedersen SS. Estimated risk of cross-infection with *Pseudomonas aeruginosa* in Danish cystic fibrosis patients. *Acta Paediatr Scand* 1989;78:395-404.
- 2 Schiøtz PO, Beck B, Pedersen M. How to evaluate clinical parameters at a glance. *Acta Paediatr Scand* 1982 (suppl 301):121-4.
- 3 Høiby N, Friis B, Jensen K, Koch C, Møller NE, Støvring S, Szaff M. Antimicrobial chemotherapy in cystic fibrosis patients. *Acta Paediatr Scand* 1982 (suppl 301):75-100.
- 4 Szaff M, Høiby N. Antibiotic treatment of *Staphylococcus aureus* infection in cystic fibrosis. *Acta Paediatr Scand* 1982;71:821-6.
- 5 Szaff M, Høiby N, Flensburg EW. Frequent antibiotic therapy improves survival of cystic fibrosis patients with chronic *Pseudomonas aeruginosa* infection. *Acta Paediatr Scand* 1983;72:651-7.
- 6 Høiby N, Schiøtz PO. Immune complex mediated tissue damage in the lungs of cystic fibrosis patients with chronic *Pseudomonas aeruginosa* infection. *Acta Paediatr Scand* 1982 (suppl 301):63-73.
- 7 Høiby N, Döring G, Schiøtz PO. Pathogenic mechanisms of chronic *Pseudomonas aeruginosa* infections in cystic fibrosis patients. *Antibiot Chemother* 1987;39:60-76.
- 8 Pedersen SS, Jensen T, Høiby N, Koch C, Flensburg EW. Management of *Pseudomonas aeruginosa* lung infection in Danish cystic fibrosis patients. *Acta Paediatr Scand* 1987;76:955-61.
- 9 Jensen T, Pedersen SS, Nielsen CH, Høiby N, Koch C. Comparison of the efficacy and safety of ciprofloxacin and ofloxacin in the treatment of chronic *Pseudomonas aeruginosa* in cystic fibrosis. *J Antimicrob Chemother* 1987;20:585-94.
- 10 Jensen T, Pedersen SS, Garne S, Heilmann C, Høiby N, Koch C. Colistin inhalation therapy in cystic fibrosis patients with chronic *Pseudomonas aeruginosa* lung infection. *J Antimicrob Chemother* 1987;19:831-8.
- 11 Koch C, Hjelt K, Pedersen SS, et al. Retrospective clinical study of hypersensitivity reactions to aztreonam and six other beta-lactam antibiotics in cystic fibrosis patients receiving multiple treatment courses. *Rev Infect Dis* (in press).
- 12 Pedersen SS, Jensen T, Osterhammel D, Osterhammel P. Cumulative and acute toxicity of repeated high-dose tobramycin treatment in cystic fibrosis. *Antimicrob Agents Chemother* 1987;31:595-9.
- 13 Littlewood JM, Miller MG, Ghoneim AT, Ramsden CH. Nebulized colomycin for early *Pseudomonas* colonization in cystic fibrosis. *Lancet* 1985;i:865.
- 14 Schönheyder H, Jensen T, Høiby N, Andersen P, Koch C. Frequency of *Aspergillus fumigatus* isolates and antibodies to *Aspergillus* antigens in cystic fibrosis. *Acta Pathol Microbiol Immunol Scand (Sect B)* 1985;93:105-12.
- 15 Schönheyder H, Jensen T, Høiby N, Koch C. Clinical and serological survey of pulmonary aspergillosis in patients with cystic fibrosis. *Int Arch Allergy* 1988;85:472-7.
- 16 Groth S, Stafanger G, Dirksen H, Andersen JB, Falk M, Kelstrup M. Positive expiratory pressure (pep-mask) physiotherapy improves ventilation and reduces volume of trapped gas in cystic fibrosis. *Bull Eur Physiopathol Respir* 1985;21:339-43.
- 17 Falk M, Kelstrup M, Andersen JB, et al. Improving the ketchup bottle method with positive expiratory pressure (PEP). *Eur J Respir Dis* 1984;65:423-32.
- 18 Corey M, McLaughlin FJ, Williams M, Levison H. A comparison of survival, growth, and pulmonary function in patients with cystic fibrosis in Boston and Toronto. *J Clin Epidemiol* 1988;41:583-91.
- 19 Suter S, Schaad UB, Roux-Lombard P, Girardin E, Grau G, Dayer J-M. Relation between tumor necrosis factor- α and granulocyte elastase- α 1-proteinase inhibitor complexes in the plasma of patients with cystic fibrosis. *Am Rev Respir Dis* 1989;140:1640-4.
- 20 Finkelstein SM, Wielinski CL, Elliott GR, et al. Diabetes mellitus associated with cystic fibrosis. *J Pediatr* 1988;112:373-416.
- 21 Lanng S, Thorsteinsson B, Erichsen G, Nerup J, Koch C. Glucose tolerance in cystic fibrosis. *Arch Dis Child* (in press).
- 22 Riordan JR, Rommens JM, Kerem B-S, et al. Identification of the cystic fibrosis gene: cloning and characterization of complementary DNA. *Science* 1989;245:1066-73.