Thorax

Editorials

Maintenance treatment of chronic *Pseudomonas aeruginosa* infection in cystic fibrosis

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Thirty years ago *Staphylococcus aureus* and not *Pseudomonas aeruginosa* was considered to be the most important lung pathogen in cystic fibrosis.[1] Those who believed that *P aeruginosa* was a pathogen in cystic fibrosis thought that various virulence factors such as exotoxin A, exoenzyme S, elastase, alkaline protease, phospholipase C, lipopolysaccharide and phenazine pigments were responsible for the lung tissue damage by drawing parallels with acute *P aeruginosa* infections in patients with burns or leukaemia.[2] Only acute exacerbations, frequently caused by a virus,[3] were therefore treated with antibiotics, although invasive disseminating *P aeruginosa* infection including bacteraemia was never found in cystic fibrosis.[4] However, a very pronounced antibody response to *P aeruginosa* antigens, including its virulence factors, was detected in patients with cystic fibrosis and the pathogenesis of the lung tissue damage was subsequently found to be caused by immune complex mediated inflammation dominated by polymorphonuclear leucocytes releasing proteolytic enzymes.[5–7] Since the annual mortality of cystic fibrosis patients with chronic *P aeruginosa* infection in the Danish Cystic Fibrosis Centre increased to nearly 20% in 1974, a comprehensive therapeutic approach was started to try to reduce the inflammation by (1) reducing the antigenic load by treating the patients with intravenous antibiotics regularly for two weeks every three months (maintenance therapy = chronic suppressive therapy), (2) reducing the antibody titres by plasmapheresis, and (3) the use of nebulised corticosteroids. The use of nebulised steroids was not successful at that time, probably because the dose of steroid used was too small[8]; a recent study with a larger dose was found to be effective in reducing inflammation.[9] Attempts to reduce the antibody titres by plasmapheresis were not successful as it was only possible to reduce the titre of anti-pseudomonas antibodies by 50–80% for a period of a few weeks (unpublished results). However, Szaff *et al*[10] found reduction of the antigenic load with intravenous antibiotics to be successful in 58 patients with cystic fibrosis (2.9 courses/year in 1976–80, approximately every three months) compared with 51 historical controls (one course/year in 1971–75 against acute exacerbations). This study included all patients with chronic *P aeruginosa* infection defined as an increase in the number of precipitating antibodies to these bacteria.[5] A follow up study in 1985[11] showed an increase from a five year survival of 54% to a 10 year survival of 90% from the onset of chronic *P aeruginosa* infection and a decrease in the annual mortality from 10–20% to 1–2%. The addition of nebulised colistin, prevention of cross infection in the clinic, and early aggressive treatment of the initial *P aeruginosa* infection further improved survival.[12]

In this issue of *Thorax* Elborn *et al*[13] report a prospective randomised multicentre study in which they compared elective and symptomatic treatment with intravenous antibiotics of cystic fibrosis patients infected with *P aeruginosa.* No benefit of the elective approach was found. This is hardly surprising since the difference in the amount of intravenous antibiotic used in the two groups of patients was only 45%, 24%, and 33% in the one, two, and three year periods of the study, whereas the difference in each year during the five year maintenance treatment period reported by Szaff *et al*[10] in 1983 was 190%. The bacteriological effect obtained by Szaff *et al*[10] was higher than that achieved in current studies, with 35–36% being free of *P aeruginosa* at the end of the treatment period, a few for up to three months.[10] This probably reflects the higher bacteriological efficacy of treating the chronic infection early[14] and the lower level of resistance 20–25 years ago.[15] Furthermore, whereas none of the patients in the study by Szaff *et al* received nebulised antibiotics, these were given to 40% of the symptomatic patients and 25% of the elective group in the study by Elborn *et al*, further decreasing the difference between the two arms of the study.[13] Another major difference between the two studies is the early treatment approach used by Szaff *et al.* All new chronically infected cystic fibrosis patients were treated regularly from the onset of the infection during the maintenance treatment period, since onset of infection before puberty was found to be associated with a poor prognosis,[10] and the major benefit on the survival of the patients was maintenance of lung function in the younger patients as confirmed by Elborn *et al.*[13]

Several reports have shown the benefit on lung function of the treatment of *P aeruginosa* infection in patients with cystic fibrosis[16 17] but, although the proteolytic activity in the lungs decreases during treatment, it is still significant between courses.[17] The addition of daily nebulised colistin[18] to the maintenance regime[12] or the use of four weekly cycles of on/off nebulised tobramycin[19] has further improved the maintenance of lung function in these patients, but a subsequent analysis of the placebo group in the study by Ramsey *et al*[19] showed that treatment of exacerbations only did not arrest the progressive decline in lung function in patients with cystic fibrosis.[20] An important conclusion of the study by Elborn *et al*[13] is the suggestion that many patients with advanced disease need 3–4 annual courses of antibiotics for respiratory exacerbations.

However, therapeutic findings from other studies indicate that the decline in lung function continues to take place between courses but can be diminished by the intensive use of nebulised antibiotics and steroids.[9 18 20] The major side effects of the intensive use of antibiotics in cystic fibrosis are the development of resistance, allergy to β-lactam antibiotics, possible ototoxicity and renal toxicity caused by aminoglycosides (although this has not yet been a significant problem), cost, and compliance of patients, as also reported by Elborn *et al*.[13] New efficient anti-pseudomonas antibiotics and new treatment strategies are therefore needed for patients with cystic fibrosis.[21–24]

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Diagnosis of lung cancer: FOB before CT or CT before FOB?

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Any patient presenting to a respiratory physician with a possible diagnosis of lung cancer requires a rapid and accurate histological diagnosis, together with enough staging information to enable a correct management plan to be arranged. Standards for these processes have been suggested.[1] In practice it is incumbent upon physicians to assess each case and to determine the optimum combination of sampling and imaging tests that will be likely to achieve a firm diagnosis and staging at the minimum inconvenience to his or her patients, and with a minimum of delay which is known to be very distressing to them.[2]

Since the advent of fibreoptic bronchoscopy (FOB) in 1974, and with its current very wide availability, most physicians would consider this as their first investigation after a clinical assessment and plain radiology. Selection would be influenced by the latter, so that lesions clearly falling into the category of small solitary pulmonary nodules would be far more likely to be investigated by computed tomographic (CT) scanning and fine needle aspiration biopsy (FNA). For lesions of less than 2 cm in diameter FNA is superior to bronchoscopy even if imaging is used to guide the transbronchial biopsy or transbronchial needle aspiration.[3 4]

The probability that a lesion, thought by a physician to be accessible to bronchoscopy, can actually be diagnosed in this way is not easy to ascertain. However, a recent UK multicentre prospective study of 1660 consecutive cases investigated by FOB because of a prior likelihood of lung cancer showed that a definite tumour was seen in 57%.[5] In a further 20% the appearances were very suggestive of a tumour. Thus, overall, one in five of these tests was negative. The proportion with a positive histological examination at bronchoscopy is likely to have been between 75% (diagnosis within seven days of bronchoscopy) and 85% (diagnosis up to 14 days). Only one in eight patients (15%) had had a prior CT scan, and whether or not this guided the bronchoscopist at all is not known.

This large study with a sensitivity for bronchoscopy of about 77% and a definite histological diagnosis rate of