Thorax

Editorials

Treatment of *Staphylococcus aureus* in cystic fibrosis

J S Elborn

A number of treatments for cystic fibrosis have evolved over the past four decades, based on the experience of clinicians involved in the care of these patients. Some of these treatments were developed without the benefit of large randomised controlled trials which would have been difficult to perform at the time. The value of prophylactic antibiotic treatment against *Staphylococcus aureus* in the management of infants and children is an example of a logical practice which has developed on the basis of experience, but which requires careful review as to its efficacy and potential deleterious effects.

Pulmonary infection with *S aureus* is a frequent problem in patients with cystic fibrosis, particularly during the first decade of life.[1] Cross sectional studies show that in this age group, 25–30% of patients culture *S aureus* from sputum.[2] This may be an underestimate as cough swabs in children unable to expectorate are often negative and infection may only be detected by bronchoalveolar lavage in such circumstances.[3] Infection with *S aureus* is usually associated with symptoms, but asymptomatic carriage is also common.

The approach to the treatment of patients with cystic fibrosis with *S aureus* infection of the airways varies.[4] In some centres patients are started on oral antistaphylococcal medication from diagnosis,[5] while in others continuous antimicrobial treatment is started when the first infection with *S aureus* occurs.[6] Treatment is then usually continued into adulthood and is not adjusted when *Pseudomonas aeruginosa* or other chronic Gram negative infection occurs.[5 6] Some centres only treat patients with an antistaphylococcal antibiotic for symptomatic exacerbations or if a sputum culture is positive, and treatment is continued until there is symptomatic improvement and eradication of the organism from sputum culture.[7] In these centres long term antibiotics are not used and fewer than 10% of patients become chronically colonised with *S aureus*.[1]

In the systematic review by McCaffery *et al*[8] in this issue of *Thorax* these approaches to treatment are explored. They conclusively confirm that antistaphylococcal treatment consistently achieves sputum clearance of *S aureus* in patients with cystic fibrosis. Several antibiotics appear to be effective in eradicating *S aureus*, though none of the studies compared antibiotic treatment with a placebo. McCaffery *et al* also conclude that prophylactic antistaphylococcal treatment in young children with cystic fibrosis is likely to be of clinical benefit. This conclusion is based mainly on a single study performed in 38 patients over two years by Weaver *et al*.[9] Long term prophylactic antibiotic treatment reduced the frequency of isolates of *S aureus* from sputum culture compared with intermittent therapy. The only clinical improvements in this study were a reduction in cough frequency and in the number of antibiotic courses and hospital admissions. Measurements of pulmonary function, which are difficult to perform in infants, were not significantly different.[10] Two other studies with similar numbers, though of a shorter duration, also failed to demonstrate any important clinical advantage in continuous over intermittent antimicrobial therapy.

A potential disadvantage of prophylactic antistaphylococcal treatment is the suggestion of early acquisition of *P aeruginosa* reported in two studies included in the review, though this was not seen in the study by Weaver *et al*. This organism is a key factor in the amplification of pulmonary inflammation and lung injury and is associated with a much worse prognosis than intermittent infection with *S aureus*. The evidence for a predisposition to *P aeruginosa* infection in patients on prophylaxis is weak but, if confirmed in an adequately powered study, the value of long term prophylactic antistaphylococcal treatment would be in considerable doubt. In addition, prophylaxis with cephalexin may result in a change from non-mucoid *P aeruginosa* to the more virulent mucoid phenotype which is associated with a poorer prognosis. There may therefore be a case for stopping such treatment after isolation of *P aeruginosa* from sputum.

A second problem with long term prophylaxis is the development of resistant strains. This is confirmed in the review by McCaffery *et al*.[8] Treatment with cephalosporins, macrolides, and tetracycline lead to increased resistance but this does not seem to be such a problem with flucloxacillin. Intermittent treatment is not associated with an increase in resistant organisms.[7]

It is therefore important for an adequately powered, randomised, placebo controlled trial to be performed comparing prophylactic treatment with careful intermittent antistaphylococcal therapy in patients with cystic fibrosis during the first five years of life. Preservation of lung function is the most relevant clinical end point currently available for short term assessment of treatment of lung disease in cystic fibrosis. A positive effect on lung function has not been reported for antibiotic prophylaxis against *S aureus*. The most effective and safe antibiotic should be chosen, and the evidence from this review suggests that flucloxacillin is likely to be the most appropriate one. Clinical and microbiological end points—particularly lung function, antimicrobial resistance, and rate of acquisition of *P aeruginosa*—would be important outcome measures. Such a study has been performed with cephalexin but unfortunately it was not reported in a peer reviewed journal and so is not included in the systematic review. It is quoted as a personal communication in a review of the management of cystic fibrosis in which it is indicated that prophylaxis for 5–7 years results in no clinical advantage compared with intermittent therapy other than a reduction in *S aureus* infection, but at the cost of an increase in *P aeruginosa* infection.[11]

Antibiotic prophylaxis for *S aureus* has not been shown conclusively to be more effective than prompt treatment of symptoms or positive sputum culture and may have

important detrimental effects. We should aim to keep all patients with cystic fibrosis free from pulmonary infection with *S aureus*, but this should not be at the expense of early acquisition of *P aeruginosa* which may worsen prognosis.

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Duplicate publication, redundant publication, and disclosure of closely related publications

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We have recently become aware of two cases of publication of closely related data in papers submitted concurrently to *Thorax* and to another journal, without disclosure of the existence of the related paper. One of these concerns papers by Girault *et al*[1 2] and relates to a study of two forms of assisted ventilation in which the data published in *Thorax*[1] represent part of a study also published in *Chest*.[2] In the review process of the *Thorax* paper, which dealt with characteristics of assist control ventilation in patients with COPD, the associate editor and external reviewers all commented on the fact that data comparing assist control ventilation with pressure support ventilation would enhance the paper, and this comment was forwarded with other feedback to the authors. The authors duly responded with a revised manuscript which did not include pressure support ventilation data, and did not disclose either in the manuscript or in the accompanying covering letter that a comparison of assist control and pressure support ventilation in these patients was, in fact, available and contained in a paper already under consideration (and subsequently published) by *Chest*. We consider this to represent duplicate and/or redundant publication, with failure by the authors to disclose the existence of related additional data from the same study to us.

The other case relates to papers on the presence and potential source of matrix metalloproteinases in bronchoalveolar lavage samples from patients with emphysema and healthy controls published by Finlay *et al* in *Thorax*[3] and in the *American Journal of Respiratory and Critical Care Medicine*.[4] These two papers, which present results of different analyses relating to closely related hypotheses carried out on biological samples from the same cases, were under consideration by the two journals concurrently without disclosure of the existence of either related publication to either journal editor. It is our opinion that the common origin of the samples used in these studies should have been acknowledged, and that the existence of another closely related manuscript with another journal should have been disclosed explicitly to both journal editors.

As editors we understand that multiple analyses or investigations of existing datasets or biological resources are commonplace, and would regard this to be perfectly acceptable so long as this is made clear in the manuscript. Disclosure is crucial in these circumstances, however, so that editors and readers know that samples or data used in different papers are not independent and can interpret findings accordingly. We ask all authors submitting papers to *Thorax* to inform us of any related publications and submissions to other journals, at any stage of the review process of papers being considered by *Thorax*.

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Executive Editors

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