

## 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.<sup>1</sup> Cross sectional studies show that in this age group, 25–30% of patients culture *S aureus* from sputum.<sup>2</sup> 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.<sup>3</sup> 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.<sup>4</sup> In some centres patients are started on oral antistaphylococcal medication from diagnosis,<sup>5</sup> while in others continuous antimicrobial treatment is started when the first infection with *S aureus* occurs.<sup>6</sup> Treatment is then usually continued into adulthood and is not adjusted when *Pseudomonas aeruginosa* or other chronic Gram negative infection occurs.<sup>5, 6</sup> 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.<sup>7</sup> In these centres long term antibiotics are not used and fewer than 10% of patients become chronically colonised with *S aureus*.<sup>1</sup>

In the systematic review by McCaffery *et al*<sup>8</sup> 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*.<sup>9</sup> 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.<sup>10</sup> 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*.<sup>8</sup> 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.<sup>7</sup>

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.<sup>11</sup>

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.

J S ELBORN

Adult Cystic Fibrosis Centre,  
Belfast City Hospital,  
Belfast BT9 7AB, UK

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- 8 McCaffery K, Oliver RE, Franklin M, et al. Systematic review of antistaphylococcal antibiotic therapy in cystic fibrosis. *Thorax* 1999;54:000-0.
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## Duplicate publication, redundant publication, and disclosure of closely related publications

John Britton, Alan J Knox

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*<sup>1</sup> and relates to a study of two forms of assisted ventilation in which the data published in *Thorax*<sup>1</sup> represent part of a study also published in *Chest*.<sup>2</sup> 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*<sup>3</sup> and in the *American Journal of Respiratory and Critical Care Medicine*.<sup>4</sup> 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*.

JOHN BRITTON  
ALAN J KNOX

Executive Editors

- 1 Girault C, Chevron V, Richard J-C, Daudenthun I, Pasquis P, Leroy J, Bonmarchand G. Physiological effects and optimisation of nasal assist-control ventilation for patients with chronic obstructive pulmonary disease in respiratory failure. *Thorax* 1997;52:690-6.
- 2 Girault C, Richard J-C, Chevron V, Tamion F, Pasquis P, Leroy J, Bonmarchand G. Comparative physiologic effects of noninvasive assist-control and pressure support ventilation in acute hypercapnic respiratory failure. *Chest* 1997;111:1639-48.
- 3 Finlay GA, Russell KJ, McMahan KJ, D'arcy EM, Masterson JB, Fitz-Gerald MX, O'Connor CM. Elevated levels of matrix metalloproteinases in bronchoalveolar lavage fluid of emphysematous patients. *Thorax* 1997;52:502-6.
- 4 Finlay GA, O'Driscoll LR, Russell KJ, D'arcy EM, Masterson JB, Fitz-Gerald MX, O'Connor CM. Matrix metalloproteinases expression and production by alveolar macrophages in emphysema. *Am J Respir Crit Care Med* 1997;156:240-7.

# Imaging in the evaluation of emphysema

R J H Robertson

The role of imaging in the assessment of emphysema has assumed increased importance since the advent of surgery as one of the potential therapeutic options. The chest radiograph had tended to be dismissed because it did not correlate well with pulmonary function tests, but pulmonary function tests may be normal in mild emphysema.<sup>1</sup> The chest radiograph may be normal too, but more often in chronic bronchitis than in true emphysema. Signs of hyperinflation include a flattened diaphragm, particularly one depressed to the level of the seventh rib anteriorly or below, while on the lateral film there may be an increased anteroposterior diameter of the chest and increased retrosternal and retrocardiac lucency. Other signs of emphysema include peripheral pruning of vessels, although this is lost with the onset of cor pulmonale when the vessels appear to become more numerous and larger.<sup>2 3</sup>

Ventilation and perfusion isotope scanning have been used for some years to assess patients with limited cardiorespiratory reserve undergoing lung resection for carcinoma, when the percentage contribution of different areas of the lung can be calculated to predict postoperative lung function. As perfusion scanning alone correlates with pulmonary function tests, the ventilation scan may not be required.<sup>4</sup> More recent studies<sup>5 6</sup> have shown that single photon emission computed tomographic (SPECT) scanning, possibly with surface rendered images, can provide further detail in patients being assessed for lung volume reduction surgery (LVRS).

Computed tomographic (CT) scanning has advanced the radiographic investigation of emphysema by demonstrating areas of low attenuation along with reduction in the vessels. Different thresholds have been used to define the level below which emphysema is said to be present, ranging from -900 HU to -960 HU. CT scans also give information on the type of emphysema. Paraseptal emphysema is represented by a series of thin walled cysts that affect the peripheral 1-2 cm of the lung. This type of emphysema does not usually affect respiratory function, except that these thin walled cysts may enlarge to become significant bullae. Spontaneous pneumothorax may occur. In comparison, centrilobular (CLE) and panlobular emphysema (PLE) do affect lung function once a significant proportion of the lung is affected. CLE is the more common type and tends to occur in the upper third of the lungs, while PLE occurs more commonly in the lower third of the lung. Alpha-1-antitrypsin deficiency is one of the causes of PLE. In the early stages of CLE involvement of the central portion of the lobule is seen which progresses to involve the entire lobule as the disease becomes worse. PLE affects the whole lobule and mild cases may be difficult to distinguish from normal lung, but as it progresses the low attenuation areas and the reduction in vessels become more obvious. Recent studies have correlated the distribution of emphysema with their effect on lung function and in this issue of *Thorax* Nakano *et al* have contributed further to this knowledge.

In assessing patients for LVRS several papers have correlated the findings of preoperative radiology with outcomes.<sup>8-11</sup> Hyperinflation must be present and this is best shown by the plain film. Factors favouring a good outcome include upper lobe emphysema and marked heterogeneity in the pattern of emphysema, although

Gierada *et al*<sup>6</sup> emphasise that quantification of heterogeneity is difficult. Whilst uniformly severe emphysema represents low heterogeneity, and large bullae with normal lungs elsewhere represent high heterogeneity, in between these extremes visual assessment is subjective and more quantitative work of the type performed by Nakano *et al* is required. Part of the reason why upper lobe emphysema is more favourable in LVRS is that it has been shown, by a comparison of HRCT scanning with pulmonary function tests, that lower zone emphysema affects lung function more than upper zone emphysema.<sup>12</sup> Nakano *et al* found that the inner half of the lung is more often affected by emphysema than the outer half, and that abnormality of the inner segment may have a greater effect on lung function. This could usefully be studied in relation to outcomes in LVRS. Whilst reviewing HRCT scanning, negative factors affecting outcomes such as pleural disease and bronchiectasis should be noted. The HRCT scan should be supplemented by either consecutive thick section or spiral CT scans to search for lung nodules. In 148 patients Rozenshtein *et al*<sup>13</sup> found pulmonary nodules in 11% of their patients, and just under half of these (5%) were found to be stage 1 lung cancers. These nodules can be resected at the time of LVRS.

Radiographic assessment is only part of the work up of patients with emphysema for LVRS. Nevertheless, the role of imaging is emphasised by these recent papers correlating outcomes of surgery with radiographic findings. By further subdividing the lung into inner and outer segments the work by Nakano *et al* may in time further refine the role of imaging in patient selection for LVRS.

R J H ROBERTSON

*The General Infirmary at Leeds,  
Great George Street,  
Leeds LS1 3EX,  
UK*

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