Prospective randomised study to compare empirical treatment versus targeted treatment on the basis of the urine antigen results in hospitalised patients with community-acquired pneumonia

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Community-acquired pneumonia (CAP) is often misdiagnosed and improperly treated. Since it is not a reportable disease we do not have exact figures, but data from the USA suggest that there are approximately four million cases per year resulting in more than 600 000 hospitalisations, 64 million days of restricted activity and 45 000 deaths annually. The overall yearly cost associated with CAP is estimated at US\$9–10 billion.

The lack of rapid, sensitive and specific methods to diagnose the aetiological pathogen in a particular patient with CAP means that the physician must often institute antimicrobial treatment without knowing with any degree of certainty what the pathogen is. Given the large number of potential aetiological agents—such as bacteria (*Streptococcus pneumoniae*, *Haemophilus influenzae*, *Staphylococcus aureus*), atypical organisms (*Mycoplasma pneumoniae*, *Chlamydophila pneumoniae*, *Legionella* species) and viruses—this represents a significant problem, particularly for patients ill enough to require admission to hospital.

A careful history and physical examination plus laboratory tests and procedures such as sputum Gram stain and culture, blood cultures and chest radiography have been shown to be unreliable in identifying the pathogen responsible for pneumonia in most patients with CAP.

Streptococcus pneumoniae, which is arguably the most important cause of CAP, can be particularly difficult to diagnose. Its identification in sputum may simply represent colonisation and its isolation

from blood is woefully insensitive.¹ The diagnosis of Legionnaire's disease in patients with CAP is dependent upon culture and serological testing, both of which have their problems.² The development of urinary antigen tests for both pneumococcal and *Legionella* antigens has helped to expedite and improve the diagnostic process. The overall sensitivity of the pneumococcal urinary antigen test is <80%, but can reach 90% or higher in patients with pneumococcal bacteraemia and those with high-risk pneumonia.³ The specificity in adult patients with CAP can exceed 95%.^{4–5} False positives have been seen in children with chronic respiratory disease colonised with *S pneumoniae* and in patients who had a prior episode within the previous 3 months.⁶

Urine antigen tests available for *Legionella* only detect *L pneumophila* serogroup 1. The tests have a sensitivity of 70–90% and a specificity approaching 99% for this particular pathogen.

One of the main issues in the treatment of CAP is whether empirical therapy or pathogen-directed therapy is better. Now that at least some reasonably rapid diagnostic tests such as the urinary antigen tests described above are available, studies can be carried out to assess the merits of an empirical versus a directed treatment approach.

Arguments in favour of an empirical approach include: (1) the aetiological pathogen is not known with certainty; (2) there may be multiple pathogens in a particular patient; and (3) combination treatment may provide a benefit in certain cases, while those in favour of a directed treatment approach include: (1) less antibiotic selection pressure; (2) may lessen antimicrobial resistance development; and (3) lower costs.

My own feeling is that, for sicker patients in particular, the arguments in support of empirical treatment prevail. We certainly know that, in most cases, the cause of the pneumonia is unknown when the patient is first seen and assessed. We also know that, in certain patients, more than one pathogen may be found which implies that broader antimicrobial coverage may be required. What complicates the argument in support of directed treatment somewhat is the fact that, for pneumococcal bacteraemia, there are data from a number of studies which suggest that combination treatment, particularly with a β -lactam and a macrolide, result in better outcomes.^{7–9} A number of explanations have been offered to account for these findings, including an additive or synergistic effect, the role of microbial tolerance, the presence of unsuspected pathogens or an immunomodulatory effect by the macrolides.

Many of these considerations plus data from a large number of clinical trials dealing with treatment of CAP helped in formulating the various treatment regimens suggested by the Infectious Diseases Society of America/American Thoracic Society CAP guidelines.¹⁰

The study by Falguera *et al*¹¹ in this issue of *Thorax* (see page 101) is an interesting one and their goals are laudable. Essentially, the authors were attempting to determine whether or not results from urine antigen tests can be used as the basis of antimicrobial treatment for hospitalised patients with CAP. They used a number of end points including both clinical and economic outcome measures and concluded that the information derived from such antigen testing “does not provide benefits in terms of patient outcome or cost effectiveness”. As they point out, very few studies in the published literature have attempted to address the question of empirical versus targeted treatment based on urinary antigen testing.

A study by Guchev *et al*¹² involving military trainees in Russia and focusing on *S pneumoniae* found no statistically significant difference between empirical treatment with a macrolide (clarithromycin) and targeted treatment with amoxicillin. However, the study did not use a randomised design and virtually all patients had only mild to moderate disease.

A randomised controlled trial by van der Eerden *et al*¹³ was based on both pneumococcal and *Legionella* urinary antigens. The authors concluded that empirical antibiotic treatment has comparable

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clinical efficacy to pathogen-directed treatment. However, fewer than 50% of the patients had pneumonia severity indices of class IV or V.

There are a number of issues that must be taken into account when considering the conclusions of Falguera *et al.* These have to do with the treatment and randomisation plans and the sample size. It appears that, of the 177 patients studied, all were treated at the outset of the study with a β -lactam plus azithromycin or a respiratory fluoroquinolone. Only when clinically stable 2–6 days after admission was assignment to an empirical or targeted treatment regimen carried out based on the results of the urine antigen tests. Since the results of such tests are usually available within a few hours, why was a decision not made much sooner? Also, although the term “severe CAP” is often used in this study, only one patient required admission to an ICU. For most patients with CAP admitted to a hospital ward and not requiring ICU treatment, either regimen mentioned above would be effective assuming that there are no significant resistance issues. This means that, before receiving the first dose of a pathogen-directed regimen, the 25 patients with antigen positive results would have received multiple doses of appropriate antimicrobial therapy. This clearly would have a confounding effect on the outcome and make it difficult (if not impossible) to assess any targeted treatment effects.

The sample size was also small and no sample size calculations were provided. Overall, there were only 177 patients in the study and only 25 in the targeted treatment arm. These numbers certainly suggest that a negative result may be because of a type II error.

There is one statistically significant difference noted—namely, with clinical relapse as the outcome. Three of the 152

patients (2%) in the empirical treatment arm relapsed compared with three of 25 patients (12%) in the targeted treatment arm. However, in one of the three patients treated with amoxicillin for a positive urine antigen for *S pneumoniae*, amoxicillin resistant *Escherichia coli* was isolated from the blood. The authors speculate as to whether the antigen test result was a false positive or whether a dual infection (*S pneumoniae*, *E coli*) existed.

Although they certainly deserve credit for trying, the study by Falguera *et al* unfortunately does not satisfactorily answer the question as to whether or not the results of urine antigen tests can be used to direct antimicrobial treatment regimens. What is needed are studies that address this question but which use a design that will minimise confounding issues and maximise potential benefits to be accrued from these rapid diagnostic tests. A much shorter duration of initial treatment consisting perhaps of only one dose should be used, and then urine antigen test results may be employed as the basis for continuation with an empirical antimicrobial regimen or switching to directed therapy.

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