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# Biomarkers and community-acquired pneumonia

Jeremy S Brown

Community-acquired pneumonia (CAP) is common, and the delivery of optimum care to patients with CAP is important to limit the associated substantial mortality and morbidity. Although severity assessment of patients presenting with CAP using clinical scores such as the CURB65 (Confusion, Urea nitrogen, Respiratory rate, Blood pressure, 65 years of age and older) or Pneumonia Severity Index (PSI) scales aids management, there are many other areas in which the care of patients with CAP could be improved. For example, improved accuracy of identifying patients at risk of death (especially the significant proportion of deaths in patients with low clinical severity scores) or complications such as empyema would improve the stratification of patients for different intensities of management, and there are few data on how to decide the duration of antibiotic treatment for individual patients. Biomarkers may help with some of these questions, and in this month's *Thorax* there are two articles (*see pages 587* and *pages 592*) on the use of biomarkers in patients with CAP<sup>1,2</sup> that join a series of often seemingly contradictory papers in this area published over the past few years. What are the main overall messages that can be concluded from the published research into biomarkers and CAP, and are their results convincing enough now to influence how patients with CAP are managed?

The National Institutes of Health definition of a biomarker is: "a characteristic that is objectively measured and evaluated as an indicator of normal biologic processes, pathogenic processes,

or pharmacologic responses to a therapeutic intervention." However, this definition would include clinical parameters such as temperature or respiratory rate, and in general a biomarker is given a narrower definition of a biochemical feature that can be used to diagnose or assess the progress of disease or the effects of treatment. As such, blood urea levels for the CURB65 score and PaO<sub>2</sub> (arterial oxygen tension), pH and blood chemistry results for the PSI are examples of biomarkers already incorporated into guidelines for the management of CAP. In contrast, most recent research into biomarkers for CAP has concentrated on the markers of inflammation C-reactive protein (CRP) and procalcitonin (PCT).<sup>1–8</sup> Both CRP and PCT are acute phase reactants with low circulating levels normally, but which rapidly increase during inflammatory disease sometimes to markedly high levels. CRP is produced by the liver in response to proinflammatory cytokines (especially interleukin 6 (IL6)), and PCT is produced by the liver, kidneys and monocytes after stimulation by proinflammatory cytokines and by bacterial products. Importantly, both can be measured relatively cheaply and quickly, although CRP measurement is routinely available more widely than PCT. Various cytokines (eg, tumour necrosis factor  $\alpha$ , IL1, IL6, IL8 and IL10), free cortisol and a range of alternative prohormones to PCT (eg, proatrial natriuretic peptide, provasopressin and proadrenomedullin) have also been assessed as biomarkers of inflammation in patients with CAP,<sup>9–11</sup> but the data on these are limited compared with those for CRP and PCT, and their measurement is generally not routinely available.

What are the potential roles for biomarkers of inflammation in managing CAP? Biomarkers could be helpful in

several areas, including: (1) confirming the diagnosis of CAP; (2) identifying the potential causative agent; (3) assessing severity, mortality risk and the potential for complications; and (4) identifying when a patient is better, or conversely identifying those with complications. In addition, biomarkers may be able to identify which severely unwell patients are most likely to benefit from new therapeutic interventions based on immunomodulation, such as activated protein C treatment, but at present this is not possible and will be discussed no further in this editorial.

A significant infection such as CAP should almost always lead to the release of proinflammatory cytokines, which will in turn cause an increase in biomarkers of inflammation. Biomarkers of inflammation would perhaps then be a more reliable indicator of infection than a pyrexia or raised white cell count, and several studies have looked at the utility of CRP and PCT for assisting the diagnosis of CAP.<sup>8,12</sup> These studies suggest that, as expected, a diagnosis of CAP is unlikely unless there has been a significant increase in CRP or PCT (eg, >40 mg/l or 0.1  $\mu$ g/l, respectively). Conversely, in patients with a clinical suspicion of CAP the diagnosis is very likely if the patient has very high CRP or PCT levels (eg, >200 mg/l or 1.0  $\mu$ g/l, respectively).<sup>8</sup> However, in most patients, a clinical diagnosis of CAP is not difficult and will often be made without the benefit of blood test results, so the utility of a biomarker of inflammation to support the diagnosis of CAP may be limited to specific situations. These might include patients who are afebrile at presentation, in whom a raised CRP or PCT could confirm the possibility of infection, or patients with underlying parenchymal lung diseases such as idiopathic pulmonary fibrosis in whom the clinical or radiological evaluation of the presence of new consolidation is difficult. At present, data on the role of biomarkers in these specific clinical scenarios are lacking.

Biomarkers of inflammation may help indicate the causative organism in CAP.

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Infections with extracellular bacteria such as *Streptococcus pneumoniae* and *Staphylococcus aureus* are particularly proinflammatory, compared with fastidious organisms such as *Mycoplasma* and *Chlamydia*. In addition, PCT release is reduced by cytokines produced in response to viral infections.<sup>12</sup> Hence lower levels of biomarkers of inflammation might suggest viral, *Mycoplasma* or *Chlamydia* CAP, and very high levels suggest infection with *S pneumoniae* or *S aureus*. However, in practice, there is marked overlap in CRP and PCT levels in patients with CAP caused by the different microorganisms, and it is unlikely that a single biomarker of inflammation will be discriminatory enough to target antibiotic treatment to specific organisms.<sup>13, 14</sup> More effective biomarkers for identifying the aetiology of CAP could be unusual intermediate metabolites whose levels are altered by a specific microorganism (as shown for *Pneumocystis*),<sup>15</sup> or a proteomics approach to analyse simultaneously a wide variety of host and microbial products that might give a characteristic signature pattern for particular microbial species.

The majority of the recent articles on biomarkers of inflammation and CAP have investigated their role for assessing CAP severity and predicting outcome. The rationale for this use of biomarkers of inflammation is that higher levels of inflammation reflect either a greater bacterial load (so a more severe infection) or an excessive inflammatory response that will have negative effects on the host by driving more extensive consolidation or contributing to the pathophysiology of septic shock. The study by Menendez *et al*<sup>2</sup> adds to the increasingly extensive literature on the role of biomarkers of inflammation for assessing the severity of CAP and predicting mortality.<sup>3–6, 8–10, 16</sup> The first message to draw from this report is that in patients with CAP the levels of CRP or PCT gave just as good information as measuring cytokine levels, suggesting that there is no advantage in performing expensive and technically challenging cytokine measurements over measuring CRP or PCT. The second message is that in patients with CRP levels >250 mg/l and a CURB65 (Confusion, Respiratory rate, Blood pressure, 65 years of age and older) or CURB65 score of 3+, the mortality was around 15% greater than for patients with a CRP <250 mg/l. In patients with a PSI score of IV or V the differences were 8.4% and 11.4%, respectively. These data support the findings of Chalmers *et al* who recently reported that

a CRP <100 mg/l is a strong negative predictor for mortality,<sup>3</sup> and of other investigators who have shown associations between high levels of PCT and other biomarkers of inflammation with mortality.<sup>4, 5, 9, 10, 16</sup> Interestingly, a low level of PCT was associated with a low mortality even in patients at high risk according to their PSI score.<sup>4</sup> Taken together, these data provide strong evidence that biochemical evidence of a strong inflammatory response identifies high risk patients with CAP. Which biomarker and what cut-off points are the most effective independently or in conjunction with clinical scoring is not yet clear. Some differences between biomarkers are apparent—for example, repeated studies show that PCT levels, but curiously not CRP levels, correlate well with CURB65, CURB65 or PSI score, suggesting that PCT could be a viable alternative to clinical scoring for overall risk stratification.<sup>2, 4, 5</sup> Another important question is whether the usefulness of biomarkers of inflammation for predicting mortality is limited to high risk groups (eg, CURB65 scores 3+), or whether they could be used to stratify patients with CAP with low clinical severity scores further into high and low risk groups.

The study by Chalmers *et al*<sup>1</sup> suggests a clinical scoring system for identifying patients at risk of developing complicated parapneumonic effusion and empyema, one of the most common complications of CAP.<sup>1</sup> An important component of this score is CRP, with almost all patients with complicated parapneumonic effusions or empyemas having a CRP >100 mg/l on admission. These data support previous publications showing strong associations between high levels of biomarkers of inflammation and complications of CAP.<sup>3, 6</sup> Furthermore, previous publications by Menendez *et al* and Chalmers *et al* show that persisting high levels of CRP levels (presumably due to ongoing inflammation and probable infection) 3 or 4 days, respectively, after admission is a marker for complications or treatment failure of CAP.<sup>3, 6</sup> Hence repeating the measurement of CRP could identify patients with CAP who are failing to respond to treatment, who would then be investigated for complications such as complicated parapneumonic effusion and empyema and/or have their treatment altered. The concept that normalisation of the levels of biomarkers of inflammation indicates treatment success has been developed further by Christ-Cain and colleagues in a potentially very important controlled trial in which the duration of antibiotic treatment for CAP was

determined by PCT levels measured on days 1, 4, 6 and 8.<sup>7</sup> In the active arm, antibiotic treatment was discouraged once PCT levels were <0.25 µg/l, and for patients in this arm of the study the median duration of antibiotic treatment was 5 days compared with 12 days for the control arm. Despite these large differences in antibiotic use, there were no differences in clinical outcome between the groups. How long patients with CAP should be treated with antibiotics is not clear, and these data suggest that using biomarkers of inflammation to tailor antibiotic treatment could avoid the risks of undertreating some patients whilst substantially reducing overall antibiotic use.

Should the management of CAP be modified to take account of these recent data on biomarkers of inflammation? Although much of the research on biomarkers does not address how these tests can be used in practice, the papers in this edition of *Thorax* in conjunction with other recent publications do provide important pointers on how biomarkers of inflammation could be used to improve management of CAP. The new data suggest that high levels of biomarkers of inflammation in conjunction with clinical scoring using CURB65 or PSI could help further characterise patients at risk of death and other complications, and, furthermore, that repeat measurements (at least for CRP) can identify patients who are likely to develop complications such as empyema. Directed use of biomarkers could also safeguard against errors in the care of patients in whom the clinical assessment has been suboptimal. Perhaps a future guideline would suggest measurement of CRP or PCT (whichever is locally available) on admission to strengthen the basis for the diagnosis of CAP (eg, CRP >40 mg/l), and to help stratify patients at low risk (eg, CRP <100 mg/l) or high risk (eg, CRP >250 mg/l). Persisting high levels of the inflammatory biomarker 4 days after admission would then identify patients requiring longer than a 5 day course of antibiotics and who also need investigations for complications. This use of biomarkers may not be too different from the present practice of many clinicians, but would have more clearly defined implications for patient management at each stage. Exactly which biomarker is most appropriate and what cut-off levels should be used to affect the management decisions requires further clarification. Furthermore, any changes to CAP guidelines to include the use of biomarkers along the lines described above would

ideally need support from prospective trials.

**Competing interests:** None.

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# Breast feeding and childhood asthma

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Asthma is the most chronic disease of childhood and the leading cause of morbidity in children globally as measured by emergency department visits, hospitalisations and days of missed school.<sup>1</sup> Susceptibility to asthma may be increased by factors present early in life, including low birth weight, preterm birth, young maternal age and male gender. Environmental allergens including household smoking, house dust mite, grasses or pollens are also implicated. Conversely, early exposure to respiratory infections may be protective, although certain infections are suspected to increase the risk. Against this complex aetiological background, there is some evidence that breast feeding may protect against the development of asthma in children.<sup>2–3</sup>

In this issue of *Thorax*, a birth cohort study by Scholtens and colleagues assesses whether the association between breast feeding and asthma measured longitudinally from 1 to 8 years of age is influenced by maternal and paternal allergy (*see page 604*). The main finding of the study confirmed that breast feeding for >16 weeks was significantly associated with

reduced asthma prevalence from 3 to 8 years without evidence of attenuation and regardless of family history.<sup>4</sup>

The study population consisted of 3963 Dutch children born in 1996/1997 who participated in the Prevention and Incidence of Asthma and Mite Allergy (PIAMA) birth cohort study and who were followed every year for 8 years. Asthma was defined as at least one attack of wheeze and/or dyspnoea and/or prescription of inhalation steroids in the last year. Chronic asthma was defined as asthma diagnosis at 8 years with asthma diagnosis in at least two other years. Specific immunoglobulin E (IgE) to common airborne allergens and bronchial hyper-responsiveness were measured according to a standard protocol. Breast feeding was measured at 3 months and at 1 year, and was defined as the duration of any breast feeding (no breast feeding, 1–16 weeks breast feeding and breast feeding for >16 weeks). In this study, the investigators took advantage of the longitudinal analytical method of generalised estimating equations (GEE) to study the associations between breast feeding and repeated measures of the respiratory outcomes every year until 8 years of age. Adjustment was made in all models for child age, gender, maternal and paternal allergy, maternal education and smoking during pregnancy, as well as current

parental smoking. In addition, the analysis was stratified by maternal and paternal allergy. Missing data were imputed several times because 10% of baseline data were missing in this study and imputation did not make any difference to the final outcome of the study.

Scholtens and colleagues found that asthma risk was lower in children breast fed for >16 weeks compared with those not breast fed. Children breast fed for the longer duration had significantly fewer chronic asthma symptoms, and having an allergic or non-allergic mother did not change these associations. Breast feeding for >16 weeks was inversely associated with sensitisation to airborne allergens at 8 years, although this was not significant, and there was no association observed for bronchial hyper-responsiveness. From ages 3 to 8 years, breast feeding was associated with a lower asthma risk at all years, and maternal or paternal allergy did not affect the association between breast feeding and asthma. Because breast feeding has been associated with protection against early respiratory infections,<sup>5</sup> the observed association between breast feeding and asthma at early ages may be mediated by the protection against infections afforded by breast feeding. Although breast feeding is shown to be protective against lower respiratory tract infection during infancy, such protection has not been demonstrated for asthma in all studies. Issues pertaining to study design, analytical methods and theoretical problems such as confounding have greatly complicated the interpretation and comparison of studies. Furthermore, asthma has a complex phenotype in which numerous genetic and environmental

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