Predicting bacteraemia or rapid identification of the causative pathogen in community acquired pneumonia - where should the priority lie?

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Word count: 1730
References: 29

Conflicts of interest: none

Community acquired pneumonia (CAP) remains amongst the most common causes of infectious disease related death world-wide. However, despite its clinical importance the existing routine microbiology tests for CAP pathogens have significant limitations, lacking sensitivity for identifying the causative pathogen and only altering management in a minority of patients. For example, blood cultures identify a pathogen in 10% or less of CAP cases [1,2] and results are usually only available after 24 hours. Clinicians are therefore still required to prescribe broad-spectrum antibiotics for the first 24 – 72 hours, which is the period of highest risk for clinical deterioration and death [3,4]. Even when bacteria are cultured this only occasionally leads to a change in treatment and may miss co-infection [2,5]. These limitations have led to suggestions that patients admitted with CAP do not require routine microbiological testing with management decisions based solely on clinical factors. However, not identifying the causative pathogens in CAP has important implications. From a public health perspective, not performing microbiological testing could result in failure to identify important changes in microbial aetiology or changes in anti-microbial resistance patterns. In the absence of microbiological testing all patients would be treated with prolonged broad-spectrum antibiotics that may not be required if, for example, *Streptococcus pneumoniae* was the causative pathogen, thereby unnecessarily increasing drug cost and potentially promoting development of antimicrobial resistance or anti-microbial related complications such as *Clostridium difficile* diarrhoea [6]. Finally, the relatively rare CAP patient infected with a drug-resistant pathogen such as community acquired methicillin resistant *Staphylococcus aureus* or *Pseudomonas aeruginosa* may not be identified, increasing the chance of a poor outcome.

In this issue of the *European Respiratory Journal*, Amaro *et al.*[7] report prospective data from a well characterised cohort of 917 immunocompetent patients on the characteristics of blood culture positive versus negative in CAP patients infected with *S. pneumoniae*, the most frequently isolated pathogen in this disease and which is frequently associated with septicaemia [8]. Indeed, Amaro *et al.*[7] found that 362 (39%) of patients with pneumococcal CAP had positive blood cultures, a higher rate of positive culture than reported in other studies [8]. If bacteraemia is associated with increased risk of septic shock and mortality in hospitalised cases of *S. pneumoniae* CAP, then early detection by blood cultures would be clinically important. Furthermore prediction of patients at risk of bacteraemic disease before culture results are available would also be clinically useful, potentially leading to increased monitoring (e.g. high dependency care) and use of adjuvant therapy [9,10]. This

study by Amaro *et al.*[7] is one of the largest sets of prospectively collected data available on the clinical characteristics associated with blood culture positive pneumococcal CAP, and provides new data on the clinical value of routine blood cultures for patients admitted to hospital with CAP.

Amaro *et al.*[7] make some interesting observations. Negative blood cultures were more likely in patients over 65 years of age, those suffering from chronic respiratory disease, the use of inhaled corticosteroids and in nursing home residents. Older age and chronic lung disease are both associated with a substantially increased risk of *S. pneumoniae* CAP, so the negative correlation with positive blood cultures for these groups is a slightly unanticipated. There are several potential explanations for this observation; a higher proportion of these individuals could be treated with antibiotics before admission; due to vaccine recommendations these patients may be more likely to have received the pneumococcal vaccine that protects against septicaemia (but not pneumonia) caused by vaccine-serotypes [11]; and furthermore, due to their underlying lower physical reserve against illness these patients may be more likely to be admitted due to a milder episode of CAP than younger patients without comorbidities. Another interesting observation is that direct comparison of the clinical features of the pneumococcal CAP patients with positive blood cultures to those with negative blood cultures reveals relatively small differences. Although patients with positive blood cultures were more ill, with higher respiratory and heart rates, lower oxygen saturations, and higher C-reactive protein (CRP) and creatinine levels the absolute differences to blood culture negative patients were small and not likely to have major biological significance. As pneumonia complicated by septicaemia is generally considered a more serious infectious disease than pneumonia alone these data are surprising, and perhaps indicate that for *S. pneumoniae* the additional negative effects of septicaemia over pneumonia is more limited than previously thought.

Following multivariate regression analysis the presence of pleural effusion, multi-lobar involvement on chest radiograph and a CRP > 20 mg/dl were independently associated with a positive blood culture and were incorporated into a predictive model. When all three parameters were present, the model had an area under the receiver operating characteristic curve of 0.69 (95% CI 0.63-0.75) to predict a positive blood culture for patients with pneumococcal CAP, suggesting sufficient but not good discriminatory ability of the model. Of the included variables, CRP>20 mg/dl had the highest sensitivity, whilst the presence of a pleural effusion and multi-lobar

infiltrates had increased specificity. Hence the presence of a high CRP, pleural effusion and multi-lobe disease is a reasonable marker for *S. pneumoniae* septicaemia in patients with known pneumococcal CAP. However this will have little clinical utility unless these parameters also differentiated pneumococcal septicaemia from all patients with CAP (not just pneumococcal CAP), or a point of care test for *S. pneumoniae* such as urinary antigen detection was used routinely. Previous studies are consistent with the present study, with pleural effusions and multi-lobar infiltrates associated with an increased proportion of positive blood cultures, and increased age and the presence of COPD associated with negative blood cultures [12–14]. These studies also identified additional factors associated with positive blood cultures including male gender, congestive heart failure, alcohol and drug abuse, hypoalbuminaemia, hyponatraemia, tachycardia, and hypotension [13,14] not corroborated by Amaro *et al.* [7]. Overall, these data do provide a strong degree of confidence that effusions and multi-lobe disease are positively and chronic lung disease and older age negatively associated with blood culture positive *S. pneumoniae* CAP. However, these clinical associations probably lack adequate sensitivity or specificity to be a particularly useful clinical tool for guiding different approaches to therapy for patients with CAP.

One curious observation by Amaro *et al.*[7] is that a positive blood culture was not associated with poorer outcomes; although 30-day mortality was slightly higher in the positive blood culture group this was not statistically significant. This result is congruent with the limited differences in severity markers between blood culture positive and negative patients. However, previous studies found that positive blood cultures in pneumococcal pneumonia were associated with an increased risk of septic shock and mortality [12,15]. Furthermore, a secondary analysis of the Community Acquired Pneumonia Organization (CAPO) database demonstrated an increased mortality amongst blood culture positive pneumococcal pneumonia patients [14]. Technical differences may explain the discrepancy in the significance of a positive blood culture for *S. pneumoniae* on mortality. For example, in the Amaro *et al.*[7] study the overall mortality was relatively low, reducing the power of the study to identify differences in mortality between blood culture positive and negative patients. Furthermore, the older age and increased incidence of chronic lung disease may have offset any increased mortality associated with more severe disease in blood culture positive patients. False negative blood culture results due to pre-admission antibiotics or insensitive culture techniques could also potentially explain the lack of association of positive blood cultures with poor outcome. Conversely, the CAPO

database study may have been confounded by HIV since blood culture positive patients without HIV did not have significant differences in the risk of mortality [14], and in the Capelastegui *et a*l.[12] study a higher proportion of blood culture negative patients received dual antibiotic therapy including a macrolide which is associated with improved outcomes [16,17]. At present the clinical relevance of a positive blood culture for pneumococcal CAP remains unclear, but may not be as important as previously thought.

The data from the studies of pneumococcal CAP clearly highlight that improved diagnostic techniques are required for pathogen detection including the presence of bacteraemia. Rapid immunochromatographic tests (ICT) such as the Binax NOW® antigen assay and novel novel multiplex urinary antigen tests increase identification of *S. pneumoniae* in patients with CAP [18–20]. Although not licensed for blood testing, Binax NOW® can also detect bacteraemia with high sensitivity and is useful for the assessment of negative conventional subcultures [21]. Molecular diagnostics such a polymerase chain reaction (PCR) do not depend on growth of the bacteria and therefore result in more positive results than culture and are not affected by prior antibiotic use [22,23]. Several genes have been targeted for the detection of *S. pneumoniae* by real-time (RT)-PCR and a test combining highly conserved genes (e.g. *lytA, ply, psaA, cpsA, wgz)* is likely to be highly specific [24,25]. When combined with other molecular techniques such as *rnpB* sequencing or conventional culture the diagnostic accuracy increases [26]. RT-PCR for *S. pneumoniae* also has prognostic implications since $>10^3$ *S. pneumoniae* DNA copies/ml was associated with increased risk of septic shock, need for mechanical ventilation and increased mortality [27]. Another molecular diagnostic test that has shown promise for the detection of *S. pneumoniae* is recombinase polymerase amplification (RPA) that does not require thermocycling so could be used as a point of care test [28]. As CAP may be caused by several other pathogens other than *S. pneumoniae* multiplex PCR assays that can simultaneous identify several bacterial and viral pathogens will be advantageous, and will help identify co-infections [22,29].

In summary, the study by Amaro *et al*.[7] on the clinical significance of a positive blood culture in patients presenting with pneumococcal CAP perhaps provides support for those who believe that it is not necessary to do microbiology tests in CAP. However, apart from the broader importance of microbiological testing in patients with CAP discussed in the opening paragraph, it is probably still premature to state that *S. pneumoniae* bacteraemia has little clinical relevance. Larger studies

preferably using improved diagnostic techniques will be necessary to fully clarify the clinical implications of bacteraemia in patients presenting with *S. pneumoniae* CAP. Better microbiological tests are needed for CAP that can rapidly identify the causative pathogen(s), preferably combined with prognostic information, quantification of pathogen load, and detection of mutations associated with antibiotic resistance. Until these tests are routinely available and implemented in clinical practice, conventional cultures will remain an important diagnostic microbiological tool for patients admitted with CAP.

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