Intensive Care Med (2008) 34:981–984
DOI 10.1007/s00134-008-1088-6

EDITORIAL

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Biomarkers in the diagnosis of pneumonia in the critically ill: don't shoot the piano player

Received: 2 March 2008
Accepted: 2 March 2008
Published online: 8 April 2008

This editorial refers to the article available at:
http://dx.doi.org/10.1007/s00134-008-1087-7.

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Sir: The diagnosis of pneumonia in critically ill patients remains an area of much uncertainty. Despite two decades of very intensive efforts and many highly sophisticated study designs and debates, the key issue as to whether quantitative cultures of respiratory samples *independently* predict the presence of pneumonia and the need for antimicrobial treatment in a patient with suspected pneumonia still could not be resolved consensually [1–3]. Moreover, the investigation of the relative role of noninvasive and invasive diagnostic tools exerted highly conflicting results [3]. An approach focusing on the impact of diagnostic procedures on clinical outcomes and antimicrobial drug consumption, rather than on operative characteristics of diagnostic tests, was launched by Spanish and French authors, again generating conflicting results [4, 5]. To date, we feel that diagnosing pneumonia in the critically ill to a large extent means to deal with uncertainties, and that algorithms should be open for individual decision making [6].

The most recent Canadian multicentre study which corrected for several evident flaws of the four previous studies in terms of design and patient numbers, albeit not without newly introduced flaws, did not find a difference in terms of clinical outcomes between invasive and noninvasive diagnostic strategies (the latter including even *qualitative* cultures of tracheobronchial aspirates!) and clearly supports the more sceptical view which recommended not to rely on quantitative cultures alone in decision making [7]. Somewhat surprisingly, the evident conclusion was not acknowledged by the accompanying editorial, hinting at a clear need for better diagnostic approaches in order to make sure rapid appropriate initiation of antimicrobial treatment and at the same time to reduce microbial selection pressure [8].

In 2004 Gibot and colleagues [9] opened a new paradigm by examining the diagnostic value of the inflammatory marker soluble triggering receptor expressed on myeloid cells (sTREM-1), rather than quantitative cultures in bronchoalveolar lavage fluid (BALF). TREM-1 is an activating receptor expressed on the surface of neutrophils and mature monocytes when stimulated by bacteria or fungi, leading to amplification of the inflammatory response. They found that sTREM-1 was more accurate than any clinical or laboratory findings in separating patients with community- or hospital-acquired pneumonia from those without pneumonia [9]. Subsequently, the authors could demonstrate that sTREM-1 was a useful marker of systemic infection. In patients who presented with clinically suspected infection and fulfilled at least two criteria of the systemic inflammatory response syndrome (SIRS), systemic sTREM-1 could differentiate patients with and without underlying infection [10]. The usefulness of sTREM-1 in BALF in patients with suspected pneumonia was confirmed in four small series by others [11–14]. In addition, serial determinations were shown to reflect

the development of VAP [12]. The value of systemic sTREM-1 varied considerably in the series reported, most probably due to the presence and severity of sepsis-related infection [12, 15, 16]. Do these findings indicate that the new paradigm of diagnosing pneumonia in critically ill patients has finally succeeded?

This is clearly not the case. Perhaps inevitably, researchers have to simplify periodically the experimental set-up in order to achieve a new point of view from which to restart. This is clearly legitimate, and, in fact, it generated a new perspective in our context; however, it is time now to remember key lessons learned in the past VAP studies. Firstly, there is no gold standard for reference which patient has pneumonia, at least in VAP [3]. Secondly, for several reasons quantitative cultures are an estimate rather than a precise measurement of bacterial load in BALF [17]. Finally, even when patients with community-acquired pneumonia are used as positive and healthy volunteers as negative reference to calculate the operative characteristics, these values are by no means directly applicable to the ventilated population which is characterized by multiple potential confounders in terms of predisposition, non-pulmonary infections, host response, and organ dysfunction (especially ARDS). On the other hand, sTREM-1 clearly has been shown to have limitations itself; it can be increased in noninfectious conditions or remain low in patients with true infection [18]. In fact, Gibot and collegues [9] presented a clear example of circular reasoning in their original paper. They established the presence of pneumonia by relying on clinical judgment and quantitative cultures, and found a good predictive value of the clinical pulmonary infection score (CPIS) > 6 (as compared with which sTREM-1 was found to be superior). They failed to realize that the truly meaningful analysis would have been to correlate quantitative cultures with sTREM-1 and evaluate their relative contribution to confirm a clinical suspicion of pneumonia rather than a definite diagnosis (which cannot be made in the absence of a robust reference).

Does this mean that the paradigm has failed? Again, the answer is no; however, it is important the recognize that biomarkers, such as sTREM-1, cannot resolve the diagnostic dilemmas on their own as long as there is no clear gold standard for VAP and the many limitations of BALF sampling and processing are not overcome. Biomarkers could be useful, however, as a complementary tool within a well-designed diagnostic work-up. When used as systemic markers of sepsis, serial measurements may provide a tool for the evaluation of treatment response in order to change treatment regimens or to shorten antimicrobial treatment courses [18]. Beyond these perspectives, the potential of biomarkers, such as sTREM-1, may even reveal unexpected avenues in other fields.

In this issue of "Intensive Care Medicine", El-Solh et al. show that sTREM-1 levels in BALF can be a biomarker to identify the presence of pathogens in aspiration pneumonia and may therefore guide antimicrobial treatment decisions [19]. Since the patient population involved is quite peculiar in terms of underlying diagnoses and absence of antimicrobial treatment, these results await further confirmation. Nevertheless, we think that the present work provides important clues how to investigate appropriately biomarkers as tools for the prediction of aspiration pneumonia and pneumonia in the critically ill.

In fact, aspiration syndromes are difficult to manage. An effort should be made to distinguish aspiration pneumonia, i. e. pulmonary infection as a result of the inhalation of colonized oropharyngeal material, from aspiration pneumonitis, i. e. acute lung injury after the inhalation of usually sterile gastric contents [20]; however, a strict differentiation may not be possible in every case, and much confusion may arise from the mix of "apples, oranges and tangerines" [21]. In fact, most patients with aspiration syndromes receive antimicrobial treatment, although such treatment is usually not indicated in aspiration pneumonitis. The presence of pathogens above the threshold in BALF may identify frank pneumonia but is subject to the same limitations as recognized for patients with suspected VAP; thus, a biomarker may be of potential help in identifying patients in need for antimicrobial treatment.

The question, however, is how to overcome the problem of a lack of a reference for the evaluation of the biomarker. The appropriate strategy is to circumvent the problem and gain additional information from different approaches. In a first step, El Solh et al. [19] calculated the predictive power of sTREM-1 in predicting significant BALF culture results. They found sTREM-1 in BALF to predict BALF-culture positive aspiration pneumonia with an area under ROC of 0.87 (95% CI 0.78–0.94). A threshold of 250 μg/ml differentiated culture-positive from culture-negative aspiration pneumonia with a sensitivity of 65.8% and a specificity of 91.9%. In a second step, they correlated the results of BALF cultures and sTREM-1 values. The correlation showed a considerable level of agreement ($r = 0.51$, $p < 0.001$) and identified 20 of 75 cases with discordant results: 12 patients had high bacterial indices but sTREM-1 levels below the threshold of 250 μg/ml; and 8 patients had levels above the threshold but non-significant or negative culture results. The meaning of these results remains doubtful and ideally would be the starting point for further controlled studies comparing the impact of antimicrobial treatment of such patients on relevant clinical outcomes. Since this will be difficult to achieve, these patients should probably be treated; thus, the determination of sTREM-1 would be clinically helpful by identifying all patients with probable pulmonary infection and by establishing more confidence to withhold treatment in those without any evidence of infection (i. e. non-significant or negative culture results and sTREM1 below the threshold).

In our view, it is important to realize what the specific and important contribution of biomarkers in the diagnosis of pulmonary infection truly could be, not only in the context of pulmonary aspiration syndromes but also of pneumonia in the critically ill in general. Since the starting point of any diagnostic evaluation always relies on clinical suspicion, biomarkers should not aim to compete with clinical diagnostic criteria for suspicion of pneumonia. This point has also unanimously been made by Tang and collegues in a recent metaanalysis of procalcitonin in the diagnosis of sepsis (vs. SIRS) in an otherwise very controversial dispute [22–25]. Since microbiological investigation is indispensable in order to estimate the probability of the presence of pneumonia and to identify the underlying pathogen and its susceptibility pattern, biomarkers must not replace quantitative cultures and susceptibility testing. The intention to replace clinical and microbiological diagnosis would mean to "shoot the piano player". The real clue of biomarkers as markers of infection other than pathogen detection could be to provide independent additional information on the clinical problem, thereby increasing the validity of clinical estimates. We most recently incorporated data on procalcitonin into such an approach in patients with community-acquired pneumonia [26]. Such an approach will not overcome all uncertainties in diagnosing pneumonia in the critically ill, but it will have the potential to minimize them considerably. We believe that this perspective justifies every effort to further explore the paradigm of biomarkers in the area of pulmonary infections.

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