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Biomarkers in community-acquired pneumonia: can we do better by using them correctly?

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INTRODUCTION

Community-acquired pneumonia (CAP) is responsible for a great part of the infectious disease burden worldwide.[1] Although the scientific knowledge on the diagnosis and management of CAP has advanced considerably, there are still gaps and room for improvement. The arrival of biomarkers has generated considerable excitement in the field of medicine, and some biomarkers have been extensively tested in CAP. Herein, we discuss what can be done to move forward in the area, highlighting what we must bear in mind when using biomarkers for clinical purposes and research (Figure 1).

IDEALLY, WHAT DO WE NEED FROM A BIOMARKER IN CAP?

A biomarker is a biological characteristic that is objectively measured and used as an indicator of a physiological process, pathological process or pharmacological response to a therapeutic intervention.[2] Ideally, a biomarker of infection must possess characteristics that facilitate the diagnosis, prognosis, and follow-up. That means that a biomarker should give an indication of the presence of an infection in a rapid and reliable manner, guiding the decision to start antibiotic therapy, always as a complement to the clinical history taking and physical evaluation. In addition, as therapy leads to clinical improvement, the levels of the biomarker should reflect that improvement and should inform decisions regarding the duration of antibiotic therapy. However, persistently altered levels of the biomarker should raise the suspicion of treatment failure or the development of another infectious complication.[3]

In severe infections such as CAP, we need biomarkers that can help us identify patients at a higher risk of a worse outcome, who should be promptly admitted to the hospital or ICU.[1] Although several biomarkers have been studied in CAP, none have been definitively demonstrated to be useful for predicting patient-reported outcomes in CAP.

RECENT ADVANCES IN THE LITERATURE

Most biomarkers are dynamic proteins in the body. Therefore, we cannot interpret a C-reactive protein (CRP) level of 25 mg/L, for example, without considering the starting point ascertained as the onset of infection (i.e., the stimulus for upregulation of the pro-inflammatory biomarker), because, given the CRP dynamic, it could still be low if the stimulus was recent. In fact, it has been reported that, early in the lung infection process (< 3 days after the self-reported symptom onset), CRP levels are lower, whereas procalcitonin levels are higher, than thereafter (≥ 3 days after the self-reported symptom onset). That finding has strong correlation with what is known about the half-life of these biomarkers, as well as their response to stimulus. There is a need for further research in this area, which has direct implications for clinician reasoning in the interpretation of a blood test result.[4] To date, there has been only one study evaluating the influence of time from initial symptoms when validating the initial value of a biomarker for CAP, resulting in limitations on the interpretation of previous studies. Therefore, clinicians have to be careful not to rely on biomarkers alone when deciding whether or not to initiate antibiotic therapy.[1,5]

The use of new molecules or methods for evaluating the inflammatory or immune response in patients with CAP is evolving. In this issue of the JBP, Zhu et al.[6] evaluated two new molecules as prognostic markers in CAP: the NACHT domain-, leucine-rich-repeat- and PYD-containing protein 3 (NLRP3); and the leucine-leucine 37 (LL-37) peptide, a fragment of the cathelicidin protein precursor and an inflammatory regulator. The authors showed that the CAP patients with higher NLRP3 values or lower LL-37 values had higher serum CRP levels and higher white blood cell counts, as well as showing greater severity (as determined by the Pneumonia Severity Index), higher NLRP3 values and lower LL-37 values both being associated with the combination of higher NLRP3 values and lower LL-37 values being associated with higher 30-day mortality in such patients. The authors argued that these could be new targets for CAP treatment.

Another recent finding that has received considerable attention is the incidence of cardiovascular complications after an episode of CAP. In addition, biomarkers traditionally used in cardiology have been applied to CAP. Moving forward in this field, another study in this issue of the JBP, conducted by Akpınar et al.,[7] studied the prognostic value of the N-terminal pro–B-type natriuretic peptide (NT-proBNP) in hospitalized CAP patients without the main factors associated with NT-proBNP increase, such as heart failure, pulmonary hypertension, and acute kidney injury. The authors observed that NT-proBNP levels correlated with the Pneumonia Severity Index and with the mental

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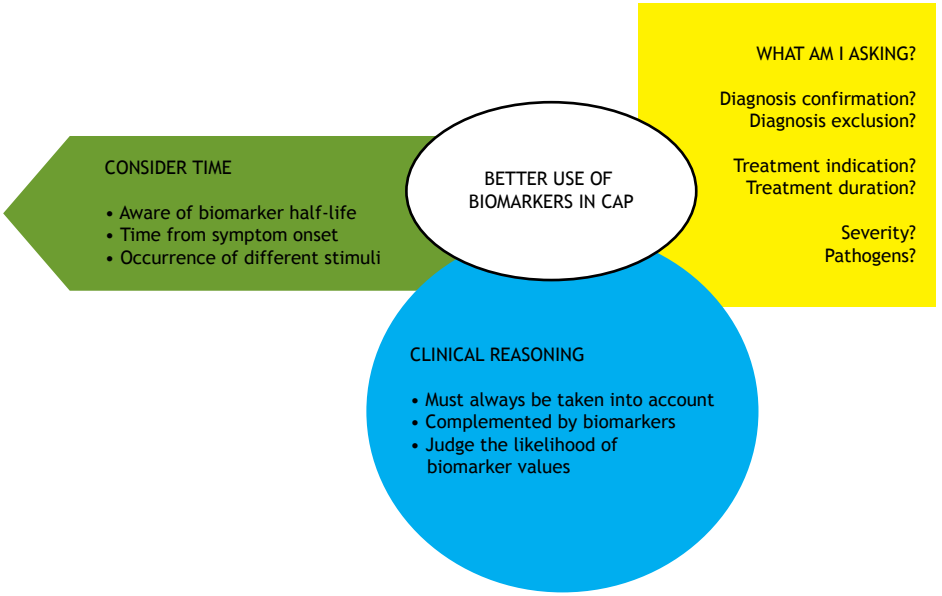

Figure 1. How can we improve the use of biomarkers in clinical practice and research for patients with community-acquired pneumonia (CAP)? Three aspects that clinicians and researchers must always consider when ordering a biomarker test or interpreting its results in a patient with CAP.

Confusion, **U**rea, **R**espiratory rate, **B**lood pressure, and age ≥ **65** years (CURB-65) score. They also found that, after adjustment for potential confounders in a multivariable analysis, higher NT-proBNP levels were associated with worse outcomes, including ICU admission and 30-day mortality. That novel finding raises the question of where cardiovascular biomarkers could be used in order to predict not only general worse outcomes for CAP but also specific complications, such as cardiovascular events. The prediction of specific events could target the subgroup of patients in need of preventive measures, such as antiplatelet therapy or atherosclerotic plaque stabilization.[7] Specifically, in a baboon model of severe pneumococcal pneumonia, the authors observed direct cardiac damage that could explain the elevation of cardiac biomarkers in CAP.[8]

SHOULD WE RESUSCITATE "OLD" BIOMARKERS?

Because CAP is commonly diagnosed by clinicians, simple, accessible biomarkers are needed. In one recent study,[9] information from complete blood counts was used in order to identify CAP phenotypes and their association with prognosis. For example, red blood cell distribution width has been associated with a poor prognosis and the need for ICU admission in different populations of patients with CAP.[9] In addition, a lymphopenic CAP phenotype, defined as < 724 lymphocytes/mm^3 at diagnosis, has been associated with higher mortality.[10] There is a need for further research on how to implement this knowledge to improve clinical decision-making, as well as on how to incorporate them into prognostic tools, such as the CURB-65 score, in patients with CAP.[11]

In conclusion, we need to use appropriate methods for the clinical application of scores. The normal evaluations by sensitivity, specificity, and ROC curve are not enough. We should use nomograms, analysis of pre- and post-test probabilities, and decision-curve analysis.[12] In addition, repeated measurement of biomarker concentrations, with an assessment of relative variations, before and during antibiotic therapy, could be more informative than is a single value. Therefore, the identification of patterns of response in some biomarkers could help differentiate between favorable and unfavorable clinical courses.[3] This can be helpful for the individualization of the duration of antibiotic therapy or the early identification of patients who are at risk for complications of CAP.

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