

LESS IS MORE IN INTENSIVE CARE



# Biomarkers in the ICU: less is more? No

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In recent years, the use of biomarkers in the ICU has increased exponentially. Only a few of them are used in clinical practice. However, as any measurement that helps to make clinical decisions, these biomarkers have detractors and defenders. Due to space constrictions, we decided to give arguments in favor of using biomarkers only in two frequent medical conditions with high morbidity and mortality in ICU, such as pneumonia and sepsis.

## Pneumonia

Most of the information about biomarkers in pneumonia comes from procalcitonin (PCT), which is the most frequent biomarker currently used in clinical practice. PCT is an acute-phase reactant primarily produced by the liver in response to bacterial infections. Cytokines associated with viral infections attenuate PCT induction, but some elevation in its expression can occur in atypical pathogen pneumonia. Thus, patients with lower respiratory tract infections, including those with lung infiltrates, can often have antibiotics safely withheld when PCT levels are low, provided that clinical judgment supplements biomarker measurements.

PCT levels may vary during illness, with higher levels in patients presenting within 3 days from symptoms onset [1]. In documented influenza cases, PCT levels do not have a sufficient positive predictive value to indicate a bacterial coinfection; however, they have a high negative predictive value and could help rule out bacterial coinfections. PCT measurements may be inaccurate in renal failure, which can falsely elevate PCT levels by interfering with their elimination. Moreover, some dialysis

membranes can remove PCT, which can lead to falsely low measurements (Figure 1). Taking into account all the considerations mentioned above, both PCT measurements and clinical judgment have to be included in the initial management of CAP, including severe CAP [2]. The second indication of PCT is the duration of antibiotic treatment. In the ProCAP study, serial measurements of PCT were used to guide treatment duration, which was 55% shorter with PCT guidance than in the control group, although the duration in the control group was longer than current standards (12 days vs. 5 days for the PCT group). A study of 1359 Emergency Department patients (68% with CAP) from six hospitals showed that PCT guidance reduced antibiotic treatment duration, use, and side effects compared to standard care [3]. Furthermore, a patient-level meta-analysis of 2910 patients showed that PCT guidance reduced antibiotic treatment duration to 5.7 days from 6.2 days in controls ( $p < 0.0001$ ) [4]. In another randomized study of 1546 ICU patients, PCT guidance reduced the duration of antibiotic treatment and increased the number of antibiotic-free days compared to control, although the number of CAP patients was not specified [5].

Blood C reactive protein (CRP) is another acute-phase reactant produced by the liver that shows a good correlation with interleukin [6]. It is more influenced by antibiotic treatment and corticosteroids than PCT. Although it is very inexpensive, its lack of specificity precludes its use for withholding antibiotics or shorten the antibiotic duration. However, it has been successfully used to stratify patients in randomized clinical trials to search for an inflammatory phenotype [6].

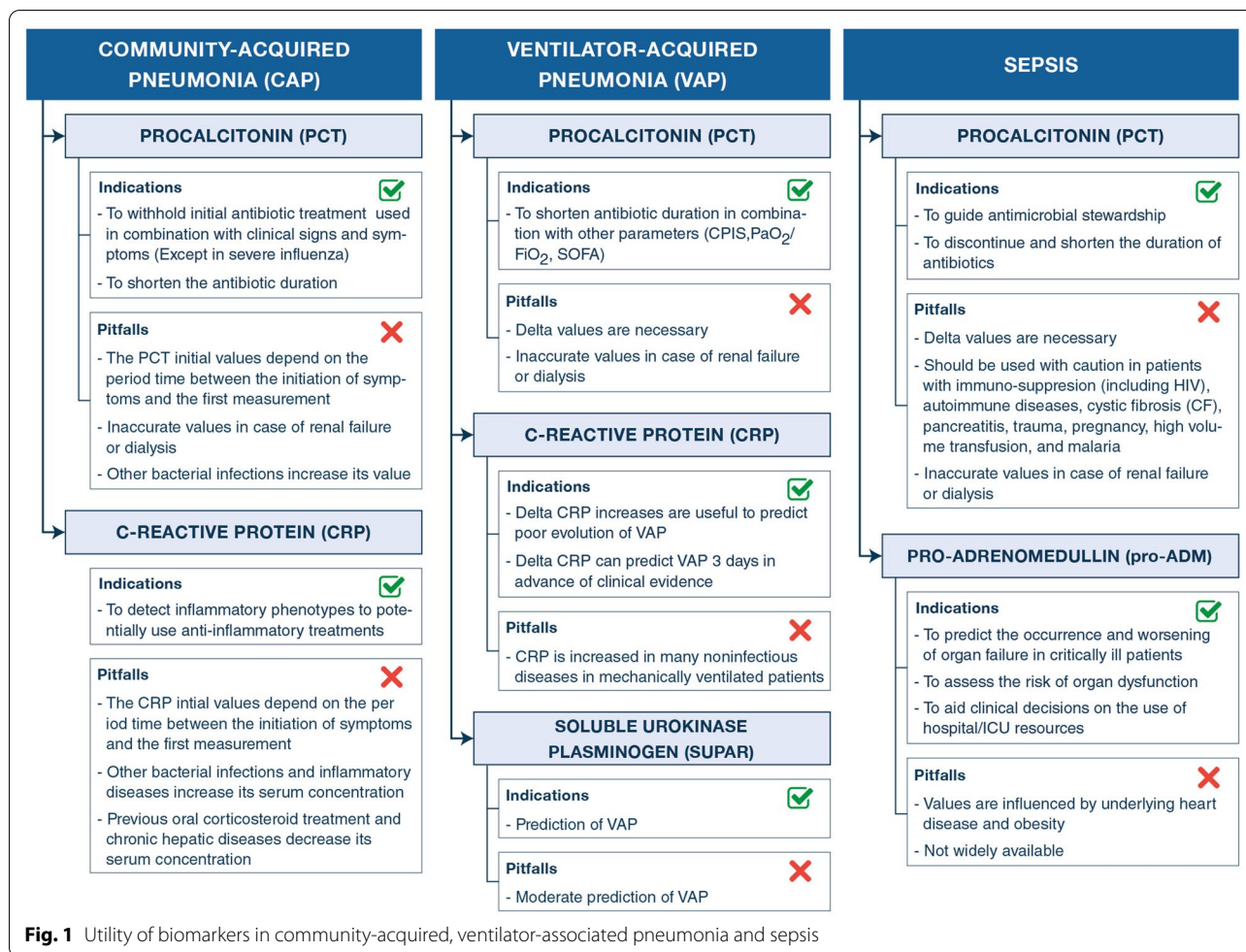
The diagnosis of ventilator-associated pneumonia (VAP) and the duration of antibiotic treatment are two important clinical challenges in which biomarkers can be useful. As in CAP, PCT is the best-studied biomarker in VAP. The lack of utility of PCT measurements in VAP diagnosis has been well proven in several observational studies. The main reason for explaining these findings is

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that other non-infectious diseases or infections outside the lung can increase PCT values in patients on mechanical ventilation. The recent ERS/ESICM/ESCMID/ALAT [7] guidelines do not recommend the use of biomarkers for the diagnosis of VAP. However, they do suggest that PCT can be useful to guide treatment duration or prolong it in several circumstances, such as inappropriate antibiotic treatments, infections caused by multidrug-resistant/extensively drug-resistant microorganisms, or when using second-line antibiotics such as colistin and tigecycline. CRP is not used to diagnose or guide antibiotic treatments in VAP due to its low specificity. Some groups have found an excellent prediction of evolution when measuring the delta variations of CRP over time [8]. The BioVAP is a multicenter study that investigated the kinetics of biomarkers to predict VAP, and found that CRP and CRP slopes over time were good indicators of VAP occurrence. This finding was not shown with PCT and Pro adrenomedullin (Pro-ADM) [9]. Finally, the soluble urokinase plasminogen receptor (SUPAR) was also investigated in the same cohort. Plasma SUPAR levels

were elevated three days before VAP, but its predictive level was moderate [10].

In summary, biomarkers are not useful for diagnosis in VAP, and they cannot replace clinical and microbiological evaluation. However, PCT measurements using predetermined algorithms are helpful in guiding the duration of antibiotic treatment, decreasing or prolonging treatment in particular circumstances.

### Sepsis

Procalcitonin (PCT) is the most studied biomarker in sepsis, with a cut-off value of 1.1 ng/ml [sensitivity of 77% and specificity of 79%; area under the receiver operating characteristic curve of 0.85 (95% CI 0.81–0.88)] used for diagnosis of sepsis, depending on pre-test probability [11]. A single measurement of PCT for early diagnosis is clinically useful when sepsis-3 criteria are used [12, 13]. The combination of using sepsis biomarkers and clinical variables, known as ‘bioscores’, improves early detection [14].

An initial measurement of PCT should be obtained at the time of diagnosis, as well as serial measurements to aid antimicrobial stewardship algorithms. This can lead to improved diagnostic interventions, therapeutic approaches, and patient outcomes. PCT-guided therapy should be implemented with caution in patients with immunosuppression, cystic fibrosis, pancreatitis, trauma, pregnancy, high volume transfusion, renal dysfunction, and malaria [15].

A drop to levels  $<0.5$  ng/ml or by at least 80–90% of the peak in combination with clinical improvement can be used to support the clinical decision to reduce antimicrobial exposure, thus avoiding antibiotic-related side effects [5]. Plasma levels of sepsis biomarkers have also been studied to predict the severity of illness and prognosis.

The use of sepsis biomarkers in precision medicine is promising. The heterogeneity of sepsis has led to the use of biomarkers to stratify patients according to the severity of the host response. Mid-region fragment of proadrenomedullin (MR-proADM) directly reflects levels of adrenomedullin, a potent vasodilator agent with immune-modulating and metabolic properties that increases in sepsis. Recently, the association has been reported between a higher clearance of MR-proADM levels during intensive care unit (ICU) stay and favorable outcomes, with survivors showing a plasma level drop to 1.65 nmol/L 48 h after admission and lower levels on day 5 compared to non-survivors. The role of MR-proADM in the early identification of severe cases at higher risk of organ dysfunction has been evaluated, irrespective of the location of the infection source. Furthermore, MR-proADM is used to aid clinical decisions regarding the use of hospital and ICU resources, having the highest predictive value for mortality compared to PCT, C-reactive protein, Sequential Organ Failure Assessment (SOFA) scores, and lactate [16].

In summary, the identification of an accurate diagnostic, predictive, or prognostic marker for pneumonia and sepsis would significantly improve our understanding of these heterogeneous diseases. Recent progress in several areas of biomarkers research, including advances in the development of point-of-care testing technologies, has the potential to transform the application of biomarkers as a chip at the bedside for diagnosis, risk stratification, molecular phenotyping, and monitoring therapeutic response in more personalized medicine.

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#### Compliance with ethical standards

#### Conflicts of interest

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