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LESS IS MORE IN INTENSIVE CARE

Biomarkers in the ICU: less is more? Yes

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In 1900, Dr. Camac wrote in the Journal of the American Medical Association "Rarely in our science is that any one finding is the open sesame to the secrets of the disease" [1]. In 2020, these words remain relevant, as a reminder that the complexities of both pathophysiology and patient care have always rendered any one test only a part of the puzzle. Regarding biomarkers, definitions vary, with most broad and encompassing many test types [2]. We focus on laboratory-based biomarkers, and contend that before widespread adoption of a given biomarker, we should ask four questions—what is the pretest probability for the diagnosis we are considering, are factors present that interfere with interpretation of the result, will I change management based on the result, and what will the outcome benefit be (Table 1)? We further contend that for many biomarkers, robust answers to these questions are lacking and support this position with illustrative examples of novel and commonly used biomarkers in the ICU.

Procalcitonin: *What is the pretest probability for the diagnosis we are considering?*

Procalcitonin is a biomarker generally elevated in bacterial but not viral infection, and there is much interest in its potential to decrease antibiotic use. Like any test, procalcitonin is best used in cases of diagnostic uncertainty, as low or high pretest probability alone can guide decisions and will heavily affect posttest probability. Procalcitonin also generally correlates with severity of illness and signs of infection and thus may provide only modest additional information to guide decisions. As such, though multiple randomized trials have shown procalcitonin-guided antibiotic de-escalation can reduce antibiotics in the ICU and other areas [3], the average reduction in ICU trials is only 1–1.5 days, and not all trials have shown reduction [4, 5]. Use in select patients where etiology is in doubt and the clinician is prepared to follow procalcitonin guidance could be the most impactful.

Brain natriuretic peptide (BNP): *Are factors present that interfere with interpretation of the result?*

BNP and its N-terminal fragment (NT-proBNP) are excellent markers of cardiac stress and loading. However, in the critical patient the heart is rarely the sole affected organ and the predictive ability of BNP for outcome in non-cardiac pulmonary conditions remains unclear. For example, although BNP has ~ 90% specificity to diagnose transfusion-associated circulatory overload, in severe ICU cases, sensitivity and specificity drop to < 60% [6]. Natriuretic peptides are also elevated in severe transfusion-related acute lung injury [7] and in critically ill patients without acute heart failure and correlate poorly with pulmonary capillary wedge pressure [8]. BNP levels are also generally lower in obesity, and patients with pulmonary disease, renal dysfunction, and atrial fibrillation can have high BNP levels without heart failure. Lastly, although sequential BNP measurement to guide fluid and diuretics in cardiac ICU patients is common, American Heart Association guidelines state the usefulness of BNP- or NT-proBNP-guided therapy for acutely decompensated heart failure is not well established.

Troponin: *Will I change management based on the biomarker result?*

Troponin became the dominant cardiac biomarker due to three key factors—the existence of a clinical gold standard for acute coronary syndromes, specificity to myocardial injury and ischemia, and extensive observational and interventional studies showing troponin provided incremental diagnostic value and outcome benefit. However,

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Table 1 Questions to consider before ordering biomarker testing in the ICU

Question	Example	Comments
What is the pretest probability for the diagnosis we are considering?	Procalcitonin	Low or high pretest probability alone can guide decisions and will heavily affect posttest probability If used, best used in cases of diagnostic uncertainty, and commitment to act on result
Are factors present that interfere with interpretation of the biomarker result?	Brain natriuretic peptide	Limited sensitivity and specificity for heart failure in critically ill patients Levels affected by common conditions such as obesity, renal dysfunction, and atrial fibrillation
Will I change management based on the biomarker result?	Troponin	Established utility for acute coronary syndromes was due to key factors that do not exist in general critical care Higher levels of troponin are associated with worse outcome, but this fact is not actionable
Will the outcome be benefited by biomarker guided decisions?	suPAR	Although higher levels of suPAR are associated with higher rates of death and acute kidney injury, provision of suPAR risk stratification information to clinicians had minimal impact on decisions and no impact on outcome, in a randomized trial

in critical care there is no gold standard for many conditions, multiple organs and pathophysiologic pathways are affected, and much biomarker research demonstrates only correlation. For example, higher levels of troponin itself are associated with worse outcome in critical illness, but this association is not actionable [9]. Prominent troponin investigators have warned clinicians should take care when deciding even when to order a novel test to avoid "erosion of the importance of the clinical findings [and basic tests]," it is "easy to show prognosis…[yet] difficult to show prognostic value," and that even now "integration of troponin…with clinical decision pathways…remains an area of active investigation" [10]. Thus, the history of troponin suggests we be thoughtful about when to order a novel test and how to interpret it, be specific in what we want a biomarker to do, and be cautious in our expectations.

Soluble urokinase-type plasminogen activator receptor (suPAR): *Will the outcome be benefited by biomarker guided decisions?*

suPAR is expressed on immunologically active cells, and an elevated serum level reflects immune system activation. From stem cell transplantation to asymptomatic aortic stenosis, patients with higher suPAR levels have higher mortality [11, 12], and a recent study found high suPAR levels associated with acute kidney injury [13]. What to do with these findings however remains unclear. An emergent department trial used suPAR to aid risk stratification, but found provision to physicians of suPAR levels and instructions on interpretation did not improve outcomes. Notably, 79.4% of physicians stated suPAR influenced their decision making in < 10% of cases or never [14].

In summary, though many biomarkers are clearly associated with disease and outcomes, actionability and incremental value beyond clinical judgment and basic tools are often lacking. This pattern is seen with many novel diagnostics in every field of medicine. For example, despite intense interest in genetic testing, two recent studies found polygenic risk scores provided minimal incremental predictive value for coronary artery disease [15]. Even for established tools such as mammograms and troponin, debate still exists on their optimal use, and we should not lose sight of the additional cost of widespread biomarker use.

Our intent is not to wholly devalue biomarkers, nor discourage research. In oncology, success has been achieved, with novel biomarkers allowing some patients to avoid chemotherapy, and others to have more targeted treatment. We simply recommend that clinically, biomarkers be used only when doubt exists despite sound clinical judgment and traditional tools, and clinicians are prepared to act on the result. We agree with the Choosing Wisely Campaign, which urges thoughtful consideration of when to order and how to use tests. Academically, we recognize how to "test a test" is challenging, and that a test by itself cures nothing, and must be tied to treatment. We agree with the biomarker qualification work by the European Medicines Agency and U.S. Food and Drug Administration, which categorize biomarkers based on their specific purposes, and highlight the need to develop evidentiary standards for their intended use.

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Authors contribution
Drs. Huang and Ramirez jointly conceived, wrote, and approved the manuscript.

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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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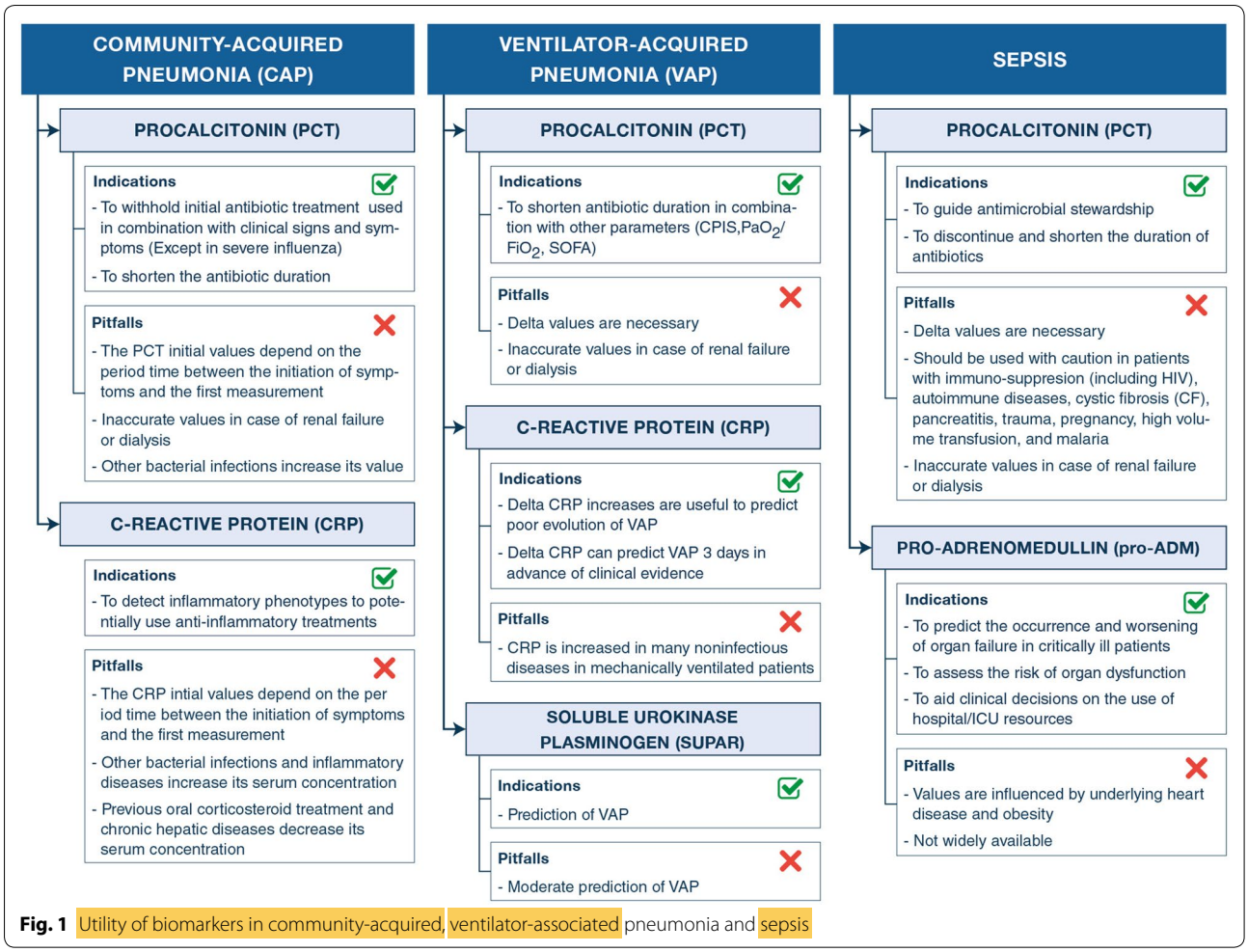

Fig. 1 Utility of biomarkers in community-acquired, ventilator-associated pneumonia and sepsis

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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