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Biomarkers

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Biomarkers of Infection in the Intensive Care Unit

Biomarkers are an area of rapid discovery in critical care medicine today. They have the potential to improve our ability to identify and manage patients at increased risk of organ failure and death. This article provides an overview of biomarkers of infection in the intensive care unit.

The heterogeneity of sepsis makes its identification challenging in the acute setting. As is common with many critical illnesses, rapid diagnosis and rapid institution of therapy are necessary to reduce mortality. The administration of active antibiotics is one of the principal modifiable risk factors for mortality in the septic patient, with the benefits most pronounced in the patient with shock (Kumar et al. 2006; Taylor et al. 2021). Conversely, our ability to identify the potentially infected patient remains imperfect. Approximately 40% of adult inpatients with features of the systemic inflammatory response syndrome are not infected (Comstedt et al. 2009), and a third of patients who receive broad-spectrum antibiotics in emergency settings for suspected sepsis do not have bacterial infections (Shappell et al. 2021). As the slow-moving pandemic of antimicrobial resistance (AMR) continues to challenge health systems around the world, critical care clinicians are becoming aware of the risks of antibiotic overuse, both in terms of increased rates of AMR and as a potential cause of direct patient harm (Vaughn et al. 2019).

At the bedside, we rely on a variety of features to identify sepsis. The term "biomarker" generally refers to some manner of laboratory assay to assist in this identification as well as to guide therapy. Biomarkers do not need to be laboratory-based, of course; fever and leukocytosis are biomarkers, and indeed the absence of fever has been associated with delayed recognition and worse outcomes in sepsis (Kaukonen et al. 2015; Dias et al. 2021). The inadequacy of our existing biomarkers, however, has led investigators to study other assays in an attempt to improve our diagnostic abilities.

Procalcitonin (PCT) is produced by parafollicular cells of the thyroid and by neuroendocrine cells in the lungs and gut, the production of which is increased in the presence of tumour necrosis factor alpha (TNF-α), interleukin (IL)-1 and IL-6 and inhibited by interferon gamma (IFN-γ). As TNF-α, IL-1, and IL-6 are associated with bacterial infections and IFN-γ with viral infections, it has been postulated that PCT can serve as an effective biomarker for bacterial infection (Assicot et al. 1993). PCT is clearly associated with disease severity in infected patients, with elevated levels corresponding to increased risk for 28-day mortality, the need for invasive ventilation, and shock requiring vasopressors (Self et al. 2016; Huang et al. 2008); Ramirez et al. 2011; Bloos et al. 2011). The Multicenter Procalcitonin Monitoring Sepsis (MOSES) study, a randomised trial of PCT-guided therapy conducted in 13 US hospitals, evaluated patients admitted to the ICU with sepsis and septic shock. Those participants with decreases in PCT levels ≤80% at 4 days had an increased risk of death compared with those patients whose PCT levels declined >80% (PPV for death, 29.5%; NPV 81.1%) (Schuetz et al. 2017). Similarly, declines in PCT of 80% or more from admission baselines are associated with decreased rates of in-hospital death (Schuetz et al. 2013).

Durations of antibiotic therapy in patients with sepsis are often arbitrary and may appear to be simple multiples of the numbers of days in a week or fingers on a human hand (Spellberg and Rice 2023). PCT-guided algorithms have been shown to be effective tools to personalise the duration of antimicrobial therapy in patients with bacterial infections in the ICU. The PRORATA and SAPS II trials demonstrated overall reductions in antibiotic treatment durations (from 14.3 to 11.6 days, and from 9.3 to 7.5 days, respectively) in critically ill patients without negative effects on mortality (Bouadma et al. 2010; de Jong et al. 2016). These results have not been consistent across all studies, with some trials demonstrating either no significant benefit or increased usage of broad-spectrum therapy using PCT guidance (Jensen et al. 2011; Shehabi et al. 2014). Some of these inconsistencies may be due to differences in the algorithm used, however. In the 2014 study by Shehabi et al. for example, the cut-off PCT value for antibiotic discontinuation was 0.1 ng/mL, lower than the 0.25-0.5 ng/mL levels used in other trials, while the 2011 study by Jensen et al. permitted not only antibiotic cessation with lower levels of PCT but antibiotic broadening and intensification with increasing levels. Like any algorithm, the outputs matter as much as the inputs.

Attempts have been made to use PCT to distinguish between viral and bacterial causes of community-acquired pneumonia (CAP). When integrated into a diagnostic strategy that included the use of commercially available multiplex molecular testing for common viral and bacterial pathogens, patients with CAP in one prospective study who had both low serum PCT levels (≤0.1 ng/mL) and testing that identified only viruses received fewer antibiotics and had

shorter hospitalisations than the comparator group. However, a large observational study in the United States was unable to identify a PCT cut-off level that safely excluded bacterial disease in patients with CAP, with a negative predictive value for bacterial pathogens of only 82.4%, even at PCT levels of <0.1 ng/mL, considerably lower than the more routine cut-off levels of 0.25-0.5 ng/mL . High levels of PCT may occur in patients with purely viral pneumonias, with murine models indicating that the suppression of PCT expression by IFN-γ may be overcome by high IL-6 levels in severe disease (Gautam et al. 2020; Carbonell et al. 2021). Similar findings have been noted in patients with 2019 coronavirus disease (COVID-19), dengue, malaria, and candidaemia, suggesting that PCT may be more closely linked to an infection's severity than to the nature of the inciting pathogen (Tong-Minh et al. 2022; Thanachartwet et al. 2016; Cortegiani et al. 2019; Hesselink et al. 2009).

The data for PCT usage as a biomarker appears strongest for its use as a tool for individualised antibiotic cessation. In 2019, a patient-level meta-analysis of 13 randomised trials of PCT-guided treatment durations in patients with bacteraemia described overall reductions in antibiotic days without increased mortality (Meier et al. 2019). In order to be effective, however, PCT guidance needs to be a part of an integrated antimicrobial stewardship programme with institutional support.

Other than lactate, C-reactive protein, and leukocytosis, procalcitonin is likely the most widespread sepsis biomarker in current usage. However, additional novel markers are an area of active investigation. Proadrenomedullin is a precursor of adrenomedullin, a product of vascular endothelial cells with varied effects on the cardiovascular system including vasodilator and diuretic functions. The majority of proADM studies utilise measurements of a middle region of the peptide (MR-proADM) without known biological activity. MR-proADM is predictive of organ injury and death in the emergency department (ED) and ICU settings, correlating well with Sequential Organ Failure Assessment (SOFA) scores (similar to PCT but with perhaps greater precision) (Piccioni et al. 2021). Unlike PCT, MR-proADM lacks the ability to discriminate between viral and bacterial pathogens and indeed is not specific for infection per se; rather, MR-proADM is best viewed as a marked of impending organ failure independent of aetiology, including in patients with heart failure (Maisel et al. 2011) and in the perioperative setting (Schoe et al. 2015). The theoretical benefit of MR-proADM, accordingly, may be in its ability to detect patients at high risk of decompensation early, with a hope for potential early intervention and improved outcomes.

> **"the inadequacy of our existing biomarkers has led investigators to study other assays in an attempt to improve our diagnostic abilities"**

Presepsin is a N-terminal fragment of soluble CD14 (sCD14), a Toll-like receptor (TLR) molecule that identifies pathogen-associated molecular patterns as a key component of the innate immune system. Among CD14's specific biological functions is as a coreceptor for the binding and recognition of lipopolysaccharide (LPS), or endotoxin, a key component and virulence factor on the outer membrane of gram-negative bacteria. As such, presepsin may be somewhat more specific for gram-negative than gram-positive bacterial infections, although it is elevated in both (Massan et al. 2015). Similar to PCT, presepsin declines with effective antibiotic therapy and has utility in distinguishing bacterial sepsis from other causes of organ failure and shock (Kweon et al. 2014). A meta-analysis of nine studies suggested that its discriminative properties are insufficient to rule out infection in a high-risk patient, however, despite a relatively high AUROC of 0.85-0.89 (Wu et al. 2015). However, the upregulation and expression of presepsin may occur rapidly than that of PCT, suggesting that its utility in an acutely decompensating patient could be superior (Ulla et al. 2013).

Pancreatic stone protein (PSP) is a 14 kDA polypeptide synthesised by the exocrine pancreas that functions as an acute phase reactant in the setting of tissue damage, possibly promoting repair after injury (Dusetti et al. 1995). Despite this apparently nonspecific trigger, PSP elevations seem to be relatively specific for infection compared with other inflammatory insults, including burns and chronic obstructive pulmonary disease exacerbations (Klein et al. 2021; Scherr et al. 2013). Similar to presepsin, PSP upregulation occurs earlier than PCT and may precede the formal diagnosis of sepsis (Niggemann et al. 2021). As the data supporting PSP are largely observational, its utility in direct management remains to be determined.

Perhaps most exciting in contemporary biomarker research is the monocyte distribution width (MDW). Along with neutrophils, cells of the monocyte-macrophage lineage respond early to new infections. The MDW does not require a new assay to measure; rather, it is a parameter readily available (although not routinely reported) when obtaining a standard complete blood count (CBC), or haemogram, with a leukocyte differential. Multiple observational studies have demonstrated an increased sensitivity for the diagnosis of sepsis in the emergency department with the use of MDW, often combined with SOFA scores or total leukocyte counts, with the cut-off for an abnormal MDW usually >20.0 (Jo et al. 2022; Kim et al. 2022; Hausfater et al. 2021; Woo et al. 2021; Cusinato et al. 2022). MDW appears to be pathogen-agnostic and does not distinguish between bacterial and viral causes of sepsis, with evidence for elevations in severe influenza and SARS-CoV-2 infections (Badaki-Makun et al. 2022). Similarly, elevated MDWs in trauma patients at the time of ICU admission are associated with the risk of future multiorgan failure (Marcos-Morales et al. 2022). Although MDW similarly lacks prospective validation in an interventional

trial, its advantages seem clear: MDW could provide rapidly actionable data that do not require additional diagnostic testing beyond a routine CBC, avoiding the attendant delays in results. Biomarkers are an area of rapid discovery in critical care medicine today. I will make a small editorial assertion here: the best biomarkers in the ICU are the eyes, ears, hands, and brain of a skilled intensivist. Despite this, these markers have the potential to improve our ability to identify and manage patients at increased risk of organ failure and death. Further prospective interventional trials are needed to determine which biomarkers, and in which combinations, will best serve our patients' needs.

> **"the best biomarkers in the ICU are the eyes, ears, hands, and brain of a skilled intensivist"**

Conflict of Interest

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