Review Article

Biomarkers in intensive care unit infections, friend or foe?

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Abstract: Antibiotic misuse is a crucial problem for critically ill patients. Biomarkers have emerged as tools to assist the clinician in antimicrobial therapy decisions among critically ill patients in intensive care units (ICU). They are useful for early identification of infection, timely initiation of antimicrobial therapy, and prompt evaluation of treatment course or duration. However, until now, an ideal biomarker has not yet been identified. The combination of procalcitonin (PCT), C-reactive protein (CPR) and other biomarkers may overcome their insufficiencies, with the high sensitivity of CRP compensating for the low sensitivity of PCT. Biomarkers could not predict antimicrobial resistance, and development of molecular diagnosis brings new challenges. The most important thing for the clinician is to understand the advantages and disadvantages of different methods so that to use them reasonably.

Keywords: Biomarker; sepsis; procalcitonin (PCT); critically ill patients; antibiotic stewardship

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Optimal antibiotic use is crucial in critically ill patients, especially in the setting of the rising level of antibiotic resistance. Many aspects were analyzed, such as early identification of pathogens, the choice of empiric treatment, de-escalation, pharmacokinetics/pharmacodynamics, and duration (1). Antimicrobial stewardship has been recommended and implemented in intensive care unit (ICU) for rapid identification and optimal treatment of bacterial infections, avoiding unnecessary broad-spectrum antibiotics, and shortening the duration of therapy (2). Biomarkers serve as useful tools to optimize antibiotic therapy among critically ill patients (2). However, the benefits and limitations of biomarkers for clinical decision-making remain controversial (3).

What is biomarker?

The definition of a biomarker is "*a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to therapeutic intervention.*" (4). Many studies have reported almost 200 different biomarkers related to infectious diseases, and also may be used in sepsis, such as C-reactive protein (CRP), procalcitonin (PCT), IL-6, etc. Professor Vincent and his colleague reviewed 3,370 references covering 178 different biomarkers (2). Many researchers are familiar with some of them, but some others not. Novel or traditional biomarkers such as CRP, PCT, IL-6 have been evaluated for diagnosis and prognostication of sepsis.

Why is there a need for biomarkers?

Infection is a common clinical problem in critically ill patients. Fifty-one percent of ICU patients are considered infected, and the prevalence of multidrug resistance was

positively correlated with the length of ICU stay (5). Mortality and morbidity associated with sepsis remain unacceptably high. Sepsis is a severe and frequent complication with a complex pathophysiological process. Traditionally, the approach to sepsis diagnosis was based on clinical signs and symptoms of sepsis, such as fever, tachycardia, and tachypnea, supported by relevant microbiological data. However, these are usually not objective indicators. In order to aid diagnosis, biomarkers of sepsis can potentially be used for prognostication to predict the development of organ dysfunction, to guide antibiotic therapy and to evaluate treatment response (2).

For sepsis, each hour of delay in antimicrobial administration was associated with an average decrease in survival of 7.6% (6). In 2018, the Surviving Sepsis Campaign (SSC) had updated the sepsis "hour-3 bundle" for "hour-1 bundle" (7). Two recommendations of the bundles include obtaining blood cultures and administering broad-spectrum antibiotics (7). However, the traditional microbiological method may take a longer time for the result to come back. The turnaround time for blood culture is about 24–48 hours or longer. Unfortunately, studies indicated that the accuracy of clinician decisions to start antimicrobials were disappointing. The experimental treatment was inaccurate in most cases (54%) (8). Another study indicated that the accuracy of empiric diagnosis varies for different infectious sites. For such as gastrointestinal and respiratory tract sources, clinicians' diagnostic accuracy is much better than urinary tract sources and skin and soft tissues.

Moreover, for intravascular sources, the accuracy is disappointing, just about 56% (9). Precision treatment remains unclear in the early stages of sepsis. In order to change the situation, rapid serological detection and molecular diagnostic methods have been developed, but there is another crucial thing to consider, availability. Novel molecular diagnosis methods such as next-generation sequencing (NGS) (10,11), matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF MS) (12), Filmarray (13), can deliver far more accurate, and rapid diagnosis and provide the value to monitor the clinical status of sepsis (14). However, in many hospitals, they are unavailable and costly. Biomarkers could be alternative options.

What is an ideal biomarker?

What is an ideal biomarker? First, they can be used to rule out infection; second, biomarkers are also markers of disease severity; third, repeated measurements can be helpful to evaluate a patient's clinical course (15). There are still no perfect biomarkers. In some infectious diseases such as HBV, HIV, brucellosis, and Helicobacter pylori infection, biomarkers have been handy tools. Many biomarkers can be used in sepsis, but they have limited ability to distinguish sepsis from other inflammatory conditions. Sepsis is an extremely complex pathophysiology process that involves the balance of inflammatory and anti-inflammatory processes, humoral and cellular reactions, and circulatory abnormalities. Various biomarkers indicate different stages of human response (2,16,17). Given the complexity of the sepsis response, Pierrakos and his colleagues concluded that it would be unlikely to identify a single ideal biomarker (2). After 5 years, Jensen and his colleagues showed similar conclusion (18). Each biomarker has limited sensitivity and specificity. So, research is still being done to find a better one.

How to do better under existing conditions in early identification?

As known, finding a better one is not an easy thing. Under existing conditions, there are two possible ways to address this dilemma. One way is to establish a bundle of diagnostic methods, including signs, symptoms, medical images, physical examinations, biomarkers, and even clinical experiences. The other way is to use two or more biomarkers combination in order to increase sensitivity and specificity of early diagnosis.

Multivariate analysis revealed that the combination of CRP, PCT and the sepsis-related organ failure (SOFA) score in the bioscore had an area under the curve (AUC) of 0.790 (95% CI, 0.739–0.834, P<0.001) (19). A bioscore of ≥2.65 was considered to be statistically significant in making a positive diagnosis of sepsis (19). Serum concentrations of PCT, soluble triggering receptor expressed on myeloid cells-1 (sTREM-1) and the high-affinity immunoglobulin-Fc fragment receptor I (FcγRI) CD64 on neutrophils (PMN CD64 index) were higher in patients with sepsis compared with all others (P<0.001 for the three markers) (20). The bioscore performed better than each biomarker (20). Another study revealed a similar result. CD64 showed a better positive probability for the identification of sepsis in ICU than CPR or PCT. Moreover, the combination of CRP, PCT, and CD64 improved diagnostic accuracy for sepsis (21). In a multi-center cohort study, they evaluated

the reliability and discriminant ability of 47 leukocyte biomarkers as predictors of sepsis (22). Individually, a single leukocyte biomarker expression was associated with subsequent sepsis, but the combination had no clinically relevant predictive validity (22). The multivariate analysis of the surgical cohort showed that the combination of PCT and HLA-DRA (encoding the non-polymorphic region of the alpha-chain of the HLA-DR molecule) improved the identification of sepsis in surgical patients (23).

Biomarker in sepsis combined with multiple organ damage

Sepsis is a syndrome characterized by a series of clinical manifestations and is frequently complicated by multiple organ damage such as acute kidney injury (AKI), cholestasis, encephalopathy (24). Presence of these complications suggests a severe condition and increased mortality.

A pilot study enrolled 33 patients with abdominal surgery, and 22 patients among them developed sepsis with varying degrees of AKI (25). A panel including serum neutrophil gelatinase-associated lipocalin (NGAL), urinary NGAL, calprotectin, SOFA score could predict in-hospital mortality with an AUROC of 0.911 (25). NGAL was human neutrophil lipocalin or lipocalin2, that was first identified as a 25 kDa protein in the secondary granules of human neutrophils (26). In bacterial bloodstream infection, NGAL is released and can be detected (27). Studies have been proven to be a valuable biomarker for early identification of AKI (28). This study illustrated that biomarkers related to AKI might be helpful to predict the complication of organ damage in critical illness. There are some other studies about biomarkers related AKI, such as cytochrome c oxidase subunit B (COX5b) (29), serum PARK7 (30), IL-8 Levels (30), and Alpha1-microglobulin (31).

The liver can release inflammatory mediators such as acute-phase proteins, cytokines, coagulants as a response to sepsis. These substances facilitate the clearance of pathogenic organisms and toxins (32,33). CD39 expression on macrophages limits P2X7-mediated pro-inflammatory responses, and combinations of a P2X7 antagonist and adenosine A2A receptor agonist are hepatoprotective during the acute phase of abdominal sepsis (34). Retinol-binding protein-4 (RBP4) (35), plasma endothelin-1 (36), and C-terminal proendothelin-1 (37) were proven to have potential value in sepsis-induced liver damage.

Other biomarkers might be used in different settings. For example, D-lactate, intestinal fatty acid-binding protein (FABP) and citrulline could be used for acute intestinal ischemic injury (38), and growth arrest-specific gene 6 (Gas6) was used for acute lung injury (39). Interleukin 27 was identified as a sepsis diagnostic biomarker in critically ill children, but not for lung injury (40).

Biomarker in antibiotic stewardship

The Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America published the guidelines for the Antibiotic Stewardship Program (ASPs) (41). The panel suggested the use of serial PCT measurements as a stewardship tool to decrease exposure and shorten the duration of antibiotic therapy, without worsening clinical outcomes (41).

A prospective, multicenter, randomized, controlled, open-label intervention trial was conducted to evaluate the efficacy and safety of the PCT-guided antibiotic treatment. The study enrolled 1,575 patients in ICUs. In the PCT-guided group, the median duration of treatment was 5 days, which was 2 days shorter than the standard-of-care group. The 1-year mortality rate was 36%, which was much lower than the latter (42). Similarly, systematic reviews and meta-analysis revealed similar results. The 30-day mortality rate was significantly lower in PCT-guided patients than in control patients with acute respiratory infections. Besides, PCT guidance was also associated with a reduction in antibiotic exposure and antibiotic-related side-effects (43). Moreover, another system review gave the same conclusion (44).

PCT has been used for several years. The specificity and sensitivity of PCT for the diagnosis of sepsis are not completely convincing (45,46), but more and more evidence showed that serial PCT measurements might be a choice for de-escalation of empirical therapy, prognosis and cost assessment (47,48).

Biomarkers for predicting resistance

In the traditional view, biomarkers could predict patients with or without infection (15), could predict infectious severity (43), could help to reduce treatment duration and cost (42,49), but biomarkers could not predict resistance. Predicting resistance is a crucial issue for empiric therapy.

A study evaluated secretome profile analysis of multidrug-resistant (MDR), monodrug-resistant, and drug-susceptible *Mycobacterium tuberculosis* in order to find some proteins as potential biomarkers for drug-susceptible

identification (50). They found some proteins such as putative prophagephiRv2 integrase, etc. which might suggest putative roles in controlling the anti-tuberculosis ability, but the results were not validated (50). Another study revealed that MDR tuberculosis (MDR-TB) strains contained specific antigens. Five bands from the MDR-TB fractions were not observed in drug-sensitive-TB fractions. These proteins might be potential diagnostic antigens (51).

The antimicrobial resistant profiles of common pathogens such as *Klebsiella pneumoniae* and *Staphylococcus aureus* are directly related to clinical decision. However, until now, professionals still depend on traditional culture and antimicrobial susceptibility testing systems. Researchers tried some molecular diagnostic methods such as PCR-based testing methods. By these methods, it is possible to detect genes related to resistance such as carbapenemase genes of *Klebsiella pneumoniae* and *mecA* gene of methicillin-resistant *Staphylococcus aureus* (MRSA) (52). However, genotypic resistance was sometimes different from phenotypic resistance, and even there would be further verified by phenotypic resistance profiles (52). Biomarkers which could predict phenotypes might be more useful and make fewer mistakes. Unfortunately, there is still a long way to go.

Compared to direct evidence, indirect evidence may be the other direction. A study was conducted to analyze volatile organic compounds (VOCs) of bacteria. It aimed to identify and compare the VOCs of antibiotic-resistant and standard strains of *Escherichia coli*, *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Acinetobacter baumannii*, and *Klebsiella pneumoniae* (53). This study demonstrated that resistant strains of bacteria produced VOCs were different from those of the standard strains (53). Another study *in vitro* showed that different interferon (IFN) subtypes played different roles for MRSA infection. IFN-β reduces host susceptibility to MRSA infection, while IFN-α increases susceptibility (54). This indicated different bacterial resistant species infection after influenza virus infection.

Biomarkers for neonatal sepsis

Neonatal sepsis is a leading cause of global mortality in children younger than 1 year (55). The initial, clinical presentation is often subtle and nonspecific. There are many studies about using biomarkers to predict neonatal sepsis (56). Based on the timing of the infection, neonatal sepsis is classified into early-onset sepsis (EOS) (≤3 days of life) and late-onset sepsis (LOS) (4–30 days) (57,58). Pathogens associated with EOS and LOS are similar, but not the same (59). For EOS, the pathogens are mostly transmitted from mothers to infants during the intrapartum period, and LOS may be caused by vertically or horizontally acquired pathogens from the environment after birth (59). This review summarized some biomarkers validated in neonatal sepsis. Similar to their utilization in adult sepsis, there are excellent prospects for CRP, and PCT, for the treatment of neonatal sepsis (60).

A large multicenter, randomized controlled trial assessed PCT-guided decision making for suspected EOS (56). Compared with the standard group, the duration of antibiotic therapy of the PCT group was reduced (55.1 *vs.* 65.1 h) (56). This study showed the critical role of PCT in antibiotic stewardship. The meta-analysis and systematic review also revealed that the combination of PCT and CRP or presepsin alone improves the accuracy of the diagnosis of neonatal sepsis (61).

However, PCT has some limitations. PCT level is elevated in non-infected newborns requiring neonatal resuscitation and in infants born to mothers with chorioamnionitis (59,62). In healthy neonates, PCT level is affected by maternal *Streptococcus agalactiae* (GBS) colonization and prolonged rupture of membranes ≥18 h (59,63). Therefore, it is possible to try harder in the setting of a more accurate cutoff valve in neonatal sepsis.

Conclusions

Clinical practice needs to balance the benefits of an earlier infectious identification, appropriate empirical and targeted therapy, and right duration with harms. Clinicians and investigators have been exploring ideal biomarkers for the balance. Perfection is approachable, but it cannot be reached. PCT and CRP have been most widely used, but none has sufficient specificity or sensitivity for rapid diagnosis and treatment of infection or sepsis. Previous studies suggested that biomarker combination would be helpful to improve diagnostic performance. The combination may be more accurate and sensitive, would be more useful in clinical practice for adult and children patients. There are some limitations of PCT, CRP, or combined with other factors. Biomarkers could not predict resistant. With the development of molecular diagnosis, biomarkers would not be the only choice for rapid diagnosis. In conclusion, biomarkers are both friend and foe. The most important thing for clinical practice is to understand the advantages and disadvantages of different

methods so that to use them reasonably.

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Footnote

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