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 units (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
What is an ideal biomarker? First, they can be used to...
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 (COX3b) (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 prophage phiRv2 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 presepin 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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