Biomarkers of Infection and Inflammation

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LEARNING OBJECTIVES

1. Define the term "biomarker."
2. Describe the traditional, newer, and future biomarkers of sepsis discussed in this article.
3. Identify the emergent biomarkers of chronic wound infections, pneumonia, and invasive fungal infections discussed in this article.

ABSTRACT

Biomarkers, or biological markers, have been tested in the clinical laboratory for decades. More recently, there has been a surge in research studies aimed at identifying biomarkers of infection and inflammation. One of the foremost motivators in this expansion of research is the quest to find ideal biomarkers for sepsis. Traditional, yet still relevant, laboratory markers of infection and inflammation consist of the white blood cell count, erythrocyte sedimentation rate, and C- reactive protein. Newer biomarkers that are currently available in the clinical laboratory and used for the evaluation of sepsis include lactate and procalcitonin, whereas 2 promising emergent biomarkers for the evaluation of sepsis, pentraxin 3, and presepsin, are presented. Beyond sepsis, promising emergent biomarkers for chronic wound infections, pneumonia, and invasive fungal infections are also discussed.

ABBREVIATIONS: BDG - 1,3-β-D-glucan, CD14 - cluster of differentiation 14, CRP - C-reactive protein, ESR - erythrocyte sedimentation rate, FDA - Food and Drug Administration, GM - galactomannan, IL - interleukin, PCT - procalcitonin, PTX3 - pentraxin 3, WBC - white blood cell.

INDEX TERMS: biomarker, infection, inflammation, sepsis.

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INTRODUCTION TO BIOMARKERS

Identification of microorganisms and their antimicrobial susceptibility patterns are the primary objectives of a microbiology department. Other laboratory departments (in particular clinical chemistry and hematology) have played a supportive role in the diagnosis of infection with the detection and quantification of circulating markers known as biomarkers. As the microbiology department has evolved because of technological advances, we have also seen a boom in research to discover superior biomarkers of infection and inflammation.

The term biomarker can have different meanings depending upon the context, thus in 2001 it was standardized as "a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention."[1] With this definition, biomarkers encompass results of laboratory testing, imaging techniques (eg, magnetic resonance imaging), and recordings of physiological tests (eg, blood pressure, electrocardiogram).[2-6] Biomarkers are often classified by their application for diagnostic, predictive, and prognostic purposes; monitoring of treatment; pharmacodynamic response; and safety.[2] Diagnostic biomarkers detect the presence of disease, whereas prognostic biomarkers are used in identifying the probability of disease recurrence or progression. Predictive biomarkers aid in identifying those who will respond to therapy.[2,7] Monitoring of treatment biomarkers is used to assess the status of a disease. Biomarkers that change in concentration upon exposure to a medical product are known as pharmacodynamic response biomarkers.[2,7,8] Lastly, safety biomarkers indicate the presence or risk of an adverse event due to medical intervention.[2,4]

BIOMARKERS IN THE CLINICAL LABORATORY

For this review, the definition of a biomarker provided by the National Cancer Institute (part of the National Institutes of Health), "a biological molecule found in blood, other bodily fluids, or tissues that is a sign of a normal or abnormal process, or of a condition or disease," will be used, as it is more specific to laboratory testing.[9] Biomarkers have been detected since the beginning of the 20th century, yet the term is relatively new.[6,10] Examples of established biomarkers include pancreatic enzymes (amylase and lipase), acute myocardial infarction markers (creatine kinase-MB and cardiac troponin), kidney metabolites (creatinine and urea), liver enzymes (alanine aminotransferase and aspartate aminotransferase), and tumor markers (prostate-specific antigen and cancer antigen 125).[6,10] Biomarker research has expanded over the past few decades due to their potential to improve success

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rates in drug development and advances in -omic (genomics, transcriptomics, proteomics, peptidomics, and metabolomics) technologies.[11] Nevertheless, the number of biomarkers cleared by the US Food and Drug Administration (FDA) has not increased. According to Pavlov (2013), this is due to the lengthy and challenging process of going from biomarker discovery to FDA clearance for clinical testing.[11]

The FDA has a pathway for developing disease-related biomarkers that consists of a multistep process.[4] A simplistic description would be to describe the pathway occurring in 4 main phases. The first phase is discovery and consists of exploratory studies that are performed to identify promising biomarkers.[4,11] The second phase is analytical validation that includes analysis of performance metrics, ensuring the test is reliable, reproducible, and of adequate sensitivity and specificity. The next phase is clinical validation that focuses on how well the test measures a clinical feature of the disease, disease outcome, or outcome of treatment. The final phase is clinical utility and is established by how well the test either confirms a diagnosis, improves patient outcomes, determines appropriate treatment, or monitors treatment.[4] Assay development is interwoven within the phases, as it is a continuous process that begins after discovery but can be modified throughout any phase of the process.[11]

The multiphase process described above is a long and arduous journey that can take up to 10 years from discovery phase to clearance by the FDA.[11] Researchers encounter many challenges throughout this lengthy process. Major challenges include relatively high false- positive rates, lack of rigorous validation studies, or scarcity of data showing significant contribution to clinical practice.[11] With each phase, the financial burden increases, and often industry enters after the second phase to provide financial support. Industry involvement presents new challenges, such as ownership of intellectual property.[11]

This article focuses on biomarkers of infection (primarily bacterial infections) and inflammation. Biomarkers of inflammation are included as they typically rise in response to an infection. The presentation of these biomarkers will begin with a brief review of conventional laboratory makers of infection and inflammation (Table 1), which will be followed by a review of more recent biomarkers used for the diagnosis and prognosis of sepsis (Table 2). Finally, emergent or promising biomarkers for bacterial and fungal infections that are prevalent in the literature will be succinctly presented (Table 2).

Table 1. Traditional biomarkers used in infection and inflammation

Biomarker	Detection of
WBC Count	Bacterial infection
ESR	Inflammation
CRP	Bacterial infection and inflammation
Serological markers	Bacterial and viral infection

TRADITIONAL LABORATORY MARKERS OF INFECTION AND INFLAMMATION

Traditional or established laboratory markers consist of hematological parameters of infection, inflammatory response markers, and serological markers of bacterial and viral infections. Hematological parameters, such as the white blood cell (WBC) count, have long been used as biomarkers of infection and inflammation. As the role of leukocytes is to protect the host against infectious agents and provide an immune defense, an elevated WBC count is often an early biomarker of infection.[12,13] The leukocyte differential, another component of the complete blood count, also provides insight into infectious disease states.[12]

Two traditional markers of infection and/or inflammation include the erythrocyte sedimentation rate (ESR) and

Table 2. Newer biomarkers for sepsis and future biomarkers of infection and inflammation

Biomarker	Detection of	Commonly Used to Detect	Promising Use
Procalcitonin	Bacterial infection	Sepsis	Pneumonia and other bacterial infection
Lactate	Bacterial infection	Sepsis	
Pentraxin 3	Bacterial infection		Sepsis
Presepsin	Bacterial infection		Sepsis and other bacterial infection
Human neutrophil elastase	Bacterial infection		Bacterial wound infection
Cathepsin G	Bacterial infection		Bacterial wound infection
Interleukin-6	Bacterial infection		Pneumonia
Galactomannan	Fungal infection		Various fungal species
1,3-β-D-glucan	Fungal infection		Various fungal species
D-arabinitol	Fungal infection		*Candida* species
Gliotoxin	Fungal infection		*Aspergillus fumigatus*

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C-reactive protein (CRP). The ESR, introduced by Westergren in 1921, remains a customary test in the hematology department and measures the rate at which erythrocytes fall in a vertical column over a specified period of time.[14-16] It is an indirect measure of the acute phase reaction and is increased in inflammation. The ESR is nonspecific and may be influenced by several factors, for example, the presence of acute phase proteins, quantity of erythrocytes, and levels of plasma proteins.[12,15] Regardless, a common cause of an elevated ESR is an infectious agent.[12] The clinical value of ESR has been debated because of its lack of specificity; however, it remains a commonly ordered test.[17-20]

CRP is an acute-phase plasma protein and is a member of the pentraxin protein family.[15] CRP plays a significant role in the host defense (innate immunity) against pathogenic bacteria by recognizing bacteria and activating the complement cascade or triggering opsonization leading to phagocytosis.[15,21] The concentration of CRP in serum quickly rises in response to infection (bacterial and parasitic) or tissue injury (traumatic necrosis and malignancies).[21] The rise can be 1000-fold above the normal value and may be proportional to the intensity of the inflammatory process.[15,21,22] Because of its rapid response in an acute inflammatory process, it is a valuable marker of the acute phase response.[21] CRP is often considered a better marker than ESR because of its sensitivity and rapid detection of changes in the acute phase reaction for disease.[23]

Serological markers are established biomarkers that aid in the diagnosis of infectious disease through the identification of the causative agent or the indication of infection.

Serodiagnosis is based on "the principle that the reaction between an antibody and an antigen will result in a recordable event" with a goal of identifying "an antigen or antibody in order to help determine the etiologic importance of a particular microorganism."[24] For brevity, serological markers will be discussed globally in relation to bacterial and viral infections.

Serological testing may be used to directly identify bacterial agents, such as *Treponema pallidum, Borrelia burgdorferi* (causative agent of Lyme disease), *Coxiella burnetii,* and *Rickettsia* and *Streptococcus* species.[25] In addition, serological testing, often in the form of an immunoassay, is commonly used in the diagnosis of viral infections caused by hepatitis viruses and the human immunodeficiency virus.[26,27] For many years, serological testing was primarily performed in the microbiology department; however, because of advances in technology, most serological assays are performed today on automated clinical chemistry analyzers.[27]

NEWER BIOMARKERS OF INFECTION AND INFLAMMATION: SEPSIS

Febrile illness resulting from bacterial infection is a common cause of hospitalization and is a contributing factor in the growth of biomarker research.[28] The overwhelming concern of any bacterial infection is progression to sepsis because of its high mortality rate. Worldwide sepsis is responsible for 30 million cases, resulting in 8 million deaths.[29] To date, there is not a gold standard test for sepsis, yet several researchers are looking at emergent biomarkers with optimism.[30] The quest for an ideal biomarker of bacterial infection, especially sepsis, is a marker that allows for early diagnosis, aids in prognosis, and/or provides guidance in treatment.[28]

To date, approximately 200 biomarkers have been studied in the evaluation of sepsis, with CRP, procalcitonin (PCT), and lactate being the most commonly ordered.[31] PCT has been an orderable test for years, but it was recently rediscovered as a biomarker for bacterial infections.[32,33] PCT is a prohormone or precursor to calcitonin (the hormone that regulates calcium concentration), and it is not normally released into the bloodstream unless stimulated by infection and inflammation.[34,35] PCT production is stimulated directly by bacterial endotoxins or indirectly by inflammatory mediators and rises quickly after the onset of infection.[35-37] PCT levels increase significantly in systemic infections, such as sepsis, thus it is a reliable biomarker for early diagnosis of sepsis and/or for response to therapy.[35] PCT does have a major limitation: It is elevated in pneumonia and other infectious diseases, including those of the lower respiratory and urinary tracts, as well as in postsurgical and abdominal infections.[35,37,38]

Lactate is another common biomarker for sepsis. Elevated serum lactate levels (hyperlactatemia) are often seen in patients with severe sepsis, thus it is often measured to monitor patients that are at high risk of impending septic shock.[31] Lactate formation during sepsis is often due to inadequate oxygen delivery resulting in tissue hypoxia, but there are other etiologies (eg, underlying disease, drug, toxins) that can contribute to elevated levels that must be taken into consideration.[39] Elevated lactate levels indicate tissue hypoperfusion and are correlated with an increased mortality rate in patients with sepsis.[39-41]

Both PCT and lactate have been included as recommended biomarkers in the *Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock: 2016.*[42] The initiative of this campaign is to decrease the mortality of patients due to sepsis.[42] In the quest for ideal biomarkers for sepsis, it is becoming more apparent that no single, gold-standard biomarker may exist, as biomarkers are now often studied in groups (panels of multiple biomarkers) due to increased sensitivity and specificity for disease detection when measured collectively.[3,43]

FUTURE BIOMARKERS OF INFECTION AND INFLAMMATION: SEPSIS

As numerous biomarkers are being studied for the diagnosis and prognosis of sepsis, only 2 promising biomarkers,

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pentraxin 3 (PTX3) and presepsin, will be presented. PTX3 is an acute phase protein and member of the pentraxin superfamily of proteins. PTX3 is stored in the granules of neutrophils and released in inflammatory conditions.[44] During inflammatory processes, PTX3 can be produced by a variety of cells, including endothelial cells, mononuclear phagocytes, and dendritic cells.[44-46] PTX3 aids in pathogen recognition, promotion of phagocytosis, and complement activation.[47] In sepsis, PTX3 levels significantly increase often within 24 hours of infection, making it a valuable diagnostic biomarker.[46-49] In addition, research studies have found that PTX3 levels will remain elevated if treatment is not effective and will continue to rise if the infection worsens (severe sepsis and septic shock), thus indicating the prognostic value of this biomarker.[46-49]

Presepsin is the soluble form of cluster of differentiation 14 (CD14) that has been investigated for almost 2 decades as a biomarker for sepsis.[33,50] CD14 is expressed on the membrane of monocytes and macrophages and is a pattern recognition molecule (aiding in pathogen recognition) of the innate immune system.[51,52] After recognition, soluble CD14 is released, resulting in presepsin formation, and levels in circulation may reflect systemic inflammation.[32,34,51] Presepsin is normally present in low concentration in healthy individuals and has been shown to increase in bacterial infections with significant increases observed in systemic bacterial infections.[51,52] Some studies indicate that presepsin might have better sensitivity and specificity than currently used biomarkers for sepsis.[50,53] Additional studies are evaluating the utility of presepsin as a biomarker for other bacterial infections, for example, pneumonia and bacterial meningitis.[54]

Numerous research studies have focused on cytokines required to initiate and maintain the inflammatory response.[55,56] Many of the inflammation-promoting cytokines (eg, interleukin [IL]- 3, IL-6, IL-8, IL-27, IL-37) are being studied as possible biomarkers for bacterial infections, specifically sepsis.[57-61] Additionally, innate immune system cells, such as neutrophils and monocytes, are being further evaluated as promising biomarkers that would be used in conjunction with more traditional biomarkers.[62,63] In comparison to traditional biomarkers, the use of biomarkers in sepsis is in its infancy, and more research is required.[30]

FUTURE BIOMARKERS OF INFECTION AND INFLAMMATION: OTHER INFECTIONS

Biomarkers are being investigated for a variety of other bacterial and fungal infections. Chronic wound infections are a growing problem worldwide and a life-threatening complication for patients.[64] Early identification of bacterial wound infections, especially in patients that do not have the classic clinical signs of inflammation and purulent secretions, can prevent progression to severe infection and/or sepsis.[65] Quantifying enzyme activity in wound fluid is being investigated, as it could allow for early detection of bacterial infection. Two potential enzyme biomarkers are being studied; the human neutrophil elastase and cathepsin G.[64,65] These enzymes are secreted into the wound as an immune-mediated response to infection.[65] Neutrophil elastase and cathepsin G are proteases stored in neutrophil azurophilic granules that are released during inflammation and help degrade bacteria during phagocytosis.[64,66] Researchers are also investigating other enzymes and proteins as possible emergent biomarkers of bacterial wound infections.[65]

Pneumonia is one of the most common lower respiratory tract infections and is a leading cause of mortality worldwide.[67-69] For bacterial pneumonia, timely antibiotic treatment is important for prognosis. The ideal biomarker for bacterial pneumonia either indicates inflammation or is released from the lung due to infection.[67] The most widely used biomarkers for diagnosis and prognosis of bacterial pneumonia include CRP and PCT, although both can be elevated in other bacterial infections and conditions.[67,68] PCT is often used to guide the initiation and duration of antibiotic treatment.[70] Novel biomarkers for pneumonia are continually sought out with several studies investigating the potential of IL-6, a cytokine in the acute phase response that is elevated in patients with pneumonia.[67,71-73]

Invasive fungal infections are of worldwide importance because of an increasing immunosuppressed population and increasing numbers of transplant recipients.[74] Current methods of diagnosis of invasive fungal infections are routinely used but have limitations. The major limitation of traditional microbiological methods of diagnosis is the time necessary for fungal culture growth, whereas traditional serological methods (including immunodiffusion and fungal antigen detection) can have low sensitivity and/or specificity.[74,75] Matrix-assisted laser desorption ionization time of flight, a more recently utilized identification technique, also requires growth in culture first.[75] Because of the limitations of traditional and current testing, the development of alternative rapid tests (that do not need growth in culture), such as biomarkers and molecular-based tests, are growing.[75]

For more than 2 decades, research has been ongoing for 2 fungal biomarkers: galactomannan (GM) and 1,3-β-D-glucan (BDG).[75,76] GM is a cell-wall polysaccharide that is released from hyphae of *Aspergillus* spp and other fungi in body fluids. There are FDA-approved immunoassays for the detection of GM in serum and bronchoalveolar lavage.[74-76] Another circulating biomarker of fungal infection is BDG, a cell wall glucose polysaccharide found in the majority of fungi.[74-76] The BDG assay can detect a variety of clinically important fungi except for *Cryptococcus* spp, *Blastomyces dermatitidis*, and the *Mucorales* group, as they either lack BDG entirely or produce it at minimal levels.[75-77] Both biomarkers have limitations, so it is recommended to use them in conjunction with clinical symptoms and other test results.[74] Possible future biomarkers for invasive fungal infections include D-arabinitol,

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a metabolite of most pathogenic *Candida* species, and gliotoxin, a metabolite released by *Aspergillus fumigatus*.[75,77,78]

SUMMARY

Biomarker detection can identify disease states while also providing information about the progression of infection and prognosis for recovery. Biomarkers have been tested in clinical laboratories for decades, but due to the push for personalized medicine and the advances in -omics technology, biomarker research has seen significant growth despite the limited number of biomarkers cleared by the US FDA. Biomarker assays need to be available at a relatively low cost, be reliable, be reproducible, be sensitive, be specific, and provide information that is not already available from a clinical assessment. A single biomarker or a multiple-biomarker panel that meets the above criteria is still being sought for infection and inflammation.

Worldwide health concerns, in particular sepsis, have seen significant research into finding the gold standard biomarker(s). To date, only PCT and lactate are recommended for clinical testing; however, hundreds have been investigated for their potential as an emergent sepsis biomarker, including PTX3 and presepsin. Emergent biomarkers have also been identified for other disease states, including pneumonia, wound infections, and fungal infections. This review has pertained primarily to biomarkers of infection and inflammation, yet it is worth noting from the literature review conducted that biomarkers are being investigated for a multitude of diseases and conditions.

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