Review Article

Septicemia: An Extreme Host Response to a Global Healthcare Problem

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The invasion of the bloodstream by an infectious agent, is one of the most serious and life threatening conditions and a growing worldwide healthcare concern. In addition, there has been significant controversy regarding the risk factors associated with the development of blood stream infections, the classification of these infections, diagnostic criteria and treatment. Many other factors such as the infecting microorganism and geographical location play an intricate role in the development of blood stream infections. This paper is an introduction to a series of reviews concerning the changing laboratory diagnostics of sepsis from traditional microbiology, to molecular diagnostics and automation, and a variety of physiologically relevant biomarkers.

An understanding of the brief history, definition of and ambiguity associated with the classification of sepsis and related blood stream infections including septic shock and the systemic inflammatory response syndrome (SIRS) is necessary in order to examine the use of traditional microbiological methods, the use of biomarkers and the introduction of molecular diagnostics and automation in the evolution of sepsis management in order to improve patient care, prognosis and treatment of sepsis in a global healthcare environment.

Key words: septicemia, sepsis, severe sepsis, bloodstream infections, septic shock

Introduction

The invasion of the bloodstream by an infectious agent, is one of the most serious and life threatening conditions and a growing worldwide healthcare concern. The World Health Organization identified sepsis as a global health problem in 2017 adopting a resolution to improve the diagnosis, management and prevention of sepsis.[1] Many risk factors are associated with the development of sepsis including age, with extremely old or young patients more often affected and patients with immunosuppressive diseases such as cancer or acquired immunodeficiency syndrome (AIDS), diabetes, alcohol abuse as well as any condition that alters the integrity of the skin can predispose a patient to the development of sepsis.[1] Improvements in medical care for critically ill patients with various cancers and immunocompromised patients (i.e. AIDS or transplant associated) provide the ideal conditions for an infectious agent to invade the bloodstream and disseminate to other areas of the body causing extensive damage to various organ systems and in many cases death. These infections result in a high rate of morbidity and mortality between 15 and 30%.[2] The incidence of sepsis is dependent on the specific definition used for the condition, the infecting microorganism, the reporting mechanism and the requirement for organ support or intensive care treatment for the patient.[1] Variation in the incidence rate of blood stream infections (BSI's) is reportedly different based on geographical location with high-income from countries reporting up to 2.8 million deaths per year

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sepsis. For example, the United Kingdom reports a 27% prevalence of sepsis in total intensive care unit (ICU) admissions and the United states reports a prevalence of 12%.[1,3] Reportedly, BSI's account for approximately 15% of all health care associated infections, which can be defined as the acquisition of an infection or has a central line for ≥ 48 hours.[4] Community acquired BSI's also occur and are present or develop prior to hospital admission. Approximately 80% of all cases of sepsis may arise from community acquired blood stream infections.[1] The classification of BSI's as either hospital acquired, health-care associated or community acquired infection are used to identify the risk factors associated with BSI as well as for epidemiological and infection control prevention practices.

History and Definitions

The term sepsis, comes from the Greek word for putrefaction or decay of organic matter and can be traced back to more than 2700 years ago in the medical literature.[5] The presence of any substance in the blood stream is referred to asemia which is also derived from the Greek word meaning blood.[6] This terminology includes bacteremia, the presence of bacteria in the blood; viremia, the presence of a virus in the blood; parasitemia, the presence of a parasite in the blood or fungemia, the presence of fungi in the blood. Whether the presence is transient, intermittent, or continuous, these conditions can lead to sepsis or septicemia. Septicemia is then further defined as not only the presence of an infectious agent in the blood stream but also the development of an infection as a result of the microorganism reproducing and eventually leading to injury or illness to the patient.[6] These definitions are primarily derived from the traditional methods for diagnosis of the infection that is defined by the microbiology laboratory and does not consider the medical definition of sepsis as it relates to the physiological status of the patient.

Sepsis was medically defined in the early 1990's by a panel of experts based on four systemic inflammatory response syndrome (SIRS) criteria, including tachycardia (heart rate > 90 beats per minute), tachypnea (respiratory rate > 20 breaths per minute), fever or hypothermia (>38°C or < 36°C). Leukocytosis (white blood cells > 12000/ mm^3), leukopenia (white blood cells < 4000/ mm^3) or bandemia (10% immature neutrophils). SIRS is further defined as a documented or suspected blood stream infection with evidence of two or more of the previously listed criteria.[3,5,6,7] Signs and symptoms of SIRS in addition to these criteria may include hyperventilation leading to excess loss of carbon dioxide from the body and subsequent respiratory alkalosis (a condition caused by the loss of acid leading to an increase in pH), skin lesions, change in mental status, and diarrhea.[6] Severe sepsis was then further defined as sepsis complicated by acute organ dysfunction that can lead to septic shock. Clinically, septic shock manifests with additional signs and symptoms including acute respiratory distress, renal failure, disseminated intravascular coagulation, and tissue destruction.[5,7] Septic shock has been reported to cause more than 40% of hospital related patient mortality rates.[7] This condition is mediated by the production of bacterial exotoxins, the presence of bacterial endotoxin and the host's inflammatory response including the production of cytokines such as tumor necrosis factor and other interleukins. The host's overall inflammatory response to a blood stream infection that results in the development of septic shock is one of the most serious complications associated with sepsis.

As sepsis progresses, it is believed to be important to utilize standard criteria to help monitor the progression and treatment of these patients in order to prevent further infection and systemic organ damage and dysfunction that can lead to death. In order to develop standardization associated with the diagnosis of sepsis, organ dysfunction was clinically classified using a system referred to as the Sequential (Sepsis-related) Organ Failure Assessment Score (SOFA).[1,5] The SOFA score utilizes specific functional criteria to assess the respiratory system, central nervous system, liver function, cardiovascular system, coagulation and renal system in BSI's. Multiple studies have examined the effectiveness of using the SOFA score for the diagnosis and prognosis associated with BSI. These studies suggest that there is a high correlation with sequential systemic monitoring of organ dysfunction and an increase in the SOFA score within the first 48 hours of admission to an intensive care unit with a mortality rate of > 50%.[8] Additional organ function scoring systems exist, including the mid-regional proadrenomedullin

(MR-proADM) and the APACHE II system, but there has been no standardization or complete agreement on the use of these methods.

Since the development of the original SOFA scoring system, severe sepsis as well as the clinical parameters for organ dysfunction have been eliminated from the definitions and recommendations for the diagnosis of sepsis.[10] The 2016 task force addressing the Third International Consensus Definitions of Sepsis and Septic Shock (Sepsis-3) updated the definitions using large sets of data to the following:

Sepsis

(a) Life-threatening organ dysfunction by a dysregulated host response to the infection.

(b) Organ dysfunction as identified by an acute change in total SOFA score ≥ 2 points.

Septic Shock

(a) Sepsis with underlying circulator and cellular/metabolic abnormalities that are profound enough to increase mortality.

(b) Clinically defined sepsis with persisting hypotension requiring vasopression to maintain mean arterial pressure ≥ 65 mm Hg and with serum lactate > 22 mmol/L.[5,7]

In addition to updating and improving these definitions, the task force also used the SOFA score to develop a quick SOFA that could be performed rapidly at the bedside of the patient. The qSOFA (quick SOFA) includes three components that include an assessment of the patient's respiratory rate (≥ 22 breaths per minute), altered mental state and a systolic blood pressure of 100 mm Hg or less.[5,10] These criteria on the surface seem rather simple, non-labor intensive and can be used in a variety of settings from the hospitalized patient to the emergency room in order to improve diagnosis and patient care.

There are however, significant limitations when using the Sepsis-3 definitions and qSOFA for the diagnosis and initiation of treatment for sepsis. These limitations are associated with the data collection process and analysis being limited to mostly resource rich countries such as the United States as previously indicated in this document. This makes it difficult to apply the criteria universally to patient populations and medical care in other countries. Secondly, most of the data that has been collected applies to the adult population lacking data or predictive value associated with pediatric blood stream infections and patients after the first 48 hours in ICU.[5,11] As a result, SOFA has not been universally or globally accepted as the best practice in the diagnosis, management and treatment for sepsis or septic shock.

Lastly, and arguably not any less important, is the fact that sepsis has been primarily treated as a consequence associated with patient comorbidity or predisposition for the development of sepsis in conjunction with the characteristics or virulence factors of the infecting organism without consideration for the patient's natural immune defense mechanisms and physiological influence. Additional factors such as the patient's genetic make-up, likely influence the risk for the development of sepsis similarly to any other advanced disease process. Studies indicate that genetic influences or alternate alleles for inflammatory cytokines such as TNF-α and regulatory cell surface markers on immune cells also play a role in the development of sepsis.[1,12]

Laboratory Diagnosis

Primary care providers and clinicians are ultimately responsible to initiate the proper treatment and procedures in any case of suspected sepsis or septic shock. However, the clinical diagnostic laboratory and ancillary laboratory services play a crucial role in this decision, as well as insuring a rapid and accurate diagnosis for proper therapeutic management of the infections. Laboratory diagnosis of BSIs have historically relied on microbiological culture-based methods. However, it is very clear that not any one single method has demonstrated sufficient clinical success to be considered the "gold standard" for the diagnosis of BSI's. Advances in medical technology and the implementation of molecular based testing, has rapidly improved this process along with the use of biomarkers to assist in the recovery and identification of the infecting microorganism, the guidance of antimicrobial therapy, the removal of vascular lines and the implementation of other clinical interventions. These methods however, are not mutually exclusive and should be used in combination to insure proper diagnosis.

Specimen collection requires a standardized procedure including proper antisepsis, timing and number of cultures, volume of sample, the proper use of anticoagulants and proper media. Pathogen detection and identification using culture-based

methods rely more heavily on proper specimen collection without contamination than the newer methods in molecular microbiology or other non-culture based laboratory tests.[6] Only 60-65% of the etiologic agent of infection is identified in patients with positive blood cultures using culture-based methods.[6] This may be due to several factors that include the administration of antibiotics prior to specimen collection, the organism failure to grow in the culture media, the organism is a slow-grower such as in fungenemia, insufficient specimen volume, or the culture was contaminated during collection. As a result, a variety of non-culture based nucleic acid-based methods have been developed in recent years that include direct hybridization or amplification techniques. These techniques not only detect genetic markers that can be used to identify the suspected pathogen but may also detect antibiotic resistance genes to avoid improper treatment of the infection.

In addition to microbiological culture and non-culture-based methods, hematological and biochemical parameters are available and can enhance the diagnosis of sepsis. This would include a complete blood count, metabolic panel that includes liver and renal function tests, and coagulation tests. These laboratory tests identify the signs of SIR's and evaluate the immune status of the patient. Additional biomarkers such as procalcitonin and lactate may also be used to diagnose sepsis and predict the success or failure of antimicrobial treatment.[13,14] Because sepsis is a multifactorial process that involves a systemic inflammatory response and various organ systems, the pattern of host response biomarkers can also be used to determine the patient's condition, provide supportive therapy and provide prognostic value. RNA expression patterns (transcriptomes) have been used to discriminate sepsis from non-infectious conditions in critically ill patients.[6]

Sepsis biomarkers, including patterns of inflammatory cytokines, can be used to diagnose sepsis, provide prognostic value and theranostic value to individualize patient treatment.[1,5,12] One example is TNF-α, a pro-inflammatory cytokine that plays a major role in response to infection as well as mediating the release of many other inflammatory molecules. When a pathogen enters the blood stream, a multitude of immune cells that includes lymphocytes, monocytes and macrophages begin to secrete a series of cytokines such as TNF-α. TNF-α is predominantly produced by macrophages (activated monocytes), in response to infection. This results in an elevation of the cytokine during infection. However, serum levels of TNF-α have been shown to inversely correlate with the survival from severe sepsis.[15] In other words, when the levels of TNF-α increase in the blood stream in some patients the likely-hood of survival from sepsis decreases. This unexpected inverse correlation, prompted a series of studies that examined the levels of expression of TNF-α as well as other proinflammatory cytokines in sepsis and septic shock. A study by O'Keefe indicated that a single nucleotide polymorphism in the promoter for TNF-α alters the level of transcription of the gene in response to infection and inflammatory disease and is related to poor patient outcomes, including the development of sepsis.[12] The study examined SNP variation in the promoter for TNF-α in 152 patients with severe trauma. The study demonstrated that patients with a G-A SNP at -308 in the genetic sequence was associated with a four-fold greater risk for the development of sepsis. This particular genetic change results in upregulation or increased transcription of TNF-α.[16] When compared to other traditional risk factors such as age or transfusion of blood products within the first 24 hours following trauma, the SNP was a stronger risk factor and more predictive for the development of sepsis.[13] There are conflicting studies in the literature related to TNF-α as it relates to the development of sepsis in different patient populations.[16]

The human inflammatory response is not unlike the complex factors that influence sepsis and relies on the expression of many other cytokines such as TNF-α. It is reasonable to expect variation in the expression and levels of cytokine production in different patient populations as well as in response to different infecting organisms. Additional studies have examined other inflammatory cytokines that include a variety of interleukins, interferons, selectins, and macrophage inflammatory proteins in response to different types of microorganisms such as Gram-positive, Gram-negative and fungal infections.[17] Different types of blood stream pathogens seem to demonstrate alternate cytokine profiles independent of a standard control group, that may be useful in early detection of sepsis.[17] These studies support the evidence that the

development of sepsis and septic shock is influenced by the types of infecting organisms and the patient's genetic make-up. This further supports the need for the development of advanced technology, molecular methodologies, the use of biomarkers and personalized medicine in the future of our understanding of the development, diagnosis, and management of sepsis.

Summary

Despite the advances in laboratory diagnostics and medical treatment, there remain no clear, reliable laboratory-based criteria for the absolute prediction of a patient's response and outcome associated with a BSI. The Surviving Sepsis Campaign (http://www.survivingsepsis.org) is a group of international critical care and infectious disease professionals whose mission is to improve the diagnosis, treatment and outcome in cases of sepsis and septic shock. It provides guidance on rapid diagnosis and intervention using a 24-hour sepsis pathway and a critical 6-hour course of action.[18] This series of papers is intended to provide a review of traditional microbiological techniques, an overview of some of the more recent, rapid molecular methodologies and the use of representative biomarkers in the diagnosis and management of sepsis. Despite advances in medical laboratory diagnostics, blood cultures remain the standard for the identification and diagnosis of sepsis and septic shock.[18]

It is clear that sepsis and septic shock are all dynamic and ambiguous definitions when it comes to the patient's genetic predisposition, comorbidities, infecting organisms and the level or progression of medical care available to a patient. Despite all the efforts in advanced diagnostics, prognostics and treatment, sepsis will continue to remain a global problem as a result in an increase in patient survival from critical illnesses and the emergence of antibiotic resistance. The ultimate goal is to continue to collect evidence-based data in order to improve patient care, reduce length of stay and medical costs in an overall effort to reduce mortality rates associated with blood stream infections.

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