Sepsis – An Impendence That Needs a Global Solution

Know Safety – No Infection

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ABSTRACT

Sepsis has been called a hidden public health disaster. Sepsis arises from the host response to infection, which is directed to kill the invading pathogens. It is an extreme response to an infection and one of the most common causes of multiorgan failure. The human body sends a flood of chemicals into the bloodstream to fight the threat. This causes widespread inflammation which, over time, can slow blood flow and damage the organs. Sepsis is clinically diagnosed by a combination of clinical signs, laboratory tests and microbiologically confirmed by the detection of bacteria in blood by culture. Early and aggressive management with appropriate antimicrobials and rapid and complete hemodynamic stabilization has been shown to be associated with improved outcomes. Detecting sepsis early and starting immediate treatment is often the difference between life and death.

Keywords: *Staphylococcus aureus* bacteria, septic shock, 25-hydroxyvitamin D, hospital-acquired infection, bloodstream infections, cytokines, anion gap

Saving patients from sepsis is a race against time. Sepsis is a clinical syndrome characterized by a systemic response to infection.

The lungs, kidneys and cardiovascular system are the most affected organs during sepsis and septic shock. It was found that blood glucose levels influence the mechanisms of "tolerance" against infections. In several cases where the disease tolerance fails, the clinical symptoms of sepsis often show more dramatic courses than classical infections.

The term "septic shock" refers to an elevated lactate level of >2 mmol/L. Bloodstream infections remain a major cause of morbidity and mortality despite the availability of potent antimicrobial therapy and advances in supportive care. It is estimated that Gram-negative bacilli are the cause of approximately a quarter to half of all bloodstream infections. Gram-negative sepsis carries a mortality rate of 12-38%.

Sepsis may lead to systemic vasodilation, organ injury, shock and death. Sepsis is a major public health burden in the United States. Interleukin (IL)-10 as an initial biomarker can help clinicians consider more aggressive antimicrobials for rapid bacterial load reduction in high-risk *Staphylococcus aureus* bacteria patients. *S. aureus* virulence is multifactorial, dependent on numerous toxins.

Sepsis is said to be present if a focus has developed from which pathogenic bacteria invade the bloodstream thus causing subjective and objective symptoms.

The hemodynamic, metabolic and immune changes seen in sepsis occur through mediators and cytokines that play a role in intercellular signal transmission. Cytokines show their effects not only by entering the systemic circulation but also by their direct cell-to-cell relationship and by very small concentrations.

Microorganisms do not need to pass into the blood for the development of sepsis. The local or systemic extension of signal products and toxins of the pathogen might initiate sepsis.

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The diagnostic uncertainty may contribute to delays in the initiation of lifesaving therapies and overuse of antimicrobial agents.

The biomarkers and molecular diagnostics are useful for the assessment of the host response and clinical management of sepsis. Bloodstream infections are associated with significant morbidity and mortality risks. Delayed administration of effective antibiotics increases the mortality risk.

There has been a decrease in the incidence of late-onset sepsis (LOS) over the past decade, still 34% of all extremely low birth weight infants develop LOS. The intestinal microbiota has increasingly been considered to play a pivotal role in LOS. Vitamin D plays an integral role in the functioning of the immune system.

Clinical applications of these discoveries are encouraging. An individual-level meta-analysis of randomized, controlled trials demonstrated that vitamin D supplementation reduces the risk of acute respiratory infections.

HISTORY

The term "sepsis" was introduced by Hippocrates in the fourth century BC, and it meant the process of decay or decomposition of organic matter. In the 11th century, Avicenna used the term "blood rot" for diseases linked to the severe purulent process.

The terms "septicemia" and "blood poisoning" referred to the microorganisms or their toxins in the blood and are no longer used.

The currently used terms depend on the microorganism present in blood. It is termed bacteremia if bacteria are present in the blood at abnormal levels, viremia for viruses and fungemia for fungi.

Certain mice have been found to be immune to the endotoxin-induced shock and the genetic locus for the same was found to be lipopolysaccharides. The mice were highly susceptible to infection by Gram-negative bacteria. These observations were later linked in 1998 by the discovery of the toll-like receptor gene 4 (TLR4).

Septic shock is a potential consequence of bacteremia. It is a clinical condition characterized by inadequate tissue perfusion. Most patients with septic shock have infections caused by Gram-negative enteric bacteria, *Pseudomonas aeruginosa* or *Neisseria meningitidis*. It is also associated with disease caused by Gram-positive bacteria, viruses, rickettsiae and fungi.

There was controversy over the use of mouse models in sepsis research. Hence, to continue research, one approach is to focus more on studying biopsies and clinical data from people who have had sepsis, and identify biomarkers and drug targets for intervention.

The pathogenesis of sepsis and septic shock begins with the proliferation of the microorganisms at the infection site. The microorganisms may invade the bloodstream directly or may proliferate locally and release various products into the bloodstream. These products include both structural components of the microorganisms.

"Black Death", one of the most devastating pandemics in human history, was caused by septicemia due to *Yersinia pestis*.

The increase in the number of invasive procedures being performed has led to an increased rate of sepsis. Sepsis arises from the host response to infection, which is directed to kill the invading pathogens.

NEXT-GENERATION OF SEPSIS TRIALS

S. aureus, Escherichia coli, Klebsiella, Proteus, Serratia, Pseudomonas, fecal streptococci, *Candida* are commonly occurring microorganisms in hospital-acquired infections. Respiratory infection-causing organisms are *S. aureus, Streptococcus pyogenes,* Gram-negative bacilli, *Klebsiella, Pseudomonas, Haemophilus influenzae. Streptococcus pneumoniae, Moraxella catarrhalis* and respiratory viruses. Bloodstream infections are caused by *Staphylococcus epidermidis, S. aureus,* enterococci, Gram-negative bacilli, *Candida albicans. Candida, Shigella* spp. and Rotavirus cause gastrointestinal infections. Similarly, urinary tract infections are caused by *E. coli, Klebsiella, Proteus, Serratia, Pseudomonas,* fecal streptococci, *C. albicans.*

Some patients may develop surgical site infections and stitch abscess after discharge from the hospital. Most of the infections are caused by enterococci, other non-hemolytic streptococci, anaerobic cocci, Bacteroides and gas gangrene-producing clostridia. The widespread use of antibiotics, chemotherapeutic agents, antiseptics and aseptic techniques in hospitals have produced selective pressures so that sensitive microorganisms die out and those that are resistant multiply, spread and infect patients and become predominant in patients, hospital staff and hospital environment.

Cellulitis caused by *S. aureus, S. pyogenes* or *Streptococcus agalactiae* can lead to bacteremia in about 2% of patients. Skin breakdown in bed-ridden patients (bed sores) or peripheral vascular disease from diabetes are common

causes of infected skin ulcers, which can provide a portal of entry for bacterial invasion of the bloodstream, often resulting in polymicrobial bacteremia. Some of the most commonly reported offending organisms are *Proteus mirabilis, E. coli, S. aureus, Bacteroides fragilis, Pseudomonas* spp., *Clostridium* spp.

Over the past 30 years, the prognosis for patients with severe sepsis and septic shock has improved substantially, because of the care and use of antimicrobial agents.

In the early stage of sepsis development, the main symptoms are from a decrease in systemic vascular resistance due to vasodilation. The late stage of sepsis development is caused by the body being unable to meet the oxygen demands of tissues. Tissue damage and lactic acidosis can occur, causing a hypovolemic state. Carnitine is an amino acid derivative synthesized endogenously from the essential amino acids lysine and methionine.

L-carnitine is decreased in sepsis. Carnitine is stored mainly in muscles. It has an important role in facilitating medium-chain and long-chain fatty acid transport from the cytosol into the mitochondria for β-oxidation and energy generation. It also stimulates pyruvate dehydrogenase complex activity and the Krebs cycle, increasing branched-chain amino acid oxidation in muscles. Sepsis and endotoxemia cause impaired lipid metabolism and hepatic energy generation from fatty acid oxidation. This could, in infants, lead to l-carnitine deficiency.

THE MECHANISM INVOLVED IN THE DEVELOPMENT OF SEPTIC SHOCK

Disturbances in temperature regulation may be due to direct central nervous system (CNS) effects or in the case of early febrile response, mediated by IL-1 and tumor necrosis factor (TNF) released from macrophages (e.g., IL-1, IL-8 and interferon-γ). There may be direct effects on vascular endothelial function and integrity. There is depression of cardiac muscle contractility by TNF, myocardial depressant factor and other well-defined serum factors and impairment of protein C anticoagulant pathway, resulting in disseminated intravascular coagulation. The resultant alterations in blood flow and capillary permeability lead to progressive organ dysfunction.

LACTATE AND ANION GAP

The lactate exits the cells and moves to the liver, where it is oxidized back to pyruvate and is converted to glucose via the Cori cycle.

Serum lactate measurement is useful in screening sepsis. Elevated lactate will raise the anion gap. This anion gap helps to measure lactate concentration. Lactic acidosis is the common cause of metabolic acidosis. Lactic acidosis results in excess lactic acid production. Increased lactate production obstructs the supply of tissue oxygenation and results in a defect of mitochondrial oxygen utilization. The anion gap is a good but not confirmatory screening test to identify the elevated lactic levels.

The anion gap is calculated by subtracting the serum concentrations of chloride and bicarbonate (anions) from the concentrations of sodium and potassium (cations):

$$= ([Na^+] + [K^+]) - ([Cl^-] + [HCO–3]) = 20 \text{ mEq/L}$$

Lactic acidosis in sepsis and septic shock has traditionally been explained as a result of tissue hypoxia when whole body oxygen delivery fails to meet whole body oxygen requirements.

BIOTECHNOLOGY FOR MOLECULAR DIAGNOSIS OF SEPSIS

Surviving sepsis should be the goal of every physician and survival with a good quality of life is the priority. Advances in the field of molecular biology will lead to interesting therapies and the coming years are going to witness directed therapies against the complex mediators of sepsis and personalized care.

There are many biomarkers that can be used in sepsis, but none has sufficient specificity or sensitivity to be routinely employed in clinical practice.

A combination of several sepsis biomarkers may be more effective, but this requires further evaluation. Molecular diagnostic tests (MDT) have been associated with significant decreases in mortality risk in an American antimicrobial stewardship program (ASP). Significant decrease in mortality risk was also seen for studies including Gram-positive organisms, Gram-negative organisms and multiple organism types. In addition, molecular rapid diagnostic testing (mRDT), which includes tests such as polymerase chain reaction (PCR), matrix-assisted laser desorption/ionization-time of flight (MALDI-TOF) mass spectrometry and peptide nucleic acid fluorescent *in situ* hybridization (PNA-FISH), has improved on conventional microbiologic methods, reducing time to organism identification, optimizing antimicrobial therapy, and subsequently improving clinical outcomes, including mortality rates.

American ASP guidelines recommended the use of rapid diagnostic testing (RDT) with ASP to improve clinical outcomes.

RESEARCHERS STRUGGLE TO DEVELOP NEW TREATMENT OF SEPSIS

Sepsis should be treated as a medical emergency. Deliver high-flow oxygen. Take blood cultures. Administer intravenous (IV) antibiotics. Measure serum lactate and order a full blood count. Start IV fluid replacement. Commence accurate measurement of urine output.

Antimicrobial agents remain the mainstay of treatment of bacteremia. Broad-spectrum antimicrobial agents are frequently used for initial empiric therapy and a combination of agents may be used to ensure coverage of several possible pathogens. Use the most effective agent against the responsible pathogen while minimizing the potential for adverse reactions and the emergence of antimicrobial resistance.

For infection caused by some pathogens such as *Enterococcus faecium, P. aeruginosa*, etc., a cell wall active agent such as β-lactam is combined with an aminoglycoside, resulting in a synergistic antimicrobial effect and improved clinical outcome. Along with antimicrobial therapy, drainage of infected fluid and removal of an infected intravascular catheter may be essential to achieving cure of the infection. Treatment of comorbid conditions such as diabetes is helpful for gaining control of infection.

Antisepsis therapy is used by aiming at blocking the cascade of events that result in sepsis, shock and death. Antisepsis therapy is used in combination with antimicrobial agents. Unfortunately, even with treatment, 30-50% of patients with sepsis die usually because of underlying illness in addition to sepsis. Resuscitation with IV fluids to maintain tissue perfusion is a fundamental method for the management of the septic patient.

In a patient with septic shock who does not respond to fluid support, along with fluids, respiratory therapy with oxygen is used. Drotrecogin alfa, also known as activated protein C, has been shown in clinical trials to decrease mortality in patients with septic shock. Drotrecogin alfa may also decrease chemotaxis of white blood cells by interfering with the interaction between the leukocytes and endothelium of blood vessels.

Glucocorticoids have long been of interest in the treatment of sepsis. A large number of investigational agents aimed at blocking the action of TNF and other cytokine mediators of sepsis have been studied in the treatment of sepsis.

NEW APPROACHES IN THE DISCOVERY OF NOVEL SEPSIS TREATMENT

The Surviving Sepsis Campaign (SSC) is an international collaboration established in 2002, aimed at improving outcomes in severe sepsis and especially at reducing the relative mortality. It is now firmly established that the earlier patients receive appropriate antimicrobials, the better the outcome, which means that treatment should be discussed with an expert and initiated as soon as possible rather than for instance, left until the next drug round. After recognizing sepsis, administration of 100% oxygen, taking blood cultures administration of IV antibiotics, starting fluid resuscitation, checking the hemoglobin and lactate, and placing and monitoring a urinary catheter must be done. It is with the initial recognition and management of sepsis that greatest gains can be made, and these ideas are now actively promoted by intensive care departments to non-specialist areas.

Manipulation of inflammatory mediators involved in sepsis has been proposed as a therapeutic modality, but laboratory studies have proved it difficult to translate into clinical advances. High dose steroids, antibodies against endotoxin, TNF antagonists and IL-1 receptor antagonists, all of which showed promise in animal models, have failed in clinical trials. However, administration of recombinant human activated protein C has been shown to improve the outcome of sepsis in adult patients, who on clinical grounds, are deemed at a high risk of death.

OPENING THE DEBATE ON THE NEW SEPSIS TREATMENT

The use of corticosteroids as adjunctive therapy in sepsis has been the cause of much controversy. The current recommendation is that steroids given as IV hydrocortisone in a dose of 100 mg twice a day are only used in adult patients requiring escalating catecholamine doses. An important mechanism is that corticosteroids up-regulate androgenic receptors thus augmenting the catecholamine effects. Severe sepsis may be associated with both hypo- and hyperglycemia. Children and malnourished patients are particularly prone to hyperglycemia.

EARLY RECOGNITION AND MANAGEMENT OF SEPSIS

Early recognition of the problem is crucial and management obviously requires considerably more than antimicrobial therapy. Other primary therapeutic measures include maintenance of adequate tissue

perfusion through careful fluid and electrolyte management and the use of vasoactive amines. It is also evident that protein C replacement may ameliorate coagulopathy.

Early effective fluid resuscitation is the key for the correction of sepsis-induced tissue hypoperfusion. Sepsis-induced hypoperfusion may be manifested by acute organ dysfunction and decreased blood pressure and increased serum lactate. A strategy of keeping the mean arterial pressure (MAP) >60 mmHg and ensuring lactate clearance with close hemodynamic monitoring is the goal in the initial resuscitation phase. It is unclear when vasopressors should be started during the resuscitation. The initial management of infection requires forming a probable diagnosis, obtaining cultures and initiating appropriate and timely empirical antimicrobial therapy and source control (draining pus, if appropriate). The speed of administration of appropriate antimicrobials is very important and outcomes are directly dependent on the time of antibiotic administration after the onset of sepsis.

CONCLUSION

Sepsis is one of the most challenging frontiers in internal medicine. With the increased expertise in providing organ support, increased awareness of sepsis, its early recognition and initial management, mortality is showing a downward trend. The focus should disseminate the evidence for early recognition and management of severe sepsis.

Care for critically ill patients requires a frequent reassessment of patient's condition, related treatments and repeated concomitant appreciation of overall condition and treatment goals is crucial. Sepsis, and particularly severe sepsis and septic shock, carry high mortality and merit vigorous and expert treatment. It is important to treat infection appropriately, but antimicrobials are just one among a variety of therapeutic strategies. Experience with immunomodulatory drugs has been disappointing, but further advances in our understanding of this complex condition may reveal new opportunities for intervention.

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SARS-CoV-2: People Who do not Yet Display Any Symptoms Transmitted Nearly 10% of Infections

People can transmit the virus even before symptoms begin, a scenario known as presymptomatic transmission. It has been estimated that the proportion of such people who had not yet developed symptoms transmitted around 10% of the cases.

The serial interval (time between one person developing the symptoms of a condition and a second person becoming infected and developing symptoms) for SARS-CoV-2 has been reported to be approximately 4 days… (*Medical News Today*)