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Advance Aspects of Sepsis: An Overview

Rupanshi Sharma*, Vaishali Mangal

Siddhartha Institute of Pharmacy, Uttarakhand Technical University, Dehradun (India)

ABSTRACT

It is defined as the generalized inflammatory response elicited by an infectious process. Systemic inflammatory response syndrome(SIRS) is defined as the presence of two or more of the following: (1) temperature greater than 38°C (100.4°F) or less than 36°C (96.8°F); (2) pulse rate greater than 90 beats/min; (3) respiratory rate greater than 20 breaths/min (4) Partial pressure of carbon dioxide (PCO_2) < 32 mm and (5) WBC count greater than 12,000/mm^3 or less than 4,000/mm3, or greater than 10% immature band forms. Severe sepsis is manifested by organ dysfunction (i.e. hypo perfusion, tissue hypoxia, lung injury, etc.), while septic shock is a type of severe sepsis marked by hypotension despite fluid resuscitation. Sepsis frequently occurs after hemorrhage, trauma, burn or abdominal surgery. The outcome of sepsis and septic shock has not significantly improved in recent decades despite the development of numerous drugs and supportive care therapies. To reduce sepsis-related mortality, a better understanding of molecular mechanism(s) associated with the development of sepsis and sepsis-related organ injury is essential. There is increasing evidence that Toll-like receptors (TLRs) play a key role in the mediation of systemic responses to invading pathogens during sepsis. However, the role of TLRs in the development of sepsis and in sepsis-related organ injury remains debatable.

KEY WORDS: Sepsis, Infectious process, Systemic inflammatory response, Organ dysfunction

***Corresponding author:**
Rupanshi Sharma
Siddhartha Institute of Pharmacy,
Uttarakhand Technical University, Dehradun (India)
E-mail: vaishalimangalpharmacy@gmail.com
Mob. No. 09024935998

INTRODUCTION

Sepsis has been defined as a clinical syndrome consisting of a severe infection with fever, leukocytosis or leucopenia, elevated cardiac output, and reduced systemic vascular resistance. Different microbes like bacteria, viruses, fungi etc. can cause sepsis in which bacteria are the most common. Infections in the lungs (pneumonia), bladder (Pain in the lower pelvic area & genital area), kidneys (urinary tract infections), skin (cellulitis), abdomen (such as appendicitis), and other areas (such as meningitis) can spread and lead to sepsis. Infections that develop after surgery can also lead to sepsis[1].

Sepsis and its consequence, septic shock and multiple organ dysfunction syndrome (MODS) represent a sequence of a syndrome encompassing multiple pathological processes including systemic inflammation, coagulopathy and systemic vascular collapse[2]. High level of mortality in sepsis occurs due to multiple organ failure in which main reasons are inability of circulatory system to provide adequate blood supply, oxygen and nutrient delivery to the tissues[1]. Calves with infectious diarrhoea of newborn calves (9 to 10 days of age) is characterized by watery white or yellowish diarrhoea, rapid onset and high mortality caused by rotavirus, coronavirus, enterotoxigenic E. coli and Cryposporidium parvum are particularly susceptible to gram negative sepsis because E. coli bacterial numbers normally increase 5 to 10,000 fold in the duodenum, jejunum and ileum within a short period of time (hours) after the onset of diarrhoea. Sepsis also occurs frequently in neonatal animals as horses with colic, cows with displacement of abomasum and abomasal volvulus.

Severe sepsis definition = sepsis-induced tissue hypoperfusion or organ dysfunction (any of the following thought to be due to the infection)

Sepsis-induced hypotension

Lactate above upper limits laboratory normal

Urine output < 0.5mL/kg/hr for more than 2 hrs despite adequate fluid resuscitation

Acute lung injury with PaO_2/FIO_2 < 250 in the absence of pneumonia as infection source

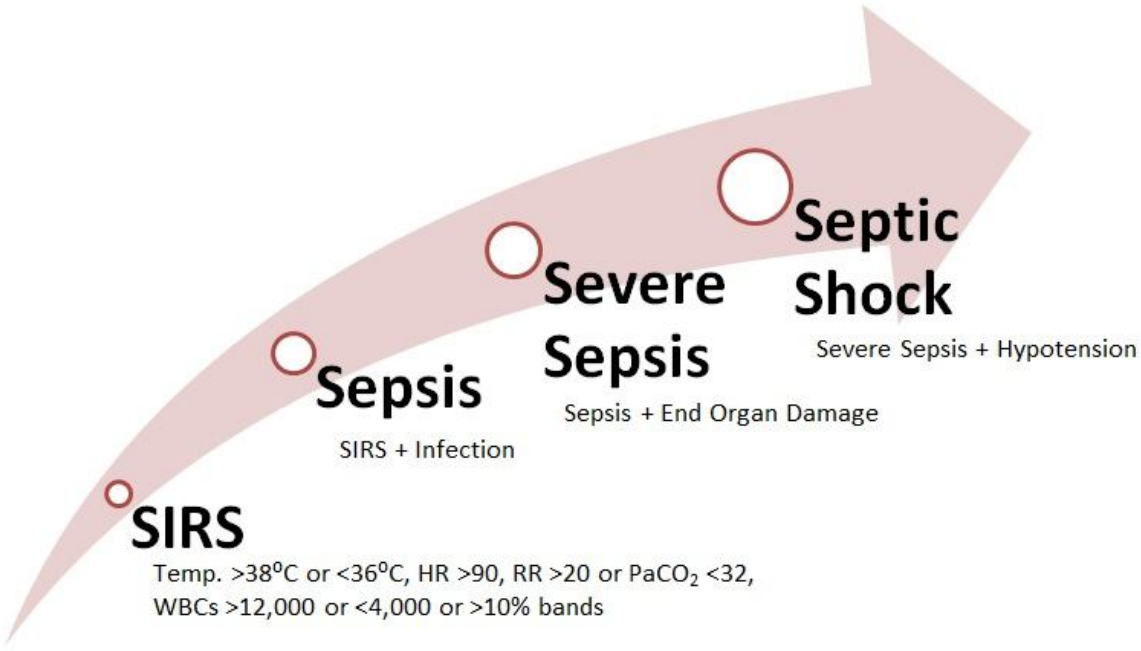
Acute lung injury with PaO_2/FIO_2 < 200 in the presence of pneumonia as infection source

Creatinine > 2.0mg/dL (176.8 µmol/L)

Bilirubin > 2mg/dL (34.2 µmol/L)

Platelet count < 100,000 µL

Coagulopathy (international normalized ratio > 1.5)[3].



EPIDEMIOLOGY

In India, the major illnesses leading to the death of children under five are Diarrhoea (20%), Acute Respiratory Infections (ARI – 19%), Measles (4%), with neonatal conditions accounting for 45% of all under five deaths (HIV accounts for only 1% of child deaths). The major causes of neonatal mortality in India are due to: prematurity (35%), sepsis and pneumonia (25%) and asphyxia (23%). Neo-natal mortality (at 45 per 1000 live births) constitutes almost 79% of the Infant Mortality Rate (IMR). Rates vary dramatically from state to state. India also accounts for 35% of the developing world's LBW (low birth weight) babies and 40% of children with malnutrition. In 2006, 41% of children, under five, in India were underweight[4].

The morbidity and mortality of septic shock remain high in patients admitted to intensive care units, with mortality rate varying between 30% and 70% [5]. In Indian context, hospital mortality and 28-day mortality of severe sepsis were found to be 65.2% and 64.6%, respectively within the period of June 2006 to June 2009[6]. Mortality due to severe sepsis is very high, up to 29% and accounts for about 215000 deaths with calculated costs $16.7 billion per year in the US[7]. In India, hospital mortality and 28-day mortality of severe sepsis were 65.2% and 64.6%, respectively[6]. Altered systemic and pulmonary vascular tones in sepsis occur directly or indirectly through the release of numerous mediators as cytokines (tumor necrosis factor-alpha, interleukin-1), histamine, platelet- activating factor, thromboxane, leukotrines and nitric oxide (NO)[8].

ROLE OF NITRIC OXIDE IN SEPSIS

Nitric oxide (NO) plays an important role in the regulation of vascular tone. Low physiological level of NO is produced from L- arginine by constitutively expressed eNOS and nNOS whereas large production of NO by iNOS is induced by bacterial products, macrophages and some other cells[9]. NO-induced vasodilatation and loss of vascular tone have been implicated in the cardiovascular failure in septic shock. Indeed, experimental studies have suggested that iNOS-derived NO plays an important role in host defense and organ protection[10].

PATHOPHYSIOLOGY

Along with increase in expression and activity of iNOS, protein tyrosine kinase has been implicated in pathophysiology of sepsis and septic shock[11]. The receptor tyrosine kinase participates in transmembrane signaling, whereas the intracellular non-receptor tyrosine kinases take part in signal transduction to the nucleus. Endotoxin, causes the phosphorylation of tyrosine kinases in macrophases and other cells[12], resulting in the release of pro-inflammatory cytokines including tumour necrosis factor α (TNF- α), interleukin-1(IL-1) and interferon-γ (IFN- γ)[13] via the activation of transcription factor NF-kB. An enhanced formation of TNF-α, IL-1 and other cytokine mediates both circulatory collapse as well as multiple organ dysfunctions like liver and kidney injury[14]. During inflammatory responses, neutrophil migrates into tissues leading to release of reactive oxygen species (ROS), which also activate src- protein tyrosine kinases pathway[15]. It was found that caveolin-1 has role in activation and translocation of NF-kB via LPS-stimulated TLR-4 activated interleukin-1 receptor-associated kinase 4 (LPS–TLR4–IRAK4) pathway which leads to increase in expression and activity of iNOS, TNFα, ICAM-1 after 2 hours of LPS stimulation in primary culture of mouse lung endothelial cells[16].

The imbalance between the production of reactive oxygen species (ROS) and their effective removal by non-enzymatic and enzymatic antioxidant systems could induce endothelial dysfunction with alterations of vascular tone, increases in cell adhesion properties (leukocytes and platelet adhesion), increase in vascular wall permeability and a pro-coagulant state. Increasing evidence supports the idea that the principal cause of endothelial dysfunction during sepsis is cell injury. ROS and RNS contribute to mitochondrial dysfunction by a range of mechanisms and induce both necrotic and apoptotic cell death[17].

Altered systemic and pulmonary vascular tones in sepsis occur directly or indirectly through the release of numerous mediators as cytokines (tumor necrosis factor-alpha, interleukin-1), histamine, platelet- activating factor, thromboxane, leukotrines and nitric oxide (NO)[8]. Nitric oxide (NO) and

peroxynitrite are crucial components implicated in vasoplegia and vascular hyporeactivity observed in septic shock. Vascular ATP-sensitive and calcium-activated potassium channels are activated during shock and participate in hypotension.

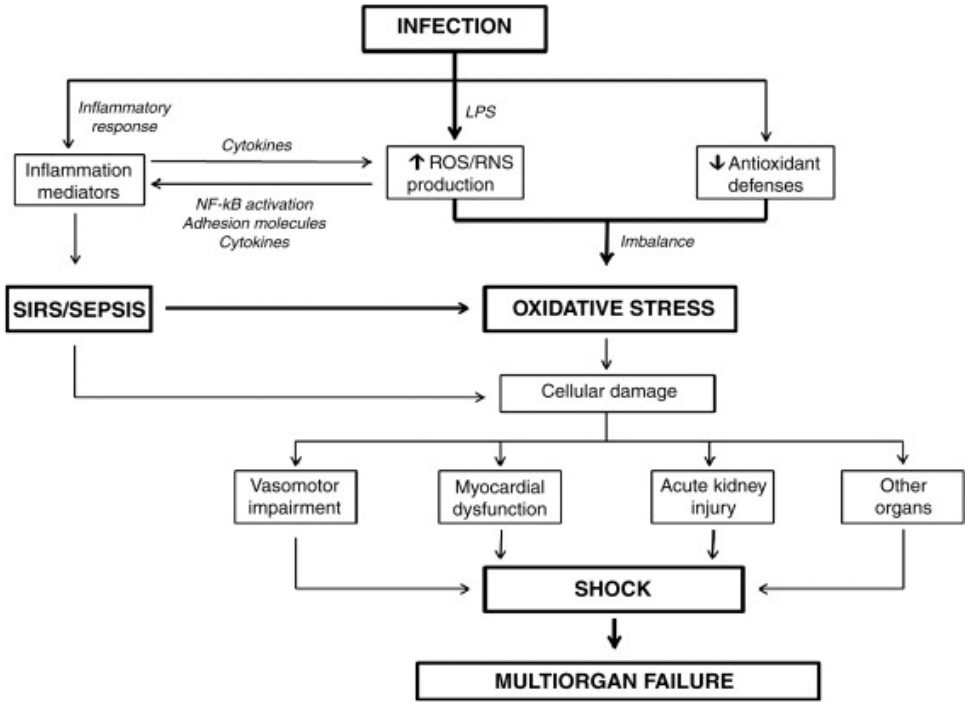


Figure 1: Pathophysiology of sepsis

SYMPTOMS

The symptoms of sepsis are not caused by the germs themselves. Instead chemicals released by body cause the response. A bacterial infection anywhere in the body may set off the response that leads to sepsis. Common places where an infection might include: the bloodstream, the bones (common in children), the bowel (usually seen with peritonitis), the kidneys (upper urinary tract infection or pyelonephritis), the lining of the brain (meningitis), the liver or gallbladder, the lungs (bacterial pneumonia), the skin (cellulitis) and for patients in the hospital, common sites of infection include intravenous lines, surgical wounds, surgical drains, and sites of skin breakdown known as bedsores (decubitus ulcers).

In sepsis, blood pressure drops, resulting in shock. Major organs and body systems, including the kidneys, liver, lungs, and central nervous system, stop working properly because of poor blood flow. A change in mental status and very fast breathing may be the earliest signs of sepsis. In general, chills,

confusion or delirium, hypothermia, light-headedness due to low blood pressure, rapid heartbeat, shaking, and warm skin, bruising or bleeding may also occur. Some patients who have sepsis develop a rash on their skin. The rash may be a reddish discoloration or small dark red dots seen throughout the body. Sepsis may also develop pain in the joints of the wrists, elbows, back, hips, knees, and ankles[18].

A person with sepsis will look very sick. The infection is often confirmed by a blood test. However, a blood test may not reveal infection in people who have been receiving antibiotics. Some infections that can cause sepsis cannot be diagnosed by blood tests. Other tests that may be done include: blood differential, blood gases, kidney function tests, platelet count and fibrin degradation products, to check for bleeding risk, white blood cell count. Infection may be documented or suspected blood cultures need not be positive. Other sources (e.g., urine and sputum) may be positive, but just a suspicion is good enough. In 2002, the definition was broadened to define sepsis as documented or suspected infection with any of the SIRS criteria or 1 or more of the following[3].

- Significant edema or positive fluid balance (> 20 mL/kg over 24 hours);
- Hyperglycemia (plasma glucose > 120 mg/dL) in the absence of diabetes;
- Inflammatory variables: plasma C-reactive protein > 2 SD above the normal value or plasma procalcitonin > 2 SD above the normal value;
- Mixed venous oxygen saturation (SVO2) > 70%; and
- Cardiac index > 3.5 $L \cdot \cdot min^{-1} \cdot M^{-23}$ [19].

RISK FACTORS

Very young people and elderly people, anyone who is taking immunosuppressive medications (such as transplant recipients), people who are being treated with chemotherapy drugs or radiation, people who have had their spleen surgically removed (the spleen helps fight certain infections), people taking steroids (especially over the long term), people with longstanding diabetes, AIDS, or cirrhosis, someone who has very large burns or severe injuries, people with infections such as: pneumonia, meningitis, cellulitis, urinary tract infection[20].

The following factors increase your infant's chance of developing neonatal sepsis:

- Premature birth—more than three weeks before due date
- Early labor—more than three weeks before your due date
- Infant is in distress before being born
- Infant has a very low birth weight
- Infant has a bowel movement before being born and fetal stool is in the uterus

- Amniotic fluid surrounding the infant has a bad smell or the infant has a bad smell right after being born
- Male babies have a greater risk for neonatal sepsis than female babies
- Pregnancy conditions or mother's health issues that increase your infant's chance of sepsis include:
- Labor complications resulting in traumatic or premature delivery
- Water that broke more than 18 hours before giving birth
- Fever or other infections while you are in labor
- Need for a catheter for a long time while you are pregnant
- Presence of group B streptococcal bacteria in vaginal or rectal areas
- Many courses of prenatal steroids
- Prolonged internal monitoring during labor and delivery[21]

TREATMENT

The patients usually admitted to intensive care unit (ICU) in hospital. Antibiotics are usually given through a vein (intravenously). Oxygen and large amounts of fluids are given through a vein. Other medical treatments include: Medications that increase blood pressure, Dialysis if there is kidney failure, A breathing machine (mechanical ventilation) if there is lung failure.

Vasopressors are second line agents in the treatment of severe sepsis and septic shock; we prefer intravenous fluids as long as they increase perfusion without seriously impairing gas exchange. However, intravenous vasopressors are useful in patients who remain hypotensive despite adequate fluid resuscitation or who develop cardiogenic pulmonary edema[22].

In severe septic shock, we prefer to use norepinephrine in most patients. However, we find phenylephrine (a pure alpha-adrenergic agonist) to be useful when tachycardia or arrhythmias preclude the use of agents with beta-adrenergic activity [3,23].

Drotrecogin alpha (activated) was approved in 2001 by the US Food and Drug Administration for the treatment of patients with severe sepsis who are at high risk for death[24].

Glucocorticoids: Glucocorticoids have long been investigated as therapeutic agents in sepsis because the pathogenesis of sepsis involves an intense and potentially deleterious host inflammatory response.

Nutrition: There is consensus that nutritional support improves nutritional outcomes in critically ill patients, such as body weight and mid-arm muscle mass. However, it is uncertain whether nutritional support improves important clinical outcomes (e.g., duration of mechanical ventilation, length of stay, mortality), or when nutritional support should be initiated.

Intensive insulin therapy: Hyperglycemia and insulin resistance are common in critically ill patients, independent of a history of diabetes mellitus. As a result, intensive glycemic control should be studied[25].

Interventions

Antibiotic interventions

Select empiric monotherapy based on coverage of predictable

pathogens determined by focus (organ) of infection

Select antibiotic with low resistance potential

Select antibiotic with a good safety profile

Non-antibiotic interventions

Administer aggressive and effective intravascular volume replacement

If pressors are needed, give volume replacement before pressors

Restore normothermia with heating blanket

Surgical intervention if sepsis is related to intra-abdominal organ perforation or obstruction or abscess. For infected devices, remove the device[26].

OVERALL MANAGEMENT OF SEVERE SEPSIS AND SEPTIC SHOCK

Table:1 Therapies used in the treatment of severe sepsis and septic shock[27]

First line treatment	Second line treatment
• Stabilize airway • Assess perfusion • Begin goal-directed fluid resuscitation • Initiate vasoactive agents (if needed) • Place central venous catheter and arterial canula (if needed) • Obtain antimicrobial cultures • Administer empiric appropriate antibiotics • Consider source control	• Institute corticosteroids if appropriate • Assess need for activated protein C • Initiate intravenous insulin for hyperglycemia • Administer blood products for anemia • Institute lung-protective ventilation strategies • Evaluate for nutrition • Initiate prophylatic measures (e.g.for venous thromboembolism and gastrointestinal hemorrhage)

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CLINICAL TRIALS: WHY HAVE THEY FAILED?

Some of the reasons why clinical trials of anti-sepsis therapies may have failed

- Inadequate pre-clinical testing
- Ineffective agents
- Inadequate doses
- Inappropriate timing of intervention
- Patient populations too heterogeneous
- Inadequate characterization of the sepsis response[28]

CONCLUSION

Although there is some treatment available for sepsis but this is the thrust area of research due to unavailability of pre-clinical & clinical trials on sepsis. The development of effective therapies for sepsis raises fundamental and unprecedented challenges for clinical researchers. The biologic processes that produce clinical sepsis are intimidatingly complex; they play a fundamental adaptive role in the survival of multicellular organisms in a potentially hostile environment, and their activation can occur in a wide range of acute diseases.

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