

**Review Paper**

**SEPSIS: CAUSES, SYMPTOMS, DIAGNOSIS AND TREATMENT/PREVENTION PROCEDURES**

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**ABSTRACT:** Current studies were performed to evaluate the causes, symptoms, diagnosis and treatment/prevention procedures of sepsis. Major cause of sepsis includes skin infection, urinary tract infection, dental or gums infection, respiratory illness, pneumonia (bacterial infection); blood stream infection and an increase in antibiotic resistance. People with diabetes, kidney failure or under treatment in intensive care unit (ICU) are easily infected. More than 60% sepsis prevails in adults aging greater than 65 years; children under age 5-12 are also at risk of infection. The symptoms of sepsis include shivering, chill fever, pale clammy skin, difficulty in breathing and low platelets count. Sepsis can lead to organ failure including lungs, kidney, heart and liver and death. Sepsis is diagnosed by X-rays, CT scan, blood pressure tests, respiratory secretion testing and tests of wound culture, urine and stool samples. It can be treated by using antibiotics, oxygen therapy, anti-infectious management, fluid resuscitation and vascular medication. Sepsis can be prevented by keeping scraps and wounds clean and getting vaccination against potential infections and good hygiene practices.

**Key words:** Sepsis; organ failure; urinary infection; treatment; antibiotics; prevention.

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**INTRODUCTION**

The word sepsis was used for the first time by Hypocrites (ca.460-370 BC). Sepsis originated from the Greek word “sipi” meaning “make rotten” (Hotchkiss Karl, 2003). A US American ICU specialist namely Roger C Bone (1941-1997) defined sepsis as “an invasion of microorganisms and/or their toxins into the bloodstream, -along with the organism's reaction against this invasion (Russell, 2006). Sepsis is a systemic inflammatory response syndrome (SIRS) (Sartelli *et al.*, 2018) and life- threatening organ dysfunction caused by dysregulated host response to infection (Wirz *et al.*, 2018). Our immune system is responsible to defend us against various diseases and infections. However, sepsis may be developed when specific chemicals are released into blood stream by our immune system in order to fight against an infection, which ultimately results in inflammation throughout the whole body (Adam, 2002). Sepsis can also lead to organ failure and death (Lelubre and Vincent, 2018). Sepsis is worldwide problem arising from overwhelming inflammatory response to infection (Quader, 2017). It is progressed very quickly so an urgent medical aid is vital in order to diagnose and treat the signs of this condition. This fatal disease commonly attacks the neonates, children (Fleischmann-Struzek *et al.*, 2018) and surgical patients. Sepsis is a big challenge

to clinician's researches, healthcare systems and societies throughout the world (Perner *et al.*, 2017).

The current studies were performed to investigate and review the causes, symptoms, diagnosis, treatment and prevention procedures of sepsis.

**SUSCEPTIBILITY TO INFECTION/ SEPSIS:** The older adults are at greater risks of infection/sepsis because the immune system is weakened with the passage of age (immunosenescence) (Lefaivre *et al.*, 2011). The risk factors commonly associated specifically with sepsis in older adults include cognitive impairment, malnutrition, frailty and institutionalization. The diseases such as chronic liver failure, congestive heart failure, diabetes mellitus, malignancies, chronic obstructive pulmonary disease increase the possibility/risk of infections and subsequent sepsis. Children under age 5-12 are also at risk of infection (Paladugu *et al.*, 2002).

**MAJOR CAUSES OF SEPSIS:** Sepsis is caused by serious infection leading to overwhelming inflammation. Virus, bacteria, fungi, protozoans, can cause infections. Skin disorders, bladder infection, urinary tract infection or kidney failure are the major causes of sepsis (Tsai *et al.*, 2006); the other sources include pneumonia (a bacterial infection), viral respiratory illness (due to common cold virus) and dental abscess (gums infection) (Baltussen Kindler, 2004). During dialysis treatment of kidney patients when the blood stream infections and

immune system chemicals are discharged into blood stream and the entire body of patient, also cause septic shocks (Tsai *et al.*, 2006).

**CAUSES OF SEPSIS IN NEWBORN BABIES:** When babies get blood infection within the first month of life it is termed as “neonatal sepsis”. Neonatal sepsis is further classified in terms of timings of the infections according to whether the infection was initiated during the birth procedure or in later birth. It is still the major cause of infant deaths; however, the baby can be recovered completely if the disease is diagnosed and treated on time (in early stages) (Campbell, 1990).

**CAUSES OF SEPSIS IN OLDER ADULTS:** Sepsis may be caused by any kind of infection from the flue to an infected bud bite; however, the most common reasons of sepsis infections are respiratory disorders; pneumonia or urinary tract infection among the older adults. The major cause of sepsis in older adults is immune system dysfunctioning with aging (Lefaivre *et al.*, 2011).

**SYMPTOMS:** On the basis of blood examination, the suspected symptoms of sepsis include the liver damage, chronic renal damage, respiratory damage, unexplained metabolic acidosis, altered consciousness and the bacteremia e.g., chills, fever, hypotension, tachypnea (Nishida *et al.*, 2018). Sepsis may have severe affects on the entire body and may cause the aching in whole body, discomfort and pain, shivering, pain and difficulty in breathing, feeling sleepy, very low blood temperature-below 96.8 F, low blood pressure, feeling fizzy, nausea, vomiting and diarrhea *etc.* It causes decrease in urination, low platelets count, and heart rate may be increased to more than 90 beats per minute; newborn babies not breast feeding well, abdominal swelling and vomiting may also be results of sepsis (Garfield, 2006). Sepsis may target the immune system by directly changing the life span and affecting on the function of effector cells which are accountable for homeostasis, immune surveillance maintenance against lethal pathogens, tissue regeneration and wound treatment (Delano Ward, 2016).

**DIAGNOSIS OF SEPSIS:** It is difficult to identify the sepsis because there is no absolute test for its diagnosis (Dantes Epstein, 2018). Sepsis is a global healthcare issue and a major reason of death. It should be diagnosed in earlier stages in order to prevent its conversion into septic shocks, which have about 40% or more mortality rate (Napolitano, 2018). The diagnosis of sepsis is based on simple measurements like type of infection, breathing rate, heart rate and body temperature (Rodwin, 2011). Some specific tests can be performed to find the type and location of infections in the body. These tests include the ultrasound scanning, X-rays, CT scan, imaging studies, blood pressure test, testing the sample of mucus, phlegm or saliva, respiratory secretion testing, urine and stool sample testing and the testing of wound culture, where a

small sample is taken for tests from the fluid, skin or tissues of the affected area (Rowe *et al.*, 2009). Following methods can be followed to diagnose the sepsis:

**BLOOD TEST:** Blood tests are performed to evaluate the infectious agents from the affected parts and from other body fluids. A blood sample drawn from different sites can be tested to diagnose the sepsis or nature of infection. The PCT level is a sign of alarm indicating impaired oxygen availability, electrolyte imbalance, abnormal liver or kidney functioning, evidence of infection and clotting problems (Ospina-Tascón *et al.*, 2008).

**pH MEASUREMENT AND TEMPERATURE CORRECTION OF BLOOD GAS:** For the evaluation of pH and blood gas, the blood sample is preheated to normal body temperature (37 °C) and then pH and individual partial pressures of carbon dioxide and oxygen are measured (Fisher *et al.*, 1994).

**MEASUREMENT OF PROCALCITONIN LEVEL:** Procalcitonin is the best biomarker for differentiation between non-infectious and infectious inflammatory states. Procalcitonin (PCT) is a blood test frequently performed if there is a suspecting of bacterial sepsis, a severe systematic infection that can become life threatening. The PCT normal level is zero; any elevation in PCT may be considered as abnormal. The patients with severe septic shocks and sepsis have normally high PCT levels. The elevated level of PCT >2ng/ml or >10ng/ml is indicative of an increased risk/possibility of organ dysfunction and is a sign of serious alarm indicating the need of urgent treatment of the patient (Warren *et al.*, 2001).

**MEASURING LACTATE LEVEL IN BLOOD:** Lactic acid test is used to measure the lactic acid level in blood. Lactic acid is produced in the body by red blood cells and muscles. The carbohydrates in the body break down into carbon dioxide and water at normal oxygen level. However, the carbohydrates are broken down to produce lactic acid and energy when oxygen level is low (Döcke *et al.*, 1997). Normal lactate serum level is 2mmol/L (18.2mg/dl); serum lactate level greater than 2mmol/L is an important indicator of septic shock. Lactate level is increased during strenuous exercises, heart failure, liver damage or sepsis which lowers the flow of oxygen and blood (Pinsky *et al.*, 1993).

**TREATMENT OF SEPSIS:** Sepsis is a major public health issue and is commonly associated with mortality. However, the mechanisms by which sepsis causes multiple organ dysfunction are not still well understood, and so the therapy remains reactive and nonspecific (Gómez Kellum, 2019). The treatment of sepsis commonly involves a prolonged stay in the intensive care unit (ICU) and costly complex therapies. More than one

million Americans are attacked by sepsis and about 15-30% die every year (Hershey Kahn, 2017). The sepsis patients are about 2 to 3 times more likely to be readmitted in the hospital as compared to the patients of other diseases including chronic obstructive pulmonary disease, pneumonia, and heart failure. Also readmissions due to sepsis are more expensive as compared to the readmissions caused by the other conditions (Mayr et al., 2017). Sepsis is considered to be the most expensive treatment in U.S.A. hospitals according to the Agency for Healthcare Research and Quality (AHRQ) (Mathias et al., 2017). For the treatment of severe sepsis and septic shock, vitamin C and corticosteroids are used intravenously in routine clinical practices. The sepsis patients have low vitamin C levels in their blood and can be balanced with intravenous vitamin C; 6.0 g vitamin C per day is recommended (Marik et al., 2017). The recent clinical experimental data reveals that the administration of vitamin C is cost effective and a suitable adjuvant therapy in order to minimize mortality (Teng et al., 2018). High potency dose of sodium selenite has been used to treat the sepsis by reducing oxidative stress. The important therapy known as procalcitonin-guided antimicrobial therapy can accelerate the diagnosis of sepsis (Keh et al., 2016).

Sepsis is a life threatening diseases but life is possible after sepsis e.g., about 1.4 million people are survived in each year after sepsis in the USA. During treatment, one can face body ache, difficulty in sleeping, hair loss, brittle nails, depression and poor concentrations. In case of severe sepsis antibiotics are directly injected into the veins. To reduce the risk of death or serious complications, the antibiotic treatment should be started within the first hour of diagnosis. After 2-4 days antibiotics may be replaced by tablets (Ochoa et al., 1991). The sepsis bundles may be used for improving the outcomes in patients. A new sepsis “hour-1 bundle,” based on the 2016 guidelines was developed. This bundle states that (1) Measure the lactate level (2) Obtain blood cultures before the use of antibiotics (3) Use the broad spectrum antibiotics (4) Start rapid administration of 30ml/Kg crystalloid for hypotension or lactate  $\geq 4$ mmol/L (5) Apply vasopressors if patient is hypotensive during or after fluid resuscitation to maintain the mean arterial pressure (MAP) $\geq 65$  mmHg (Levy et al., 2018).

**ANTIBIOTICS:** Different organisms such as fungi, virus and bacteria can cause the infection which may lead to sepsis. However, the most cases of sepsis are reported by bacterial infections (Brun-Buisson et al., 1995) so sepsis is usually treated with antibiotics and intravenous fluids (Rhodes et al., 2017). Antibiotics are abundantly used medicines in neonatal intensive care units (NICU). Neonatal sepsis is very common infection which takes place in NICU. It has been observed that septicemia is the main cause of neonatal morbidity and mortality globally.

It may be narrated as “a clinical syndrome recognized by symptoms of bacteraemia in the first month of life” and later onset of sepsis (Nagesh et al., 2017).

Following antibiotics are mostly recommended for the treatment of sepsis; Imipenem and Cilastatin (Primaxin), Ampicillin and Sulbactam (unasin), Piperacillin and Tazobactam (zosyn), Cefepime (maxipime), Cefotaxime (claforan), Ceftazidime (fortaz), Meropenem (Merrem), Ceftriaxone (Rocephin) (Abraham et al., 1995).

After the diagnoses of sepsis, the patients should receive immediate antibiotic treatment even when the bacterial infection is still not confirmed by tests (Stoll et al., 2002). Various antibiotics perform better against different kinds of bacteria. But because the identification of specific bacteria is time taken procedure so the patient is initially given a broad spectrum antibiotic which is simultaneously effective against different types of bacteria; laterally the patient may be switched to the more targeted antibiotic (Calandra et al., 1990). The selection of a suitable antibiotic for sepsis treatment, depends on its availability, nature of infected parts and the ability of patient to resist against certain bacteria (Damas et al., 1992). If patient is suffering from mild sepsis then the patients are recommended to receive antibiotics at home but in case of severe sepsis the antibiotics are given intravenously in hospital (Hotchkiss et al., 1999). By using this method the medicine is quickly entered into the patient blood stream and the patient may respond to the treatment in few hours or days.

If a test confirms that the cause of sepsis is a viral infection then patient is switched to an antiviral medicine. Patient must take an intravenous antifungal drug if fungal infection is causing sepsis. The fungal infection which may lead to sepsis includes the fungal infection in lungs, the fungal skin infection, yeast infection and vaginal infection (Sprung et al., 1984).

**INTRAVENOUS FLUIDS:** After sepsis, it is not possible to maintain the healthy blood pressure only by medication because sepsis and septic shock can cause lowering in blood pressure level (Danner et al., 1991). If the blood pressure is lower than 90\60 millimeter of Hg (mm\Hg), then the patient is given intravenous (I.V.) fluids in the hospital. These fluids increase the volume of blood and reduce the risk of dehydration, both of which are the major reasons of low blood pressure. The confusion, clammy skin, rapid pulse and shallow breathing are the symptoms of too low blood pressure (Sprung et al., 2008). Low blood pressure treatment is compulsory because in this situation it is difficult for the blood to transport oxygen to various body parts so some organs may also be damaged due to less supply of oxygen. The blood volume can be maintained during sepsis by the use of various IV fluids. Such fluids contain

normal saline having minerals like sodium. (Meakins *et al.*, 1977).

**OXYGEN THERAPY:** The blood demands greater oxygen during sepsis so the affected patients are mostly placed on mechanical ventilators; it is done to give relief to their bodies and lungs and to enhance the ability of healing (Suter *et al.*, 1992). Sepsis may cause damage not only to kidneys but also to lungs, heart and other organs. To avoid such damages, the doctors have the choice of hemodynamic monitoring and have close eyes on patient condition. This machine has the ability to evaluate the blood pressure in the arteries, heart and veins (Briegel *et al.*, 1999). Hypoglycemia is experienced by people with severe sepsis and septic shock; the diabetes patients are at greater risk. It is observed that the combination of inflammation and stress can cause higher glucose level and induce resistance (Bollaert *et al.*, 1998).

The broad spectrum antibiotics and IV fluids provide first response in many people having sepsis; some people do not respond to initial treatment so steroids such as sterapred (prednisone)- are added to their treatment plan to keep their blood pressure up. Inflammation is reduced by this medication. However, this method is not advantageous in every case as only few people are recovered through it (Munoz *et al.*, 1991). When blood pressure is not increased even by using IV fluids then the doctors may use another therapy; here the blood pressure is forcefully increased by using vasopressors (Vincent *et al.*, 2006).

**ANTI-INFECTIOUS MANAGEMENT:** Earlier antimicrobial therapy provided the basis of anti-infective therapy for sepsis. Several recommendations were given by the Surviving Sepsis Campaign (SSC) regarding antimicrobial therapy of sepsis, all of which have recommendations of lower grade and low quality of evidence. After collecting at least two sets of blood cultures, it is necessary to administrate broad spectrum antimicrobial therapy (Fourrier *et al.*, 1992). Time management plays a *vital* and crucial role for such patients because delay in antimicrobial therapy results in increase of mortality rate. According to SSC recommendations, the 1<sup>st</sup> dose of antibiotics should be applied within the first hour of sepsis diagnosis. However, there may be a significant rise in mortality rate when improper antimicrobial therapy is administrated; so it is necessary to apply the broad spectrum coverage (Mira *et al.*, 1999). Generally, broad-spectrum carbapenems (e.g., or doripenem, imipenem/cilastatin or meropenem) or extended-range penicillin/ $\beta$ -lactamase inhibitor combination (e.g., ticarcillin/clavulanate or piperacillin/tazobactam) are the recommended drugs as first option. However, there may also be the choice of third- or higher-generation cephalosporins depending upon the patient condition (Rhodes *et al.*, 2017). Patients

having very high risks of mortalities i.e., septic shocks are recommended to receive a special therapy which may be avoided in cases of no shock sepsis. Proper antibiotics must be chosen as first choice when the combination of therapies are administrated (Marik Sibbald, 1993). However, it has been reported that several infections e.g., *Aureus bacteremia*, *tuberculosis*, *invasive candida* infections, *endocarditis*, demand longer time duration for antimicrobial therapy (Rhodes *et al.*, 2017).

**FLUID RESUSCITATION:** Septic shock is generally accompanied by severe hypovolemia so fluid resuscitation is a very important element of hemodynamic stabilization. First choice is the recommendation of crystalloid solutions with initial intravenous fluids bolus of 30ml/kg. Hemodynamic parameters are monitored on regular basis until the patient status is improved by fluid administration (Rhodes *et al.*, 2017). Patients with acute respiratory distress syndrome are recommended the conservative fluid administration. The balance saline or crystalloid solutions may be the equivalent choice as recommended by SSC. There are no clear recommendations demonstrating the preference of a specific crystalloid solution. However, some adverse effects e.g., renal dysfunctioning and hyperchloremic acidosis are associated with high sodium chloride load (Rochweg *et al.*, 2014).

**VASOACTIVE MEDICATION:** Sepsis is commonly accompanied by arterial hypotension which persists mostly after/during fluid resuscitation. In order to achieve the minimum of 65mmHg arterial blood pressure, the first choice vasopressor is norepinephrine. However, norepinephrine is replaced by dopamine as an alternative medication in some cases (Abraham *et al.*, 2005).

**PREVENTIONS:** The risk of sepsis can be reduced by adopting some general precautionary approaches (Noone *et al.*, 1974); these precautions are especially important for the older people and also for those who are at greater risk of infections. For potential infections like pneumonia and flu, vaccination may be advised by the doctor (Landry *et al.*, 1997). Good hygiene practices such as hand washing and keeping the wounds and scrapes clean *etc.* are highly important in this regard (Michard *et al.*, 2000). Always stay alert and get urgent medication in cases of any possible symptoms of sepsis (infection) such as disorientation, confusions, rapid breathing rash, rapid heart rate, fever chills *etc.* In neutropenic patients, the gram negative sepsis can be reduced by sterilizing gentamicin with nystatin and bowel aerobic flora with polymyxin. Patients can also be prevented from N-meningitides and S-pneumonia by immunization (Askanazi *et al.*, 1980). Sulfamethoxazole-trimethoprim is used for children with leukemia (Michard *et al.*, 2000).

The burn patients should be treated with sulfamylon or sulfadiazine prophylactically (Lorenz *et al.*, 2002).

**Conclusions:** Sepsis is a life threatening disease but life is possible if proper treatment is administered on time. However, about 60% of survivor experiences long term decline in cognitive and physical balance. Sepsis is majorly treated by antibiotics and intravenous (I.V.) fluids. During treatment, one can face body ache, difficulty in sleeping, hair loss, brittle nails, depression and poor concentrations. The symptoms of sepsis include shivering, chill fever, pale clammy skin, difficulty in breathing and low platelets count. It can also lead to failure of organs e.g., lungs, kidney, heart and liver. Sepsis can be diagnosed by different tests i.e., blood test, physical examination, CT scan and X-ray imaging etc. The risk of sepsis can be reduced by adopting some general precautionary approaches. Major causes of sepsis include skin infection, urinary tract infection, dental or gums infection, respiratory illness, pneumonia (bacterial infection); blood stream infection and an increase in antibiotic resistance. People with diabetes, kidney failure or under treatment in intensive care unit (ICU) are easily infected. More than 60% sepsis prevails in adults aging greater than 65 years; children under age 5-12 are also at risk of infection.

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