Review Paper:

Sepsis: One of Medicine's Most Elusive Syndrome – A Systematic Review and Current Therapeutic Management

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Abstract

Sepsis is a complex condition and can be defined as life-threatening organ dysfunction caused by a dysregulated host response to infection, leading to tissue hypoperfusion and organ failure culminating in death. In fact, since the early development of medicine, sepsis continues to represent a major health issue globally, with a mortality rate not less than 20% and rising prevalence. This review will discuss the most recent technologies and strategies in diagnosing and managing sepsis: Infection Control, Host Response Modulation and Hemodynamic Management. It discusses EGDT, Machine Learning (ML), Nanotechnology, HMGB1-targeted therapy, the role of sedatives, catheters, tubes, nutrition, glucose management and oxygen therapy. The pathophysiology of sepsis involves the complex interplay of immune activation and subsequent endothelial dysfunction, complement system activation, coagulation abnormalities and disturbances of metabolism, all contributing to widespread tissue damage and organ failure, if not treated.

This review also talks about diagnostic tools and biomarkers for the diagnosis of sepsis, severe sepsis and septic shock. Nanotechnology-based diagnostic techniques such as biosensors and bioreceptors, are very significant in identifying biological or chemical reactions in a patient suffering from sepsis, while in the management, antibiotics (within one hour) should be administered in all cases. Fluid resuscitation is also needed because fluid loss is very common in sepsis and often vasopressors are needed to maintain adequate perfusion pressure.

Keywords: Sepsis, Novel management, Recent advancement, Early detection, EGDT.

Introduction

Acute organ failure and a higher risk of mortality are linked to sepsis, a complicated illness that arises as a dysregulated host response to an infection. Given that this sickness needs rapid treatment, it is important to comprehend the presenting symptoms. Sepsis is still one of the leading causes of death worldwide and is rather common. Thus, sepsis is a serious public health issue[43]. Sepsis is a potentially lethal sickness that arises when the body reacts to an infection by damaging its tissues and organs[106]. The phrase "one of the oldest and most elusive syndromes in medicine" has been used[7]. "Sepsis, according to Hippocrates, is the process by which wounds fester, marshes produce filthy air and flesh rots[68].

After Semmelweis, Pasteur and others confirmed the germ theory, sepsis was reframed as a systemic illness, sometimes referred to as "blood poisoning," and thought to be caused by pathogenic organisms invading the host and then spreading via the bloodstream. Even if the instigating infection was successfully eradicated, many sepsis patients died, proving that germ theory was unable to adequately explain the pathophysiology of sepsis with the development of modern medicines. Therefore, scientists proposed that the pathophysiology of sepsis was driven by the host rather than the germ[23]. Sepsis may now be identified and treated more quickly because of a significant amount of research and enhanced clinical procedures during the last 30 years.

A revised definition was created in 2016 that placed more emphasis on identifying organ failure in the setting of infection[97]. A resolution to improve sepsis care, detection and prevention was voted by the World Health Assembly and WHO in 2017, designating sepsis as a global health priority[88].

Definition

Sepsis was defined internationally by the year 1991 as "the systemic inflammatory response (SIRS) to a microbial infection" (BOX 1) where SIRS is defined as at least two of the following symptoms: fever or body temp below 95°C, high white blood cell count, leukopenia, or neutrophilia, rapid breathing, or rapid heartbeat[107]. Sepsis can result from a variety of infectious causes and septicaemia is not a required situation nor a useful word, according to a 1992 international definition of sepsis which defined sepsis as a systemic inflammatory response to an infection[107]. The board instead named the term "severe sepsis" to refer to situations in which acute organ failure complicates sepsis and "septic shock" were defined as sepsis exacerbated by either hyperlactatemia or low blood pressure that is resistant to fluid replacement.

Most of these concepts were approved by a second consensus panel in 2003[65], with the caveat that signs of a SIRS, such as rapid heartbeats or an elevated white-cell

count, can occur in several infectious and non-infectious conditions and therefore do not help in distinguishing sepsis from other conditions. To describe the infection-related disease that is made worse by immediate organ failure, the phrases "severe sepsis" and "sepsis" are thus sometimes used interchangeably.

Sepsis along with septic shock were defined by the Third International Consensus in 2016. These days, sepsis is described as both "an infection associated with organ injury distant from the site of infection" and "life-threatening organ dysfunction caused by a dysregulated host response to infection." However, septic shock is still classified as a subtype of sepsis when the death risk is significantly elevated and the anomalies in metabolism are serious enough to significantly raise the death risk. This necessitates the administration of vasopressors due to hypotension that endures throughout volume resuscitation[97]. In the absence of hypovolemia six vasopressors are needed to keep the mean arterial pressure (MAP) at 65 mmHg or higher and the serum lactate level at 2 mmol/l[55].

Box 1 | 1991 Criteria for sepsis, severe sepsis and septic shock

The following definitions come from the 1991 Consensus Conference of the American College of Chest Physicians and Society of Critical Care Medicine.

Infection- The presence of germs or their penetration into the tissue is referred to as infection.

Sepsis- The SIRS to infection, or sepsis, is characterized by at least two of the following:

- Hypothermia
- Rapid heartbeats (90 beats per minute)
- A partial CO_2 pressure of less than 32 mmHg or a respiratory rate of more than 20 breaths per minute
- WBC counts greater than 12,000 or less than 4,000 per millilitre

Severe sepsis- Sepsis linked to hypotension, hyperfusion, or organ failure is referred to as severe sepsis. Lactataemia, oliguria, or a change in mental state are examples of end organ hypoperfusion disorders.

Septic shock- Sepsis accompanied by hypotension and irregular perfusion even when proper fluid (volume) replacement is administered and is known as septic shock. Lactic acidosis, oliguria, or a sudden change in mental state are examples of perfusion anomalies.

Epidemiology

In the United States, the incidence of severe sepsis was approximately 750000 cases per year (300 cases per 100,000 population), or 2·26 cases per 100 hospital discharges,[8] according to 2001 research by Angus and colleagues[8]. Sepsis incidence rose by 7.3% yearly in Catalonia between 2008 and 2012, from 167.2 per 100,000 in 2008 to 261.8 per 100,000 in 2012, according to research[38]. According to reports, sepsis kills 148.1 people out of every 100,000 as of 2017[13]. This amounts to around 8 million fatalities annually. By 2017, 48.9 million sepsis cases were there, out of which 11.0 million deaths occurred globally due to sepsis, accounting for around 20% of all deaths, according to Rudd et al[91].

In high-income nations, its rate of mortality ranges from 15% to 30%, but in low-income ones, it might reach up-to 50% or more[36]. One of the costliest illnesses to treat is sepsis. Sepsis costs around $1.3 billion annually in Ontario, Canada and $27 billion annually in the United States before the Coronavirus illness 2019 pandemic[40]. Sepsis has an in-hospital mortality rate of up to 20% and an average hospital stay that is twice as long as any other deadly illness[1]. The emergency room treats around 80% of septic cases, with the other patients being sent to other hospital departments[89].

In the intensive care unit (ICU), where it affects around 30% of patients and varies greatly by geographic location, sepsis is also very important[93]. Fifty-five percent of all sepsis patients needed intensive care unit hospitalization, according to research conducted in the United States with over 170,000 cases[89].

Clinical Features: Acute organ malfunction and infection are the hosts reaction to an infection in sepsis. Death, acidosis and multiple organ failure can result from this cause, sepsis most frequently occurs in the lung (accounting for 64% of cases), abdomen (20%), circulation (15%) and malfunction[32]. Infections obtained in the community and diseases linked to healthcare facilities can result in severe sepsis and septic shock. Breathlessness, colorlessness, restlessness, excretion, anorexia, respiratory rate of ≥22/min, altered mental state, rapid heartbeats and lack of oxygen are some of the symptoms, along with a temperature of >38°C. Pneumonia-induced sepsis is characterized by sputum production, irregular breath sounds and hypothermia below 36 °C[45]. About half of all cases begin with pneumonia, although urinary tract and intra-abdominal infections may occur first[3].

Risk Factor

The risk of sepsis and septic shock grows with age, it is distributed in two ways, with infants having a higher risk and young adults having a lower risk. Additionally, because of underdeveloped immunity, the risk increases once again beyond the age of sixty[70]. Sepsis and septic shock are linked to a higher chance of male gender. Because oestrogens have protective effects on cardiovascular and immunological response, the reduced incidence of sepsis in females may be explained[34]. Sepsis and septic shock are made more likely by immunosuppressive drugs and comorbidities[12,34].

Seasons can also have an impact on sepsis and septic shock, with a greater incidence in the winter. This is because lung infections, which are risk factors for sepsis, are more common in the winter[25]. Additionally, hunger, poorness, illiteracy, the duration of the period between the occurrence of symptoms and the initiation of sepsis management and infection incorrect diagnosis are associated with sepsis and septic shock[12].

Box 2 | Signs and symptoms as per WHO[113]

Common signs and symptoms include:

- Hyperthermia or Hypothermia and shivering
- Unsureness
- Problem with breathing
- Skin becomes clammy and sweaty
- Severe body pain
- Tachycardia, weak pulse, or hypotension
- Less urine output.

Symptoms for children include:

- Rapid breathing
- convulsions
- colourless skin
- Feeling lazy
- Problem in getting up from bed
- Sensation of coldness to the touch

For children below 5 years of age, it can cause difficulty in feeding, often vomiting or decrement in urination.

Pathophysiology

Sepsis is a complicated and sometimes fatal illness brought on by the body's overreaction to an infection. A unregulated host action to an infection, which turns into extensive inflammation, immune system dysfunction and eventually organ failure, is what defines its pathogenesis. (Fig. 1)

Box 3 | Risk Factors as per WHO[113,22]

Anyone suffering from an infection, severe trauma, or significant non-communicable disease has the potential to develop sepsis, however, certain groups are more susceptible than others such as:

- Elder or aged persons
- Pregnant women
- New born baby
- Patients admitted in hospital
- Patients in ICU
- Patients with poor immune systems (ex. In case of HIV, cancer, etc.)
- Patients with severe medical conditions (for example CKD, AKD, cirrhosis, etc.).

Immune System Activation and Dysregulation: The onset of sepsis is triggered by an infection that activates the immune system. “Pathogen-Associated Molecular Patterns (PAMPs) from the infectious agents are identified by the host's pattern recognition receptors (PRRs), leading to an exaggerated immune response[5,61]. This action is identified by the reveal of pro-inflammatory cytokines, resulting in a "cytokine storm”[28]. The immune system's overreaction can damage host tissues and organs, a phenomenon known as collateral damage. During this phase, the body also experiences systemic inflammation, fever and shock, which can progress to “Multiple Organ Dysfunction Syndrome (MODS)[74,80].

Endothelial Dysfunction and Microcirculatory Failure: Endothelial cells, which cover the blood vessels, run an important part in managing vascular homeostasis[77]. In sepsis, these cells become activated and shift to a pro-inflammatory state[47]. The cytokine storm damages the endothelial cells, leading to impaired vascular permeability and dysregulated vascular tone[31,47,53,77]. The endothelial injury disrupts the glycocalyx layer, which normally protects the endothelium and regulates leukocyte adhesion[79,102]. The loss of the glycocalyx enhances leukocyte and platelet adhesion, contributing to microvascular thrombosis[63]. These microvascular clots further exacerbate organ dysfunction by impairing blood flow and oxygen delivery[16].

Aggregated System Activation: The aggregated system, a part of the non-specific immune system response, is also activated in sepsis. This immune system improves the capacity of antibodies and phagocytic cells to clean microorganism and injured cells. However, in sepsis, more activation of the aggregated system leads to the production of anaphylatoxins (e.g. C5a) which exacerbate inflammation and contribute to tissue damage[6]. The complement system also interacts with the coagulation cascade, promoting thrombosis and further contributing to microvascular dysfunction[24].

Coagulation Abnormalities: Sepsis induces a hypercoagulable state characterized by the widespread stimulation of the coagulation cascade[96]. Tissue factor (TF) released from damaged endothelial cells and immune cells initiates coagulation, leading to the formation of fibrin-rich clots[48]. These clots obstruct blood mobility in the small vessels, resulting in tissue hypoxia and organ dysfunction. Simultaneously, the body's natural decoagulant systems such as the protein C system, are impaired, further promoting coagulation. This dysregulated coagulation can lead to distributed intravascular coagulation, a serious condition where clotting and bleeding take place simultaneously[86].

Metabolic Changes and Cellular Dysfunction: As sepsis progresses, cellular metabolism becomes increasingly impaired. The combination of hypoxia, mitochondrial dysfunction and altered metabolic pathways leads to anaerobic glycolysis and the accumulation of lactic acid, contributing to metabolic acidosis. These metabolic changes, coupled with impaired oxygen utilization, result in cellular energy failure and exacerbate organ dysfunction[13].

In summary, the pathogenesis of sepsis includes a complicated interplay of immune stimulation, endothelial dysfunction, complement system activation, coagulation abnormalities and metabolic disturbances. This cascade of events leads to widespread tissue damage, organ failure, and, if not promptly treated, death.

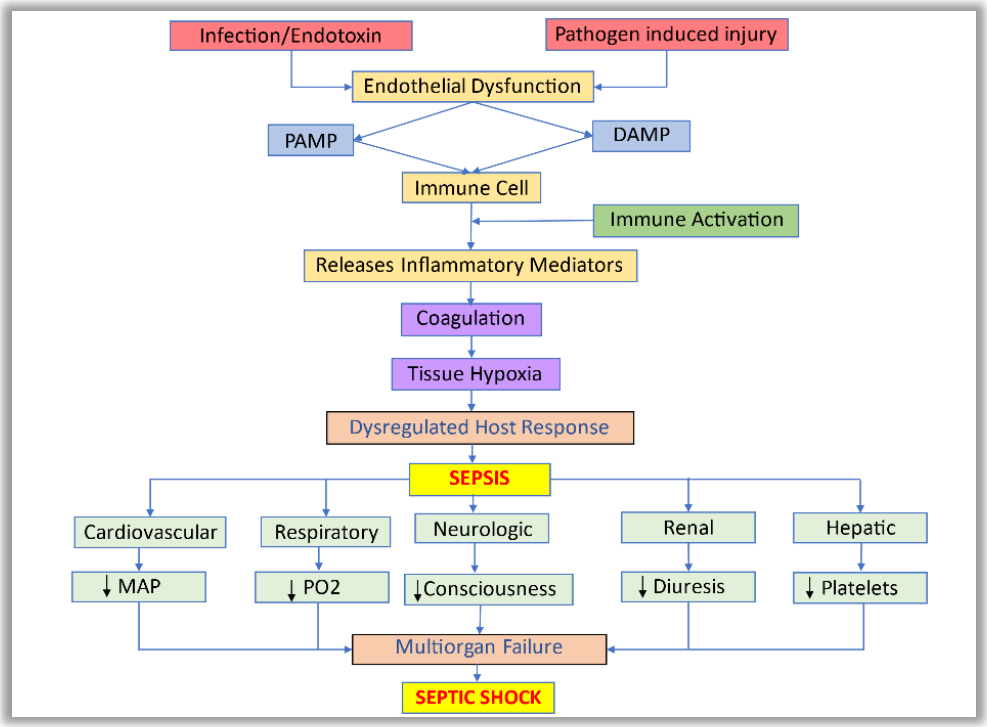

Fig. 1: Showing pathophysiology of Sepsis

Diagnosis

Box 4 | Diagnostic Benchmark for Sepsis and Septic Shock[64,65]

Sepsis (Verified or non-verified infection)
General markers:
- Body temperature more than 38.3°C
- Body temperature less than 36°C
- Rapid heartbeats (more than 90 beats per minute)
- Rapid breathing (more than 30breaths per minute)
- Confusion
- Considerable edema or fluid gains is more than fluid loss
- Increased glucose level (6.7 mmol/L when no diabetes)

Inflammatory markers:
- WBC (White Blood Cell) count, more than 12,000/mm^3
- WBC (White Blood Cell) count, less than <4000/mm^3
- Normal white blood cell counts with more than 10% immature forms
- Raised plasma C-reactive protein (more than 2 SD above the normal range)
- Increased plasma procalcitonin (more than 2 SD the normal range)

Leucocyte surface markers:
- Cell Surface antigen (CD11b)
- Intercellular Adhesion Molecule (ICAM-1)
- Cell Surface Antigen 63
- Cell Surface Antigen 64
- Cell Surface Antigen 66b

Leucocyte products:
- Cell Surface-adhesion Soluble L-selectin Antigen 62L
- Cell Surface-adhesion Soluble L-selectin Antigen 62P

Box 4 | Continued[64,65]

Hemodynamic markers:
- Hypotension (systolic blood pressure, less than 90mm Hg, while mean arterial pressure is less than 70mm Hg)
- Increased SvO2 more than 70%
- Increased cardiac output more than 3.5 liter/min/square meter of body-surface area

Peptides:
- Either Monocyte or macrophage
- TNF-α
- IL 1α and IL 1β
- IL 6, IL8, IL10 and IL 18

Elongated cellular products:
- Soluble vascular cell adhesion molecule (sVCAM-1=CD106)
- Soluble E-selectin (=CD62E)

Organ-dysfunction markers:
- Low concentration of oxygen in artery.
- Production of small amount of urine (less than 0.5ml/kg/hr)
- Elevated creatinine level (value greater than 0.5mg/dl)
- Problem in clot formation
- Paralysis in bowl movement
- Depletion of platelets count in the blood (less than 100,000/mm3)
- Elevated serum bilirubin level (value greater than 4 mg/dl)

Differential tissue-perfusion:
- More lactate acid in blood (more than 1 mmol/L)
- Declined capillary fulfilment

Acute phase reactants:
- C reactive protein
- Iron storing protein
- Iron binding protein present in milk
- Neopterin
- Precursor of calcitonin harmone
- Apolipoproteins

Severe sepsis:
- Sepsis along with organ dysfunction

Septic shock:
- Sepsis as well as hypotension

Inflammation and infection along with either hypothermia or hyperthermia with a rectal temperature of less than 38.5°C or more than 35°C respectively, are diagnostic criteria for sepsis. Hypothermia may be established by one of the following signs of reduced organ function, but not tachycardia. elevated blood lactate level, hypoxemia and altered mental state. For infants as well as children with paediatric ranges of 75% to 80%, a mixed vein-oxygen limit level greater than 70% is considered normal. Children often have a cardiac index between 3.5L and 5.5L per minute per square meter[7,65].

Box no. 4 lists a few criteria for diagnosing sepsis and septic shock[64,65]. In contrast to a confined microbial infection, sepsis has a dysregulated, broad host response with ambiguous indications and symptoms[109]. Patients who are hypoxic and on antibiotic therapy after surgery may have a low platelet count but no infection symptoms, or they may be over-diagnosed with sepsis, which is often misdiagnosed in these patients[109].

Though their previous clinical application is restricted by the analysis time of 24 to 48 hours[20], culture reports from biological fluids, especially blood, are a confirming and reliable diagnostic approach in addition to diagnosis based on symptoms. Both infection and inflammation raise C-reactive protein (CRP), an acute-phase protein that is often studied. Its application in the diagnosis of sepsis, is limited by its lack of specificity, despite its great sensitivity. Often reported measure, procalcitonin (PCT), is produced after systemic inflammation caused by a bacterial infection and may be more specific than CRP[49].

Use of Nanotechnologies in the diagnosis of sepsis

Sepsis is commonly detected with biosensors that track chemical or biological reactions. Biosensors are devices that

provide a signal proportional to the levels of analytes in biological material. Among the several components that comprise biosensors generally are analytes, bioreceptors, signal transducers and display screens[67]. Biosensors use a limited number of samples to measure tiny signals from different body fluids[44]. CRP, PCT and Interleukin-6 are among the few biomarkers which have successfully been used in the clinical diagnosis of sepsis (box 4)[51,103].

Management of Sepsis

Infection control: The actual source of sepsis is infection which also starts and maintains immunological dysregulation. Therefore, every effort must be made to remove both the illness and its cause. Even in situations when an infection cannot be conclusively confirmed and no any particular bacterium is withdrawn which can take place in more than 30% of sepsis forbearers (patients), antibiotics should always be administered[62,94].

Antibiotics: Initial antibiotic administration is recommended exclusively in serious sepsis such as septic shock. Nonetheless, the idea is that antibiotics ought to be given within an hour of sepsis being diagnosed[98]. Adequate antimicrobial treatment must be begun right away and not postponed until culture data are acquired. According to the uncertain source of sickness, flora and resistance trends[59,114], patients should be administered with broad-spectrum antibiotic treatment that may occupy all plausible species. Particularly in the most severe instances, combination antimicrobial treatment is better than single-agent therapy[71,100]. The selection of antimicrobials should be reassessed when culture results are obtained and wherever feasible, de-escalation to a smaller range should be carried out. This strategy will lower expenses, minimize toxicity, aid stop the emergence of medication resistance and maximize therapeutic efficacy[60].

Source Removal: Source control or also called as source removal, which is regarded as best practice in the management of sepsis, involves removing diseased tissue, draining an abscess, or removing an infected equipment. Open surgery or percutaneous drainage can be used to manage the source. Inadequate early source management was linked to a 28-day mortality increase from 26·7% to 42·9%, according to observational data[18,69]. Future RCTs are unlikely to challenge this conventional method since source removal is an important footprint in the therapy of sepsis.

Hemodynamic management

Fluids are always part of hemodynamic therapy and vasoactive drugs are mostly given when shock is present:

IV Fluids: Since sepsis is often accompanied by both exterior and internal fluid losses, fluid therapy is always required. Because sepsis is usually linked to vasodilation, which raises blood volume, patients may also be dehydrated as a result of consuming less fluids[110]. Salvation, optimization, stability and de-escalation[63] are the four stages of hemodynamic therapy for patients with sepsis and septic shock. Providing rapid hemodynamic support to avoid organ damage and shock is the main goal of these four stages.

Before monitoring is achieved during the salvage phase of therapy, a large amount of fluid should be administered[33]. In the optimization stage, a customized strategy is required. When a patient is severely asleep and on mechanical ventilation, passive leg lifting and other indicators of fluid responsiveness might be useful. Although it is not as simple, it is possible to evaluate the changes in stroke volume during passive leg lifting. The most effective method for customizing fluid treatment is often a fluid challenge strategy. A reduced accelerated phenomenon, in which the balance of fluid should turn negative, must be carried out following the stabilization phase[33].

Early goal-directed treatment (EGDT): Early goal-directed treatment (EGDT) is one facet of sepsis care that is becoming more and more contentious. When compared to traditional therapy, which lacked clear objectives for assessing the quality of the response, Rivers et al[90] demonstrated in landmark single-center research that EGDT helped forbearers with septic shock in the ED setting to minimize death. By titrating hemodynamic resuscitation with intravenous fluids, dobutamine and packed RBC transfusion, the EGDT approach aimed to maintain a central venous oxygen saturation (ScvO2) of more than 70%. However, larger, more recent multicentre studies were unable to support these positive results, may be as a result of the control group's superior patient care[66].

Vasoactive drugs: To prevent persistent hypotension, which can impede tissue perfusion, vasoactive medications are also commonly needed and initiated concurrently with fluid delivery. Because it has fewer side effects and mortality, noradrenaline is advised over dopamine[29,30].

As an inotropic drug, dobutamine is frequently combined with noradrenaline to enhance cardiac results and O_2 delivery to the group of cells. Analyzing variations in blood lactate levels can assist in determining how well the resuscitation worked[54]. Vasopressor assistance is frequently necessary to maintain perfusion pressure in individuals suffering from septic shock. The majority of forbearers with septic shock who need vasopressor therapy, should start with an arterial pressure of 65 mm of Hg.

In contrast to a lower aim (65–70 mm Hg), Asfar and colleagues showed that a higher blood pressure 80 to 85 mm Hg was not linked to improved survival[14]. Selepressin[92] and angiotensin II[56] are two novel vasopressors that were released in 2017–18.

According to initial research, these medications effectively raise blood pressure and lower noradrenaline dosage, which may offer a novel way to lessen the need for catecholamines in septic shock.

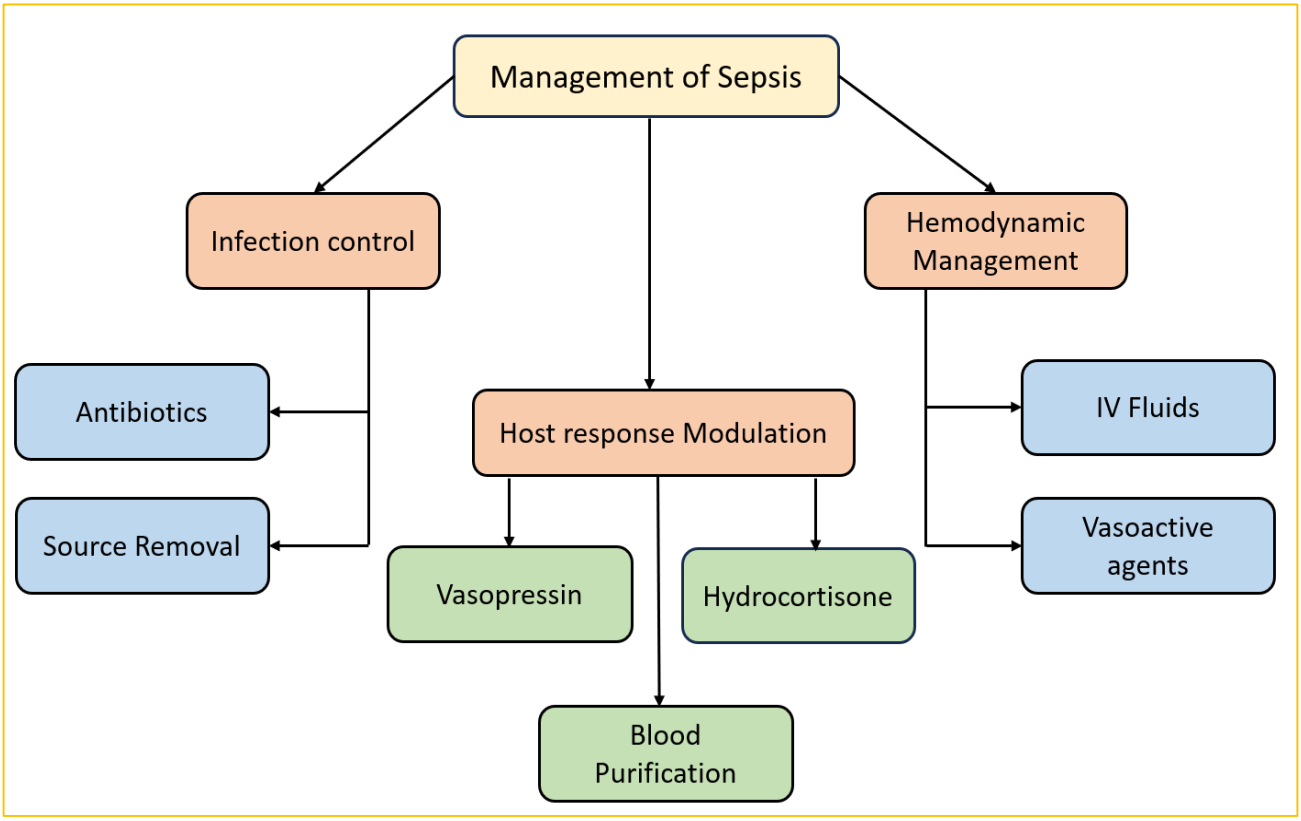

Fig. 2: Showing management of Sepsis

Modulation of the host response

Hydrocortisone: There are current issues with using corticosteroids in sepsis patients. Early research suggested that using high doses of methylprednisolone[9] followed by lower doses of hydrocortisone may be beneficial, but bigger trials have not confirmed this conclusion[101]. Guidelines from the Society of Critical Care Medicine and the European Society of Intensive Care Medicine, as well as systematic reviews[10,46,82], indicate that the use of corticosteroids may be good for sepsis patients, but only in cases when shock is present. People with serious septic shock, often characterized by the requirement for comparatively large noradrenaline dosages to fulfill mean arterial pressure approximately or above 1µg/kg/min are the only ones who should get corticosteroid treatment[50].

Nonetheless, using steroids in septic shock had shown positive results in two sizable, multicentre trials. In the first, the Adrenal multicentre research, which had 3800 patients, the glucocorticoid group saw shorter durations of shock and intensive care unit stays than the placebo group, but the primary endpoint indicated a negative improvement[79]. Consequently, modest dosages of hydrocortisone did not enhance the survival rate; nevertheless, the patients were not terribly sick as seen by the 29% placebo fatality rate[105].

An addition of hydrocortisone along with fludrocortisone was linked to a decreased all-source of 90-day mortality when contrast to the placebo in the second, larger multicentre study, which involved 1241 patients[11]. However, multicentre research in France showed that patients treated with hydrocortisone had significantly reduced ICU, hospital and 6-month mortality rates, while the placebo group had a mortality rate over 50% and a mean lactate level of 4 mmol/l.80. Therefore, a daily dose of 200 mg of hydrocortisone is recommended for patients with severe septic shock[39].

Vasopressin: Vasopressin can also be employed to modify the host's reaction. The hormone vasopressin affects water metabolism and renal function. Vasopressin is administered a dose of 0.03–0.05 units per minute to patients with sepsis to replace insufficient vasopressin levels. Vasopressin is normally given as a second-line drug when noradrenaline is not working. However, when given to patients in septic shock early on, it can enhance renal function, raise urine production, lower fluid requirements and lessen the creation of oedema[111].

Blood Purification: Excess medicine and endotoxins can be eliminated using the extracorporeal purification of blood which also has considerable logic. However, none of the existing modulations has consistently reduced mortality.

It is not advised to begin renal replacement treatment prior to the development of renal failure[81]. The polymyxin B hemoperfusion method is a new treatment strategy for endotoxin elimination that is currently being studied but has shown mixed outcomes. exhibiting a non-significant rise in mortality in subsequent studies, while it demonstrated an improvement[27] in results during the early trials[26,83].

Table 1
Selected clinical biological response modifiers used in clinical trials for severe sepsis or septic shock

Action	Category	Type of Study	Agent	Result
Endocrine Abnormalities[112]	Vasopressors	Prospective RCT	Arginine vasopressin	ineffective
Endocrine Abnormalities[12]	Corticosteroids	Meta-analysis	Corticosteroid	Ineffective or Moderate effect
Endotoxin[28]	Monospecific antibody	Prospective RCT	HA-1A	ineffective
CD14[15]	Monospecific antibody	Prospective RCT	IC14	Not clear
TNF[1,25]	Monospecific antibody	Prospective RCT	BAY 1351	ineffective
TNF[2,42]	Immunoadhesin	Prospective RCT	Lenercept, Etanercept	ineffective
IL-1[78]	Receptor antagonist	Prospective RCT	Anakinra	ineffective
Nitric oxide[17]	L-N-methylarginine	Prospective RCT	546C88	Moderate effect
Nitric oxide[85]	Reducing agents	Prospective RCT	Methylene blue	Moderate effect
Intravascular Coagulation[3]	Tissue factor pathway inhibitor	Prospective RCT	Tifacogin	ineffective
Intravascular Coagulation[18]	Antithrombin	Prospective RCT	Antithrombin	ineffective
Intravascular Coagulation[73]	Anti-tissue factor antibody	Prospective RCT	ALT-836	ineffective
Intravascular Coagulation[115]	Heparin	Meta-Analysis	Heparin salt	Moderate effect

A list of certain clinical biological response modifiers is given in table 1 which has been used for septic shock and serious sepsis patients in several lessons. The target, drug class, study type, name of the drug and result are mentioned.

Other forms of assistance

Employing sedatives: Many hospitals have now put procedures in place to reduce needless sedation after realizing that excessive sedative usage is likely to be hazardous[57, 99]. While early movement of severely sick patients enhances delirium and functional result and shortens the time of mechanical breathing, awake individuals are better equipped to recover[95].

Catheters and tubes: Ventilator-associated pneumonia rates have declined, in part due to better oral hygiene and endotracheal tube engineering that reduces biofilm development and microaspiration[41]. Nosocomial infections have decreased leading to advancements in intravascular catheter design, placement method, maintenance and prompt removal, as well as criteria for eliminating unneeded urine catheters[87,104].

Lung protective ventilation: It was demonstrated in 2000 that reduced tidal volume breathing significantly improved survival in ARDS patients,[4] with an absolute decrease in in-hospital mortality of 8.9%. Follow-up research revealed that this effect also applied to sepsis patients with ARDS[37]. Over the past 15 years, a significant contributor to better result for people with sepsis and acute respiratory distress syndrome has been the use of low tidal volume and lung protective ventilation.

Glucose control and nutrition: The optimal time and level of nutritional assistance in sepsis therapy are still up for debate. Recent trials have shown little benefit from intensive enteral or parenteral supplementation, despite prior data, suggesting enteral feeding may prevent infection problems. Enteral nutrition is thus advised by the surviving sepsis campaign (SSC) as tolerated[58].

Although sepsis patients frequently have hyperglycemia, it is unclear what the ideal glucose goal is. In critically sick patients, it has been demonstrated that aiming for glucose levels between 80 and 110 mg/dL increases 90-day mortality. The SSC now advises taking insulin to keep blood glucose levels below 180 mg/dL as a result[52,75].

Recent advancements in the management of sepsis

Oxygen therapy for sepsis: Considering the respiratory issues that are typically linked to sepsis, oxygen treatment is one of the most important management measures for the condition. Severe sepsis causes acute respiratory distress and acute respiratory distress syndrome (ARDS), that is characterized by an insufficient oxygen supply that prevents oxygen from reaching tissues and organs. Oxygen

supplementation prevents organ failure, increases blood oxygen levels and enhances oxygen transport to tissues.

To prevent problems, a proper oxygen level is crucial in sepsis. While hyperoxia, or excessive oxygen consumption, can result in oxidative stress that harms cells and tissues, hypoxia causes malfunction in several organs. This oxidative stress raises inflammation and might be one of the contributing causes to the increased risk of blood clotting and possible consequences connected with DIC. Oxygen treatment needs to be closely watched to ensure that it increases oxygen saturation in a balanced manner without having any negative side effects[72].

Role of HMGB1 for sepsis: Since high mobility group box 1 (HMGB1) is involved in all events that occur during inflammation, it is crucial in the treatment of sepsis. It is a nuclear protein that mediates inflammation and is either actively produced by immune cells during an inflammatory response or passively through sepsis-induced cell death. Elevated HMGB1 levels contribute to the characteristics of organ damage and are linked to systemic inflammatory responses.

HMGB1 targeting is emerging as a significant therapeutic option for sepsis treatment. HMGB1 inhibition lowers the heightened inflammatory response, which in turn regulates organ damage brought on by sepsis. A number of tactics have been used including the use of inhibitors, anti-HMGB1 antibodies and natural substances like glycyrrhizin, which reduce inflammation brought on by HMGB1. By improving survival in sepsis, these have led to the downregulation of downstream pro-inflammatory pathways and the prevention of tissue damage[35].

Use of nanotechnology: Nanotechnology offers promising approaches in the treatment of sepsis. Innovations in diagnostics and therapy may be provided through nanotechnology. Electrochemical and magnetic biosensors are among the most sensitive and speedy nanotechnology-based detection tools for the biomarkers of sepsis, for example, procalcitonin and C-reactive protein. The nano sensors facilitate an early diagnosis with much more accuracy and speed than conventional methods, thus guiding prompt therapeutic interventions.

Therapeutically, nanoparticle-based drug delivery systems improve drugs' solubility and stability and biodistribution within the body. They are very powerful in enhancing the effects of antibiotics by targeting the drug-resistant pathogen.

Nanoparticles can simultaneously deliver antibiotics and anti-inflammatory agents so that infection and inflammation in sepsis will be treated well. Furthermore, nanotechnology can enhance targeted drug delivery to specific tissues or pathogens reducing side effects while maximizing the efficacy of the treatment. Antimicrobial peptides and other molecules functionalized nanoparticles enhance the delivery and targeting of the pathogen, leading to better control of sepsis-related complications[81].

Machine Learning (ML): With the aid of massive applications in managing sepsis, ML enables its early detection, predictability of disease progression and enhanced clinical decision-making. The identified early signs of sepsis before symptoms evolve are aided through real-time analysis based on essential indication and different therapeutic data applied in the working of ML systems. This will further help to predict the occurrence of risk of developing sepsis and its expansion towards septic shock and mortality, thus providing reasons for clinicians to prioritize the treatment of higher-risk patients.

Apart from this, ML will assure adherence to guidelines to treatment by making the critical interventions on time like antibiotics and fluid administration, very crucial in optimizing survival. Furthermore, ML will be able to lower healthcare costs through efficient use of its resources and by minimizing inappropriate treatments or prolonged hospital stay[76].

Discussion

Despite a vast evolution of progress in medical care, sepsis represents a grand global health challenge with a great rate of disease and death. The review focuses on the pathophysiology of sepsis, the challenges associated with its diagnosis and the evolving strategies for managing it. Early and accurate detection is critical as sepsis progresses rapidly and has tremendous potential for causing life-threatening organ dysfunction. One of the landmark findings has been reviewed concerning the role of Machine Learning (ML) and nanotechnology in shifting the paradigm identification and management of sepsis.

In the analysis of large amounts of clinical data in real-time, ML-based systems have proved quite excellent at the early detection of sepsis, enhancement of adherence to treatment protocols and consequential mortality reduction. In addition, nanotechnology has improved diagnostic sensitivity with sophisticated biosensors and enhanced therapeutic efficacy with targeted drug delivery. These technologies hold much promise in managing sepsis including earlier diagnosis and tailoring of therapy or the management of sepsis. Another area of great interest is the modulation of host response using HMGB1-targeted therapies with the potential to reduce inflammation and organ damage. The inhibition of HMGB1 may potentially serve as an efficient strategy in mitigating the over-exuberant host immune response characterizing sepsis, presenting with this a new therapeutic target that could complement the antimicrobial therapies and the supportive therapies.

This is a step forward in this direction, yet there is still a gap in the real incorporation and implementation of treatment protocols, especially in low-resource settings. Though sepsis

bundles and EGDT have enhanced the result, compliance along with these guidelines varies. There is, hence, growing concern regarding stronger implementation strategies including educational initiatives, hospital-wide sepsis programs and the actual incorporation of technological advancement.

Conclusion

Sepsis remains a leading concern in the global health agenda with a considerable burden of mortality and significant healthcare expenses, especially in the acute care environment. This review addresses insights gained on the pathophysiology of sepsis and importance of early detection. Potentially promising new technologies may contribute to better management of sepsis. At the same time, with all of these advances, sepsis still remains a complex and multifaceted syndrome whose early diagnosis and timely intervention would prevent most undesirable secondary dysfunction and mortality effects.

Integration of ML and nanotechnology in the care of sepsis holds potential for improving early diagnosis, predicting progression of disease and refining the precision of therapeutic interventions. This set of technologies associated with conventional treatments like antibiotics, fluid resuscitation and vasopressor support, actually presents a more comprehensive approach in addressing sepsis. With these targeted inflammatory mediators such as HMGB1 and more, comes the new capability to modulate the host response, to decrease excessive inflammation, and, ultimately, to improve patient outcomes. Again, these advances need to be translated into clinical practice and should be further studied depending on standardizing protocols and ensuring easier access in low-resource settings.

In summary, with sustained improvement in sepsis management, there is a need for further research and innovative ideas to significantly reduce deaths involving sepsis leading to improved survival outcomes. Better care will also be achieved around the world. Sepsis management in the future should be guided by the integration of advanced diagnostics and targeted therapies with increased adherence to evidence-based guidelines to foster an even higher rate of survival as well as quality of care for patients with sepsis.

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