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Sepsis management: A paradigm shifts towards novel therapies

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Abstract
Sepsis remains the life threatening clinical condition with medical and economy burden healthcare units and hospitals globally. Despite of all clinical efforts and medical techniques, treatment and management of sepsis remains limited over the past three decades. With advances in understanding the evolution and pathophysiology of sepsis, it has been found that occurrence of sepsis cannot be attributed to pathogen only, but also alterations in immune response play a significant role in generation of sepsis. Treatment of sepsis involved early identification of patients at risk with prompt diagnosis and administration of appropriate antibiotics with all-purpose supportive care. This approach contributed to improved prognosis in management of sepsis and reducing the overall mortality rate. With the ongoing research and advances in clinical medicine, it has been investigated that more ameliorate measures have yet to yield better results. This review is aimed to provide outline about the immune pathophysiology and the progress made in the development of targeted therapy for management of sepsis over the decades with focus on more promising avenues for future research.

Keywords: sepsis, antibiotics, clinical medicine, treatment, diagnosis

1. Introduction
Sepsis can be described as the systemic inflammatory response characterized by the simultaneous activation of inflammation and coagulation in response to microbial insult through the release of proinflammatory cytokines, procoagulants and adhesion molecules from immune cells [1]. Alternatively, sepsis can be defined as the "life-threatening organ dysfunction caused by a dysregulated host immune response to infection" [2]. It is the potential threat to global public health safety and economic security [3]. The most severe form of sepsis is septic shock that refers to a state of circulatory failure, arterial hypotension, multi-organ failure and eventually death [4]. Mortality rate varies from about 20% in patients with sepsis and 60-80% in case of patients affected with septic shock [5]. Sparse data from India described that sepsis is major cause of deaths with intensive care unit mortality, hospital mortality and 28-day mortality were 56%, 63.6%, and 62.8%, respectively in a study conducted with Indian tertiary care hospital [6]. A tentative extrapolation of data suggested that 31.5 million cases of sepsis and 19.4 million cases of severe sepsis occurred globally each year, with potentially 5.3 million deaths annually [7]. Treatment of sepsis involved prompt diagnosis and administration of appropriate antibiotics with all-purpose supportive care [8]. Increasing antibiotic resistance has resulted in further research on new treatment modalities in addition to classical treatments. It has been suggested that use of heavy dose of antibiotics may worsen the condition as it kill bacteria and releases LPS in large amount leading to septic shock in patients treated for severe infections caused by Gram-negative bacteria [9].

2. History of sepsis
The word Sepsis had its origin from the ancient Greek word which means the decomposition of animal- or plant-based organic materials by bacteria and the very first use of the word 'sepsis' was about 2700 years ago in Homeric poems as 'sepo' [σηπω], meaning 'I rotted.'

3. The Genesis of sepsis
There is significant evidence of sepsis-associated acute mortalities in hospitals due to inappropriate medical care or mismanagement. It becomes very important to understand the underlying causes, etiology, pathophysiology involved in the manifestation of sepsis that may culminate in death also.

3.1. Etiology of sepsis: Role of endotoxins

LPS is a pro-inflammatory constituent of the outer membrane of Gram-negative bacteria. Endotoxins play a pivotal role in many pathophysiological conditions and diseases in animals and often times they are the leading cause of severe illness and death in variety of animal species [10]. Endotoxaemia refers to the presence of endotoxins in the systemic circulation. During septicaemia, microbes invade normally the sterile parts of the body leading to systemic illness [11]. Gram-negative bacteria, especially *E. coli*, play a crucial role in the development of endotoxaemia among livestock [12]. In a current study it is found that the endotoxin liberated during bacteriolysis or periods of rapid growth and enters general circulation and causes adverse systemic reactions. Endotoxaemia is the circulatory disturbance due to microbial insult leading to multiple organ dysfunctions such as cardiovascular, respiratory and haemostatic and biochemical changes and may eventually result in death and is a significant cause of mortality in farm animals [13].

3.2. Pathophysiology of sepsis and septic shock

For the diagnosis and management of sepsis it is very important to gain knowledge about the underlying mechanism for molecular cascade of the systemic inflammatory response involved in the pathophysiology of sepsis. Innate immunity acts as the first line of defense against pathogens which involves the recognition of pathogen-associated molecular patterns (PAMPs) by pattern recognition receptors expressed by immune cells of the host. The outer membrane of Gram-negative bacteria has LPS that act as a well-characterized PAMP. During bacterial infection, once the LPS is released to the blood, it is sensed by immune cells and removed by the mononuclear phagocyte system [14]. Though the endotoxins don't affect host cells directly but they enhance the various cells like endothelial and smooth muscle cells, polymorphonuclear granulocytes, platelets, thrombocytes and monocytes to produce cell bound or soluble mediators [15]. Consequently, these cells once activated, release the inflammatory mediators including cytokines, platelet activating factor, thromboxane A2, prostaglandins, leukotrienes, proteinases, toxic oxygen metabolites and vasoactive amines to the bloodstream. The released cytokines are responsible for many of the pathophysiologic events of endotoxaemia [16]. LPS is extracted from bacterial membranes by a protein named LPS binding protein (LBP) present in the bloodstream and eventually binds with the endotoxin component of bacterial LPS and then passed to a membrane-bound receptor (mCD14) on mononuclear cells. CD14 then presents LPS to the toll-like receptor-4 (TLR-4) on the mononuclear cell membrane. The lipid A (endotoxin) component of LPS is recognized by Toll-like receptor 4 (TLR4) and its co-receptor myeloid differentiation factor-2 (MD-2) on host innate immune cells that subsequently shape the adaptive immune response [17]. The resulted complex (LPS–LBP– mCD14–MD-2 complex) is then internalised and LPS is destroyed during the process. This process triggers the cascade of intracellular signalling pathways. The most prominent signalling pathways include the phosphorylation of mitogen activated protein kinases (MAPKs) and the activation of transcription factors such as nuclear factor-kappa B (NF-κB) and interferon regulatory factors (IRFs), which in turn stimulate production of pro-inflammatory cytokines like TNFα and IL-6 [18].

Some of the soluble CD14 receptors (sCD14) are shed into the bloodstream and play an important role in the pathogenesis of endotoxaemia. Increased serum concentrations of sCD14 are responsible for the severity of clinical signs associated with endotoxaemia [19]. The ability of TLR4 to recognize a variety of molecular patterns important for host defense but if not controlled can make the host vulnerable to excessive or unwanted inflammatory responses like inappropriate TLR4 activation can cause allergy and excessive activation of transcription factor NFκB can lead to septic shock [20, 21]. Some of the activated genes are involved in synthesis of cyclooxygenase 2, nitric oxide, endothelial adhesion molecules and chemokines. The circulating levels of the eicosanoids like arachidonic acid metabolites, thromboxane A2 and prostacyclin are responsible for the haemodynamic abnormalities [15]. Sepsis result in multiple organ dysfunctions, shock and disseminated coagulopathy which ultimately lead to death.

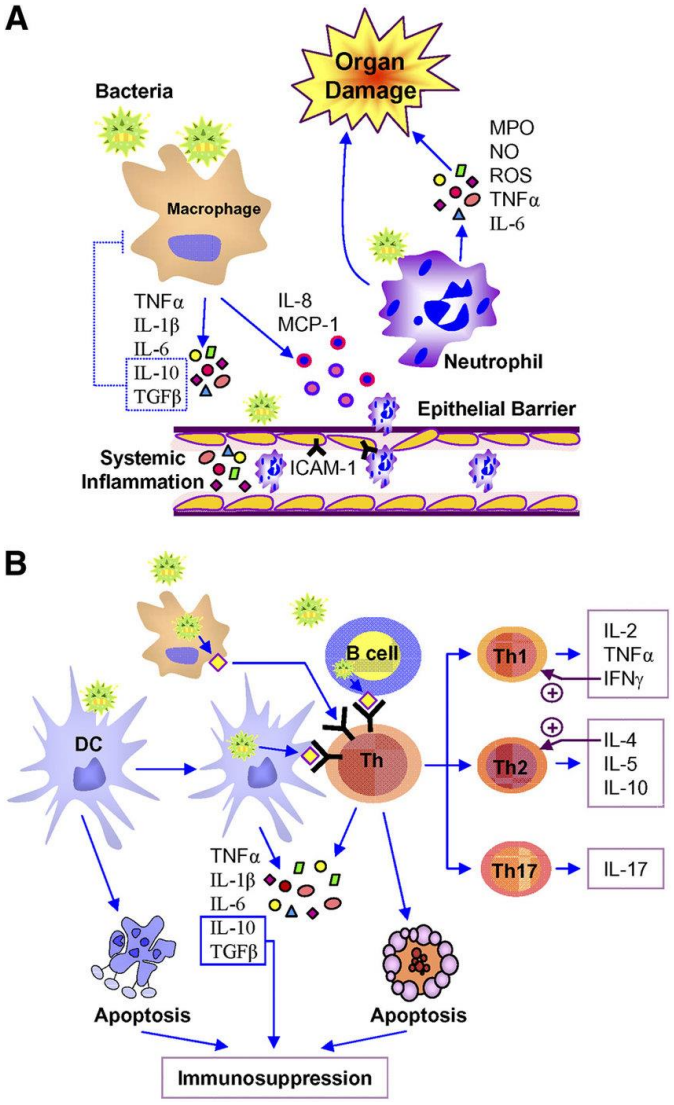

Fig 1: Innate and adaptive immune responses involved in pathophysiology of sepsis [22].

4. Management of sepsis: Therapeutic concepts

Sepsis remains a challenge for global health security and endotoxemia acts as one of the leading causes of high mortality in large animals [23]. Over the past years, several therapeutic strategies had been designed for the effective treatment of sepsis. The literature supports the evidences for improved prognosis with advances in strategies employed.

However, only a few of these therapies proved to be effective and the choice of best therapy still remain a topic of debate.

4.1. Casual therapy: Antibiotics & Supportive care

Bactericidal Gram-negative antimicrobial agents were always the first choice of treatment in case of bacterial infection causing endotoxaemia. It was discovered in a study that the antibiotic levofloxacin had good potential to treat bacterial diseases in sheep when administered at rate of 3 mg/ kg in experimentally induced endotoxaemia model of sheep [24]. One of the approaches applied for the treatment of endotoxaemia was the LPS inactivation which was attained by neutralisation of endotoxin through administration of bactericidal antibiotic like Polymyxin B that specifically targets active portion of LPS and neutralised its biological activity. Treatment with polymyxin B to attenuate clinical endotoxaemia was found to be effective in reducing LPS induced lethalities in sheep [25]. Effects of intravenous polymyxin E (colistin) administration on ovine experimental endotoxaemia were evaluated and found that polymyxin E could be used as an anti-endotoxic drug against the *E. coli* induced endotoxaemia in sheep [26]. The use of antibiotics to effectively control Gram negative infections was popular but may lead to rise in antibiotic resistance [27].

Fluid resuscitation was employed as the therapeutic intervention in septic shock in order to meet perfusion deficits and prevented multi organ dysfunction [28].

4.2. Immune therapy

Scientific approaches based on anti-endotoxin or anti-LPS immunotherapy had gained considerable interest as potential therapeutic mode for improving survival in Gram-negative bacteraemia [29]. In the first approaches for the treatment of sepsis, the anticytokine therapies were directed that included use of monoclonal antibodies against TNF-α, sTNFRs, IL-1Ra, and soluble IL-1 receptors. Murine monoclonal antibodies against TNF-α were known to reduce the detrimental effects of LPS including the haematological and clinical responses in horses [30, 31]. The treatment protocol involving administration of anti-LPS antibodies was an old approach that was renewed by improvements and advancements in monoclonal antibody technology. However, murine and rabbit polyclonal TNF-α antibodies did not prove to be so effective when tested in vivo in equines, but did decrease the activity of TNF-α when tested in vitro [32, 33]. It was shown in vitro studies that inhibition of TNF-α-converting enzyme (TACE) prevented the release of TNF-α from human monoblastoid tumour cell line (U973 cells) and equine bone marrow-derived macrophage cell line referred to as e-CAS cells [34]. Also, experimental work was done on studying the cytokine –modulating and anti-inflammatory effects of ketamine in equine macrophage cell line. The major finding was that ketamine significantly inhibited the LPS-induced cytokine production in equine macrophage cell line with its prominent effect on LPS-binding to TLR4 (extracellular), on the MAPK pathway (intracellular) and on NF-κB (intranuclear) activation [35]. A significant decrease in mortality was seen in experimental mice with polymicrobial sepsis after administration of anti-TLR4 antibodies [36]. Several trials based on the anticytokine therapy were conducted and they revealed that a consistent decrease in mortality was observed in human patients [33].

4.3. Immune-modulation based therapies

Antimicrobial peptides (AMPs) were found to be effective strategy for preventing and controlling microbial infections by both direct microbial killing and modulation of innate immune system thereby reducing LPS induced detrimental responses. Human lactoferrin peptide 1–11 (hLF 1–11), a derivative of the human lactoferrin was found to possess antimicrobial activity and lead to modulation of the inflammatory immune response, thus prevented harmful effects of sepsis [37, 38, 39]. A series of studies were conducted suggesting the protective effects of ethyl pyruvate on endotoxin-induced experimental sepsis, but the exact underlying mechanism remained elusive [40].

During the initial phases of sepsis, there is oxidative stress in the patient creating immune imbalance and cellular dysfunction due to toxic free radical production. It was investigated that treatment with peroxide scavenger mannosylated polymeric albumin manganese dioxide (mSPAM) nanoassembly had significantly reduced the neutrophilic infilteration and other leukocytes in a local endotoxemia animal model. Hence, the mSPAM nanoassembly system served as a potent anti-inflammatory agent and could be further anticipated as a successful application in treatment of various inflammation-related diseases in future [41].

4.4. Steroids in sepsis treatment

Over the past decades' corticosteroids had been extensively used for endotoxaemia and sepsis treatment. Betamethasone at the dose of 1mg/kg significantly reduced the circulating levels of acute phase proteins and inflammatory cytokines [42]. The known benefits of non-steroidal anti-inflammatory drugs (NSAIDs) as analgesic, anti -inflammatory and antipyretic were clearly indicated as they suppressed the production of thromboxane and prostaglandins and reduced the acute haemodynamic response to endotoxaemia [19].

4.5. Newer modalities in sepsis treatment

The improved therapeutic interventions included the use of novel neutrophil extracellular traps (NETs) directed therapy for sepsis treatment. Based on the beneficial effects of novel NET-targeting approach, a monoclonal antibody modified in FC portion was developed that decreased the bacterial dissemination and improved the survival outcome in murine sepsis models [43]. Treatment with ethyl pyruvate proved to be effective in giving protection against lethal endotoxemia and decreased the release of IL-1α and IL-1β. Similar results were observed in the mouse cecal ligation and puncture (CLP) peritonitis sepsis model contributing to the further explanation of the protective action of ethyl pyruvate [44]. The administration of domain-specific polyclonal and monoclonal antibodies had promising potential for clinical management of inflammatory conditions. Till date for the clinical management of sepsis, antibody-based strategies had been attempted to antagonize proinflammatory cytokines but no attempt been made to target proteins that interact with the pathogenic mediators. In a current finding, tetranectin (TN) domain-specific monoclonal antibodies were developed that effectively inhibited TN/HMGB1 interaction and their cellular uptake thereby attenuated the sepsis induced TN depletion and tissue injury and hence rescued animals from lethal sepsis [45].

5. Conclusion

The effective management of sepsis can be done with the prompt diagnosis and application of newer treatment protocols in clinical medicine. With the ongoing research and advances in molecular biology and medical field, the more ameliorate measures have yet to yield better results in future and help to reduce overall mortality rate due to sepsis.

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