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Immunomodulatory Therapies in Sepsis Management

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Abstract

Sepsis is a life-threatening condition caused by a dysregulated immune response to infection. It affects over 25 million individuals annually. A more severe subset, septic shock, is characterized by persistent low blood pressure and hospital mortality rates that exceed 40%. While early mortality from sepsis has significantly declined in recent years, many survivors of the initial hyperinflammation and organ damage face long-term complications, including secondary infections. Despite extensive clinical trials aimed at this stage of the disease, there are currently no therapies specifically designed for sepsis.

Traditional treatment approaches often fail to address immune dysregulation, emphasizing the need for innovative therapeutic strategies. Immunomodulatory therapy offers potential in sepsis management by reestablishing immune balance and reducing excessive inflammation. This review explores the pathophysiology of sepsis, current treatment challenges, advancements in immunomodulatory agents, and novel approaches for managing the condition. Notably, colostrum and lactoferrin, known for their immunomodulatory properties, exhibit strong anti-inflammatory and antioxidant effects. Their ability to target both the immune system and pathogens positions them as promising candidates for sepsis treatment. The review reports clinical trial outcomes of colostrum and lactoferrin, their safety profiles, and the implications for future research and clinical practice.

Although immunomodulatory therapies show significant promise in improving sepsis outcomes, successful implementation will require further research, collaboration, and integration into established clinical protocols.

Keywords

Sepsis, Cytokines, Immunomodulation, Colostrum, Lactoferrin.

1. Introduction

1.1 Sepsis Definition

Sepsis is a life-threatening condition that results from an abnormal immune response to infections such as respiratory, urinary, or skin infections.[1, 2]. In sepsis, there are two immune-modulated phases, including an early hyper-inflammatory phase, in response to the infection, which is characterized by massive cytokine release that eventually causes extensive tissue damage. Then, it is followed by an immunosuppressive phase through which a progressive dysregulation of the immune response happens [3].

1.2 Sepsis Implications on Global Health

Sepsis is one of the biggest causes of morbidity and mortality worldwide. The World Health Organization reports that, according to 2020 data from the Global Burden of Disease Study, there were 48.9 million cases, and 11 million deaths related to sepsis which accounted for a fifth (20%) of all global mortalities. Even those who survive often suffer from long-term disability resulting in decreased physical and mental functioning capacities [4, 5]. In low- and middle-income countries especially, sepsis represents a significant burden due to limited healthcare resources and higher prevalence rates for infections [5]. In addition, certain populations such as infants, pregnant women, elderly adults, and people with chronic health problems are more susceptible to developing septicemia.

1.3 Pathophysiology of Sepsis

The pathophysiology of sepsis is complicated, although some patients mount a productive immune response to fight infection, others deteriorate into a dysregulated state. Hence, we discussed some of the several sepsis interrelated pathological mechanisms that lead to tissue damage (Figure1).

1.3.1 Immune Response Dysregulation

Sepsis is mainly induced by immune dysfunction that transforms from an initial excessive inflammatory response, specific to pathogenic factors such as infection, into immune paralysis or immunosuppression [6]. Infections trigger the innate immune system which then releases pro-inflammatory cytokines like Interleukin-1 (IL-1), Interleukin-6 (IL-6), and Tumor necrosis factor- alpha (TNF-α) from neutrophils and macrophages [7]. Cytokines are essential in controlling infections but during sepsis, the immune response becomes overwhelming and unregulated leading to systemic inflammatory response syndrome (SIRS) instead of a localized response resulting in multiple organ dysfunction [8].

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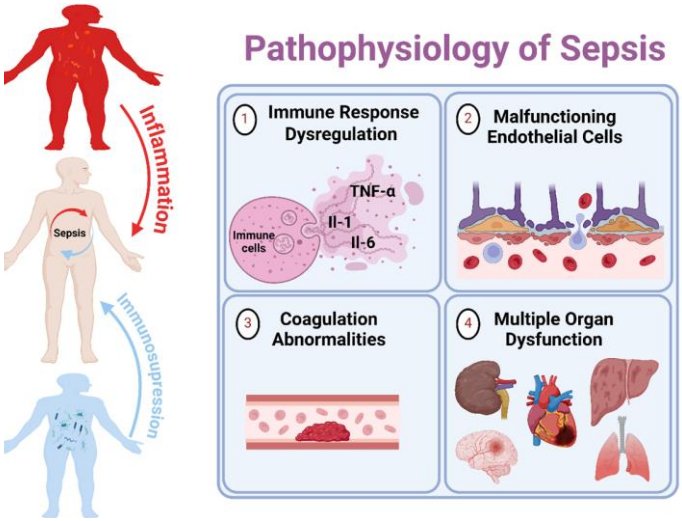

Figure 1. The schematic diagram illustrates the possible pathways of sepsis**.**

1.3.2 Malfunctioning Endothelial Cells

It is another theory that explains tissue damage during sepsis. The inflammatory response to the released cytokines leads to altered functioning of the endothelial cell lining (ECL) with increasing blood vessel permeability. As a consequence, extracellular fluid and proteins leak into the surrounding tissues hence causing edema and lowered tissue perfusion [9]. Hypoperfusion is described as tissue hypoxia that results from an inadequate supply of blood to organs and represents the main reason for organ failure during sepsis.[10]

1.3.3 Coagulation Abnormalities

Sepsis interferes with the natural blood clotting process by up-regulating procoagulant mechanisms while down-regulating natural anticoagulants simultaneously [11]. The coagulation cascade is initiated, and the fibrinolysis mechanisms are inhibited leading to the formation of intravascular thrombi and eventually causing disseminated intravascular coagulation (DIC). The subsequent impairment in blood flow further worsens organ malfunction.[12]

1.3.4 Multiple Organ Dysfunction (MODS)

Excessive inflammation, damage to endothelial cells, disordered blood clotting as well as the suppression of the immune system contribute to MODS. Thus, acute respiratory distress syndrome and acute renal failure can develop. If not intervened promptly they may lead to rapid progression into a septic shock which if untreated could result in death [13].

2. Sepsis Current Treatment Approaches

Managing sepsis entails rapidly identifying and treating the root infection as well as giving supportive care to stabilize important functions of the body. Below are the current approaches:

2.1 Antibiotic Therapy

The choice of the best antibiotic is crucial for saving lives and controlling infections and depends on which antibiotic(s) work best against specific infections [14]. Treatment should be initiated by broad-spectrum antibiotics then the antibiotic of choice is given depending on identification of the source of the infection based on culture results [15]. Beta-lactam's extended or continuous infusion and therapeutic drug monitoring (TDM) can help in obtaining therapeutic levels of antimicrobials. Common antibiotics for treating gram-positive infections include vancomycin and linezolid [15]. For gram-negative infections, there are more options, including broad-spectrum penicillins (like piperacillin/tazobactam), third- or fourth-generation cephalosporins, imipenems, and aminoglycosides [15]. However, overuse of antibiotics has contributed to the emergence of antibiotic-resistant bacteria making infections more difficult to treat. Widespread administration of antibiotics might sometimes fail, requiring stronger drugs with potentially harmful side effects [16, 17]. The six most frequently used antibiotics are levofloxacin, ceftazidime, ciprofloxacin, cefotaxime, ceftriaxone, and erythromycin showed an average resistance above 50%[16] .

2.2 Fluid Resuscitation

Swift provision of fluids is critical to offset the low blood pressure and the inadequate blood flow to organs. International consensus guidelines recommend administering at least 30 ml/kg of isotonic crystalloid fluids to restore blood volume and improve organ functions [17]. Nevertheless, determining the appropriate volume of fluid resuscitation and the timing of its administration remain difficult tasks. Too low or too high amounts of fluid can increase organ dysfunction and mortality in patients with severe sepsis and septic shock [18].

2.3 Vasopressors

When the blood pressure remains persistently low, despite adequate fluid resuscitation, medications to increase the blood pressure like norepinephrine (NE) are given to ensure that essential organs perfuse well [19]. The immediate administration of NE could enable achieving the desired initial mean arterial pressure (MAP) quicker and reduce the likelihood of volume overload. The available data suggests an initial target MAP of 65 mmHg. In cases of refractory hypotension, increasing NE up to doses ≥1 µg/kg/min could be an option.[20]

2.4 Septic Source Control

Source control aims at removing or controlling an infection's source, discontinuing ongoing contamination as well as restoration of the premorbid anatomy and function [21]. Therefore, it is important to drain pus or open or percutaneously remove infected /necrotic tissue (debridement), establish diverting 'ostomies', remove the obstruction, etc. to improve patient's outcomes by finding out and treating the cause of infection at its root [22]. Not all goals may be required for every infection, and strategies can be applied selectively based on the type of infection.[22]

2.5 Supportive Care

Providing support for damaged organs is crucial in treating sepsis and increasing survival rates. This can involve normalization of blood glucose in diabetics (a continuous IV infusion of insulin (starting dose 1 to 4 units/hour) is titrated to maintain glucose between 110 and 180 mg/dL (7.7 to 9.9 mmol/L)), using a ventilator for lung problems, dialysis for kidney failure, and other

treatments to help organs function properly [23]. Moreover, corticosteroids may be used in severe cases of sepsis.[24]
Sepsis is a highly heterogeneous condition, where host factors (age, biological sex, comorbidities, and genetics), infection etiology, host response dysregulation, and MODS can all result in different disease manifestations, progression, and response to treatment, which make it challenging to develop a single treatment plan for all patients [25]. Moreover, most treatments focus on stabilizing the patient rather than correcting the body's abnormal immune response.[26]
Great strides have been made in sepsis treatment; however, several daunting challenges persist as well. Delayed diagnosis, antibiotic resistance, and ineffective treatments highlight the need for new therapies against sepsis-induced host derangements [27]. Consequently, recent studies aim at developing such targeted therapies that address both infection as well as detrimental immune responses within the host [28].

3. Immunomodulatory Approaches in Sepsis Management

As a therapy intervention, immunomodulatory treatments could be promising specifically in sepsis because it can be viewed as an approach that targets the 'broken' immune response rather than the pathogen [29]. Immunomodulation aims at achieving better performance by regulating the immune reaction in patients to establish a more efficient immune response not aggressive enough to damage the human tissue [28].

3.1 How Immunomodulatory Drugs Act in Sepsis

Some of the most important aspects to understand about the pharmacology of immunomodulatory agents include the mechanisms of drug action of these agents and their effects on the immune responses of the body.

3.1.1 Anti-inflammatory agents

In the early phases of sepsis development, these agents help to regulate inflammation. Research has been extensively done mainly on the impacts of steroids, particularly hydrocortisone in the suppression of systemic inflammation and the stabilization of blood flow among septic patients [24]. According to the guidelines of the Surviving Sepsis Campaign 2012, about 200 mg/day of hydrocortisone should be given to treat patients with septic shock if adequate fluid resuscitation cannot restore hemodynamic stability plus vasopressor therapy is above considered stabilizing [30]. Moreover, other studies indicate that hydrocortisone dosed 75–150 mg/day appears to reverse shock as effectively 200–400 mg/day and may cause a lower frequency of adverse events [24].

3.1.2 Cytokine Blockade

Reduction in the impact of pro-inflammatory cytokines may result in increased survival rates in some animal sepsis models. The antagonists of TNF-α, IL-1β, and IL-6 are now in the investigative phase, carrying out the preclinical to early phase II trials for the treatment of infections [31]. Anakinra, a widely recognized IL-1 receptor antagonist, is utilized in the treatment of several hyper-inflammatory disorders, such as Still's disease, juvenile idiopathic arthritis, and familial Mediterranean fever. It is highly effective in treating cytokine storm syndrome, including cytokine release syndrome and macrophage activation syndrome [32]. Sarilumab is a fully human monoclonal antibody (MCA) that inhibits the binding of IL-6 to its α receptor. It is approved by the FDA for the treatment of ankylosing spondylitis and moderate to severe rheumatoid arthritis. It is considered a safe and well-tolerated medication, with a recommended dosage of up to 200 mg every two weeks [33].

3.1.3 Immunostimulatory Agents

On the other hand, interferons and granulocyte-macrophage colony-stimulating factor (GM-CSF) may be used in the late phases of sepsis to overcome immunosuppression and restore normal immune response to clear any further infections efficiently [34]. The Mesenchymal stem cells (MSCs) have immunomodulatory function and the ability to support tissue repair. These cells can reduce inflammation and promote the healing of damaged tissues within the body [35]. MSCs may enhance the production of anti-inflammatory cytokines while decreasing pro-inflammatory ones. Furthermore, these studies have shown that MSCs can suppress the overexpression of TNF-α and IL-6 caused by sepsis while boosting the expression of IL-4 and IL-10 in both septic rats and lipopolysaccharides -treated Kupffer cells, thus alleviating organ damage associated with sepsis [36].

3.2. Challenges in Implementing Immunomodulatory Therapies for Sepsis in Clinical Settings

Implementing immunomodulatory therapies of sepsis into the clinical setting is encumbered by several significant obstacles:

1. Heterogeneity of septic patients

Septic patients exhibit diverse underlying conditions and immune profiles, making the development of universal treatments highly challenging. This variability necessitates personalized therapeutic strategies [37].

2. Optimal timing of administration

Determining the ideal timing for immunomodulatory therapy administration is challenging. Administering them too early or too late may be ineffective or even harmful, highlighting the importance of precise timing [38].

3. Selection of inappropriate patients

Selecting the appropriate patients for suitable immunomodulatory interventions is challenging due to the lack of reliable biomarkers and the heterogeneous nature of sepsis. This has been a major factor contributing to the failure of most clinical trials [39].

4. Safety Considerations: Risks and Precautions
Most immunomodulatory drugs, including colostrum and lactoferrin, are considered safe. However, some, like toll-like receptor 4 antagonists, have been linked to a higher risk of severe side effects, emphasizing the necessity of rigorous safety evaluations.[40]

5. Translational Challenges
The gap between preclinical models and human sepsis has created challenges in translating successful animal trials into

effective treatments for humans, highlighting the need for more relevant study models.[39]
Although the implementation of immunomodulatory therapies for sepsis in clinical settings presents several challenges, colostrum and lactoferrin possess properties that help overcome these barriers, making them viable options for sepsis treatment.

3.3 Promising Immunomodulatory Agents in Sepsis Management

Colostrum and lactoferrin, immunomodulatory and antimicrobial agents, are safe and promising treatments for sepsis due to their ability to target both the immune system and pathogens, helping to balance inflammation and immunosuppression [41-43]. No contraindications have been observed with colostrum administration, even at high concentrations, in both humans and animals [44]. However, some studies have reported lactose intolerance and sensitivity to milk proteins, leading to minor gastrointestinal issues such as nausea, flatulence, diarrhea, unpleasant taste, and skin rash [45]. Additionally, lactoferrin is generally considered a safe supplement for sensitive groups, including children and pregnant individuals [46-48]. However, excessive doses of lactoferrin may cause mild and common side effects, such as stomach pain, vomiting, reduced appetite in children, and constipation [49].

3.3.1 Colostrum

Colostrum, the first type of milk produced by mammals, is rich in nutrients and bioactive ingredients like lactoferrin. It binds to iron and has antimicrobial effects. Further, it contains immunoglobulins such as (IgA, IgG, IgM) with IgG being the most abundant that provides passive immunity by neutralizing infections. IgA protects the respiratory and gastrointestinal tracts [50, 51], while growth factors like Epidermal growth factor, Insulin-like growth factor-1, and Transforming growth factor-β promote tissue regeneration and have anti-inflammatory properties [52, 53]. Other components include cytokines (interleukins and tumor necrosis factor) and antioxidants (vitamins A and E) that help in immune responses and protect against oxidative stress respectively [54, 55].

Colostrum exhibits anti-inflammatory effects by balancing pro- and anti-inflammatory cytokines like IL-10, reducing systemic inflammation, and preventing the harmful effects of sepsis and organ damage [41, 56]. Colostrum reduced IL-1β activation of Nuclear factor kappa-B (NF-κB) showing that it has the potential to prevent inflammation in the intestine by blocking the NF-κB signaling pathway as mentioned by Playford and Weiser [52]. It also enhanced immune cell functions, including neutrophil activity, macrophage phagocytosis, and T-cell maturation, helping the body fight infections [42, 57, 58]. Colostrum's antimicrobial action arises from immunoglobulins and antimicrobial peptides that inhibit the growth of bacteria, fungi, and viruses. It also promoted pathogen clearance by boosting immune functions thus reducing the risk of severe infections [59, 60].

Some studies have confirmed that colostrum could be a promising treatment for sepsis, as it targets pathogens, besides its immunomodulatory effects, helping to regulate inflammation and prevent subsequent immunosuppression. A pilot study by Cross, Opal [61] using neutropenic rats challenged orally with Pseudomonas aeruginosa, revealed that administration of hyperimmune bovine colostrum enriched in antibodies and non-immune bovine colostrum improved survival, reduced bacterial burden from the liver, lung, and spleen. Therefore, they are effective supplements that improve the outcome from lethal gut-derived disseminated infection and reduce transmission of Gram-negative bacilli from the gastrointestinal tract. Further a study conducted by Döhler and Nebermann [62] on rats challenged orally with a suspension of Escherichia coli to induce enterogenic endotoxemia showed that administering either pure bovine colostrum or lactoferrin-enriched bovine colostrum effectively neutralized endotoxins and bacteria. This was determined by assessing plasma endotoxin activity and bacterial contamination in mesenteric lymph nodes and peritoneal lavages.

Oropharyngeal administration of colostrum may help lower the risk of necrotizing enterocolitis, late-onset sepsis, feeding intolerance, and mortality in preterm infants. It can also accelerate the achievement of full enteral feeding and promote faster recovery to birth weight. Colostrum should be given within the first 2 hour after birth, as early administration maximizes the absorption of immunoglobulins and other protective components essential for the infant's immune defense [63]. The recommended frequency for administration is every 4 hours, with an optimal duration of 8 to 10 days [64].

3.3.2 Lactoferrin

Lactoferrin, an iron-binding glycoprotein found in colostrum and various secretions like saliva, sweat, semen, and tears, plays a key role in immune modulation by depriving bacteria of the iron they need for growth [65]. It also has antioxidant properties and helps reduce free radical production therefore limiting tissue damage during inflammation [43]. Lactoferrin modulates immune responses by blocking bacterial endotoxins, especially lipopolysaccharides (LPS) and regulating the immune system during sepsis [66]. It has anti-inflammatory effects by suppressing the release of cytokines like TNF-α and IL-6, which are involved in excessive inflammation [67, 68]. Lactoferrin enhances neutrophil function, macrophage activity, and lymphocyte differentiation leading to the development of an effective immune response to infections.[70 ,69]
Lactoferrin also exhibits direct antimicrobial action against bacteria, viruses, and fungi [71]. It destabilizes bacterial membranes and inhibits viral binding to host cells, contributing to infection prevention [72, 73]. Additionally, lactoferrin works synergistically with antibiotics by inhibiting bacterial biofilms, making bacteria more susceptible to treatment, which is crucial for managing antibiotic-resistant infections in sepsis [74]. Several studies have confirmed these findings. For instance, a study by Venkatesh, Pham [75] on neonatal Wistar rats subcutaneously infected with C. albicans and S. epidermidis (2×10^8 CFUs) demonstrated that intraperitoneal administration of lactoferrin significantly improved survival in the coinfection group, increasing survival rates by 16.1% at a dose of 40 mg/kg and 15.1% at 300 mg/kg. Additionally, research by Kruzel, Harari [76] on mice injected with endotoxin showed that endotoxemia and endotoxin-induced mortality were linked to an oxidative burst and excessive production of inflammatory mediators. However, intraperitoneal administration of lactoferrin one hour before LPS exposure significantly suppressed LPS-induced TNF-α, IL-6, IL-10, and nitric oxide production, thereby reducing tissue inflammation and preventing organ failure. Recent findings also suggest that lactoferrin enhances immune

cell function, improving neutrophils' bacteria-killing activity and stimulating a beneficial macrophage response essential for controlling infection and inflammation [77]. Furthermore, a study by Ochoa, Loli [78] found that administering bovine lactoferrin at 200 mg/kg/day to infants with a birth weight below 2500 g and 2000 g effectively lowered the risk of late-onset sepsis, with the most significant protective effect observed in infants weighing under 1500 g, particularly those not fed human milk .

Enteral administration of lactoferrin within the first 7 days of life has been linked to a lower risk of sepsis and necrotizing enterocolitis in preterm infants [79]. A standard regimen involves a daily dose of 200 mg/kg, mixed with breast milk or formula. This supplementation typically continues for around 12.5 days, corresponding to the average hospital stay for very low birth weight infants [80].

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