REVIEW ARTICLE

PATHOPHYSIOLOGY OF SEPSIS

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ABSTRACT

Background: Sepsis, a systemic inflammatory response to infection, resulting in organ failure and death. Pathogenic microbial agents trigger cascades of events in sepsis by stimulating the host's immune system. Macrophages require surface receptors to present pathogenic molecule to Toll-like receptors (TLR$_s$) to be activated and release proinflammatory cytokines such as tumour necrosis factor (TNFα) and interleukins (IL-1β, IL-6 and IL-8) together with activation of the coagulation cascades. In the last three decade, several basic science and clinical researches have been conducted in order to improve treatment and survival of patients with sepsis. The main aim of this review is, thus, to highlight recent advances in the pathophysiology of sepsis for effective management of the problem.

Sources and Methods: More than 200 literatures of both experimental models of sepsis as well as clinical trials that were published from 1990 to 2011 were reviewed. Medline search was done based on the following key words; sepsis, systemic inflammatory response syndrome (SIRS), pathophysiology of sepsis, sepsis and coagulation, treatment of sepsis, mediator cytokines, multiple organ dysfunction syndrome (MODS) were performed. Both original publications and review articles were utilized.

Results: Both preclinical and clinical models reserches on sepsis have shown significant development in the identification of diagnostic molecules such as cytokines and cell surface receptors that are potential biomarkers of sepsis in the clinical settings. Certain advancements have also been made in the understanding of the pathophysiologic, immunologic and biochemical pathway of sepsis. Despite these significant advances in the pathophysiology of sepsis, the mortality rate is still high, 30% to 50%.

Conclusion: To win the war against sepsis, the pathophysiology of sepsis should be clearly elucidated. Early administration of broad spectrum antibiotics, effective source control, maintenance of normal glucose levels and goal-directed hemodynamic resuscitation are the cornerstone of successful management of sepsis.

Key works: SIRS, Sepsis, Severe Sepsis, Septic Shock, Pathophysiology.
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INTRODUCTION

Sepsis, severe sepsis, septic shock represents progressive stages of the same illness-a systemic response to infection mediated via macrophage derived cytokines (1). Severe sepsis and septic shock are major challenges in intensive care units (ICU) (2). Severe sepsis is associated with a mortality rate of 25 - 30% and mortality due to septic shock is 50-85% (3).

Pathogenic microbial agents trigger cascades of events in sepsis by stimulating the host's immune system. Severe sepsis is characterized by over activation of the host's immune system resulting in production of excessive inflammatory and anti-inflammatory cytokines that may result activation of the intravascular coagulation, systemic inflammation, systemic vasodilatation, increased capillary permeability and apoptosis that lead to the development of progressive multiple organ failure and ultimately death (4).

Endotoxin (lipopolysaccharide, LPS) from Gram-negative bacteria, peptidoglycan and flagellan from Gram-negative and Gram-positive bacteria, lipotechoic acid (LTA) from Gram-positive bacteria, mannan from fungi, and other antigens from infectious agents stimulate macrophages and monocytes to release tumour necrosis factor alpha (TNF-α), resulting in a cascade of cytokine release (5, 6). Following the release of TNF-α, other pro-inflammatory cytokines, including interleukins (IL-1β, IL-6) are released into the circulation (7). These cytokines trigger numerous additional pro-inflammatory events from endothelial cells and leukocytes (5). TNF-α acts in conjunction with IL-1β to produce the clinical signs of the systemic inflammatory response syndrome described in table 1, and their synergistic effects are probably responsible for the hypotension and resultant organ dysfunction seen early in the course of severe sepsis (8, 9, 10). Over the last 20 years, although there are promising therapeutic options supported by research evidences to improve survival of patients with sepsis, the overall result is without success, perhaps because of the complexity of pathogenesis of sepsis and basic pathophysiological differences between actual human sepsis and experimental animal models (11, 12).

Pathophysiology of sepsis is complex processes that encompass interaction of proinflammatory and anti-inflammatory cytokines, humoral, cellular, and circulatory involvement resulting from dysregulation of the immune response to infection and associated with hematological, hemodynamic and metabolic disturbances (9, 11).

Clear understanding of the pathophysiologic scope of the problem is the most essential aspect for researchers to look for effective therapies and for clinicians to manage it properly. Therefore, the main aim of this descriptive review is to elucidate the pathophysiology of sepsis for easy management of the problem.

SOURCES AND MATERIALS

More than 200 literatures of both experimental models of sepsis as well as clinical trials that have been published from 1990 up to 2011 were reviewed to organize this descriptive review. Medline search was made only in English language using the following key words; sepsis, SIRS, pathophysiology of sepsis, pathogenesis of sepsis, epidemiology of sepsis, sepsis and coagulation, treatment of sepsis, mediators cytokine, MODS were performed. Both original publications and review articles were utilized.

RESULTS

Flow chart

200 Literatures were reviewed, however,

        Old articles published before 1990

        Articles written in French and Deustche

        Articles that were not freely accessible were excluded

70 Articles were included

SEPSIS: TERMS AND DEFINITIONS

The American College of Chest Physicians/Society of Critical Care Medicine (ACCP/SCCM) consensus committee agreed on a set of definitions to create a universal understanding (13).

SIRS, sepsis, severe sepsis and septic shock represent the continuum of the same systemic response with increasing severity of the disease process (14).

By consensus, SIRS is defined as a widespread inflammatory response to a variety of severe clinical injuries. This syndrome is clinically indicated by the presence of 2 or more of the following: temperature $>38^{\circ}$C or $<36^{\circ}$C; heart rate >90/min; respiratory rate >20/min or $PaCO_2 <32$ mm Hg; White blood cell count $>12 \times 10^9$/L or $<4 \times 10^9$/L, or with $>10\%$ immature (band) forms (13, 15).

There are conditions that may produce systemic inflammatory response syndrome and organ dysfunction without any evidence of infection. These include tissue trauma, burn, and pancreatitis. (16).

As presented in table 1, sepsis is defined by the clinical signs of a systemic response to infection (17). In sepsis, the clinical signs of SIRS are presented together with definitive evidence of infection (18). Patients who have sepsis with acute organ dysfunction are considered to have severe sepsis (19). Sepsis is considered to be severe when it is associated with organ dysfunction, hypo-perfusion or hypotension. The manifestations of hypoperfusion may include, but are not limited to, lactic acidosis, oliguria and an acute alteration in mental status. (17,19). Septic shock is severe sepsis with hypotension, which represents a systolic blood pressure (SBP) < 90 mmHg or mean arterial pressure (MAP) < 70 mmHg or a SBP decrease by >40 mmHg below normal for age in the absence of other causes of hypotension (13, 15).

EPIDEMIOLOGY OF SEPSIS

Sepsis affects 1.8 million people worldwide every year and on average each case costs more than US$22,000 to treat (20). The incidence of sepsis in the United States has been estimated to be 750,000/year (300 cases per 100,000 populations) with a mortality rate of 28% to 50%, resulting in an economic expense of nearly US$17 billion annually (17). As shown in table 2, the incidence of sepsis is bigger than that of other diseases. It is the second leading cause of death among patients in non-coronary intensive care units and the 10th leading cause of death overall in the United States (21, 22). A greater number of sepsis cases are caused by infection with gram-positive organisms than gram-negative organisms, and fungal infections now account for 6% of cases (17). The annual incidence of sepsis is increasing by 8%. This upsurge has been attributed to such risk factors, including an increased in number of aging population, emergence of antibiotic resistant microbial pathogens, the use of immunosuppressant drugs, an increased in invasive medical interventions, an increased in the rate of HIV AIDS infection (21).

ETIOLOGY OF SEPSIS: MICROBIAL CAUSATIVE AGENTS

The source of infection resulting in sepsis is most frequently bacterial, (23). Recent studies described that there has been a shift of causative agents of sepsis from the predominant Gram-negative bacterial infection in the late 1970s and 1980s to Gram-positive bacteria at present (17). Gram-positive and polymicrobial infection accounted for 30%-50% and 25% of cases respectively (Table 3) (24).

The most common sites of infection are the lungs (40%), abdomen (30%) and urinary tract (10%). The high rate of pulmonary infection may reflect frequent and prolonged use of mechanical ventilation and the rising occurrence of nosocomial pathogens encountered in intensive care facilities (25).

Gram-negative bacilli, mainly E.coli, Klebsiella species, Enterobacter, Proteus and Pseudomonas aeruginosa) are the commonest microbes isolated from patients with sepsis and septic shock (26). Lipopolysaccharide (LPS, endotoxin) is an important component of the outer membrane of Gram-negative bacteria and has a pivotal role in inducing sepsis. (27). Gram-negative infection usually occurs in the lung, abdomen, and the urinary tract (23).

Gram-positive cocci, mainly Staphylococci (Staphylococcus aureus, and Coagulase Negative Staphylococci) and Streptococci (Streptococcus pyogenes, Streptococcus pneumoniae, Viridians Streptococci) are the commonest cause of Gram-positive sepsis (28). They are usually responsible for infection of blood stream, skin, soft tissues and respiratory tract. Staphylococcus aureus produce Toxic Shock Syndrome Toxin (TSST) that results in septic shock and Streptococcus pyogenes produce Streptococcal pyrogenic exotoxin A (SEA) (29).

Gram-positive organisms cause sepsis by at least two mechanisms: by producing exotoxins that act as superantigens and by their cell wall components that can stimulate immune cells. (28). Superantigens are molecules that bind to MHC class II molecules of antigen presenting cells and T-cell receptors. In doing so, they activate large number of T-cells to produce massive amount of proinflammatory cytokines. Staphylococcal enterotoxins, toxic shock syndrome toxin-1, and Streptococcal pyrogenic exotoxin A are examples of bacterial superantigens (30, 31).

Gram-positive bacteria without exotoxin can also induce septic shock, by stimulating the innate immune system through similar mechanisms to those in Gram-negative sepsis. Indeed, toll-like receptors (TLR-2) has been shown to mediate cellular responses to heat killed Gram-positive bacteria and their cell wall structure (peptidoglycan, lipoproteins, lipoteichoic acid, and phenol soluble modulin) (32).

PATHOPHYSIOLOGY OF SEPSIS

Sepsis, sever sepsis, septic shock and multiple organ failure are complex processes that encompasses pro-inflammatory, anti-inflammatory, humoral, cellular, and circulatory involvement resulting from dysregulation of the immune response to infection (28). The pathophysiologic process has been linked to the contribution of apoptosis or programmed cell death, which may have an important role in the organ dysfunction. (29).

The pathogenesis of sepsis involves a complex interaction between the host immune system and the infecting microorganisms (33). Bacteria and their products trigger cascades of cellular response in the host's body that involve several cell types (leukocyte, mast cells, endothelial cells and platelets), and several cellular pathways (pro-inflammatory, anti-inflammatory, coagulation cascades, complement activation, adhesion and apoptosis) (34).

The normal immune response to bacterial infection is a complex inflammatory process that attempts to localize and limit the spread of the infection and repair the tissue (27). This response involves the activation of phagocytes and endothelial cells to produce both pro-inflammatory and anti-inflammatory mediators. The balance between these groups of mediators helps to protect the host against the invading pathogens and to facilitate tissue healing. Sepsis comes when the balance is lost, in which the inflammatory response to infection produced in excess and extends beyond the infected site causing generalized functional alterations (35). Due to exaggerated immune response to the invading pathogen, widespread inflammatory mediators and vasodilators are released (36). Inflammatory cytokines such as TNFα, IL-1β, and IL-6, are secreted by the monocytes and macrophages. Tissue factor (TF) is expressed by monocytes and the damaged vascular endothelium. Coagulation is activated with release of thrombin and the formation of the fibrin clot in order to wall off the spread of the infection (35).

Circulatory problem arises from the combination of vasodilatation, capillary leakage, and reduced myocardial contractility. Organ failure may be the first clinical sign of severe sepsis, as the consequences of the excessive products of inflammatory mediators. Mortality rates increase with the increase of failed organs (21).

The clinical manifestation of sepsis is the consequence of complex groups of mediators secreted by the immune cells in response to pathogens such as LPS (endotoxin) produced by bacteria (33, 37, 38). Free LPS that is formed from degradation of Gram-negative bacteria cell wall, once in the circulation binds with LPS binding protein (LBP), to form a complex (39). This complex then binds to monocyte/macrophage cell surface receptor, CD_{14} and TLR_4 that result in cellular activation and secretion of inflammatory cytokines (40). Prominent among the central mediators of sepsis produced in response to LPS activation of receptors are TNFα, IL-1β, IL-6, eicosanoids, platelet activating factor (PAF), oxygen free radicals and nitric oxide (41).

These primary cytokines and many other intermediate and distant mediators interact with each other, setting into motion of complex cascades of reactions and series of local and systemic inflammatory response (39, 40). Secretion of TNF-α maily from macrophages is particularly strongly stimulated by LPS and it is believed that this mediator, but not LPS directly, is one primary agent, which sets in motion a pronounced cellular, metabolic and vascular changes occurred during sepsis (41, 42). Serum TNF-α and IL-1β reach toxic level in mice and human volunteers within 1-2 hours after LPS infusion (43)

Patients with severe sepsis exhibited biphasic hemodynamic and immunological response. (a) The early, hyperdynamic phase is characterized by increased cardiac output, tissue perfusion, and decreased vascular resistance. The hallmark of this early phase is the pro-inflammatory state that is mediated primarily by neutrophils, macrophages, and monocytes that have been stimulated by microbes (44); followed by (b) Hyporeponsive phase (cold phase, vasoconstricted phase): a period of immunodepression in which anti-inflammatory cytokines are produced in order to counterbalance inflammatory mediators resulting in immune-paralysis (45). It is characterized by cold extremities, hypotension, small pulse pressure, low cardiac output, high SVR and low cardiac contractility. It is associated with loss of phagocytic functions, and decreased Th_1 cytokine release (44, 46). Persistence of this hypo responsiveness is associated with increased risk of nosocomial infection and death (47, 48). Immunoparalysis: CD_4 lymphocytes play a key role in the inflammatory response during sepsis. Early in the process of sepsis, these cells assume a T-helper-1 (TH_1) phenotype, where they produce large amounts of the pro-inflammatory mediators, including IF-γ, TNF-α, and IL-2 (49). T-lymphocytes may evolve over time to a T-helper-2 (TH_2) phenotype, whereby the CD_4 lymphocytes produce anti-inflammatory cytokines, including IL-10, IL-4, and IL-13 (50). These cytokines dampen the immune response and can lead to the deactivation of monocytes. Additionally, TNF-α released early can cause apoptosis of lymphocytes in the gut, leading to further immune suppression (51).

Sepsis-triggered immunological cascade is multimodal: initial systemic inflammatory response syndrome (SIRS; excessive pro-inflammatory, but no/low anti-inflammatory mediators), intermediate homeostasis with a mixed anti-inflammatory response syndrome (MARS; both pro-inflammatory and anti-inflammatory mediators)

and final compensatory anti-inflammatory response syndrome (CARS; excessive anti-inflammatory, but no/low pro-inflammatory mediators) (52, 53, 54).

The balance between pro-inflammatory and anti-inflammatory mediators derived from the innate immune system defines the progression and severity of infection. If unbalanced, an overproduction of endogenous pro-inflammatory mediators, including cytokines, platelet activating factor, oxygen radicals and nitric oxide, synergistically interact to mediate hypotension, multiple organ failure and death (53). Progression from sepsis to septic shock coincides with an increase in circulating levels of pro-inflammatory cytokines such as TNF-α, IFN-γ, IL-1β, and IL-6 (39). Administration of TNFα in animal models mediates sepsis typical to endotoxin and removal of TNF-α from animals challenged with LPS using pharmacological strategies significantly improves survival (41).

The pathophysiology of sepsis can be initiated by the outer membrane component of Gram-negative organisms (e.g., lipopolysaccharide [LPS], lipid A, endotoxin) or Gram-positive organisms (e.g. lipoteichoic acid, peptidoglycan), as well as fungal, viral, and parasitic components (55, 56). Signalling by these mediators occurs via a family of transmembrane receptors known as toll-like receptors (TLRs) (57). Within the monocytes, nuclear factor-κB (NF-κB), is activated, which leads to the production of pro-inflammatory cytokines, TNF-α, and IL-1β. TNF-α and IL-1β lead to the production of toxic downstream mediators, including prostaglandins, leukotrienes, platelet-activating factor, and phospholipase A_2 (56). These mediators damage the endothelial lining, leading to increased capillary leakage. Finally, activated macrophages and neutrophils release nitric oxide, a potent vasodilator that leads to septic shock (58).

Pathogenic molecules derived from microbial infectious agents that can bind with specific receptors on immune cells to activate production of cytokines and chemokines are collectively called pathogen associated molecular pattern (PAMP) (57). The common PAMPs are surface molecules such as, lipopolysaccharide (LPS), peptidoglycan (PGN), lipoteichoic acid (LTA), unmethylated bacterial DNA (CpG DNA), lipoarabinomannan (LAM) of mycobacterium, viral ds RNA, flagellin, lipopeptides, mannans and zymosan of yeast and choline-containing phosphoglycolipids and internal motifs released during bacterial lysis such as heat shock proteins and DNA fragments (59).

Recognition of PAMPs by PRRs results in the activation of different intercellular signalling cascades that in turn lead to the expression of various effecter molecules (57). Immune cells recognize microbes though pattern recognition receptors (PRRs) on the cells (59). Toll-like receptors (TLRs) are among PRRs and activate immune cells to produce pro-inflammatory cytokines and chemokines (60). Toll-like receptors regulate antimicrobial host defense mechanisms and play a central role in the activation of innate immunity (61). Toll-like receptors are a family of cellular surface protein receptors that recognize pathogenic molecules of various micro-organisms. Bacterial components including lipopolysaccharide, lipoteichoic acid, flagellin and other cell wall components interact with Toll-like receptors. Different microbial pathogenic products bind to different receptors. TLR2 and TLR6 have been shown to react with lipoteichoic acid, TLR4 specifically recognizes lipopolysaccharide, and TLR5 with flagellin (62). These findings implicate that the innate immune response is tailored in a pathogen specific manner (61). In the initial phase of infection, Toll-like receptors activate the innate immune system; as a result invading pathogens are destroyed by macrophages, natural killer cells and complement system. In the second phase, Toll-like receptors form an important link between innate immunity and adaptive immunity, by activating T and B lymphocytes to produce cytokines (63, 64, 65, 66).

TREATMENT OF SEPSIS

Current treatment of severe sepsis involves early appropriate antibiotic therapy, surgical drainage of infected site, mechanical ventilation, optimizing oxygen delivery to patients with lactic acidosis, adequate fluid resuscitation (colloids, crystalloids and other plasma expanders), administration of vasopressors (dopamine, noradrenaline) to improve cardiovascular parameters, tight glycemic control, blood transfusion in case of low haemoglobin (< 7 g/dl), use of low dose corticosteroid, and supportive therapy. Despite all these therapeutic applications, mortality remains high; therefore, the search endeavour in sepsis should be scaled up to find appropriate immune-modulatory therapies with remarkable survival records (68, 69, 70).

CONCLUSION

Although there are promising therapeutic options supported by research evidences to improve survival of patients with sepsis, the overall result is without success, perhaps for two major reasons: the complexity of pathogenesis of sepsis and basic pathophysiological differences between actual human sepsis and experimental animal models. The pathophysiology of sepsis involves a complex interaction of inflammatory mediators, activation of host cells to release inflammatory and counter-inflammatory mediators. Multiple derangements exist in sepsis involving several different organs and systems. Having a clear understanding of the

pathophysiology of sepsis is a precondition for an effective management of the problem. The early administration of empirical antibiotic therapy, effective source control, and goal-directed hemodynamic resuscitation are the cornerstone of successful management. Further large scale study on sepsis is recommended.

ACKNOWLEDGMENTS

REFERENCES

1. Bone RC, Grodzin CJ, Balk RA. Sepsis: a new hypothesis for pathogenesis of the disease process. Chest 1997; 112: 235-43.
2. Bernard GR, Vincent JL, Laterre PF, LaRosa SP, Dhainaut JF, Lopez-Rodriguez A, Steingrub JS, et.al.Efficacy and safety of recombinant human activated protein C for severe sepsis. N Engl J Med. 2001; 344: 699-709.
3. Dellinger RP, Carlet JM, Masur H, Gerlach H, Calandra T, Cohen J, et al. Surviving sepsis: Campaign guidelines for management of severe sepsis and septic shock. Crit Care Med. 2004; 32: 858-873.
4. Okazaki Y. and Matsukawa A. *Pathophysiology of sepsis. Recent Patents on Inflammation & Allergy Drug Discovery* 200; *3:* 26-32.
5. van der Poll T, van Deventer SJH. Cytokines and anticytokines in the pathogenesis of sepsis. *Infect. Dis. Clin. N. Am.* 1999; 13: 413–426.
6. van der Poll T. Immunotherapy of sepsis. *Lancet Infect. Dis.* 2001; 1:165–174.
7. Thijs LG, Hack CE. Time course of cytokine levels in sepsis. *Intensive Care Med.* 1995; 21(Suppl 2): S258.
8. Matthay MA. Severe sepsis: a new treatment with both anticoagulant and anti-inflammatory properties. *N. Engl. J. Med.* 2001; 344:759–762
9. Marik PE and Varon J. Sepsis. In *Irwin and Rippe's Intensive Care Medicine*, ed. RS Irwin, JMRippe, 2003; 5:1822–3183.
10. Rice TW and Bernard GR. Therapeutic intervention and targets for sepsis**.** Annu. Rev. Med. 2005; 56: 225–248.
11. Horn KD. Evolving strategies in the treatment of sepsis and systemic inflammatory response syndrome (SIRS). *QJ Me. 1998; 91: 265-277.*
12. Bauer PR. Microvascular response to sepsis:- clinical significance. *Pathophysiology 2002; 8(3): 141-148.*
13. Bone RC, Balk RA, Cerra FB, Dellinger RP, Fein AM, Knaus WA, et al. Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. The ACCP/SCCM Consensus Conference Committee. College of Chest Physicians/Society of Critical Care Medicine. Chest 1992; 101: 1644-1655.
14. Balk RA**.** Optimum Treatment of Severe Sepsis and Septic Shock: Evidence in Support of the Recommendations. DM 2004; 168-212
15. Levy MM, Fink MP, Marshall JC, Abraham E, Angus D, Cook D, et al, for the International Sepsis Definitions Conference. 2001 SCCM/ESICM/ACCP/ATS/SIS International Sepsis Definitions Conference. Crit Care Med 2003; 31: 1250-1256.
16. Llewelyn M, Cohen J. Diagnosis of infection in sepsis. Intensive Care Med. 2001; 27:S10-S32.
17. Angus DC, Linde-Zwirble WT, Lidicker J, Clermont G, Carcillo J, Pinsky MR. Epidemiology of severe sepsis in the United States: analysis of incidence, outcome, and associated costs of care. Crit Care Med. 2001; 29:1303-1310.
18. Martin GS, Mannino DM, Eaton S, Moss M. The epidemiology of sepsis in the United States from 1979 through 2000. N Engl J Med. 2003; 348:1546-1554.
19. Brun-Buisson C, Meshaka P, Pinton P and Vallet B. EPISEPSIS: a reappraisal of the epidemiology and outcome of severe sepsis in French intensive care units. *Intensive Care Med. 2004;* 30*: 580-588.*
20. Slade E, Tamber PS, Vincent JL. The surviving sepsis campaign: raising awareness to reduce mortality. *Crit. Care. Med 2003; 7:1-2.*
21. Parrillo JE*,* Parker MM*,* Natanson *C*, Suffredini AF, Danner RL, Cunnion RE, et al. Septic shock in humans. Advances in the understanding of pathogenesis, cardiovascular dysfunction, and therapy. Ann Intern Med. 1990; 113: 227-242.
22. Natanson C, Esposito CJ, Banks SM. The sirens´ songs of confirmatory sepsis trials: selection bias and sampling error. *Crit Care Med. 1998; 26(12):1927-1931.*
23. Offord R. Causes and features of sepsis. *Hospital Pharmacists. 2002; 9: 93-96.*
24. Annane D, Bellissant E & Cavaillon JM. Septic shock: seminar. *Lancet 2005;365:63-78.*

25. Annane D, Aegerter P, Jars-Guincestre MC and Guidet B. Current epidemiology of sepsis. The CUB-Rea network. *Am J Respir Crit care Med. 2003; 168: 165-172.*

26. Worthley LIG. Shock: a review of pathophysiology and management. Part II. *Crit Care and Resuscitation. 2000; 2: 66-84*

27. Horn KD. Evolving strategies in the treatment of sepsis and systemic inflammatory response syndrome (SIRS).*Q J Med. 1998; 91:265-277.*

28. Balk RA. Severe sepsis and septic shock: definitions, epidemiology, and clinical manifestations. Crit Care Clin 2000; 16: 179-192.

29. Cohen J. The immunopathogenesis of sepsis. *Nature. 2002; 420: 885-891.*

30. Lavoie PM, Thibodeau J, Erard F and Sekaly RP. Understanding the mechanism of action of bacterial super antigens from a decade of research. *Immunol Res 1999; 168: 257-69.*

31. Papageorgieo AC and Acharya KR. Microbial supper antigens from structure to function. *Trends Microbial 2000; 8: 369-375.*

32. Wang JE. Peptidoglycan and lipoteichoic acid from *Staphylococcus aureus* induce TNF-α, IL-6 and IL-10 in T-cells and monocytes in human whole blood model. *Infect Immun 2000; 68: 3965-3970.*

33. Kox WJ, Volk T, Kox SN & Volk HD. Immunomodulatory therapies in sepsis. *Care Med. 2000; 26: 124-128.*

34. Patel GP, Gurka DP, Balk RA. New treatment strategies for severe sepsis and septic shock.Curr Opin Crit Care. 2003; 9(5): 390-396.

35. Martin GS, Mannino DM, Eaton S, Moss M. The epidemiology of sepsis in the United States from 1979 through 2000. N Engl J Med 2003; 348: 1546-54.

36. Hollenberg SM, Ahrens TS, Annane D, Astiz ME, Chalfin DB, Dasta JF, Heard SO, Martin C, Napolitano LM, Susla GM, Totaro R, Vincent JL, Zanotti-Cavazzoni S. Practice parameters for hemodynamic support of sepsis in adult patients: 2004 update. Crit Care Med. 2004;32(9):1928-1948.

37. Fanton MJ & Golenback DT. LPS-binding proteins and receptors. *J Leuk. Biol. 1998;64:25-32.*

38. Krishnagopalan S & Dellinger RP. Innovative therapies for sepsis. *Biodrugs 2001; 15(10): 645-654.*

39. Ye X. & Liu SF. LPS regulated constitutive and inducible transcription factor activities differentially in vivo in the rat. *Biochem. & Biophys. Res. comm. 2001; 288(4): 927-932.*

40. Freeman BD, & Natanson C. Anti-inflammatory therapies in sepsis and septic shock. *Expert. Opin. Investig. Drugs. 2000; 9(7): 1651-1663.*

41. Wang H, Yang H, Czura CJ, Sama AE & Tracey KJ. HMGB$_1$ as a late mediator of lethal systemic inflammation.*Am J Respir. Crit. Care Med. 2001; 164: 1768-1773.*

42. Anel RL & Kumar A. Experimental and emerging therapies for sepsis and septic shock. *Expert. Opin. Investig. Drugs. 2001; 10(8): 1471-1475.*

43. Zonatti S & Kumar A. Cytokine modulation in sepsis and septic shock. *Expert. Opin. Investig. Drugs. 2002; 11(8): 1061-1075.*

44. Wesche-Soldato DE, Lomas-Neira JL, Perl M, Jones L, Chung CS and Ayala A. The role and regulation of apoptosis in sepsis *J Endot. Res. 2005; 11: 375.*

45. Wichterman KA, Baue AE, Chaudry IH. Sepsis and septic shock – a review of laboratory models and a proposal. *J Surg Res* 1990; 29: 189–201.

46. Unsinger J, Kazama H, McDonough JS, Griffith TS, Hotchkiss RS, Ferguson TA. Sepsis-induced apoptosis leads to active suppression of delayed-type hypersensitivity by CD8+ regulatory T cells through a TRAIL-dependent mechanism. J Immunol. 2010;184(12): 6766-72.

47. Lefemine A, Acuff R Vo N and WaycasterM. Delayed hypersensitivity on a surgical service. *J Am Coll Nutr. 1998; 7 (5): 355-359.*

48. Bone RC. Immunologic dissonance: a continuing evolution in our understanding of the systemic inflammatory response syndrome (SIRS) the multiple organ dysfunction syndrome (MODS). *Ann Intern Med 1996;* 125:60-87.

49. Hotchkiss RS, Tinsley KW, Swanson PE, Schmieg RE, Hui JJ, Chang KC, Osborne DF, Freeman BD, Cobb JP, Buchman TG and Karl IE. Sepsis-Induced Apoptosis Causes Progressive Profound Depletion of B and CD41 T Lymphocytes in Humans. *J. Immunol.* 2001;166: 6952-6963

50. Reddy RC, Chen GH, Tekchandani PK and Standiford TJ. Sepsis-induced immune- suppression: From bad to worse. Immunol Res. 24: 2001; 273-287.

51. Lyn-Kew K, Standiford TJ. Immunosuppression in sepsis. Curr Pharm Des. 2008;14(19):1870-1881.

52. Danner RL, Elin RJ, Hosseini JM, Wesley RA, Reilly JM, Parillo JE. Endotoxemia in human septic shock. Chest. 1991; 99:169–175.

53. Davies MG and Hagen PO. Systemic inflammatory response syndrome. Review article. *British Journal* of *Suqer.* 1997; 84: 920-935.

54. Marcin FO, Welch K, Siddoqui J and Remick DG. SIRS/MARS/CARS continuum in sepsis. *The Journal of Immunology,* 2006; 177: 1967–1974**.**

55. Deborah JSK, Marcin FO, Catherine V, Shinichiro K and Daniel GR.Annu. The Pathogenesis of Sepsis. Rev. Pathol. Mech. Dis. 2011; 6:19–48.

56. Cinel and Opal SM. Molecular biology of inflammation and sepsis: A primer. Crit Care Med. 2009; 37 (1): 291–304.

57. Doughty L. Pathogen Associated Molecular Patterns, Pattern Recognition Receptors and Pediatric Sepsis. The Open Inflam. J. 2011; 4(Suppl 1-M5): 31-48.

58. LaRosa SP. Sepsis: Menu of new approaches replaces one therapy for all. Cleve Clin J Med. 2002; 69: 65-73.

59. Denk S, Perl M, Huber-Lang M. Damage- and Pathogen-Associated Molecular Patterns and Alarmins: Keys to Sepsis? Eur Surg Res 2012; 48:171–179.

60. Lewis DH, Chan DL, Pinheiro D, Armitage-Chan E and Garden OA. The Immuno-pathology of Sepsis: Pathogen Recognition, Systemic Inflammation, the Compensatory Antiinflammatory Response and Regulatory T Cells. J Vet Intern Med. 2012; 26: 457–482.

61. Kopp EB, Medzhitov R. The Toll-receptor family and control of innate immunity. Curr Opin Immunol. 1999; 11: 13-18.

62. Liang, MD, Bagchi, A, Warren HS, Tehan MM, Trigilio JA, Beasley-Topliffe L, Tesini B, Lazzaroni JC, Fenton M, Hellman J. Bacterial Peptidoglycan-Associated Lipoprotein: a potent Toll-like Receptor-2 Agonist that is shed into serum and is synergistic with LPS. J. Infect Disease. 2005; 191:939-948.

63. Modlin RL, Brightbill HD, Godowski PJ. The Toll of innate immunity on microbial pathogens. New Engl J Med 2000; 340: 1834-1835.

64. Hack CE, Aarden LA, Thijs LG. Role of cytokines in sepsis. Advances Immunol 1997; 66: 101-95.

65. Hack CE, Thijs LG. Role of inflammatory mediators in sepsis. In: Dhainaut JF, Thijs LG, Park G, eds. Septic Shock. London: WB Saunders, 2000: 41-127.

66. Yang H, Wang H, Tracey KJ. HMG$_1$ rediscovered as a cytokine. Shock 2001; 15: 247-53.

67. Sharma S and Kumar A. Septic shock, multiple organ failure, and acute respiratory distress syndrome. Current Opin Pulm Med. 2003, 9:199-209.

68. Rivers E, Nguyen B, Havstad S,: Early goal-directed therapy in the treatment of severe sepsis and septic shock. N Engl J Med. 2001; 345: 1368-1377.

69. Cross AS & Opal SM. A new paradigm for the treatment of sepsis: is it time to consider combination therapy? *Ann Intern Med 2003; 138:502-505*.

70. Bornstein SR and Briegel JA. New Role for Glucocorticoids in Septic Shock: Balancing the Immune Response. Am J Respir Crit Care Med. 2003; 167: 485–489.

Table 1:- Standard definition of sepsis and related terms (13, 15).

Terms	Definitions
1. SIRS	*The systemic inflammatory response to a wide variety of severe clinical insults (infection, pancreatitis, ischemia, trauma, autoimmunity and others), manifested by 2 or more of the following*
	Core Temperature: $<36\,^oC$ or $>38\,^oC$
	Heart Rate: >90 beats/min
	Respiratory Rate: >20 breaths/min or $PaCO_2 <32$ mm Hg
	WBC count: $<4,000/mm^3$ or $>12,000/mm^3$ or $>10\%$ Immature neutrophils (band) forms.
2. Sepsis	*The systemic inflammatory response to infection. It is SIRS plus documented infection.*
3. Severe Sepsis	*(Sepsis + ≥ 1 organ failure)* *Sepsis associated with organ dysfunction, hypoperfusion or hypotension. Hypoperfusion may include, but not limited to, lactic acidosis, oliguria, or an acute alteration in mental status.*
4. Septic Shock	*A subset of severe sepsis and defined as sepsis induced hypotension despite adequate fluid rescusitation along with perfusion abnormalities that may include but not limited to, lactic acidosis, oliguria, or an acute alteration in mental status. Hypotension responds to inotropic or vasopressor agents.*
5. MODS	*Presence of altered organ functions in an acutely ill patients such that homeostasis cannot be maintained without intervention.*
6. Sepsis-induced Hypotension	*A systolic BP < 90 mm Hg or a reduction of ≥ 40 mm Hg from baseline in the absence of other causes for hypotension*

Table 2:- Incidence of sepsis in comparison with other diseases worldwide.

HIV AIDS	17/100,000 inhabitants
Colon carcinoma	50/100,000 inhabitants
Breast cancer	110/100,000 inhabitants
Cardiac insufficiency	196/100,000 inhabitants
Sepsis	300/100,000 inhabitants

Table 3: Estimated frequency of pathogens in sepsis (24)

Pathogens	Frequency
Gram-positive bacteria	30 –50%
Staphylococcus aureus	20-35%
Other Staphylococcus spp	1-3%
Streptococcus pneumoniae	9-12%
Other Streptococcus spp	6-11%
Enterococcus spp	3-13%
Other Gram positive bacteria	2-7%
Gram-negative bacteria	25-30%
E.coli	9-17%
Pseudomonas aerugiosa	8-15%
Klesiella pneumoniae	2-7%
Other enterobacter spp	6-16%
Other Gram negative bacteria	8-29%
Fungus	3-5%
Protozoa (parasites)	1-3%
Virus	**2-4%**

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