WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 8.453
Volume 14, Issue 1, 538-550. Review Article ISSN 2277–7105

SEPSIS- ORGAN DYSFUNCTION (A CELL DEATH): CAUSES, PATHOPHYSIOLOGY, CLINICAL IMPACTS, SPECTRUM OF SEPSIS AND ETIOLOGY OF SEPSIS

***Pushpendra, Amisha Gautam, Dr. Neeraj Bhandari, Sanjoti and Aanchal Chandel**

Arni School of Pharmacy, Arni University Kathgarh, Indora Distt Kangra HP Pincode 176401.

Article Received on
14 Nov. 2024,

Revised on 04 Dec. 2024,
Accepted on 25 Dec. 2024

DOI: 10.20959/wjpr20251-35096

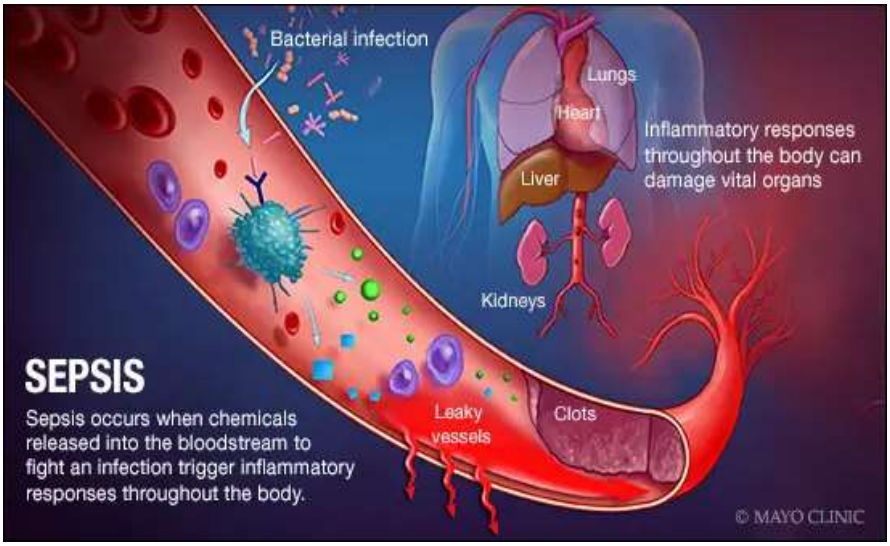
***Corresponding Author**
Pushpendra
Arni School of Pharmacy,
Arni University Kathgarh,
Indora Distt Kangra HP
Pincode 176401.

ABSTRACT

A dysregulated host response to infection is the hallmark of sepsis, a potentially fatal illness that causes extensive inflammation, organ dysfunction, and, if left untreated, multiorgan failure. It causes a large number of hospital admissions and high mortality rates, making it a serious worldwide health concern. Although bacterial, viral, fungal, and parasitic illnesses can cause sepsis, the most frequent origins are infections of the lungs, urinary tract, abdomen, and circulation. The production of pro-inflammatory mediators, microvascular dysfunction, and immunological suppression are the results of the intricate interactions between microbial factors and host immune responses that characterise the pathophysiology of sepsis. The vague nature of its symptoms makes diagnosis difficult, however clinical criteria including the presence of infection and high inflammatory markers are frequently used. Improving survival results requires early detection and timely treatment with broad-spectrum antibiotics, fluid resuscitation, and organ support. The management of sepsis is still a clinical issue despite advancements in critical care, and research is still being done to find biomarkers for early identification, comprehend immunological systems, and create targeted medicines. In order to lower the incidence of sepsis and enhance patient outcomes, prevention techniques such as immunisation, infection control procedures, and the prudent use of antibiotics are essential.

INTRODUCTION

One of the leading causes of death for patients admitted to the intensive care unit (ICU) is sepsis. The numerous comorbidities and underlying illnesses that these patients present with make diagnosis very challenging in this context.(1,2) Since the inaugural con sensus conference in 1991, the criteria of sepsis and septic shock that centre on the host's inflammatory response have not changed. Experts have revised the definitions due to advances in our understanding of the pathophysiology of sepsis, which is now defined as a host reaction to infection that involves changes in non-immunological pathways (cardiovascular, autonomic, neurological, humoral, metabolic, and clotting) in addition to the activation of pro- and anti-inflammatory responses. The Sepsis-3 conference in 2016 defined septic shock as a "subset of sepsis in which underlying circulatory and cellular/metabolic abnormalities are profound enough to substantially increase mortality" and sepsis as "life-threatening organ dysfunction caused by a deregulated host response to infection."(3) Sundaram et al. examined the incidence of neonatal sepsis in a north Indian tertiary care centre over two time periods (epochs 1–1991–1996 and 2–2001–2006). They discovered that while the incidence of early onset sepsis remained constant, the incidence of late onset sepsis rose from 12–16.5 per 1000 live births ($p<0.001$).(4) These definitions have served as the foundation for the last 25 years of research on sepsis and have influenced the development of clinical trial design, clinical recognition, and management. Nonetheless, there have been concerns raised regarding the SIRS criteria's sensitivity and specificity.(5,6) As has the argument that sepsis, septic shock, SIRS, and severe sepsis are not distinct clinical entities but rather occur along a continuum.(7) An increasing amount of research indicates that the death rate rises with each hour that antimicrobial intervention is postponed, highlighting the significance of prompt diagnosis and treatment beginning. (8-10). Differentiating sepsis from disease states (like inflammation) that share clinical indications (like a change in vitals), symptoms (like fever), and molecular manifestations (like a dysregulated host response) is a significant obstacle to early detection.[11,12]



PATHOGENESIS AND PATHOPHYSIOLOGY

According to a prominent early trial, human volunteers who received an infusion of LPS experienced considerable myocardial depression and left ventricular dilatation within five hours.[13] A seminal study revealed that patients with established septic shock actually have higher gross coronary perfusion, despite the earlier belief that SICM was pathologically similar to coronary artery disease.[14] Since then, a number of myocardial depressant factors have been identified, such as cytokines, complement cascade components, pathogen-associated molecular patterns, endogenous damage-associated molecular patterns, oxidative stress, aberrant calcium movement within cells, mitochondrial dysfunction, myocyte apoptosis, autonomic dysregulation, and altered nitric oxide metabolism.[15,16] Additionally, sepsis causes the endothelium glycocalyx to shed, which results in vascular leakage, coagulation, and inflammation and is linked to negative consequences.[17,18] An understudied SICM mechanism is the endothelium's ability to induce myocardial oedema and heterogeneous microvascular flow once it is disturbed. Using cardiac magnetic resonance imaging and histology, a recent study shown that myocardial oedema could partially account for the increase in cardiac troponin observed in SICM.[19]

Cause

Infections in the respiratory and genitourinary tracts are the most frequent infectious causes of sepsis in the elderly.3, 9 Infections of the skin, soft tissues, and gastrointestinal tract are less frequent causes; the latter is linked to the highest death rate among older persons.[22] Gram-negative organism infections are more common in older persons than in younger adults. According to Martin and colleagues3, the likelihood of a gram-negative infection was

1.31 times higher in older persons (65 years of age) than in those under 65 (95% CI, 1.27–1.35). Escherichia coli is the most often found bacterium by urine culture in individuals who have sepsis from a urinary source (50%) in these patients.[9] Older adults are more susceptible to infection from other gram-negative bacteria, including Proteus species, Klebsiella species, and Pseudomonas species, even though E. coli is the most common cause of UTI in both younger and older adults.[23] Gram-positive bacteria such as Staphylococcus aureus, Enterococci, and Streptococci are frequently seen in older persons with bloodstream infections.[24] 12.3% of a cohort of 60-year-olds with pneumonia-related sepsis had a positive culture for methicillin-resistant S. aureus (MRSA), whereas 16.9% had a positive culture for methicillin-sensitive S. aureus.[25]

Clinical impacts

Numerous clinical studies have demonstrated that the incidence, clinical presentation, and outcome of severe sepsis in the elderly are unique, which may be explained by the pathophysiological factors previously addressed.[26]

According to a recent assessment of the epidemiology of sepsis in the elderly by Girard et al., the incidence of sepsis rises with age. When Angus et al. examined the epidemiology of sepsis in 192,980 individuals, they discovered that there were 3 cases per 1000 people. In patients over 85, the incidence rose to 26 cases/1000 population, which is more than 100 times greater than the incidence for individuals between the ages of 5 and 14.[27]

Regarding the microbiological pattern of sepsis in the elderly, Martin et al. discovered that older patients had a higher prevalence of pulmonary and genitourinary infections as well as an increased risk of infections from Gram-negative organisms.[28] Even when the symptoms of a systemic inflammatory response are thoroughly examined, the clinical picture of sepsis in the elderly might be difficult to detect. Elderly individuals frequently exhibit a milder inflammatory response at first, which abruptly worsens as they approach septic shock.[29] In the elderly, fever and other early indicators of a systemic inflammatory response may be diminished or non-existent. Fever was absent in 13% of elderly patients and 4% of young and adult patients, according to Gleckman et al.'s research of 192 patients with bacteraemia who were older than 65 and 128 bacteraemia patients younger than 65.[30] Castle et al. assessed 26 elderly individuals' body temperature trends throughout the course of 69 infectious episodes.[31] Even though 89% of the infectious episodes had a peak body temperature higher than 37.2°C, 47% of them had a fever response that was attenuated with a peak body

temperature below 101°F (38.3°C). The authors recommended that residents in nursing homes be given a lower fever threshold.[32] Miller et al. looked into the potential causes of this reduced fever response and discovered that elderly mice had a reduced hypothalamus response to TNF-alpha. It's possible that other indicators of a systemic inflammatory response will also be lessened.[33] A logistic regression analysis that took into account 16 common clinical or biological signs revealed that four variables were significantly and independently associated with bacteraemia in the elderly: fever, altered general state, rapid onset of infection, and clinical indication of the source of infection. Chassagne et al. (1996) found statistically fewer symptoms in elderly infected patients compared to young ones. Other writers noted that older patients frequently have non-specific clinical manifestations of infection, such as delirium, weakness, anorexia, malaise, falls, and urinary incontinence.[34]

SPECTRUM OF SEPSIS

When nomenclature aids in our comprehension of a disease's pathogenesis, it is significant. As nomenclature has influenced the design of randomised, controlled trials and, ultimately, the prognosis of sepsis, this is also true for sepsis. A suspected or confirmed infection combined with a systemic inflammatory response syndrome (such as fever, tachycardia, tachypnea, and leukocytosis) is known as sepsis.[35] Sepsis with organ dysfunction (hypotension, hypoxaemia, oliguria, metabolic acidosis, thrombocytopenia, or obtundation) is referred to as severe sepsis. Severe sepsis with hypotension in spite of proper fluid resuscitation is known as septic shock. The two most frequent reasons why individuals with sepsis die are septic shock and multiorgan failure.[36] Severe sepsis and septic shock are linked to fatality rates of 25–30% and 40–70%, respectively. In the US, there are over 750,000 instances of sepsis annually.[37-39] Due to an ageing population, a growing number of patients with weakened immune systems, patients undergoing lengthy, high-risk surgery, and patients infected with organisms resistant to treatment, the frequency is rising.[40]

ETIOLOGY OF SEPSIS

The most common cause of infection that leads to sepsis is bacteria.[41] According to recent research, the majority of sepsis-causing bacteria have shifted from Gram-negative infections in the late 1970s and early 1980s to Gram-positive infections nowadays.[42] Thirty to fifty percent and twenty-five percent of cases, respectively, were caused by gram-positive and polymicrobial infections.[43] The abdomen (30%), urinary tract (10%), and lungs (40%) are the most frequently infected areas. The increased prevalence of nosocomial pathogens found

in intensive care units and the frequent and extended use of mechanical ventilation may be the causes of the high rate of lung infection.[44] The most prevalent microorganisms found in sepsis and septic shock patients are gram-negative bacilli, primarily E. Coli, Klebsiella species, Enterobacter, Proteus, and Pseudomonas aeruginosa.[45] Gram-negative bacteria's outer membrane contains lipopolysaccharide (LPS, endotoxin), which is essential for causing sepsis.[46] Gram-negative infections typically affect the urinary tract, abdomen, and lungs. The most frequent cause of Gram-positive sepsis is caused by gram-positive cocci, primarily Streptococci (Streptococcus pyogenes, Streptococcus pneumoniae, and Viridians Streptococci) and Staphylococci (Staphylococcus aureus, and Coagulase Negative Staphylococci).[47] They typically cause infections in the respiratory system, skin, soft tissues, and bloodstream. Streptococcus pyogenes produces Streptococcal pyrogenic exotoxin A (SEA), while Staphylococcus aureus produces Toxic Shock Syndrome Toxin (TSST), which causes septic shock.[48] The production of exotoxins, which function as superantigens, and the components of their cell walls that have the ability to activate immune cells are the two main ways that gram-positive organisms induce sepsis. Super antigens are substances that attach to T-cell receptors and antigen-presenting cells' MHC class II molecules. By doing this, they trigger the production of a significant quantity of proinflammatory cytokines by a big number of T-cells. Bacterial superantigens include toxic shock syndrome toxin-1, streptococcal pyrogenic exotoxin A, and staphylococcal enterotoxins.[49,50] By activating the innate immune system through pathways akin to those in Gram-negative sepsis, Gram-positive bacteria devoid of exotoxins can likewise cause septic shock. In fact, it has been demonstrated that toll-like receptors (TLR-2) mediate the cellular reactions to heat-killed Gram-positive bacteria and their cell wall structure.[51]

FOCUS ON SEPSIS

According to the most recent study, sepsis remains a significant clinical and research issue in critical care. In 2018, the Surviving Sepsis Campaign bundle was revised.[52] Although the 1-hour bundle is acceptable and sensible from the standpoint of the patient, there is not much high-quality data to support some of its individual components. In the most recent Surviving Sepsis Campaign guideline, a panel of global specialists representing the European Society of Intensive Care Medicine and the Society of Critical Care Medicine outlined research goals.[53] Fluid resuscitation, quick diagnostic testing, empirical antibiotic combination therapy, long-term outcomes, predictors of organ dysfunction, and the application of personalised medicine in sepsis were the top six research objectives. The past year has seen a large number of

studies on the burden of sepsis. Infection and sepsis were major causes of hospital and intensive-care unit (ICU) admission and mortality in a large countrywide cohort study conducted in Germany, where over one out of four patients admitted to the hospital had an infection diagnosis.[54] In a European observational study, the percentage of sepsis patients admitted to the intensive care unit (ICU) did not change over a ten-year period from 2002 to 2012, but the severity of the condition appeared to rise.[55] The standardised sepsis-related mortality rate, according to a Chinese population-based study, was 67 fatalities per 100,000 people, which equates to about 1 million sepsis-related deaths in China in 2015.[56] There appears to be a lack of public knowledge of sepsis in spite of these concerning statistics, as well as the fact that there are an estimated 30 million instances of sepsis and 6 million fatalities from sepsis worldwide each year. Compared to other medical illnesses including myocardial infarction, asthma, and breast cancer, fewer than 30% of Irish persons surveyed knew what sepsis was.[57] Numerous studies have been conducted on the importance of early detection and prediction of people at risk of sepsis, including the negative outcomes linked to sepsis. Discrimination of leukocyte surface biomarkers was evaluated in a multicentre cohort research conducted in UK emergency rooms and intensive care units.[58] Unfortunately, the majority of the evaluated biomarkers exhibited low clinical predictive validity and poor performance. Accordingly, in a French multicenter cohort trial, no combination of biomarkers outperformed CRP alone, and circulating biomarkers were found to discriminate poorly between patients with and without sepsis.[59] Although the use of intravenous immunoglobulin as adjuvant therapy in sepsis has strong biological justification (i.e., altered immunoglobulin and B-lymphocyte homeostasis in sepsis), the quality of the data supporting its use is very low, with no conclusive evidence of either benefit or damage.[60,61] Accordingly, the authors requested that more research is needed prior to using intravenous immunoglobulins as adjuvant therapy in patients with sepsis. Another promising intervention which has failed to improve the outcome of patients with sepsis is polymyxin B hemoperfusion.[62] A slight but unclear advantage of polymyxin hemoperfusion was observed in patients with high endotoxin activity, according to a post hoc analysis of the EUPHRATES trial.[63] But as an accompanying editorial points out, this finding's validity and clinical consequences are merely hypotheses.[64]

CONCLUSION

Sepsis is a potentially fatal illness brought on by the body's overreaction to an infection. It happens when the immune system overreacts, causing widespread inflammation that, if left

untreated, can cause tissue damage, organ failure, and even death. Given how quickly sepsis can worsen, early detection and prompt action are essential to better results. In order to promote organ function and stabilise blood pressure, treatment often consists of a mix of medicines, fluids, and antibiotics. In order to lower the risk of sepsis, preventive measures like immunisation, good cleanliness, and prompt infection management are crucial. Improving survival rates and reducing long-term problems for those afflicted by this disorder depend on early medical care and awareness of its signs.

REFRENCES

1. Novosad SA, Sapiano MRP, Grigg C, et al. Vital signs: epidemiology of sepsis: prevalence of health care factors and opportunities for prevention. Morb Mortal Wkly Rep., 2016; 65(33): 864–9.
2. Vincent J-L, Rello J, Marshall J, et al. International study of the prevalence and outcomes of infection in intensive, 2009; 302(21): 1303–10.
3. Singer M, Deutschman CS, Seymour CW, et al. The third international consensus definitions for sepsis and septic shock (sepsis-3). JAMA, 2016; 315(8): 801.
4. Sudaram V, Kumar P, Dutta S, et al. Blood culture confirmed bacterial sepsis in neonates in a north Indian tertiary care center: changes over the last decade. Jpn J Infect Dis., Jan. 2009; 62(1): 46-50.
5. Churpek MM, Zadravecz FJ, Winslow C, Howell MD, Edelson DP. Incidence and prognostic value of the systemic inflammatory response syndrome and organ dysfunctions in ward patients. Am J Respir Crit Care MED.
6. & Vincent J-L, Opal SM, Marshall JC, Tracey KJ. Sepsis definitions: time for change. Lancet pmid.
7. Ulloa L, Tracey KJ. The "cytokine profile": a code for sepsis. Trends Mol Med :j. molmed. pmid.
8. Ferrer R, Martin-Loeches I, Phillips G, Osborn TM, Townsend S, Dellinger RP, et al. Empiric antibiotic treatment reduces mortality in severe sepsis and septic shock from the first hour: results from a guideline-based performance improvement program. Crit Care Med., 2014; 42: 1749–55. doi: 10.1097/CCM.0000000000000330
9. Weiss SL, Fitzgerald JC, Balamuth F, Alpern ER, Lavelle J, Chilutti M, et al. Delayed antimicrobial therapy increases mortality and organ dysfunction duration in pediatric sepsis. Crit Care Med., 2014; 42: 2409. doi: 10.1097/CCM.0000000000000509

10. Pruinelli L, Westra BL, Yadav P, Hoff A, Steinbach M, Kumar V, et al. Delay within the 3-hour surviving sepsis campaign guideline on mortality for patients with severe sepsis and septic shock. Crit Care Med., 2018; 46: 500. doi: 10.1097/CCM.0000000000002949
11. Lever A, Mackenzie I. Sepsis: definition, epidemiology, and diagnosis. BMJ., 2007; 335: 879–883. doi: 10.1136/bmj.39346.495880.AE
12. Al Jalbout N, Troncoso Jr R, Evans JD, Rothman RE, Hinson JS. Biomarkers and molecular diagnostics for early detection and targeted management of sepsis and septic shock in the emergency department. J Appl Lab Med., 2019; 3: 724–9. doi: 10.1373/jalm.2018.027425
13. Parrillo JE, Parker MM, Natanson C, Suffredini AF, Danner RL, Cunnion RE, et al. Septic shock in humans. Advances in the under standing of pathogenesis, cardiovascular dysfunction, and therapy. Ann Intern Med., 1990; 113: 227–42.
14. DhainautJF, Huyghebaert MF, MonsallierJF, Lefevre G, Dall'Ava Santucci J, BrunetF, etal. Coronaryhemodynamicsandmyocardial metabolism of lactate, free fatty acids, glucose, and ketones in pa tients with septic shock. Circulation, 1987; 75: 533–41.
15. Ehrman RR, Sullivan AN, Favot MJ, Sherwin RL, Reynolds CA, Abidov A, et al. Pathophysiology, echocardiographic evaluation, biomarker findings, and prognostic implications of septic cardio myopathy: a review of the literature. Crit Care., 2018; 22: 112.
16. LvX, WangH. Pathophysiologyofsepsis-inducedmyocardial dys function. Mil Med Res., 2016; 3: 30. More indepth lookat pathophysiology.
17. Uchimido R, Schmidt EP, Shapiro NI. The glycocalyx: a novel diagnostic and therapeutic target in sepsis. Crit Care, 2019; 23: 16.
18. Smart L, Bosio E, Macdonald SPJ, Dull R, Fatovich DM, Neil C, et al. Glycocalyx biomarker syndecan-1 is a stronger predictor of respiratory failure in patients with sepsis due to pneumonia, com pared to endocan. J Crit Care, 2018; 47: 93–8.
19. Vasques-Nóvoa F, Laundos TL, Madureira A, Bettencourt N, Nunes JPL, Carneiro F, et al. Myocardial edema: an overlooked mechanism of septic cardiomyopathy? Shock, 2019.
20. Moher D, Liberati A, Tetzlaff J, et al.; PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Ann Intern Med., 2009; 151: 264–269.
21. Stang A. Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandom ized studies in meta-analyses. Eur J Epidemiol, 2010; 25: 603–605.

22. Leligdowicz A, Dodek PM, Norena M, et al. Association between source of infec tion and hospital mortality in patients who have septic shock. Am J Respir Crit Care Med., 2014; 189(10): 1204–13.
23. Das R, Towle V, Van Ness PH, et al. Adverse outcomes in nursing home residents with increased episodes of observed bacteriuria. Infect Control Hosp Epidemiol, 2011; 32(1): 84–6.
24. Blot S, Cankurtaran M, Petrovic M, et al. Epidemiology and outcome of nosoco mial bloodstream infection in elderly critically ill patients: a comparison between middle-aged, old, and very old patients. Crit Care Med., 2009; 37(5): 1634–41.
25. Kreger BE, Craven DE, Carling PC, et al. Gram-negative bacteremia. III. Reas sessment of etiology, epidemiology and ecology in 612 patients. Am J Med., 1980; 68(3): 332–43.
26. Girard, T.D.; Opal, S.M.; Ely, E.W. Clin. Infect Dis., 2005; 40: 719-727.
27. Angus, D.C.; Linde-Zwirble, W.T.; Lidicker, J.; Clermonte, G.; Carcillo, J.; Pinsky, M.R. Crit. Care Med., 2001; 29: 1303-1310. Carcillo, J.; Pinsky, M.R. Crit. Care Med., 2001; 29: 1303-1310.
28. Martin, G.S.; Mannino, D.M.; Eaton, S.; Moss, M. N. Engl. J. Med., 2003; 348: 1546-54.
29. Chassagne, P.; Perol, M.B.; Doucet, J.; Trivalle, C.; Menard, J.F.; Manchon, N.D.; Moynot, Y.; Humbert, G.; Bourreille, J.; Bercoff, E. Am. J. Med., 1996; 100: 65-70.
30. Gleckman, R.; Hibert, D. JAMA, 1982; 248: 1478–1481. Castle, S.C.; Norman, D.C.; Yeh, M.;
31. Miller, D.; Yoshikawa, T.T. J. Am. Geriatr. Soc., 1991; 39: 853–857. Miller, D.; Yoshikawa, T.; Castle, S.C.; Norman, D. J. Gerontol., 1991; 46: M176-179.
32. Rajagopalan, S.; Yoshikawa, T.T. Med. Clin. North Am., 2001; 85: 133–147.
33. Krabbe, K.S.; Bruunsgaard, H.; Quist, J.; Hansen C.M.; Møller, K.; Fonsmark, L.; Madsen, P.L.; Kronborg, G.; Frandsen, U.; Ander sen, H.Ø.; Skinhøj, P.; Pedersen, B.K. Eur. J. Anaesthesiol., 2001; 18: 572-575.
34. Bone RC, Balk RA, Cerra FB, et al. Def initions for sepsis and organ failure and guidelines for the use of innovative thera pies in sepsis. Chest, 1992; 101: 1644-55.
35. Russell JA, Singer J, Bernard GR, et al. Changing pattern of organ dysfunction in early human sepsis is related to mortality. Crit Care Med., 2000; 28: 3405-11.
36. Bernard GR, Vincent JL, Laterre PF, et al. Efficacy and safety of recombinant hu man activated protein C for severe sepsis. N Engl J Med., 2001; 344: 699-709.
37. Annane D, Aegerter P, Jars-Guincestre MC, Guidet B. Current epidemiology of septic shock: the CUB-Rea Network. Am J Respir Crit Care Med., 2003; 168: 165-72.

38. 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.
39. Hotchkiss RS, Karl IE. The pathophys iology and treatment of sepsis. N Engl J Med., 2003; 348: 138-50.
40. 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.
41. Offord R. Causes and features of sepsis. Hospital Pharmacists, 2002; 9: 93-96.
42. Annane D, Bellissant E & Cavaillon JM. Septic shock: seminar. Lancet, 2005; 365: 63-78.
43. 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.
44. Worthley LIG. Shock: a review of pathophysiology and management. Part II. Crit Care and Resuscitation, 2000; 2: 66-84.
45. Horn KD. Evolving strategies in the treatment of sepsis and systemic inflammatory response syndrome (SIRS).Q J Med., 1998; 91: 265-277.
46. Balk RA. Severe sepsis and septic shock: definitions, epidemiology, and clinical manifestations. Crit Care Clin., 2000; 16: 179-192.
47. Cohen J. The immunopathogenesis of sepsis. Nature, 2002; 420: 885-891.
48. 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.
49. Papageorgieo AC and Acharya KR. Microbial supper antigens from structure to function. Trends Microbial, 2000; 8: 369-375.
50. 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.
51. Levy MM, Evans LE, Rhodes A. The surviving sepsis campaignbundle: 2018 update. Intensive Care Med., 2018; 44: 925–928.
52. Coopersmith CM, De Backer D, Deutschman CS, Ferrer R, Lat I, MachadoFR, Martin GS, Martin‐Loeches I, Nunnally ME, Antonelli M, Evans LE, Hellman J, Jog S, Kesecioglu J, Levy MM, Rhodes A. Surviving sepsiscampaign: research priorities for sepsis and septic shock. Intensive CareMed., 2018; 44: 1400–1426.

53. Fleischmann‐Struzek C, Mikolajetz A, Schwarzkopf D, Cohen J, HartogCS, Pletz M, Gastmeier P, Reinhart K. Challenges in assessing theburden of sepsis and understanding the inequalities of sepsis outcomesbetween National Health Systems: secular trends in sepsis and infectionincidence and mortality in Germany. Intensive Care Med., 2018; 44: 1826–1835.
54. Vincent JL, Lefrant JY, Kotfis K, Nanchal R, Martin‐Loeches I, Wittebole X, Sakka SG, Pickkers P, Moreno R, Sakr Y, Icon Investigators S and Investigators S. Comparison of European ICU patients in 2012 (ICON) versus2002 (SOAP). Intensive Care Med., 2018; 44: 337–344.
55. Weng L, Zeng XY, Yin P, Wang LJ, Wang CY, Jiang W, Zhou MG, Du B, ChinaCritical Care Clinical Trials G. Sepsis-related mortality in China: a descriptive analysis. Intensive Care Med., 2018; 44: 1071–1080.
56. Kerrigan SW, Martin-Loeches I. Public awareness of sepsis is still poor: we need to do more. Intensive Care Med., 2018; 44: 1771–1773.
57. Shankar-Hari M, Datta D, Wilson J, Assi V, Stephen J, Weir CJ, Rennie J, Antonelli J, Bateman A, Felton JM, Warner N, Judge K, Keenan J, Wang A, Burpee T, Brown AK, Lewis SM, Mare T, Roy AI, Wright J, Hulme G, Dimmick I, Gray A, Rossi AG, Simpson AJ, Conway Morris A, Walsh TS Early PREdiction of sepsis using leukocyte surface biomarkers: the ExPRES-sepsis cohort study. Intensive Care Med., 2018; 44: 1836–1848.
58. Parlato M, Philippart F, Rouquette A, Moucadel V, Puchois V, Blein S, Bedos JP, Diehl JL, Hamzaoui O, Annane D, Journois D, Ben Boutieb M, Esteve L, Fitting C, Treluyer JM, Pachot A, Adib-Conquy M, Cavaillon JM, Misset B, Captain Study G. Circulating biomarkers may be unable to detect infection at the early phase of sepsis in ICU patients: the CAPTAIN prospective multicenter cohort study. Intensive Care Med., 2018; 44: 1061–1070.
59. Shankar-Hari M, Madsen MB, Turgeon AF Immunoglobulins and sepsis. Intensive Care Med., 2018; 44: 1923–1925.
60. Welte T, Dellinger RP, Ebelt H, Ferrer M, Opal SM, Singer M, Vincent JL, Werdan K, Martin-Loeches I, Almirall J, Artigas A, Ignacio Ayestaran J, Nuding S, Ferrer R, Sirgo Rodriguez G, Shankar-Hari M, Alvarez-Lerma F, Riessen R, Sirvent JM, Kluge S, Zacharowski K, Bonastre Mora J, Lapp H, Wobker G, Achtzehn U, Brealey D, Kempa A, Sanchez Garcia M, Brederlau J, Kochanek M, Reschreiter HP, Wise MP, Belohradsky BH, Bobenhausen I, Dalken B, Dubovy P, Langohr P, Mayer M, Schuttrumpf J,

Wartenberg-Demand A, Wippermann U, Wolf D, Torres A. Efficacy and safety of trimodulin, a novel polyclonal antibody preparation, in patients with severe community-acquired pneumonia: a randomized, placebo-con-trolled, double-blind, multicenter, phase II trial (CIGMA study). Intensive CareMed., 2018; 44: 438–448.

61. Dellinger RP, Bagshaw SM, Antonelli M, Foster DM, Klein DJ, Marshall JC, Palevsky PM, Weisberg LS, Schorr CA, Trzeciak S, Walker PM, Investiga-tors ET Effect of targeted polymyxin b hemoperfusion on 28-day mortality in patients with septic shock and elevated endotoxin level: the EUPHRATES randomized clinical trial. JAMA., 2018; 320: 1455–1463.
62. Klein DJ, Foster D, Walker PM, Bagshaw SM, Mekonnen H, Antonelli M. Polymyxin B hemoperfusion in endotoxemic septic shock patients without extreme endotoxemia: a post hoc analysis of the EUPHRATES trial. Intensive Care Med., 2018; 44: 2205–2212.
63. Pickkers P, Russell JA Treatment with a polymyxin B filter to capture endotoxin in sepsis patients: is there a signal for therapeutic efficacy? Intensive Care Med., 2019; 45: 282–283.