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A Comprehensive Review on Liver Sepsis and Its Effect on Human Physiology

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Abstract

Sepsis is a common disease which morbidity and mortality rate in the recent years remain high. Sepsis disease is common in growing population and its irregular affects patient with cancer and underlying immunosuppression. Sepsis in its severe form causes multi-organ dysfunctions that produce a state of severe immune dysfunction and catabolism. No specific medication targeting the mediators of sepsis has yet proven effective. The liver acts a double-edged sword in sepsis. It remains a leading cause of death in United States the world health assembly and WHO made sepsis disease a global health priority in recent year. Sepsis irregular effect on organs like liver damage remains imprecise no specific therapy has yet not proven to control this irregular effect. Mortality rates of sepsis and septic shock have not improved in the past decade. The Surviving Sepsis Campaign (SSC) guidelines released in 2017 emphasize early recognition and treatment of sepsis, in an effort to reduce the burden of sepsis worldwide. No single solution is likely to be beneficial, and sepsis continues to be an entity that should receive high priority for the development of precision health approaches for treatment. Review concluded the impact of sepsis severity in the recent year, a diagnostic tool the influence of outcome as well as pathophysiological effects, including the cellular event leading to liver dysfunction. Finally, the role of liver is host immune response to sepsis and therapeutic considerations with the weakness of the relevant specific approach are examined.

Keywords: Liver, Catabolism, Immunosuppression, Precision, Sepsis.

Introduction

Sepsis is the clinical syndrome defined by the presence of infection and systemic inflammatory response to infection and the results from a complex interaction between the host and infectious agents, identified by the activation of multiple inflammatory pathways, with a great risk of mortality. Sepsis causes cellular and metabolic changes, with the beginning of septic shock with positive blood cultures (sepsis-17%, severe sepsis-25%, septic shock-69%)[1].Sepsis is the most common cause of patient mortality in intensive care units, with a global incidence of approximately 18 million cases per year and a mortality rate of (28–40%) .

The annual number of sepsis-related deaths in the United States was 258000 people, according to sepsis Alliance (an organization whose goal is to raise awareness of this condition to facilitate its early detection and treatment for successful outcomes)[2].To promptly recognize and manage higher risk patients, several risk stratification models have been adopted such as Sequential Organ Failure Assessment (SOFA) [3].Sepsis induces profound changes in the function of the normal liver. The balance of hepatic metabolic activity may be shifted rapidly in response to systemic inflammation with an ‘‘acute phase reaction (APR) [4].

Sepsis can evolve to multiple organ dysfunction syndromes (MODS) [5]. Sepsis is moderately important as it is seen in 10 of 1000 hospitalized patients and multiple organ dysfunction syndrome (MODS) develops in 30% of these patients; mortality is observed in 20% of patients with sepsis and 60-80% of patients with septic shock [6]. Multiple organ failure must include one or more of the following conditions: cardiovascular disorders, respiratory, neurological, hepatic, hematologic system disorders and other organ dysfunction.Early diagnosis and treatment are must due to high mortality rates. Cancer patients are nearly 10 times more susceptible to sepsis than are patients without cancer and sepsis- caused deaths account for 8.5% of all deaths among cancer patients. Sepsis is a serious clinical condition that represents a patient’s response to a sever infection and has a very high mortality rate. Normal immune and physiologic

responses eradicate pathogens, and the pathophysiology of sepsis is due to the inappropriate regulation of these normal reactions [7].

Septic shock is called infectious shock or toxicoseptic, bacterial shock or bacteremia. A retrospective, observational study including more than 100,000 patients with severe sepsis in Australia and New Zealand found that hospital mortality decreased steadily throughout the last decade [8]. A report published an international registry of patients with severe sepsis demonstrates some basic characteristics of the septic disease process on the basis of data from more than 11,000 patients from 37countries. The hospital community is increasing the development of multidisciplinary approaches and shared protocols with simple interventions that might dramatically change the management of the patients.

Several new approaches have been reported to reduce mortality rates in severe sepsis. These include the application of low tidal volume in acute respiratory distress syndrome (ARDS), plasma glucose control, goal-oriented treatment (central venous pressure, mean artery pressure, hourly urine output, and central venous oxygen saturation) started in the early period (in emergency service), and corticosteroid treatment at mean doses.Besides pharmacological treatment approaches, early and appropriate antibiotic treatment and cardiovascular support have great importance in sepsis treatment.

The liver is the largest gland in the human body and plays a central role in metabolic and immunological homeostasis. This organ is responsible for over 200 functions, such as detoxification, storage, energy production, nutrient conversion hormonal balance, and coagulation. These important physiological functions make the liver a critical organ for host survival following severe injury such as sepsis. Evidence has shown that liver dysfunction and failure, particularly serious complications in sepsis, directly contribute to disease progression and death [9].

Pathophysiology

Sepsis progresses from a localized infection to mild systemic inflammation and on to septic shock, the cardiovascular system undergoes major perturbations that are well known to intensive care practitioners. Sepsis is the culmination of complex interactions between the infecting microorganism and the host immune, inflammatory, and coagulation responses [10].The sepsis syndrome or SIRS can be explained by three mechanisms, all of which involve the release of mediators (table1) that result in systemic inflammatory response[11-13]. The mechanisms of inflammation are given as follows;

- The Pro-inflammatory Response.
- Failure of the Compensatory Anti-inflammatory Response (CARS) to Act.
- Immuno-paralysis

Table 1: Pro-inflammatory and anti-inflammatory mediators of sepsis

Proinflamatory mediators	**Anti-inflammatory mediators**
TNF-α	IL-1Ra
IL1b, IL-2, IL-8, IL-15	IL-4
Neutrophil elastase	IL-10
IFN-γ	IL-13
Thromboxane, platelet-activating factor	Type II IL-1 receptor
Vasoactive neuropeptides	Transforming growth factor-β
Plasminogen activator inhibitor-1	Epinephrine phospholipase A_2
Prostaglandins, prostacyclin	Epinephrine phospholipase A_2
Free radical generation	Soluble TNF-α receptor
Soluble adhesion molecules	Leukotriene B_4-receptor antagonist
Tyrosine kinase, Protein kinase	LPS-binding protein
H_2S, NO	Soluble recombinant CD-14
HMGI protein	--

The theory behind this mechanism relates to the excessive release of pro-inflammatory mediators that cause inflammation and result in the clinical picture of SIRS [14].Host defence can be categorized according to innate and adaptive immune system responses. Naturally, immune system responds rapidly by means

of pattern-recognition receptors e.g., toll-like receptors [TLRs] that interact with highly conserved molecules present in microorganisms [15].Binding of TLRs to epitopes on microorganisms stimulates intracellular signalling, increasing transcription of pro-inflammatory molecules such as tumor necrosis factor α (TNF-α) and interleukin-1β, as well as anti-inflammatory cytokines such as interleukin-10[16]. Proinflammatory cytokines up-regulate adhesion molecules in neutrophils and endothelial cells. Although activated neutrophils kill microorganisms, they also damage endothelium by releasing mediators that increase vascular permeability, leading to the flow of protein-rich edema fluid into the lung and other tissues. In addition, activated endothelial cells release nitric oxide, aninflential vasodilator that acts as a key mediator of septic shock [17].

T-cell subgroups are relatively in sepsis. Helper ($CD4^+$) T cells can be categorized as type 1 helper (Th1) or type 2 helper (Th2) cells. Th1 cells generally secrete pro-inflammatory cytokines such as TNF-α and interleukin-1β, and Th2 cells secrete anti-inflammatory cytokines such as interleukin-4 and interleukin-10, depending on the infecting the burden of infection and other factors [18].

Gram-negative and Gram-positive bacterial infections with endotoxin releasethe effects of the release of endotoxins, such as lipopolysaccharides (LPS), are commonly expected to occur during Gram-negative infections, uniformly in Gram-positive infections, lip- oteichoic acid (LTA) is expected to be released. Both toxins affect macrophage function and that result in the production of mediators. This process an inflammatory response by the body in response to infections(figure1).

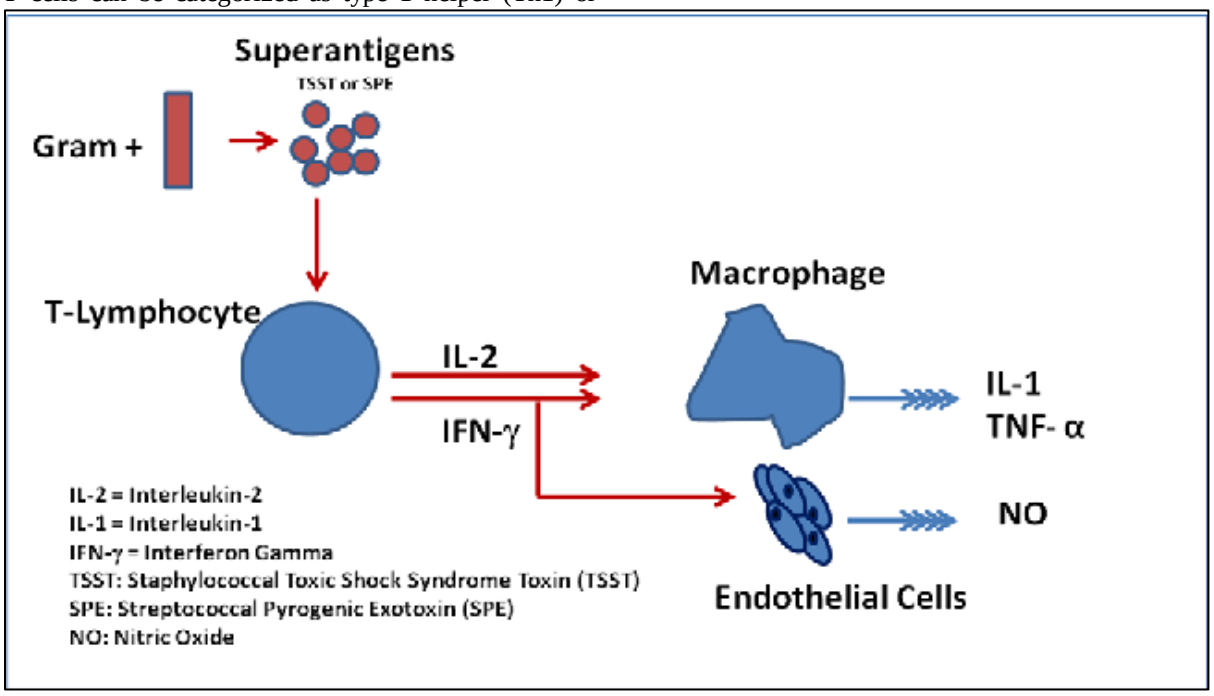

Figure1: Effect of exotoxin (superantigen) on the release of mediators of inflammation
Source: https://ai2-s2-public.s3.amazonaws.com/figures/2017-08-08/eb2b1ba13df572398fbc728c3994f2af31d99e11/3-Figure2-1.png.

An imbalance between pro-inflammatory response and anti-inflammatory response is believed to occur on during infection. This permit the pro-inflammatory mediators to generatean uncontrolled excessive inflammatory process to pro-inflammatory cytokines, anti-inflammatory mediators inhibit inflammation by inhibiting TNF-α, augmenting acute-phase reactants and immunoglobulins, and inhibiting T-lymphocyte functions. Anti-inflammatory mediators also inhibit activation of coagulation system. The anti-inflammatory response serves as a negative feed-back mechanism to down-regulate the synthesis of pro-inflammatory mediators and vary their effects, thereby restoring homeostasis and preventing SIRS. SIRS results from a great pro-inflammatory response. By contrast, an excessive compensatory anti-inflammatory reaction (CARS) that results in an inappropriate

immune suppression. If an imbalance develops between SIRS and CARS, homeostasis is violated and a clinical progression towards multi-organ dysfunction may occur.

The liver plays a major role in clearing bacteria, in mediating inflammatory responses, and in coagulating, which may regulate renal failure, acute lung injury, acute respiratory distress syndrome, coagulopathy. Bacterial clearance is one of the most important processes for the survival of patients with sepsis. As the organ responsible for sterilizing and detoxifying the blood stream, the live plays a critical role in bacterial and toxin clearance in sepsis(figure 2) [19].

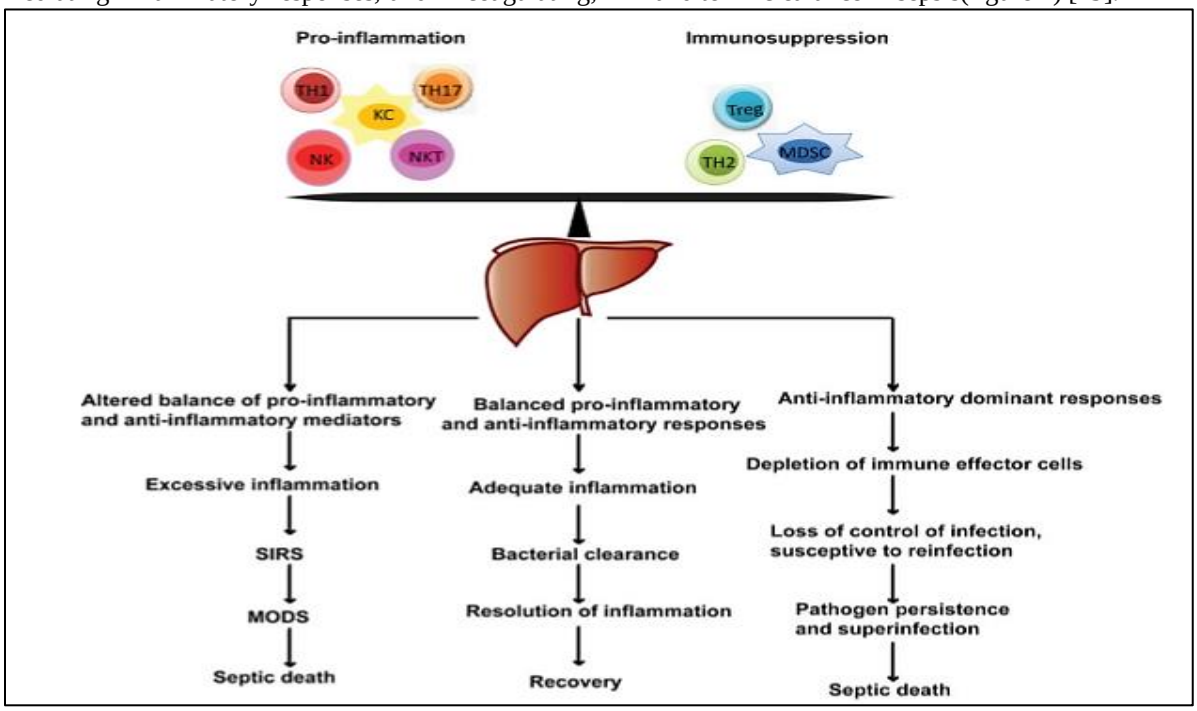

Figure 2: Effect of pro-inflammation and immunosuppression on the liver
Source: https://encrypted-tbn0.gstatic.com/images?qtbn:ANd9GcR-uY3A853O_ sOPUAJ8BcttCR-GBV6MGqOf2LAlyvzPmeZSgGpUHQ

Clinical Diagnosis

Current commendation for recognizing both sepsis and septic shock is the use of the SOFA scores [Sequential (Sepsis-Related) Organ Failure Assessment]. SOFA is a simple system, which uses available parameters in daily clinical practice to identify dysfunction or failure of the key organs as a result of sepsis. SOFA (quick SOFA) was developed[20, 21]. Laboratory tests are required to help in diagnosing sepsis, distinguish it from other conditions, and evaluate and monitor organ function, blood oxygenation and the acid-base balance. Other visualize tests are needed to evaluate the state of various organs, detect complications and identify the location of the infection (table 2). These tests are usually X-rays, CT scans or ultrasounds [22].

Table 2: Diagnostic criteria of sepsis

Diagnostic criteria	Threshold
Fever	>38.3°C
Tachycardia	>120/minute
Systolic blood pressure	<90 mmHg
Procalcitonin	>0.5 ng/ml
Bandemia	>5%
Lymphocytopenia	$<0.5 \times 10^3$ul
or neurophil/lymphocyte ratio	>10
Thrombocytopenia	$<150 \times 10^3$ul
Lactate	>2.0 meq/l

Biomarkers

Sepsis biomarkers have various principal applications. They can be used to rule out infection. It is often believed that these markers can help identify the presence of infection, but this is not their real value [23]. Indeed, no sepsis biomarker can be entirely specific for infection, because similar pathways can be activated in the absence of an infection. use of biomarkers has been demonstrated in many studies during the last 10 years, from the initial landmark study by Christ-Crain and colleagues, showing that the use of procalcitonin (PCT) levels could reduce antibiotic therapy in suspected lower tract infections [24] to the more recent analysis of the Procalcitonin-Guided Antibiotic Therapy and Hospitalisation in Patients (ProHOSP) with lower respiratory tract infections study, which showed that PCT use could decrease antibiotic prescription in patients with heart failure presenting to an emergency department [25].Biomarkers can be useful to rule out, rather than rule in, infection), a sepsis marker should not be used to escalate antibiotic therapy; this approach has been shown to be associated with increased organ failure [26]. PCT is a particularly good severity marker in sepsis, with levels well related to mortality rates [27]. HLA-DR and functional inactivation of monocytes, and have established that the decreased expression of HLA-DR may be a sign of severe immunosuppression (considering sepsis not as a pro-inflammatory disorder but as an immune disorder including inflammation and immunosuppression) [28-30].

More than 170 sepsis markers have been proposed [31].PCT is one of the best, and it is certainly the most widely studied, but there is nothing magic about it, and it is definitely not perfect. Combining information collected from several biomarkers may be more useful,[32]and adding circulating biomarker levels to information about the cellular response[33] and the degree of cell activation [34]may be a good future approach to help optimize our anti-infective strategies.Procalcitonin has a shorter half-life than CRP, and PCT levels rise shortly in cases of bacterial infection. This favourable kinetics may allow earlier diagnosis of sepsis and better monitoring of its progression.

CRP(C - reactive protein) is an acute-phase protein produced by the liver, although it can also be synthesized byother cells like alveolar macrophages. Its plasma concentration remains stable in healthy patients, but its levels increase after trauma, inflammation, and other stimuli related to tissue damage. Bacterial infections are strong stimuli that produce a rapid rise in CRP levels in a few hours. Interleukin-6 (IL-6) is thought to be the main mediator stimulating the production of CRP, but other cytokines, such as interleukin-1 (IL-1) and tumour necrosis factor alpha (TNF-a), also produce it. Changes in plasma levels of CRP may be useful in the diagnosis and prognosis of infection; a fall in plasma levels indicates infection resolution. Its short half-life of about 19 h makes CRP a useful tool in the monitoring of the inflammatory response, infection, and antibiotic therapy. In addition, CRP laboratory tests are less expensive than cytokine measurements [35]. Isolated CRP values can be helpful in diagnosing sepsis [36]**.** Prolcalcitonin and C-reactive protein biomarkers are pro-inflammatory biomarkers that highly used in the study.

Lactate is the marker of hypo-perfusion par excellence generally used for organ dysfunction. Increase in serum lactate levels deducible progress to organ dysfunction and are associated with an increased mortality rate from 35% to 70%. Hyperlactatemia is considered a severe sepsis marker, as it reflects poor tissue perfusion. Studies have established the use of lactate as amarker for diagnosis, prognosis, and treatment of tissue hypoxia in shock. Lactate bio- kineticsis also used as a prognostic marker in sepsis. A patient with severe sepsis with significant hypo perfusion (lactate4mmol/l) is considered to be in shock even without the necessary hypotension [37-39].The absence of blood lactate clearance is an independent sign of death.

Other biomarkers like cell-free DNA (cf-DNA), but a great work in this area remains to be done. cf-DNA comprises short fragments of DNA found in plasma and released from the cells due to necrosis or apoptosis. Thecf-DNA has recently increased attention and it is currently being investigated as a biomarker in patients. cf-DNA levels are great in sepsis patients than in healthy controls &also in non-survivors. Cell death is a common event in sepsis but it is not sepsis-specific, so cf-DNA has been looked over as a prognostic biomarker.

Management of Sepsis

Allopathic medication system

Observational data from several studies of sepsis and septic shock show that timely administration of appropriate antibiotic therapy is associated with improved patient outcomes. The difficulties that clinicians face with diagnosing infection, especially when a patients initially present to need a care, and the high rate of over-diagnosis of sepsis, and thus risks

promoting the excess antibiotic use and causing unintended harm.Although several studies have shown the detrimental effects of even small delays in antibiotic administration, it is important to consider antimicrobial keeping as an essential concomitant of sepsis management, and that unnecessary antibiotic use should be avoided. Rapid de-escalation of antimicrobial therapy will allow clinicians to feel more comfortable with sepsis measures that encourage rapid administration of broad-spectrum antibiotics immediately after identification of a patient with sepsis or septic shock.

Antibiotic-related risks, such as Clostridium difficile infection, acute kidney injury, hepatitis, cytopenias, rash, and selection for drug-resistant pathogens, have beenwell described, but more indirect effects, including mitochondrial toxicity and altering the microbiome, are less well appreciated. A recent study that diminished effectiveness of checkpoint inhibitors in treating different cancers during concurrent antibiotic use highlights a potential off-target antibiotic-related adverse effect.

Surviving Sepsis Campaign: International guidelines for management of sepsis,2017 recommendations state that intravenous antimicrobials should be provided as soon as possible after the recognition of sepsis (ideally within 1 hour).An elementary choice should include a broad-spectrum cover (with either a single agent or a combination of agents).The antibiotic spectrum should be decrease when pathogens have been isolated and sensitivities established, or when clinical progress allows it.Dosing process of antimicrobials should be optimized on the basis of accepted pharmacokinetic and pharmacodynamic principles.De-escalation of antimicrobials should be considered daily and at the earliest stage when the clinical situation permits.

Homeopathic medications system

Homeopathic medicines are about two centuries. Homeopathic treatment may be a useful additional therapeutic measure with a long-term benefit for severely septic patients admitted to the intensive care unit. Some of the homeopathic medicines given sepsis are (table 3).

Table 3: The useful homeopathic medicines used in sepsis

Homeopathic medication	Indications
Apismellifica	Oedema Extreme dyspnoea
Arsenicum album	Weakness, Anxiety, restlessness
Baptisia	ARDS , Sepsis Hot skin
Belladonna	High temperature with sweat Red discoloration face
Bryonia	Pneumonia, pain in the chest
Carbo vegetabilis	Respiratory insufficiency ARDS
Crotalushorridus	Purpura haemorrhagica Haemorrhages
Lachesis muta	Septic shock
Lycopodium clavatum	Fever, afternoon Distension, abdominal
Pyrogenium	Bad odour

In future innovative technologies may help accelerate time to diagnosis and optimal treatment selection for patients with possible sepsis. Proper use of antibiotics in patients with sepsis is of paramount importance to minimize the contribution of poor antibiotic stewardship to this emerging problem.

Conclusion

Despite recent therapeutic breakthroughs, mortality rates remain high in sepsis patients and much more remains to be done to advance our understanding and treatment of sepsis. The liver plays acentral regulatory role in sepsis and homeostasis. Addressing the disturbance of liver functions, such as immune response, metabolism, excretion,coagulationand detoxification, is importantfortheprognosis andultimate survival of sepsis patients. In this review, we summarized sepsis morbidity and mortality rate in a recent year. The pathophysiological condition of sepsis and how it affects the liver. Recent clinical diagnosis including homeopathic medication and antibiotic

medication is also been discussed. No further therapeutic medication is been developed to enhance the role of the liver in sepsis.

References

1. Pop-Began V.,PaunescuV., GrigoreanV.,Pop-BeganD.,PopescuC., Molecular Mechanisms In the Pathogenesis of Sepsis, J Med Life 2014;7:2:38-41.
2. Yan J.,Li S., Li S.,The Role of the Liver in Sepsis,Int Rev Immunol2014;33:6:498-510.
3. Yang HS., Hur M., Yi A., Kim H., Lee S., Kim SN.,Prognostic Value of Presepsin in Adult patients with sepsis: Systematic Review and Meta-analysis,PLOS One2018;13:1:1-12.
4. WillamB.,The Liver in Systemic Disease: Sepsis and Critical Illness, Clinical liver Disease a Multimedia Review Journal2016; 7:4:88-91.
5. Nesseler N., Launey Y., Aninat C., Morel F., Mallédant Y., Seguin P.,Clinical review: The Liver in Sepsis,Crit Care 2012;16:5:235.
6. Polat G.,Ugan RA., Cadirci E, Halici Z.,Sepsis and Septic Shock: Current Treatment Strategies and New Approaches,Eurasian J Med2017; 49:1:53–58.
7. Stearns-Kurosawa DJ., Osuchowski MF., Valentine C., Kurosawa S., Remick DG., The Pathogenesis of Sepsis,Annu Rev Pathol 2011;6:19–48.
8. Loeches IM.,Levy MM., Antonio Artigas., Management of Severe Sepsis: Advances, challenges, and current status,Drug Des DevelTher 2015;9:2079–2088.
9. CanabalJM., Kramer DJ., Management of Sepsis in patients with Liver Failure, Curr Opin Crit Care 2008;14:2:189–197.
10. Bone RC., Grodzin CJ., Balk RA., Sepsis: a new hypothesis for pathogenesis of the disease process, Chest 1997 Jul; 112:1:235-243.
11. Glauser MP., Zanetti G.,Baumberger JD.,Cohen J.,Septicshock: Pathogenesis, Lancet 1991;338:732–736.
12. SagyM., Al-Qaqaa Y., Kim P., Definitions and Pathophysiology of sepsis., Curr Probl PediatrAdolesc Health Care 2013;43:10:260-263.
13. Modlin RL., Brightbill HD., Godowski PJ., The toll of innate immunity on microbial pathogens, N Engl J Med 1999;340:1834-1835.
14. Brown MA.,Jones WK., NF-kappaB action in sepsis: the innate immune system and the heart, Front Biosci 2004;9:1201-1217.
15. James AR.,Management of Sepsis.,NEngl J Med 2006; 355:1699-1731.
16. Abbas AK.,MurphyKM.,SherA.,Functional diversity of helper T lymphocytes, Nature 1996 ;383:787-793.
17. Protzer U., Maini MK., Knolle PA., Living in the liver: hepatic infections, Nat Rev Immunol 2012;12:3:201–213.
18. Doerr F.,Badreldin AM.,Heldwein MB.,A comparative study of four intensive care outcome prediction models in cardiac surgery patients,JCardiothoracSurg2011;1-8.
19. Minne L., Abu-Hanna A.,deJongeE., Evaluation Of SOFA-based models for predicting mortality in the ICU: A systematic review, Crit Care 2008;12:6:161.
20. Rello J.,Sánchez FV., Rodriguez MR.,Moyano S.,Sepsis: A Review of Advances in Management,AdvTher 2017; 34:11:2393–2411.
21. Paul EM., Don't miss the diagnosis of sepsis,Crit Care2014; 18:5:529.
22. Christ-Crain M., Jaccard-Stolz D., Bingisser R., Gencay MM., Huber PR., Tamm M., Muller B.,Effect of procalcitonin-guided treatment on antibiotic use and outcome in lower respiratory tract infections: clusterrandomised, single-blinded intervention trial, Lancet 2004;363:600–607.
23. Schuetz P., Kutz A., Grolimund E., Haubitz S., Demann D.,Ogeli A., *et al*.,ProHOSP Study Group Excluding infection through procalcitonin testing improves outcomes of congestive heart failure patients presenting with acute respiratory symptoms: results from the randomized ProHOSP trial,Int J Cardiol 2014;175:464–472.
24. Jensen JU.,Hein L.,Lundgren B.,Bestle MH.,Mohr TT.,Andersen MH.,*et al*.,ProcalcitoninAnd Survival Study (PASS) GroupProcalcitonin-guided interventions against infections to increase early appropriateantibiotics and improve survival in the intensive care unit: a randomized trial,Crit Care Med 2011;39:2048–2058.
25. Ugarte H.,Silva E.,Mercan D.,De Mendonça A., Vincent JL.,Procalcitonin used as marker of infection in the intensive care unit,Crit Care Med 1999;27:498–504.
26. Juskewitch JE., Abraham RS., League SC., Monocyte HLA-DR expression and neutrophil CD64 expression as biomarkers of infection in critically ill neonates and infants,Pediatr R 2015;78:6:683–690.
27. Cazalis MA.,Friggeri A.,Cavé L.,Decreased HLA-DR antigen-associated invariant chain (CD74) mRNA expression predicts mortality after septic shock,Crit Care 2013;17:6:28.

28. Vester H.,Dargatz P.,Huber-Wagner S.,Biberthaler P.,Griensven M.,HLA-DR expression on monocytes is decreased in polytraumatizedpatients,EurJ Med 2015;1-9.

29. Pierrakos C.,Vincent JL.,Sepsis biomarkers: a review,Crit Care 2010; 1-18.

30. Charles PE., Gibot S., Predicting outcome in patients with sepsis: new biomarkers for old expectations,Crit Care 2014;18:108.

31. Guerin E., Orabona M., Raquil MA., Giraudeau B., Bellier R., Gibot S., *et al*.,Circulating immature granulocytes with T-cell killing functions predict sepsis deterioration,CritCare Med 2014;42:2007–2018.

32. Dimoula A., Pradier O., Kassengera Z., Dalcomune D., Turkan H., Vincent JL., Serial determinations of neutrophil CD64 expression for the diagnosis and monitoring of sepsis in critically ill patients, Clin Infect Dis 2014;58:820–829.

33. Povoa P., Coelho L., Almeida E., Fernandes A., Mealha R, Moreira P.,C-reactive protein as a marker of infection in critically ill patients, Clin Microbiol Infect 2005;11:101-8.

34. Hofer N., Zacharias E., Muller W., Resch B., An update on the use of C-reactive protein in early-onset neonatal sepsis: current insights and new tasks, Neonatology2012;102:25–36.

35. Rhee C., Murphy MV., Li L., Platt R., Klompas M., Centres for Disease Control and Prevention Epicentres Program, Lactate testing in suspected sepsis: trends and predictors of failure to measure levels. Crit Care Med 2015;43:8:1669–1676.

36. Holder AL., Gupta N., LulajE.,Predictors of early progression to severe sepsis or shock among emergency department patients with nonseveresepsis,Int J Emerg Med 2016;1-11.

37. Frass M., Linkesch M., Banyai S., Resch G., Dielacher C., Lobl T., *et al*.,Adjunctive Homeopathic Treatment In Patients with Severe Sepsis: A Randomized, Double-blind, Placebo-controlled Trial in an Intensive Care unit,Homeopathy 2005; 94:2: 75-80.

38. Cecconi M., Evans L., Levy M., Rhodes A., Sepsis and septic shock,Lancet 2018; 392:10141:75-87.

39. Klompas M., Calandra T., Singer M., Antibiotics for Sepsis-Finding the Equillibrium, Jama 2018;320:14:1433-1434.

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