Review of: "Perspectives on the Immune System in Sepsis"

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Sepsis and Septic shock is one of the conditions in intensive care unit that is associated with a high mortality around 40%, despite following surviving sepsis guidelines and appropriate therapy. There has been a lot of research in the management of sepsis, but unfortunately with negative overall results. This may be because of a lot of heterogeneity in inclusion of patients with sepsis. Our current understanding regarding the pathophysiology of sepsis is incomplete and this article presents the varied spectrum of dynamic interactions of the immune system that may explain complex heterogeneity underlying sepsis in an individual patient. Even though the current definition of Sepsis as defined by Sepsis IV guidelines is as simple as “dysregulated host immune response to infection” with an elevated SOFA score, the complex network of immune system interactions has to be understood inorder to decrease morbidity and mortality. This article begins with the changing paradigms of definition of Sepsis including the old SIRS criteria to the current definition of SOFA criteria followed by a brief discussion of biomarkers, their utility in diagnosis and prognosis. The pathobiology of sepsis in terms of both initial pro-inflammatory phase and subsequent anti inflammatory phase has been described with focus on transcriptome, metobolome and proteome.

Major transcription changes in sepsis is described with respect to NF-kB that promotes gene transcription and how a 29 mRNA test out perfoms the APACHE scoring in predicting clinical outcomes. Also described is the utility and disadvantages of using micro RNAs as inflammatory markers and the influence of long non coding RNAs on M1/M2 polarization, differential TLR activation. The article also gives a brief update on “Lethe” an example of pseudogene lnc-RNA that inhibits NF-kb via begative feedback.

Post Sepsis Immunoparalysis phase is described with emphasis on pathogenesis followed by different therapeutic strategies that target molecular pathogenesis e.g the use of ethyl pyruvate to ameliorate sepsis induced immunosuppression.

Overall an excellent article describing the molecular pathogenesis of sepsis. Can be published after reviewing my following suggestions:

As per the recent publication on June 23, 2022 "N Engl J Med 2022; 386:2387-2398
DOI: 10.1056/NEJMoa2200644"- the LOVIT trail, intravenous vitamin C increases mortality in sepsis and hence not recommended.

Unlike the animal experiments, IV glutathione has not been shown to improve mortality. I request the authors to include some of the human trial data regarding glutathione and vitamin C .