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

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The morbidity & mortality associated with sepsis and septic shock continues to be unacceptably high despite advancements in critical care medicine in the past few decades. As per WHO, the mortality is estimated to be about 27% in patients diagnosed with sepsis and 42% in patients with septic shock in the ICU[1]. Sepsis involves a dysregulated host immune response to infection, promoting complex interaction between various pro and anti-inflammatory cytokines which could result in life threatening organ failures and death [2]. We also see that the response to a pathogenic stimulus is variable across population groups, age and comorbidities. Early diagnosis of sepsis is crucial for improving the survival rate; however, traditional screening tools and biomarkers lack sensitivity and specificity [3].

The challenges in accurately diagnosing sepsis and limited treatment options have led to an increase in research activities related to identifying biomarkers like procalcitonin(PCT) and CRP which are currently being used in sepsis management. Despite scores of molecules studied till date, an ideal biomarker for sepsis helping in the diagnostic, prognostic and therapeutic aspects is yet to be evolved at this stage. Genetic predisposition to sepsis or complications of sepsis is well known. The current trend in research is to identify the contribution of various culprit genes which in turn code for culprit RNAs that are involved in the pathogenesis of sepsis. In this mini review at Queios, Felician Stancioiu et al. briefly summarize the current state of development and utilization of the above-mentioned genetic profiles in the management of septic patients.

Many studies have been done on this front and it has been observed that various miRNAs and lncRNAs are involved in the manifestations of sepsis. MicroRNAs (miRNAs) are small non-coding RNAs and few of them are specific for sepsis. It has been seen that sepsis leads to dysregulation of several miRNAs, such as miR-146a, miR-223, miR-16, and miR-150. They have also been detected in blood samples in septic patients. [4,5].A meta-analysis done in 2020, concluded that circulating miRNAs, especially for miR- 223, are potential markers for distinguishing sepsis from SIRS and healthy controls[6].

In continuation with the promising research of genetics and sepsis, the 29 mRNA test has been described by the investigators in the PROMPT trial. The PROMPT trial was a multicentric trial done in 397 adult patients who presented to the emergency department with signs of acute infection and a minimum of one vital sign change. This study incorporated cut-off values to allocate patients into interpretation bands. The rule in - bacterial band showed a specificity of 98%

compared to 94% for the PCT- band (>0.5 µg/L); the rule out bacterial band showed a sensitivity of 95% for the RNA test compared to 86% for PCT. For the detection of viral infections, it demonstrated a specificity of 93% for the rule in band and a sensitivity of 96% for the rule out band. It has also shown to be promising in distinguishing between bacterial and viral infections. The authors have also shown that it is not affected across population sub groups. They have also used the test in detecting secondary infections in patients with SARS-CoV-2. The 29 mRNA test has been shown to perform better in point of care diagnosis of sepsis in few studies. [7]

Protein-coding genes are also investigated as diagnostic signatures for sepsis. Long non-coding RNA (lncRNA) is a category of RNAs longer than 200 base pairs in length with little potential of encoding proteins [8].Studies revealed that lncRNAs regulate inflammation-related genes and may serve as potential biomarkers or signatures for sepsis diagnosis. Few researchers are trying to identify specific signature lncRNAs for sepsis. SepSiglnc signature for sepsis which contains 14 lncRNAs for sepsis has been identified by Zheng et al.[9] thus many miRNAS and lncRNAs are being studied and future looks promising both in early diagnosis and treatment of septic patients based on genetic markers.
Though the above mentioned studies are quite promising, we still need further large studies in heterogeneous populations/conditions across the globe helping further evaluation and validation.
However, it is worth noting that the sensitivity/specificity/positive and negative predictive values for various other genetic markers are not uniformly fool-proof. This is very likely due to the extremely complex inflammatory pathways involving diverse molecules (few or many yet to be even identified at this stage) in varying quantities with the net effect of individual molecules on one another is impossible to ascertain at this stage. This complexity is compounded by significant heterogeneity in patient population including age, sex, race, co-morbidities, the nature of toxins by microbials, the pathophysiology & chronology of individual infection; and drugs administered to treat an individual patient.
The genetic association in various autoinflammatory conditions has been very strong and the treatment options have moved from blanket non-specific immunosuppression to target therapies With the ongoing research on genetic influence of sepsis pathophysiology, we hope to have timely diagnosis of sepsis, differentiate between various pathogens like bacteria, virus and fungus , have targeted therapy for organ dysfunction, reduce the overuse or abuse of antibiotics and have appropriate antibiotic stewardship. However, currently, Genetic studies require complex and costly equipment and expertise which could make universal accessibility extremely challenging. These tests would be of any utility only when available at bedside with rapid results. Moreover, the short term/long term side effects of therapeutic interventions at genetic level in septic patients also need to be watched carefully.

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