Review

Precision Medicine in Sepsis and Septic Shock

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The entire spectrum from systemic inflammation to septic shock is a continuum of dysregulated host response to a stimulus[1]. Sepsis is one the leading causes of mortality worldwide despite structured and protocolized therapies like fluid resuscitation, infection control and establishment of organ support. But does one size fit all? Can we predict the clinical course and outcome of all patients with sepsis? Do all the septic patients have the same clinical management? The answer to these questions is precision medicine.

Precision medicine[2] is based on the concept of matching the treatment options as close as possible to patient's clinical, genetic, and physiological characteristics so that there is improvement in disease state and overall reduction in mortality[3,4]. The need for precision medicine has been on a rise as most trials indicate that applying same kind of treatment strategies to a heterogenous group of patients does not provide uniform favorable response, but targeted therapy according to subgroups shows positive outcome[5]. The best example of application of precision medicine is in oncology where the chemotherapeutic agents are targeted to specific tumor genetics. But as sepsis is a heterogenous disease and the progression changes very rapidly, it is very difficult to apply this knowledge in managing these critically ill patients.

Strategies for precision medicine in sepsis:

As sepsis evolves rapidly over time, the strategies should also be very sensitive and specific to the disease state. The major targets for strategies that have been tried in sepsis management are: biomarkers, hemoadsorption, omics and immunoglobulins.

Biomarkers*:*

They can be used to stratify patients based on the prognosis and severity of the disease[6]. The role of biomarkers can be divided into following stages: prediction of sepsis before clinical symptoms, discriminate sepsis from non-infective causes, prediction of response to therapy and prediction of possible side effects of therapy.

Procalcitonin (PCT) is among the most widely used biomarker for predicting sepsis[7], suggesting bacterial infection and defining the duration of therapy[8]. It has been a reliable indicator of mortality in major observational trials[9] if the level of PCT does not reduce by 80% with therapy.

C-Reactive Protein (CRP) has also been used extensively to identify the presence of systemic inflammation[10] and also used as a marker of sepsis in neonates[11]. But its poor sensitivity in adults has reduced the utility.

Other immunological biomarkers which have been used for early detection of sepsis are presepsin, interleukin-6 and interleukin-8.

Non-septic acute kidney injury (AKI) can be detected very early with the help of tissue inhibitor of metalloproteinase-2 and insulin such as growth factor binding protein 7 (TIMP-2)*(IGFBP7)[12].

Omics:

The technology to differentiate septic patients based on their genotype and phenotype should help in individualizing specific therapies to a subgroup of patients. This is the basis of genomic, epigenomic, transcriptomics, metabolomics and proteomics studies of a septic patient. These studies are involved in identifying patients at risk for clinical deterioration and unfavorable outcome[13]. It was observed that patients with increased expression of subtype gene 1 is associated with increased prevalence of sepsis.[14] This will also help us in differentiating between bacterial and viral cause of infection. The combination of biomarkers and the omics technologies could significantly help in personalizing the treatment approaches for individual septic patients,

although this technology has still not been attempted in clinical practice.

Immunoglobulins (Igs):

Downregulation of Igs in sepsis is not well understood but has been associated with increased mortality. Administration of IgM-IgA enriched Igs have shown promising results specifically in patients with low IgG levels, although it has still not been endorsed by surviving sepsis campaign (SSC)[15].

Endotoxin/cytokine hemadsorption:

Endotoxin is released from gram negative bacterial cell wall and their increased presence has been associated with severity of sepsis. The hemadsorption techniques have targeted this knowledge to reduce the concentration of endotoxins and cytokines in blood. The EUPHAS trial[16], ABDOMIX trial[17], EUPHRATES trial[18] have all failed to show any major benefit of endotoxin adsorption. Well-constructed trials can help in identifying the true space for all these therapies especially in patients with high endotoxin or cytokine load.

The heterogenous nature of sepsis makes it very difficult to individualize the therapies. These precision-based techniques if used in correct manner can help in implementing specific treatment for specific subset of patients. Further research is warranted before we extrapolate this knowledge into clinical practice.

Conflict of Interest: None

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