EDITORIAL

Pediatric Sepsis – Sailing the Unchartered Waters with Omics

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Sepsis is a global health priority and a leading cause of morbidity and mortality in children. Our understanding of sepsis and septic shock has advanced over the decades, and the same is reflected in the definitions of sepsis over the years. Recently, greater emphasis has been laid on identifying the dysregulated host response in sepsis and septic shock that leads to multiple organ injuries and results in increased mortality. Various clinical and laboratory scores of organ dysfunction criteria have been validated both in adults and children with sepsis. The latest Phoenix sepsis score developed for children is a composite 4-organ system model including cardiovascular, respiratory, neurologic and coagulation dysfunction.[1] The complex pathways involved in the progression from infection to sepsis and septic shock, are still poorly understood, and vary with age, severity of infection, adequacy of treatment, appropriate choice of antimicrobials, source control, genetic variability and susceptibility, and immune mechanisms, amongst others.[2] Children with sepsis behave differently to adults with respect to the pathophysiology, age-specific vital parameters, different sets of pediatric comorbidities, and developmental age-dependent immune function alterations.[1] The perception of sepsis and septic shock as a clinical syndrome alone precluded a deeper understanding of the molecular mechanisms involved. Complex disease states such as septic shock are not centered on a single factor and result from an interplay of a multitude of factors, and we are far from unravelling the intricacies involved. Understanding the molecular basis of sepsis and the pathways involved has both diagnostic and therapeutic implications for us. It will not only facilitate early identification of sepsis using biomarkers, help in characterization of subgroups who would need aggressive measures predict disease progression, but also help us to target some of the key molecular pathways involved in sepsis progression. "One size fits all" approach would definitely not be applicable to such a heterogenous disease state, and thus, a better understanding of these processes would pave the way for Precision medicine in sepsis, so that we could identify patient subtypes within sepsis who form a relatively homogenous group and who would benefit from targeted therapeutic interventions.[3]

Various biomarkers, inflammatory markers, organ dysfunction scores in sepsis have been developed and have become integral to our bedside management. In our quest to characterize the pathways in sepsis progression precisely, genetics and omics approach have been applied. Omics approach refers to a comprehensive or global assessment of a given set of molecules, and the first omics discipline genomics focused on the study of genomes in its entirety, providing a framework for studying the specific genetic variants that contribute to a disease state. Transcriptomics refers to the qualitative and quantitative analysis of the RNA levels in the biological system, and aims to study the differential gene expression patterns, and also temporal changes in the expression of genes during the evolution of disease states. The study of real-time dynamic changes in gene expression over a time period is an advantage of such RNA-based strategies compared to DNA studies.[4]

Host response to infection begins with the detection of microorganisms via the interaction between pathogen-associated molecular patterns (PAMPs), damage associated molecular patterns (DAMPs) and pattern recognition receptors (PRRs) present on the cells. The role of transcriptomics starts by studying the messenger RNA expression transcripts involved in these processes, which regulate host responses to infection.[5] As our understanding deepens, we have also realized that non coding RNAs, namely microRNAs and long noncoding RNAs (microRNA sponges) play crucial roles in their regulatory effect on messenger RNA and modulate the response on downstream cellular pathways.[6,7] The study of these RNA transcripts is not quite straight-forward, as the expression patterns are unique to the specific cell type that is under study, and there are dynamic changes in the process with time. Nevertheless, some of these molecules have been validated as molecular biomarkers in sepsis. To name a few, the HLA-DRA gene is considered a promising mRNA surrogate marker for immunosuppression in sepsis patients, and miR-150 has been studied as a marker to differentiate sepsis and non-infectious systemic inflammatory response syndrome.[8,9] Transcriptomics has also been utilized as a prognostic tool to identify those who would progress to organ failures such as septic shock, acute respiratory distress syndrome, acute kidney injury and the derivation of endotypes within sepsis who share common biologic processes and have distinct molecular signatures. Identifying endotypes within sepsis would help in risk stratification as well as the use targeted host-directed therapies in certain subsets of patients.[10,11] Inflammopathic, adaptive and coagulopathic endotypes were identified and coagulopathic endotype was associated with the highest mortality rate. Pediatric septic shock endotypes A and B have been defined based on gene profiling

corresponding to glucocorticoid receptor signaling and the adaptive immune system. Endotype A was independently associated with organ failure burden as well as increased mortality, and it was also realized that there are temporal changes in endotype assignment as sepsis progresses.[12]

In the current edition, Lalitha et al., have studied transcriptomic profiling of pediatric septic shock in an Indian cohort, and have looked at the differences between survivors and non-survivors among children with septic shock, and also non-septic controls.[13] This is a significant step towards utilizing RNA sequence profiling in children in our setting, and would pave the way for more research directed in this area. Lymphocyte mediated immunity was found to be low in sepsis non-survivors. Various mechanisms such as lymphocyte apoptosis, cellular trafficking to inflamed tissues and reduction in lymphopoiesis have been postulated to result in Lymphopenia in sepsis and is associated with increased mortality.[14] The authors have also found overexpression of coagulation and complement pathways in children who progressed to septic shock, which translates into activation of the coagulation system, resulting in disseminated intravascular coagulation. Apart from the previously reported genes that have been identified as prognostic markers in sepsis-TAP2, GPR18, PCSK9, new molecular signatures have been identified in this small cohort, which would need validation in a larger population. More such studies in larger group of pediatric cohorts in different settings would add to the existing knowledge and facilitate the creation of models based on molecular signatures.

Application of the transcriptomics data to clinical practice is not without its challenges. Identifying the precise molecular signatures that are clinically relevant is a daunting task, and advancements in machine learning have helped us in a great extent to analyze the large sets of data created and perform high-throughput analysis of the molecules. Integrated omics approach that combines data from other disciplines such as genomics, metabolomics, lipidomics would help us to build multi-modal platforms for early diagnosis, prognosis, therapeutic selection of patients with sepsis. Once such data is available and is validated in a large cohort of population, we could have a panel of molecular markers to diagnose, predict sepsis progression and identify population who would benefit from targeted treatment strategies. The next big task would be to make it commercially available at bedside that could help us in guide real-time patient management. Future research would continue in this direction, as we sail through the unchartered waters in search of the magic bullet.

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