HHS Public Access

Author manuscript

Curr Opin Pediatr. Author manuscript; available in PMC 2020 June 01.

Published in final edited form as:

Curr Opin Pediatr. 2019 June ; 31(3): 322–327. doi:10.1097/MOP.0000000000000753.

Precision medicine in pediatric sepsis

Mihir R. Atreya, MD, MPH[1] and **Hector R. Wong, MD**[1,2]

[1]Division of Critical Care Medicine, Cincinnati Children's Hospital Medical Center, Cincinnati, OH, USA

[2]Department of Pediatrics, University of Cincinnati College of Medicine, Cincinnati, OH, USA

Abstract

Purpose of review: Pediatric sepsis is a heterogeneous state associated with significant morbidity and mortality, but treatment strategies are limited. Clinical trials of immunomodulators in sepsis have shown no benefit, despite having a strong biological rationale. There is considerable interest in application of a precision medicine approach to pediatric sepsis to identify patients who are more likely to benefit from targeted therapeutic interventions.

Recent findings: Precision medicine requires a clear understanding of the molecular basis of disease. 'Omics data' and bioinformatics tools have enabled identification of endotypes of pediatric septic shock, with corresponding biological pathways. Further, using a multi-biomarker based approach, patients at highest risk of poor outcomes can be identified at disease onset. Enrichment strategies, both predictive and prognostic, may be used to optimize patient selection in clinical trials, and identify a sub-population in whom a therapy of interest may be trialed. A bedside to bench to bedside model may offer clinicians pragmatic tools to aid in decision making.

Summary: Precision medicine approaches may be used to sub-classify, risk-stratify, and select pediatric patients with sepsis who may benefit from new therapies. Application of precision medicine will require robust basic and translational research, rigorous clinical trials, and infrastructure to collect and analyze big data.

Keywords

precision medicine; personalized medicine; pediatric sepsis; pediatric septic shock

Introduction:

Pediatric sepsis is a leading cause of infant and child morbidity and mortality across the world.[1] The prevalence of pediatric sepsis has increased over the past two decades,[2] and an increasing number of pediatric patients have co-morbid conditions.[1] Over time, mortality from pediatric sepsis has greatly decreased with vaccines, antibiotics, and supportive care. Contemporary data approximate mortality from pediatric severe sepsis to be 8–10%.[2]

Corresponding author: Hector R. Wong, MD, Cincinnati Children's Hospital Medical Center, Division of Critical Care Medicine, MLC2005, 3333 Burnet Avenue, Cincinnati, OH, 45229, USA, Tel: 513-636-4259, Fax: 513-636-4267, Hector.Wong@cchmc.org.

Conflict of interest: Dr. Wong and Cincinnati Children's Hospital Medical Center hold United States patents for the PERSEVERE biomarkers and the endotyping strategy described in this manuscript.

Sepsis serves as the final common pathway for children suffering various infections, and is thought to be due to a dysregulated host response to an infectious agent. At present, diagnosis of pediatric sepsis still relies on systemic inflammatory response syndrome (SIRS) criteria and suspicion of infection.[3] This approach toward recognition of sepsis has high sensitivity, but suffers from a lack of specificity and does not identify the biological underpinnings leading to pathology. Thus sepsis and septic shock, as currently defined, represents a heterogeneous group of patients with varied underlying pathophysiological mechanisms.[4]

At present, the management of septic shock is limited to fluid resuscitation, supportive care, and achieving source control of infection. Over the last 5 decades, over 100 clinical trials to modulate the host response in sepsis have shown no benefit.[5] Given the underlying heterogeneity, it is conceivable that a subset of the population may benefit from a given therapy and another potentially harmed, contributing to a net equivocal effect. Furthermore, pediatric sepsis differs from adult sepsis, with developmental age playing a key role in the host response to sepsis,[6,7] and interventions that show promise in adults may not show similar results in pediatric patients.[8]

Precision medicine refers to approaches that match the ‘right treatment strategy’ to the ‘right patient group’. There is considerable interest in its application to pediatric sepsis to reduce associated morbidity and mortality.[9] This review provides a summary of research relying on systems biology and bioinformatics to enable use of precision medicine in pediatric sepsis. Sub-classification of pediatric sepsis, risk stratification, and enrichment strategies for enrollment in clinical trials are emphasized. Finally, challenges to the successful application of precision medicine in pediatric sepsis are highlighted.

Precision medicine versus personalized medicine:

Personalized and precision medicine refer to endeavors that seek to identify an individual’s inherent risk, including genetic and environmental factors, and customize therapies accordingly. To an extent, personalized medicine is practiced every day in the intensive care unit. Medical providers use clinical examination findings to identify groups of patients that may benefit from a given therapy. For instance, patients with delayed capillary refill and high diastolic blood pressures are considered to have ‘cold shock’, and patients with flash capillary refill and low diastolic blood pressures are considered to have ‘warm shock’. Here, clinical exam findings are used as a surrogate for underlying pathophysiology- cold shock thought to be due to high systemic vascular resistance (SVR) and warm shock due to low SVR. Based on an underlying assumption, therapies are customized. For instance, milrinone, a vasodilator, may be considered in those with ‘cold shock’, and vasopressors such as norepinephrine or vasopressin may be considered for patients with ‘warm shock’.

The term precision medicine is preferred over personalized medicine, with a concern that the latter could be misinterpreted to imply therapies that are customized to an individual patient, rather than a groups of individuals.[10] This approach has been effective in development of growing number of therapeutic and biological agents against other heterogeneous groups of diseases such as cancer.[11, 12] Use of precision medicine in critical illness, such as sepsis,

however poses unique challenges. The dynamic and multi-directional nature of host immune response in sepsis, evolution of gene expression profiles over time in the same patient, and the limited window of opportunity between detection and outcome during which a intervention may be instituted are particularly daunting.[13]

Review of literature:

Precision medicine requires a clear understanding of the molecular basis of disease. Recent developments in systems biology have equipped us with tools to begin to disentangle the complex interconnected phenomenon at a cellular/sub-cellular level. 'Omics data' has enabled us to gain new insights into the pathobiology of pediatric sepsis. Transcriptomics or gene expression analysis relies of the identification of differences in the complete set of mRNA transcripts produced by the genome using high throughput methods such as microarray or RNA-seq. Genomics refers to the study of the entire genome, proteomics refers to the study of proteins in cell/tissue, and metabolomics refers to the study of small cell metabolites in cell/tissue/body fluid.[14] The exponential growth of data produced from these fields necessitates advanced statistical and bioinformatics tools to meaningfully interpret data. An unbiased analysis of such datasets may facilitate generation of hypothesis and identification of novel pathways that can be subject to further study.

Transcriptomics:

Over a decade ago, using discovery-oriented transcriptomics, whole blood RNA was first used to identify genes that were up- and down-regulated in a cohort of pediatric patients with septic shock compared with normal controls.[15,16] These patients were also noted to have a unique gene expression signature compared to those who meet SIRS criteria without infection or those with sepsis but without evidence of shock.[17]

By utilizing bioinformatics tools, 100 genes with the strongest predictive value were used to identify subclasses of pediatric septic shock (subclass A,B, and C).[18–20] A large proportion of genes corresponded to pathways related to the adaptive immune system and the glucocorticoid receptor pathway, and found to be repressed in patients categorized as subclass A.[18] Others genes repressed corresponded to zinc homeostasis[18] and mitochondrial genes.[21] These patients were noted to be phenotypically distinct; patients belonging to subclass A were younger, had higher illness severity, lower co-morbidity, and independently associated with increased risk of complicated course (defined as persistence of two or more organ failure at Day 7 of septic shock or 28-day mortality).[18, 20]

The identification of endotypes-a subset of a disease state based on pathophysiological mechanism, may assist in identifying patients who are more suited for a particular treatment.[22] By using a multiplex messenger RNA quantification platform (NanoString, Seattle, WA) and computer-assisted image analysis, pediatric septic shock patients were classified into two endotypes (endotype A and B), that corroborate with above mentioned subclasses.[23] In recent iterations, the process of identifying endotypes has been further simplified, and utilizes as few as 4 genes.[24] Patients categorized as endotype A, relative to endotype B, were noted to have repression of genes corresponding to glucocorticoid receptor signaling, and

use of adjunctive corticosteroids in this group was associated with a 4-fold increase in mortality.[23] Endotypes may also evolve and switch during critical illness. Pediatric patients who have persistence of endotype A were noted to have a higher risk of poor outcomes.[25]

Analogous sepsis endotypes have been identified in adults by making use of inter-individual variations in host response to sepsis.[26] There exists a weak positive correlation between sepsis response signatures in adults (SRS1 and SRS2) and pediatric endotypes (A and B).[27] The lack of substantial overlap between adults and children likely reflect developmental differences in host response. However, a combination of the two approaches may provide age-dependent prognostic information. Pooled analysis of adults and pediatric datasets have led to the identification of unique subtypes of sepsis.[28] Other research groups have had yet different approaches to transcriptomic data; using analytic tools, researchers have sought to identify new molecular targets[29] and dysregulated pathways at the individual level.[30]

Genomics:

Several gene association studies have evaluated single nucleotide polymorphisms (SNPs) in pediatric sepsis and septic shock, and have been previously summarized.[31] Genome-wide association studies (GWAS), examine a large number of SNPs simultaneously, and identify common variants associated with specific disease states.[32] GWAS studies conducted in neonates with sepsis have been unable identify any SNPs with genome wide significance.[33]

While no gene association study has to date altered the care of patients in the pediatric intensive care unit (PICU), these types of studies remain an important avenue to explore mechanistic pathways. In a recent study, Walley and colleagues evaluated the role of proprotein convertase subtilisin/kexin 9 (PCSK9), a regulator of lipid metabolism, and found that in adults with septic shock, subjects with at least one loss-of-function (LOF) variant of the PCSK9 gene were noted to have a survival benefit.[34] However, in pediatric patients with septic shock, the association appears to be reversed,[35] and presents an opportunity to conduct further experimental studies.

Study of genetic polymorphisms may also serve as a tool to infer causality in observational studies of biomarkers in sepsis, and identify pathways amenable to targeted therapies.[36] Instrument variable analysis and specifically Mendelian randomization make use of genetic variants that are associated with exposure of interest to infer causality between exposure and outcome. Because genetic variants are determined at gametogenesis and not associated with confounding factors, differences in outcome are attributed to the exposure of interest.[37]

Metabolomics:

Nuclear magnetic resonance (NMR) spectroscopy based metabolomics have been used to segregate survivors and non-survivors of pediatric septic shock, in addition to identifying distinct metabolic profiles of patients with septic shock, SIRS, and healthy controls.[38] Similar methods have been used in neonates.[39] A combined metabolomics and inflammatory protein mediator based approach has been proposed that may help risk stratify patients and predict which patients will require care in the PICU.[40]

Proteomics:

Recent studies have used proteomic approaches to differentiate late onset neonatal sepsis where clinical diagnosis remains a challenge.[41] If validated, such an approach may serve to improve clinical decision making by helping in early and accurate diagnosis and targeting high risk infants.

Integrated omics approach:

Emerging fields of such as epigenomics, microbiomics, and lipidomics hold promise. Recently, an 'integrated omics' approach has been proposed, wherein data from multiple complementary sources are used to understand biological pathways holistically, which may otherwise be lost in one-dimensional analyses, and ultimately help drive drug discovery.[42] Additionally, pharmacogenomics and pharmacometabolomics may help decipher variation in response to drug therapies.

Risk stratification:

Currently available physiological scoring tools that incorporate clinical and laboratory parameters approximate illness severity but provide little information about risk of poor outcome at disease onset. Biomarkers are defined as accurate and reproducible tests, performed on bodily fluids, which provide clinicians with an objective assessment of the patients' health, disease, or response to a therapeutic intervention.[43] Broadly, they may be classified as diagnostic, monitoring, stratification, and surrogate biomarkers. A review of biomarkers in pediatric sepsis have been previously published.[44–46] Of those used in clinical practice, C-reactive protein, procalcitonin, and lactate are used as diagnostic and monitoring biomarkers.[44]

Stratification biomarkers may help identify patients and highest risk of poor outcome. Taken alone, any given biomarker may provide limited information. A combination of biomarkers may provide a more comprehensive understanding of patients' inherent risk. Based on the previously described transcriptomic studies,[15,16,18] multiple serum protein biomarkers with known biological mechanism were used to derive and validate a risk stratification tool to identify pediatric patients with septic shock with highest risk of 28 day mortality – PERSEVERE (Pediatrics Sepsis Biomarker Risk Model).[47] PERSEVERE was noted to provide more information than existing physiology based scoring system[48] and have also been validated for use in patients with distinct clinical phenotypes of septic shock.[49] Subsequent versions which included mRNA biomarkers in addition have been able to improve the performance of this risk stratification tool.[50]

Enrichment:

The selection of patients with heterogeneous disease, such as sepsis, for enrollment in clinical trials of therapeutic interventions remains a significant challenge. Enrichment strategies refer to efforts to select a study population in which a drug or an intervention is more likely to be effective, as compared to an unselected population.[51] Broadly, enrichment strategies may be classified as predictive and prognostic. Predictive enrichment refers to the

selection of patients who are more likely to respond to an intervention based on underlying biology. This requires an understanding of causal mechanisms and limited by extant knowledge of disease. Prognostic enrichment refers to the selection of patients who are at higher risk of disease related event. For instance, patients at risk of sepsis related organ dysfunction or mortality.[51]

A combination of predictive and prognostic enrichment can help optimize patient selection. Where biologically appropriate, targeted therapies may be used in selected high risk patients. Subjects deemed to have low risk of disease-related events may be randomized to receive standard care. In a proof of concept study, such an approach was deployed to identify a subset of pediatric septic shock patients who may respond to corticosteroids.[52] For predictive enrichment, based on gene-expression analysis each patient was allocated to one of 2 septic shock endotypes. For prognostic enrichment, the PERSEVERE biomarker risk model was used to estimate a baseline mortality probability for each patient. In this cohort, in patients with endotype B and intermediate to high PERSEVERE based mortality, the use of corticosteroids was independently associated with a more than 10 fold reduction in risk of complicated course. It is important to note that use of PERSEVERE alone in prior studies was not able to detect benefit of steroids in the study population.[53] If validated in clinical trials, such a strategy may help provide definitive answers to important questions in the field.

Challenges to precision medicine in pediatric sepsis:

Application of precision medicine approach in pediatric sepsis requires simultaneous advancement in three interconnected areas –pre-clinical studies, clinical trials, and implementation science.[54] Robust basic and translational research is necessary to identify novel molecular targets. Rigorous clinical trials in humans are required to test safety and efficacy of new therapies. Infrastructure to collect, analyze and store big data, to conduct clinical trials, and implement scientific advances into practice will be essential.

A key challenge to application of precision medicine in pediatric sepsis is the time frame within which clinicians must reach an accurate diagnosis and identify patients most likely to benefit from an intervention. Molecular diagnostics hold promise in rapid diagnosis of infection.[55] With gene-expression data becoming available within a matter of hours, this approach may help provide clinicians with real time data.[23] Further gene-expression mosaics that provide ‘heat maps’ may enable clinicians to visually predict endotypes with a reasonable degree of confidence.[55, 56]A bedside to bench to bedside approach may offer clinicians pragmatic tools to aid in decision making

Conclusions:

Precision medicine approaches in pediatric sepsis aim to identify patients who are most likely to benefit from a potential therapeutic intervention. Based on perturbations in shared biological pathways, groups of patients may be sub-classified into endotypes and those at risk of poor outcomes identified. Finally, select patients based on their inherent risk may be subject to receive therapeutic interventions in clinical trials. Successful application of precision medicine in clinical practice will require rigorous testing and validation.

Acknowledgements:

none

Financial support and sponsorship:

NIH R35 GM126943, R01 GM108025, R21 HD092896

References and recommended reading:

Papers of interest, within the annual period of review, have been highlighted as:

* of special interest

** of outstanding interest

1. Weiss SL, Fitzgerald JC, Pappachan J, et al. Global epidemiology of pediatric severe sepsis: the sepsis prevalence, outcomes, and therapies study. Am J Respir Crit Care Med. 2015;191(10):1147–1157. doi:10.1164/rccm.201412-2323OC [PubMed: 25734408]
2. Hartman ME, Linde-Zwirble WT, Angus DC, Watson RS. Trends in the epidemiology of pediatric severe sepsis*. Pediatr Crit Care Med J Soc Crit Care Med World Fed Pediatr Intensive Crit Care Soc. 2013;14(7):686–693. doi:10.1097/PCC.0b013e3182917fad
3. Goldstein B, Giroir B, Randolph A, International Consensus Conference on Pediatric Sepsis. International pediatric sepsis consensus conference: definitions for sepsis and organ dysfunction in pediatrics. Pediatr Crit Care Med J Soc Crit Care Med World Fed Pediatr Intensive Crit Care Soc. 2005;6(1):2–8. doi:10.1097/01.PCC.0000149131.72248.E6
4. Iskander KN, Osuchowski MF, Stearns-Kurosawa DJ, et al. Sepsis: multiple abnormalities, heterogeneous responses, and evolving understanding. Physiol Rev. 2013;93(3):1247–1288. doi:10.1152/physrev.00037.2012 [PubMed: 23899564]
5. Marshall JC. Why have clinical trials in sepsis failed? Trends Mol Med. 2014;20(4):195–203. doi:10.1016/j.molmed.2014.01.007 [PubMed: 24581450]
6. Wynn JL, Cvijanovich NZ, Allen GL, et al. The influence of developmental age on the early transcriptomic response of children with septic shock. Mol Med Camb Mass. 2011;17(11–12):1146–1156. doi:10.2119/molmed.2011.00169 [PubMed: 21738952]
7. Raymond SL, López MC, Baker HV, et al. Unique transcriptomic response to sepsis is observed among patients of different age groups. PloS One. 2017;12(9):e0184159. doi:10.1371/journal.pone.0184159 [PubMed: 28886074] * This is a pooled analysis of transcriptomic datasets that shows differences in host response to sepsis among patients of different age groups
8. Nadel S, Goldstein B, Williams MD, et al. Drotrecogin alfa (activated) in children with severe sepsis: a multicentre phase III randomised controlled trial. Lancet Lond Engl. 2007;369(9564):836–843. doi:10.1016/S0140-6736(07)60411-5
9. Coopersmith CM, De Backer D, Deutschman CS, et al. Surviving Sepsis Campaign: Research Priorities for Sepsis and Septic Shock. Crit Care Med. 2018;46(8):1334–1356. doi:10.1097/CCM.0000000000003225 [PubMed: 29957716]
10. Toward Precision Medicine: Building a Knowledge Network for Biomedical Research and a New Taxonomy of Disease. Washington, D.C.: National Academies Press; 2011. doi:10.17226/13284
11. Jackson SE, Chester JD. Personalised cancer medicine. Int J Cancer. 2015;137(2):262–266. doi:10.1002/ijc.28940 [PubMed: 24789362]
12. Roper N, Stensland KD, Hendricks R, Galsky MD. The landscape of precision cancer medicine clinical trials in the United States. Cancer Treat Rev. 2015;41(5):385–390. doi:10.1016/j.ctrv.2015.02.009 [PubMed: 25864024]
13. Maslove DM, Wong HR. Gene expression profiling in sepsis: Timing, tissue, and translational considerations. Trends Mol Med. 2014;20(4):204–213. doi:10.1016/j.molmed.2014.01.006 [PubMed: 24548661]

14. Wafi A, Mirnezami R. Translational -omics: Future potential and current challenges in precision medicine. Methods San Diego Calif. 2018;151:3–11. doi:10.1016/j.ymeth.2018.05.009

15. Wong HR, Shanley TP, Sakthivel B, et al. Genome-level expression profiles in pediatric septic shock indicate a role for altered zinc homeostasis in poor outcome. Physiol Genomics. 2007;30(2): 146–155. doi:10.1152/physiolgenomics.00024.2007 [PubMed: 17374846]

16. Cvijanovich N, Shanley TP, Lin R, et al. Validating the genomic signature of pediatric septic shock. Physiol Genomics. 2008;34(1):127–134. doi:10.1152/physiolgenomics.00025.2008 [PubMed: 18460642]

17. Wong HR, Cvijanovich N, Allen GL, et al. Genomic expression profiling across the pediatric systemic inflammatory response syndrome, sepsis, and septic shock spectrum. Crit Care Med. 2009;37(5):1558–1566. doi:10.1097/CCM.0b013e31819fcc08 [PubMed: 19325468]

18. Wong HR, Cvijanovich N, Lin R, et al. Identification of pediatric septic shock subclasses based on genome-wide expression profiling. BMC Med. 2009;7:34. doi:10.1186/1741-7015-7-34 [PubMed: 19624809]

19. Wong HR, Wheeler DS, Tegtmeyer K, et al. Toward a clinically feasible gene expression-based subclassification strategy for septic shock: proof of concept. Crit Care Med. 2010;38(10):1955–1961. doi:10.1097/CCM.0b013e3181eb924f [PubMed: 20639748]

20. Wong HR, Cvijanovich NZ, Allen GL, et al. Validation of a gene expression-based subclassification strategy for pediatric septic shock. Crit Care Med. 2011;39(11):2511–2517. doi: 10.1097/CCM.0b013e3182257675 [PubMed: 21705885]

21. Weiss SL, Cvijanovich NZ, Allen GL, et al. Differential expression of the nuclear-encoded mitochondrial transcriptome in pediatric septic shock. Crit Care Lond Engl. 2014;18(6):623. doi: 10.1186/s13054-014-0623-9

22. Lötvall J, Akdis CA, Bacharier LB, et al. Asthma endotypes: a new approach to classification of disease entities within the asthma syndrome. J Allergy Clin Immunol. 2011;127(2):355–360. doi: 10.1016/j.jaci.2010.11.037 [PubMed: 21281866]

23. Wong HR, Cvijanovich NZ, Anas N, et al. Developing a Clinically Feasible Personalized Medicine Approach to Pediatric Septic Shock. Am J Respir Crit Care Med. 2015;191(3):309–315. doi: 10.1164/rccm.201410-1864OC [PubMed: 25489881]

24. Wong HR, Sweeney TE, Lindsell CJ. Simplification of a Septic Shock Endotyping Strategy for Clinical Application. Am J Respir Crit Care Med. 2017;195(2):263–265. doi:10.1164/rccm. 201607-1535LE [PubMed: 28084830] ** This study highlights the ability to streamline the identification of pediatric septic shock endotypes. Four genes were sufficient to sub-classify patients with sepsis.

25. Wong HR, Cvijanovich NZ, Anas N, et al. Endotype Transitions During the Acute Phase of Pediatric Septic Shock Reflect Changing Risk and Treatment Response. Crit Care Med. 2018;46(3):e242–e249. doi:10.1097/CCM.0000000000002932 [PubMed: 29252929] ** This study demonstrates temporal changes in endotypes of pediatric septic shock. Patients demonstrate considerable switch in endotypes between day 1 and day 3 of sepsis.

26. Davenport EE, Burnham KL, Radhakrishnan J, et al. Genomic landscape of the individual host response and outcomes in sepsis: a prospective cohort study. Lancet Respir Med. 2016;4(4):259–271. doi:10.1016/S2213-2600(16)00046-1 [PubMed: 26917434]

27. Wong HR, Sweeney TE, Hart KW, Khatri P, Lindsell CJ. Pediatric Sepsis Endotypes Among Adults With Sepsis. Crit Care Med. 2017;45(12):e1289–e1291. doi:10.1097/CCM. 0000000000002733 [PubMed: 28991828] * This study compares pediatric and adult transcriptomic approaches in adults with sepsis

28. Sweeney TE, Azad TD, Donato M, et al. Unsupervised Analysis of Transcriptomics in Bacterial Sepsis Across Multiple Datasets Reveals Three Robust Clusters. Crit Care Med. 2018;46(6):915–925. doi:10.1097/CCM.0000000000003084 [PubMed: 29537985] * This is a pooled analyses of transcriptomic datasets that includes children and adults with sepsis

29. Li Y, Li Y, Bai Z, Pan J, Wang J, Fang F. Identification of potential transcriptomic markers in developing pediatric sepsis: a weighted gene co-expression network analysis and a case–control validation study. J Transl Med. 2017;15. doi:10.1186/s12967-017-1364-8 [PubMed: 28100276] * This study uses analytic tools to identify novel transcriptomic markers

30. Li B, Zeng Q. Personalized identification of differentially expressed pathways in pediatric sepsis. Mol Med Rep. 2017;16(4):5085–5090. doi:10.3892/mmr.2017.7217 [PubMed: 28849000] * This study uses statistical tools to identify dysregulated pathways at individual level

31. Wong HR. Genetics and genomics in pediatric septic shock. Crit Care Med. 2012;40(5):1618–1626. doi:10.1097/CCM.0b013e318246b546 [PubMed: 22511139]

32. Kingsmore SF, Lindquist IE, Mudge J, Gessler DD, Beavis WD. Genome-wide association studies: progress and potential for drug discovery and development. Nat Rev Drug Discov. 2008;7(3):221–230. doi:10.1038/nrd2519 [PubMed: 18274536]

33. Srinivasan L, Page G, Kirpalani H, et al. Genome-wide association study of sepsis in extremely premature infants. Arch Dis Child Fetal Neonatal Ed. 2017;102(5):F439–F445. doi:10.1136/archdischild-2016-311545 [PubMed: 28283553]

34. Walley KR, Thain KR, Russell JA, et al. PCSK9 is a critical regulator of the innate immune response and septic shock outcome. Sci Transl Med. 2014;6(258):258ra143. doi:10.1126/scitranslmed.3008782

35. Atreya M, Wong HR. PCSK9 gene variants and septic shock outcomes in a pediatric cohort In: Basic/Translational Reseach Critical Care, Pediatric Academic Societies. San Francisco, CA; 2017.

36. Trinder M, Genga KR, Kong HJ, et al. Cholesteryl Ester Transfer Protein Influences High-Density Lipoprotein Levels and Survival in Sepsis. Am J Respir Crit Care Med. 10 2018. doi:10.1164/rccm.201806-1157OC

37. Eckerle M, Ambroggio L, Puskarich M, et al. Metabolomics as a Driver in Advancing Precision Medicine in Sepsis. Pharmacotherapy. 2017;37(9):1023–1032. doi:10.1002/phar.1974 [PubMed: 28632924] * This is a review of metabolomics research in sepsis

38. Mickiewicz B, Vogel HJ, Wong HR, Winston BW. Metabolomics as a novel approach for early diagnosis of pediatric septic shock and its mortality. Am J Respir Crit Care Med. 2013;187(9):967–976. doi:10.1164/rccm.201209-1726OC [PubMed: 23471468]

39. Fanos V, Caboni P, Corsello G, et al. Urinary 1H-NMR and GC-MS metabolomics predicts early and late onset neonatal sepsis. Early Hum Dev. 2014;90:S78–S83. doi:10.1016/S0378-3782(14)70024-6 [PubMed: 24709468]

40. Mickiewicz B, Thompson GC, Blackwood J, et al. Development of metabolic and inflammatory mediator biomarker phenotyping for early diagnosis and triage of pediatric sepsis. Crit Care Lond Engl. 2015;19:320. doi:10.1186/s13054-015-1026-2

41. Chatziioannou AC, Wolters JC, Sarafidis K, et al. Targeted LC-MS/MS for the evaluation of proteomics biomarkers in the blood of neonates with necrotizing enterocolitis and late-onset sepsis. Anal Bioanal Chem. 2018;410(27):7163–7175. doi:10.1007/s00216-018-1320-3 [PubMed: 30141021]

42. Langley RJ, Wong HR. Early Diagnosis of Sepsis: Is an Integrated Omics Approach the Way Forward? Mol Diagn Ther. 2017;21(5):525–537. doi:10.1007/s40291-017-0282-z [PubMed: 28624903] ** This is an excellent review of ‘omic’ approaches in sepsis and highlights the need for integration of datasets.

43. Strimbu K, Tavel JA. What are Biomarkers? Curr Opin HIV AIDS. 2010;5(6):463–466. doi:10.1097/COH.0b013e32833ed177 [PubMed: 20978388]

44. Standage SW, Wong HR. Biomarkers for pediatric sepsis and septic shock. Expert Rev Anti Infect Ther. 2011;9(1):71–79. doi:10.1586/eri.10.154 [PubMed: 21171879]

45. Sandquist M, Wong HR. Biomarkers of sepsis and their potential value in diagnosis, prognosis and treatment. Expert Rev Clin Immunol. 2014;10(10):1349–1356. doi:10.1586/1744666X.2014.949675 [PubMed: 25142036]

46. Jacobs L, Wong HR. Emerging infection and sepsis biomarkers: will they change current therapies? Expert Rev Anti Infect Ther. 2016;14(10):929–941. doi:10.1080/14787210.2016.1222272 [PubMed: 27533847]

47. Wong HR, Salisbury S, Xiao Q, et al. The pediatric sepsis biomarker risk model. Crit Care Lond Engl. 2012;16(5):R174. doi:10.1186/cc11652

48. Wong HR, Weiss SL, Giuliano JS, et al. Testing the prognostic accuracy of the updated pediatric sepsis biomarker risk model. PloS One. 2014;9(1):e86242. doi:10.1371/journal.pone.0086242 [PubMed: 24489704]

49. Wong HR, Cvijanovich NZ, Anas N, et al. PERSEVERE-II: Redefining the pediatric sepsis biomarker risk model with septic shock phenotype. Crit Care Med. 2016;44(11):2010–2017. doi: 10.1097/CCM.0000000000001852 [PubMed: 27513537]

50. Wong HR, Cvijanovich NZ, Anas N, et al. Improved Risk Stratification in Pediatric Septic Shock Using Both Protein and mRNA Biomarkers. PERSEVERE-XP. Am J Respir Crit Care Med. 2017;196(4):494–501. doi:10.1164/rccm.201701-0066OC [PubMed: 28324661] ** This study incorporates mRNA biomarkers to PERSEVERE and demonstrates an improved ability to risk stratify pediatric patients with septic shock.

51. Wong HR. Intensive care medicine in 2050: precision medicine. Intensive Care Med. 2017;43(10): 1507–1509. doi:10.1007/s00134-017-4727-y [PubMed: 28236258] ** This is a review of enrichment strategies for enrollment in clinical trials.

52. Wong HR, Atkinson SJ, Cvijanovich NZ, et al. Combining prognostic and predictive enrichment strategies to identify children with septic shock responsive to corticosteroids. Crit Care Med. 2016;44(10):e1000–e1003. doi:10.1097/CCM.0000000000001833 [PubMed: 27270179]

53. Atkinson SJ, Cvijanovich NZ, Thomas NJ, et al. Corticosteroids and pediatric septic shock outcomes: a risk stratified analysis. PloS One. 2014;9(11):e112702. doi:10.1371/journal.pone. 0112702 [PubMed: 25386653]

54. Seymour CW, Gomez H, Chang C-CH, et al. Precision medicine for all? Challenges and opportunities for a precision medicine approach to critical illness. Crit Care Lond Engl. 2017;21(1):257. doi:10.1186/s13054-017-1836-5* This is a review of challenges to application of precision medicine in critical illness

55. Riedel S, Carroll KC. Early Identification and Treatment of Pathogens in Sepsis: Molecular Diagnostics and Antibiotic Choice. Clin Chest Med. 2016;37(2):191–207. doi:10.1016/j.ccm. 2016.01.018 [PubMed: 27229637]

Key Bullet Points

- Advances in systems biology, bioinformatics, and availability of ‘omics’ data have enabled the use of a precision medicine approach to pediatric sepsis.
- Based on shared biological pathways, distinct endotypes or subclasses of pediatric septic shock can be identified.
- Pediatric sepsis patients can be risk stratified at disease onset by utilizing a multi-biomarker model.
- Prognostic and predictive enrichment strategies can be used to optimize selection of patients in clinical trials of adjunctive therapies in pediatric sepsis.
- Application of precision medicine will require robust basic and translational science, rigorous clinical trials, and infrastructure to collect and analyze big data.