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# Precision Medicine in the Pediatric Cardiac Intensive Care Unit

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## Abstract

Advances in structural and functional genomics have paved the way for precision medicine in critically ill children. Patients with congenital heart disease are especially susceptible to various critical pathophysiologic states as they navigate the challenges of palliative and reparative cardiac surgeries. In addition to the stress of cardiopulmonary bypass, they also experience sepsis and acute respiratory distress syndrome which contributes to the overall morbidity and mortality. Enhanced understanding of the genomic mechanisms associated with these critical illnesses can lead to future research aiding the development of a personalized care management approach for this high-risk subgroup of critically ill children.

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## Introduction

Precision medicine and genomics have changed the way we treat and stratify adults and children in the intensive care unit (ICU). With the advances in computational analytics, data mining, and cost reduction the use of genomics in heterogeneous diseases like sepsis and acute respiratory distress syndrome (ARDS) have shown promising results. Although up to 30% of children with congenital heart disease (CHD) have an underlying structural genetic disorder, there are limited functional genomic studies involving children with CHD when critically ill. In this commentary, we will discuss how functional genomics have advanced the pathophysiologic understanding of cardiopulmonary bypass (CPB), sepsis, ARDS, and future directions.

## Cardiopulmonary Bypass

CPB is an extracorporeal circulatory machine to sustain oxygen delivery to tissues during cardiac procedures. When plasma is exposed to the non-endothelial lining of the CPB circuit it activates the immune system and releases pro-inflammatory cytokines leading to fever, vasodilation, and capillary leak. In an attempt to restore the immune system to homeostasis, the compensatory anti-inflammatory response syndrome (CARS) is also triggered which can lead to immunosuppression and increased susceptibility to secondary infections [1]. Multiple studies that show characteristics of CARS such as low levels (<30%) of HLA-DR on circulating monocytes and low TNF – alpha on ex vivo stimulation are associated with postoperative infections and mortality [2,3]. Twenty-five percent of children with CHD have critical congenital heart disease (CCHD) and require cardiac surgery with CPB in the first few days of life. Transcriptomic data of neonates with hypoplastic left heart syndrome undergoing cardiac surgery with CPB show an altered inflammatory response when pre and post-CPB samples were compared. Patients who develop postoperative low cardiac output syndrome (LCOS) had differential regulation of inflammatory pathways (IL signaling, PDGF, NOTCH1, NGF, GPCR) and metabolic pathways (heme metabolism, oxidative phosphorylation, protein metabolism including amino acid and derivatives, fatty acid metabolism, TCA cycle, and respiratory electron transport chain) (Figure 1), compared to those who did not develop LCOS [4]. Neonates requiring CPB have the challenge of an immature immune system that has a reduced inflammatory response to pro-inflammatory triggers (i.e. CPB) and reduced neutrophil chemotaxis towards lipopolysaccharides increasing the chances of infection postoperatively [5]. In addition, the first 3 months of life have proven to be critical for naïve B cells, natural killer (NK) cells, and dendritic cells as they converge to an adult-like phenotype, and environmental exposures can imprint on these cells and lead to alterations of the immune system later in life [6]. Given the significant immunologic overlap between CPB and sepsis, we postulate the way the immune system responds to CPB may be an indication of how the immune system will respond when stressed (i.e., sepsis). Further genomic studies can help identify which children have an immunosuppressive response to CPB which can help stratify high-risk children and attempt immunostimulatory therapy.

## Sepsis

Sepsis is an imbalance of the immune system in response to infection that leads to organ failure. Similar to the response to CPB, individuals with sepsis have a hyper inflammatory response followed by CARS and can later lead to a persistent inflammatory/immunosuppressed and catabolism syndrome (PICS). The molecular heterogeneity of sepsis

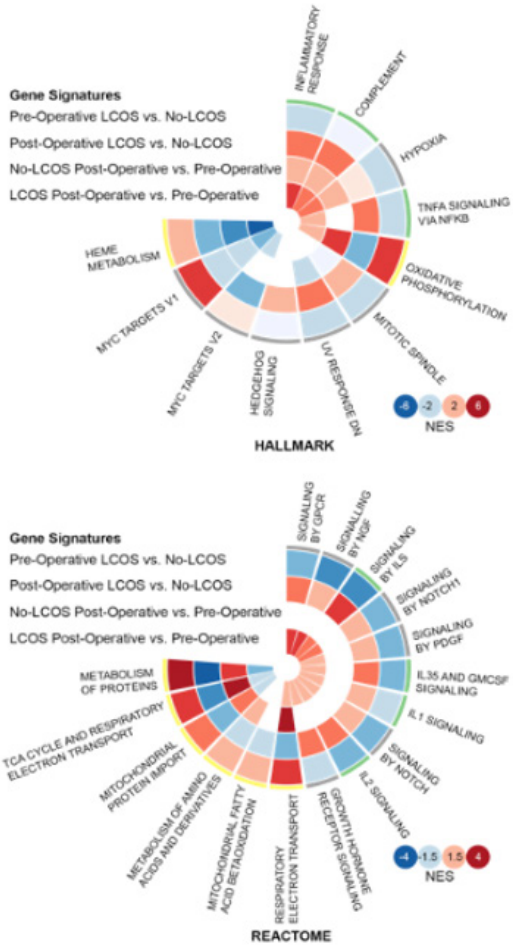


**Figure 1:** HALLMARK an REACTOME pathways showing Normalized Enrichment Scores (NES) of various pathophysiological pathways. From outside of circle to the inside: outermost circle compares NES scores in Pre-Operative samples of patients who developed LCOS vs No-LCOS, the next circle compares NES scores in Post-Operative samples of patients who developed LCOS vs patients who did not, the next inner circle compares NES scores between Pre and Post-Operative samples of patients who did not develop LCOS, the innermost circle compares NES scores between Post-Operative and Pre-Operative samples of patients who developed LCOS. (Total n=13 patients with 2 sample from each patient [pre-operative and post-operative]).

has led to many genomic studies to help classify endotypes within sepsis and improve early identification and management. Sweeney et al pooled data from 14 bacterial sepsis transcriptomic datasets (n = 700) from 8 different countries and developed and validated a 33-messenger RNA profile to distinguish 3 sepsis endotypes: inflammopathic, coagulopathic, and adaptive [7]. The coagulopathic endotype demonstrated the highest mortality in both bacterial and viral (COVID-19) sepsis. On the contrary, the adaptive endotype had the lowest mortality and the least number of clinical manifestations. Of the 14 datasets (n = 700), 5 datasets (n =236) were solely in children, with the largest study including 188 children admitted to the paediatric intensive care for sepsis or septic shock. Using transcriptomic analysis, two paediatric sepsis endotypes were identified using only 4 genes (JAK2, PRKCB, SOS2, and LYN). Endotype A showed increased odds of mortality and independently showed corticosteroid use had higher odds of mortality. In addition, Wong HR, et al. (2017) developed a transcriptomic model to predict acute kidney injury (AUC 0.95), renal replacement therapy, and renal recovery [8-10]. Consistent with the concept of balancing the immune system when suffering from sepsis, Burnham KL, (2017) et al. collected serial samples on days 1, 3, and 5 and found 46% of patients oscillated from sepsis response 1 (SRS1) to sepsis response 2 (SRS2) [11]. Determining whether sepsis is in the hyper inflammatory phase or the immunosuppressed phase will be highly important to try therapeutic interventions like GM-CSF. These sepsis endotypes and prediction models can help with prognostic enrichment for clinical trial enrollment and predictive enrichment for immunomodulatory therapies in the future.

## Acute Respiratory Distress Syndrome

ARDS is an acute lung injury leading to respiratory failure from fluid-filled alveoli causing oxygenation issues. Common etiologies for development of ARDS in paediatric cardiac ICU are pneumonia, aspiration, sepsis and CPB. The heterogeneity of ARDS is significant and separate severity scores have been developed for both adults and children given the vast differences in epidemiology and pathophysiology [12]. In adults, the Berlin definition uses physiologic values to calculate the ratio of partial pressure of oxygen in arterial blood to fraction of inspired oxygen (P/F ratio). In children, the paediatric acute lung injury consensus conference (PALICC) definition is used which calculates the oxygenation index or oxygenation saturation index [13,14]. However, these severity scores do not inform clinicians about ongoing biologic processes occurring at the molecular level. Since there are no randomized controlled trials in children with ARDS, management has been extrapolated from adult literature. The ARDS Network trial showed low tidal volume (6 ml/kg) and minimizing plateau pressure (<30 mmHg) reduced mortality and ventilator days which has been the standard of care in the paediatric ICU for lung-protective ventilation. By adding genomics to the ARDS stratification, Calfee and colleagues identified two phenotypes for adult ARDS, one being a hyper inflammatory response which correlated with higher mortality [15]. They also found the hyper inflammatory phenotype responded better to higher PEEP settings, resulting in less mortality, more organ failure free days, and more ventilator free days. Similarly, Yehya N, et al. (2020) derived 3 sub phenotypes in paediatric ARDS with differing mortality rates and immune responses [16]. As we start using ARDS phenotypes in clinical trials, recommendations about ventilator strategies and neuromuscular blockade may change.

## Future Directions

More genomic studies are needed in the ICU to enhance our understanding of the underlying pathophysiology when critically ill and develop novel therapeutic interventions. Functional genomic studies will augment both prognostic and predictive enrichment thereby improving patient selection for clinical trials and optimizing selective therapies. As we continue to collect more data and validate results, rapid analysis for endotype stratification will allow genomics to be used by clinicians at the bedside as a point of care test. Incorporating epigenetics into these studies would be useful to determine which environmental exposure is causing harm or benefit. Lastly, systematic review and meta-analyses of the publicly available genomic data on the NCBI GEO database can potentially identify novel pathophysiologic pathways associated with various critical illnesses in children, paving way for future therapeutic interventions.

## References

1. Bronicki RA, Hall M (2016) Cardiopulmonary bypass-induced inflammatory response: Pathophysiology and treatment. Pediatr Crit Care Med 17: S272-S278. https://doi.org/10.1097/PCC.0000000000000759

2. Cornell TT, Sun L, Hall MW, Gurney JG, Ashbrook MJ, et al. (2012) Clinical implications and molecular mechanisms of immunoparalysis after cardiopulmonary

bypass. J Thorac Cardiovasc Surg 143: 1160-1166. https://doi.org/10.1016/j.jtcvs.2011.09.011

3. Allen ML, Peters MJ, Goldman A, Elliott M, James I, et al. (2002) Early postoperative monocyte deactivation predicts systemic inflammation and prolonged stay in pediatric cardiac intensive care. Crit Care Med 30: 1140-1145. https://doi.org/10.1097/00003246-200205000-00031

4. Jain PN, Robertson M, Lasa JJ, Shekerdemian L, Guffey D, et al. (2021) Altered metabolic and inflammatory transcriptomics after cardiac surgery in neonates with congenital heart disease. Sci Rep 11: 1. https://doi.org/10.1038/s41598-021-83882-x

5. Raymond SL, López MC, Baker HV, Larson SD, Efron PA, et al. (2017) Unique transcriptomic response to sepsis is observed among patients of different age groups. PLoS One 12: e0184159. https://doi.org/10.1371/journal.pone.0184159

6. Olin A, Henckel E, Chen Y, Lakshmikanth T, Pou C, et al. (2018) Stereotypic immune system development in newborn children. Cell 174: 1277-1292. https://doi.org/10.1016/j.cell.2018.06.045

7. Sweeney TE, Azad TD, Donato M, Haynes WA, Perumal TM, et al. (2018) Unsupervised analysis of transcriptomics in bacterial sepsis across multiple datasets reveals three robust clusters. Crit Care Med 46: 915. https://doi.org/10.1097/CCM.0000000000003084

8. Stanski NL, Stenson EK, Cvijanovich NZ, Weiss SL, Fitzgerald JC, et al. (2020) PERSEVERE biomarkers predict severe acute kidney injury and renal recovery in pediatric septic shock. Am J Respir Crit Care Med 201: 848-855. https://doi.org/10.1164/rccm.201911-2187OC

9. Wong HR, Sweeney TE, Lindsell CJ (2017) Simplification of a septic shock endotyping strategy for clinical application. Am J Respir Crit Care Med 195: 263-265. https://doi.org/10.1164/rccm.201607-1535LE

10. Stanski NL, Wong HR (2020) Prognostic and predictive enrichment in sepsis. Nat Rev Nephrol 16: 20-31. https://doi.org/10.1038/s41581-019-0199-3

11. Burnham KL, Davenport EE, Radhakrishnan J, Humburg P, Gordon AC, et al. (2017) Shared and distinct aspects of the sepsis transcriptomic response to fecal peritonitis and pneumonia. Am J Respir Crit Care Med 196: 328-339. https://doi.org/10.1164/rccm.201608-1685OC

12. Wilson JG, Calfee CS (2020) ARDS subphenotypes: Understanding a heterogeneous syndrome. Crit Care 24: 1-8. https://doi.org/10.1186/s13054-020-2778-x

13. Orloff KE, Turner DA, Rehder KJ (2019) The current state of pediatric acute respiratory distress syndrome. pediatr allergy. Immunol Pulmonol 32: 35-44. https://doi.org/10.1089/ped.2019.0999

14. Smith LS, Zimmerman JJ, Martin TR (2013) Mechanisms of acute respiratory distress syndrome in children and adults: a review and suggestions for future research. Pediatr Crit Care Med 14: 631-643. https://doi.org/10.1097/PCC.0b013e318291753f

15. Calfee CS, Delucchi K, Parsons PE, Thompson BT, Ware LB, et al. (2014) Subphenotypes in acute respiratory distress syndrome: Latent class analysis of data from two randomised controlled trials. Lancet Respir Med 2: 611-620. https://doi.org/10.1016/S2213-2600(14)70097-9

16. Yehya N, Varisco BM, Thomas NJ, Wong HR, Christie JD, et al. (2020) Peripheral blood transcriptomic sub-phenotypes of pediatric acute respiratory distress syndrome. Crit Care 24: 681. https://doi.org/10.1186/s13054-020-03410-7