SEARCHING FOR A PEDIATRIC SEVERE SEPSIS PHENOTYPE: WE MIGHT INDEED BE THERE

Hector R. Wong, MD
Division of Critical Care Medicine, Cincinnati Children’s Hospital Medical Center and Cincinnati Children’s Research Foundation, Department of Pediatrics, University of Cincinnati College of Medicine, Cincinnati, OH

Dear Editor

The recent editorial in PCCM by Drs. Workman and Larsen (1) provides an opportunity to clarify recent efforts to develop stratification strategies for children with severe sepsis. The editorial is correct in stating that our discipline needs clinical tools to identify children at risk for poor outcome from severe sepsis “before it is too late, so that the inevitable never happens.”

The Pediatric Sepsis Biomarker Risk Model (PERSEVERE) uses a panel of five biomarkers to estimate baseline mortality risk among children with severe sepsis (2, 3). The editorial describes the PERSEVERE biomarkers as being “genomic”. This descriptor implies that the biomarkers reflect gene variants and genetic predisposition to illness severity. This is imprecise. The PERSEVERE biomarkers are proteins measured from blood samples. As such, they provide a global signal of the host response to severe sepsis to reliably and reproducibly estimate mortality risk. Further, the biomarkers are measured during the first 24 hours of presentation with severe sepsis, a clinically relevant time point for mortality risk stratification. While some of the almost 800 subjects studied thus far may have been children in whom there was delayed recognition of severe sepsis, they all nonetheless reflect our real world patients who would benefit from early mortality risk stratification.

Distinct from PERSEVERE, there is a strategy to endotype children with severe sepsis (4). Endotypes are biologically defined subclasses of clinical syndromes that differentiate a heterogeneous cohort based on differing molecular pathobiology. Pediatric severe sepsis endotypes “A” and “B” are defined by a 100-gene expression signature. Analogous to PERSEVERE, the endotyping genes are measured within the first 24 hours of a severe sepsis diagnosis and they reflect gene expression in response to severe sepsis, rather than gene variants per se and genetic predisposition to more severe illness. Allocation to endotype A is independently associated with mortality and greater organ failure burden, even after accounting for age, illness severity, and co-morbidity burden. Because the endotyping genes reflect adaptive immunity and glucocorticoid receptor signaling, endotyping has the potential to go beyond mortality risk stratification; it can potentially inform therapeutic...
decisions. Indeed, prescription of corticosteroids is independently associated with increased odds of poor outcome among endotype A patients (4). Conversely, when endotyping is combined with PERSEVERE-based mortality risk stratification, there is an identifiable group of children who might benefit from corticosteroids (5).

Thank you to Drs. Workman and Larsen. Their well-written editorial provides an ideal forum to clarify the intent and details of recent efforts to stratify children with severe sepsis.

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**References**


