spectrum of VEGF influences on other organs and tissues will have to be considered to minimize the risks of systemic side effects (13, 14). It will also be important to understand the intrinsic mechanism for the elevation of VEGF_{165b} protein in the demonstrated absence of an elevation in the corresponding mRNA, because therapeutic modulation of the natural pathway of VEGF_{165b} elevation may arguably allow for a more controlled intervention than external delivery. This report also demonstrates that lung fibroblasts are responsive to stimulation with VEGF variants, despite decreased expression of VEGF receptor proteins in patients with IPF and nonexpression of receptor 2, which is commonly considered to be the most active VEGF receptor. The mechanisms through which the variants exert their actions in fibroblasts each need to be characterized, and the possibility of differential use of the receptors by splice variants in a disease-related fashion needs to be considered.

It remains to be seen whether further work will lead to a realistic therapeutic modality based on manipulation of VEGF-A isoforms, but Barratt and colleagues have succeeded in substantially expanding our understanding of IPF pathophysiology by outlining the contributions of nonvascular effects of VEGF-A isoforms (12). ■

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A Biosignature Predicting Complicated Course in Children Presenting with Septic Shock Why PERSEVERE?

Severe sepsis and septic shock have been identified in approximately 3% of children hospitalized at major U.S. pediatric centers, and sadly, more than 8% of those children died (1). If results of a blood test could be obtained on the first hospital day of septic shock diagnosis to consistently and accurately predict mortality, how would this test influence clinical practice? In this issue of the *Journal*, Wong and colleagues (pp. 494–501) show that their Pediatric Sepsis Biomarker

Risk Model (PERSEVERE) (2) had improved mortality risk stratification after incorporating information on mRNA expression levels of four additional genes (3). The improved PERSEVERE-XP had excellent ability to discriminate between survival and death, with an area under the receiver operator characteristic curve of 0.85–0.95 and replication in a smaller independent test cohort (3).

Mortality risk stratification across groups of patients has been used for decades in pediatric critical care for quality benchmarking purposes (4). Use of composite biomarker scores to influence

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individual patient care, however, requires a higher level of precision, validity, and reliability (5). This goal is unlikely to be attainable in patients with sepsis, given the heterogeneity introduced by infectious etiologies, patient characteristics, and variability in care delivery. PERSEVERE-XP's positive likelihood ratio for identifying 28-day all-cause mortality in children during their first 24 hours of hospitalization for septic shock was only 5; it accurately predicted death in 27/29 fatalities, but falsely predicted death in 66 survivors (3). It was a useful predictor of survival, however, with a positive likelihood ratio of 11. Survival prediction could be helpful for reassuring overwhelmed parents, and for excluding patients from interventions with high risk for potential harm.

For the original PERSEVERE (2), from 80 genes associated with mortality from mRNA expression data, they tested 12 related proteins with biological support for association with sepsis pathophysiology that could be measured in sera. Five of these (C-C motif chemokine ligand 3, heat shock protein 70, IL-8, granzyme B, and matrix metalloproteinase 8) plus age composed PERSEVERE (6). A temporal model called tPERSEVERE was later developed using biomarker values on the first and third day of septic shock presentation to predict "complicated course," defined as persistence of two or more organ failures on Day 7 or death within 28 days (7). However, validation of tPERSEVERE in an independent cohort failed; investigation revealed two septic shock endotypes characterized by excessive inflammation and by immune suppression. Because assessment of performance of PERSEVERE in multiorgan failure (MOF) endotypes revealed good performance in thrombocytopenia-associated MOF (TAMOF), but poorer performance in MOF without thrombocytopenia, PERSEVERE-II incorporated platelet count (8).

Wong and colleagues used a data-driven restricted strategy (9) to choose among the 68 septic shock-associated genes not previously tested, for evaluation for inclusion in PERSEVERE-XP. Gene network analysis identified 18 genes associated with the highest scoring pathway connected to the pleiotropic transcription factor tumor protein 53 (*TP53*) that they chose for further testing (3). Because they could not test protein levels of these genes, mRNA expression levels were tested using a classification and regression tree (CART). Those that improved the performance of PERSEVERE were included. In PERSEVERE-XP, Wong and colleagues have identified a collection of features, or a biosignature (10), detectable on the admission day of children presenting with septic shock that is associated with overall 28-day all-cause mortality. This biosignature includes expression levels of four genes associated with DNA damage repair and/or with destruction of irreversibly damaged cells (3). Therefore, in some children, the response to cellular damage on their admission day could portend their ultimate survival.

Sepsis is a construct with an evolving consensus-based definition that includes invasive infection along with varying degrees and types of organ dysfunction (11, 12). Biomarkers and scores that diagnose the degree of organ dysfunction (e.g., creatinine, lactate, oxygenation index, Pediatric Risk of Mortality III score) on admission may accurately predict worse outcome, but are unlikely to identify new biological pathways or treatment targets. Although the score incorporating thrombocytopenia (PERSEVERE-II) performed almost as well as XP (3) in stratifying mortality, platelet count is a diagnostic biomarker of hematologic organ failure and is

therefore part of MOF diagnosis (13). Incorporation of organ failure-related biomarkers for identification of sepsis-related endotypes, however, might eventually substratify patients for precision therapies. In adult patients with acute respiratory distress syndrome, for example, Calfee and colleagues identified a hyperinflammatory subphenotype that may have influenced a patient's response to a ventilator strategy (14). The ability to predict future complications in patients with sepsis, such as development of secondary infections, may also eventually lead to preventive interventions (15).

Although 90% of the children in the PERSEVERE-XP cohort survived, MOF persisted for 7 or more days in more than half of these children. Those falsely predicted to die had a significantly worse number and persistence of organ failures. Markedly decreasing septic shock-related pediatric mortality will always be a goal, but speeding up organ recovery in survivors and improving their longer-term outcome could also be achievable. Aside from supportive care, there are currently no therapies shown to improve pediatric sepsis outcomes. To move the field forward, it is essential to better understand the biologic processes underlying and driving persistence of organ damage. PERSEVERE-XP offers new insight into the pathophysiology of pediatric septic shock. With further work, the novel *TP53*-related associations could lead to development of theranostics, molecular diagnostic markers to ultimately guide treatment decisions. ■

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