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DOI: 10.1097/PCC.0000000000002433

The authors reply:

The coronavirus disease 2019 (COVID-19) pandemic has stretched institutional resources in some locations necessitating novel solutions. Our recent article (1), published in *Pediatric Critical Care Medicine*, perspective provided guidance to adapt PICUs to care for infected adults. Rodriguez-Rubio et al (2) highlight an important alternative role for pediatric intensivists outside the PICU in supporting adult ICUs in the fight against the COVID-19 pandemic. Pediatric intensivists are comprehensively trained in principles of critical care (e.g., respiratory physiology and mechanical ventilation) which can be easily transposed to adult patients making them qualified to oversee care in an adult ICU as described (2). Our recent perspective (1) should provide pediatric providers with clinical guidance important in caring for adult patients with COVID-19 and highlight common adult situations rarely encountered in pediatrics. This guidance can be applied in an adult or pediatric hospital. A number of the issues raised by Christian and Kissoon (3) can be overcome if pediatric intensivists oversee the care of adults with COVID-19 in a primary adult setting.

This appears to be the strategy used in Spain and Italy (2). An interesting alternative recently reported (4) is the care of adults with COVID-19 within a PICU located in a primarily adult hospital. In these situations, the hospitals had in place the supplies and systems needed to care for adults. Likewise, there exist academic pediatric hospitals which are connected by halls or bridges to adult centers readily permitting the use of adult consultants and equipment/supplies overcoming many of the challenges pointed out by Christian and Kissoon (3). We agree with these authors that these approaches are preferred prior to bringing adults into a PICU where the care of adults is uncommon.

In a COVID-19 surge, one must consider whether the scarcity lies in trained personnel or appropriately equipped critical care settings, or both. Admitting adults to a PICU in a children's hospital is sensible when ICU equipped spaces with optimal monitoring, gases, vacuum, etc. are scarce. This avoids creating ad hoc ICUs in schools or stadiums which have been proposed for surge capacity but have clear limitations. Adults brought to a pediatric setting may benefit from services uncommon in adult hospitals such as pet, art, music, and "child life" therapies and rooms designed to permit a family member to remain during the hospitalization. Thousands of adults have

died in heartbreaking isolation from their loved ones without any form of solace in their final days—a situation rarely permitted in pediatric hospitals.

A "one size fits all approach" is unlikely to be universally effective or feasible during this pandemic. However, the pandemic does provide an opportunity to consider related non-pandemic patient care issues such as where and how to care for adults with congenital heart disease, cystic fibrosis, sickle cell, or muscular dystrophies where pediatric providers/hospitals may have greater expertise. We appreciate the innovative approaches and dedication exhibited by our colleagues in Spain and Italy as they bravely confront this pandemic and prove that pediatric intensivists can save lives regardless of the age.

The authors have disclosed that they do not have any potential conflicts of interest.

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DOI: 10.1097/PCC.0000000000002517

Pediatric Sepsis: Subphenotypes to Enrich Clinical Trial Entry Criteria

To the Editor:

We read with great interest the article by Carcillo et al (1) published in a recent issue of *Pediatric Critical Care Medicine*. Studies with biomarkers in adults with sepsis and acute respiratory distress syndrome (ARDS) have shown that identification of specific subphenotypes could lead to a better identification of patients that could be more responsive to interventions. In ARDS, a combination of biomarkers and clinical data improved the understanding of the patient profiles and may influence entry criteria of clinical trials. Recent trials support that the presence of ARDS subphenotypes may demand distinct treatment approaches, regarding, for example, fluid management or other specific therapies (2). In Statins for Acutely Injured Lungs for Sepsis study (3), two subphenotypes (hyper-inflammatory subphenotype or not) were tested for distinct treatment response to statin. Although the use of statin did not show treatment effect, hyper-inflammatory subphenotype patients had higher mortality

and validated subphenotypes previously described and their usefulness for patients' stratification. More recently, Seymour et al (4) analyzed more than 20,000 adult patients deriving different sepsis subphenotypes, and the results suggested that these subtypes may help to comprehend the distinct responses to treatments and outcomes.

Carcillo et al (5) previously hypothesized that three inflammatory phenotypes tested in the adult population could be applied to pediatric patients. In a prospective cohort multicenter study, published in 2017, they compared children with severe sepsis with one of these three phenotypes: 1) immunoparalysis-associated multiple organ failure (MOF); 2) thrombocytopenia-associated MOF; and 3) sequential MOF with hepatobiliary dysfunction; to children with severe sepsis and none of these phenotypes, hypothesizing that these phenotypes were associated to higher inflammation and worst outcomes, but this hypothesis had to be still confirmed in other multicenter studies of pediatric MOF patients. In 2016, Manzoli et al (6) had already showed that early MOF and later immunoparalysis were associated with worst outcomes, higher incidence of nosocomial infections, and death in septic pediatric patients. This phenotyping could be used in randomized controlled trial for earlier-outcome assessment and randomization could focus on more severe patients with worse outcomes.

Carcillo et al (1) also described other interesting findings of this very well designed study, including evaluation of non-specific biomarkers that have been used for a long time in the assessment of septic patients, such as C-reactive protein (CRP) and ferritin, incorporated into phenotypic evaluation. The authors found higher CRP and ferritin levels in children with MOF and any of the phenotypes (and worse outcomes) when compared with MOF patients without any phenotype. These results corroborate previous literature. Our research group published recently (7) a prospective cohort of septic children showing that patients with worse outcomes had higher CRP and Pediatric Logistic Organ Dysfunction scores than the ones with better outcomes. Therefore, CRP, an old and nonexpensive biomarker, available in most units, can be a good prognosis marker too, especially when dynamically evaluated and associated with other biomarkers. Also, another prospective pediatric sepsis cohort has shown that higher serum ferritin values were significantly associated with unfavorable outcomes (8). This leads us to think that stratification of patients may be feasible at the bedside and be remembered and encouraged, even in low- and medium-resource settings.

The phenotyping of patients through the use of biomarkers gives us, not only a path for future trials, but also the possibility of stratifying patients to predict outcomes and to implement earlier clinical management and individualized treatment, in an attempt to improve outcomes in pediatric sepsis.

The authors have disclosed that they do not have any potential conflicts of interest.

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DOI: 10.1097/PCC.0000000000002422

The authors reply:

We thank our Brazilian colleagues for their supportive letter by Lanzotti and Salluh (1) highlighting and endorsing the evolving research paradigm shift to considering pediatric sepsis-induced multiple organ failure as a group of targetable inflammation pathobiology phenotypes rather than a “one size fits all” monolithic syndrome highlighted in our recent article published in *Pediatric Critical Care Medicine* (2). Management of pediatric septic shock has long been based on targeting hemodynamic subphenotypes related to hypovolemia, euvolemia, or fluid overload; normal, hypodynamic, or hyperdynamic cardiac function; vasodilation, vasoconstriction, or normal systemic vascular resistance; high lactatemia or normal lactatemia; and compensated (normotensive) or uncompensated (hypotensive) shock. We previously showed that managing these targetable subtypes with the goal of maintaining central venous oxygen saturation greater than 70% reduced mortality from pediatric septic shock from 42% to 11% (3). In our ongoing investigations, we ask whether we can have further survival effects on the remaining 11% who die of multiple organ failure by targeting inflammation subphenotypes (2)?