

insufficient; long-term survival with adequate functional and neurodevelopmental outcome is more important.

Understanding the epidemiology and consequences of nosocomial infection is the first step toward improving outcomes. In order to do this effectively, reliable definitions must be established and used consistently. Prospective, multicenter studies can then be conducted using shared protocols which may help identify preventive and treatment strategies. There are a number of aspects of contemporary ECMO which could be improved with such an approach. The principal complications which need to be addressed in infants are hematologic in nature, such as thrombosis and hemolysis. In adolescents and adult patients, nosocomial infection is arguably more important, particularly during venoarterial ECMO. There is little reason to believe that multicenter collaborative efforts could not attempt to address both simultaneously. Nonetheless, children receiving ECMO for congenital heart disease, particularly those who recently underwent cardiac surgery, have a number of unique characteristics which are likely to affect their risk factors for infection and subsequent outcomes. It is important that this group is studied separately. The pediatric cardiac critical care community is well placed to do so as we aim to tailor effective infection prevention strategies to each child's unique clinical profile.

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Pediatric Sepsis in the Time of Coronavirus Disease 2019*

Humanity, like armies in the field, advances at the speed of the slowest.—Gabriel Garcia Marquez, *Love in the Time of Cholera* (1)

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The volume of data and studies on coronavirus disease 2019 (COVID-19) disease caused by the novel coronavirus severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has grown at a pace as unprecedented as the pandemic itself. Statistics and findings change weekly. Although pediatric cases have thankfully remained a small minority (1.7–2%) of overall worldwide COVID-19 cases (2), the potential for severe illness in children remains and grows. Rapidly published

pediatric case series have identified severe critical COVID-19–related illnesses associated with primary SARS-CoV-2 infection and findings consistent with a phenotype of pediatric sepsis or septic shock (3). In addition, a small but growing number of pediatric patients have demonstrated a form of hyperinflammatory multiple organ involvement suggestive of postinfectious host involvement with SARS-CoV-2. This entity, termed pediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2 (PIMS-TS) (4) or multisystem inflammatory syndrome in children (MIS-C) (5, 6), can bear varying features suggestive of Kawasaki disease or toxic shock syndrome. PIMS-TS or MIS-C heralds a separate potential pediatric sepsis phenotype.

Description of these COVID-19–related findings comes on the heels of the recent publication of the long-awaited Surviving Sepsis Campaign (SSC) International Guidelines for the Management of Septic Shock and Sepsis-associated Organ Dysfunction in Children (7). These guidelines provide the most detailed and evidence-based review to date on the diagnosis and management of pediatric sepsis. The guidelines were developed to provide consistency in the care of pediatric sepsis, an entity still associated with high morbidity and mortality worldwide (8, 9). In this issue of *Pediatric Critical Care Medicine*, authors of the pediatric SSC guidelines have now quickly stepped in to review

*See also p. e1031.

Key Words: coronavirus disease 2019; multisystem inflammatory syndrome in children; pediatric inflammatory multisystem syndrome temporally associated with severe acute respiratory syndrome coronavirus 2; pediatric sepsis; surviving sepsis

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the veritable whirlwind of adult and pediatric publications on data, case series and therapeutic interventions, and provide recommendations for COVID-19 management (10). The perspectives from the SSC task force authors from assessment of non-COVID-19 sepsis are quite valuable in assessing the new sepsis manifestations of the pandemic. The authors' conclusions are clear: care for COVID-19 sepsis should primarily follow management principles of other causes of pediatric sepsis.

The most important application of the SSC guidelines is the reminder that recognition of sepsis is the primary step of management. Sepsis still may present in subtle and nonspecific manner in children. Although COVID-19 has captured the diagnostic eye of clinicians worldwide, the fact remains that non-COVID sepsis still likely outnumbers COVID-19 sepsis by over 10 to 1 (10). Weiss et al (10) nicely compare and contrast characteristics of COVID-19 sepsis, PIMS-TS/MIS-C, and non-COVID-19 sepsis in Table 1. They also emphasize the impact of COVID-19 on the multiple indirect effects of the virus' toll in increasing the number of sepsis cases worldwide (11).

The basics of sepsis management remain the same, regardless of the etiology. The authors emphasize that the six key SSC guideline management steps should be followed. They emphasize management of hypoxemia as this may be more common in acute COVID-19 illness, but of course just as important to address in non-COVID-19 illness. SSC guidelines on fluid administration and management still pertain, with no evidence of differing approaches, whether COVID or non-COVID.

The taskforce authors also encourage attention to obtaining cultures and beginning antibiotics until bacterial cultures return negative in patients with suspected COVID-19 sepsis. Amid so much attention to COVID-19, we must remain vigilant to the "horses" that presage the relative zebra of COVID-19. Potential misdiagnosis of other treatable conditions has already been reported (12). Most importantly, a primary bacterial infection remains the most common cause of pediatric sepsis. Given current provider focus toward the potential presence of COVID-19, the authors caution against premature exclusion of alternative or concurrent pathogens for which early antimicrobial therapy is critical and for which evidence of outcome benefit is greatest in the SSC guidelines (7). One must also remain vigilant for a treatable coinfection (13). Approximately half of COVID-19 pediatric patients in one recent Chinese study had either bacterial or viral coinfection (14).

The recommendations for management of sepsis-associated myocardial dysfunction in the SSC guidelines remain the same for acute COVID-19 infection. However, the prevalence of myocardial dysfunction in COVID-19 sepsis and PIMS-TS/MIS-C may be greater than in non-COVID-19 sepsis, as noted by higher reported levels of troponin and brain natriuretic peptide (15). Therefore, earlier attention to diagnostic cardiac evaluation in sepsis patients in this era is in order.

The authors briefly note the plethora of efforts that have been rapidly implemented as therapies in COVID-19 sepsis, including remdesivir, corticosteroids, convalescent plasma (16), IV immunoglobulins, plasma exchange (17), and other therapies. These efforts have varying levels of evidence and experience to support them, and they wisely refrain from recommendations.

They also emphasize consultation with infectious disease and other subspecialists to determine the best current adjunctive approaches and the importance of clinical trial enrollment.

We are reminded amid this pandemic battle that the most useful weapons for COVID-19 sepsis remain those proven for broader use. In the time of COVID-19, the "slowest" measures in our armamentarium remain our surest.

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