2016 Update for the *Rogers' Textbook of Pediatric Intensive Care*: Recognition and Initial Management of Shock

Julie C. Fitzgerald, MD, PhD[1]; Scott L. Weiss, MD, MSCE[1]; Niranjan Kissoon, MD[2]

Objective: To review important articles in the field of pediatric shock and pediatric septic shock published subsequent to the Fifth Edition of the *Rogers' Textbook of Pediatric Intensive Care*.

Data Sources: The U.S. National Library of Medicine PubMed (www.ncbi.nlm.nih.gov/pubmed) was searched for combination of the term "pediatric" and the following terms: "sepsis, septic shock, shock, antibiotics, extracorporeal membrane oxygenation, and steroid." The abstract lists generated by these searches were screened for potential inclusion. The authors were also aware of a number of key recent articles in pediatric shock, and these were also screened.

Study Selection and Data Extraction: Promising articles published subsequent to the fifth edition of the textbook were included based on the consensus of the authors and via the peer review process.

Data Extraction: Articles were grouped by category. Each author was assigned categories and extracted data from articles in that category. All authors contributed to final review of extracted data.

Data Synthesis: Articles in the following categories were included: epidemiology and recognition of shock; laboratory markers of shock; antimicrobial therapy; vasoactive therapy; extracorporeal therapies; mortality patterns, prediction, and risk stratification; bundled approaches to shock recognition and management; and corticosteroid use.

Conclusion: Research efforts in pediatric shock have largely centered on pediatric septic shock, with significant progress in the understanding of sepsis epidemiology, the use of extracorporeal therapies in critically ill children with sepsis, the role of hyperlactatemia and risk stratification in pediatric septic shock, and the impact of bundled care for pediatric sepsis, including evaluation of individual bundle elements such as the optimal timing of antibiotic administration and vasoactive medication choice. A consistent theme in the literature is the beneficial role of a bundled approach to septic shock recognition and management to improve both care and outcomes. (*Pediatr Crit Care Med* 2016; 17:1073–1079)

Key Words: emergency management; pediatric critical illness; sepsis

This article contributes to a series of updates to the Fifth Edition of *Rogers' Textbook of Pediatric Intensive Care*. Only articles published subsequent to the fifth edition and thought to advance our understanding and approach to pediatric shock care were considered in this review. Thus, this targeted review is not meant to be comprehensive but to inform readers of developments that may further our understanding or dictate a change in practice. Based on our review and the article intent, we found exciting, robust, and new information pertaining to the epidemiology and recognition of shock, largely centered on septic shock. Additionally, data have emerged to identify timing of death, gaps in care, and methods to risk stratify that may lead to more aggressive and earlier interventions.

Other exciting work provided new evidence in areas which we previously relied on consensus of experts only. For instance, the role of lactate in sepsis in children is now bolstered by studies pointing to its clinical role, while we have a better understanding of the alteration in mitochondrial function during sepsis. In addition, the timing of antimicrobial therapy and choice of vasoactive agents have now been supported by pediatric studies.

Recent evidence on predictors of mortality in both high- and low-resource utilization areas of the world allow us to better understand where targeted interventions may make a difference. In addition, our understanding of the role of extracorporeal therapies as well as the controversial use of corticosteroids in sepsis and septic shock are now being

[1]Department of Anesthesia and Critical Care, The Children's Hospital of Philadelphia, University of Pennsylvania Perelman School of Medicine, Philadelphia, PA.

[2]Department of Pediatrics, BC Children's Hospital and Sunny Hill Health Centre for Children, University of British Columbia, Vancouver, BC, Canada.

Dr. Weiss is funded by an NIGMS K award (K23GM110496) and has received honoraria for lectures from ThermoFisher Scientific. Dr. Kissoon has received funding from the Muskoka Project of the Canadian Government and Grand Challenges of Canada.

Dr. Weiss received funding from lecturing for ThermoFisher Scientific, and received royalties from Up-To-Date. The remaining authors have disclosed that they do not have any potential conflicts of interest.

For information regarding this article, E-mail: nkissoon@cw.bc.ca

DOI: 10.1097/PCC.0000000000000942

bolstered by some direct evidence. Furthermore, meticulous and robust quality improvement projects have elucidated some beneficial approaches to shock recognition and management. These include the use of rapid improvement cycles as well as electronic activation alerts and protocols. Finally, although not pediatric-specific, a comprehensive "roadmap for future research" in sepsis provides insight into how to unravel the pathobiology and address the thorny issues of sepsis recognition and management on a global scale (1).

EPIDEMIOLOGY AND RECOGNITION OF SHOCK

Several large studies have reported on the occurrence and outcomes of septic shock among children who require intensive care. The first study, by Schlapbach et al (2), examined 97,127 children younger than 16 years admitted to PICUs in Australia and New Zealand between 2002 and 2013. Patients were identified using diagnostic codes that have been implemented within the Australia and New Zealand Pediatric Intensive Care registry, and sepsis was defined using consensus criteria (3). Overall, 6.9% of patients had invasive infections, 2.9% had sepsis, and 2.1% had septic shock with the standardized frequency increasing over time in each category. Seventeen percent of the children with septic shock died, with a nonsignificant trend toward lower mortality over time. Notably, the combination of invasive infection, sepsis, and septic shock accounted for over one-quarter of all PICU deaths. In multivariable analyses, oncologic conditions, bone marrow transplantation, chronic neurologic disorders, and illness severity scores were independently associated with mortality.

The second was the Sepsis Prevalence, Outcomes, and Therapies (SPROUT) study, which was an international prospective point prevalence study conducted on 5 days throughout 2013–2014 at 128 sites in 26 countries (4). The SPROUT study prospectively screened 6,925 PICU patients using consensus criteria for severe sepsis and septic shock and found a prevalence of 8.2% (95% CI, 7.6–8.9%) and PICU mortality rate of 24%. Prevalence and mortality ranged 6–23% and 11–40%, respectively, across geographic regions. Seventeen percent of survivors exhibited at least new moderate disability at hospital discharge.

Similarly, using data from 43 U.S. children's hospitals in the Pediatric Health Information System (PHIS) database between 2004 and 2012, Ruth et al (5) reported a 7.7% prevalence of severe sepsis among PICU admissions with an associated mortality of 14.4%. Balamuth et al (6) also used 2004–2012 PHIS data to investigate hospital-wide sepsis prevalence and mortality using two different *International Classification of Diseases*, Ninth Revision, Clinical Modification code strategies, noting a seven-fold higher prevalence and three-fold lower mortality for patients identified using combination codes for infection plus organ dysfunction compared to sepsis-specific codes. For those patients with sepsis-specific codes, whom this same group has shown to be a more reliable indicator of true severe sepsis (7), mortality was 21.2%.

Together, these large epidemiologic studies highlight the persistent burden of septic shock among children requiring intensive care, with a mortality rate of 14–24% within PICUs that exceeds estimates from population-based registries and approaches ICU mortality rates reported in adults. In particular, the study by Balamuth et al (6) emphasizes that the more commonly reported pediatric sepsis mortality rates of 2–8% (8–10) are likely to be diluted by the inclusion of large numbers of children with mild sepsis who do not require critical care. Indeed, Kissoon and Uyeki (11) emphasized that sepsis-related pediatric deaths are likely to be substantially underestimated worldwide—especially in resource-limited settings—because childhood deaths due to infections outside of the neonatal period are currently categorized by infection type even though the unifying feature of nearly all of these deaths is that they are due to sepsis.

Neither of the two above studies accounted for sepsis- or shock-related deaths prior to hospital or PICU admission. Cvetkovic et al (12) studied 627 consecutive referrals of children up to age 16 years for severe sepsis/septic shock to a regional PICU transport service in North Thames, United Kingdom, between 2005 and 2011. Of the 130 children who died within 1 year of the initial referral, 55% died within 24 hours including half of these deaths occurring prior to PICU admission. The majority of these early deaths reflected unsuccessful shock resuscitation with cardiac arrest. Although the high occurrence of fulminant meningococcal septic shock in this study (one-third of deaths) may limit generalizability to other regions, the authors pointed out that delayed or inadequate resuscitation is problematic in many of these cases (13, 14). In addition, these findings raise concern that hospital-based epidemiologic studies and PICU-based interventional trials may inadvertently exclude many patients with fulminant shock at high risk for poor outcomes, and that future clinical trials, quality improvement efforts, and education need to be directed to the pre-PICU environment.

An ongoing challenge to the early recognition of septic shock in children is the lack of "gold-standard" criteria to define either sepsis or shock. In the SPROUT study, 31% of PICU patients diagnosed with severe sepsis or septic shock by the treating physician did not meet published consensus criteria for these conditions, even though mortality remained high at 17% for these patients (15). Recently, updated definitions and criteria were developed to better integrate sepsis pathobiology with content-valid clinical criteria for sepsis and septic shock in adults (16). Rather than using nonspecific systemic inflammatory response syndrome (SIRS) criteria, Sepsis-3 now recommends prompt evaluation for infection-induced organ dysfunction for adult patients with tachypnea, abnormal mentation, or hypotension. However, this approach has not yet been recommended for children and whether simplifying criteria to suspect sepsis can improve early recognition and enhance resuscitation in a manner that improves outcomes remains to be tested.

LABORATORY MARKERS OF SHOCK

The optimal marker to identify shock and determine response to resuscitative therapies remains controversial. While serial blood gas and lactate evaluations are widely used to compliment the clinical assessment of systemic perfusion, strong data supporting the utility of hyperlactatemia and lactate clearance in pediatric shock have been lacking. Two recent studies by Scott et al (17, 18) have shed additional light on the potential utility of lactate testing to aid physician diagnosis and management of shock in the emergency department setting. In a prospective cohort study of 239 children less than 19 years with SIRS, those with venous lactate greater than or equal to 4 mmol/L had a relative risk of 5.5 (95% CI, 1.9–16.0) of developing organ dysfunction within 24 hours of presentation and had a longer duration of organ dysfunction than patients without elevated lactate (median, 6 vs 2 d) (18). In a separate study, Scott et al (17) found that normalization of lactate to less than 2 mmol/L within 4 hours of septic shock presentation was associated with a lower adjusted risk of persistent organ dysfunction at 48 hours (adjusted risk ratio, 0.47 [0.29, 0.78]). However, lactate clearance of at least 10% over 2–4 hours was not associated with decreased organ dysfunction at 48 hours. Two important notes about the 2016 Scott et al (17) study are that 1) the overall median lactate level was relatively low at 2–3 mmol/L and 2) the subgroup with lactate normalization had a significantly lower initial median lactate compared to the nonnormalization group (2.0 vs 3.6 mmol/L) suggesting normalization was a potential surrogate for lower illness severity. Although these studies provide new data about the potential diagnostic and prognostic utility of lactate measurements in pediatric septic shock, there remain insufficient data testing lactate-guided shock resuscitation algorithms or comparison of lactate to more direct measures of cardiac output or regional blood flow assessments in children. Furthermore, even if hyperlactatemia does indicate a higher "relative" mortality risk, several studies have also shown unacceptably high mortality in children with septic shock without hyperlactatemia (19, 20).

The recently published updated definition of adult septic shock extends prior notions of septic shock as a state of acute circulatory failure to a condition with both circulatory and cellular metabolic abnormalities (16). Although Sepsis-3 recommends using hyperlactatemia to identify "cellular metabolic abnormalities" in adults, the task force conceded that blood lactate levels are unlikely to capture the complete picture of metabolic derangements in patients with shock. However, elevated lactate often represents an inability to cells to effectively utilize oxygen to make energy (adenosine triphosphate [ATP]) through mitochondrial aerobic metabolism. New pediatric data along these lines were provided by Weiss et al (21) by measuring direct alterations in mitochondrial respiration in peripheral blood mononuclear cells (PBMCs; lymphocytes and monocytes) from 13 children with septic shock and multiple organ dysfunction and 11 PICU controls without sepsis or organ dysfunction. This study demonstrated that bioenergetic reserve (i.e., ability of PBMCs to use oxygen to make ATP in response to a stress-induced increase in metabolic demand) was decreased and mitochondrial proton leak (i.e., oxygen utilization uncoupled from ATP production) was increased in septic shock. Decreased bioenergetic reserve also inversely correlated with central venous oxygen saturation. Furthermore, changes in mitochondrial membrane potential on day 1–2 were associated with duration of organ dysfunction. This small study supports the concept that cellular metabolic abnormalities are present in pediatric septic shock, though more study is needed to determine its contribution to shock-induced organ dysfunction and clinical outcomes. In adult septic shock, three recent large randomized trials found that universal central venous pressure (CVP)-, $Scvo_2$-, and lactate-guided therapy through a central venous catheter was not superior to standardized protocols with more selective measurement of these variables (22–24). Whether peripheral blood markers or other noninvasive hemodynamic or metabolic assessments will further improve resuscitation of shock in children is not yet clear.

ANTIMICROBIAL THERAPY

Adult literature and the Surviving Sepsis Campaign support rapid administration of antimicrobial therapy in septic shock. However, literature on the impact of shorter time to antimicrobial therapy on outcome in pediatric sepsis is limited. Two retrospective cohort studies performed in PICUs have now been published examining this question. Weiss et al (25) studied 130 patients with severe sepsis treated in a single PICU over a 1-year period. PICU mortality in the cohort was 12%. Median time from sepsis recognition to antimicrobial administration was 140 minutes, and 18% received antimicrobials in the first hour. After adjusting for severity of illness, the odds ratio (OR) of death at PICU discharge was 4.84 (95% CI, 1.45–16.20) for delays in antimicrobial administration greater than 3 hours. Antimicrobial delays greater than 3 hours were also associated with fewer organ failure-free days in this cohort, but not with ventilator-free days or PICU length of stay.

In contrast, van Paridon et al (26) did not find an association between timing of antimicrobial administration and outcome. This study examined 79 children treated in a single PICU meeting a pragmatic definition of sepsis. Included patients had SIRS, suspected or proven bacterial or fungal infection treated with antibiotics, and had an arterial or central venous line. A subset of 44 patients had septic shock, defined as an infusion of an inotrope or vasopressor. One-year mortality for the whole cohort was 6%. Median time from presentation to appropriate antimicrobial administration was 115 minutes, and 25% received antimicrobials in the first hour. There was no association between time to antimicrobials and PICU length of stay or 1-year mortality.

While the study by van Paridon et al (26) did not confirm the association seen by Weiss et al (25), this could be related to sample size, different inclusion criteria, and different primary outcome measures. Van Paridon et al (26) included a broader sample of patients with sepsis, whereas Weiss et al (25) focused only on severe sepsis with resulting discrepancies in mortality.

Additionally, in the van Paridon (26) study, patients expected to not survive more than 24 hours were excluded, which could have eliminated a subset of patients that might have been impacted by timing of antimicrobial administration. Further rigorous, prospective, multicenter study is needed regarding timing of antimicrobial therapy and outcomes in pediatric shock.

VASOACTIVE THERAPY

Multiple components of the recommended bundle of initial resuscitative care in pediatric shock (e.g., timing of antimicrobials, choice and volume of fluid resuscitation, and vasoactive infusion therapy) are based on expert opinion, extrapolation of adult data, and uncontrolled pediatric studies. A study by Ventura et al (20) offers new direct pediatric data. These authors performed a single center, double-blind, randomized controlled trial evaluating dopamine versus epinephrine as the first-line vasoactive infusion for fluid-refractory pediatric septic shock. This is the first randomized trial comparing initial choice of vasoactive infusions in pediatric septic shock. The study was done in a PICU in Brazil, and 120 children 1 month to 15 years old were enrolled and randomized. Patients with ongoing clinical signs of hypoperfusion after 40 mL/kg of fluid resuscitation were randomized to receive either dopamine (starting at 5 μg/kg/min and escalating in two dose increments to 10 μg/kg/min) or epinephrine (starting at 0.1 μg/kg/min and escalating in two dose increments to 0.3 μg/kg/min). Escalations were performed every 20 minutes if the patient's hemodynamics had not met protocolized targets until the maximum dose was reached. Open-label vasoactive medications were then added and titrated by the treating clinician if the patient remained unresponsive to study drug at the maximum dose.

Baseline characteristics in the two groups were similar. Mortality rate was lower in the epinephrine group (7%) than the dopamine group (14%; $p = 0.033$). The OR of death for patients in the dopamine group compared to the epinephrine group was 6.5 (95% CI, 1.1–37.8). Systolic blood pressure, mean arterial blood pressure (MAP), and MAP-CVP were higher in the epinephrine group at 6 hours after randomization and at the end of resuscitation, suggesting either that epinephrine is more effective than dopamine to reverse shock, or that achieving higher blood pressures during resuscitation, potentially explained more by differences in dose escalation rather than different drugs, may improve survival. There was also an increased odds of healthcare-associated infection in the dopamine group (OR, 67.7; 95% CI, 5.0–910.8). More hyperglycemia was seen in the epinephrine group. The study vasoactive medication was delivered either via peripheral IV catheter or intraosseous line while central venous access was secured. There were no extravasation injuries observed in either group. Although this study is limited by being performed at a single center and using a dose titration of vasoactive infusions that may not be equivalent across groups, the results are still compelling and warrant further study. The dose titration period was also aggressive, and patients unresponsive to escalating therapy after 60 minutes on the protocol were moved to open-label therapy. Interestingly, for those who required vasoactive medications in addition to the study drug, no additional dopamine was used.

The Vasoactive Inotrope Score (VIS) is a score that attempts to normalize dosages of different vasoactive infusions to enable comparison of degree of hemodynamic support between patients receiving different or multiple vasoactive medications. This score has been shown to be a predictor of morbidity and mortality after cardiopulmonary bypass surgery in children. Haque et al (27) retrospectively evaluated 71 children with fluid-refractory septic shock admitted to a PICU in Pakistan. In this cohort, higher VIS was associated with mortality, and all children with VIS greater than 20 died. The authors suggest that VIS is a simple tool that can be used as an outcome predictor, especially in resource-limited settings.

EXTRACORPOREAL THERAPIES

In 2009, the American College of Critical Care Medicine clinical practice parameters for hemodynamic support of pediatric septic shock were updated. The update included continued recommendation for consideration of extracorporeal membrane oxygenation (ECMO) support for refractory shock and a new recommendation for fluid removal through diuretics, peritoneal dialysis, or continuous renal replacement therapy (RRT) for those with signs of fluid overload once adequately fluid resuscitated. Ruth et al (28) performed a retrospective cohort study examining the outcomes of children with severe sepsis treated in PICUs at 43 children's hospitals in the PHIS database who were supported with ECMO or RRT. Overall hospital mortality was 47.8% for those supported with ECMO, 32.3% for those treated with RRT, and 58% for those receiving both therapies.

The authors found that patients with severe sepsis were more likely to receive ECMO support between 2009 and 2012 compared to 2004 through 2008 (OR, 1.18; 95% CI, 1.06–1.33), and a lower likelihood of receiving RRT in 2009–2012 compared to 2004–2008 (OR, 0.64; 95% CI, 0.59–0.69). They also found a 6% annual decrease in mortality in patients with severe sepsis treated with these extracorporeal therapies. A similar improvement in mortality was seen for the subset of patients with severe sepsis and malignancy treated with extracorporeal therapies. Mortality for patients with severe sepsis treated with ECMO correlated inversely with center volume of ECMO cases. These data are supportive of the idea that while the mortality remains high for patients with severe sepsis requiring extracorporeal support, steady improvement in outcomes is evident.

MORTALITY PREDICTION AND RISK STRATIFICATION

Early risk stratification using biomarkers is a promising method to identify patients at higher risk for morbidity and mortality who would be candidates for more aggressive interventions or for clinical trial enrollment. Acute kidney injury (AKI) is common in severe sepsis and associated with poor outcome. Wong

et al (29) measured AKI biomarkers in a derivation cohort of 241 children with septic shock and a separate test cohort of 200 children with septic shock to determine a risk stratification model using Classification and Regression Tree analysis. The model predicts septic AKI at day 3 of septic shock, and the authors postulate that identification of these at risk patients could inform clinical decision making.

The risk stratification final model included the presence of AKI on day 1, and biomarkers elastase 2, matrix metalloproteinase 8, and proteinase 3. In the test cohort, 29% of patients identified as at intermediate to high risk had septic AKI at day 3, versus only 2% of the patients identified as low risk by the model. The model had excellent performance in the derivation cohort (area under the curve [AUC] of 0.95 and sensitivity of 93%) and very good performance in the test cohort (AUC of 0.83 and sensitivity of 85%). In both cohorts, the model added to predictive ability of the presence of septic AKI on day 1. In the combined cohort (derivation and test cohorts), the model was more predictive of septic AKI on day 3 than other mortality prediction models (Pediatric Risk of Mortality or PEdiatRic SEpsis biomarkEr Risk modEl, a biomarker-based mortality prediction model), reflecting that the model developed was biologically plausible and predictive of AKI rather than a simple reflection of illness severity.

Early prediction of morbidity and mortality is important for risk stratification in patients with severe sepsis. It is well recognized that patients have not returned fully to baseline health at hospital discharge, and are at risk for subsequent rehospitalization and mortality. Determining factors that impact postdischarge mortality may help providers identify patients that would most benefit from close follow-up while recovering from sepsis.

Wiens et al (30) derived risk prediction models for postdischarge mortality in a population of 1,242 children in Uganda hospitalized for acute infections using readily measured variables. The final model for postdischarge mortality prediction included mid-upper arm circumference, time since last hospitalization, oxygen saturation, abnormal Blantyre Coma Scale score, and HIV-positive status. The AUC for mortality prediction was 0.82, and the authors estimated that 35% of children would be identified as high risk for mortality. Although the predictive model may not generalizable to more developed regions with different infectious disease patterns, this study exemplifies how region-specific predictors of postdischarge mortality may help to identify a vulnerable population for close follow-up to decrease long-term morbidity and mortality.

BUNDLED APPROACHES TO SHOCK RECOGNITION AND MANAGEMENT

Recognition and management bundles are increasingly being used to enhance resuscitation of pediatric septic shock. Although a bundled approach has been emphasized for adult septic shock through the Surviving Sepsis Campaign for several decades, the application of these bundles to pediatric patients has been less pervasive. In the last 5 years, several studies have demonstrated that a bundled approach to shock recognition and management can increase adherence to guidelines, decrease time to therapy, and improve outcomes in pediatric septic shock (10, 31, 32). For example, Paul et al (33) showed that improved adherence to a five-component sepsis bundle that included timely 1) recognition of septic shock, 2) vascular access, 3) administration of IV bolus fluid, 4) antibiotics, and 5) vasoactive agents (when necessary) within 60 minutes was associated with a decrease in mortality from 5% to 2%.

More recently, Balamuth et al (34) compared the sensitivity and specificity of routine physician judgment versus an automated electronic algorithmic alert to recognize children with severe sepsis/septic shock in a large academic pediatric emergency department. The electronic alert was based on vital signs, high-risk comorbid conditions, altered mentation, and abnormal perfusion. The electronic algorithmic alert was more sensitive (92.1%) than physician judgment (72.7%) but less specific, resulting in more than 3,000 false-positive sepsis activation alerts. The authors concluded that a routine alert embedded within the electronic health record may be best used to trigger a rapid bedside clinician assessment for sepsis in order to maximize sepsis recognition without overextending available resources. Similarly, Akcan Arikan et al (35) demonstrated that an electronic sepsis recognition alert combined with rapid clinician assessment and implementation of a protocolized resuscitation bundle was associated with a lower rate of AKI (54% preintervention vs 29% postintervention) and mortality (8.3% vs 1.7%). Along these lines, Tuuri et al (36) demonstrated that a similar approach using a paper-based septic shock screening tool at emergency department triage could also improve time to critical interventions when coupled with rapid bedside clinician assessment of positive screens for continuation of a septic shock resuscitation bundle. This may be a more feasible approach at smaller institutions with fewer information technology resources.

Two recent studies highlight the role that simulation can play in improving recognition and resuscitation of pediatric shock. Investigators from International Network for Simulation-Based Pediatric Innovation, Research and Education and Improving Pediatric Acute Care Through Simulation demonstrated high variability in adherence to pediatric guidelines across pediatric emergency department teams using a simulated case of an infant in septic shock (37). Notably, teams with greater composite experience achieved the highest guideline adherence, highlighting the importance of reiterative experience in shock management. Given the relatively low frequency of shock among pediatric acute illness, simulation may help to optimize bedside implementation of management bundles. Qian et al (38) demonstrated that repetitive simulation team training could effectively improve compliance with resuscitation bundles and reduce the time to critical interventions for children with septic shock.

CORTICOSTEROID USE

Corticosteroid use is currently recommended in refractory septic shock; however, the benefit remains unproven and controversial. Wong et al (39) compared gene expression in

children with septic shock who did ($n = 70$) and did not ($n = 110$) receive corticosteroid therapy in a retrospective observational study. Notably, gene expression related to the adaptive immune response was down-regulated in both groups compared to normal controls, but to a greater extent in patients who received corticosteroids. While cause-and-effect cannot be determined from study, the authors raised concern that treatment with corticosteroids may repress adaptive immunity in patients with septic shock.

This group has also used gene expression to identify subclasses of patients with septic shock with different morbidity and mortality, but have now moved this technology closer to the bedside using a messenger RNA technology that can provide results on expression of the 100 subclass-defining genes in 8–12 hours (40). Using test and validation cohorts of children with septic shock, the authors were able to reliably assign patients to subclasses with different morbidity and mortality rates based on their gene expression profile using samples collected within the first 24 hours of PICU presentation with septic shock. Interestingly, Wong et al (40) also found that corticosteroids were associated with increased mortality in the higher risk subclass of patients. The authors conclude that this technology has the potential to identify a subset of patients who may not respond favorably to adjunctive corticosteroid therapy.

FUTURE RESEARCH DIRECTIONS

The Lancet Commission on Research has laid the groundwork for a very thoughtful and ambitious agenda in sepsis research globally. Furthermore, thoughtful commentaries on the research that is needed for neonates in resource-poor areas as well as for the poorest in the world are exciting new developments that may change our understanding and approaches to sepsis in the next few years (41, 42). The authors emphasize the disappointing reality that, despite numerous promising drugs, there remain no specific antisepsis treatments and management relies mainly on recognition and aggressive organ support. In resource-rich countries, unraveling the pathobiology of sepsis and ensuring earlier recognition will take precedence, while in resource-poor countries, creative solutions to implement basic life-saving resuscitative therapies and antibiotics are the priority. Innovation in sepsis care as well as in adaptive clinical trial design will be increasingly important.

CONCLUSIONS

There have been a remarkable number of recent studies in the field of pediatric shock recognition and management, although research has largely centered on severe sepsis and septic shock. The notable breadth of international contributions in this field is particularly enlightening given the global public health impact of sepsis and shock on children. While there has been significant progress in the understanding of sepsis epidemiology and use of extracorporeal therapies in critically ill children with sepsis, the role of hyperlactatemia and risk stratification in pediatric septic shock, and the optimal timing of antibiotic administration, more work is clearly needed. Importantly, the consistent theme of a beneficial role for a bundled approach to septic shock recognition and management to improve both care and outcomes should drive their inclusion into future updates of pediatric shock guidelines. A roadmap to relevant research offers possibilities to improve knowledge and outcomes.

REFERENCES

1. Cohen J, Vincent JL, Adhikari NK, et al: Sepsis: A roadmap for future research. *Lancet Infect Dis* 2015; 15:581–614
2. Schlapbach LJ, Straney L, Alexander J, et al; ANZICS Paediatric Study Group: Mortality related to invasive infections, sepsis, and septic shock in critically ill children in Australia and New Zealand, 2002-13: A multicentre retrospective cohort study. *Lancet Infect Dis* 2015; 15:46–54
3. Goldstein B, Giroir B, Randolph A: International pediatric sepsis consensus conference: Definitions for sepsis and organ dysfunction in pediatrics. *Pediatr Crit Care Med* 2005; 6:2–8
4. Weiss SL, Fitzgerald JC, Pappachan J, et al; Sepsis Prevalence, Outcomes, and Therapies (SPROUT) Study Investigators and Pediatric Acute Lung Injury and Sepsis Investigators (PALISI) Network: Global epidemiology of pediatric severe sepsis: The sepsis prevalence, outcomes, and therapies study. *Am J Respir Crit Care Med* 2015; 191:1147–1157
5. Ruth A, McCracken CE, Fortenberry JD, et al: Pediatric severe sepsis: Current trends and outcomes from the Pediatric Health Information Systems database. *Pediatr Crit Care Med* 2014; 15:828–838
6. Balamuth F, Weiss SL, Neuman MI, et al: Pediatric severe sepsis in U.S. children's hospitals. *Pediatr Crit Care Med* 2014; 15:798–805
7. Balamuth F, Weiss SL, Hall M, et al: Identifying pediatric severe sepsis and septic shock: Accuracy of diagnosis codes. *J Pediatr* 2015; 167:1295–1300.e4
8. Hartman ME, Linde-Zwirble WT, Angus DC, et al: Trends in the epidemiology of pediatric severe sepsis. *Pediatr Crit Care Med* 2013; 14:686–693
9. Odetola FO, Gebremariam A, Freed GL: Patient and hospital correlates of clinical outcomes and resource utilization in severe pediatric sepsis. *Pediatrics* 2007; 119:487–494
10. Paul R, Neuman MI, Monuteaux MC, et al: Adherence to PALS sepsis guidelines and hospital length of stay. *Pediatrics* 2012; 130:e273–e280
11. Kissoon N, Uyeki TM: Sepsis and the global burden of disease in children. *JAMA Pediatr* 2016; 170:107–108
12. Cvetkovic M, Lutman D, Ramnarayan P, et al: Timing of death in children referred for intensive care with severe sepsis: Implications for interventional studies. *Pediatr Crit Care Med* 2015; 16:410–417
13. Launay E, Gras-Le Guen C, Martinot A, et al: Suboptimal care in the initial management of children who died from severe bacterial infection: A population-based confidential inquiry. *Pediatr Crit Care Med* 2010; 11:469–474
14. Ninis N, Phillips C, Bailey L, et al: The role of healthcare delivery in the outcome of meningococcal disease in children: Case-control study of fatal and non-fatal cases. *BMJ* 2005; 330:1475
15. Weiss SL, Fitzgerald JC, Maffei FA, et al; SPROUT Study Investigators and Pediatric Acute Lung Injury and Sepsis Investigators Network: Discordant identification of pediatric severe sepsis by research and clinical definitions in the SPROUT international point prevalence study. *Crit Care* 2015; 19:325
16. Singer M, Deutschman CS, Seymour CW, et al: The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). *JAMA* 2016; 315:801–810
17. Scott HF, Brou L, Deakyne SJ, et al: Lactate clearance and normalization and prolonged organ dysfunction in pediatric sepsis. *J Pediatr* 2016; 170:149–155.e1

18. Scott HF, Donoghue AJ, Gaieski DF, et al: The utility of early lactate testing in undifferentiated pediatric systemic inflammatory response syndrome. *Acad Emerg Med* 2012; 19:1276–1280
19. de Oliveira CF, de Oliveira DS, Gottschald AF, et al: ACCM/PALS haemodynamic support guidelines for paediatric septic shock: An outcomes comparison with and without monitoring central venous oxygen saturation. *Intensive Care Med* 2008; 34:1065–1075
20. Ventura AM, Shieh HH, Bousso A, et al: Double-Blind Prospective Randomized Controlled Trial of dopamine versus epinephrine as first-line vasoactive drugs in pediatric septic shock. *Crit Care Med* 2015; 43:2292–2302
21. Weiss SL, Selak MA, Tuluc F, et al: Mitochondrial dysfunction in peripheral blood mononuclear cells in pediatric septic shock. *Pediatr Crit Care Med* 2015; 16:e4–e12
22. Mouncey PR, Osborn TM, Power GS, et al; ProMISe Trial Investigators: Trial of early, goal-directed resuscitation for septic shock. *N Engl J Med* 2015; 372:1301–1311
23. Yealy DM, Kellum JA, Huang DT, et al; ProCESS Investigators: A randomized trial of protocol-based care for early septic shock. *N Engl J Med* 2014; 370:1683–1693
24. Peake SL, Delaney A, Bailey M, et al; ARISE Investigators; ANZICS Clinical Trials Group: Goal-directed resuscitation for patients with early septic shock. *N Engl J Med* 2014; 371:1496–1506
25. Weiss SL, Fitzgerald JC, Balamuth F, et al: Delayed antimicrobial therapy increases mortality and organ dysfunction duration in pediatric sepsis. *Crit Care Med* 2014; 42:2409–2417
26. van Paridon BM, Sheppard C, G GG, et al; Alberta Sepsis Network: Timing of antibiotics, volume, and vasoactive infusions in children with sepsis admitted to intensive care. *Crit Care* 2015; 19:293
27. Haque A, Siddiqui NR, Munir O, et al: Association between vasoactive-inotropic score and mortality in pediatric septic shock. *Indian Pediatr* 2015; 52:311–313
28. Ruth A, McCracken CE, Fortenberry JD, et al: Extracorporeal therapies in pediatric severe sepsis: Findings from the pediatric healthcare information system. *Crit Care* 2015; 19:397
29. Wong HR, Cvijanovich NZ, Anas N, et al: A multibiomarker-based model for estimating the risk of septic acute kidney injury. *Crit Care Med* 2015; 43:1646–1653
30. Wiens MO, Kumbakumba E, Larson CP, et al: Postdischarge mortality in children with acute infectious diseases: Derivation of postdischarge mortality prediction models. *BMJ Open* 2015; 5:e009449
31. Cruz AT, Perry AM, Williams EA, et al: Implementation of goal-directed therapy for children with suspected sepsis in the emergency department. *Pediatrics* 2011; 127:e758–e766
32. Larsen GY, Mecham N, Greenberg R: An emergency department septic shock protocol and care guideline for children initiated at triage. *Pediatrics* 2011; 127:e1585–e1592
33. Paul R, Melendez E, Stack A, et al: Improving adherence to PALS septic shock guidelines. *Pediatrics* 2014; 133:e1358–e1366
34. Balamuth F, Alpern ER, Grundmeier RW, et al: Comparison of two sepsis recognition methods in a pediatric emergency department. *Acad Emerg Med* 2015; 22:1298–1306
35. Akcan Arikan A, Williams EA, Graf JM, et al: Resuscitation bundle in pediatric shock decreases acute kidney injury and improves outcomes. *J Pediatr* 2015; 167:1301–1305.e1
36. Tuuri RE, Gehrig MG, Busch CE, et al: "Beat the shock clock": An interprofessional team improves pediatric septic shock care. *Clin Pediatr (Phila)* 2016; 55:626–638
37. Kessler DO, Walsh B, Whitfill T, et al; INSPIRE ImPACTS investigators: Disparities in adherence to pediatric sepsis guidelines across a spectrum of emergency departments: A multicenter, cross-sectional observational in situ simulation study. *J Emerg Med* 2016; 50:403–415.e1
38. Qian J, Wang Y, Zhang Y, et al: A Survey of the first-hour basic care tasks of severe sepsis and septic shock in pediatric patients and an evaluation of medical simulation on improving the compliance of the tasks. *J Emerg Med* 2016; 50:239–245
39. Wong HR, Cvijanovich NZ, Allen GL, et al: Corticosteroids are associated with repression of adaptive immunity gene programs in pediatric septic shock. *Am J Respir Crit Care Med* 2014; 189:940–946
40. Wong HR, Cvijanovich NZ, Anas N, et al: Developing a clinically feasible personalized medicine approach to pediatric septic shock. *Am J Respir Crit Care Med* 2015; 191:309–315
41. Molyneux E, Gest A: Neonatal sepsis: An old issue needing new answers. *Lancet Infect Dis* 2015; 15:503–505
42. Riviello ED, Sugira V, Twagirumugabe T: Sepsis research and the poorest of the poor. *Lancet Infect Dis* 2015; 15:501–503