Pediatric Critical Care Management of Septic Shock Prior to Acute Kidney Injury and Renal Replacement Therapy

James D. Fortenberry, MD

Summary: A high index of suspicion for bacterial sepsis and recognition of the potential for rapid deterioration is essential for impacting patient outcome. Meningococcemia produces a stereotypical clinical and biochemical constellation of profound septic shock and purpura fulminans with marked inflammatory disturbance and a complex disruption of coagulation. Meningococcal infections preferentially affect infants and young children, but adolescents are also at risk. Aggressive fluid resuscitation, hemodynamic management, and clinical monitoring are based on understanding of pathophysiologic disturbances typical of the pediatric cardiovascular response and guided by evidence-based guidelines. Appropriate antibiotic choice is important, and corticosteroid use may be beneficial. A variety of efforts to manipulate the coagulation abnormalities may be considered, although evidence is lacking. Extracorporeal support remains a consideration both for the failing cardiorespiratory systems but also potentially for the use of plasma exchange. A team approach between the intensivist and subspecialist is important in managing the frequent multiorgan complications seen with meningococcemia.

Semin Nephrol 28:447-456

Keywords: *Septic shock, meningococcemia, children, septic acute kidney injury, pediatric sepsis, corticosteroids*

The clinical case of an adolescent with meningococcal sepsis described by Symons and Picca[1] represents a complex scenario both commonly faced and feared by pediatric intensivists. Management in such situations often changes during the first few hours and days of ICU admission, especially with respect to fluid management and provision of vasoactive medications. The child with septic shock is likely to require multiple specialty disciplines to achieve success in treatment of its complex manifestations. Understanding pathophysiologic and biochemical mechanisms can help guide management of the general sepsis process and those findings specific to meningococcal infection, as well as potential multiorgan failure.

THE PROBLEM OF SEPSIS IN CHILDREN

Sepsis remains a major cause of morbidity and mortality for both adults and children. The World Health Organization estimates that infection-related sepsis is the leading killer of children worldwide.[2] Worldwide, 1.6 million neonates die each year from infection.[3,4] In the United States alone, current estimates suggest that more than 750,000 sepsis cases occur annually, with 65% of patients admitted to intensive or intermediate care units, and an annual cost of treatment of more than $17 billion dollars.[5] Approximately 42,000 of these annual cases of sepsis occur in children, with an estimated annual cost for care of more than 2 billion dollars.[6] Recent data suggest that although progress has been made in the intensive care of sepsis, much work remains to be done

Division of Pediatric Critical Care Medicine, Emory University School of Medicine, Critical Care and Pediatric ECMO, Children's Healthcare of Atlanta, Atlanta, GA.

Address reprint requests to James D. Fortenberry, MD, FCCM, FAAP, Associate Professor of Pediatrics, Chief, Division of Pediatric Critical Care Medicine, Emory University School of Medicine, Medical Director, Critical Care and Pediatric ECMO, Children's Healthcare of Atlanta, 1405 Clifton Rd NE, Atlanta, GA 30322. E-mail: james.fortenberry@choa.org

0270-9295/08/$ - see front matter

 doi:10.1016/j.semnephrol.2008.05.004

to improve outcome. Severe sepsis hospitalization has almost doubled,[5] and mortality from the disease also has increased significantly. In children 0 to 4 years of age, severe sepsis hospitalization of males increased from 26.4 to 51.3 per 100,000 from 1993 to 2003.[5] Mortality rates for this group increased from 5.4 to 9.5 per 100,000 during the same period. Case fatality rates have decreased overall, likely owing to overall improvements in antibiotics and critical care. However, rates remain unacceptably high (20.6 to 18.4 per 100 severe sepsis cases in the 0-4 age group). Of children hospitalized with sepsis in the United States, 10.3% will die.[6]

Significant differences exist between adults and children with sepsis regarding epidemiology, physiologic response, and associated underlying diseases. However, for both children and adults, death from sepsis is related primarily to the development of multiple organ failure (MOF), defined as the failure of 3 or more organ systems.[7] The development of MOF in sepsis significantly increases mortality rates, and increasing numbers of organ dysfunction have been correlated with increasing likelihood of death.[7] Although simple measures such as early antibiotics and fluid resuscitation are making inroads into decreasing mortality rates, MOF remains a persistent final common pathway to death and a target for prevention or improved treatment. A large body of evidence has highlighted the importance of microvascular coagulation in the pathogenesis of MOF/sepsis.[8-12] Products resulting from microbial sepsis, including endotoxin, exotoxin, and peptidoglycans activate cellular and biochemical pathways aimed at eliminating the pathogenic insult.[13] This leads to activation of the kinin and complement systems, the release of secondary inflammatory mediators tumor necrosis factor-α, interleukin-1, interleukin-6, interleukin-8, and the expression and release of tissue factor (TF) from macrophages and neutrophils. TF levels are reported to be higher in the blood of severely septic patients who have organ dysfunction compared with those who do not.[14] TF triggers activation of the extrinsic coagulation pathway through conversion of factor VII to VIIa, resulting in the generation of intravascular thrombin, which has been shown to appear early in the course of sepsis.[15] Thrombin is responsible for a number of key findings in septic patients, including consumption of coagulant and anticoagulant proteins (including protein C and antithrombin III), activation of platelets, and activation of endothelial cells via binding to a specific thrombin receptor.[15,16]

The interaction of these factors with endothelial cells is critical to the development of microvascular thrombosis. Thrombin/thrombomodulin binding, and activation of protein C, produces a net anticoagulant effect by virtue of inactivating activated factor V and factor VIII. However, further activation of endothelial cells results in a significant decrease in the expression of thrombomodulin (by as much as 80%) on the cell surface.[11] Moreover, under these conditions endothelial cells elaborate additional TF and plasminogen activator inhibitor type-1 (PAI-1), which is associated with potent antifibrinolytic effects. Studies performed in patients with sepsis have shown early release of profibrinolytic tissue plasminogen activator, followed by elaboration of PAI-1 as sepsis progresses to MOF.[10] Progressive activation of the coagulation system (increasing TF, thrombin-antithrombin complexes (TAT), PAI-1, thrombomodulin (TM), and decreasing plasmin/plasmin inhibitor complex) increases with further progression to disseminated intravascular coagulopathy. Disseminated intravascular coagulopathy is a strong predictor of MOF and death in patients with sepsis.[17] The net result of these changes is the conversion of the normal microvascular milieu from an anticoagulant/profibrinolytic condition to a markedly procoagulant/antifibrinolytic state. This conversion ultimately leads to the development of microvascular thrombosis, tissue hypoperfusion, and resultant organ failure.

MENINGOCOCCAL SEPSIS: CLINICAL FEATURES

Infections with *Neisseria meningitidis* can produce a prototypical form of pediatric septic shock with stereotypical inflammatory and coagulation responses representative of the pattern described earlier. Meningococcal sepsis remains one of the most feared in the pediatric intensive care unit. *Neisseria* infections are responsible for greater than 500,000 cases of sep-

tic shock annually worldwide, with an annual incidence of approximately 1/100,000 in the United States.[18,19] Of 13 serogroups, types A, B, C, Y, and W-135 are the most common. Outbreaks typically are sporadic, but can occur in epidemic fashion, with great variability in incidence dependent on worldwide region. From 60% to 90% of cases occur in children and adolescents, with almost half involving children 2 years of age or younger.[19] Infections in adolescents have decreased with improved availability and use of vaccines before college entrance. Although most meningococcal infections manifest as meningitis, approximately 10% of cases present as meningococcal sepsis.[20]

The clinical course of meningococcemia is a rapid one, emphasizing the need for rapid assessment, aggressive treatment, and recognition that further organ deterioration can and probably will occur even with the initiation of antibiotics. Severe meningococcemia progresses rapidly, with time from onset of fever until profound shock as short as 12 hours.[19] Initial symptoms include nonspecific fever, rash, myalgias, and lethargy. Meningeal signs may be present, but absence of meningitis generally is associated with a more rapid course and worse prognosis. The classic petechial rash is a typical feature in about 80% of cases and may be seen while the patient's mental status is normal. If treated early, symptoms may not progress further, but progression can occur and should be recognized by tachycardia, decreased perfusion, prolonged capillary refill, and depressed mental status with worsening limb ischemia and purpura. This shock state is generated by release of the gram-negative meningococcal endotoxin, resulting in diffuse activation of both the inflammatory and coagulation cascades. The subsequent endothelial cell injury produces marked capillary leak, myocardial dysfunction, peripheral vasoconstriction, and microvascular thrombosis.

Although meningococcemia still carries a high mortality rate, outcomes have improved over recent decades, in part related to improved vaccines, and likely also to improvements in general intensive care unit management approaches.[21] Meningococcal sepsis carries a mortality rate in the range of 10% to 30% even with aggressive therapy,[18] with deaths usually in patients with refractory shock and organ failure or from adult respiratory distress syndrome (ARDS). Despite many efforts directed at specific therapy described later, no single magic bullet to arrest meningococcemia has been found. However, emphasis on rapid fluid resuscitation, goal-directed therapies, and occasional use of adjunctive therapies may be responsible. As mortality rates improve, emphasis also must be placed on decreasing morbidity.

PEDIATRIC SEPSIS: FLUID RESUSCITATION AND USE OF VASOACTIVE AGENTS

The primary approach to pediatric septic shock based on best available evidence and expert consensus have been codified recently in sepsis guidelines developed by the American College of Critical Care Medicine (ACCM) (Fig. 1).[22] These guidelines still emphasize early, aggressive fluid resuscitation as the best available therapy in shock. A variety of studies have supported the premise that early intervention during the septic shock golden hour can improve outcomes in children.[23-25] Treatment can be with either normal saline, lactated Ringer's solution, or human albumin. Most authorities reserve albumin for patients who do not respond to crystalloids. A goal-directed approach to titrating fluids likely is critical in outcome. A landmark study[26] showed improved mortality rates with fluid management directed at maximizing central venous oxygen saturation. Recent Brazilian studies have preliminarily shown improved survival in children receiving aggressive resuscitation and management via a similar goal-directed approach (J.A. Carcillo, personal communication). The prominent hemodynamic problem in meningococcal sepsis also involves maintenance of adequate circulating volume in early stages of treatment. Thus, aggressive fluid resuscitation is the key treatment principle in meningococcemia. Volume resuscitation can be titrated to clinical examination, and to measurement of adequate central venous pressures (CVP), and mixed venous oxygen saturations (SvO_2) from central venous catheters placed early in the course of resuscitation. CVP and SvO_2 measurements can pro-

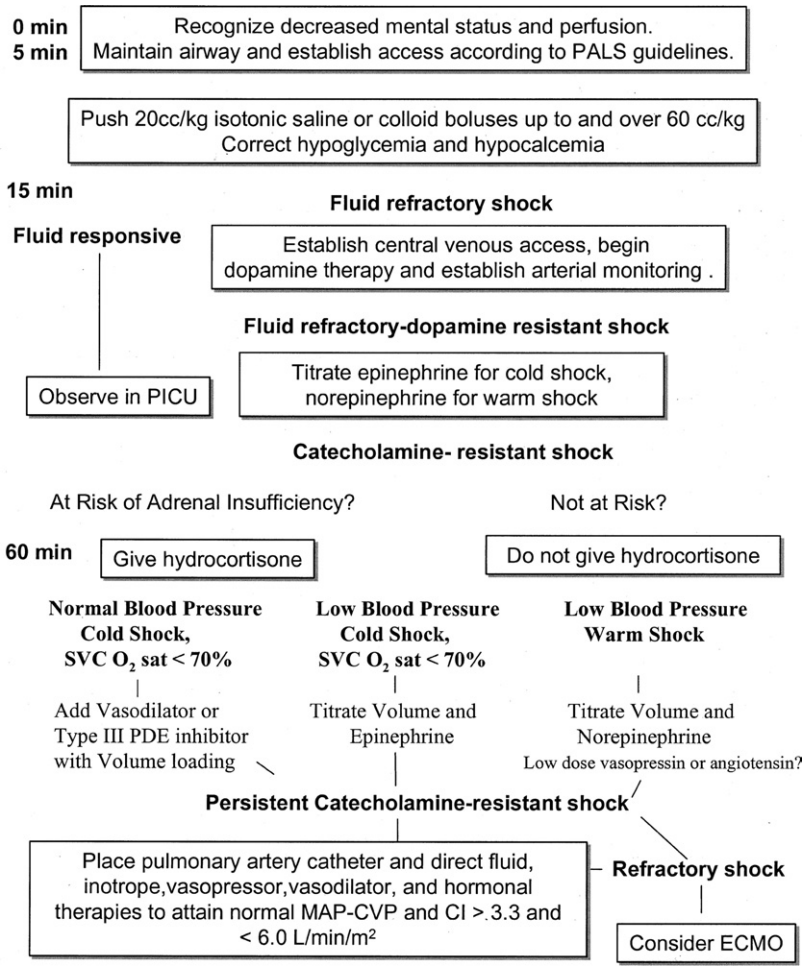

Figure 1. Recommendations for stepwise management of hemodynamic support in infants and children with goals of normal perfusion and perfusion pressure (mean arterial pressure (MAP) - CVP. Proceed to next step if shock persists. PALS, pediatric advanced life support; $SVCO_2$, superior vena cava oxygen; PDE, phosphodiesterase; CI, cardiac index. Copyright © Society of Critical Care Medicine, European Society of Intensive Care Medicine, and International Sepsis Forum. Reproduced by permission of the publisher.[22]

vide a helpful assessment of sufficiency of fluid resuscitation. Echocardiographic evaluation also can provide a noninvasive assessment of ejection fraction and ventricular filling adequacy. In the patient described by Symons and Picca in this issue,[1] fluid volumes of up to 120 to 140 mL/kg may be necessary in the acute resuscitation phase to adequately keep up with intravascular losses and filling requirements.

Although aggressive early fluid resuscitation is key, a lack of resolution of fluid overload later in the disease course could be responsible for, or at least associated with, worsening outcomes.[27,28] However, these concerns should not lead one to undertreat early. Likely the impact of fluids on outcome is bimodal, with early undertreatment and late fluid overload both associated with worsening outcomes.

Children with meningococcemia frequently require inotropic and vasopressor support in addition to aggressive fluid resuscitation. An understanding of mechanisms of shock in this setting is integral to determine selection of the optimal agent. Adults with septic shock typically show vasomotor paralysis with vasodilation and overall increased cardiac output. On the other hand, children with septic shock display more heterogeneous hemodynamic responses.[22,29] As opposed to adults, low cardiac output and decreased oxygen delivery are more common and more likely to be associated with mortality; low cardiac output and high systemic

Table 1. Definitions of Shock

Cold or warm shock: decreased perfusion including decreased mental status, capillary refill >2 seconds (cold shock) or flash capillary refill (warm shock), diminished (cold shock) or bounding (warm shock) peripheral pulses, mottled cool extremities (cold shock), or decreased urine output <1 mL/kg/h
Fluid-refractory/dopamine-resistant shock: shock persists despite >60 mL/kg fluid resuscitation in first hour and dopamine infusion to 10 μg/kg/min
Catecholamine-resistant shock: shock persists despite use of catecholamines epinephrine or norepinephrine
Refractory shock: shock persists despite goal-directed use of inotropic agents, vasopressors, vasodilators, and maintenance of metabolic (glucose and calcium) and hormonal (thyroid and hydrocortisone) homeostasis

vascular resistance (SVR) occurs in 58% of a series of 50 children with septic shock in comparison with only 22% with low cardiac output and low SVR,[29] although some patients did develop a high-output, low sustained virologic response state as well. Thus, the choice of agents must be predicated on the estimated degree of diminished vascular resistance and cardiac function. Pulmonary artery catheters rarely are used now in pediatric patients, and so assessment is dependent on a combination of blood pressure measurement, CVP and arterial pressure monitoring, SvO_2 measurement, echocardiographic assessment, and the time-honored physical examination. For instance, the patient described in the Symons and Picca narrative[1] manifests a low blood pressure, wide pulse pressure, decreased perfusion, and capillary refill. These features are consistent with a description of warm shock as defined in the ACCM guidelines (Table 1).[22] He also might be expected to have increased CVP, low systemic venous oxygen saturation, and decreased ejection fraction by echocardiogram. The clinical examination and objective measurements in combination suggest him to be in a low-cardiac-output state with the need of a vasoactive agent both with primary inotropy (β-receptor activity) to improve cardiac output, as well as a degree of vasoconstriction (α-receptor) to maintain adequate organ perfusion pressure.

ACCM guidelines include general recommendations for choice of vasoactive agents in fluid-refractory shock. Current ACCM guidelines suggest dopamine as the first choice. If resistant to dopamine, epinephrine is recommended to titrate for cold shock and norepinephrine for warm shock. Further inotropic therapy is titrated as noted in Figure 1, with addition of vasodilators and/or milrinone (a phosphodiesterase III inhibitor with additional lusitropic function) in patients with adequate blood pressure and increased oxygen consumption. Vasopressin is an additional pressor agent that has become increasingly used in catecholamine-resistant shock as an adjunct to either norepinephrine or epinephrine because of its addition mode of pressor action via vasopressin receptors. In the setting of meningococcemia, the high potential for extremity ischemia and thrombosis necessitates titration of vasoconstriction to minimal levels if possible. Agents with peripheral vasodilating effects, such as milrinone, may be added as tolerated by blood pressure.

PEDIATRIC SEPSIS: OTHER THERAPIES

The patient in the Symons and Picca narrative[1] is not intubated at present. However, given his degree of shock, acidosis, and progressive respiratory distress, irrespective of advancing pulmonary edema, a strong case could be made for earlier endotracheal intubation and mechanical ventilation to decrease overall oxygen consumption and nonessential use of cardiac output.

Antibiotics are an essential aspect of management in meningococcemia and should be administered empirically as early as possible in the disease course. Likely, however, they do not mitigate the initial proinflammatory and coagulopathic cascades that have been activated, and it has been suggested that initial antibiotics may initially aggravate these responses as a result of lysis of organisms. Current recommended empiric antibiotic use should be based on age and potential organisms responsible for sepsis, even if meningococcemia is suspected. With the increase of community-acquired methicillin-resistant *Staphylococcus aureus* in many areas of the United States, empiric addition of vancomycin to a standard broad-spectrum cephalosporin is recommended in children and adolescents presenting with septic shock. Other broad-spectrum choices may need to be made in the child with known immunosuppression. Ceftriaxone has been used in many algorithms for empiric treatment of pediatric sepsis. However, recent reports of deaths associated with concomitant use of ceftriaxone and calcium-containing solutions, allegedly owing to in vivo calcium chelation, have led the Food and Drug Administration to issue an alert that included recommendations to avoid administration of ceftriaxone within 48 hours of completion of calcium-containing infusions, including parenteral nutrition, regardless of whether drug delivery occurs through separate catheters.[30,31] Given the high incidence of need for calcium replacement in severe sepsis or meningococcemia, the alternative use of cefotaxime as a first-line cephalosporin has been recommended. Ceftriaxone (with its advantage of longer dosing intervals) could be used later at more stable points of the meningococcal disease resolution.

Empiric use of corticosteroids is controversial in pediatric septic shock.[32] Several studies have shown a high incidence of absolute or relative adrenal insufficiency in both children and adults with septic shock, even in the absence of other risk factors such as chronic steroid use as chemotherapy. In meningococcemia, adrenal hemorrhage has been described classically as the Waterhouse-Friderichsen syndrome. However, even in the absence of hemorrhage and necrosis, reports evaluating adrenal function in meningococcemia generally have found decreased response. Pediatric studies have shown significantly lower cortisol levels[33] in meningococcemia nonsurvivors than in survivors, as well as blunted corticotropin response.[34] Low serum cortisol and high adrenocorticotropic hormone levels also were associated with higher vasopressor requirements[34] and poorer outcome.[35] Current national adult sepsis guidelines[36] have recommended empiric use of steroids in septic shock based on a large adult trial finding improved survival with use of a low-dose steroid regimen in patients not responding to adrenocorticotropic hormone stimulation.[37] However, the negative results of the recently reported adult sepsis steroid replacement trial[38] may call for reassessment of routine use in septic shock. Pediatric trials are notably absent. Empiric corticosteroids have been recommended for pediatric patients with catecholamine-resistant shock at specific risk of adrenal sufficiency,[22] which include children with suspected meningococcemia.

Purpura fulminans is an ominous but frequent feature of systemic meningococcemia.[39] The coagulopathy and microthrombosis is responsible for a great degree of morbidity seen in survivors. Skin loss, amputations, and brain vascular injury are seen in varying degrees. The pathophysiology of the coagulopathy is complex. Disseminated intravascular coagulation results from excessive activation of the coagulation cascade and associated down-regulation of the fibrinolytic system. Concentrations of anticoagulants such as protein C and antithrombin III are decreased, and tissue factor pathway inhibitor is increased. The complex disturbances produce tendencies both for hemorrhage and tissue microthrombosis.[39] A variety of maneuvers have been aimed at treating the various disruptions of procoagulant and anticoagulant function, including tissue effects of purpura fulminans, with variable success. One approach to generalized control and replacement of factors is through the use of plasma exchange, which is described in a recent review.[40] Many clinicians routinely replace depleted factors with fresh-frozen plasma and platelets, but concern exists that one is merely fueling the fire with products that will be consumed in microthrombosis. One approach is to provide replacement

only in the case of active bleeding or with platelet counts of less than 20,000/mm^3. More directed replacement with activated protein C has been shown to be effective in some settings of adult sepsis and has suggested benefits in pediatric meningococcemia.[41] However, a recent multicenter trial of activated protein C was halted in children because of a lack of effect and concern for increased bleeding risk.[42] Heparin infusion has been used in an effort to avoid microthrombosis, but no strong evidence supports it use. Tissue plasminogen activator also has been used to overcome inhibition of endogenous tissue plasminogen activator, but a retrospective review in children suggested increased risk of intracerebral hemorrhage.[43] Topical nitroglycerine applied to ischemic digits may provide local improvement in perfusion, but care must be taken to avoid hypotension.

As noted previously, ongoing fluid management in the child with severe meningococcemia is problematic. Although decreasing additional fluid would be preferred, capillary leak syndrome may lead to ongoing tissue losses, requiring repeated fluid boluses and higher rates. Diuretic use may not be tolerated in the face of hypotension and poor perfusion. The preponderance of evidence now confirms that low-dose dopamine does not improve urine output in sepsis. Furthermore, increasing concern has been raised that use of dopamine may be immunosuppressive because of its effect on prolactin secretion and thus T lymphocyte activity.[44] Thus, one may consider discontinuing dopamine if another pressor/inotrope is needed or if able to wean dopamine to lower doses. Glucose-containing fluids are used initially in management because hypoglycemia can occur, particularly in infants. However, close monitoring of serum glucose levels and strict glycemic control has been suggested to improve outcomes in adults. Persistent hyperglycemia has been associated with increased mortality in critically ill children,[45] but the impact of control with insulin on outcome has not been shown yet in children.

DEVELOPMENT OF MULTIPLE ORGAN FAILURE AND EXTRACORPOREAL SUPPORT

Disease progression to multiple organ dysfunction markedly increases likelihood of death. Renal function in meningococcemia typically worsens for several reasons. Acute kidney injury in septic shock, although once thought to be primarily a hemodynamic disease induced by ischemia, likely is associated with inflammatory response.[46] Bilateral cortical necrosis is noted in some patients.[47] Likely, tendencies for microvascular thrombosis predispose to this finding. Increasing renal insufficiency and increasing serum creatinine levels correlate with decreased levels of the von Willebrand factor cleaving protease ADAMTS-13 in adults with septic shock, in a pattern similar to thrombotic thrombocytopenic purpura.[48] In one series of 209 children admitted with meningococcemia, 21 developed oliguric acute renal failure necessitating renal replacement therapy. Twelve of these patients survived, 4 developed some form of persistent abnormality of renal kidney.[49] Management of renal failure is in part dictated by hemodynamic stability. Although diuretics may be attempted to improve urine output, acute diuresis likely will not be well tolerated, particularly early in the resuscitative course. Furosemide infusions may produce diuresis with improved hemodynamic tolerance. However, renal replacement therapy will provide better overall fluid management and assist in decreasing massive fluid overload, and is discussed in another review in this issue.

If the patient described in the Symons and Picca case study[1] did not respond to all the earlier-described maximal hemodynamic support, extracorporeal support could be considered. Extracorporeal membrane oxygenation (ECMO) has a well-established record of potential benefit in neonatal and pediatric respiratory failure, and for emergent temporary cardiac support.[50] ECMO provides artificial respiratory and/or cardiac support via introduction of an artificial oxygenator and circulation of blood by either venoarterial or venovenous support. However, the role of ECMO is less certain in the treatment of refractory shock, sepsis, and MOF.[51] Individual pediatric center case series have suggested benefit. A recent review of 45 children with septic shock (including 12 with meningococcemia) described survival to hospital discharge in 21 of 45 children receiving

ECMO support after failure of maximal conventional therapy.[52]

Two series of pediatric experience with ECMO in meningococcal sepsis have reported a somewhat divergent experience. One study[53] described 12 children with meningococcal disease and a high predicted likelihood of death who received ECMO support. In 7 patients, ECMO was provided rapidly for intractable shock; in 5 other patients ECMO was required later for severe ARDS. Six of the 12 patients actually required cardiopulmonary resuscitation before ECMO. Overall, 8 of the 12 patients survived (6 functionally normal), including 4 of 7 intractable shock patients and all 5 ARDS patients. The investigators concluded that ECMO should be considered to support patients with meningococcal disease failing conventional measures for refractory shock or respiratory failure, given the otherwise high likelihood of death. A more recent meningococcal ECMO series was less encouraging, but also did suggest that ECMO was more effective for respiratory indications. Another study[54] reported 11 children with meningococcal sepsis and a high predicted mortality rate who were treated with ECMO. Overall, 6 of 11 survived. All 5 children with ARDS who received venovenous ECMO survived. However, of 6 children with refractory shock and organ failure receiving ECMO (all venoarterial), only 1 survived. Although recognizing study limitations, the investigators affirmed the use of ECMO in meningococcal-associated ARDS but urged caution in its use for refractory shock. Based on accumulated experience, ACCM guidelines recommend the physician "consider ECMO" in the child with meningococcemia and refractory shock (Fig. 1).

SUMMARY

Meningococcemia is a manifestation of septic shock with potentially high morbidity and mortality rates in children. Rapid recognition is essential to have the opportunity to impact outcome. Aggressive fluid resuscitation and hemodynamic management can improve organ perfusion. The use of corticosteroids and agents to manipulate coagulation dysfunction are reasonable, but their benefits remain to be proven. Extracorporeal support through ECMO can be considered. The use of continuous renal replacement therapies and plasma exchange also offer further potential benefits with the support of nephrology consultants.

REFERENCES

1. Symons JM, Picca S. Acute kidney injury and dialysis in children: illustrative cases. Sem Neph. 2008;28: 431-5.
2. Watson RS, Carcillo JA. Scope and epidemiology of pediatric sepsis. Pediatr Crit Care Med. 2005;6 Suppl: S3-5.
3. The World Health Care Report. Fighting disease, fostering development. Geneva: World Health Organization; 1996.
4. The World Health Care Report. Changing history. Geneva: World Health Organization; 1996.
5. Dobrovsky VY, Martin AA, Sunderram J, et al. Rapid increase in hospitalization and mortality rates from severe sepsis in the United States: a trend analysis from 1993 to 2003. Crit Care Med. 2007;35:1244-50.
6. Watson RS, Carcillo JA, Linde-Zwirble WT, et al. The epidemiology of severe sepsis in children in the United States. Am J Respir Crit Care Med. 2003;167: 695-701.
7. Leclerc F, Leteutre S, Duhamel A, et al. Cumulative influence of organ dysfunctions and septic state on mortality of critically ill children. Am J Respir Crit Care Med. 2005;171:348-55.
8. Nguyen T, Hall M, Han Y, et al. Microvascular thrombosis in pediatric multiple organ failure: is it a therapeutic target? Pediatr Crit Care Med. 2001;2:187-96.
9. Hinshaw LB. Sepsis/septic shock: participation of the microcirculation: an abbreviated review. Crit Care Med. 1996;24:1072-8.
10. Grinnell BW, Joyce D. Recombinant human activated protein C: a system modulator of vascular function for treatment of severe sepsis. Crit Care Med. 2001;29 Suppl:S53-61.
11. Massignon D, Lepape, Bienvenu J, et al. Coagulation/ fibrinolysis balance in septic shock related to cytokines and clinical state. Haemostasis. 1994;24:36-48.
12. Degan JL. Hemostatic factor and inflammatory disease. Thromb Haemost. 1999;82:858-64.
13. Bierhaus A, Chen J, Liliensiek B, et al. LPS and cytokine-activated endothelium. Semin Thromb Hemost. 2000;26:571-87.
14. Iba T, Kidokoro A, Yagi Y. The role of endothelium in changes in procoagulant activity in sepsis. J Am Coll Surg. 1998;187:321-9.
15. Coughlin SR, Vu TH, Hung DT, et al. Characterization of a functional thrombin receptor. J Clin Invest. 1992; 89:351-5.
16. Mammen EF. The haemotological manifestations of sepsis. J Anitimicrob Chemother. 1998:41 Suppl A:17-24.
17. Levi M, Cate HT. Disseminated intravascular coagulation. N Engl J Med. 1999;34:586-92.

18. Stephens DS, Greenwood B, Brandtzaeg P. Epidemic meningitis, meningococcaemia, and Neisseria meningitides. Lancet. 2007;369:2196-210.
19. Kirsch EA, Barton P, Kitchen L, Giroir B. Pathophysiology, treatment and outcome of meningococcemia: a review and recent outcome. Pediatr Infect Dis J. 1996;15:967-79.
20. Dhanani S, Cox P. Infectious syndromes in the pediatric intensive care unit. In: Fuhrman B, Zimmerman J, editors. Pediatric critical care medicine. Philadelphia: Mosby; 2006. p. 1374-93.
21. Stephens DS. Conquering the meningococcus. FEMS Microbiol Rev. 2007;31:3-14.
22. Carcillo JA, Fields AI, ACCM Task Force Committee. Clinical practice parameters for hemodynamic support of pediatric and neonatal patients in septic shock. Crit Care Med. 2002;30:1365-78.
23. Carcillo JA, Davis AL, Zaritsky A. Role of early fluid resuscitation in pediatric septic shock. JAMA. 1991; 266:1242-5.
24. Booy R, Habibi P, Nadel S, et al. Reduction in case fatality rate from meningococcal disease associated with improved healthcare delivery. Arch Dis Child. 2001;85:386-90.
25. Han YY, Carcillo JA, Dragotta MA, Bills DM, Watson RS, Westerman ME, et al. Early reversal of pediatric-neonatal septic shock by community physicians is associated with improved outcome. Pediatrics. 2003; 112:793-9.
26. Rivers E, Nguyen B, Haystad S, Ressler J, Muzzin A, Knoblich B, et al. Early goal-directed therapy in the treatment of severe sepsis and septic shock. N Engl J Med. 2002;345:1368-77.
27. Goldstein SL, Currier H, Graf JM, et al. Outcome in children receiving continuous venovenous hemofiltration. Pediatrics. 2001;107:1309-12.
28. Foland JA, Fortenberry JD, Warshaw BL, et al. Fluid overload before continuous hemofiltration and survival in critically ill children: a retrospective analysis. Crit Care Med. 2004;32:1771-6.
29. Ceneviva G, Paschall A, Maffei F, Carcillo JA. Hemodynamic support in fluid-refractory pediatric septic shock. Pediatrics. 1998;102:e19.
30. US Food and Drug Administration. Information for healthcare professionals. [cited 2007 November 28] Available from: http://www.fda.gov/cder/drug/InfoSheets/HCP/ceftriaxone.htm.
31. Faust SN, Pollard AJ, Nadel S, Ninis N, Levin M. Ceftriaxone drug alert: no longer for first line use in meningococcal sepsis (letter). Arch Dis Child. 2008;93: 184-5.
32. Zimmerman JJ. A history of adjunctive glucocorticoid treatment for pediatric sepsis: moving beyond steroid pulp fiction toward evidence-based medicine. Pediatr Crit Care Med. 2007;8:530-9.
33. Riordan FA, Thomson AP, Ratcliffe JM, et al. Admission cortisol and ACTH levels in children with meningococcal disease: evidence of adrenal insufficiency? Crit Care Med. 1999;27:2257-61.
34. Hatherill M, Tibby SM, Tillard T, et al. Adrenal insufficiency in septic shock. Arch Dis Child. 1999;80: 51-5.
35. De Kleijn ED, Joosten KF, Van Rijn B, et al. Low serum cortisol in combination with high ACTH concentrations are associated with poor outcome in children with severe meningococcal disease. Pediatr Infect Dis J. 2002;21:330-6.
36. Dellinger RP, Carlet JM, Masur H, Gerlach H, Calandra T, Cohen J, et al. Surviving Sepsis Campaign guidelines for management of severe sepsis and septic shock. Crit Care Med. 2004;32:858-73.
37. Annane D, Sebille V, Charpentier C, et al. Effect of treatment with low doses of hydrocortisone and fludrocortisone on mortality in patients with septic shock. JAMA. 2002;288:862-71.
38. Sprung CL, Annane D, Keh D, Moreno R, Singer M, Freivogel K, et al. Hydrocortisone therapy for patients with septic shock. N Engl J Med. 2008;358:111-24.
39. van Deuren M, Brandtzaeg P, van der Meer JW. Update on meningococcal disease with emphasis on pathogenesis and clinical management. Clin Microbiol Rev. 2000;13:144-66.
40. McMaster P, Shann F. The use of extracorporeal techniques to remove humoral factors in sepsis. Pediatr Crit Care Med. 2003;4:2-7.
41. deKleijn E, de Groot R, Hack CE, Mulder PG, Engl W, Moritz B, et al. Activation of protein C following infusion of protein C concentrate in children with severe meningococcal sepsis and purpura fulminans. Crit Care Med. 2003;31:1839-47.
42. Nadel S, Goldstein B, Williams MD, Dalton H, Peters M, Macias WL, et al. Drotrecogin alfa (activated) in children with severe sepsis: a multicentre phase III randomized clinical trial. Lancet. 2007;369:836-43.
43. Zenz W, Zoehrer B, Levin M, Fanconi S, Hatzis T, Knight G, et al. Use of recombinant tissue plasminogen activator in children with meningococcal purpura fulminans: a retrospective study. Crit Care Med. 2004;32:1777-80.
44. Bailey AR, Burkett KR. Effect of low-dose dopamine on serum concentrations of prolactin in critically ill patients. Br J Anaesthesia. 1997;78:97-9.
45. Srinivasan V, Spinella PC, Drott HR, Roth CL, Helfaer MA, Nadkarni V. Association of timing, duration and intensity of hyperglycemia with ICU mortality in critically ill children. Pediatr Crit Care Med. 2004;5:329-36.
46. Abraham E, Singer M. Mechanisms of sepsis-induced organ dysfunction. Crit Care Med. 2007;35:2408-16.
47. Marotto M, Marotto P, Sztajnbok, Seguro A. Outcome of acute renal failure in meningococcemia. Ren Fail. 1997;19:807-10.
48. Martin K, Borgel D, Lerolle N, Feys HB, Trinquart L, Vanhoorelbeke K, et al. Decreased ADAMTS-13 is associated with a poor prognosis in sepsis-induced organ failure. Crit Care Med. 2007;35:2375-82.
49. Slack R, Hawkins K, Gilhooley L, Addison M, Lewis M, Webb NJ. Long-term outcome of meningococcal sep-

sis-associated acute renal failure. Pediatr Crit Care Med. 2005;6:477-9.
50. Bartlett RH, Roloff DW, Custer JR, Younger JG, Hirschl RB. Extracorporeal life support: the University of Michigan experience. JAMA. 2000;283:904-8.
51. Fortenberry JD, Paden ML. Extracorporeal therapies in sepsis: experience and promise. Semin Pediatr Infect Dis. 2006;17:72-9.
52. MacLaren G, Butt W, Best D, Donath S, Taylor A. Extracorporeal membrane oxygenation for refractory septic shock in children: one institution's experience. Pediatr Crit Care Med. 2007;8:447-51.
53. Goldman A, Kerr S, Butt W, et al. Extracorporeal support for intractable cardiorespiratory failure due to meningococcal disease. Lancet. 1997;349:466-9.
54. Luyt DK, Pridgeon J, Brown J, et al. Extracorporeal life support for children with meningococcal septicemia. Acta Pediatr. 2004;93:1608-11.