Treatment of septic shock and use of drotrecogin alfa (activated) in children

Expert Rev. Anti Infect. Ther. 7(7), 769–772 (2009)

Giuseppe A Marraro
Associate Professor, Anesthesia and Intensive Care, University of Milano, f. Director of Anesthesia and Intensive Care Department and Pediatric Intensive Care Unit, Fatebenefratelli and Ophthalmiatric Hospital, Milano, Italy
Fax: +39 027 0040 4589
gmarraro@picu.it

"Death is often attributed to the comorbidities rather than to sepsis itself, resulting in nearly half of the deaths remaining unattributed to sepsis."

Severe sepsis is a complex syndrome and often life-threatening condition caused by the body's systemic response to an infection, and is accompanied by single or multiple organ dysfunction or failure, leading to death [1].

Sepsis often develops in children with pneumonia, trauma, surgery, burns or cancer, and is frequently underdiagnosed at an early stage when it is still potentially reversible. Sepsis and infection may be present at the same time and, indeed, infection is a prerequisite for sepsis, but the two are not synonymous – infection is the invasion of a tissue or organ by a pathogenic microorganism, while sepsis is the complex, systemic inflammatory response to infection [2].

In children, as in adults, the response to infection leads to the secretion of pro- and anti-inflammatory cytokines, the activation and mobilization of leukocytes, the activation of coagulation and inhibition of fibrinolysis, and increased apoptosis [3]. As a result of coagulation activation, the thrombin generated promotes fibrin deposition in the microvasculature and exacerbates ongoing inflammation via both direct and indirect mechanisms.

These innate inflammatory processes can be detrimental, resulting in cardiac dysfunction, vasodilatation, capillary injury, and micro- and macro-vascular thromboses. Despite antibiotics and intensive care, these processes frequently lead to organ dysfunction, gangrenous extremities, long-term neurologic morbidity or death [4,5].

Activated protein C is a critical, endogenous regulator of coagulation and inflammation. After activation of plasma protein C by the thrombin–thrombomodulin complex, activated protein C exerts antithrombotic and profibrinolytic effects [6]. The anti-inflammatory effects of activated protein C are, on the one hand, indirect because of the inhibition of thrombin formation and, on the other, direct via the blockage of cytokine formation, and inhibition of selectin activity and nuclear factor-β translocation [7].

"Sepsis often develops in children with pneumonia, trauma, surgery, burns or cancer..."

The incidence of severe sepsis in the USA is approximately three cases per 1000 of the population [8], with over 18 million cases worldwide each year. The number of deaths is difficult to estimate, as sepsis is a progressive syndrome, beginning with infection and leading to inflammation, organ failure and death. Death is often attributed to the comorbidities rather than to sepsis itself, resulting in nearly half of the deaths remaining unattributed to sepsis.

Sepsis can be difficult to treat as the course of sepsis varies widely from patient to patient as a result of a variety of circumstances. Older people, oncologic and debilitated patients, surgical and trauma patients, infants and children are more susceptible to infections due to age, comorbidities, the use of invasive surgical techniques and problems associated with hospital admission.

Mortality rates and recovery can be improved by early accurate diagnosis and treatment of sepsis patients. Delay in antibiotic therapy, for example, increases mortality by 10–15% [9,10].

EXPERT REVIEWS

 10.1586/ERI.09.65 ISSN 1478-7210

The rapid diagnosis and management of sepsis is essential for successful treatment. The sepsis patient is usually already critically ill and requires immediate care to avoid rapid deterioration. The management of sepsis patients involves a variety of therapeutic interventions [11,12]. Currently available strategies for the management of a child with sepsis include:

- Identification and diagnosis: patient identification, diagnosis and rapid identification of causative organisms or pathologic condition (e.g., recent trauma, surgical invasive procedure, and so on) are essential elements for the proper management of sepsis [13];
- Appropriate antimicrobial therapy: timely administration of antibacterial therapy is crucial for the management of children with sepsis [14];
- Hemodynamic support: hemodynamic therapy, in the form of rapid fluid resuscitation, should be commenced to reverse hypotension, hypovolemia and organ dysfunction, and to restore effective tissue perfusion and cellular metabolism as soon as possible [15,16];
- If fluid resuscitation fails to restore adequate arterial pressure and organ perfusion, vasopressors, and potentially inotropes, should be administered. Care must be taken when starting patients on vasopressor or inotropic therapy, since studies have indicated that their administration causes detrimental effects, including impaired splanchnic blood flow and oxygenation, reduced pH, and negative effects on growth and thyroid hormones [17–19];
- Ventilation support: an estimated 25–42% of adult sepsis patients develop acute respiratory distress syndrome (ARDS), which requires mechanical ventilation (MV) [20]. Pediatric considerations included a more likely need for intubation and MV due to low functional residual capacity. Despite developments of newer ventilation supports over the last decade, the mortality rate associated with ARDS that needs artificial ventilation may exceed 40%;
- Protective lung strategy: older approaches to MV employed high tidal volumes (10–15 ml/kg ideal body weight [IBW]), which have been associated with stretch-induced lung injury and high mortality rates. The use of low tidal volumes (6 ml/kg/IBW) has been shown to reduce the risk of mortality in ARDS patients by 22% and increase the number of ventilator-free days in the first 28 days compared with conventional treatment [21]. Protective lung ventilation strategy must be planned in order to reduce ventilation-induced lung injury and improve survival [22].
- Glycemia control: hyperglycemia associated with insulin resistance is common in critically ill children and may lead to severe infections, polyneuropathy, multiple organ failure and death. In recent studies, intensive insulin therapy reduced in-hospital mortality, incidence of acute renal failure, episodes of septicemia, incidence of bloodstream infections, abnormal levels of inflammatory markers, prolonged use of antibiotics, median number of red cell transfusions required, risk of polyneuropathy, length of stay in the intensive care unit, and requirements for prolonged MV [23,24];
- Supportive therapies: goal-directed hemodynamic support combined with targeted pharmacological and immunological therapies and use of low-dose steroids [25] are critical elements for the proper management of sepsis. Proper nutrition accompanied by effective supportive therapies (prophylaxis against stress ulcers, administration of anticoagulants and dialysis) must be provided. The child must be treated by highly qualified physicians and nursing staff.

Use of drotrecogin alfa (activated)

In children, as in adults, acquired deficiencies in protein C are found in most patients with severe sepsis and are associated with an increased risk of mortality. Moreover, the diminished or even absent expression of endothelial thrombomodulin imposes an additional severe restriction on activated protein C generation. Altogether, both the levels and activation of protein C are diminished considerably during severe sepsis.

Pediatric patients with severe sepsis manifest sepsis-induced coagulopathy, including protein C deficiency comparable to that seen in adults with severe sepsis, and drotrecogin alfa (activated) could improve survival, as demonstrated in adults with severe sepsis [26].

> **"In children, as in adults, acquired deficiencies in protein C are found in most patients with severe sepsis and are associated with an increased risk of mortality."**

Drotrecogin alfa (activated) is a natural anticoagulant, also known as activated protein C, which is manufactured as a recombinant human protein. Drotrecogin alfa (activated) is an antithrombotic and profibinolytic agent that also possesses anti-inflammatory and antiapoptotic properties. Drotrecogin alfa (activated) produced dose-dependent reductions in the levels of markers of coagulation and inflammation in patients with severe sepsis.

The pharmacokinetics, pharmacodynamic effects and safety profile of drotrecogin alfa (activated) in pediatric patients are similar to those in adult patients [27].

Nadel *et al.* did not record any efficacy of drotrecogin alfa (activated) in children with severe sepsis; serious bleeding events were similar between treated and control groups and the overall safety profile was acceptable, except in children younger than 60 days [26].

In another study, subgroups at higher risk of death were identified and the change in protein C level from baseline was predictive of survival [28]. The most significant complication observed when using drotrecogin alfa (activated) in children with severe sepsis was bleeding. Risk factors for serious bleeding appeared to be multiple organ failure, thrombocytopenia and coagulopathy.

Bleeding is a more common complication in drotrecogin alfa (activated)-treated patients than in placebo recipients, and many of the episodes of bleeding are procedure related. De Backer demonstrated that bleeding did not outweigh the benefits of drotrecogin alfa (activated), as there was an overall survival benefit, provided only patients at high risk of death from sepsis were treated with drotrecogin alfa (activated) [29].

At present, drotrecogin alfa (activated) in children with severe sepsis does not result, as in adults, in a difference in the resolution of vasopressor-dependent hypotension versus placebo, and most patients continued to require vasopressor support after 72 additional hours of treatment. Treatment did not reduce 28-day all-cause mortality and in-hospital mortality or improve organ function compared with placebo, although there was a lower percentage change in D-dimers, and increases in protein C levels were numerically greater on extended infusion. The risk of severe bleeding imposes an accurate selection of patients to treat and the reduction, before and after treatment, of invasive methodologies that could increase this severe complication [30–32].

The future

Despite the projected increase in the treatment of sepsis in children in the future, there are specific opportunities to improve the management of the condition. Improvements can be made by identifying patients earlier through the use of globally accepted definitions, treating with the most appropriate medication and adopting agreed standards of care – all these initiatives will assist in reducing mortality. To identify patients with severe sepsis, clinicians should use less-invasive measures of hemodynamics and blood-flow monitoring, molecular techniques for identifying infectious agents, refined scoring systems, biomarkers and genetic screening. The use of early goal-directed therapies improves survival in patients with severe sepsis and these principles should help guide the resuscitative efforts. There should be support of oxygenation, and if mechanical ventilatory support is necessary, a lung-protective ventilatory support strategy should be used [33,34].

Drotrecognin alfa (activated) as an antithrombotic agent that will also restore the normal fibrinolytic pathways and reduce inflammation and possibly apoptosis could be helpful in selected patients. In the near future, we need controlled clinical trials to confirm the efficacy of drotrecogin alfa (activated), assess its side effects, possible safe indication and cost–benefit (therapy is very costly). Without placebo-control studies, definitive conclusions on the efficacy and safety of the treatment are not possible [28,35].

Patients with vasopressor-dependent septic shock should be treated with steroid replacement therapy that should be continued in those patients in whom the cortisol concentration is less than 25 g/dl. Hyperglycemia must be tightly controlled in severely ill patients in order to reduce infectious complications. Prevention of organ dysfunction, complications of critical illness and secondary infections should be a priority in patients with severe sepsis and septic shock.

Financial & competing interests disclosure

The author has no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

No writing assistance was utilized in the production of this manuscript.

References

1 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.* 167, 695–701 (2003).

2 Brun-Buisson C. Epidemiology of severe sepsis. *Presse Med.* 35(3 Pt 2), 513–520 (2006).

3 Hack CE, Zeerleder S. The endothelium in sepsis: source of and a target for inflammation. *Crit. Care Med.* 29(7 Suppl.), S21–S27 (2001).

4 Anderson MR, Blumer JL. Advances in the therapy for sepsis in children. *Pediatr. Clin. North Am.* 44, 179–205 (1997).

5 Butt W. Septic shock. *Pediatr. Clin. North Am.* 48, 601–625 (2001).

6 Bajzar L. Thrombin activatable fibrinolysis inhibitor and an antifibrinolytic pathway. *Arterioscler. Thromb. Vasc. Biol.* 20, 2511–2518 (2000).

7 Faust SN, Heyderman RS, Levin M. Coagulation in severe sepsis: a central role for thrombomodulin and activated protein C. *Crit. Care Med.* 29(7 Suppl.), S62–S67 (2001).

8 Angus DC, Linde-Zwirble WT, Lidicker J *et al.* Epidemiology of severe sepsis in the United States: analysis of incidence, outcome, and associated costs of care. *Crit. Care Med.* 29, 1303–1310 (2001).

9 Sharma VK, Dellinger RP. Treatment options for severe sepsis and septic shock. *Expert Rev. Anti Infect. Ther.* 4, 395–403 (2006).

10 Girbes AR, Beishuizen A, Strack van Schijndel RJ. Pharmacological treatment of sepsis. *Fundam. Clin. Pharmacol.* 22, 355–361 (2008).

11 Raghavan M, Marik PE. Management of sepsis during the early 'golden hours'. *J. Emerg. Med.* 31, 185–199 (2006).

12 Dellinger RP, Levy MM, Carlet JM *et al.* Surviving Sepsis Campaign: international guidelines for management of severe sepsis and septic shock: 2008. *Crit. Care Med.* 36, 296–327 (2008).

13 Rivers EP, Coba V, Whitmill M. Early goal-directed therapy in severe sepsis and septic shock: a contemporary review of the literature. *Curr. Opin. Anaesthesiol.* 21, 128–140 (2008).

14 Iregui M, Ward S, Sherman G *et al.* Clinical importance of delays in the initiation of appropriate antibiotic treatment for ventilator-associated pneumonia. *Chest* 122, 262–268 (2002).

15 Oliveira CF, Nogueira de Sá FR, Oliveira DS *et al.* Time- and fluid-sensitive resuscitation for hemodynamic support of children in septic shock: barriers to the implementation of the American College of Critical Care Medicine/Pediatric Advanced Life Support Guidelines in a pediatric intensive care unit in a developing world. *Pediatr. Emerg. Care* 24, 810–815 (2008).

16 Brierley J, Carcillo JA, Choong K *et al.* Clinical practice parameters for hemodynamic support of pediatric and neonatal septic shock: 2007 update from the American College of Critical Care Medicine. *Crit. Care Med.* 37, 666–688 (2009).

17 De Backer D, Creteur J, Silva E *et al.* Effects of dopamine, norepinephrine, and epinephrine on the splanchnic circulation in septic shock: which is best? *Crit. Care Med.* 31, 1659–1667 (2003).

18 Ruggiero MS. Effects of vasopressin in septic shock. *AACN Adv. Crit. Care* 19, 281–287 (2008).

19 Choong K, Kissoon N. Vasopressin in pediatric shock and cardiac arrest. *Pediatr. Crit. Care Med.* 9, 372–379 (2008).

20 Sevransky JE, Levy MM, Marini JJ. Mechanical ventilation in sepsis-induced acute lung injury/acute respiratory distress syndrome: an evidence-based review. *Crit. Care Med.* 32(11 Suppl.), S548–S553 (2004).

21 The Acute Respiratory Distress Syndrome Network. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. *N. Engl. J. Med.* 342, 1301–1308 (2000).

22 Marraro GA. Protective lung strategies during artificial ventilation in children. *Paediatr. Anaesth.* 15, 630–637 (2005).

23 NICE-SUGAR Study Investigators, Finfer S, Chittock DR, Su SY *et al.* Intensive versus conventional glucose control in critically ill patients. *N. Engl. J. Med.* 360, 1283–1297 (2009).

24 Fahy BG, Sheehy AM, Coursin DB. Glucose control in the intensive care unit. *Crit. Care Med.* 37, 1769–1776 (2009).

25 Valoor HT, Singhi S, Jayashree M. Low-dose hydrocortisone in pediatric septic shock: an exploratory study in a third world setting. *Pediatr. Crit. Care Med.* 10, 121–125 (2009).

26 Nadel S, Goldstein B, Williams MD *et al.* Researching Severe Sepsis and Organ Dysfunction in Children: a Global Perspective (RESOLVE) study group. Drotrecogin alfa (activated) in children with severe sepsis: a multicentre Phase III randomised controlled trial. *Lancet* 369, 836–843 (2007).

27 Barton P, Kalil AC, Nadel S *et al.* Safety, pharmacokinetics, and pharmacodynamics of drotrecogin alfa (activated) in children with severe sepsis. *Pediatrics* 113(1 Pt 1), 7–17 (2004).

28 Goldstein B, Nadel S, Peters M *et al.* ENHANCE: results of a global open-label trial of drotrecogin alfa (activated) in children with severe sepsis. *Pediatr. Crit. Care Med.* 7, 200–211 (2006).

29 De Backer D. Benefit–risk assessment of drotrecogin alfa (activated) in the treatment of sepsis. *Drug Saf.* 30, 995–1010 (2007).

30 Dhainaut JF, Antonelli M, Wright P *et al.* Extended drotrecogin alfa (activated) treatment in patients with prolonged septic shock. *Intensive Care Med.* 35, 1187–1195 (2009).

31 Martin G, Brunkhorst FM, Janes J *et al.* The international PROGRESS registry of patients with severe sepsis: drotrecogin alfa (activated) use and patient outcomes. *Crit. Care* 13, R103 (2009).

32 Lorenz BD, Smith TD, Laessig K *et al.* Recombinant activated protein C and risk of bleeding. *Crit. Care Med.* 37, 2141–2142 (2009).

33 Rivers EP, Ahrens T. Improving outcomes for severe sepsis and septic shock: tools for early identification of at-risk patients and treatment protocol implementation. *Crit. Care Clin.* 24(3 Suppl.), S1–S47 (2008).

34 Balk RA. Optimum treatment of severe sepsis and septic shock: evidence in support of the recommendations. *Dis. Mon.* 50, 168–213 (2004).

35 Ahishakiye D, Lorent S, De Backer D *et al.* Drotrecogin alfa (activated) for severe sepsis: could we consider a shorter treatment period in patients with a favorable course? *J. Crit. Care* (2009) (Epub ahead of print).