Supportive therapy of sepsis in children

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In the recent years, sepsis is the leading cause of death in children worldwide. Antibiotic therapy and hemodynamic support are the basis of treatment given to patients who survive circulatory failure and organ dysfunction. However, these patients may still suffer from many complications such as pulmonary embolism or stress ulcer. Although there is no clear evidence to quantify the importance of such complications on outcome, the anticipated impact is huge, having in mind the exhausted physiologic reserves of critically ill patients. Therefore, the critical patients who are being treated for severe sepsis in intensive care units, in addition to basic therapy, often also receive diverse forms of supportive therapy. This review summarizes the current evidence regarding the application of supportive therapy, which is included in international and domestic guidelines for the diagnosis, prevention and treatment of sepsis, severe sepsis and septic shock.

Key words: sepsis, supportive therapy, children

INTRODUCTION

Despite the improvement of the understanding of the pathophysiology and treatment, in recent years, sepsis is the leading cause of death in children worldwide. The most significant cause of death in severe sepsis and septic shock is multiorgan dysfunction, which occurs due to a progressive tissue hypoperfusion. Antibiotic therapy and hemodynamic support are the basis of treatment given to patients who survive circulatory failure and organ dysfunction. However, these patients may still suffer from many complications such as pulmonary embolism or stress ulcer. Although there is no clear evidence to quantify the importance of such complications on outcome, the anticipated impact is huge, having in mind the exhausted physiologic reserves of critically ill patients. Therefore, the critical patients who are being treated for severe sepsis in intensive care units, in addition to basic therapy, often also receive diverse forms of supportive therapy.

Supportive therapy is the application and implementation of various therapeutic procedures such as the administration of blood, blood products and immunoglobulins, mechanical lung ventilation, nutrition, sedation and muscle relaxation, stress ulcer and deep venous thrombosis prophylaxis, renal replacement therapy, and other. There are few pediatric studies that have monitored the effects of supportive therapy on outcome of patients with severe sepsis.

CORTICOSTEROIDS

Evidence for the use of corticosteroids in severe sepsis and septic shock has often been conflicting. The Surviving Sepsis Campaign (SSC) guidelines recommend considering corticosteroid therapy in children with fluid-refractory, catecholamine-resistant shock and suspected or proven absolute adrenal insufficiency.

Patients who persist with shock in spite of rapid fluid administration and continuous infusions of catecholamine may have adrenal insufficiency, and approximately 25% of children with septic shock have absolute adrenal insufficiency. Patients at risk for absolute adrenal insufficiency include purpura fulminans, recent or chronic treatment with corticosteroids, hypothalamic or pituitary abnormalities, or adrenal insufficiency (congenital or acquired).

Initial treatment is hydrocortisone infusion given at stress doses 50 mg/m²/day or 2 mg/kg/day, intermittent or continuous infusion, maximum dose 50 mg/kg per day.
No large randomized controlled trials (RCT) examining corticosteroids use in pediatric septic shock have been completed. However, a meta-analysis of small trials showed no benefit attributable to corticosteroid therapy 7.

**BLOOD PRODUCTS AND PLASMA THERAPIES**

Hemoglobin is essential for tissue oxygen delivery and important in the overall management of the septic child who is haemodynamically unstable (poor cardiac output, low mean arterial pressure) with impaired oxygen delivery 8. The optimal hemoglobin for a critically ill child with severe sepsis is not known. The SSC guidelines suggested a hemoglobin concentration of >10 g/dL should be maintained in these patients. Once a shock has been resolved, a lower transfusion threshold may be appropriate 4. In an intensive care unit trial of transfusion thresholds, subgroup analysis of children with haemodynamically stable sepsis showed no significant differences in mortality, length of stay, or progressive organ failure between restrictive and liberal transfusion thresholds (hemoglobin <7 g/dLv <9.5 g/dL, respectively). 9,3

A randomised controlled trial of early goal-directed therapy for pediatric septic shock using the threshold hemoglobin of (=10 g/dL for patients with SvO2 saturation less than 70% in the first 72 h of pediatric ICU admission, showed improved survival in the multimodal intervention arm 10.

In pediatric patients with severe sepsis, current guidelines recommend that platelets should be administered prophylactically when counts are = 10 x 10^9/L in the absence of apparent bleeding, as well when counts are = 20 x 10^9/L if the patient has a significant risk of bleeding. Higher platelet counts (= 50 x 10^9/L) are advised for active bleeding, surgery, or invasive procedures 4.

Plasma transfusions are frequently prescribed for critically ill children, although their indications lack a strong evidence base. Plasma transfusions are largely driven by physician conceptions of need, and these are poorly documented in pediatric intensive care patients 11. Plasma is infused with the goal of correcting laboratory clotting abnormalities, but only in the presence of active bleeding or before surgical or invasive procedures.

The SSC guidelines suggest the use of plasma therapies in children to correct sepsis-induced thrombotic purpura disorders, including progressive disseminated intravascular coagulation, secondary thrombotic microangiopathy, and thrombotic thrombocytopenic purpura.

Severe sepsis is characterized by activation of the coagulation cascade, the formation of micro-thrombi and consumption endogenous anticoagulant substances. Anti-thrombin III is a potent natural anticoagulant with strong anti-inflammatory action. Therefore, it is believed that the application of antithrombin may be of benefit in patients with sepsis. Results of clinical studies showed that the application of antithrombin III has no effect on 28-day mortality in patients with severe sepsis.

The use of activated protein C is not recommended in children with sepsis.

**IMMUNOGLOBULINS**

The application of immunoglobulin in the treatment of sepsis has been an open question for years. Results of larger multicenter RCT in adult and children with sepsis, severe sepsis or septic shock found no benefit for intravenous immunoglobulin (IVIG) 12. The Surviving Sepsis Campaign guidelines suggested not using intravenous immunoglobulins in pediatric patients with severe sepsis or septic shock. Intravenous polyvalent immunoglobulin M (enriched IVIG) due to its anti-bacterial, anti-inflammatory and immunomodulatory properties, has been investigated as one of these potentially valid adjunctive therapies. In adult septic patients, the use of IgM-eIVIG as an adjuvant to antibiotic therapy has led to a significant reduction in disease severity or mortality rate in intensive care units. Both retrospective and prospective trials suggests that IgM/ enriched IVIG may be beneficial in adult postoperative patients with severe sepsis (Table 1) 13,14,15,16. However, the reduction in mortality associated with the use of polyclonal enriched preparations as adjunctive therapy of sepsis in children needs to be confirmed by new research that would include a large number of respondents.

**GLUCOSE CONTROL**

In sepsis, infants are at risk for developing hypoglycemia because glycogen stores can become depleted. Therefore, it is important to monitor and treat hypoglycaemia with a continuous infusion of intravenous dextrose 10% normal saline (4 to 6 mg/kg/min or 6-8 mg/kg/min in newborns) to provide age appropriate glucose delivery 17.

Hyperglycaemia is common as part of the stress response to sepsis or as a side effect of corticosteroid treatment. Current practice regarding management of hyperglycaemia in this setting varies among institutions. Tight control, which is a treatment that targets blood glucose of 4.0-7.0 mmol/L, did not improve major clinical outcomes, while increasing the risk of hypoglycaemia 18.

Children are generally more prone to hypoglycemia when treated with insulin, therefore, insulin therapy should be used cautiously 1. The SSC recommend a protocolised approach to blood glucose management in pediatric patients with severe sepsis, commencing insulin dosing when two consecutive blood glucose levels are > 180 mg/dL 4,18.

**HYPOCALCAEMIA**

Hypocalcaemia is common in children with severe sepsis or septic shock. American College of Critical Care Medicine (ACCM) guidelines for the treatment of septic shock in children include a recommendation for the correction of metabolic abnormalities, including hypocalcaemia 19.

Children with persistent shock in association with an ionized calcium < 1.1 mmol/L (4.8 mg/dL) or symptomatic hypocalcemia should undergo correction with calcium gluconate 10% solution in a dose of 50 to 100
TABLE 1

<table>
<thead>
<tr>
<th>Requirements</th>
<th>Comments and Concepts</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severity</td>
<td>Persistance of septic shock or severe sepsis with &gt;2 organ dysfunctions after initial resuscitation/treatment</td>
<td>Heinrich et al (14)</td>
</tr>
<tr>
<td>Timing</td>
<td>As early as possible. Effects are expected if treatment is initiated within the first 6h of sepsis</td>
<td>Berlot et al (15)</td>
</tr>
<tr>
<td></td>
<td>Late start of treatment (48h) is not recommended</td>
<td>Expert opinion</td>
</tr>
<tr>
<td>Target groups/subgroups with the highest benefit probability</td>
<td>Abdominal infections in surgical patients (peritonitis) presumably Gram-negative bacterial infections</td>
<td>Rodriguez et al (16)</td>
</tr>
<tr>
<td>Dosage (80kg)</td>
<td>50ml/h for the first 6h (15g), followed by 15ml/h for 72h (54g), daily re-evaluation.</td>
<td>Expert opinion</td>
</tr>
<tr>
<td>Exclusion criteria</td>
<td>Standing DNR order of limitation of therapy, incurable metastatic malignant diseases, neutropenia due to hematological malignancies and according to SPC.</td>
<td>Expert opinion</td>
</tr>
</tbody>
</table>

mg/kg (0.5 to 1 mL/kg), up to 2 g (20 mL) by slow intravenous infusion. Calcium chloride 10% in a dose of 10 to 20 mg/kg (0.1 to 0.2 mL/kg), maximum dose 1 g (10 mL) provides an equivalent dose but should only be administered through the central line.

VENTILATION STRATEGIES

Timely intubation and mechanical ventilation based on clinical parameters rather than laboratory indices are crucial. As intubation and mechanical ventilation reduce respiratory-muscle oxygen demand and decrease the risk of aspiration. Based on data from adult patients lung-protective ventilation should be used. Multiple trials have now shown the benefit of a high positive end-expiratory pressure and low tidal-volume (6 to 8 mL/kg) approach. The goal of mechanical ventilation is to maintain a reasonable level of oxygenation while keeping the fraction of oxygen in inspired gas (FiO₂) below 0.6, allowing for some hypercapnia with the buffered pH 7.25.

Numerous trials have shown no preferences regarding ventilation modes (volume and pressure controlled), if the principles of protective ventilation have been equally followed.

Stress ulcer prophylaxis is commonly used in children who are mechanically ventilated, usually with H₂ blockers or proton pump inhibitors, although its effect is not known.

NUTRITION

A hypermetabolic state such as sepsis, in concert with bed rest and inactivity, may result in malnutrition. Enteral nutrition has been advocated as a means of reducing villous atrophy with increased intestinal permeability, with consequent reduction in the incidence of gut translocation and septic complications. Patients with sepsis who require pressors and narcotics often have a degree of gastroparesis and thus may benefit from transpyloric feeding, which may be associated with a shorter time interval to full strength feeds and decreased incidence of nosocomial pneumonia. The European Society of Parenteral and Enteral Nutrition recommends that if critically ill patients are not expected to be feeding within 3 days, enteral nutrition should be commenced.

Parenteral feeding should be used in children who cannot tolerate enteral nutrition.

SEDATION, ANALGESIA, NEUROMUSCULAR BLOKADE

Deep sedation is common in mechanically ventilated patients and current guidelines recommend use of sedation in critically ill mechanically ventilated patients with sepsis.

In patients with sepsis, the administration of intermittent sedation, daily sedative interruption, and systematic titration decrease the duration of mechanical ventilation.

Propofol should not be used for long-term sedation in children younger than 3 years because of the reported association with fatal metabolic acidosis. The use of etomidate and dexmedetomidine during septic shock should be discouraged, or at least considered carefully, because these drugs inhibit the adrenal axis and the sympathetic nervous system, respectively, both of which are needed for hemodynamic stability. ACURASYS studies results suggest the benefits of short-term myorelaxation (up to 48h) at an early phase of severe ARDS. Muscle relaxation allows protective lungs ventilation by less biorrather that results in a lower concentration of proinflammatory cytokines. Patients receiving neuromuscular
BICARBONAT THERAPY

Routine bicarbonate administration for treatment of lactic acidosis in sepsis is subject to ongoing debate. Current guidelines suggest that bicarbonate therapy is not beneficial in cases of metabolic acidosis in sepsis and may even cause harm by worsening intracellular acidosis. The use of bicarbonate can cause a load of sodium and fluids, increases lactate and CO₂ and causes reduction in serum ionized calcium. Severe acidemia in sepsis contributes to hemodynamic instability, which is the result of reduced myocardial contractility, arterial vasodilation, and impaired responsiveness to catecholamines.

Etiologic treatment is essential in metabolic acidosis, but optimization of oxygen delivery to tissues and reduction of tissue oxygen demand through sedation and mechanical ventilation are parts of the therapeutic strategy. However, the benefit of bicarbonate administration in metabolic acidosis in sepsis is controversial and remains a matter of debate in clinical practice.

DIURETICS AND RENAL REPLACEMENT THERAPY

The Surviving Sepsis Campaign has recommended the use of diuretics to reverse fluid overload when shock has resolved and if diuretics were unsuccessful than use continuous venovenous hemofiltration (CVVH) or intermittent dialysis to prevent > 10% total body weight fluid overload.

Continuous renal replacement therapy (CRRT) has become the preferred modality for the management of critically ill-children with sepsis induced acute kidney injury (AKI) and fluid overload (F.O), especially in developed countries. Different modes of CRRT eliminates the compulsion for fluid restriction and allows the provision of medications, blood products, and nutrition in critically ill children with multiorgan failure. Another potential use of CRRT is the removal of inflammatory cytokines and endotoxins in septic patients. One retrospective study of critically ill children with multiple-organ dysfunction syndrome reported that patients with less fluid overload before continuous venovenous hemofiltration had better survival. The critically ill children treated in an intensive care unit, in addition to basic therapy, often receive various forms of supportive therapy. It is beneficial in some cases, whereas in some other, such as advanced multiple-organ dysfunction, it does not contribute to survival. In order to estimate the overall effect of various forms of supportive therapy on the outcome of the treatment, additional trials are necessary.

SAŽETAK

POTPORNA TERAPIJA SEPSE KOD DECE

Uprkos poboljšanju razumevanja patofizijologije i lečenja, sepsa je poslednjih godina vodeći uzrok smrtnosti kod dece širom sveta. Antibiotička terapija i hemodimanska potpora predstavljaju osnovu lečenja, ali se kod bolesnika koji prežive cirkularnom insuficijenciju i organsku disfunkciju mogu javiti brojne komplikacije poput plućne embolije ili stes ulkusa. Iako u literaturi ne postoje jasni dokazi o uticaju ovih komplikacija, on je nesumnjivo značajan imajući u vidu smanjenje fiziološke rezerve ovih bolesnika. Zbog toga kritično oboleli koji se leže od teške sepsa u jedinicama intenzivnog lečenja često dobijaju poed osnovne i raznovrsne oblike potpore terapije. Ovaj pregled sumira trenutne dokaze u vezi primene potpone terapije, a koji su sadržani u medijunaradnim i domaćim smernicama za dijagnostiku, prevenciju i lečenje sepsa, teške sepsa i septičnog šoka.

Ključne reči: sepsa, potporna terapija, deca

REFERENCES


