Management of neonatal sepsis in term newborns

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Abstract

Neonatal sepsis is a common and deadly disease. It is broadly defined as a systemic inflammatory response, occurring in the first four weeks of life, as a result of a suspected or proven infection. Yet, more reliable and consistently applied diagnostic criteria would help improve our knowledge of the disease epidemiology. Several therapeutic attempts to control systemic inflammation in sepsis were unsuccessful. Immediate empirical administration of broad-spectrum anti-microbials, aggressive fluid resuscitation, and vaso-active or inotropic support (or both) are the mainstays of the therapeutic management of neonatal sepsis.

Introduction

Worldwide, 360,346 neonates died from sepsis and other infections in 2011 [1]. By definition, "neonatal" pertains to the first four weeks postnatal, whether born prematurely or at term. This article will pay particular attention to neonatal sepsis in term babies and review recent evidence published over the last two years. We will also focus our discussion on the management of neonates admitted to the pediatric intensive care unit (ICU) for a neonatal sepsis.

1. Diagnostic criteria of neonatal sepsis

In 2005, the International Pediatric Sepsis Consensus Conference defined sepsis as a "systemic inflammatory response syndrome (SIRS) in the presence of or as a result of suspected or proven infection" [2]. A SIRS is considered present if at least two of the following four criteria are observed, one of the two being abnormal temperature or leukocyte count:

• Core temperature of more than $38.5\,^{\circ}$C or less than $36\,^{\circ}$C.

• Tachycardia, or bradycardia for children younger than 1 year old.

• Mean respiratory rate of more than 2 standard deviations (SDs) above normal for age or mechanical ventilation for an acute process not related to underlying neuromuscular disease or the need for general anesthesia.

• Leukocyte count elevated or depressed for age (not secondary to chemotherapy-induced leukopenia) or more than 10% immature neutrophils.

The diagnostic criteria listed above were developed to improve the diagnosis of pediatric sepsis, from newborns to adolescents up to 18 years of age; the diagnostic value of these criteria has not been estimated in neonatal sepsis.

Other diagnostic criteria have been suggested. In 2010, a group of European experts suggested a list of seven clinical and six laboratory parameters defining late-onset neonatal sepsis. In a prospective study, Lutsar et al. [3] showed that the predictive value of these criteria to recognize cases of culture-proven late-onset neonatal sepsis was 61% (95% confidence interval (CI) 52% to 70%), which is almost equivalent to tossing a coin. Classic sepsis criteria, such as impaired peripheral perfusion, increased oxygen requirement, and mottled skin, were observed in only 40% of affected children! Hence, a more reliable list of diagnostic criteria for neonatal sepsis should be developed and validated, which should probably include not only clinical data but

also laboratory parameters like cord blood level of procalcitonin or interleukin (IL)-6 or both [4,5].

2. Septic states
Experts in critical care medicine defined three septic states: sepsis, severe sepsis, and septic shock [2,6]. Does it make sense? Leclerc *et al*. showed that there is an added prognostic value if one differentiates these three septic states: the hazard ratios of mortality were 7.43 (95% CI 1.01 to 54.8) in critically ill children with sepsis, 27.40 (95% CI 3.26 to 230.4) in patients who contracted severe sepsis, and 61.40 (95% CI 7.8 to 486.1) in those with septic shock [7]. Clearly, the frequency of these three septic states must be taken into account in all randomized controlled trials (RCTs) where the efficacy of a treatment is studied in critically ill children, including neonates. The relationship between SIRS, sepsis, severe sepsis, septic shock, and multiple organ dysfunction syndrome (MODS) is illustrated in Figure 1.

3. Epidemiology
There are good studies on the epidemiology of severe sepsis, but not on sepsis, probably because many studies were based on a public database using International Classification of Diseases, Ninth Revision (ICD-9) codes. The Centers for Medicare & Medicaid Services (www.cms. gov) do not reserve an ICD-9 code for sepsis, but do so

Figure 1. Relationship between systemic inflammatory response syndrome (SIRS), sepsis, severe sepsis, septic shock, and multiple organ dysfunction syndrome (MODS).

Upper panel: relationship according to infectious etiology. Lower panel: Venn diagram.

for severe sepsis (995.92) and septic shock (785.52 and 998.02). In 1995, the incidence rate of severe neonatal sepsis and septic shock in 7 American states was 3.6 cases per 1,000 of population with a case fatality rate of 10.3%; about one third of severe neonatal sepsis was observed in term babies [8,9]. Similarly, 62 neonates were admitted to the pediatric ICU Sainte-Justine Hospital over a 1-year period (2010); frequency rates were 50% (n = 31) for SIRS alone, 29% (n = 18) for sepsis, 11% (n = 7) for severe sepsis, and 6% (n = 4) for septic shock [10].

By definition, early-onset sepsis happens within the first week after birth (some would say in the first 72 hours of life [11]). Its incidence in the UK is about 0.5 per 1,000 term births; the mortality rate is about 10%, and severe permanent disability is frequently observed in survivors [12]. Late-onset sepsis occurs between the 8th and the 89th day after birth. In a prospective study conducted in Taiwan, 17% of late-onset neonatal sepsis cases (118 out of 713) were detected in term neonates rather than premature babies.

4. Sepsis-related complications
Sepsis can cause many severe complications happening while the patient is in the ICU, like acute lung injury, cardiac dysfunction, capillary leak syndrome, coma, critical care neuromyopathy, thrombosis, coagulopathy, hemorrhage, hepatic failure, renal failure, reactive hemophagocytic syndrome, hyperglycemia, nosocomial infections, MODS, and death [13]. The epidemiology of these complications is not so well determined. These acute complications may be compounded by alteration of drug pharmacokinetics in sepsis. For example, Pettersen *et al*. [14] showed that clearance of pantoprazole was profoundly decreased in SIRS and sepsis. Moreover, many drugs have a large volume of distribution and decreased clearance in neonates, more so than in older patients [11]. Actually the effect of SIRS, sepsis, MODS, and age on the pharmacology of many drugs given to critically ill neonates remains to be ascertained.

After the ICU stay, numerous long-term complications are also described in the literature, such as persistent inflammation [15]; severe chronic pain [16]; neurodevelopmental problems [17]; ICU-acquired weakness [16,18]; stress ulcer-related upper gastro-intestinal bleeding [19]; persistent renal dysfunction [20,21]; sleeping problems and post-traumatic stress disorder [22]; depression, acute stress disorder, and anxiety [23]; and poor quality of life of the patients or their family or both [16,24]. Experts in critical care medicine coined the terms "post-intensive care syndrome" (PICS) [25] and "post-intensive care syndrome-family" (PICS-F) [23] to raise
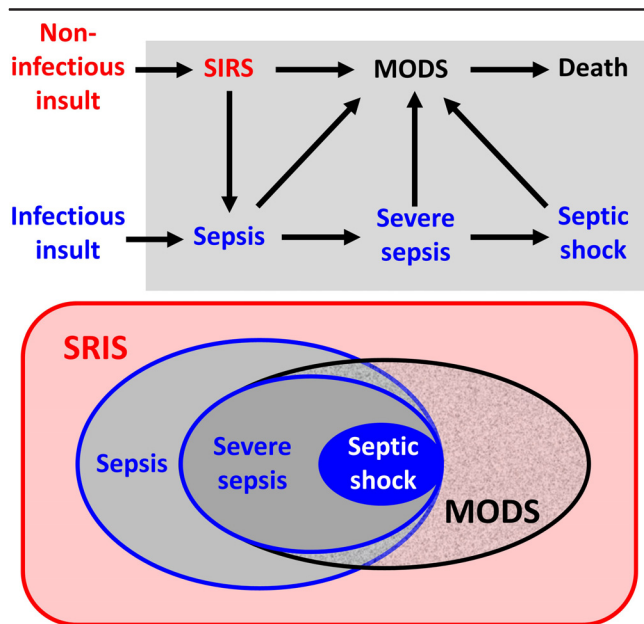
attention to these frequently under-recognized chronic and devastating conditions. The epidemiology and the clinical impact in neonates of sepsis-related long-term sequelae — PICS and PICS-F — are unknown. The risk of long-term neuropsychological deficits and educational difficulties is higher in school-aged children admitted for septic illness and meningo-encephalitis compared with children admitted for other ICU-related illnesses [26]; it is unknown whether this holds true in newborns.

5. Management

Sepsis, by definition, is caused by an infection; not surprisingly, there is a consensus that an anti-infectious agent must be given as early as possible to all patients with sepsis [27]. Over the past 20 years, a large number of RCTs have attempted to control the systemic inflammatory storm characterizing sepsis with little success. Supportive care of dysfunctional organs is therefore the mainstay of therapy, which might include mechanical ventilation, fluids, vasopressors or inotropes (or both), and blood transfusion.

5.1. Treatment against infectious agents

There is no clear consensus on the management of term newborns with sepsis, and this probably explains the large variation in the practice pattern observed among British practitioners [12]. However, anti-microbial agents are unequivocally the cornerstone therapy of sepsis.

Most cases of early-onset sepsis in term newborns are caused by Group B *Streptococcus*, but Gram-negative bacteria are not rare. The most common choice of antibiotics in 125 UK hospital guidelines was a combination of benzylpenicillin and intravenous gentamicin [12].

Most cases of late-onset sepsis are attributable to *Staphylococcus species* and Group B *Streptococcus*, but about one third are caused by Gram-negative organisms (*Klebsiella spp*, *Escherichia coli*, etc.) [28]. In a prospective study of 113 consecutive newborns with late-onset neonatal sepsis, Lutsar *et al.* [3] found more than 18 different empiric antibiotic regimens; most included ampicillin, a third-generation cephalosporin, or meropenem, plus an aminoglycoside or vancomycin. Current management of late-onset neonatal sepsis is extremely variable. An ongoing large RCT compares meropenem versus standard care [29].

There is a consensus that antibiotics must be started as soon as possible once a neonatal sepsis is suspected, but there is a debate as to when they should be stopped [30]. Intravenous antibiotics are usually prescribed for 21 days for cases of neonatal meningitis and for 10 to 14 days in other severe neonatal infections. There is more and more

concern that antibacterial agents are overused. There is indeed a risk to undertreat an infection if the course of antibiotics is too short, but keeping antibiotics for a prolonged time is associated with the emergence and spread of resistance to antibiotics. Some experts are also concerned by long-term effects on microbiota implantation and possible impact on future child health [31]. In 2013, the World Health Assembly underlined the risk of antibiotic resistance to global health security [32]. Can we stop antibiotics sooner, at least in patients for whom the source of sepsis is unclear or no germs have been found (or both)? Some investigators believe that markers like progression over time of procalcitonin levels or of neutrophil counts might be good indicators to stop antibiotics. A large multicenter RCT evaluating whether procalcitonin levels could be used to guide antibiotic therapy in adults with non-microbiologically proven sepsis was interrupted early because of failure to demonstrate benefit [33]. In the Procalcitonin and Survival Study (PASS), procalcitonin-guided anti-microbial escalation in the ICU did not improve survival and resulted in prolonged ICU stay and more organ damage [34]. No studies have been undertaken in neonates.

5.2. Treatment aiming to control the systemic inflammatory process

Sepsis is a systemic response to fight off pathogens. However, this systemic inflammatory process can become uncontrolled, resulting in MODS and death. Thus, it makes sense to try to control the SIRS in patients with sepsis.

More than $1 billion has been spent to complete RCTs aiming to find a magic bullet that would modulate the inflammation the right way and that would improve the outcome of patients with sepsis. High levels of cytokines like tumor necrosis factor-alpha (TNFα), IL-1, IL-10, and platelet-aggregating factor (PAF) are observed in patients with sepsis; however, all RCTs using molecules active against these cytokines (anti-IL-1, anti-IL-10, and anti-PAF) were negative, as were RCTs on recombinant human soluble thrombomodulin [35] and on recombinant bactericidal permeability-increasing protein (BPI) [36]. Some molecules were detrimental, like nitric oxide synthase inhibitors [37] and recombinant tissue factor pathway inhibitor [37]. However, one large RCT using activated protein C in adults with sepsis — the Protein C Worldwide Evaluation in Severe Sepsis (PROWESS) study — was positive [38]. Thereafter, an RCT conducted in 477 children reported no positive effects and more severe hemorrhage, including intracranial bleeding [39]. Actually, the PROWESS study in adults was probably a false positive: two other RCTs reported no difference at all in the outcome of adults in septic shock [40,41]. A meta-analysis recommends that activated protein C not be

used to treat neonatal sepsis [42]. In any case, activated protein C is now withdrawn from the market.

At present, there is no evidence that mediator modulation therapy works. Nonetheless, is there any hope that we can find a magic bullet? In 2013, Qiu *et al.* published a meta-analysis reporting that anti-TNF (anti-TNFα-Ab and anti-TNFα receptors) "produces a modest decrease in the risk of mortality of patients with sepsis" (relative risk 0.93, 95% CI 0.88 to 0.98) [43]. The conclusion was that "a definitive trial demonstrating the potential benefit of such agents might require at least 10,000 patients with sepsis" [43]. Would it make sense to undertake such a large-scale RCT for such a small effect size? Maybe not. Actually, there is a lot of redundancy and interactions between all pro- and anti-inflammatory mediators; it is hard to believe that modulating only one of them will cure patients with sepsis. Many experts in critical care medicine believe that there will not be any "magic bullet" and that a more general approach against the SIRS would be better. Many non-specific treatments of sepsis have been advocated.

The immune system of patients with severe SIRS is overwhelmed. Recent studies demonstrated that an impairment of patients' immune system called immunoparalysis could be the main contributor to the late mortality of patients with sepsis. Reduced expression of human leukocyte antigen (HLA)-DR on monocytes (mHLA-DR), lymphocyte apoptosis, and attenuated TNFα production are some of the underlying evoked mechanisms. In theory, it would thus make sense to attempt to enhance the capacity of the immune system in cases of neonatal sepsis. We should discuss at least three treatments: colony-stimulating factors (CSFs), immune globulins (IgGs), and optimal nutrition. (a) CSFs can increase neutrophil and macrophage counts. In theory, they should be useful in patients with neutropenia. In practice, a meta-analysis reported that the different types of CSFs do not seem to work in neonatal sepsis [44]. Granulocyte-CSF (G-CSF) and granulocyte-macrophage CSF (GM-CSF) cannot be recommended in neonatal sepsis. (b) IgGs are effective in adults with sepsis [45] but not in low-birth weight newborns (<1,500 g) [46] or in newborns with gestational ages of 31 to 42 weeks [47]. (c) A meta-analysis on the efficacy of immuno-modulating diets reported that they had no effect on mortality or length of stay of critically ill patients [48]. On the other hand, there were data suggesting that standard nutrition with added nutriments might be useful in critically ill adults [49]. An RCT published in 2013 reported that early provision of glutamine did not improve clinical outcomes; glutamine supplementation was even associated with an increased mortality in critically ill adults with MODS [50].

The optimal nutrition strategy and the best feeding route (enteral or parenteral or both) remain to be determined in patients with sepsis, including neonates.

Non-specific "cleaning" of inflammatory mediators to remove "bad humors" by extracorporeal blood purification techniques is another avenue. A meta-analysis of RCTs reported that, overall, blood purification techniques — hemofiltration, hemoperfusion, plasma exchange (i.e., plasmapheresis), or hemodialysis — decrease the mortality rate of patients with sepsis: risk ratio (RR) 0.69, 95% CI 0.56 to 0.84. The most positive effect was attributable to 10 RCTs on polymyxin B hemoperfusion (RR 0.63, 95% CI 0.50 to 0.80) and two RCTs on plasma exchange (RR 0.63, 95% CI 0.42 to 0.96) [51]. The efficacy of blood purification techniques must be estimated by a large RCT before they can be strongly recommended [52]. This holds true also in neonatal sepsis: the cost/benefit ratio should be different in neonates and infants since the risk of mortality is much lower in this population than in adults, while the technical risks should be at least similar to, if not higher than, those in adults (for example, more difficult intravenous access) [53].

Increased mortality is associated with both high and low cortisol levels. In the '80s, a large RCT proved that high-dose steroids (up to 30 mg/kg per day of methylprednisolone) increase mortality in cases of severe sepsis and septic shock [54]. However, some intensivists still believed that normal-dose steroids can be useful. In 2002, an RCT reported that a 7-day treatment with low-dose hydrocortisone (50 mg every 6 hours) and fludrocortisone (50 μg once daily) decreased 28th-day mortality in adults with septic shock and relative adrenal insufficiency [55]. In 2008, the Corticosteroid Therapy of Septic Shock (CORTICUS) RCT reported negative results [56]. Although it is clear that high-dose corticosteroid treatment provides no benefit and possibly harm in patients with sepsis, the role of corticosteroid treatment in patients with severe sepsis and septic shock remains controversial, and results from recent trials are contradictory [57]. At present, other large RCTs are being conducted that should bring about clear responses on the question in adults —for example, the Adjunctive Corticosteroid Treatment in Critically Ill Patients with Septic Shock (ADRENAL) study [58] — and children (NCT00732277), but none of these RCTs was conducted specifically in neonates.

5.3. Supportive care
The last update of the "Surviving Sepsis Campaign Guidelines for Management of Severe Sepsis and Septic Shock" was published in 2012 [59]. Key recommendations

included broad-spectrum empiric anti-microbial therapy within 1 hour of the recognition of sepsis, infection source control, septic work-up (at least urine, blood, cerebrospinal fluid cultures, and lung x-rays), and hemoglobin target of 7 to 9 g/dL in stable patients.

In cases of severe sepsis and septic shock, recommendations also included early initial resuscitation (<6 hours after first medical recognition of severe sepsis) with crystalloids (at least 30 mL/kg within 3 hours), ± vaso-active or inotropic agents or both (first-line norepinephrine, ± epinephrine, ± dobutamine if signs of cardiac dysfunction). The goal in adults is to maintain a mean arterial pressure of at least 65 mm Hg; in neonatal and pediatric sepsis, physical examination therapeutic endpoints such as capillary refill of not more than 2 seconds, normal peripheral pulses, urine output of more than 1 mL/kg per hour, or normal mental status might be more reliable endpoints than blood pressure to assess the adequacy of resuscitation. Albumin can be given in cases of refractory shock. Hydrocortisone is also an option in children with fluid- and catecholamine-resistant shock and with suspected or proven adrenal insufficiency, even though its efficacy remains to be determined (see above). Vasopressin and blood glucose control were also suggested, but two RCTs conducted in children failed to demonstrate any clinical benefit from the use of vasopressin [60] and tight glycemic control (72 to 126 mg/dL or 4.0 to 7.0 mmol/L versus less than 216 mg/dL or less than 12.0 mmol/L) [61]. Once shock is resolved, continuous veno-venous hemofiltration or intermittent hemodialysis can be considered in patients with refractory fluid overload (>10%). These guidelines should be implemented as soon as neonatal sepsis is suspected [27].

Guidelines are derived from expert opinions, but some key aspects of supportive care in severe sepsis have been evaluated by RCTs, such as goal-directed therapy and transfusion thresholds. The concept of "early-goal directed therapy" was suggested in 2001: Rivers *et al.* [62] randomly assigned 266 adults with severe sepsis or septic shock during the first 6 hours in the emergency department either to be monitored with central venous oxygen saturation (ScvO$_2$) or not. In patients allocated to ScvO$_2$ monitoring, a bundle of treatment was advocated in order to maintain the ScvO$_2$ over 70%; this bundle included, in sequential order, mechanical ventilation, fluid bolus up to 80 mL/kg, vasoactive drugs (dobutamine and vasoconstrictive therapy), and red blood cell (RBC) transfusion if the ScvO$_2$ was still under 70% after all of the other maneuvers were done. The mortality rates were 30.5% with early goal-directed therapy and 46.5% in controls. The reproducibility of these data was evaluated in the "Protocolized Care for Early Septic Shock" (ProCESS) study: protocol-based resuscitation—with or without

ScvO$_2$ monitoring—of adults treated for septic shock in the emergency department; protocol-based treatment did not improve outcomes (mortality and need for organ support) [63]. In children, De Oliveira *et al.* [64] completed an RCT involving 102 Brazilian children with severe sepsis or fluid refractory shock. The goal and bundle were similar to those of the study by Rivers *et al.* [61]. The mortality rates were 11.8% with early goal-directed therapy and 39.2% in controls. As few neonates were enrolled in the study (mean age of more than 5 years), generalizability to neonatal sepsis would need to be confirmed.

Improving oxygen delivery is one of the central goals of supportive care; this can be done by increasing the hemoglobin level. However, RBC transfusions are not perfectly safe [65]. What is the optimal RBC transfusion threshold of patients with sepsis? If less evidence for the ideal transfusion threshold in unstable patients is available, Transfusion Requirements in Pediatric Intensive Care Units (TRIPICU) explored that question in stable or stabilized children (mean arterial pressure of not less than 2 SDs below the mean for age and cardiovascular support — pressors/inotropes and fluids — not increased for at least 2 hours) [66]. The incidence rate of new and progressive MODS, including deaths, in a subgroup analysis of 137 patients with sepsis, severe sepsis, and septic shock was unchanged (13 in both arms), which suggests that a restrictive RBC transfusion strategy (hemoglobin threshold of 7 g/dL) may be safe in stable or stabilized children and neonates with sepsis, even if they are in septic shock [67]. Transfusion requirements in unstable neonates and infants with sepsis are unknown.

Conclusions

Early anti-microbial administration and supportive care are the mainstays of treatment of neonatal sepsis. More reliable diagnostic criteria are required: rapid identification of high versus low infectious risk newborns might be useful in order to expose to antibiotics only infected newborns and to stop antibiotics as soon as possible.

The treatment of neonatal sepsis is inconsistent. Many controversies in its management remain: even the duration of antibiotic therapy is a matter of debate. There is an urgent need for well-done RCTs and for the development of evidence-based guidelines for the management of neonates with sepsis.

Abbreviations

CI, confidence interval; CSF, colony-stimulating factor; ICD-9, International Classification of Diseases, Ninth Revision; ICU, intensive care unit; IL, interleukin; MODS, multiple organ dysfunction syndrome; PAF,

platelet-aggregating factor; PICS, post-intensive care syndrome; PICS-F, post-intensive care syndrome-family; PROWESS, Protein C Worldwide Evaluation in Severe Sepsis; RBC, red blood cell; RCT, randomized controlled trial; RR, risk ratio; ScvO$_2$, central venous oxygen saturation; SD, standard deviation; SIRS, systemic inflammatory response syndrome; TNF, tumor necrosis factor.

Disclosures

The authors declare that they have no disclosures.

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