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Septic Shock in Neonates

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1. Introduction

Every year 1.6 million of newborn infants die from sepsis (Lawn et al 2000). The prevalence of sepsis, meningitis, and other confirmed bacterial infections has been estimated to range between 1 to 5/1000 live births. Preterm infants are 20 times more likely to get infection than term infants with a prevalence of 1/230 (Haque KN 2003). Very low birth weight infants, evaluated and treated for infections are around 50% of all admissions to neonatal intensive care (Stoll et al 2003).

Sepsis is responsible for 30–80% increased risk of neuro-developmental impairment and 30–100% increase in odds for poor head growth and long term morbidity (Stoll et al 2004). 45% of late deaths in the Neonatal Intensive Care Unit (NICU) are caused by an infectious disease (Ince 2005). Despite assistance progress, mortality rates from sepsis have not declined over the last three decades (Haque 2003).

While the incidence of sepsis is known, the true incidence of septic shock in neonates has not been well documented. It is estimated to be around 1–5% of all infants with proven severe sepsis (Haque 2004). Kermorvant-Duchemin E. et al. (2008) reported septic shock in 1.3% of extremely low birth weight newborns with an associated mortality peaking at 71%.

2. Definition and risk factors

Infection, far from being a homogeneous condition, reflects a continuum from fetal inflammatory response syndrome to sepsis, severe sepsis, septic shock, multiorgan failure, and death. The difficulty for the clinician is to define precisely the phase in which his/her patient is at any given moment as the patient may move from one phase to another imperceptibly (Haque 2007).

Definition of sepsis derives from the international consensus definitions that have been adapted for pediatric and neonatal use, including term neonates (0–7 days) and newborns (1 week to 1 month) (Carcillo et al 2002, Goldestein et al 2005) (tab 1 and 2). Sepsis is a complex entity, with wide variations in clinical, laboratory parameters and outcome. Septic shock is a

condition of inadequate tissue perfusion secondary to cardiovascular dysfunction occurring in the course of suspected or certain systemic infection, requiring fluid resuscitation or inotropic support (Goldstein et al 2005, Haque 2007). This definition, valid for newborns born > 37 weeks gestation, is problematic for preterms due to immaturity of organ systems and transitional physiology (Jones 2008). For these reasons, the hemodynamic response to septic shock and optimum clinical interventions in preterm neonates are not well understood.

Risk factors for a neonate to develop septic shock have not been described in detail, but they overlap those for sepsis. Prenatal risk factors include maternal intrapartum fever, chorioamnionitis or prolonged rupture of membranes, treatment with steroids, group B *Streptococci* recto-vaginal colonization. A few days after aspiration of infected amniotic fluid during the birth, the neonate may manifest with signs and symptoms of neonatal shock. Gram-positive germs as group B *Streptococci* are those most frequently described as causative agents in early neonatal sepsis, even if, more recently, some gram-negative agents have been frequently described (*Escherichia coli*, *Klebsiella spp.*, *Enterobacter spp.*). This probably is due to the intrapartum use of antibiotics directed against gram-positive pathogens that allows gram-negative flora's outbreak (Schrag et al 2007). Other microbes include *Listeria monocytogenes*, coagulase-negative staphylococci (ConS) (22%) and nonpyogenic streptococci (9%) (Muller-Pebody et al. 2011).

Post-natal risk factors include: male gender, birth weight less than 1000 g, hypogammaglobulinemia, parenteral nutrition, central venous catheters, steroids or drugs that decrease gastric acidity, prolonged duration of mechanical ventilation, hand contamination of health care personnel, mother and other family members, aspiration of feeds, and disruption of skin integrity. *Staphylococcus aureus* is the most frequent germ in late sepsis. Gram negative and ConS, almost half the isolates (45%), are the predominant pathogens associated with late severe sepsis or septic shock ((Muller-Pebody et al. 2011).). Also viruses (*herpes simplex*, *enteroviruses*) or fungi (*candida albicans*) have been associated with fulminant neonatal sepsis. Compared with ConS, Gram-negative infections are associated with a higher mortality: one-fifth of those infected by gram negatives die. (Stoll et al 2002, Gordon et al 2006).

3. Pathophysiology

The development of septic shock is associated with elevated levels of proinflammatory cytokines including IL-1 β , IL-6, IL-8 and TNF α (Lynch et al 2008). The inflammatory cytokine response to sepsis in neonates is more pronounced and faster than in adults and associated with an increase in early mortality (<48 hours), while the compensatory anti-inflammatory response system appears to be immature, with both term and preterm infants demonstrating profoundly decreased IL-10 production and a lower amount of transforming growth factor beta-positive lymphocytes, than do adults, after lipopolysaccharide (LPS) stimulation (Langer et al 2006). In addition, in the neonate eosinophils, macrophages and polymorphonuclear neutrophils have reduced surface binding components and have defective opsonization, phagocytosis and antigen-processing capabilities, leading to a generally less robust response to pathogen exposure (Urlichs et al 2006, Marodi et al 2006). Several studies indicate that the mechanisms of sepsis include excessive activation of the coagulation cascade, inhibition of endogenous natural anticoagulants, and impaired fibrinolysis (Short 2004). Within the microcirculation, this leads to fibrin deposition,

contributing to hypoperfusion that eventually results in tissue damage and organ dysfunction. On the other hand, consumption of coagulation factors and platelets promotes a bleeding tendency that may clinically manifest as petechiae, ecchymoses, and sometimes hemorrhages, all of which are associated to increased mortality. (Fourrier et al 1992, Kenet et al 2008, Levi 2010). The immune system and coagulation are closely related. Cytokines mediating neutrophils activation and migration to the tissues and extravascular compartment, generate the thrombin and fibrin deposit formation, triggering tissue factor, that is considered the main both septic shock and diffuse tissue injury mediator. That's why, disseminated intravascular coagulation (DIC) is not so rare in septic shock, resulting from the sustained thrombin generation. Thrombin, in turn, stimulates more inflammatory mediators' formation. Fibrin formation stabilizes platelet plugs, in addition to its important role in pathogens' adhesion to the leukocyte surface, facilitating phagocytosis (Levi et al 2010). The Toll-like receptors (TLRs), found in immune system cells, have a fundamental role in the septic shock pathophysiology. They can interfere with the cardiovascular system depending on the systemic inflammatory response to pathogen. They are able to detect pathogens-associated molecular patterns (PAMPs), causing the induction of pro-inflammatory and anti-inflammatory mediators, particularly cytokines. (Gao et al 2008, Gao et al 2005, Fleer et al 2007). TLRs, present in endothelial cells, alveolar epithelium cells, and cardiomyocytes, may induce TNF α and IL-1 β production, responsible for the early myocardial dysfunction in gram-negative (TLR4) and gram-positive (TLR2) germs severe sepsis. (Zhang et al 2007). Unlike in adults, TLRs genetic polymorphisms and signaling proteins (MYD88) regulating the host response to infection and different septic shock patterns, are less characterized in neonates. (Zhang et al 2007, Cornell et al 2010).

In septic shock the action of inflammatory mediators leads to damage of the capillary wall with loss of vascular tone, resulting in vasodilatation and reduction of systemic vascular resistance with low to normal blood pressure and increased systemic blood flow. Thanks to the compensatory heart rate increase, skin is well perfused and warm (warm shock). In the late phase of shock there is a reduction of myocardial contractility that leads to vasoconstriction, decreased systemic blood flow, decreased pulse volume, cold periphery, prolonged capillary refill time, and increased vascular tone in an attempt to centralize the circulation (cold shock). Shock, that is not recognized and treated, progresses from early to late stages, referred to as compensated, uncompensated, and irreversible shock. (Jones et al 2008).

The hemodynamic response to sepsis of a newborn is markedly different from that of an adult or an older child with relevant difference between the preterm and the term newborn owing to the different anatomical structure, the functional activity and excitation-contraction (Brierley et al 2008).

In the neonates, the absence of hypotension does not preclude shock that is mainly related with blood flow rather than blood pressure as the mean blood pressure may be in the normal range due to compensatory mechanisms (Cayabyab et al 2009).

In the evaluation of blood pressure, the physiological variability with age and gestational age should be taken in account (Silveira et al 2010). Despite this, 30 mmHg should be considered the absolute minimum tolerable of in the extremely premature infants. (Munro et al 2004). Furthermore in critically ill prematures, refractory hypotension may be related to patent ductus arteriosus, intraventricular hemorrhage and poor prognosis. (Carcillo et al 2002). While in healthy prematures lower mean blood pressure levels may be accepted being associated with appropriate cerebral perfusion and normal cardiac output (30), in septic shock hypotension is not permissive and need a therapeutical intervent.

The neonate is unable to increase the stroke volume or myocardial contractility in case of sepsis, due to different physiologic abnormalities: a relatively decreased left ventricular muscle mass (Joyce et al 2004), an impaired left ventricular diastolic function and alterations in mid-wall left ventricular fractional shortening (Kozak-Barany et al 2001). These differences may be mediated by alterations in calcium channel expression and activity, in ATP-sensitive potassium channel function and in β -receptor coupling (Huang et al 2006, Morrissey et al 2005).

These developmental alterations make the neonates critically dependent on increasing the heart rate to generate increased cardiac output, but unable to compensate in this manner because of their relatively higher baseline heart rate (Carcillo et al 2009).

The development of cardiovascular dysfunction and septic shock make newborn infants susceptible to sudden cardiac deterioration, also because left ventricular systolic performance is highly dependent on afterload. So the reopening of a patent ductus arteriosus and the development of persistent pulmonary hypertension (Carcillo et al 2002) may complicate the cardiovascular response to sepsis.

4. Clinical features

Septic shock should be suspected in any newborn with tachycardia, respiratory distress, poor feeding, poor tone, poor color, tachypnea, diarrhea or reduced perfusion particularly in the presence of prenatal risk factors like chorionamnionitis or prolonged rupture of membranes. (Kisson et al 2010)

The predominant clinical sign is circulatory failure that can coexist with multiple organ damage, severe coagulopathy, metabolic acidosis and electrolyte alterations. During the compensated stage blood pressure remains normal and cardiac output is maintained. Clinical signs are pallor, increased capillary refill time (refill > 2''), tachycardia, decreased urine output, mild agitation and confusion, signs of cerebral hypoperfusion. When compensatory mechanisms fail, cardiac output falls resulting in a reduction of oxygenation and increase of anaerobic metabolic mechanisms. The toe/core temperature gap widens, and the peripheries become cool and mottled, the pulse becomes small and weak, oliguria worsens to the point of anuria. The further deterioration of cerebral perfusion leads to irritability, sleepiness and impairment of conscious state. Despite intense peripheral vasoconstriction, hypotension occurs. In the meantime, the clinical condition of the newborn becomes critical. The lack of adequate resuscitation leads to a state of irreversible shock which causes the death of the baby. Furthermore, in newborn babies septic shock may be complicated by the physiological transition from fetal to neonatal circulation. Newborn septic shock is typically accompanied by acidosis and hypoxia that can lead to an increase in pulmonary resistance and persistence of the patent ductus Botallo, resulting in persistent fetal circulation which will result in right ventricle failure with right to left shunting at the atrial and ductus arteriosus levels causing cyanosis, hepatomegaly and tricuspid regurgitation. (Brierley et al 2009)

5. Diagnosis

Early recognition of neonatal shock allows to establish an adequate therapy and save lives (Han et al 2003). Ideally shock should be clinically diagnosed before hypotension occurs. Laboratory diagnosis is mainly based on controlling the blood gases, complete blood

count with differential, glucose, electrolytes, albumin, creatinine, urea, lactate, blood pyruvate, coagulation parameters, serum and urine osmolarity, cultures with susceptibility testing (blood culture, urine culture, culture catheters or drainage).

Research offers an increasing number of biological markers for early detection of sepsis, but many of them failed to differentiate between sepsis and other non septic critical illness. The most commonly available and used markers are shown in table 3 (Haque 2005).

Procalcitonine (PCT) revealed superior to C reactive protein (CRP) to differentiate children with sepsis from those with septic shock (Simon et al 2006), mainly at admission and 12 h later (Fioretto et al 2010). Baruti Garufi et al. (2010) found that the increase of PCT levels was related to the severity, course and prognosis of disease. Procalcitonin values were significantly increased in neonates with septic shock (92.5 ng/mL) compared to those with systemic inflammatory response syndrome- SIRS (41 ng/mL), neonatal sepsis (10,26 ng/mL) and purulent meningitis (9,80 ng/mL). CRP was increased without statistical differences in all stages. Casado-Flores et al. (2006) observed a stronger correlation between PCT and PRISM score in septic shock than RCP, possibly due to the kinetics of this mediator that after an approximately 2 h latency period from initial stimulus, rises to a plateau within 12–48 h and then slowly declines.

Serum lactate level is considered an important biomarker to distinguish sepsis from septic shock. Normally a small amount of lactate is produced and all healthy tissue have the capacity to convert it, in aerobic condition, to pyruvate, used for cellular metabolism. When sepsis-associated multisystem organ failure occurs, this metabolic capacity, in anaerobic condition, is decreased and lactate levels rise. In the past the lactate levels were used to distinguish between state of adequate perfusion and poor oxygen delivery. At present, as has been that lactate could be increased by others factors like adrenergic stimuli and lung injury, it became important to consider the increase lactate levels in the general clinical context while a reduction of serum lactate is still advocated as a target for treatment (Arnold et al 2009, Jones et al 2010).

Among imaging techniques: chest X-ray, ECG, ultrasound scans of brain, heart and kidney are proposed.

Minimally invasive monitoring like central vein access and arterial pressure monitoring, and non invasive tools like echocardiography are considered necessary in septic neonates.

Hemodynamic variables including (perfusion pressure mean arterial pressure [MAP], minus central venous pressure [CVP]), and cardiac output (CO) should guide resuscitation treatment.

The systemic circulation is represented by $CO = (MAP - CVP)/SVR$ (systemic vascular resistance). This relationship is important for organ perfusion.

Measurement of urine output and creatinine clearance can be also used as an indicator of adequate blood flow and perfusion pressure. Because blood pressure does not necessarily reflect CO, it is recommended that normal CO and/or SVC (superior vena cava) flow, measured by Doppler echocardiography, be a primary goal as well. (Carcillo et al 2002, Brieley et al 2009, Kluckow 2001, Kluckow et al 2000, Kluckow et al 2000)

Measurement of CO and O₂ consumption were proposed as being of benefit in patients with persistent shock because a cardiac index (CI) between 3.3 and 6.0 L/min/m² and O₂ consumption >200 mL/min/m² are associated with improved survival (Pollack et al 1985). Because low CO is associated with increased O₂ extraction, ScvO₂ saturation can be used as an indirect indicator of whether CO is adequate to meet tissue metabolic demand. If tissue

oxygen delivery is adequate, then assuming a normal arterial oxygen saturation of 100%, mixed venous saturation is >70% .

In VLBW infants, SVC blood flow measurement was reportedly useful in assessing the effectiveness of shock therapies and prognostic value because approximates blood flow from the brain. It has been observed that a value > 40 mL/kg/min is associated with improved neurologic outcome and survival. ScvO₂ saturation can be used in low birth weight infants, but may be misleading in the presence of left to right shunting through the patent ductus arteriosus. (Kluckow 2001, Kluckow et al 2000, Kluckow et al 2000)

Shock should be diagnosed before blood pressure decrease by clinical signs like hypothermia, hyperthermia, vascular alterations, tachycardia, bradycardia. Blood pressure should not be used as a marker of systemic blood flow in neonates because oxygen delivery to cells is dependent upon cardiac output and systemic blood flow than on blood pressure and a neonate may be hypotensive but still have adequate oxygen delivery.

E-selectin, a protein expressed by the endothelium after activation at sites of acute inflammation, taking part in the first step of the adhesion cascade, shows plasma levels higher in nonsurvivors than in survivors ($P = .01$) and in patients with hemodynamic dysfunction than in those without hemodynamic dysfunction ($P < .001$). (El Sayed Zaki et al 2009)

6. Management

In spite there are extensively studied multiple organ dysfunction scores and well-defined algorithmic guidelines for treatment, there is a large amount of practice variability in neonatal septic shock.

In the onset of septic shock an early and aggressive management of septic shock is needed because for each hour of delay the risk of death increases by 2 times. The immediate objective is to optimize the perfusion and delivery of oxygen and nutrients to tissues.

According to the guidelines of the American College of Critical Care Medicine, 60 min is the average time needed to provide adequate circulatory support and block the development of shock. (Brierley et al 2009). Recognize decreased perfusion, cyanosis and respiratory distress syndrome (RDS), establishing an airway for adequate ventilation and oxygenation and obtaining rapid peripheral or central venous access or intraosseous access are the first steps in managing a newborn in shock (0-5 min) (7).

It is important to remember that all babies with shock and hepatomegaly, cyanosis or pressure gap between upper and lower limbs should begin treatment with prostaglandin within 10 min, until congenital heart disease is excluded (Carcillo et al 2002, Brierley et al 2009).

A key element in the therapeutic management of septic shock is the early recognition of infection. One of the most important factors in progression from infection to septic shock is the use of inappropriate or delayed antibiotic therapy (Kumar et al 2006).

6.1 Antibiotics

After appropriate blood cultures, tests for biomarkers of sepsis, glucose and ionized calcium are made, the empirical antibiotic therapy must be established.

A term neonate or a late pre-term infant ≤ 7 days of age with sepsis should be treated with ampicillin and gentamicin within 60 min. from the suspected diagnosis (Rao et al 2006). Many NICU use Cefotaxime, as a first-line agent, but neonates treated with ampicillin/cefotaxime were more likely to die, and less likely to be discharged to home as compared to neonates treated with ampicillin/gentamicin (Clark et al 2006).

The empiric therapy for late onset sepsis (LOS) in term or late preterm infants admitted from the community after 7 days, is a combination of ampicillin and gentamicin too. In case of meningitis, cefotaxime is administered every 8 h instead of gentamicin. If there is history of prolonged hospitalization or the newborn infant has a central venous catheter (CVC) vancomycin is preferable to ampicillin. In this case, vancomycin and gentamicin/cefotaxime is preferable empiric coverage because provides additional coverage for *S. aureus* and CONS. Clindamycin is now recommended for susceptible MRSA isolates in term infants (Aneja et al 2011).

Afetrwards, once the causative organism has been identified, antibiotics can be targeted only against that organism. As Herpes simplex virus Type I is one of the causes of intractable 'shock', anti-viral (acyclovir) medication, should be initiated, even in the absence of history of maternal infection with herpes virus, in infants who either does not respond. to standard therapy or has persistent signs and symptoms of infection with negative bacterial or fungal cultures or present in septic shock. (Haque 2007).

Therapeutic plasma levels should be monitored because renal and hepatic dysfunction may lead to abnormal volumes and levels of distribution of drugs. The duration of antibiotic therapy is debatable. Serial measurements of CRP or preferably IL-6 or IL-8 are desirable to minimize resistance, super-infection, and other complications from prolonged use of antibiotics. The decision to continue or stop antibiotic therapy must be based on clinical signs plus biomarkers of sepsis and not only on negative blood culture results, that are frequently negative. Intravascular access devices potential source of severe sepsis or septic shock should be promptly removed after establishing other vascular access.

6.2 Mechanical ventilation

Respiratory failure in severe sepsis and septic shock, due to low functional residual capacity may require elective intubation and ventilation to guarantee oxygenation and tissue perfusion, trying to avoid hyperoxemia and over distention of alveoli, which is a potent inducer of IL-6 release.

6.3 Hypoglycemia and hypocalcemia

Correction of hypoglycemia and hypocalcemia should be done if needed. Hypoglycemia can cause neurological damage, if non corrected. Hyperglycemia, particularly cortisol-induced hyperglycemia, is immunosuppressive and prothrombotic. Being due to insulin resistance, which prevents glucose entering into the Krebs cycle, early institution of insulin therapy in hyperglycemic states ensures that glucose is delivered into the Krebs cycle, in particular to the cardiac muscles.

There is no consensus as to what is the ideal blood glucose level, anyhow there is consensus that it should not be lower than 30 mg/dl. Similarly, there is no agreement as to what is the upper limit of blood sugar when insulin therapy should be initiated. In pediatric patients, a glucose level of 178 mg/dL or more was associated with a 2.59 increased risk of mortality (Branco et al 2005). Other researchers noted a similar outcome in extremely low-birth-weight-infants who had glucose levels greater than 150 mg/dL.

Solutions containing 10% dextrose as maintenance fluid are adequate to provide energy (glucose 4 to 8 mg/kg/minute).

In septic shock strict glycemetic controls are needed to avoid marked blood glucose levels changes, therefore it is advisable to prevent rapid fluctuation in blood glucose levels by

giving boluses or high concentration glucose infusion. Hyperglycemia peaks appear to be related with the disease severity.

Since insulin hyperglycemia control in parenteral nutrition preterms has been responsible for hypoglycemic episodes effects, (Beardsall et al 2008) until better evidence is available, insulin is indicated in the newborn only when marked hyperglycemia is seen (> 180 mg/dL), in refractory shock and unfavorable response newborns. (Vlasselaers et al 2009)

Normalization of ionized calcium concentration should be the goal of calcium replacement, because hypocalcemia may be a reversible cause of cardiac dysfunction.

6.4 Bicarbonate therapy

There is no evidence to support the use of bicarbonate therapy in the treatment of hypoperfusion induced acidemia, during sepsis. Bicarbonate solutions are very hyperosmolar even when diluted and if infused rapidly may increase the risk of ventricular hemorrhage in the newborn, particularly the preterm infants.

6.5 Volume replacement

Septic prematures microcirculation evaluation shows that changes are already detectable 24 hours before the systemic sepsis parameters are apparent. (Weidlich et al 2009). The damage of vascular endothelium, caused by inflammatory mediators, results in vasodilation and fluid shifts into the interstitial space resulting in intravascular volume decrease. So neonates in shock often require volume replacement to maintain and/or restore adequate tissue perfusion. A significant reduction in mortality has been obtained if hemodynamic function is optimized in a few time (Rivers et al 2001). The underlying importance is the maintenance of preload and tissue perfusion.

Volume expansion could be carried with crystalloids, colloid or blood products, if hemorrhage. Actually there is a lack of consensus in the literature regarding which product is most effective than the other. In clinical practice, crystalloids have been used more extensively because they are inexpensive and fluid retention and the incidence of adverse effects (eg, intraventricular hemorrhage and infection transmission) may be lower (Lynch et al 2008, Oca et al 2003). Normal saline and lactated ringers are 2 examples of crystalloid solutions used for volume expansion. Colloid solutions contain minerals and electrolytes. They increase oncotic pressure, do not easily cross semipermeable membranes, may remain in the intravascular space longer than crystalloids and allow to use small volumes with less incidence of pulmonary edema. The colloid most commonly used for volume expansion is 5% albumin.

In term infants or older preterm infants, aggressive volume expansion (push boluses of 10–40 mL/kg up to 60mL/kg over 20 to 30 minutes should be considered (Carcillo et al 2002). To prevent reperfusion injury it is preferable to increase the total volume and rate of fluid infusion rather than give repeated boluses of fluids.

Those infants who after adequate fluid resuscitation do not self-diurese may need diuretics to prevent fluid overload. For very preterm neonates there is insufficient evidence to support early volume expansion because of a significant risk of intracranial hemorrhage associated with rapid volume expansion from fluctuations in cerebral perfusion and developing heart failure and/or pulmonary overcirculation from resultant left to right flow through a patent ductus arteriosus, specially in case of anemia. In the septic shock, when hemoglobin levels are below 12 g/dL ($Hb < 12$ g/dL), packed red blood cells transfusion is recommended.

6.6 Cardiovascular agents

Inotropes are indicated when myocardial contractility remains compromised despite adequate volume replacement (Irazuzta et al 2007). They should be administered through a peripheral or intraosseous line before central access is available. A delay in administration of inotropes was associated with a 20-fold increased mortality risk (Kisson et al 2010). Medications in this group include dopamine, dobutamine, epinephrine, and norepinephrine. During neonatal sepsis can be established a hypodynamic state with vasoconstriction that may respond better to inotrope and vasodilator therapy than adults. Both dopamine and epinephrine were found to be efficacious in improving the mean arterial blood pressure but epinephrine was associated with more short-term adverse effects such as enhanced chronotropic response, hyperglycemia requiring insulin treatment, increased plasma lactate levels and inadequate gastric mucosa perfusion (Valverde et al 2006, Levy et al 2011). Recently, a randomized controlled trial showed that dobutamine increased systemic blood flow more effectively than dopamine (Osborn et al 2002). Anyhow Dopamine remains the first-line agent in neonates, and epinephrine may be used in dopamine-resistant septic shock (Carcillo et al 2002). Dopamine: is a natural precursor of both epinephrine and norepinephrine, stimulates the dopaminergic receptors β and α , in this order, with increasing dose. The initial dose of 5-10 mcg/kg/min is recommended and incremented by 2.5 mcg/kg/min steps every 10-15 minutes (Pellicer et al 2009). The prematures may be resistant to its action due to deficient deposit of norepinephrine. A dose ≥ 10 mcg/kg/min dopamine may reduce TSH release, making difficult hypothyroidism diagnosis and producing relevant adverse effects such as tachycardia, arrhythmias, bradycardia, nausea and vomiting. If low cardiac output and high systemic vascular resistance persist, dobutamine and/or a type III phosphodiesterase inhibitor may be indicated. Dobutamine is frequently associated to dopamine in the newborn septic shock; Trough β -adrenergic effects determines vasodilation, through α -adrenergic myocardial receptors stimulation, increases heart contractility and frequency. As reduces after-load, it is particularly useful for septic shock characterized by myocardial dysfunction and high peripheral resistance. In the premature, improves the systemic blood flow, however is not superior to dopamine for septic shock hypotension reversion. Dobutamine may reduce pulmonary vascular resistance, with additional benefit for PPH. Caution is advised when using dobutamine for LV flow obstruction patients. It may cause hypotension if the infant remains hypovolemic, and in higher doses causes tachyarrhythmia. (Dempsey et al 2009). In the term or near-to-term newborn, once assured previous losses replacement and started volume resuscitation, β -adrenergic (inotropic) dose dopamine is indicated between 5-9 mcg/kg/min associated with dobutamine 2.5-10 mcg/kg/min, already during the first management hour (Brierley et al 2009, Pellicer et al 2009). If the patient does not adequately respond to these interventions, then epinephrine (0.05– 0.3 μ g/kg/min) can be infused. For extreme premature transition period shock, the best starting vasoactive drugs schedule was not yet established. (Noori et al 2009) It is very important to have service procedures standardized to control for the results. Dopamine use is safe in these patients. A combination of dopamine at low dosage and dobutamine is initially recommended. *Epinephrine* At a low dose < 0.03 mg/kg/min acts as a potent inotrope (β_1), chronotrope (α_1), and both systemic and pulmonary vasodilatator (β_2). At higher doses, has systemic and pulmonary circulation vasopressor effect (α -adrenergic). The use of *Norepinephrine* is limited in neonatal shock. It is indicated for “warm” shock (doses 0.05 to 0.5 mcg/kg/min), an uncommon condition in the newborn. Tourneux et al. obtained improved blood pressure and PPH-related hemodynamic values and positive effects on the heart and cerebral flow (Tourneux et al 2008).

6.7 Corticosteroids

Corticosteroids are often used to treat shock when volume expansion and inotropes are ineffective to raise blood pressure. They may act by improving the vessel wall sensitivity to circulating catecholamines or to exogenous vasoactive drugs, inhibiting the nitric oxide synthase enzyme expression, or suppressing immune responses. Additionally, septic newborns may develop relative adrenal insufficiency, manifested by low stress cortisol levels. (Fernandez et al 2008) Despite this, the use of corticosteroids remains relatively untested. A recent large cohort study of steroid administration to children and infants with severe sepsis showed no improvement in outcome and an increase in mortality in a subset of patients (Markovitz et al 2005).

Hydrocortisone and dexamethasone are the most used steroids. There are no specific recommendations for neonates regarding the use of dexamethasone, conversely Hydrocortisone is life saving and should be reserved for refractory shock patients, or in services missing inodilators (milrinone), in epinephrine-resistant shock, when adrenal insufficiency is suspected (Vincent 2008). The dose of hydrocortisone ranged from the “stress-dose” used in adrenal insufficiency of 1-2 mg/kg to the empirical shock dose of 50 mg/kg. (Parker et al 2004). Higher mean arterial blood pressures and less vasopressor support and volume expanders use were observed in neonates treated with low-dose hydrocortisone (NG et al 2006).

6.8 Nutrition

Severe illness causes a catabolic process, increases an infant’s metabolic requirements, specially in preterm infants owing to poor muscle mass and energy reserves. Appropriate quantities of energy, minerals, and vitamins can be provided rather by enteral feedings to reduce bacterial translocation from the gut mucosa into the circulation and preserve gut mucosal function.

7. Adjunctive treatments

7.1 Nitric oxide (iNO)

Infants with sepsis and persistent pulmonary hypertension (PPHN) may require iNO to reduce pulmonary vascular resistance and off-load the right ventricle (Roberts et al 1997). The dose of NO with the best results is generally 20 ppm.

7.2 Triiodothyronine

Is an effective inotrope in newborns in case of thyroid insufficiency (Carcillo et al 2002, Carcillo et al 2009).

7.3 Phosphodiesterase inhibitors

Phosphodiesterase inhibitors are indicated if cardiac output does not improve and high systemic vascular resistance persists.

7.4 Milrinone

Milrinone is an inodilator (inotrope/vasodilator) that exerting the selective phosphodiesterase type III inhibition, improves myocardial contractility and relaxation by effects on calcium influx, efflux, and myofilament calcium binding. In the vasculature relaxes arterial and venous smooth muscle. These properties have led to increased use of Milrinone in shocked newborns

with high peripheral vascular resistance ("cold" shock), ventricular dysfunction and normal pressure, specially with PPH, epinephrine-resistant shock with the aim to increase cardiac contractility and cardiac output (Paradisis et al 2006, Paradisis et al 2007). Milrinone due to its systemic and pulmonary vasodilator effects may need volume expansion or inotropic support during the therapy. The recommended dose is 0.75 mcg/kg/min for 3 hours, followed by 0.2 mcg/kg/min. Limited data are available about the use of milrinone in preterm infants. Milrinone failed to show significant effects in extreme low systemic flow prematures within their first 24 hours of life. In these subjects it should be used under hemodynamic control. It is also important to consider that these subjects have a glomerular filtration rate reduced by half compared to term infants in the first 2 weeks of life and that the velocity of improvement over the first several weeks of life is reduced. (Paradisis et al 2009). These differences among varying gestational age newborns make that dosing should be often renally adjusted. Lindsay et al used a loading doses of 75 g/kg and a start infusion rates of 0.75 to 1.0 g/kg/min for patients with normal renal function. The authors recommended for every increase of 0.25 g/kg/min, a 25 g/kg bolus dose be given. Because the median half-life is 1.47 hours, immediate hemodynamic effects may not be seen unless appropriate loading doses and infusion adjustments are made. (Lindsay et al 1998)

7.5 Arginine-vasopressin (AVP)

AVP and TP are 2 forms of vasopressin indicated for rescue therapy in neonates and pediatric patients in case of catecholamine-refractory shock, able to determine an increase in arterial pressure within 1 hour after administration. The meta-analysis conducted by Meyer et al. did not demonstrate a clear advantage of one drug over the other (Vincent et al 2006, Meyer et al 2008).

Endogenous AVP, released in response to hypovolemia and hypotension, shows a biphasic response in septic shock, with initial high levels followed by inappropriately low levels, that more likely occurs after 36 hours from the onset of shock in approximately one third of late septic shock patients. (Sharshar et al 2008) This justifies exogenous administration to correct hypotension in vasodilatory shock in children and also in extremely-low-birth weight infants.

The best dosages of vasopressin remain controversial. Dosages of 0.067 IU/min seem to be more effective to reverse cardiovascular failure in vasodilatory shock requiring high norepinephrine dosages than 0.033 IU/min. (Luckner et al 2007)

Low-dose vasopressin (0.04 IU/min) infusion has been shown to be effective in reversing catecholamine-resistant hypotension in adult septic shock patients. (Klinzing et al 2007). However, one should keep in mind that the pressor activity of vasopressin in the absence of shock, is minimal.

A study suggested that vasopressin is more efficient to increase urine output than norepinephrine. (Patel et al 2002). However, use of vasopressin instead of norepinephrine cannot be recommended.

7.6 Terlipressin (TP)

A synthetic AVP analogue with prolonged action and a higher affinity for vascular receptors than vasopressin. Recently resulted effective in rescue treatment of refractory vasodilatory septic shock, although few data are available. Its use has been promoted because vasopressin is not available in most European countries. It is considered as a last resort when septic patients remain hypotensive despite fluid resuscitation and high doses of catecholamine.

As a prodrug, TP is continuously converted by endopeptidases to vasoactive lysine-vasopressin with a peak level approximately 10 minutes after intravenous administration.

Accordingly, despite low plasma levels it has a prolonged action. In fact, half-life is 6 h for TP versus 6 min for VP and duration of action is 2–10 h versus 30–60 min, respectively (Kam et al 2004). This allows TP intermittent administration without hypotension rebound at drug withdrawal. An intermittent intravenous dosing schedule of approximately every 4 to 6 hours would be appropriate (Pesaturo et al 2006). Matok et al administered TP in an 8-day-old neonate with refractory septic shock to dopamine, milrinone and adrenaline, as rescue therapy (0.07 mg/kg twice a day). Rapid BP improvement and tissue perfusion without side effects, followed (Matok et al 2004). Similarly Filippi et al. used TP because of refractory hypotension in a shocked but not septic neonate, at dose of (0.02 mg/kg every 4 h) with a maximum duration of therapy of 60h. BP dramatically increased 30 min after the first bolus and diuresis was promptly re-established, indicating improvement of tissue perfusion. MAP rapidly increased so that adrenaline and norepinephrine, dopamine and dobutamine were reduced and stopped so TP was administered as the only vasopressor. No rebound hypotension occurred (Filippi et al 2008).

No evidence exists at present on the appropriate timing of TP initiation. Some data suggest that in infants TP should be administered when norepinephrine need is 0.5–2.5 µg/kg/min, probably a precocious administration may be beneficial in order to avoid episodes of severe hypotension (Filippi et al 2008, Zeballos et al 2006, Rodríguez-Núñez et al 2010). In adult preliminary clinical data on ultra low dose terlipressin infusion as first line agent, suggest that “the earlier may be the better” (Morelli et al 2008). However, the level of evidence based on the data available in the literature is very low.

Low-dose continuous infusion has also been described. (Leone et al 2008). Nunez et al obtained an increase of median MAP 30 minutes after administration and a norepinephrine infusion reduction through continuous terlipressin infusion in pediatric refractory septic shock. After a loading dose of (20 µg/kg) was administered a continuous infusion at a rate of 4–20 µg/kg/h (Rodríguez-Núñez et al 2008).

Terlipressin experimental studies showed a protective effect from capillary leakage, less rebound hypotension during weaning (Westphal Westphal et al 2009, Rehberg et al 2009, Morelli et al 2009).

Ischaemic adverse effects secondary to local vasoconstriction, as in the skin and gut were reported in children above all if TP was administered as intermittent bolus. A fact that promoted in adults the TERLIVAP study based on TP continuous infusion and significantly lower dose (1.3 µg/kg/h) to limit this adverse effects (Morelli et al 2009).

7.7 Levosimendan

Levosimendan is an extensively investigated inodilator showing cardioprotective and antiinflammatory effects. Levosimendan is a calcium-sensitizing agent acting by binding to myocardial troponin C in a calcium-dependant manner, causing a configuration change in tropomyosin. This exposes actin and myosin elements, allowing more efficient contraction. In peripheral vascular beds, levosimendan opens adenosine triphosphate-sensitive vascular potassium channels, causing hyperpolarization and vascular relaxation. This effect reduces cardiac afterload and promotes coronary vasodilation. In adults has been demonstrated benefits in low cardiac output states (Moiseyev et al 2002, Slawsky et al 2000).

Levosimendan potential utility is due to a number of reasons; it can be used with conventional inotropic agents, has a simple dosing regimen, and does not worsen the diastolic dysfunction often present in structural heart disease. Levosimendan has received little attention in the pediatric field other than 2 case reports. In both case with clinical

improvement (Luther et al 2004, Braun et al 2004). Egan et al (2006) in their experience with 19 cardiac surgical infants and children documented the improvement of myocardial contractility and perfusion, particularly when used early in the evolution of the low cardiac output syndrome, without increasing myocardial oxygen consumption and negative events. Recently Hasslacher et al (2011) showed that levosimendan reduces oxidative burst activity of PMN both in vitro and in patients with acute heart failure or septic shock with septic myocardial depression. This may contribute to the anticipated cardioprotective effects of the drug. It has a half life of 1 hour and a duration of action of 4 days. The recommended dose is 6-12 mcg over 60 min, followed by continuous infusion at 0.05 to 1 mcg / kg / min for 24 hours.

7.8 Granulocyte and granulocyte-macrophage colony stimulating factors (G-CSF, GM-CSF)

The use of G-CSF, GM-CSF has been shown to increase the number of circulating white cells but don't reduce mortality from neonatal sepsis or septic shock (Carr et al 2003).

7.9 Pentoxifylline

Pentoxifylline is a carbonic anhydrase inhibitor that has been shown to improve white cell function. In one randomized controlled trial in premature infants, was shown to significantly reduce the development of multiorgan failure, mortality and coagulopathy with improvement of blood pressure (Lauterbach et al 1999). This is currently a promising option for refractory shock dosed at 5 mg/kg/hour for 6 hours for next 5 days.

7.10 Intravenous immunoglobulin (IVIG)

Polyclonal and IgM-enriched IVIG have been shown to reduce mortality from sepsis in newborn infants. The activity of Tumour necrosis factor (TNF), a major pro-inflammatory cytokine, can be blocked by various antagonists. In a search was designed a single-domain monoclonal antibody (V_{HH}), which recognizes TNF biologically active *in vivo*. Therefore, therapeutic application of TNF- V_{HH} -ELP fusion protein was tested in humanized TNF mice and was shown to be effective in preventing death caused by septic shock. Immunomodulator agents have shown frustrating results in newborn septic shock management. (Conrad et al 2011)

7.11 Protein C (PC)

The strong activation of coagulation occurring during sepsis may cause the depletion of PC, a vitamin K dependent natural anticoagulant, which exerts a crucial role in the modulation of coagulation, fibrinolysis, and inflammation. Low PC plasma activity correlates with adverse outcomes, such as multiple organ failure and mortality. It has been considered a useful predictor of organ failure in severe sepsis and an important factor of high diagnostic and negative prognostic significance. (Shaw et al 2011, Lauterbach et al 2006, Venkataseshan et al 2007).

Recently in an animal newborn model, was demonstrated impairment of intestinal microcirculation early after induction of endotoxic shock, and its prevention through to continuous infusion of 24 μ g/kg/h activated PC (aPC). This underlines that the use of PC results in an improvement of sepsis-induced microcirculatory dysfunction. (Fischer et al 2009) and underlines the warrants of its supplementation. Whereas several studies, in adults and children, has shown some significant reduction in septic shock mortality thanks to aPC supplementation, a large clinical trial was stopped early, due the finding of an increased

incidence of intracranial bleeding in children younger than 60 days (Nadel et al 2007). In addition, the efficacy of aPC may also be different in neonates due to underlying developmental differences in the coagulation pathway. The anticoagulant effect of aPC has been shown to be decreased in neonatal cord plasma, which is due, in part, to the lower levels of tissue factor pathway inhibitor, antithrombin and protein S in neonatal versus adult plasma (Bernard et al 2001, Cvirn et al 2005). In contrast, non-activated plasma-derived human protein concentrate (PCConc) has been successfully used in paediatric, neonatal and adult patients at high-risk of haemorrhage, especially in those suffering from meningococcal septic shock (de Kleijn et al 2003). PCConc has been successfully used in term neonates and preterms at high-risk of haemorrhage with sepsis-induced coagulopathy (Fischer et al 2009, Decembrino et al 2010). Supplementation was followed by micro- and macrocirculatory, haemodynamic parameters and coagulation, improvement, increased levels of PC activity. PCConc was given intravenously as bolus administration of 200 IU/kg/day or 100 IU/kg/day followed by a daily bolus administration of 50 IU/kg every 6 h for 72 h. No adverse events were observed.

When enough prothrombotic factors are consumed, spontaneous bleeding occurs. It is important, therefore, to determine early whether the infant is in a prothrombotic or fibrinolytic phase. Appropriate coagulation studies should be undertaken. If the baby has a prolonged prothrombin time/partial thromboplastin time and low fibrinogen then it is likely to be DIC. If, however, fibrinogen levels are normal or high then it is likely to be thrombotic thrombocytopenic purpura. Even if routine use of fresh frozen plasma to correct laboratory clotting abnormalities is not recommended, some professional bodies find it useful. The transfusion of platelets is recommended when platelets are between 5000 and $30,000 \times 10^9/l$.

8. Septic shock in preterms

The therapeutic approach of very low birth weight is affected by specific hemodynamic response and multiple factors. The echocardiographic evidence of a reduction of the right and left ventricular function, leads to the use of volume expanders and inotropic to improve cardiac output, contractility and blood pressure. Parathyroid, adrenal and thyroid hormone deficit may require therapy with thyroid hormones, calcium or hydrocortisone. Immaturity of thermogenic mechanisms needs special heating measures.

During the first three days of life the extremely very low birth weight (BW < 1,000 g) frequently with maternal chorioamnionitis history, metabolic acidosis and altered perfusion in the first 24 hours of life, often present progressive respiratory worsening, tachycardia, silent ductus arteriosus. In this case, a rapid infusion of fluid above 30 mL/kg during the first 48 hours of life is responsible for left-right shunt, congestive heart failure and ventricular overload and increased mortality (Ewer et al 2003, Hamrick et al 2010) The failure to close the patent ductus is associated with increased mortality, intraventricular hemorrhage, and poor neurodevelopmental outcome.(Noori et al 2009). Ultrasonography techniques to estimate superior vena cava flow and heart output are effective to replace MBP as an evaluation tool, although not widely available.

The optimal shock oxygenation for extreme prematures it is not yet determined. If under too restricted saturation control (between 83% - 89%), they have increased patent ductus arteriosus incidence. (Noori et al 2009) On the other hand, the harmful hyperoxia effects on ischemic tissues reperfusion are also feared. In extreme prematures, saturation > 94% should

be avoided. PaO₂ should not be kept in supra-systemic levels. (Hamrick et al 2010, Weindling et al 2007)

9. Conclusion

Despite major improvements in the management of severe sepsis, neonates can develop septic shock, a critical condition associated with high morbidity and mortality. For these reasons neonatal septic shock requires emergency treatment with antibiotics, appropriate fluid resuscitation and vasoactive drugs. Knowledge of risk factors will help to identify those neonates at greatest risk for development of septic shock. In the future genomic and proteomic approaches may be helpful in early diagnosis. Although at present antimicrobial therapy and supportive care remain the foundation of treatment, it is desirable that future agents may improve outcomes, specially for particularly vulnerable premature neonates. It is estimated that intra-uterine infection, a risk factor for developing severe infection, is present in up to 35% of preterm deliveries [2].

<p>SIRS: presence of at least 2 of the following 4 criteria, 1 of which must be abnormal temperature or leukocyte count:</p> <ul style="list-style-type: none"> • Core temperature of >38.5°C or <36°C • Tachycardia, defined as a mean heart rate >2SD more than normal for age in the absence of external stimulus, chronic drugs, or painful stimuli; or otherwise unexplained persistent increase in a 0.5- to 4-h time period OR for children <1 y old: bradycardia, defined as a mean heart rate <10th percentile for age in the absence of external vagal stimulus, b-blocker drugs, or congenital heart disease; or otherwise unexplained persistent depression in a 0.5-h time period • Mean respiratory rate >2SD more than normal for age or mechanical ventilation for an acute process not related to underlying neuromuscular disease or the receipt of general anesthesia • Leukocyte count increased or decreased for age (not secondary to chemotherapy-induced leukopenia) or >10% immature neutrophils
<p>Infection: a suspected or proven (by positive culture, tissue stain, or polymerase chain reaction test) infection caused by any pathogen OR a clinical syndrome associated with a high probability of infection. Evidence of infection includes positive findings on clinical examination, imaging, or laboratory tests (eg, white blood cells in a normally sterile body fluid, perforated viscus, chest radiograph consistent with pneumonia, petechial or purpuric rash, or purpura fulminans).</p>
<p>Sepsis: SIRS in the presence of or as a result of suspected or proven infection.</p>
<p>Severe sepsis: sepsis plus 1 of the following: cardiovascular organ dysfunction OR ARDS OR 2 or more other organ dysfunctions.</p>
<p>Septic shock: sepsis and cardiovascular organ dysfunction.</p>

From Goldstein B, Giroir B, Randolph A. International pediatric sepsis consensus conference: definitions for sepsis and organ dysfunction in pediatrics. *Pediatr Crit Care Med* 2005;6(1):2-8.
 Fleer A, Krediet TG. Innate immunity: toll-like receptors and some more. A brief history, basic organization and relevance for the human newborn. *Neonatology*. 2007;92(3):145-57.

Table 1. Definition of systemic inflammatory response syndrome (SIRS), infection, sepsis, severe sepsis, septic shock

<p>Cardiovascular dysfunction: Despite administration of isotonic intravenous fluid bolus >40 mL/kg in 1h</p> <ul style="list-style-type: none"> • Decrease in BP (hypotension) <5th percentile for age or systolic BP >2SD less than normal for age <p>OR</p> <ul style="list-style-type: none"> • Need for vasoactive drug to maintain BP in normal range (dopamine >5 mg/kg/min or dobutamine, epinephrine, or norepinephrine at any dose) <p>OR</p> <ul style="list-style-type: none"> • Two of the following: Unexplained metabolic acidosis: base deficit >5.0 mEq/L Increased arterial lactate >2 times upper limit of normal Oliguria: urine output <0.5 mL/kg/h Prolonged capillary refill >5 s Core to peripheral temperature gap >3°C
<p>Pulmonary:</p> <ul style="list-style-type: none"> • PaO₂/FIO₂ <300 in absence of cyanotic heart disease or preexisting lung disease <p>OR</p> <ul style="list-style-type: none"> • PaCO₂ >65 torr or 20 mm Hg more than baseline PaCO₂ <p>OR</p> <ul style="list-style-type: none"> • Proven need for >50% FIO₂ to maintain saturation >92% <p>OR</p> <ul style="list-style-type: none"> • Need for nonelective invasive or noninvasive mechanical ventilation
<p>Neurologic:</p> <ul style="list-style-type: none"> • Glasgow Coma Score >11 <p>OR</p> <ul style="list-style-type: none"> • Acute change in mental status with a decrease in Glasgow Coma Score >3 points from abnormal baseline
<p>Hematologic:</p> <ul style="list-style-type: none"> • Platelet count <80,000/mm³ or a decline of 50% in platelet count from highest value recorded in the past 3 days (for chronic hematology/oncology patients) <p>OR</p> <ul style="list-style-type: none"> • International normalized ratio >2
<p>Renal:</p> <ul style="list-style-type: none"> • Serum creatinine >2 times upper limit of normal for age or 2-fold increase in baseline creatinine
<p>Hepatic:</p> <ul style="list-style-type: none"> • Total bilirubin >4 mg/dL (not applicable for newborn) <p>OR</p> <ul style="list-style-type: none"> • ALT 2 times upper limit of normal for age

From Goldstein B, Giroir B, Randolph A. International pediatric sepsis consensus conference: definitions for sepsis and organ dysfunction in pediatrics. *Pediatr Crit Care Med* 2005;6(1):2-8.

Table 2. Organ dysfunction criteria

- Infant 72 hours or less in age.
- Tachypnea (Respiratory rate > 60 bpm) plus either grunting/retraction or desaturations.
- Temperature instability (<36°C or > 37.9 °C)
- Capillary refill time > 3 seconds
- WBC count (< 4000 × 10⁹/L or > 34,000 × 10⁹/L)
- CRP > 10 mg/dl
- IL-6 or IL-8 > 70 pg/ml
- 16S rRNA gene PCR: Positive.
- WBC: white blood cell; CRP: C-reactive protein; IL: interleukin; rRNA: recombinant RNA; PCR: polymerase chain reaction.

From Haque KN (2005) Definitions of blood stream infection in the newborn. *Pediatr Crit Care Med* 6 (Suppl):545-549

Table 3. Two or more of the following are required to diagnose the fetal inflammatory response syndrome (FIRS)

10. References

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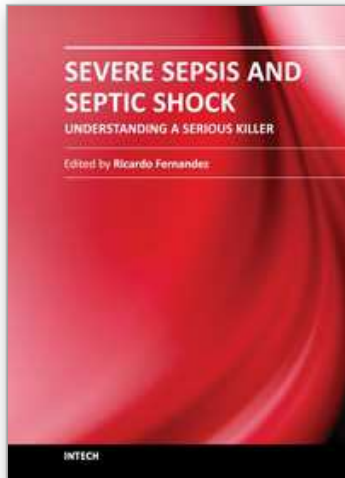
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Despite recent advances in the management of severe sepsis and septic shock, this condition continues to be the leading cause of death worldwide. Some experts usually consider sepsis as one of the most challenging syndromes because of its multiple presentations and the variety of its complications. Various investigators from all over the world got their chance in this book to provide important information regarding this deadly disease. We hope that the efforts of these investigators will result in a useful way to continue with intense work and interest for the care of our patients.

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