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Neonatal sepsis and septic shock: concepts update and review

Sepse e choque séptico no período neonatal: atualização e revisão de conceitos

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ABSTRACT

The nonspecific presentation of neonatal sepsis and systemic inflammatory response syndrome preceding septic shock delay the early diagnosis of septic shock and increase its mortality rate. Early diagnosis involves suspecting septic shock in every newborn with tachycardia, respiratory distress, difficult feeding, altered tonus and skin coloration, tachypnea and reduced perfusion, specially in case of maternal peripartum infection, chorioamnionitis or long-term membranes rupture.

This article aims to review current knowledge on neonatal period peculiarities, fetal circulation dynamics, and the pregnancy age variable.

Newborn septic shock is not just a small adult shock. In the newborn, the septic shock is predominantly cold and characterized by reduced cardiac output and increased systemic vascular resistance (vasoconstriction).

Time is fundamental for septic shock reversion. The indexed-databases literature review provides subside for the newborn management.

Keywords: Sepsis; Infant, newborn; Shock, septic; Cytokines; Systemic inflammatory response syndrome; Neonatal mortality (Public Health)

INTRODUCTION

Neonatal sepsis and the consequent septic shock have been causing increased early infantile morbidity and mortality for years. Sepsis and classic group B *Streptococcus* shock remains a relevant clinical issue, even though maternal antibiotic prophylaxis.[1] According to the World Health Organization (WHO), 130 million children are born yearly, and about 4 millions die every year, while infection causes 36% of these deaths; this is even worse in countries where critical patient resources are limited.[2] One half of very low birth weight (VLBW) newborns' deaths within the first seven days of life are from severe infection. Infection and prenatal inflammation are related to premature work and development of bronchopulmonary dysplasia.[3,4] Exposure of the premature brains to inflammatory mediators during infective episodes such as chorioamnionitis, sepsis and necrotizing enterocolitis is linked to cerebral hemorrhage, white substance injury and neurodevelopmental changes, including cerebral palsy.[3,5-9] Maternal and fetal diseases (preeclampsia, intrauterine growth restriction) and those of the newborn

(persistent ductus arteriosus, post- hypoxic-ischemic encephalopathy microvascular events) are being increasingly designed by inflammatory mediators action, which may be related to the reduced number of positive blood culture proven sepsis in the immediate neonatal phase.[3,6] To this should be added a still developing immune system, featuring gestational age-dependent differences not only from bigger children and adults, but also from other newborns.[9]

Although the systemic inflammatory response, characterized by tachycardia, tachypnea, hyperthermia and leukocytosis is more frequently triggered by infection, there are several systemic inflammatory response syndrome (SIRS) promoters during the immediate neonatal period as traumatic delivery, severe perinatal asphyxia, metabolism innate errors, surgical procedures, among other conditions also responsible for inflammatory mediators release, and these, through the pro-inflammatory events cascade, culminating in septic shock.[10-15]

A Critical Care Society pediatric intensive doctors' task force has recently coordinated an updating, leading to incorporation of some evidence-rated recommendations, being the septic shock definition based on clinical parameters and the shock graded according to the response to therapy (Chart 1). Many these recommendations were not from good quality studies and consist on consensus statements; the literature shows a drop in mortality following these guidelines implementation, thus suggesting that the biggest impact comes from the approach to care rather than from the interventions themselves.[10]

Thus, this article aims to review the main studies on neonatal septic shock, focusing on knowledge involving this phase peculiarities, fetal circulation dynamics and the gestational age variable (term, preterm and extreme preterm newborns), very important for this critical patients population management.

METHODS

Literature review based on MEDLINE (PubMed) and Scientific Electronic Library Online (SciELO). Were included different designs original articles, classic texts, letters to peer reviewed journals' editors, metanalysis and review supplements on newborn septic shock, sepsis, bacteremia, sepsis pathophysiology and immune-inflammatory response. The search source and interest focus was the neonatal period, and its peculiarities. The key words included newborn, preterm, shock, sepsis, cytokines, inflammatory response, dopamine, dobutamine, norepinephrine, epinephrine, and fetal-neonatal transition period.

Our interest to specifically review the newborn septic shock was justified by its frequency being higher during this phase of life than other causes of shock and the difficulties for appropriate therapeutic approach due to the lack of scientific evidence on the use of inotropes for newborn shock management.

Initially, a newborn septic shock definition is established. The literature review particularly focuses on the preterm newborns, as little is established on premature's septic shock diagnosis and management. The Consensus and international committees established criteria for younger (0-7 days) and older (7 days to 1 month) newborns' multi-organ dysfunction, excluding discussion on premature infants.[16,17]

The septic shock is classically defined as the presence of diagnostic criteria for sepsis associated with sustained cardiovascular dysfunction, even after infusion of at least 40 mL/kg fluids within 1 hour. Cardiovascular dysfunction frequently causes hypotension

Chart 1- Septic shock definitions (according to the Critical Care Society pediatric intensive doctors task force)

Septic shock (cold)	Reduced perfusion, including altered mental status, longer than 2 seconds capillary filling, reduced peripheral pulse, cold spotted extremities, or reduced urinary output (less than 1 mL/kg/hour).
Septic shock (warm)	Reduced perfusion, including altered mental status, shorter than 2 seconds capillary filling, wide peripheral pulse, reduced urinary output (less than 1 mL/kg/hour).
Dopamine-resistant/fluid refractory shock	Shock persists independent of fluid resuscitation = 60 mL/kg in the first hour and dopamine infusion at 10 µg/kg/min.
Catecholamine-resistant shock	Shock persists independent of catecholamines use as epinephrine or norepinephrine
Refractory shock	Shock persists independent of targeted use of inotropes, vasopressors, vasodilators and metabolic homeostatic (glucose and calcium) and hormonal (thyroid and hydrocortisone) agents.

Modified from Brierley J, Carcillo JA, Choong K, et al.[10]

(gestational age-dependent), need of vasopressor agents to maintain blood pressure, or reduced peripheral perfusion evidence.[1,16,17]

Understanding the newborn shock requires the description of the variables blood pressure (BP) and cardiac output (Q). There is a basic relationship between BP, Q and peripheral vascular resistance (PVR), which is well known and described by the formula:

$$\text{Blood Pressure} = Q * PVR$$

Thus, in patients with low Q, blood pressure may be normal if the PVR is high.

In the neonatal septic shock, low blood pressure will be likely due to low Q, as the PVR is usually high. If Q is normal and PVR is high, we may have hypertension, which may come from several causes including inappropriate intravascular volume, excessive preload, changed contractility, myocardial restriction, valvar dysfunction and arrhythmia.[17]

This review presentation has subheadings after the introduction and the methodology conceptual base, according to the proposed by pediatric committees for systematic randomized clinical trials reviews.[18] Initially the pathophysiology and inflammatory mediators and the bacterial agent roles are discussed, followed by the differences between newborns and pediatric patients' shocks, including particularities of the newborn shock, the shock and systemic blood pressure, and its volume and pharmacologic (vasopressors and inotropes) management.

Pathophysiology: the role of the mediators and bacterial agent

Several proinflammatory cytokines are produced and secreted because of the bacterial agent in the blood stream. By activating neutrophils and endothelial cells, these proinflammatory interleukins allow the leukocyte adhesion to the endothelial wall, nitric oxide production and other nitrogen and oxygen reactive species which will cause additional endothelial injury, with changes to the cells junctions causing edema, vasodilation and lost vascular tonus control. From this proinflammatory status, the picture may progress to a blood compartment immunosupression and immunopalsy status, while a hyper-inflammatory state trends to persist at the tissue level.[14,15,19]

Newborns with severe sepsis are fully impacted by the hyper-inflammation status leading to septic shock consequences. The proinflammatory cytokines such as IL-6, IL-1β and TNFα levels are significantly higher during the early neonatal sepsis, and are early neonatal infection markers.[9,15]

Studies we have conducted in the last decade already showed that the IL-6 and TNFα association may have up to 98.5% sensitivity, when the samples for cytokines are drawn early when infection is suspected.[14,20] In extreme prematures, these levels may be even higher, particularly for IL-8, a chemokine that is an important neonatal sepsis biomarker.[21,22] On the other hand, the compensatory anti-inflammatory toll-like receptors mediated response looks to be immature even in the term newborn. An example of this finding, is the insufficient interleukin-10 (IL-10) and TGFβ production.[23-25]

TNFα is considered the main both septic shock and diffuse tissue injury mediator, not only in the newborn, but also in the child and in the adult.[7,12,15] Several evidences support the TNFα role in sepsis as: both patients and experimental shock models show maximal TNFα levels between three and four hours of the experiment; TNFα-mediated hemodynamic and metabolic changes causing hypotension, intravascular coagulation, hemorrhagic necrosis and tissue injury; TNFα neutralization prevents both endotoxemia and bacteremia in animal models, even with persistent endotoxins and bacteria in the blood stream (however TNFα neutralization therapy failed to show good results in septic shock).[7,15,20]

During the infective process, the TNFα serum level is increased for the first 30 to 90 minutes after lipopolysaccharide (LPS) exposure, peaking between 3 and 4 hours, correlating well with newborn's fever and/or thermal instability.[7,26]

Thus, disseminated intravascular coagulation (DIC) is not rare in septic shock, resulting from the sustained thrombin generation, which leads to microvascular coagulation with end-organ dysfunction, and paradoxically, bleeding diathesis due to coagulation factors waste.[27,28] The immune system and coagulation are closely related. Cytokines mediating neutrophils activation and migration to the tissues and extravascular compartment generate the thrombin formation and fibrin deposit formation, triggering tissue factor. 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.[23,24,29]

Membrane receptors known as toll like receptors

(TLRs) have a fundamental role in the septic shock pathophysiology, interfering with the cardiovascular system depending on the systemic inflammatory response triggering pathogen. Those are membrane receptors found in immune system cells (dendritic cells, neutrophils and monocytes) able to detect pathogens-associated molecular patterns, usually known in the international literature as PAMPs. Are examples of PAMPs the lipopolysaccharide (LPS) endotoxin of gram-negative organisms membrane and the gram-positive bacteria teiocoico acids. By signaling molecules activation, they cause in the nucleus activation of transcription sites of appropriate genes packages to induce proinflammatory and anti-inflammatory mediators, particularly cytokines.[9,13,30]

In addition to immune system cells, these receptors are expressed in other cells, such as endothelial cells, alveolar epithelium cells, and cardiomyocytes. TLRs-induced TNFα (tumor necrosis factor – alpha), IL-1β (interleukin 1β) is responsible for the early myocardial dysfunction gram-negative (TLR4) and gram-positive (TLR2) germs severe sepsis.[23,30]

Another TLRs function is the amplification of inflammatory response by recognizing the danger-associated cell injury (DAMPs) released molecular patterns.[23,30]

TLRs genetic polymorphisms and signaling proteins (MYD88) are related to septic shock inflammatory response intensity and mortality.[30-32] Cornell et al. recently revised the complex transcriptional expression genetic factors and epigenetics regulating the host response to infection, and different septic shock patterns.[33]

Bacterial agent role

Distinct hemodynamic patterns may suggest the different pathogens in children's septic shock, with gram-negative bacteria preponderance in the cold shock, and gram-positive in the warm shock.[34] There is no such described correlation for the neonatal period. Peripheral perfusion apparently preserved (wide pulse and vasodilated extremities) in the presence of oliguria, acidemia, altered consciousness and hypotension indicating vasoplegia or warm shock, is eventually present in the transition of extreme prematures and in late *Staphylococci* sepsis in prematures, and may lead to false stability impression.[1,2,34,35]

Gram-positive germs as group B *Streptococci* are those most frequently described as causative agents in early neonatal sepsis. However, more recently some gram-negative agents have been frequently described, mainly in vertical transmission sepsis.[35,36] Data from the Centers for Disease Control and Prevention (CDC) point to that intrapartum use of antibiotics may have reduced the incidence of gram-positive sepsis, although allowing gram-negative flora's outbreak.[37]

Invasive streptococcal disease is related to absent anti-capsular maternal antibodies. When the newborn aspirates the pathogen from the vaginal canal (maternal colonization), pulmonary invasion may take place which is highly dependent on the delayed surfactant protein A gene expression, as worse as lower gestational age at birth. Next, the germ reaches the blood stream and promotes intensive systemic inflammatory response syndrome, classically described already in early sepsis. Yet the type III *Streptococcus* strain is responsible by late neonatal sepsis, and is generally associated with meningitis.[36,38]

In late sepsis, as in any other prolonged hospitalization setting, *Staphylococcus aureus* is the most frequent germ, being a gram-positive encapsulated organism, where cell wall protein A provides ability to block opsonization, and this anti-phagocytosis action impairs the natural host response, that is why persistent bacteremia is frequent and local foci difficult to treat. Multi-resistant strains (MRSA) , inclusive vancomycin-resistant, outbreak is a serious neonatal intensive care units (ICUs) issue.[38] Coagulase-negative *Staphylococci* (CNS), and its most know subtypes *S. epidermidis, S. haemolyticus, S. capitis, S. warnier* are the most frequent nosocomial infection agents in very low weight prematures. They act inducing a mild inflammatory response with lipoproteic acids, peptidoglycans and pro-albumins. The presentation is insidious, with more frequently than the for the usual pattern apneas, worsened ventilatory pattern, lethargy, thermal instability and ileum. The ability to form biofilm, an extracellular layer of proteins and polysaccharides that allows adhesion to intravascular catheters, is the main pathogenic mechanism. However, it is a very difficult task to establish when it is either an actual invasive infection, and when it is a contamination. There is no enough sensitive and specific marker to make a differentiation. It appears that the increased virulence is related to the type of genes distribution in the biofilm formation.[39,40]

Fungal sepsis is more common in the severe extreme premature under mechanic ventilation support, long term parenteral nutrition, with hyperglycemia, and exposed to previous multiple antibiotics therapy.[41] *Candida albicans* (vertical, from maternal flora) and *Candi-*

da parapsiloisis (horizontal, from nosocomial infection) are very related to vascular catheters. The prophylactic use of fluconazole in extreme prematures (birth weight below 1,000 grams and gestational age below 27 weeks) has been proven a good option for septic shock mortality prevention in this high-risk population.[42] In the Hospital de Clinicas de Porto Alegre's NICU we currently use empirical amphothericin B, based on restrict to very low birth weight preterm population risk factors, instead of prophylactic fluconazole. Doing so, we believe selecting the potential cases and avoiding superresistance.[43,44]

Newborn shock peculiarities

The neonatal and adult or older children shocks are markedly different. The postnatal period, a metabolically adjusting time, leads to relevant differences including between the preterm and the term newborn.[17,34] The vital signs evaluation during this phase has its peculiarities, as described by the International Consensus Conference on Pediatric Sepsis, which is shown adapted in the chart 2.[16]

Both, the premature and the newborn without major issues are in a hypercoagulable status, with increased microcirculation endothelial thrombomodulin receptors and reduced anticoagulation-related proteins response (activated C protein, among others).[24,28]

In the most severe cases, the extrinsic pathway is activated, promoting increased tissue factor expression in the extravascular compartment. This is likely to be the initial event in coagulation changes (DIC), with significant complement and coagulation cascade activation. It was recently shown that antithrombin, tissue inactivation factor and activated C protein are reduced in severe sepsis, and that the fibrinolytic response is changed (TNFα action). This results in microvascular thrombosis, reduced fibrinolysis, increased capillary permeability, hypoperfusion areas or unable to supply the increased tissues metabolic requirements leading to tissue hypoxia, and cytopathic hypoxia due to mitochondrial injury.[45]

Newborns and younger children have increased bleeding risks due to low circulating procoagulants K vitamin-dependent factors levels (factors II, VII, IX and X). The newborn coagulation system has all essential coagulation factors, however lesser than the adult. Platelet counts are similar between adults and children, but in younger children platelets trend to be poorly responsive to physiologic agonists.[46,47] These differences explain, at least partially, the newborn's most severe DIC cases, the increased mortality and little therapeutic response to coagulation modulators, as compared to adults and children.[1,45,48]

The newborn immune system response is frequently dependent on the innate immunity which, in turn, is functionally limited as compared to the adult and older children.[1] Circulating complement components, antimicrobial proteins expression and T-helper cell peptides are deficient. Neutrophils, macrophages, monocytes, dendritic cells functions, and reduced toll-like receptors agonists response, render the newborn, particularly the premature, highly susceptible to invader organism and septic shock.[1,8,9]

The diagnosis of newborn's septic shock is primarily medical, without delays waiting for laboratory test confirmation before starting immediate management. Age-related newborn's normal vital signs values range should be well known, as there is no direct heart output measurement available, as usually is in adults.[34,49] In the term newborn, no hypotension is required for diagnosing shock, however hypotension associated to clinical signs is septic shock until proven differently.[10] Normal blood pressure values for very low weight newborns are not well established. Few articles approach this matter; additionally, normal values are very difficult to establish in such a frequently needing mechanic ventilation, patent ductus arteriosis, and with frequent hemodynamic changes population.[50,51]

Shock and systemic blood pressure

At any age, shock is primary concerned to blood flow rather than blood pressure change and, neverthe-

Chart 2 - Newborns and older children vital signs

	Heart rate (bpm)	Respiratory rate (mov/min)	White blood cells count (103/min3)	Systolic pressure (mmHg)
0 - 7 days	<100 or >180	>50	>34 or< 5	<65
7 - 28 days	<100 or >180	>40	>19,5 or <5	<75
2 - 12 months	<90 or >180	>34	>19,5 or <5	<100

Modified from International Consensus Conference on Pediatric Sepsis. International pediatric sepsis consensus conference: definitions for sepsis and organ dysfunction in pediatrics.[16]

Chart 3 – Mean blood pressure values suggested for newborn hypotension diagnosis

Birth weight	< 1000 g	1000-1500 g	1500-2500 g	>2500 g
Gestational age	23-27 weeks	28-33 weeks	34-37 weeks	> 37 weeks
1 - 3 days	MBP < GA	< 30	< 35	< 40
4 - 7 days	< 30	< 33	< 35	< 45
> 7 days	< 30	< 35	<40	< 50

Adapted with permission from II SIBEN (Ibero-American Society of Neonatology) Hemodynamics Consensus; 2008. MBP – mean blood pressure; GA – gestational age.

less appropriate blood pressure is vital for vital organs perfusion and glomerular filtration, the absence of hypotension does not precludes shock, as BP may be in the normal range due to compensatory mechanisms.[51] This statement becomes specially complex during the neonatal period, where the blood pressure is variable with age, as thoroughly discussed in the 2008 Ibero-American Society of Neonatology Hemodynamics Consensus meeting (Chart 3).

In no infection extreme prematures, specially during the transition phase, a correlation between MBP and systemic blood flow is seen; these, when "healthy" and with lower than the usual mean blood pressures may have appropriate cerebral perfusion, normal cardiac output and no clinical or biochemical signs of shock. Some authors suggest permissive hypotension in healthy patients.[50-54]

However, hypotension is not permissive for septic shock prematures. In critically ill prematures, refractory hypotension is related to patent ductus arteriosus, intraventricular hemorrhage and poor prognosis.[8,48,53] On the other hand, hemodynamically significant ductus arteriosus appears to negatively affect the brain perfusion, adding serious concerns regarding these patients volume replacement.[55] Ultrasonography techniques to estimate superior vena cava flow and heart output are effective to replace MBP as an evaluation tool, although not widely available.[10]

Volume and pharmacologic management (vasopressors and inotropes)

Fast action for early neonatal septic shock reversion, and adopting practices aimed to early hemodynamic recovery using volume resuscitation and vasoactive drugs are associated to improved prognosis and significantly reduced mortality.[10,56]

A simultaneously implemented measures package should be preferred over stepwise management, i.e., time and targets driven management.[10] Septic prematures microcirculation evaluation shows that changes are already detectable 24 hours before the systemic sepsis parameters are apparent.[45] We should radically change our mind regarding time in critically ill neonate septic shock. A recent trial has shown that younger than 2 years-old chronically ill children are specially sensitive to short delays in volume resuscitation, and are very volume-responsive.[57] No similar trials are available in newborns, but it is reasonable to believe that the same therapeutic principles are applicable for the neonatal period, until better evidence is available.

After stable airway is assured, the priority is volume crystalloid solution replacement (saline 0.9%); careful monitoring and special attention to ductus arteriosus secondary hemodynamic instability.[49,50] First hour volume replacement limits are basically determined by the gestational age; for the term newborn, up to 60 mL/kg; in very low weight preterm newborns (BW < 1,500 grams), up to 30 mL/kg; and for extreme prematures without evidence of significant loss, up to 20 mL/kg. When these volume replacement limits are complied to, saline replacement is well tolerated, and there are no adverse effects described in newborns.[1,10,34]

The extremely very low birth weight (BW < 1,000 g) and premature who had maternal chorioamnionitis history, metabolic acidosis and altered perfusion in the first 24 hours after birth, with progressive respiratory worsening, tachycardia, silent ductus arteriosus (no sounds) is very frequent during the first three days of life. In this case, excessive or fast volume replacement may increase the shunt intensity and increase preload in a poor stretching ability and contractile strength myocardium. The failure to close the patent ductus is associated with increased mortality, intraventricular hemorrhage, and poor neurodevelopmental outcome.[58] Fast volume infusion, above 30 mL/kg during the first 48 hours of life, was associated with increased mortality.[59]

Volume replacement causes hemodilution, specially in anemic newborns or intracranial hemorrhage prematures. In the septic shock, when hemoglobin levels are below 12 g/dL (Hb < 12 g/dL), packed red blood cells transfusion is recommended. The use of 10% glucose solution as maintenance volume is required, and this

glucose infusion rate should be checked in cases with electrolytic calcium and glucose abnormalities. In septic shock it is important to avoid marked blood glucose levels changes.[60,61] The potential glucose toxicity in severe sepsis is a consensus, however its actions on the immune response, repair processes, reactive oxygen species formation and acid-basic balance changes are not completely understood. Hyperglycemia peaks appear to be related with the disease severity, however the sustained hyperglycemia effects, or marked blood glucose levels variation, are not well described. In a pediatric population, blood glucose levels above 178 mg/dL lead to a three-fold mortality increase.[61]

Insulin hyperglycemia control in parenteral nutrition preterms has been questioned due to the harmful hypoglycemic episodes effects in these newborns.[62] About 25% of insulin users critically ill pediatric patients develop hypoglycemia.[60] On the other hand, insulin appears to inhibit inflammatory response and increase immune competence, in adults. Until better evidence is available, insulin is indicated in the newborn only when, even with reduced glucose offer, marked hyperglycemia is seen (> 180 mg/dL) and in refractory shock and unfavorable response newborns.[60,62]

Offering oxygen to hypoxic tissues is a fundamental part of therapy, however 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.[63] 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.[50,52,58,63]

Pharmacological management

The pharmacologic septic shock management includes vasopressors as dopamine, norepinephrine and vasopressin, in addition to inotropes such as epinephrine, dobutamine and milrinone, and these are frequently associated aiming microcirculation and tissue perfusion restoration.[10,34,64]

Most of septic shock drugs' efficacy and safety trials were developed in adults, some in pediatric patients, and very few evidence is available in the newborn. Considering some literature on these drugs effects in preterm children, and based on the American College of Critical Care Medicine Consensus, we can summarize the newborn pharmacological management.[10,34,64]

Dopamine: Is the most used vasopressor for neonatology shock; natural precursor of both epinephrine and norepinephrine, stimulates the dopaminergic receptors beta and alpha, in this order, with increasing dose. For the initial management a 5-10 mcg/kg/min dose is recommended, to be individually adjusted according to the effects in each newborn. The dose is generally incremented by 2.5 mcg/kg/min steps every 10-15 minutes.[65] As the norepinephrine deposits are immature in the premature child, it may be found resistance to its action, in addition to pulmonary vasoconstriction proportional to systemic vasoconstriction.[10] Valverde et al. found that preterms with ≥ 10 mcg/kg/min dopamine had reduced TSH release, making difficult hypothyroidism diagnosis and producing relevant adverse effects such as tachycardia, arrhythmias, bradycardia, nausea and vomiting.[66]

Norepinephrine: Limited use in neonatal shock, indicated for "warm" shock (doses 0.05 to 0.5 mcg/kg/min), an uncommon condition in the newborn. In an observational trial (very poor evidence level) with 22 septic shock newborns refractory to volume and dopamine plus dobutamine and Persistent Pulmonary Hypertension (PPH), Tourneux et al. used norepinephrine, and found improved blood pressure and other PPH-related hemodynamic values. Later, these authors described the heart and cerebral flow performance with norepinephrine in these newborns, suggesting positive effects.[67] In adults, in who norepinephrine is largely used, it is questioned if the norepinephrine improved blood pressure would not be a function of a microcirculatory trapping, then requiring O2 mixed venous saturation during its use.[10]

Vasopressin (and its synthetic analog, terlipressin): Is a fluids homeostasis acting hormone, a potent vasoconstrictor. It is indicated in vasodilation shock, but its use in neonatology is restricted to few reported cases.[10,68] In high doses it may cause coronary, mesenteric and skin ischemia.[64] A pilot study has shown that in low doses vasopressin is safe (hyponatremia is common) in hemodynamically stable, but mechanically ventilated, children.[69]

Epinephrine: In low doses (< 0.03 mg/kg/min) is a potent inotrope (β1), chronotrope (α1) and, due to β2 receptors stimulation, has both systemic and pulmonary vasodilator effect. In higher doses, has systemic and pulmonary circulation vasopressor effect (α-adrenergic), increasing more the systemic than the pulmonary pressure. Epinephrine improves the heart output, myocardial perfusion and increases the mesenteric vascular resistance. Epinephrine adverse effects

include increased PVR leading to reduced cardiac output and tissue perfusion, hypertension, tachycardia, and necrosis due to peripheral vessels leakage. In the premature, increased glucose and lactate are transitory effects.[57] It is indicated for the refractory volume, dopamine and dobutamine resistant shock dosed as 0.05 to 0.3 mcg/kg/min.[10]

Dobutamine: Frequently associated to dopamine in the newborn septic shock; has β-adrenergic effects trending to vasodilation and α-adrenergic myocardial receptors stimulation, increasing both heart contractility and frequency. As reduces after-load, is particularly useful for septic shock characterized by myocardial dysfunction and high peripheral resistance, although the undefined effect on coronary flow and O2 myocardial offer improvement in the newborn. In the premature, improves the systemic blood flow as evaluated by echocardiography, 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 patient remains hypovolemic, and in higher doses causes tachyarrhythmia.[53]

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.[10,65] Yet for extreme premature transition period shock, the best starting vasoactive drugs schedule was not yet established.[10,57,58] It is very important to have service procedures standardized to control for the results. Dopamine use is safe in these patients.[65] We suggest using inotropic doses dopamine plus dobutamine initially, associated with more cautious volume replacement in extreme premature children.[56]

Milrinone: Selective phosphodiesterase inhibitor, with important inotropic effects while causes systemic and pulmonary vasodilation (inodilator). The successful milrinone use in septic pediatric shock with high peripheral vascular resistance ("cold" shock), ventricular dysfunction and normal pressure brought considerations on its usefulness in the newborn, specially with PPH. Indicated for the epinephrine-resistant shock, the recommended dose is 0.75 mcg/kg/min for 3 hours, followed by 0.2 mcg/kg/min. Systematic volume replacement is required, in addition to vasopressor dopamine doses. These can be used for epinephrine-refractory shock to counteract the milrinone hypotensive risk.[10,64] Paradisis et al. failed to show significant milrinone effects in extreme low systemic flow prematures within their first 24 hours of life, and thus it should be used under hemodynamic control in neonatal ICUs.[70]

Other possible drugs

Corticosteroids: They may act in the septic shock 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.[1,10] Additionally, septic newborns may develop relative adrenal insufficiency, manifested by low stress cortisol levels.[71]

Hydrocortisone therapy should be reserved for refractory shock patients, or in services missing structure to use inodilators (milrinone), in epinephrine-resistant shock, or also in suspected relative or absolute adrenal failure (ambiguous genitalia).[56]

Immunomodulator agents: Immunomodulator agents have shown frustrating results in newborn septic shock management. Immunoglobulin IV, colony-stimulating factors (rhG-CSF and rhGM-CSF), activated C protein and pentoxifylline were previously proposed immunomodulator agents for neonatal septic shock.[1,10,24]

Activated C protein, which is potentially beneficial in adult patients, failed to show benefit in children and is associated to intracranial hemorrhage in below 60 days old patients.[1] In an animal newborn model, intestinal microcirculation improvement was shown with rhAPC (commercially available human recombinant C protein) after endotoxic shock induction.[24]

Pentoxifylline, a platelet antiaggregant in prematures, has been shown to reduce mortality, circulatory impairment, coagulopathy and necrotizing enterocolitis versus placebo, and with no known adverse effects. This is currently a promising option for refractory shock dosed at 5 mg/kg/hour for 6 hours for 5 successive days.[10]

CONCLUSION

The impact of neonatal septic shock on morbidity and mortality rates is high, but some promising strategies have been evaluated involving the understanding of neonatal sepsis pathophysiology, genetic determinants and immunomodulators, many of them exclusive of the newborn. Practical institutional protocols, with measures for nosocomial infection control, hemodynamical stabilization and futurely immunomodulators, should be implemented in neonatal ICUs.

Aiming to improve the neonatal care quality, neona-

tal sepsis anticipation, prevention, early diagnosis and treatment measures are recommended to quickly revert its dramatic consequences.

RESUMO

A sepse neonatal e a síndrome da resposta inflamatória sistêmica, que antecede o choque séptico, se manifestam como um estado não específico, o que pode retardar o diagnóstico precoce do choque séptico, razão pela qual a mortalidade desta condição permanece elevada. O diagnóstico precoce envolve a suspeita de choque séptico em todo recém nascido apresentando taquicardia, desconforto respiratório, dificuldade de alimentação, tônus alterado, cor alterada, taquipnéia e perfusão reduzida, especialmente na presença de histórico materno de infecção periparto, como corioamnionite ou ruptura prolongada de membranas ovulares.

O presente artigo tem como objetivo revisar o conhecimento atual a respeito das peculiaridades do período neonatal, da dinâmica da circulação fetal e da variável idade gestacional.

O choque séptico no recém-nascido não é choque séptico do adulto pequeno. No recém-nascido, o choque séptico é predominantemente frio, caracterizado por redução do débito cardíaco e alta resistência vascular sistêmica (vasoconstrição).

O tempo é fundamental no tratamento para reversão do choque séptico. A revisão da literatura, baseada em buscas em bases indexadas, fornece subsídios para o manejo do recém-nascido.

Descritores: Sepse; Recém-nascido; Choque séptico; Citocinas; Síndrome de resposta inflamatória sistêmica; Mortalidade neonatal

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