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Research Article

Neonatal Septic Shock in a Neonatal Intensive Care Unit - Trends In Incidence and Therapeutic Challenges

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Abstract

Septic shock remains an important cause of morbidity and mortality in newborns. We performed a retrospective, observational, cohort study to determine the incidence, microorganisms and therapeutic management of Neonatal Septic Shock (NSS) in a Portuguese Neonatal Intensive Care Unit (NICU). Medical records and microbiological data were analysed. Between 2017 and 2020, 31 (3.1 %) newborns admitted to the NICU developed neonatal septic shock (3.2 per 1.000 live births); 84% preterm, 68% male, median age at presentation 11 days. Clinically, tachycardia, hypothermia and need for invasive ventilation were the main findings. Blood analysis revealed immature to total neutrophil ratio >10%, base deficit and lactate elevation and thrombocytopenia. There were 32 positive blood cultures. The most frequently isolated bacteria were gram-negative pathogens (70%), accounting for 90% of fatal cases. Therapeutic management included volume expansion and vasoactive drugs in 87%. Lethality occurred in 10 newborns, all with positive blood cultures. Analysis of death outcome showed the lower the weight, the greater the probability of death and association of gram-negative bacteria with death. Prevention, diagnosis, and treatment of NSS are an important challenge in NICU. More precise guidelines, adapted to preterm newborn unique characteristics, are necessary to optimise an early diagnosis and adequate approach.

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Introduction

Septic shock remains an important cause of morbidity and mortality in newborns, despite improved management of neonatal sepsis. According to the World Health Organization, in 2018 an estimated 15% of all neonatal deaths were due to sepsis [1]. A recent systematic review and meta-analysis found an estimate for neonatal sepsis case mortality of 17.6% [2]. Although there is a lack of data from many countries, studies show that neonatal sepsis global incidence is highest in low-income countries. Overall, the highest incidence of neonatal sepsis occurs in preterm and low-birth-weight infants [1-3]. In neonates, there is very little data on the incidence of septic shock. Kermorvant-Duchemin E. et al. (2008) reported a septic shock mortality rate of 40%, reaching 71% in extremely low-birth-weight newborns [4]. Survival of preterm infants is improving over time, but neonates are particularly vulnerable to sepsis caused by healthcare-associated infections. It is estimated that 84% of neonatal deaths due to infections could be prevented with measures such as early diagnosis and appropriate clinical intervention, so it is essential to optimise the approach [1].

According to The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3), sepsis is defined as a life-threatening organ dysfunction caused by a dysregulated host response to infection; and septic shock as a subset of sepsis in which particularly profound circulatory, cellular and metabolic abnormalities are associated with a greater risk of mortality than with sepsis alone [5]. Currently, there are no consensual definitions for neonates, or about changes in monitoring and hemodynamic characterization (progression to shock). In 2005, an International Pediatric Sepsis Consensus Conference adapted the criteria used in adults (Sepsis-2) to the paediatric age, including term newborns [6]. Modifications were later proposed to the existing definitions for premature newborns, however, these are not yet validated by consensus [7].

Shock can be described as a dynamic and unstable state and there is no single direct measure to identify it. It is characterized by inadequate tissue perfusion due to decreased oxygen delivery, increased consumption and/or inappropriate use, leading to anaerobic metabolism and accumulation of lactic acid with subsequent metabolic acidosis and eventual progression to cell death. Tissue hypoperfusion also leads to endothelial dysfunction and stimulation of inflammatory and anti-inflammatory cascades which, if not stopped, result in circulatory collapse, multiorgan failure and death. In sepsis, there is a release of vasoactive mediators that results in diffuse vasodilation and hypoperfusion. Most children who die of sepsis have refractory shock and/or multiple organ dysfunction syndrome, with many deaths occurring within the first 48-72 hours of treatment [6-10]. In the early stages of newborn shock it may be difficult to identify subtle changes occurring. For example, Blood Pressure (BP) alone is not a good measure to determine shock in the newborn: A normal value does not

imply normal perfusion and a low BP can be present in the absence of shock. When shock is clinically evident, usually the newborn is in an uncompensated state [10].

Risk factors for a neonate to develop septic shock have not been described precisely though they overlap those for sepsis and include prenatal and postnatal risk factors. Prenatal risk factors include maternal age (> 30 years), lack of prenatal care, high gravidity, maternal intrapartum fever, urinary tract infection, prolonged fetal internal monitorization, chorioamnionitis or prolonged rupture of membranes, treatment with steroids, group B Streptococci recto-vaginal colonization and meconium-stained amniotic fluid during labour. Postnatal risk factors include prematurity (< 37 weeks), low-birth-weight (<1000 grams), 5-minute Apgar score <5, resuscitation in delivery room, male gender, intravenous nutrition, central venous catheters, use of steroids or drugs that decrease gastric acid acidity, prolonged duration of mechanical ventilation, hypogammaglobulinemia, neutropenia, prolonged hospital stay and development of severe necrotizing enterocolitis [7,8].

Prevention, diagnosis, and treatment of Neonatal Septic Shock (NSS) is an important challenge in Neonatal Intensive Care Units (NICU). We aim to determine the incidence, causative microorganisms, and therapeutic management of neonatal septic shock in our NICU.

Materials and Methods

We performed an observational, retrospective, descriptive, longitudinal, cohort study of newborns in a Neonatal Intensive Care Unit (NICU), with septic shock. The study was conducted in Hospital São Francisco Xavier, Centro Hospitalar Lisboa Ocidental, a public hospital in Lisbon, Portugal, with a fourteen-bed capacity. Patients were admitted from maternity, from the emergency service or referred from other hospitals. We analysed medical records and microbiological data of newborns with septic shock, over 4 years, between 2017 and 2020.

Sepsis was defined as systemic inflammatory response syndrome in the presence of suspected or proven infection. A suspected or proven (by a positive culture, tissue stain, or polymerase chain reaction test) infection is caused by any pathogen or a clinical syndrome associated with a high probability of infection. Evidence of infection includes positive findings on clinical exam, imaging, or laboratory tests. In our study, we use Wynn and Wong septic shock definition: Sepsis and cardiovascular organ dysfunction. Cardiovascular dysfunction was defined as the need for fluid resuscitation or inotropic support to maintain BP in the normal range or 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) and prolonged capillary refill (>5 seconds or >4 seconds in preterm infants). Although some other definitions are not consensual, in our study, we defined tachycardia as a heart rate higher than 180 beats/min; hypotension as median arterial pressure less than 30 mmHg or BP <5th percentile for age; hypothermia as core temperature less than 36ºC and fever as more than 38ºC in premature infants or more than 38.5ºC in term newborns [7].

Demographic data included gender, gestational age, birth weight, age at diagnosis, isolated microorganisms, clinical and laboratory monitoring (during the first 24 hours after septic shock identification). Furthermore, all carried out interventions were collected. Outcomes evaluated were mortality, antibiotic, fluid bolus, vasopressor, hydrocortisone, immunoglobulin, bicarbonate, and blood derivatives administration.

Statistical analysis was performed with Microsoft® Excel and SPSS 28.0® and significance was indicated by p-value ≤ 0.05. The Kolmogorov-Smirnov test was used to test distribution and data were normally distributed. Qualitative variables were expressed as frequencies, percentages and 95% Confidence Intervals (CI) and continuous variables as means and Standard Deviation (SD). Chi-square test or Fisher exact test were used to compare categorical variables. Odds ratios were calculated and a logistic regression analysis was performed. A level of significance of <0.05 was assumed.

Results

Between 1 January 2017 and 31 December 2020, there were a total of 9593 live births, 990 (10.3 %) newborns admitted to the NICU and 31 (3.1 %) newborns developed neonatal septic shock (3.2 per 1.000 live births). In the group of neonatal septic shock newborns, 84% (n=26) were preterm. Mean gestational age was 31 weeks (SD 4.8), minimum 24 weeks, maximum 42 weeks. Mean birth weight was 1567g (SD 989), 55% (n=17) with less than 1500g and 39% (n=12) less than 1000g (minimum 477g, maximum 4075g) and 68% (n=21) were male (Table 1). The median postnatal age at the onset of septic shock was 11 days (minimum 5, maximum 19), and 26 cases (84%) presented after 72h of life. Clinically, 58% (n=18) were tachycardic (>180 beats/min), arterial hypotension was observed in 48% (n=15), 87% (n=27) needed invasive mechanical ventilation, 48% (n=15) had hypothermia and 16% (n=5) fever.

Variables	Mean	SD
Gestational age (weeks)	30.9	4.8
Birth weight (grams)	1567	989
	Frequency, %	**CI 95%**
Male gender	68	50-82
Heart disease	7	0-26
Genetic disease	3	0-10

Table 1: Demographic profile of newborns admitted with septic shock

Blood analysis: NiNt>20% in 81% (n=25) and >10% in 16% (n=5), CrP>10 mg/dL in 42% (n=13), base deficit >5 mEq/L in 81% (n=25), lactate >2 times upper limit in 68% (n=21), platelet count <80000/mm^3 in 61% (n=19), leucocytosis in 32% (n=10) and leukopenia 32% (n=10). Blood cultures were collected in all cases and there were 32 positive results. The most frequently isolated bacteria were gram-negative pathogens, accounting for 19 of 27 (70%). Pathogen distribution is reported in table 2. All 31 newborns had a suspected or proven infection and all of them received antibiotics: Vancomycin (59%), amikacin (49%) and meropenem (44%) were the main antibiotics used.

Therapeutic management included volume expansion and vasoactive drugs in 87% (n=27), bicarbonate in 29% (n=12), hydrocortisone in 7% (n=2) and immunoglobulin in 3% (n=1).

Lethality occurred in 10 newborns (32%), 90% preterm, median gestational age 29 weeks, all with positive blood cultures. All 10 deaths received vasoactive drugs (dopamine 100%, dobutamine 80%, epinephrine 30%), 90% had fluid boluses, two took hydrocortisone and one had intravenous immunoglobulin. Blood derivatives were

Pathogen	N	(%)	Death, No.
Acinetobacter baumani	1	3%	1
Aeromonas hydrophila	1	3%	0
Enterobacter cloacae	1	3%	1
Enterovirus	1	3%	0
Escherichia coli	8	25%	2
Klebsiella pneumoniae	3 (1 ESBL)	9%	1
Pseudomonas aeruginosa	2	6%	1
Serratia marcescens	3	9%	3
Staphylococcus epidermidis	6	19%	1
Streptococcus agalactiae	2	6%	0
Staphylococcus capitis	1	3%	0
Staphylococcus aureus	2	6%	0
Staphylococcushaemolyticus	1	3%	0
ESBL: extended-spectrum β-lactamases			

Table 2: Pathogen distribution in neonatal septic shocks (n=31).

used: red cell concentrate in 77% (n=24), platelet transfusion in 65% (n=20) and fresh frozen plasma in 32% (n=10). One patient was transferred for ECMO therapy (Table 3).

Interventions	Number (%)	Frequency, %	CI 95%
Fluid boluses	27 (87%)	87	75-100
Antibiotics	31 (100%)	100	100-100
Vasoactive drugs	27 (87%)	87	75-100
Bicarbonate	12 (29%)	29	21-57
Hydrocortisone	2 (7%)	7	0-16
IV Immunoglobulin	1 (3%)	3	0-10

Table 3: Interventions during management of septic shock of infants included (n=31)

Statistical analysis for outcome death in infants with septic shock is presented in table 4. Odds Ratios (OR) of clinical presentation statistically significant were weight <1000g (OR 7.5, CI 95% 1.39-40.25; p= 0.021), weight ≥1000g (OR 0.13, CI 95% 0.03-0.72; p= 0.021) and isolation of gram-negative bacteria (OR 12.0, CI 95%: 1.28-112.66; p=0.020). Considering clinical symptoms: tachycardia (OR 4.0, CI 95%: 0.67-23.73; p=0.235), NiNt>10% (OR 4.07, CI 95%: 0.56-29.73; p=0.296) and oliguria (OR 4.07, CI 95%: 0.56-29.73; p=0.296) might be a risk factor for death but the association is not statistically significant in this cohort. Bicarbonate administration was associated with death (OR 54.0, 95% CI: 4.9-595.52; p< 0.001).

A logistic regression analysis showed a negative correlation between weight and probability of death (B -1.038, Exp(B) 0.354, CI 95% 0.14-0.87; p=0.023) and a positive correlation between weighing <1000g and having a gram-negative infection relatively to the possibility of death (<1000g: Exp(B) 18.72, CI 95% 1.67-209.49; p=0.017; gram-negative bacteria: Exp(B) 30.36, CI 95% 1.75-527.81; p=0.019;).

Variables	Odds ratio	CI (95%)	p-value
Weight <1000g	7.47	1.39-40.25	0.021
Weight ³1000g	0.13	0.03-0.722	0.021
< 28 weeks	2.13	0.42-10.73	0.417
28-31 weeks	2.5	0.53-11.89	0.423
32-36weeks	0.36	0.04-3.54	0.634
>36 weeks	NA	NA	NA
< 3 days at diagnosis	NA	NA	NA
3-7 days at diagnosis	1.29	0.24-6.96	1
> 7 days at diagnosis	2.1	0.41-10.66	0.45
Gram negative bacteria	12	1.28-112.66	0.02
Gram positive bacteria	1.37	0.25-7.39	1
Fever (>38ºC)	NA	NA	NA
Hypothermia (<36ºC)	2	0.43-9.26	0.458
Tachycardia	4	0.67-23.73	0.235
Arterial hypotension	1.1	0.24-4.96	1
Leukocytosis	3.2	0.65-15.78	0.222
Leukopenia	0.15	0.02-1.39	0.106
NiNt>10%	4.07	0.56-29.73	0.296
NiNt>20%	0.39	0.06-2.41	0.358
Platelets <80000/uL	1.75	0.35-8.71	0.697
CrP>10mg/dL	0.47	0.10-2.34	0.452
Base deficit >5.0 mEq/L	2.81	0.28-27.97	0.634
Lactate >2 times upper limit	1.17	0.23-5.95	1
FiO2 >50%	2.57	0.52-12.72	0.28
Oliguria < 0.5mL/kg/h	4.07	0.56-29.73	0.296
Altered mental status	2	0.27-14.78	0.627
Fluid boluses	1.5	0.14-16.54	1
Vasoactive drugs	NA	NA	NA
Bicarbonate	54	4.90-595.52	<0.001
Hydrocortisone	NA	NA	NA
IV Immunoglobulin	NA	NA	NA
CrP: C-reactive protein; NA: Not Applicable (no data to calculate Odds ratio); NiNt: Immature to total neutrophil ratio.			

Table 4: Analysis for outcome death in infants with septic shock (n=31).

Discussion

Septic shock definition is not consensual, especially in premature newborns for which the hemodynamic response and clinical interventions are not well known. Neonatal sepsis, especially in premature babies, can present with subtle signs. A high degree of vigilance is necessary because when shock becomes clinically obvious is often in an uncompensated state and it can rapidly progress to multisystem organ failure and death [10,11]. Clinical surveillance with measures such as MAP, SpO_2, capillary refill and urine output and also functional echocardiography and near-infrared spectroscopy may provide important physiologic data to optimise management of septic shock [7]. In our study, hypothermia (48%), hypotension (48%), tachycardia (58%) and need for invasive mechanical ventilation (87%) were present during the first 24 hours of shock. Only 16% of patients had fever.

Blood analysis evaluations (pH, mixed venous saturation, lactate, and base deficit) are important for monitoring severity and response to therapy [7]. Our results revealed that base deficit >5 mEq/L (81%), lactate >2 times upper limit (68%), NiNt>20% (81%), CrP>10 mg/dL (42%), platelet count <80000/mm3 (61%), leucocytosis (32%) and leukopenia (32%) were present. Regarding the leucocyte count, it has a better predictive value if low (<5000/uL) or high (>40000/uL) and-NiNt has greater sensitivity compared with the absolute neutrophil count. In our cohort NiNt>20% and base deficit > 5mEq/L were more prevalent than leucocytosis, leukopenia or CrP>10mg/dL. Thrombocytopenia is frequent in neonatal sepsis, and two-thirds of patients had this finding. Not with standing, a normal leukocyte count and platelet count don't rule out the diagnosis [11,12].

When clinical and laboratory signs are detected, immediate administration of intravenous antibiotics and supportive care are needed. Before administering antibiotics, all patients had at least one blood culture obtained in the initial assessment as it is the gold standard for documentation of bacterial sepsis. Blood cultures were collected and there were 32 positive results. The most frequently isolated bacteria were gram-negative (*Escherichia coli* (25%), *Serratia marcescens* (9%) and *Klebsiella pneumoniae* (9%)) and were responsible for 90% of fatal septic shock cases (OR 12.0, CI 95%: 1.28-112.66; p=0.02). Even though *Staphylococcus epidermidis* was present in19% of cases, 2 were considered possible contaminations. *S. marcescens* (3 cases), *E. coli* (2 cases), *Acinetobacter baumani* (1 case), *Enterobacter cloacae* (1 case), *Pseudomonas aeruginosa* (1 case), *K. pneumoniae* extended spectrum beta-lactamase (1 case) and *Staphylococcus epidermidis* (1 case) were identified in fatal cases. As in our study, gram-negative agents have been frequently identified in recent years and are associated with higher mortality. According to Stoll et al. 2002 and Gordon et al. 2006, one-fifth of those infected by gram negatives die. Viruses (herpes simplex, enteroviruses) have been associated with fulminant neonatal sepsis [4,13-15]. We had one case of enterovirus isolation that needed to be transferred to another unit for ECMO treatment. There were five cases (16%) where there was no microorganism isolation, with two cases of necrotizing enterocolitis and none of them associated with death. Necrotizing enterocolitis can be associated with severe sepsis, and in some cases shock and death. All 31 infants had a suspected or proven infection and all of them received antibiotics. Vancomycin (59%), amikacin (49%), meropenem (44%), gentamicin (32%), piperacillin and tazobactam (32%), cefotaxime (27%) and ampicillin (24%) were the main antibiotics used. Antibiotics used were broad-spectrum, which were narrowed once the pathogen and its antibiotic sensitivity were characterised. Initial empiric antibiotic combinations were ampicillin plus gentamicin for early-onset sepsis, or vancomycin plus an aminoglycoside (and a third-generation cephalosporin) for late-onset sepsis.

In our study, analysis of death outcome showed the lower the weight, the greater the probability of death. Furthermore, weighing <1000g and isolation of gram-negative bacteria were statistically significantly associated with death. Additionally, weighing <1000g and having a gram-negative infection combined showed a stronger correlation of these two variables with the possibility of death. Hypothermia, hypotension, tachycardia and need for invasive mechanical ventilation were associated with death but this association was not statistically significant. Regarding blood analysis results, NiNt>10%, base deficit >5 mEq/L, lactate >2 times upper, platelet count <80000×10^9/L, and leucocytosis were associated to fatality cases and also not statistically significant. The odds of pathophysiology of sepsis in premature infants, with organs and immune system immaturity, can explain these results.

Regarding shock treatment, volume expansion and vasoactive drugs were the main interventions, in line with recommendations for treatment of septic shock. Deciding when to treat is a great challenge in neonatal cardiovascular management because it's possible to have a clinical state of hypoperfusion with or without low BP [7,10]. In our series 27 patients (87%) received fluid boluses and this intervention is poorly associated with death, with statistically significance. Three of the four that didn't receive fluid boluses had congenital cardiopathies. The volume to use is not well defined as there are no newborn trials. Volume should be used with caution, particularly in the preterm infant. Higher fluid intake has been associated with an increased risk of patent ductus arteriosus, chronic lung disease and intraventricular haemorrhage [16,17]. Dopamine was used in 27 cases (87%), dobutamine in 12 cases (39%) and epinephrine in 5 (16%). Data on inotrope use in NSS is limited but dopamine remains the primary inotrope. Use of a combination of agents is not well studied in neonatal care for sepsis and septic shock [10]. Hydrocortisone was used in 2 cases and immunoglobulin in one, all in 3 different fatal cases.

Data regarding neonatal septic shock is limited and there is no Portuguese study in this field. Regardless of our little example, this cohort study gives significant epidemiologic data and diagnostic and treatment approach in this particular population.

The limitations of this study are essentially related to the fact that it is small cohort which makes it difficult to have more accurate results and being a retrospective study. The fact that we do not have the timing of starting antibiotics, starting volume administration and vasoactive drugs meant that we could not draw some conclusions about intervention and its outcome.

Despite advances in the management of sepsis, both diagnosis and treatment remain challenging. A more precise definition, adapted to the neonatal period, is necessary to optimise an early diagnosis. Hydrocortisone and immunoglobulin were used in just a few patients of our study but may play an important role in neonatal septic shock management. However, this approach needs additional studies to understand preterm newborn unique characteristics of septic shock.

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Conflicts of Interest

The authors declare no conflict of interest.

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