

Research in Education and Rehabilitation 2020; 3(1): 1-8.

SEPSIS MONITORING IN NEONATAL INTENSIVE CARE UNIT

MONITORING SEPSE U NEONATALNOJ INTENZIVNOJ JEDINICI

Devleta Hadžić[1], Hajriz Alihodžić[2], Amina Saračević[1], Dženana Softić[1], Delila Softić[1]

[1]Klinika za dječije bolesti, Univerzitetski klinički centar Tuzla
[2]Služba hitne medicine Doma zdravlja Tuzla

Original Scientific Article

Received: 03/04/2020
Accepted: 26/06/2020

ABSTRACT

The aim of this study was to determine epidemiology, clinical implications, outcome and monitoring of neonatal sepsis in intensive care unit. A retrospective cohort study included all consecutive neonates with a positive blood culture, from those treated in Neonatal intensive care unit over one-year period, marked as the test group. The study was approved by Ethics Committee of the Institution. Clinical and demographic data were obtained from medical records and electronic database of patients, including gender, gestational age, birt weight, perinatal risk factors for neonatal sepsis, clinical presentation, laboratory findings, applied therapy and outcome. For statistical analysis were used standard methods of descriptive statistics. Of total 345 treated neonates, sepsis were confirmed on blood culture in 93 neonates (26.9%), evenly in both genders. Among the causative agents, gram positive pathogens dominated, followed by gram negative pathogens and fungi. Gestational immaturity and low birth weight were confirmed as the most significant risk factors. In laboratory findings leukopenia, thrombocytopenia and coagulation disorders were significant. The lenght of intensive treatment was significantly longer in the sepsis group. Mortality rate of neonates with sepsis was 7.5%, higher than the total sample but without statistical significance. Recovery of these neonates notedly depends on timely clinical suspicion, adequate treatment and supervision. Antimicrobial susceptibility is also important, which requires monitoring of local epidemiological data to improve treatment.

Key words: Sepsis, neonatal intensive care unit, monitoring, prevention

[1] Correspondence to:
Devleta Hadžić, Univerzitetski klinički centar Tuzla, Klinika za dječije bolesti, Prof.dr.Ibre Pašića bb, 75000 Tuzla, Bosna i Hercegovina
Phone.: ++387 35 303 733;
E-mail: devletahadzic@yahoo.com

Research in Education and Rehabilitation 2020; 3(1): 1-8.

MATERIAL AND METHODS

Sample of participant

A retrospective cohort study, which included all consecutive neonates with a positive blood culture, from those treated in Neonatal intensive care unit (NICU) of Pediatric clinic Tuzla (capacity 22 beds, level III) over one-year period (January 1 - December 31, 2019). All neonates with proven microbial isolates from blood culture were designated as the test group, which was compared with the sample of neonates treated at the same time in the NICU without positive blood culture. The study was approved by Ethics Committee of the Institution.

Method of conducting research

Clinical and demographic data were obtained from medical records and electronic database of patients treated in NICU, which included gender, gestational age, birt weight, perinatal risk factors for neonatal sepsis, clinical presentation, laboratory findings, applied therapy and outcome.

Measuring instruments

During admission, clinical status of neonates was scored by SNAP-PE (Score for Neonatal Acute Physiology - Perinatal Extension) i CRIB II (Clinical Risk Index for Babies) score (Dorling et al., 2005). Especially we analyzed predisposing factors for health care-associated infections (presence of central venous catheter, length of mechanical ventilation, parenteral nutrition, applied therapy and length of hospitalization). From laboratory findings we particularly analyzed potential markers of infection, including C-reactive protein (CRP), Complete blood cell (CBC) counts, the highest and lowest value for white blood cell (WBC) count, absolute neutrophil count (ANC), immature to total neutrophil ratio (I/T ratio), platelet count, and coagulation status. Early onset neonatal sepsis (EOS) was defined as infection that develops in first 72 hours of life, and late onset neonatal sepsis (LOS) was defined as infection that develops after 72 hours of life.

Data processing methods

For statistical analysis were used standard methods of descriptive statistics (central tendency measures, dispersion measures). Parametric and non- parametric significance tests (X^2-test, Student's t- test) as well as linear correlation method were used to test the significance of differences between the samples. Statistical hypotheses were tested at a significance level of $\alpha = 0.05$, i.e. The difference between the samples is considered significant if $p < 0.05$. We used Systat Software, Systat Inc, Evanstan, IL, USA for statistical processing of data.

Research in Education and Rehabilitation 2020; 3(1): 1-8.

RESULTS AND DISCUSSION

During the one-year period (2019), 345 neonates were treated in NICU, and their basic clinical and demographic characteristics are shown in Table 1.

Table 1. NICU admitted patients characteristics (n = 345)

Characteristics	**n**	**%**
Neonates (0-28 day of life)	345	100.0
Preterm (<37GW)	190	55.0
late preterm (34-36GW)	155	45,0
very preterm <32GW)	64	18.5
extremely preterm (<28GW)	21	6.1
low birth weight (<2500g)	104	30.1
very low birth weight (<1500g)	43	12.5
extremely low birth weight (<1000g)	14	4.1
Mechanical ventilation within NICU stay	150	43.5
Surgery within NICU stay	16	4.6
Clinically suspected sepsis	144	41.7
Confirmed sepsis on blood cultures	93	26.9
Gram positive isolates from blood culture	52	15.0
Gram negative isolates from blood culture	21	6.0
Fungal isolates from blood culture	20	5.8
MRP isolates from blood culture	8	2.31
NICU: neonatal intensive care unit; GW: gestational weeks; MRP: multidrug resistance pathogen		

Of total 345 treated neonates, clinically suspected sepsis were found in 144 neonates (41.7%). Sepsis confirmed on blood culture was found in 93 neonates (26.9%), evenly found in both genders. Suspected neonatal sepsis is a common indication for admission to the NICU, and from recent published studies we can conclude that regardless of constant progress in treatment of critically ill neonates, globally, sepsis is still one of the major causes of morbidity and mortality in neonates. It causes about 25% of all neonatal deaths, and mortality due to sepsis has increased by approximately 13.7% each year over the past 2 decades (Ozkan et al., 2014). The incidence of blood culture-proven sepsis in our NICU currently is 12 per 1000 live births, which is comparable to other reports and NICU results. Blood culture is the gold standard for the confirmation of sepsis. In advance centres, blood culture is positive in 80% of genuine sepsis. The prevalence of culture proven neonatal sepsis is different in various studies, from 10% to 50%, which depends on criteria and sampling technique, as well as from quality of health care and hospital services in various countries (Ozkan et al., 2014).
The diversity of the etiology of sepsis varies from region to region and changes over time even in the same place. This is attributed to differences in quality of life, predisposing factors for infection, and usage of antibiotics (Behmadi et al., 2016). In our study gram positive pathogens dominated, followed by gram negative pathogens and fungi. Among the causative agents were also multidrug-resistant pathogens. Our results showed that early onset sepsis was more prevalent than late onset sepsis (60% vs. 40%), which is in agreement with some reports (Behmadi et al., 2016), but different from some others (Afonso and Blot, 2017).

Research in Education and Rehabilitation 2020; 3(1): 1-8.

There were no gender differences neither in total nor in sepsis sample, although, other studies have preferred male, even to be reported the male gender as a risk factor for neonatal sepsis (Roy et al., 2014).

The risk factors for neonatal sepsis have been extensively studied (Garcia et al., 2015; Verstraete et al., 2015), and results of this study are shown in Table 2.

Table-2: Perinatal risk factors in the two observed groups

	Sepsis group		**Non-sepsis group**		
Parameter	**Mean**	**SD**	**Mean**	**SD**	**p**
GA (weeks)	32.56	3.78	36.65	3.24	**<0.001**
BW (grams)	1852.84	746.23	2841.72	805.61	**<0.001**
AS 1st minute	5.9	2.1	6.9	2.3	**0.0042**
AS 5th minute	6.91	1.32	7.73	1.61	**0.0017**
PRM (hours)	5.05	4.16	4.17	11.38	0.5121

GA- gestational age; BW-birth weight; AS 1st min- Apgar score in the first minute; AS 5th minute-Apgar score in the fifth minute; PRM- premature rupture of membranes

Multiply, the neonates are at risk of infection, and as is known, sources may originate from maternal disease, infections, interventions during pregnancy and/or childbirth, or postnatally, and come again out of the hospital, or even from the community (Shane et al., 2017). Gestational immaturity and low birth weight in our study were confirmed as the most significant risk factors for onset of neonatal sepsis. In our study maternal risk factors showed significance, especially for first birth and in vitro fertilization, that were significantly more frequent in the sepsis group compared to the total sample, but without statistical significance.

Laboratory parameters used to evaluate neonatal sepsis include infectious markers from known sepsis scoring systems, like a complete blood cell count, C-reactive protein, leukocyte count, platelet count, and others (Levit et al., 2014). Laboratory findings in neonates with sepsis in our study were leukopenia, thrombocytopenia and coagulation disorders, significantly more of the total sample (Table 3). There are different reports on the utility of laboratory parameters in the assessment of neonatal sepsis, and certainly, it is a significant tool in all sepsis scoring systems (Shane et al., 2017).

Table-3: Clinical and laboratory data of neonatal sepsis and non-sepsis cases

	Sepsis group		**Non-sepsis group**		
Parameter	**Mean**	**SD**	**Mean**	**SD**	**p**
CRP (mg/ℓ)	49.51	70.13	21.62	40.04	**0.0004**
Htc	0.52	0.16	0.51	0.14	0.5753
Leukocytes	9.13	3.72	14.11	8.43	**0.0001**
neutrophils	0.32	0.14	0.41	0.18	**0.0025**
ANC	3250.0	2240.18	6056.70	4551.28	**<0.001**
ITR	0.07	0.06	0.08	0.09	0,7834
platelets	110.66	97.57	223.27	116.60	**<0.001**
albumin	26.42	4.63	27.57	4.21	0.1021
Treatment (days)	38.19	23.14	12.40	6.93	**<0.001**
CRIB II	5.95	4.31	3.94	4.07	**0.0029**
SNAPEPE II	36.80	20.07	23.51	24.99	**0.0008**

Research in Education and Rehabilitation 2020; 3(1): 1-8.

CRP- C reactive protein; Htc- hematocrit; ANC- Absolute neutrophil count; CRIB II- Clinical Risk Index for Babies scoring system ; SNAPEPE II- Score for Neonatal Acute Physiology-Perinatal Extension.

The clinical manifestations range from subclinical to severe manifestations. The timing of exposure, neonatal immune status, and causative agent virulence influence the clinical expression of neonatal sepsis (Raymond et al., 2017). Neonatal disease severity scoring systems showed significantly higher values in neonates with sepsis in relation to the non sepsis group (Table 3). Severe clinical presentation of neonates with proven sepsis via positive blood culture, was demonstrated by the necessarily applied supportive therapy (Table 4).

Table-3: Clinical implications and outcome in the two observed groups

Variables	**Sepsis group (n=93)**	**Non-sepsis group (n=252)**	**p-value**
Early onset of sepsis (<72h)	56(60.2)		**0.0032**
Late onset of sepsis (>72 h): n (%)	37(39.8)		**0.0032**
Respiratory distress syndrome	72(77.3)	92 (36.5)	**<0.001**
Pneumonia n(%)	32(34.4)	75(29.8)	0.4125
Severe intracranial hemorrhage	6(6.5)	2(0.8)	0.0019
Initial acute renal failure	12(12.9)	16(6.3)	0.0459
Intravenous immunoglobulins n(%)	27(29.0)	2(0.8)	**<0.001**
Mechanical ventilation n(%)	78 (83.9)	72 (28.6)	**<0.001**
Parenteral nutrition n(%)	91 (97.8)	63 (25.0)	**<0.001**
Inotropes n(%)	57(61.3)	75(29.7)	**<0.001**
NICU stay in days (mean±SD)	20.7± 10.8	12,40±6,93	**<0.001**
Outcome			
Survivors n(%)	86 (92.5)	241(95.6)	0.2514
Non-survivors n(%)	7 (7.5)	11(4.3)	0.2514
SD- standard deviation; NICU-Neonatal intensive care unit			

The lenght of intensive treatment was significantly longer in the sepsis group (20.7 ± 10.8 days) compared to the total sample (12.40 ± 6.93 days). The available evidence suggests a higher incidence and mortality rate of late-onset sepsis in premature and very low birth weight neonates, but pathogen distribution and risk exposure for pathogens are similar for all neonates admitted to the NICU (Hsu et al., 2015).

Because treatment has not produced satisfactory results, modern medicine is increasingly promoting the prevention, education, responsibility and and permanent control of hospital infections (Weiss et al., 2020). Inevitably, intensive treatment, which in critically ill neonates involves invasive procedures, such as central venous catheters, mechanical ventilation, surgical interventions, in addition to parenteral nutrition and prolonged hopitalization, these are all proven risk of infection (Garcia et al., 2015), wich was also the case in our study. These are the so-called specific points of attention, given that most health-associated infections in intensive care units are associated with the use of therapeutic devices (Verstraete et al., 2015). These include ventilator associated pneumonia, catheter related infections in the bloodstream, surgical wound infections, and urinary tract infections.

Research in Education and Rehabilitation 2020; 3(1): 1-8.

Recommendations for the proper use of all appliances and medical materials (probes, catheters, suction of secretions, maintenance of venous catheters, etc.), as well as monitoring and preventing the spread of infection, are mandatory (Levy et al., 2018).

Careful monitoring of infection in our NICU has a tradition of over 15 years with carefully monitoring of microbial isolates from patients, but at the same time we following and monitoring cultures from staff and all surfaces and apparatus in the NICU (Table 5). Monitoring cultures from equipment and personnel are also necessary in an attempt to achieve the best possible infection control in a very challenging environmentthe of a neonatal and pediatric intensive care unit.

Table 4. Sepsis monitoring in NICU

Year	**2017**	**2018**	**2019**
Number of treated patients	462	485	500
Number treated neonates	332	342	345
Number of treated pediatric patients	130	143	155
Number of microbiological samples	935	1060	958
Microbiological samples in neonates	829	958	851
Microbiological samples in pediatric patients	106	102	107
Number of positive isolates	201	230	213
Number of positive isolates in neonates	159	194	160
Number of positive isolates in pediatric patients	42	36	53
Sampling of staff and equipment	138	108	160
Positive isolates from staff and equipment	22	8	10

These facts are very important for the evaluation of the spread of infection, the identification of the prevalent local agents, and the identification of the resistance of the agents to antibiotics, which is an important determinant of initial and causal treatment.

Prescribed hand hygiene, by itself, can significantly improve results (Rhodes et al., 2017). Responsible management of infection involves a careful and correct approach to controlling source of infection, activities to reduce spread of infections, and additional attention to infection prevention protocols. These are conditions for successful treatment, but also obligation to maintain prescribed standards.

CONCLUSION

Sepsis is still one of the major causes of morbidity and mortality in neonates. In our NICU affects about a quarter of treated patients with a mortality rate of about 7.5%. The incidence of blood culture-proven sepsis in our NICU currently is 12 per 1000 live births, with more prevalent early onset sepsis than late onset sepsis (60% vs. 40%) and with no gender differences. Etiologically gram positive pathogens dominated, followed by gram negative pathogens and fungi, with also some multidrug-resistant pathogens. Gestational immaturity and low birth weight were confirmed as the most significant risk factors, and also confirmed that neonatal sepsis has a risky clinical course and outcome. It endangers life, complicates treatment, prolongs NICU stay, increases costs and mortality. Recovery of these neonates depends on timely clinical suspicion, adequate treatment and supervision, so outcomes may be improved by preventative strategies, earlier and accurate diagnosis, which requires monitoring of local epidemiological data. Antimicrobial susceptibility is also important, and emphasis is on prevention trough promotion of infection control including effective hospital infection control programs, local antimicrobial stewardship program and surveillance of antibiotic resistance and (nosocomial) infections.

REFERENCES

1. Afonso, E.D.P., Blot, S. (2017). Effect of gestational age on the epidemiology of late-onset sepsis in neonatal intensive care units - a review. *Expert Rev Anti Infect Ther*, 15(10): 917-924.
2. Bandyopadhyay, T., Kumar, A., Saili, A., Randhawa, V.S. (2018). Distribution, antimicrobial resistance and predictors of mortality in neonatal sepsis. *J Neonatal Perinatal Med*, 11(2): 145-153.
3. Behmadi, H., Borji, A., Taghavi-Rad, A., Soghandi, L., Behmadi, R. (2016). Prevalence and antibiotic resistance of neonatal Sepsis Pathogen in Neyshabour, Iran. *Arch Pediatr Dis*, 4(2): e 33818.
4. Cailes, B., Kortsalioudaki, C., Buttery, J., Pattnayak, S., Greenough, A., Matthes, J., Bedford, R.A., Kennea, N., Heath, P.T. (2018). Antimicrobial resistance in UK neonatal units: neonIN infection surveillance network. *Arch Dis Child Fetal Neonatal Ed*, 103(5): F474-F478.
5. Dorling, J.S., Field, D.J., Manktelow, B. (2005). Neonatal disease severity scoring systems. *Arch Dis Child Fetal Neonatal Ed*, 90(1): F11–F16.
6. Garcia, H., Torres-Gutierrez, J., Peregrino-Bejarano, L., Cruz-Castaneda, M.A. (2015). Risk factors for nosocomial infection in a level III Neonatal Intensive Care Unit. *Gac Med Mex*, 151(6):711-9.
7. Hsu, J.F., Chu, S.M., Huang, Y.C., Lien, R., Huang, H.R., Lee, C.W., et al. (2015). Predictors of clinical and microbiological treatment failure in neonatal bloodstream infections. *Clinical microbiology and infection: the official publication of the European Society of Clinical Microbiology and Infectious Diseases*, 21(5): 482 e9-17.
8. Levit, O.B.V., Li, F.Y., Shabanova, V., Gallagher, P.G., Bizzarro, M.J. (2014). Clinical and laboratory factors that predict death in very low birth weight infants presenting with late-onset sepsis. *Pediatr Infect Dis J,* 33: 143±46.
9. Levy, M.M., Evans, L.E., Rhodes, A. (2018) The Surviving Sepsis Campaign bundle: 2018 update. *Crit Care Med*, 46: 997-1000.

10. Ozkan, H., Cetinkaya, M., Koksal, N., Celebi, S., Hacimustafaoglu, M. (2014). Culture-proven neonatal sepsis in preterm infants in a neonatal intensive care unit over a 7 year period: coagulase-negative Staphylococcus as the predominant pathogen. *Pediatrics International*, 56(1): 60–66.
11. Raymond, S. L., Stortz, J. A., Mira, J. C., Larson, S. D., Wynn, J. L., & Moldawer, L. L. (2017). Immunological Defects in Neonatal Sepsis and Potential Therapeutic Approaches. *Frontiers in pediatrics*, *5*, 14.
12. Rhodes, A., Evans, L.E., Alhazzani, W., et al. (2017) Surviving Sepsis Campaign: international guidelines for management of sepsis and septic shock. *Crit Care Med*, 45: 486-552.
13. Roy, P., Kumar, A., Kaur, I.R., Faridi, M.M. (2014). Gender differences in outcomes of low birth weight and preterm neonates: the male disadvantage. *J Trop Pediatr*, 60(6): 480-481.
14. Shane, A.L., Sanchez, P.J., Stoll, B.J. (2017). Neonatal sepsis. *Lancet*, 390(104):1770-1780.
15. Verstraete, E.H., De Coen, K., Vogelaers, D., Blot, S. (2015). Risk Factors for Health Care-Associated Sepsis in Critically Ill Neonates Stratified by Birth Weight. *Pediatr Infect Dis J*, 34(11): 1180-6.
16. Weiss, S.L., Peters, M.J., Alhazzani, W. *et al.* (2020). Surviving sepsis campaign international guidelines for the management of septic shock and sepsis-associated organ dysfunction in children. *Intensive Care Med*, 46: 10–67.