

EPIDEMIOLOGY AND CLINICAL PRESENTATION OF NEONATAL FUNGAL SEPSIS IN INTENSIVE CARE UNITS OF PEDIATRIC CLINIC TUZLA

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ABSTRACT

Introduction: Standing advances in neonatology increased survival of premature infants with the use of invasive procedures, which increases risk of infection and fungal sepsis. Risk factors for fungal sepsis are extensively studied. *Candida* is dominant, but there is increase in resistant *C. non-albicans* species. Mortality is high and requires timely suspicion of fungal sepsis, and adequate treatment to counteract the fatal outcome.

Objectives: to analyze the clinical and laboratory characteristics of neonates, treated in the neonatal intensive care unit because of microbiologically proven fungal sepsis.

Subjects and Methods: The retrospective observational study included 48 consecutive neonates, treated in intensive care unit of Pediatric Clinic Tuzla during three-year period (2016-2018), those with proven fungal sepsis, confirmed by positive blood culture. We analyzed perinatal history, clinical and laboratory presentation of disease, length of treatment and outcome. Statistical analysis applied standard methods, and the research was approved by the Ethics Committee of the institution.

Results: Of the total treated 921 neonates, confirmed fungal sepsis were found in 48 infants (5.2%), evenly distributed by gender. Of perinatal risk factors, confirmed the prematurity and low birth weight, and significant were the presence of umbilical venous catheter, parenteral nutrition, longer antibiotic therapy and mechanical ventilation. Clinically, fungal sepsis manifested as late sepsis with respiratory higher requirements, lethargy, feeding difficulties and abdominal distension. The most common laboratory abnormalities were increased CRP, leukocytosis and thrombocytopenia. Outcome: 44 neonates (91.7%) survived, while 4 neonates (8.3%) died. Antifungal therapy lasted 20.6 ± 6 days, and intensive treatment 38.2 ± 23.2 days. All isolates were *Candida species*, in vitro without resistance. In 8 neonates (16.7%) recorded a slight toxic hepatitis.

Conclusion: Recovery of neonates with fungal sepsis depend on timely clinical suspicion, adequate treatment and monitoring. Antifungal susceptibility is also important, which requires monitoring of local epidemiological data to improve treatment.

Key words: fungal sepsis, neonates, epidemiology, clinical presentation, risk factors

INTRODUCTION

Although fungal sepsis (FS) in Neonatal Intensive Care Unit (NICU) is less common than sepsis caused by Gram-positive and Gram-negative bacteria, it has a higher morbidity and mortality rate, especially in preterm infants with low birth weight, while infants who survive often have long-term neurological damage [1]. The mortality rate is different and ranges from 20-75% [2]. The risk factors for neonatal FS have been extensively studied and include prematurity, low birth weight, indwelling central venous catheter use, prolonged hospitalization, mechanical ventilation, endotracheal intubation,

parenteral nutrition, prolonged broad-spectrum antibiotic use, exposure to H₂-receptor antagonist, as well as previous *Candida albicans* colonization from mother [1-3].

Clinical presentations of FS have also been investigated as they are nonspecific in infants, and most commonly include thrombocytopenia, lethargy, glucose instability, increased requirements for ventilation or apnea [4]. It is very important for clinicians to be aware of constant risk of neonatal FS. Given the full extent of the problem, FS in critically ill infants should be considered with negative hemocultures, as early diagnosis and aggressive treatment improve overall

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outcome [5-6]. The definite diagnosis of FS is not always easy to confirm because isolation and identification of the pathogen takes time, which makes it reasonable for infants with suspected FS to be treated empirically with antifungal therapy while awaiting for the results of microbiological findings. Empirical antifungal therapy is based on local epidemiology monitoring of dominant agents in a particular unit [7-9].

Candida strains are most commonly reported as a causative agents of neonatal FS, but instead of the previously dominant (up to 80%) sensitive *Candida albicans*, a gradual increase in non-*albicans* *Candida* strains including *C. parapsilosis*, *C. tropicalis* and *C. glabrata* that show varying degrees of resistance to fluconazole and other antifungal agents have been reported [5-9]. Therefore, the recommended prophylactic administration of Fluconazole is questionable, and its routine, empirical administration as the first-line therapy may be inappropriate [2]. It is very important to have current information on neonatal fungal isolates and their patterns of antimicrobial susceptibility, and thus be guided in the choice of empirical antifungal therapy [10-14].

The aim of this study was to determine the epidemiology of FS in Intensive Care Unit of the Clinic for Children's Diseases, University Clinical Center Tuzla over a three-year period, and to analyze the clinical presentation and presence of the most common risk factors in infants with microbiologically confirmed FS. For comparative purposes, a systematic review of published studies on the epidemiology of FS in critically ill infants was used.

PATIENTS AND METHODS

A retrospective observational study included all consecutive infants with hemoculture confirmed FS from the total number of treated patients in Intensive Care Unit (ICU) of the Clinic for Children's Diseases (capacity 20 beds, level III) in the period from 1 January 2016 to 31 December 2018. All infants who had at least one positive fungi hemoculture or signs and symptoms of infections were taken into consideration in this study. Only the first episode of FS had been reported for patients with recurrent positive findings. The study also included infants undergoing treatment and those who crossed the first 28 days following birth, so that all infants with hemoculture isolated fungi were included in this study.

Clinical and demographic data were obtained from medical records and electronic database of patients treated in ICU, which included gender, gestational age, birth weight and predisposing risk factor for FS (presence of central venous catheter, length of mechanical ventilation, antibiotic therapy, parenteral nutrition and length of hospitalization). During admission, clinical status of infants was scored by SNAP (Score for Neonatal Acute Physiology), SNAP-PE (Score for Neonatal Acute Physiology - Perinatal Extension) and CRIB (Clinical Risk Index for Babies) [15].

The study was approved by Hospital's Ethics Committee. The long-term antibiotics use was considered if it exceeded 14 days of a continuous administration. Late neonatal sepsis is defined as an infection that develops after the first 7 days of life. Fluconazole was used as the first line of empirical antifungal therapy. There was no prophylactic administration of Fluconazole in neonatal unit at the time of the trial, and empirical antibiotic therapy for neonatal sepsis was Ceftriaxone, Amikacin, which was corrected by Meropenem and/or Vancomycin, depending on further clinical course and findings in the particular patient.

For comparative purposes, a systematic review of published studies on the epidemiology of FS in critically ill patients was used. Standard methods of descriptive statistics (central tendency measures, dispersion measures) were used. Parametric and non-parametric significance tests (χ^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, Evanston, IL, USA for statistical processing of data.

RESULTS

During the three-year period, 921 infants were treated in ICU, and their basic clinical and demographic characteristics are shown in Table 1. Of total 921 treated infants, FS was found in 48 infants (5.2%), evenly found in both genders. The basic clinical and demographic data of infants treated for FS are shown in Table 2. Mostly, it was about preterm infants with low birth weight with an average gestational age of 32.3 ± 3.7 and birth weight of 1852 ± 746 grams.

Table 1. Neonatal intensive care unit admitted patients characteristics (n = 921)

Characteristics	n	%
Neonates	921	100.0
Preterm (<37GW)	501	54.4
late preterm (34-36 GW)	328	35.6
very preterm (<32GW)	173	18.7
extremely preterm (<28GW)	58	6.2
low birth weight (<2500 g)	278	30.1
very low birth weight (<1500 g)	116	12.5
extremely low birth weight (<1000 g)	38	4.1
Mechanical ventilation within NICU stay	330	35.8
Surgery within NICU stay	46	4.9
Clinically confirmed sepsis	396	42.9
Confirmed sepsis on blood cultures	235	25.5
Confirmed fungal sepsis on blood cultures	48	5.2

GW - gestational weeks

Table 2. Baseline characteristics of neonates with fungal sepsis

Parametar	Mean	Minimum	Maximum	SD
Gestational age (weeks)	32.35417	25.00000	40.00000	3.789625
Birth weight (grams)	1852.083	680.0000	3770.000	746.2700
AS 1 st minute	5.904762	2.000000	9.000000	2.119074
AS 5 th minute	6.952381	4.000000	9.000000	1.321975
PRM (hours)	4.095238	1.000000	15.00000	4.134063
Postnatal age of admission to NICU (hours)	3.142857	1.000000	24.00000	5.552348
Duration of mechanical ventilation (days)	8.083333	0.00	41.00000	10.08018
Duration of NICU stay (days)	32.12500	5.000000	100.0000	18.26708
CRIB II skor	5.952381	1.000000	17.00000	4.318289
SNAPE-PE II skor	36.80952	2.000000	74.00000	20.07889

SD-standard deviation; AS 1st min-Apgar score in the first minute; AS 5th minute-Apgar score in the fifth minute; PRM- premature rupture of membranes; NICU - neonatal intensive care unit; CRIB II- Clinical Risk Index for Babies scoring system; SNAPEPE II- Score for Neonatal Acute Physiology-Perinatal Extension

Prematurity and low birth weight in our study were confirmed as the most significant perinatal risk factors for the development of fungal sepsis in critically ill infants Table 3. Little significance in our study had a vaginal birth.

Table 3. Perinatal risk factors in neonates with proven fungal sepsis

Parameter	n	%	p
Male	25	52.1	
Female	23	47.9	
Cesarean delivery	18	37.5	
Vaginal delivery	30	62.5	0.01
Preterm infants (<37GW)	42	87.5	0.009
Late Prematurity (34-36GW)	11	22.9	
Extreme prematurity (<32GW)	31	64.6	
Extreme Prematurity (<28GW)	8	16.7	
Low birth weight (<2500g)	39	81.25	0.009
Very low birth weight (<1500g)	20	41.7	
Extremely low birth weight (<1000g)	4	8.3	
AS 1 st minute <6	9	18.7	
AS 5 th minute <6	6	12.5	
Maternal infections	10	20.8	
PRM >12sati	4	8.3	

GW- gestational weeks; AS 1st min- Apgar score in the first minute; AS 5th minute-Apgar score in the fifth minute; PRM- premature rupture of membranes

The severity of illness in treated infants on admission was scored by neonatal tests (CRIB II and SNAPE-PE II), while the severe clinical picture of treated infants was confirmed by administered supportive therapy that was shown in Table 4.

Table 4. Severity of disease and interventions as risk factors for neonatal fungal sepsis

Parameter	n	%	p
Umbilical venous catheter	48	100	>0.0001
Broad spectrum antibiotics > 14 days	10	20.8	
Mechanical ventilation	43	89.6	>0.0001
Parenteral nutrition	48	100	>0.0001
Inotropes	15	31.5	
H ₂ receptor blockers	12	25	
Probiotics	12	25	
Intravenous gammaglobulins	14	29.2	
Ursodeoxycholic acid	8	16.7	
Survived	44	91.7	
Died	4	8.3	

All infants with fungal sepsis had an umbilical vein catheter, received parenteral nutrition and antibiotic therapy, and one fifth of them received prolonged a broad- spectrum antibiotic therapy. Almost 90% of them required mechanical ventilation support, and the mean ventilation support length was 8 days. Four infants underwent surgery for pneumothorax treatment. Of

the other known risk factors for the development of FS, a quarter of our patients received H₂- receptor blockers and had prolonged hospitalization. Clinically, fungal sepsis manifested as a late sepsis in all 48 patients, and the most common clinical presentation included respiratory deterioration, lethargy, feeding difficulties, and abdominal distension. (Table 5).

Table 5. Clinical presentation of neonatal fungal sepsis

Parameter	n	%	p
Late onset sepsis (> 7 days of age)	48	100	>0.0001
Increasing respiratory requirement	25	52.1	0.85
Temperature instability	5	10.4	
Poor perfusion	9	18.7	
Lethargy	22	45.8	0.65
Abdominal distension	14	29.2	
Feeding difficulties	15	31.2	
Convulsions	2	4.2	

Laboratory findings in neonates with fungal sepsis are shown in Table 6. The most common deviation in our patients was presented as an increase in C- reactive protein and leukocytes with thrombocytopenia. (Table 7).

Table 6. Laboratory findings in neonates with fungal sepsis

Parameter	Mean	Minimum	Maximum	SD
CRP (mg/L)	49.54792	1.000000	294.0000	70.13882
Hematocrit	0.506190	0.370000	0.740000	0.093353
Leukocytes	9.190476	3.400000	18.00000	3.756182
Neutrophils	0.320952	0.110000	0.630000	0.148017
Absolute neutrophil count	3250,000	920,0000	8800,000	2240,187
Platelets	110.6667	3.000000	510.0000	97.57361
Albumins (g/L)	26.42857	20.00000	41.00000	4.632186
Glucose (mmol/L)	5.447826	0.1	23.3	4.088106

SD-standard deviation; CRP- C reactive protein

Table 7. Laboratory abnormalities in neonates with fungal sepsis

Parameter	n	%	p
CRP <5 mg/ℓ	15	31.3	
CRP >5 mg/ℓ	33	68.8	0.09
Htc anemia	19	39.6	
Htc normal	21	43.8	
Htc polycythemia	8	16.7	
Leukocytes <6 x 10 ⁹ /L	17	35.4	
Leukocytes >13 x 10 ⁹ /L	31	64.6	0.09
ANC <1800	10	20.8	
ANC >13000	4	8.3	
thrombocytopenia <150 x 10 ⁹ /L	38	79.2	0.09
thrombocytosis >450 x 10 ⁹ /L	1	2.1	
Coagulation status normal	25	52.1	
Coagulation status disturbed	23	47.9	
Hypoglycemia	15	31.3	

CRP- C reactive protein; Htc- hematocrit; ANC- Absolute neutrophil count

Fluconazole prophylaxis was not included at the time of the study, but Fluconazole therapy was included when there was a clinical suspicion of fungal sepsis and before the hemoculture findings were received. All hemoculture isolates were from the candida strains group without in- vitro resistance. The duration of Fluconazole therapy averaged 20.6 ± 6 days; 11 of them received supportive platelet concentrate; 14 patients received intravenous gamaglobulin. Despite its in vitro sensitivity, Fluconazole was not effective in the treatment of two infants and it was replaced by Amphotericin B.

The outcome for 44 infants (91.7%) was favorable, while 4 infants (8.3%) died. The length of intensive care was 38.2 ± 23.2 days. The difference between infants survivors and deceased was found in the Apgar score result, that was more often statistically significant lower than 5 in deceased infants. Also, statistical significance was found in the length of intensive care that was significantly longer in survived infants. In 8 infants (16.7%) mild toxic hepatitis was recorded as a complication of the total treatment with transient enlargement of the liver, an increase in direct bilirubin and liver enzymes, which was successfully treated with supportive therapy and an oral ursodeoxycholic acid formulation.

DISCUSSION

Fungal sepsis (mainly *Candida spp.*) is an important cause of morbidity and mortality in critically ill infants [1-5]. Our study has shown that candidemia is a common problem in critically ill infants, with an overall incidence of 5.2%. This data is higher than those in the literatures of European countries reporting an incidence of 1.1-1.3% infants who were treated in intensive care union [3-9], and North and South America reporting an incidence of 0.5-1.6% [10,11], but it is lower than published data in Asia reporting an incidence of 4-7.7% [12-14]. This variability may reflect differences in neonatal clinical practice among countries, as well as in the design of the study and patients involved in it. In our study, infants with fungal sepsis were evenly arranged by gender, which was generally in concord with the published literature, or it was reported a slight advantage of male infants [1-3].

In nearly 90% of cases, it was about a preterm infants, while over 80% cases were with low birth weights, which was the most common result in published studies where dominated very immature infants (≤ 32 gestation weeks) and very low birth weight (≤ 1500 g) [1,3,5]. It is known that the risk for fungal sepsis in infants is high due to aggressive and invasive treatment, such as central venous catheters, mechanical ventilation, parenteral nutrition and prolonged hospitalization [16]. In our study all patients had an umbilical vein catheter, received parenteral nutrition and antibiotic therapy, and one-fifth of them received broad- spectrum antibiotic therapy. Almost 90% of them required mechanical ventilation, and the mean mechanical

ventilation support length was 8 days. Intravenous catheters are risk factors for *Candida* sepsis in critically ill infants because *Candida spp.* can adhere to platelets and fibrinogen on the surface, form biofilms that can be a source for systemic infection [16]. Central venous catheters and parenteral nutrition are reported to be major risk for infection with non-albicans *Candida* strains, both of which predispose to the formation of catheter biofilms. Amino acids from parenteral nutrition mediate cell differentiation, that could explain the high incidence of *Candida* in neonates with a central venous catheter receiving amino acid-rich parenteral diet [16].

Most of our patients (89.6%) were on mechanical ventilation support. Mechanical ventilation has been described as a risk factor for neonatal fungal sepsis, although there are also very rare reports describing non- invasive support with continuous positive airway pressure as a risk factor [2]. Four infants in our study underwent surgery for pneumothorax treatment. Other studies report a significantly higher proportion of surgical intervention in infants with fungal sepsis up to 44% [2], including necrotizing enterocolitis up to 25%. *Candida* sepsis has been described as an uncommon cause of intestinal perforation and necrotizing enterocolitis [2], and abdominal surgery has been reported as a risk factor for the onset of *Candida* sepsis regardless of birth weight [2].

Fungal sepsis manifested as late neonatal sepsis in all patients, which is the most common result in other studies, and only rarely *Candida* is reported as the cause of early neonatal sepsis [17]. Clinical presentation in our study included respiratory deterioration, lethargy, feeding difficulties and distension of the abdomen, which is also consistent with reports from other studies [13]. The most common laboratory results deviation in our patients were an increase in C- reactive protein, leukocytes and thrombocytopenia [13]. All hemoculture isolates in our study were from *Candida spp.* group without in vitro resistance, which is consistent with some published studies [1-3]. There are regional differences in the incidence of the most common *Candida* strains. Through a systematic literature review, we found out that four *Candida species* (*C. albicans*, *C. parapsilosis complex*, *C. tropicalis* i *C. glabrata complex*) are associated with more than 95% cases of neonatal candidemia, but the distribution of these four species is different. In general, *Candida albicans* was the dominant isolated strain in Europe [3-9] and North and South America [10-11], and non- albicans strains were dominant in Asia [12-14]. However, more recent studies report constant growth of *Candida* non-albicans strains, with a frequency higher than 50% in some neonatal intensive care unions. This is partly associated with an increase in clinical use of the azole antifungal therapy and prophylaxis [18-20], although this has also been reported in hospitals where Fluconazole has rarely been used for prophylaxis and therapy [3]. Even some earlier reports, such as the Helsinki report

[21] mention the emergence of Fluconazole resistance in a *C. parapsilosis* strain after more than 10 years of Fluconazole prophylaxis in neonatal intensive care unions. There was a high incidence of Fluconazole resistance in *C. parapsilosis* in this study, so that routine use of Fluconazole prophylaxis in this constellation is questionable. The outcome for infants (91.7%) in this study was favorable, while 4 infants (8.3%) died. Mortality rate due to neonatal fungal sepsis varied, and it is mostly high. It goes from 40% [2,-] up to 75% [22], and is considered low if it is below 20% [23]. The difference between survivors and deceased in our study was found only for the Apgar score and the length of intensive care. Mortality in other studies are mainly related to known risk factors and their correlation.

CONCLUSION

Candida sepsis is an important cause of morbidity and mortality in critically ill infants. The incidence at our hospital is 5.2 per 100 admissions to Neonatal Intensive Care Union. Perinatal risk factors for fungal sepsis are prematurity and low birth weight. The umbilical vein catheter, parenteral nutrition, antibiotic therapy and mechanical ventilation are also considered to be significant risk factors.

SAŽETAK

Uvod: Stalni napredak u neonatologiji povećava preživljavanje nedonoščadi uz primjenu višestrukih invazivnih procedura, što neminovno povećava rizik infekcije, a time i gljivične sepse. Faktori rizika za gljivičnu sepsu opsežno su proučavani. Candida je dominantan uzročnik, ali se bilježi porast rezistentnih ne-albicans vrsta. Mortalitet je visok i nalaže pravovremeno postavljanje kliničke sumnje na gljivičnu sepsu i adekvatan tretman da se preduprije loš ishod. **Cilj:** Cilj rada bio je da se analiziraju kliničke i laboratorijske karakteristike novorođenčadi liječene u intenzivnoj jedinici zbog mikrobiološki dokazane gljivične sepse.

Ispitanici i metode: Restrospektivnom opservacionom studijom obuhvaćeno je 48 konsektivne novorođenčadi, liječene u Odjeljenju intenzivne terapije Klinike za dječije bolesti Tuzla u trogodišnjem periodu (2016-2018), a koja su imala dokazanu gljivičnu sepsu, potvrđenu pozitivnom hemokulturom. Analizirani su perinatalna anamneza, klinička i laboratorijska prezentacija bolesti, dužina liječenja i ishod. U statističkoj obradi korištene su standardne metode, a istraživanje je odobreno od strane Etičkog komiteta ustanove.

Rezultati: Od ukupno liječenih 921 novorođenčeta, gljivična sepsa potvrđena hemokulturom nađena je u 48 novorođenčadi (5,2%), ravnomjerno raspoređenih po spolu. Od perinatalnih faktora rizika potvrđeni su prematuritet i niska porođajna težina, a značajni su bili umbilikalni venski kateter, parenteralna prehrana, antibiotska terapija i mehanička ventilacija. Klinički se gljivična sepsa manifestovala kao kasna sepsa sa respiratornim pogoršanjem, letargijom, teškoćama

hranjenja i distenzijom trbuha. Najčešće laboratorijske abnormalnosti bile su porast CRP, leukocitoza i trombocitopenija. Ishod za 44 novorođenčadi (91,7%) bio je povoljan, dok je 4 novorođenčadi (8,3%) umrlo. Antifungalne terapije trajala je 20,6±6 dana, a intenzivno liječenje 38,2± 23,2 dana. Svi izolati bili su iz grupe *Candida species* bez in-vitro rezistencije. Kod 8 novorođenčadi (16,7%) zabilježen je blagi toksični hepatitis.

Zaključak: Povoljan ishod novorođenčadi s gljivičnom sepsom zavisi od pravovremene kliničke sumnje, adekvatnog tretmana i nadzora. Antifungalna osjetljivost takođe je bitna za djelotvorno liječenje, stoga je važno pratiti lokalne epidemiološke podatke kako bi se olakšao izbor liječenja.

Ključne riječi: gljivična sepsa, novorođenče, epidemiologija, klinička prezentacija, faktori rizika

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