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NEONATAL SEPTICEMIA IN A NEONATAL INTENSIVE CARE UNIT*
Results of Four Years

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The outcome of congenital and nosocomial septicemia has been documented in infants who were admitted to a neonatal intensive care unit over a four-year period. The overall incidence of neonatal septicemia in the neonatal intensive care unit was 5.4 percent. Common causes of neonatal septicemia were gram-negative bacilli and staphylococci. Gram-positive microorganisms were the major causative agents for early-onset septicemia. Since the most common pathogen in cases of nosocomial sepsis was gram-negative bacillus, higher mortality rates were observed in nosocomial sepsis. The overall mortality rate in neonatal sepsis was 44.2 percent. The mortality rate in infants in whom nosocomial septicemia developed was significantly higher than in the infants in whom early-onset septicemia developed. However, as gram-negative colonization of the nursery recently changed to gram-positive microorganisms, the mortality rate is hoped to decrease. *Key words: neonatal septicemia, nosocomial infection, early-onset septicemia.*

The incidence of neonatal sepsis is between one and 10 cases per 1000 live births, and almost four-fold that in cases of preterm infants; the incidence is higher (1-5%) for infants born to mothers with chorioamnionitis[1,2]. Despite the increasing use of newer antibiotics, the mortality rate in neonatal sepsis remains 20 to 75 percent[1].

The two principal sources of newborn infection are the mother and the nursery environment. Infection is acquired from the mother transplacentally at the time of delivery or in the postnatal period[3,4]. The infections that develop in the first 48 hours of life (early-onset) are not acquired in the nursery. Such infections are defined as congenital infection or early-onset sepsis. Infections occurring after this time are defined as nosocomial (nursery-acquired)[2,3].

The reported incidence of nursery-acquired infections varies considerably and is affected by multiple factors such as nursery personnel, respiratory equipment, sinks and incubators. The most important risk factor for neonatal sepsis is low

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birth weight; others include prolonged hospitalization, invasive procedures, placement of indwelling devices and overcrowded nurseries[2-4].

The overall incidence of nursery-acquired infection is reportedly 1.4 percent, but is considerably higher in neonatal intensive care units, ranging from five to 30 percent[4-6]. This incidence varies from nursery to nursery and depends on conditions predisposing to infection.

In the present report, we evaluated the frequency of congenital and nosocomial infections in our neonatal intesive care unit (NICU) during a four-year period, the influence of birth weight on infection frequency, and the association of nosocomial infection with infant mortality.

Material and Methods

Between January 1, 1991 and December 31, 1994, 3120 newborns were admitted to the neonatal intensive care unit. All of the infants were born at the Department of Gynecology and Obstetrics of İstanbul University Faculty of Medicine. In the neonatal intensive care unit, three rooms were designated as level I, level II and level III. Indications for admission to the neonatal intensive care unit included low birth weight, prematurity, respiratory distress syndrome, aspiration of meconium, resuscitation in the labor ward, the presence of congenital anomalies, hyperbilirubinemia, perinatal asphyxia, infants of diabetic mothers, prolonged rupture of membranes and maternal peripartum infection. During this period, 2.824 preterm infants were admitted to the NICU.

For each infant enrolled in this study, the following information was recorded: maternal obstetric history, evidence of maternal infection, history of prolonged rupture of membranes (longer than 24 hours), mode of delivery, APGAR score, gestational age, birth weight, isolated organism, the onset of sepsis and its outcome. The incidence of infection, isolated microorganisms, complications and mortality rates were evaluated. Gestational age was assessed by the method of Dubowitz et al.[7] or by maternal dates. Neonates were defined as premature if the gestational age was less than 37 completed weeks. Perinatal asphyxia was defined as a five-minute Apgar score of less than seven. Each infant was examined by a neonatal fellow.

Premature rupture of membranes or maternal peripartum infection as well as resuscitation in the labor ward were accepted as risk factors, and blood cultures were obtained from these infants after delivery.

When sepsis was suspected clinically, initial tests performed included complete blood cell counts (CBC), differential leukocyte counts, C-reactive protein (CRP) and peripheral blood cultures. Other investigations were done when clinically indicated, included gastric aspirate, urine and spinal fluid microscopy and culture,

tracheal aspirate culture, stool culture, and chest or abdominal radiographs. On completion of the inital investigation for infection, antibiotics were administered intravenously. Ampicillin and an aminoglycoside were combined to treat suspected early-onset septicemia or meningitis before identification of the pathogen. The diagnosis of sepsis was made when there were positive findings on peripheral blood culture. Most infants with septicemia present with nonspecific signs and symptoms. The presence of one or more clinical features, such as lethargy, temperature instability, increased gastric aspirate, glucose intolerance or hepatosplenomegaly are diagnostic signs and symptoms. A ratio of immature to total neutrophils of greater than 0.2, white cell count of either less than 5 x 10^9/L or greater than 30 x 10^9/L, platelet count of less than 50 x 10^9/L and CRP levels greater than 1 mg/dl are positive laboratory results[8] for diagnosing neonatal septicemia in infants with clinical features.

Generally antibiotic therapy was started in infants with risk factors for infection. Also, antibiotics were discontinued within three days if the neonatal fellow considered infection to be unlikely or blood cultures were sterile. If sepsis was diagnosed, the most susceptible antibiotics were selected. Patients responding to antibiotic therapy were treated for 2-3 weeks or at least 10 days from the time of the first negative blood culture.

If sepsis was suspected clinically, lumbar puncture was performed immediately. Interpretation of biochemical values of cerebrospinal fluid (CSF) in newborn infants was difficult. Any one or a combination of the following CSF values was considered positive for meningitis: more than 32 leukocytes/mm^3, of which more than 60 percent were polymorphonuclear cells; CSF glucose less than 50 to 75 percent of a simultaneous serum glucose; protein greater than 150 mg/dl; and microorganisms on gram-stained smears of CSF[9]. The diagnosis of meningitis was made when there were positive findings in biochemical values and CSF culture. If meningitis was diagnosed, cranial ultrasonography was performed to detect ventriculitis. Ampicillin and cefotaxime were combined for initial empiric therapy of neonatal meningitis. After the pathogen was identified and its antimicrobial susceptibilities were known, the most appropriate drug or drugs were selected. Therapy for meningitis was continued for a minimum of two weeks after sterilization of CSF cultures.

Since the incubation periods of infections occurring in the neonate are not well defined, it was sometimes difficult to determine whether an infection was perinatally or nosocomially acquired. Most infections that develop in the first 48 hours of life (i.e., early-onset)ore not nosocomial, and those developing after this interval are increasingly likely to be nosocomial.

Values are expressed as mean ± SD. Statistical analyses were performed using chi-square and the Fisher exact test. The results of statistical analysis were considered significant at $p < 0.05$.

Results

During four years of retrospective study, neonatal sepsis was diagnosed in 167 infants. Sepsis was confirmed by blood cultures in 141 cases (84.6%). In 26 cases (15.4%), sepsis was diagnosed by laboratory results. The mean gestational age was 32.4 ± 2.3 weeks (25-43 weeks), and birthweights were 1,762 ± 581 g (730-4,250 g) in infants with neonatal sepsis. Forty percent (67 infants) were female and sixty percent (100 infants) were male. A total of 27 infants (16%) had neonatal asphyxia. The type of delivery in cases with sepsis was vaginal in 78.2 percent and cesarean section in 21.8 percent. The overall incidence of prolonged rupture of membranes was 2.7 percent. One hundred and fifty-three infants were premature (91.6%) and 14 infants (8.4%) were mature. The overall incidence of sepsis was 5.4 percent in the neonatal intensive care unit. The incidence of neonatal sepsis in premature infants was 5.4 percent. The incidence of neonatal sepsis according to birth weight is shown in Table I. That total infection rate in the infants with birthweights of less than 1500 g was significantly higher than that of the larger infants ($p < 0.05$) (Table I).

Table I: Neonatal Sepsis in the Unit According to Birth Weight

Birth Weight	No. of Infants	No. of Infants with Infection	Incidence (%)
< 100 g	178	19	10.6
1000-1499	530	83	15.7
1500-1999	786	41	5.2
2000-2499	1192	18	1.5
> 2500	434	6	1.4
Total	3120	167	5.4

Forty-three infants had early-onset sepsis. The remaining 124 infants were defined to have nosocomial sepsis. The nosocomial sepsis rate in the neonatal intensive care unit was four percent. Meningitis was diagnosed in 16 cases. The frequency of pathogenic organisms in infants with neonatal sepsis and meningitis is shown in Table II. The most common etiologic agents isolated from the cases of septicemia were gram-negative enteric bacilli and Staphylococcus aureus. Gram-negative microorganisms were common causes of sepsis in ventilated neonates; five cases were diagnosed in ventilated neonates.

The risk factors for early-onset sepsis, such as prolonged rupture of membranes (PROM), maternal chorioamnionitis and meconium aspiration syndrome, were evaluated. Thirty-two cases had PROM, 11 cases had maternal amnionitis and 12 cases had meconium aspiration (12 of the 43 infants with early-onset sepsis had > 1 risk factor).

A total of 16 patients had sepsis plus meningitis. Ventriculitis and hydrocephalus developed in four cases (25%) with meningitis. The isolated microorganisms are shown in Table II. The most common etiologic agents were gram-negative bacilli.

Table II: Frequency of Pathogenic Organisms in Neonatal Sepsis and Meningitis

Organism	Early-Onset Sepsis	Nosocomial Infection	Cases of Meningitis
Klebsiella pneumoniae	7	39	9
Staphylococcus aureus (MRSA)	14	16	2
Coagulase (-) staphylococci	8	17	2
E.Coli	2	2	2
K.Oxytoca	2	8	
Enterobacter	3	9	1
Group B streptococcus	4	–	–
α-hemolitic streptococcus	3	5	–
Acineto bacter	–	2	–
Total	43	98	16

A total of 43 cases of early-onset sepsis were diagnosed, with gram-positive microorganisms being the most common pathogens isolated from cultures. The most common etiologic agents isolated from the cases of nosocomial sepsis were gram-negative bacilli.

In cases of septicemia, 74 infants (44.3%) died and 93 infants (55.7%) survived. The overall mortality rate in neonatal sepsis was 44.2 percent. The mortality rates in neonatal sepsis and meningitis are shown in Table III. The mean gestational age, birth weight and duration of hospitalization of the mortality and survival groups are shown in Table IV. Smaller infants (birth weight less than 1500 g) had increased infection and mortality rates (Table V). The total nosocomial infection rate in the infants with birth weights of less than 1500 g was significantly higher than that in nthe infants greater than 1500 g at birth ($p < 0.05$). The mortality rate in infants in whom neonatal septicemia of any type developed was significantly higher than that of the infants in whom such infections did not develop (Table V). The overall mortality rate in the neonatal intensive care unit was 15.1 percent.

Table III: Mortality Rates in Neonatal Septicemia and Meningitis

	No. of Infants	No. with Mortality
Early-onset sepsis	43	11 (25%)
Nosocomial infection (late-sepsis)	124	63 (50.8%)
Meningitis	16	9 (56%)

Table IV: Epidemiologic Characteristics in Neonatal Sepsis

	Survival Group	Mortality Group
Mean gestational age (weeks)	32.8 ± 2.4	29.8 ± 2.1
Mean birth weight (g)	1874 ± 595	1382 ± 208

Table V: Mortality Rates According to Birth Weight

	With Neonatall Sepsis		Without Neonatal Sepsis	
Birth Weight (g)	No. of Infections	Mortality (%)	No. of Infants	Mortality (%)
< 1000	19	79	159	71
1000-1499	83	54	447	38
1500-1999	41	24	745	17.2
2000-2499	18	17	1174	5.4
> 2500	6	17	418	0.6

The mortality rate (50.8%) in infants in whom nosocomial septicemia of any type developed was significantly higher than the rate (25%) in cases where early-onset sepsis developed ($p < 0.05$).

The average duration of hospitalization for the total infants admitted to the neonatal intensive care unit was 13.2 days. In the infants who developed nosocomial infection, the average duration of hospitalization was 22.1 days. We were unable to determine the precise role of nosocomial infection in prolonging the duration of hospitalization because of the presence of other risk factors in the infants with long hospital stays (e.g. lower birth weight, respiratory distress syndrome, perinatal asphyxia).

Discussion

Infections are significant causes of mortality in neonates, especially for premature infants of very low birth weight. The two principal sources of newborn infection are the mother and the nursery environment. Prematurity is a common risk factor for neonatal sepsis in both early-onset and nosocomial diseases[1, 10-12]. This increased susceptibility to infection correlates with the immaturity of the premature infant's immune system, including diminished humoral and cellular responses and decreased transplacentally acquired IgG. Environmental factors in the nursery affect the risk of acquiring a nosocomial infection. Prolonged hospitalization in neonatal intensive care units predisposes infants to colonization with the potentially pathogenic gram-negative bacterial flora of the nursery and possible subsequent infection[13]. Invasive procedures and indwelling foreign bodies increase the risk of nosocomial infection in newborns[3].

In infants weighing less than 1000 g at birth, the reported incidence of sepsis is 50 percent or higher, and in infants weighing 1000-1500 g at birth the reported incidence of sepsis is 12-14 percent[2-4, 6]. We observed similar results except in infants weighing less than 1000 g at birth. We suggested that high numbers of extremely low birth weight babies had been lost in the first few days because of asphyxia, intraventricular hemorrhage and respiratory distress syndrome.

In NICUs, common causes of neonatal septicemia include gram-negative bacilli, staphylococcus aureus and coagulase-negative staphylococci. A common characteristic of nosocomial, gram-negative, enteric pathogens in newborn nurseries is antibiotic resistance. In addition, colonization and infection with methicillin-resistant S.aureus in the NICU have occurred (Table II). In recent years, a leading cause of nosocomial infections has been coagulase-negative staphylococci. Other nosocomial pathogens in low-birth weight infants in NICUs have been fungi, a finding not observed in the present study.

We observed that the gram-negative, antibiotic-resistant bacilli (particularly K. pneumoniae) were still playing the greatest role in nosocomial infections, followed by staphylococci. The main source of gram-negative infection is the nursery environment. We observed a total of four cases of group B β-hemolytic streptococcus, all infants with early-onset septicemia. We found that gram-positive microorganisms (S. aureus and coagulase-negative staphylococci) were the major causative agents (68%) of early-onset septicemia.

Factors that appear to contribute to the high rate of nosocomial infection in the unit may be considered under two categories: host factors and environmental factors. The most important host factor for nosocomial infection is low birth weight[2-4]. The nosocomial infection rate in infants with birth weights of less than 1500 g was approximately 5.5 times that in larger infants. The mortality rate in early-onset septicemia was lower than in nosocomial sepsis. Since the most common pathogens in cases of nosocomial sepsis were gram-negative bacilli, higher mortality rates were observed in nosocomial sepsis[4, 11, 14, 15]. We estimated the incidence of septicemia in the NICU to be 5.4 percent, and the nosocomial infection rate was for percent. The infection rates were lower than those in other published works[4-6, 14, 16].

The complications of neonatal sepsis include focal infection and meningitis. The mortality rate was high in infants with sepsis plus meningitis.

Amnionitis was a significant problem. Eleven of the neonates with early-onset sepsis had maternal amnionitis. The statistically significant relationship between maternal amnionitis and sepsis was previously demonstrated in our hospital[17].

The outcome of neonatal infections can be improved if illness is recognised early and appropriate antimicrobial agents are promptly administered[4]. The mortality

rate in neonatal sepsis has been reported as 12 to 30 percent[4, 11]. In our study, the overall mortality rate was 44.2 percent. Since gram-negative, antibiotic-resistant, enteric bacilli were the predominant organism in cases of neonatal sepsis, the mortality rate was high. In cases of early-onset septicemia, the mortality rate was 25 percent. Since gram-positive organisms were predominant in this type of neonatal infection, the mortality rate was lower than in nosocomial sepsis[4, 11].

Our data emphasize the clinical importance of nosocomial infections in a patient population in a NICU. Although we have continually stressed the need for good handwashing technique, appropriate use of isolation procedures and the minimal handling method, we observe nosocomial infection frequently. However, the nosocomial infection rate in our unit was not high compared to that in the literature. The main problem was gram-negative infections two years ago. The colonization of the nursery changed to gram-positive microorganisms recently, Which is hoped to result in a decrease in mortality rate.

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