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Neonatal sepsis in the neonatal intensive care unit: characteristics of early versus late onset

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Neonatal sepsis is a major cause of death in newborns despite sophisticated neonatal intensive care. This retrospective study reviewed the clinical characteristics of cases of culture-proven sepsis in a neonatal intensive care unit from January 1992 to December 2001. Patients were divided into those with onset of sepsis in the first 7 days of life (early-onset group) and those with onset after the seventh day of life (late-onset group). A total of 270 cases with 325 episodes of sepsis and 353 isolated pathogens were identified and included in the study. The male-to-female ratio was 1.4. The majority of cases of sepsis occurred in low birth weight (75.9%) and premature babies (76.7%). Late onset occurred in 71.9% of cases. Patients with late onset had a lower mortality rate than those with early onset (11.3% vs 28.9%). Coagulase-negative staphylococci (20.1%) was the most common organism isolated, but infection with *Pseudomonas aeruginosa* was associated with the highest morality rate (55.0%). Late-onset sepsis was significantly more common in very low birth weight and premature infants. The most frequently encountered pathogens in the early-onset group were group B streptococci (GBS) and *Escherichia coli*, while in the late-onset group, the organisms were coagulase-negative staphylococci and *Enterobacteriaceae*, including *E. coli*, *Klebsiella pneumoniae*, and *Acinetobacter baumannii.* GBS infection resulted in the highest mortality when the onset of sepsis was within the first 24 hours of life.

Key words: Etiology, neonatal intensive care units, risk factors, sepsis, survival analysis

With advanced neonatal intensive care, there has been a substantial improvement in neonatal mortality, especially in very low birth weight (VLBW) and premature infants [1-4]. Sepsis, however, continues to cause significant mortality and morbidity in these patients. The incidence of neonatal sepsis was 1 to 2 per 1000 live births in the United States [5]. Culture-proven sepsis may occur in up to 20% of neonatal intensive care unit (NICU) admissions [5]. There are 2 patterns of sepsis described during the first month of life, early onset and late onset.

Early-onset sepsis, presenting during the first few days of life, usually progresses rapidly and has multi-organ involvement. It is frequently associated with obstetric complications, such as premature rupture of membranes (PROM), premature onset of labor, chorioamnionitis, and peripartum maternal fever. The majority of affected newborns are premature or low birth weight (LBW) infants, and the pathogens are frequently acquired during passage through the birth canal. Mortality ranges from 5 to 50% [6].

Late-onset sepsis, occurring after the first week of life, is less severe and less frequently associated with obstetric complications. Pathogens may have originated from the maternal genital tract, but also may come from contact with human carriers after birth or with contaminated equipment or materials. Mortality is usually much lower than in early-onset sepsis. VLBW infants with prolonged hospital stay and more invasive intervention in the NICU are at increased risk for nosocomial sepsis [6]. The incidence of nosocomial sepsis in NICUs ranged from 5 to 30 per 100 patients [7]. This study analyzed the clinical characteristics and outcome in a series of patients with neonatal sepsis.

Patients and Methods

Data were collected by chart review of patients treated at Mackay Memorial Hospital, a teaching hospital with a 33-bed NICU and an active neonatal transport program.

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Between January 1992 and December 2001, a total of 8965 patients were admitted to the NICU.

Data collection

Patients with culture-proven sepsis treated in the NICU from January 1992 to December 2001 were included. Patients were excluded if the blood culture results were caused by contamination, i.e., if commensal organisms (such as Gram-positive bacilli) were cultured, if a second set of blood cultures was negative before antibiotic therapy was given, or if patients recovered without the use of antibiotics. Patients were divided into those with sepsis developing within the first 7 days of life (early-onset group) and those with sepsis developing after the seventh day of life (late-onset group).

Data collected included gender, gestational age (GA), birth weight, age at onset of sepsis, symptoms and signs, pathogens, perinatal risk factors, underlying conditions, associated infections, and outcome.

Definition

Prematurity was defined as GA below 37 weeks. LBW infants were those with birth weight less than 2500 g and VLBW babies were those with birth weight below 1500 g. If positive blood culture was obtained more than 48 hours after admission, the infection was regarded as nosocomial.

Perinatal risk factors

PROM was defined as rupture of membranes more than 24 hours prior to delivery. Maternal fever and chorioamnionitis were classified based on maternal hospital records. Other perinatal risk factors investigated included Apgar score less than 7 at 5 min; delay of initial crying; meconium aspiration syndrome; maternal eclampsia; fetal distress; hydroamninosis; cesarean section due to placenta previa, placenta abruptio or breech; unmarried mother; and cervical incompetence.

Outcome

Sepsis-related mortality was defined as death occurring within 7 days of septic episodes.

Statistical analysis

Data were analyzed with analysis of variance, chi-squared or Fisher's exact test.

Results

A total of 325 episodes of sepsis involving 353 pathogens were identified in 270 patients. Thirty two patients had 2 or more septic episodes. The incidence of sepsis was 3.01% among all NICU admissions during the study period, or 3.29 per 1000 patient days. The male-to-female ratio was 1.4. In the early-onset group, there were 76 patients (28.1%) with 76 septic episodes (23.4%) and 83 isolated pathogens (23.5%). In the late-onset group, there were 194 patients (71.9%) with 249 septic episodes (76.6%) and 270 isolated pathogens (76.5%). In the late-onset group, 240 episodes occurred at least 48 hours after admission; therefore, 96.4% of infections in the late-onset group were classified as nosocomial compared to only 22.4% in the early-onset group (n = 17).

Birth weight, gestational age and clinical presentation

The gender, GA, and birth weight of the patients are shown in Table 1. The overall mean birth weight and GA were

Table 1. Gender, gestational age and birth weight of infants with early-onset and late-onset neonatal sepsis

	Early onset n = 76 (%)	Late onset n = 194 (%)	Total n = 270 (%)	*p*
Gender				
Male:female	2.4:1	1.2:1	1.4:1	
Male	55 (72.3)	104 (53.6)	159 (58.9)	<0.005
Female	21 (27.6)	90 (46.4)	111 (41.1)	
Gestational age				
Mean	33 ± 5 weeks	30 ± 5 weeks	31 ± 5 weeks	<0.00007[a]
<37 weeks	46 (57.9)	161 (83.0)	207 (76.7)	<0.0001
≥37 weeks	30 (39.5)	33 (17.0)	63 (23.3)	
Birth weight				
Mean	2149 ± 1081 g	1549 ± 840 g	1661 ± 931 g	<0.000003[a]
≤1500 g	29 (38.2)	118 (60.8)	147 (54.4)	<0.01
>1500 g	47 (61.8)	76 (39.1)	123 (45.6)	

[a]Analysis of variance.

Table 2. Pathogens isolated from patients with early-onset and late-onset neonatal sepsis

Pathogens	Early onset (n = 83)				Late onset (n = 270)				Total	(%)	Mortality rate (%)
	Total	(%)	Death	(%)	Total	(%)	Death	(%)			
Gram-positive bacteria	41	(49.4)	6	(14.6)	119	(44.1)	6	(5.04)	160	(45.3)	7.5
CoNS	11	(13.2)	1	(9.1)	60	(22.2)	3	(5.00)	71	(20.1)	5.6
Staphylococcus aureus	3	(3.6)	0	-	41	(15.2)	2	(4.9)	44	(12.4)	4.6
GBS	15	(18.1)	3	(20.0)	3	(1.1)	0	-	18	(5.1)	16.7
Other Gram-positive organisms	12	(14.5)	2	(16.7)	15	(5.6)	1	(6.7)	27	(7.6)	11.1
Gram-negative bacteria	42	(50.6)	21	(50.0)	134	(49.6)	21	(15.7)	176	(49.9)	23.7
Escherichia coli	18	(21.7)	11	(61.1)	26	(9.6)	5	(19.2)	44	(12.5)	36.4
Acinetobacter baumannii	0	-	0	-	26	(9.6)	1	(3.9)	26	(7.4)	3.9
Klebsiella pneumoniae	3	(3.6)	0	-	22	(8.2)	1	(4.6)	25	(7.1)	4.0
Pseudomonas aeruginosa	5	(6.0)	4	(80.0)	15	(5. 6)	7	(46.7)	20	(5.7)	55.0
Other Gram-negative organisms	16	(19.3)	6	(37.5)	45	(16.7)	7	(15.6)	75	(21.2)	21.3
Fungi	0	-	0	-	17	(6.3)	0	-	17	(4.8)	0
Candida albicans	0	-	0	-	9	(3.3)	0	-	9	(2.6)	0
Candida guilliermondi	0	-	0	-	3	(1.1)	0	0	3	(0.9)	0
Other fungi	0	-	0	-	5	(1.9)	0	0	5	(1.4)	0

Abbreviations: CoNS = coagulase-negative staphylococci; GBS = group B streptococci

1661 ± 931 g (range, 520-4900 g) and 31 ± 5 weeks (range, 23-43 weeks). The majority of sepsis episodes occurred in LBW (n = 205, 75.9%) and premature (n = 207, 76.7%) infants. The mean birth weight and GA were lower in the late-onset group. In the early-onset group, there was no significant difference in the incidence of term and premature babies, but in the late-onset group sepsis occurred significantly more frequently in VLBW (60.8%) and premature infants (83.0%).

The major clinical manifestations included fever (34.1%), bradycardia (23.7%), cyanosis (22.7%), lethargy (22.7%), respiratory distress (21.8%), and apnea (18.0%).

Pathogens

Gram-positive (n = 160, 45.3%) and Gram-negative (n = 176, 49.9%) pathogens were isolated with nearly equal frequency (Table 2). Fungal infection accounted for 4.8% (n = 17) of septic episodes, all in the late-onset group. Coagulase-negative staphylococci (CoNS; n = 71, 20.1%) were the most commonly isolated organisms. *Pseudomonas aeruginosa* was associated with the highest mortality (55.0%), followed by *Enterobacter cloacae* (45.5%) and *Escherichia coli* (36. 4%). The most frequently encountered pathogens in the early-onset group were *E. coli* (18 episodes, 21.7%) and group B streptococci (GBS; 15 episodes, 18.1%). CoNS and *Enterobacteriaceae*, including *E. coli*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, were the most common pathogens in the late-onset group.

In the early-onset group, there were 15 cases of GBS sepsis in 14 infants with onset within 24 hours of age. Mortality occurred in 3 of these cases (3/14, 21.4%), whereas no babies older than 24 hours died of GBS sepsis. The high prevalence of early onset and high mortality rate in GBS sepsis were significantly greater than for other pathogens. There was no significant change in the incidence of GBS sepsis during the study period, but an increasing trend of *E. coli* sepsis was noted (Fig. 1).

For *Staphylococcus aureus* infection, methicillin-resistant strains accounted for 26 episodes (63.4%) of episodes in the late-onset group and 2 episodes (66.7%) in the early-onset group. The incidence of *S. aureus* infection was stable over the study period.

Perinatal risk factors and underlying conditions

There was no significant difference in the incidence of PROM, chorioamnionitis, maternal fever, or other perinatal risk factors between the 2 groups. Within each

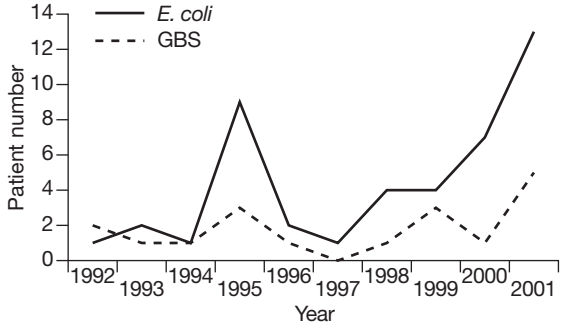

Fig. 1. Trend of infections with *Escherichia coli* and group B streptococci (GBS) from 1992 to 2001.

Table 3. Underlying conditions in patients with early-onset and late-onset sepsis

	Early onset (n = 76)	Late onset (n = 194)	Total (n = 270)	*p*
Mechanical ventilation	18	83	101	<0.005
Respiratory distress syndrome	25	123	148	<0.0001
Congenital heart disease	9	67	76	<0.00025
Intraventricular hemorrhage grade III-IV	4	17	21	>0.05
Necrotizing enterocolitis	1	17	18	<0.05
Bronchopulmonary dysplasia	6	70	76	<0.0001
Catheter usage	16	113	129	<0.0001
Total parenteral nutrition	4	126	130	<0.0001
Operation	4	51	55	<0.00025
Congenital anomaly	8	34	42	>0.05
Antibiotic therapy	16	32	48	>0.05
Steroid therapy	1	12	13	>0.05

group, there was no significant association between these perinatal risk factors and mortality; however, in the overall group, PROM was associated with higher mortality (14/51, $p<0.02$). In addition, the late-onset group had a significantly higher incidence of mechanical ventilation, respiratory distress syndrome, congenital heart disease, necrotizing enterocolitis, bronchopulmonary dysplasia, catheter use, total parenteral nutrition, and operations than the early-onset group (Table 3).

Associated infections

Meningitis developed in 11.8% of patients in the early-onset and 5.2% in the late-onset group ($p<0.05$). Other infections did not differ significantly between the 2 groups. Seventy five percent of patients with early-onset sepsis had no other associated infections. Comparison of the 2 groups revealed that although other infections were less frequent in the early-onset group, this difference did not reach significance.

Outcome

The overall sepsis-related mortality rate was 16.3%. The sepsis-related mortality rate was not significantly higher in VLBW (15.7%) infants or newborns with GA <28 weeks (17.8%), but was significantly higher in the early-onset group (28.9% vs 11.3%).

Discussion

There were more premature and VLBW infants in the late-onset group in this series, as has been reported in other studies [8-11]. Premature and VLBW infants often require aggressive management, such as intravascular catheterization and mechanical ventilation, and stay in the hospital longer. Late-onset sepsis is associated with the use of such interventions [8,9,12]. In this study, the clinical presentation was mostly nonspecific, as in previous reports [10,13,14].

As in previous studies, GBS and *E. coli* were the most frequently isolated pathogens in the early-onset group, while GBS was less common in late-onset sepsis [15,16]. In this study, almost all late-onset sepsis episodes were nosocomial infections. Although *S. aureus* has been reported as the most common nosocomial pathogen in Taiwan, with a high incidence of methicillin-resistance, in our series, CoNS was the most common isolated pathogen, as has been reported in other series [8,11,17], followed by *S. aureus*, *A. baumannii*, and *E. coli*. Neonatal sepsis caused by Gram-negative bacteria, especially *P. aeruginosa* has been reported to be associated with the highest mortality rate [7,8], as in our series. However, unlike other studies [8,18,19], the outcome of our patients with candidal infection was good.

Although GBS early-onset sepsis is associated with PROM, peak intrapartum temperature or other perinatal risk factors have been reported to have higher mortality [20], we did not find such an association in our study group. In addition, PROM, maternal fever, chorioamnionitis, and other perinatal risk factors were not associated with increased mortality in the early-onset group. In this study, late-onset neonatal sepsis was associated with use of mechanical ventilation, development of respiratory distress syndrome, congenital heart disease, necrotizing enterocolitis, bronchopulmonary dysplasia, use of intravascular catheters, and total parenteral nutrition, as previous studies have found [8,10,11].

Although early-onset sepsis has frequently been reported to be associated with pneumonia and late-onset sepsis with meningitis [6], we did not find this association in our series. On the contrary meningitis was

Table 4. Pathogens, birth body weight and mortality analysis

	≤1500 g (n = 201)			>1500 g (n = 152)		
	Total	Deaths	Mortality rate (%)	Total	Deaths	Mortality rate (%)
Gram-positive bacteria	86	4	4.65	74	8	10.8
GBS	2	1	50.0	16	2	12.5
Staphylococcus aureus	27	2	7.41	17	0	
CoNS	45	1	2.22	26	3	11.5
Other Gram-positive organisms	12	0		15	3	20.0
Gram-negative bacteria	102	22	21.6	74	20	27.0
Pseudomonas aeruginosa	14	7	50.0	6	4	66.7
Escherichia coli	23	10	43.5	21	6	28.6
Klebsiella pneumoniae	16	1	6.25	9	0	
Acinetobacter baumannii	18	0		8	1	12.5
Other Gram-negative organisms	31	4	12.9	30	9	30.0
Fungi	13	0		4	0	
Candida albicans	6	0		3	0	
Other fungi	7	0		1	0	
Total	201	26	12.9	152	28	18.4

Abbreviations: CoNS = coagulase-negative staphylococci; GBS = group B streptococci

more common in the early-onset group. The mortality rate was higher in the early-onset group, as has been previously reported [6].

Infants with signs of sepsis during the first 24 hours of life and VLBW infants have the highest mortality rate [20-22]. In our study, we found that if GBS sepsis occurred within the first 24 hours of life, the mortality was higher regardless of VLBW status. Among VLBW infants, the mortality rate was highest in those with GBS (50%), *P. aeruginosa* (50%) and *E. coli* (43.5%) sepsis (Table 4).

Antibiotic prophylaxis against GBS during labor and delivery has markedly reduced the incidence of GBS sepsis, but an increase in *E. coli* sepsis was noted in some reports [23-25]. Another study did not find a significant change in the incidence of non-GBS early-onset sepsis [5]. During the study period, no significant difference was found in the incidence of GBS sepsis, possibly because of the inconsistency of GBS prophylaxis policy in our country and the frequent use of ampicillin instead of penicillin for GBS prophylaxis [26]. In a series of patients at Yale University from the late 1940s to the mid-1960s, *E. coli* was the most common pathogen of neonatal sepsis [25]. During the late 1980s to the early 1990s, a shift in early-onset *E. coli* infection from less fulminant disease caused by ampicillin-sensitive organisms to more fulminant disease caused by ampicillin-resistant organisms was reported [27]. In our series, there was an increasing trend of *E. coli* sepsis, which was not significant on linear regression analysis.

In conclusion, late-onset sepsis is more common in the NICU and occurs mainly in premature and VLBW infants. Early-onset sepsis carries a higher mortality. In our series, GBS and *E. coli* were the major pathogens in early-onset sepsis, while CoNS was the most frequently encountered pathogen in late-onset sepsis. Overall, Gram-negative pathogens were associated with a higher mortality rate. In GBS sepsis, the highest mortality rate was found in those patients whose infection began within 24 hours after birth.

References

1. Alexander GR, Tompkins ME, Allen MC, Hulsey TC. Trends and racial difference in birth weight and related survival. Matern Child Health J 1999;3:91-9.
2. Allen MC, Alexander GR, Tompkins ME, Hulsey TC. Racial difference in temporal changes in newborn viability and survival by gestational age. Paediatr Perinat Epidemiol 2000; 14:152-8.
3. Guyer B, Maritin JA, MacDorman MF, Anderson RN, Strobino DM. Annual summary of vital statistics-1996. Pediatrics 1997; 100:905-18.
4. Alexander GR, Kogan M, Bader D, Carlo W, Allen M, Mor J. US birth weight/gestational age-specific neonatal mortality: 1995-1997 rates for whites, hispanics and blacks. Pediatrics 2003;111:e61-6.
5. Baltimore RS, Huie SM, Meek JI, Schuchat A, O'Brien KL. Early-onset neonatal sepsis in the era of group B streptococcal prevention. Pediatrics 2001;108:1094-8.
6. Klein JO. Bacterial sepsis and meningitis. In: Remington JS, Klein JO, eds. Infectious disease of the fetus and newborn infant.

5th ed. Philadelphia: W.B. Saunders; 2001:943-98.
7. Tseng YC, Chiu YC, Wang JH, Lin HC, Lin HC, Su BH, et al. Nosocomial blood stream infection in a neonatal intensive care unit of a medical center: a three year review. J Microbiol Immunol Infect 2002;35:168-72.
8. Makhoul IR, Sujov P, Smolkin T, Lusky A, Reichman B. Epidemiological, clinical, and microbiological characteristics of late-onset sepsis among very low birth weight infants in Israel: A national survey. Pediatrics 2002;109:34-9.
9. Stoll BJ, Gordon T, Korones SB, Shankaran S, Tyson JE, Bauer CR, et al. Late-onset sepsis in very low birth weight neonates: a report from the National Institute of Child Health and Human Development Neonatal Research Network. J Pediatr 1996;132: 1130-40.
10. Fanaroff AA, Korones SB, Wright LL, Verter J, Poland RL, Bauer CR, et al. Incidence, presenting features, risk factors and significance of late onset septicemia in very low birth weight infants. Pediatr Infect Dis J 1998;17:593-8.
11. Sohn AH, Garrett DO, Sinkowitz-Cochran RL, Grohskopf LA, Levine GL, Stover BH, et al. Prevalence of nosocomial infections in neonatal intensive care unit patients: results from the first national point-prevalence survey. J Pediatr 2001;139:821-7.
12. Beck-Sague CM, Azimi P, Fonseca SN, Baltimore RS, Powell DA, Bland LA, et al. Bloodstream infections in neonatal intensive care unit patients: results of a multicenter study. Pediatr Infect Dis J 1994;13:1110-6.
13. Nyhan WL, Fousek MD. Septicemia of the newborn. Pediatrics 1958;22:268-78.
14. Gluck L, Wood HF, Fousek MD. Septicemia of the newborn. Pediatr Clin North Am 1966;13:1131-48.
15. Gladstone IM, Ehrenkranz RA, Edberg SC, Baltimore RS. A ten-year review of neonatal sepsis and comparison with the previous fifty-year experience. Pediatr Infect Dis J 1990;9: 819-25.
16. Greenberg D, Shinwell ES, Yagupsky P, Greenberg S, Leibovitz E, Mazor M, et al. A prospective study of neonatal sepsis and meningitis in Southern Israel. Pediatr Infect Dis J 1997;16: 768-73.
17. Rubin LG, Sanchez PJ, Siegel J, Levine G, Saiman L, Jarvis WR. Pediatric Prevention Network. Evaluation and treatment of neonates with suspected late-onset sepsis: A survey of neonatologists's practices. Pediatrics 2002;110:e42.
18. Lee BE, Cheung PY, Robinson JL, Evanochko C, Robertson CM. Comparative study of mortality and morbidity in premature infants (birth weight, < 1,250gm) with candidemia or candidal meningitis. Clin Infect Dis 1999;28:153-4.
19. Kossoff EH, Buescher ES, Karlowicz MG. Candidemia in a neonatal intensive care unit: trends during fifteen years and clinical features of 111 cases. Pediatr Infect Dis J 1998;17:504-8.
20. Boyer KM, Gadzala CA, Burd LI, Fisher DE, Paton JB, Gotoff SP. Selective intrapartum chemoprophylaxis of neonatal group B streptococcal early-onset disease: I. Epidemiologic rationale. J Infect Dis 1983;148:759-801.
21. Vesikari T, Janas M, Gronroos P, Tuppurainen N, Renlund M, Kero P, et al. Neonatal septicemia. Arch Dis Child 1985;60: 542-6.
22. Schuchat A, Oxtoby M, Cochi S, Sikes RK, Hightower A, Plikaytis B, et. al. Population-based risk factors for neonatal sepsis group B streptococcal disease: Results of a cohort study in metropolitan Atlanta. J Infect Dis 1990;162:672-7.
23. Towers CV, Carr MH, Padilla G, Asrat T. Potential consequences of widespread antepartal use of ampicillin. Am J Obstet Gynecol 1998;179:879-83.
24. Benitz WE, Gould JB, Druzin ML. Antimicrobial prevention of early-onset group B streptococcal sepsis: estimates of risk reduction based on a critical literature review. Pediatrics 1999; 103:e78.
25. Stoll BJ, Hansen N, Fanaroff AA, Wright LL, Carlo WA, Ehrenkranz RA, et al. Changes in pathogens causing early-onset sepsis in very-low-birth-weight infants. N Engl J Med 2002;347:240-7.
26. Schuchat A, Zywicki SS, Dinsmoor MJ, Mercer B, Romaguera J, O'Sullivan MJ, et al. Risk factors and opportunities for prevention of early-onset neonatal sepsis: A multicenter case-control study. Pediatrics 2000;105:21-6.
27. Joseph TA, Pyati SP, Jacobs N. Neonatal early-onset *Escherichia coli* disease: the effect of intrapartum ampicillin. Arch Pediatr Adolesc Med 1998;152:35-40.