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Original Article

Epidemiology of neonatal sepsis in South Korea

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Abstract ***Background***: Neonatal sepsis is a severe clinical syndrome characterized by systemic signs of infection, shock and system organ failure; diagnosis is confirmed on positive culture from a normally sterile site(s). There are few reports comparing incidence, mortality, and risk factors between clinically diagnosed sepsis and that confirmed by culture.
Methods: All infants diagnosed with early- (within first 72 h after birth) or late-onset (72 h–4 weeks after birth) neonatal sepsis between 1997 and 1999 from four neonatal centers in South Korea, were investigated.
Results: The estimated incidence rate of neonatal sepsis during the 3 years was 30.5 per 1000 live births for clinical sepsis and 6.1 per 1000 live births for sepsis with positive culture, with case-fatality rates of 4.7% and 2.2%, respectively. When only early-onset sepsis was considered, the incidence and fatality rates were 25.1 per 1000 live births and 6.1% for clinical sepsis, and 4.3 per 1000 live births and 2.5% for culture-confirmed sepsis, respectively. For the 179 patients (185 causative organisms) of proven sepsis, *Staphylococcus* spp. including *S. aureus* were the most frequent isolates. In early-onset clinical sepsis, having very low birthweight (≤1500 g), a low Apgar score at 5 min (≤7), and being male were related to higher rates of case-fatality (relative risk: 11.3, 6.8 and 2.5, respectively)
Conclusions: Clinical sepsis was more common than culture-confirmed sepsis and had a higher case-fatality rate. It seems prudent to take rapid and decisive steps toward better management of the high-risk group whether the sepsis is clinically diagnosed or culture confirmed.

Key words case fatality rate, epidemiology, newborns, sepsis, South Korea.

Neonatal sepsis is a severe clinical syndrome characterized by systemic signs of infection, shock and system organ failure; diagnosis is confirmed on positive culture from normally sterile sites. Neonatal sepsis is further classified into early-onset sepsis and late-onset. Early-onset occurs in the first 72 h of life, and is usually regarded as originating from vertical transmission. Late-onset neonatal sepsis occurs from 72 h to 4 weeks after birth.[1] The incidence of sepsis in the first month of life varies by geographic area from one to four per 1000 live births in developed countries, and 2.4–16 per 1000 live births in developing countries.[2] For Korea's 54 hospitals, incidence rate estimates of neonatal sepsis, of 6.6 per 1000 live births, reported in 1997,[3] were much higher than the 1.6 per 1000 live births reported in the USA.[4]

Risk factors for neonatal sepsis include preterm delivery or low birthweight (<2500 g), premature and prolonged rupture of membranes (ROM), maternal peripartum infection, and fetal hypoxia;[5,6] in many cases the infant may acquire infection postnatally from environmental sources, such as nursery personnel, respiratory equipment, contaminated total parenteral solutions or medication vials, and incubators.[7] Central venous lines or catheters are also risk factors for late-onset sepsis in preterm infants.[7]

The case-fatality rate for culture-confirmed neonatal sepsis in Korea decreased from 24.3% (10/41) in the 1960s[8] to 7.9% (9/113)[9]–17.1% (6/35)[10] in the early 1990s, still higher than the 4% reported for the USA currently.[11] The explanations for these differences over time and location remain to be explored.

Because the diagnosis of sepsis includes clinical presentation and culture, but is usually treated empirically prior to culture results – if a culture is taken at all – culture-confirmed sepsis rates do not represent the true burden of neonatal sepsis. Further, cultures may be negative in those who have received antibiotics. Therefore, to estimate the burden of neonatal sepsis, clinical sepsis should be considered along with culture-confirmed sepsis. There are many reports on limited groups of culture-confirmed sepsis[5,12–14] but only a few reports that integrate comparisons of incidence, mortality, and risk factors between culture-confirmed and clinical sepsis, and early-onset and late-onset sepsis.

We analyzed medical records from four neonatal centers located in Seoul, Gyeonggi Province, and Daejeon over a 3 year period, 1997–1999, in order to describe the epidemiology of neonatal sepsis for culture-confirmed and clinically diagnosed cases, and early-onset and late-onset cases. We also evaluated the impact of gestational age, birthweight and other related factors on the neonatal sepsis case fatality rate.

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Methods

Population and definitions

This study included infants who were born or hospitalized for neonatal sepsis at four neonatal centers located in Seoul, Gyeonggi province, and Daejeon from 1997 to 1999. Two out of the four neonatal centers are level III centers and the other two are level II centers (level I, clinic; levels II, general hospital; level III, general hospital and the last referral center); all participating centers were located in training hospitals and have neonatology specialists. We targeted infants within the first month of life who were diagnosed as having neonatal sepsis clinically or via positive blood or cerebrospinal fluid (CSF) culture, and reviewed their hospital records retrospectively. The number of infants who were born at study hospitals during the study period was 23 768; the number of patients who were born at study hospitals (inborn) and hospitalized for neonatal sepsis in study hospitals was 868. The number of patients who were born at other hospitals (outborn) and hospitalized for neonatal sepsis in a study hospital was 412.

Neonatal sepsis was defined as a clinical syndrome characterized by systemic signs of infection and/or accompanied by bacteremia in the first month of life. Confirmed sepsis was defined as positive culture from normally sterile sites in association with clinical and laboratory findings. Clinical sepsis was diagnosed when the doctor suspected it to be sepsis based on systemic symptoms and signs, such as temperature instability, lethargy, apnea, poor feeding, and respiratory or gastrointestinal disease (e.g. tachypnea and cyanosis or vomiting, diarrhea and abdominal distention), serology and/or radiology; abnormal leukocyte count (>30 000 cells/μL or <5000 cells/μL), C-reactive protein >1.0 mg/dL, risk factors for vertical transmission and/or intrapartum administration of antibiotics, and negative culture.[15] When a patient was re-hospitalized within 3 days after discharge with the same diagnosis, the two hospitalization records were combined into one. We divided neonatal sepsis cases into groups, by whether the baby was born at a study hospital (inborn) or in another hospital but treated for sepsis at a study hospital (outborn).

Gestational age was determined by obstetrical methods, which include dating from the last menstrual period and use of prenatal ultrasonography, or estimated by a neonatologist on the basis of physical and neurologic criteria. ROM lasting longer than 18 h was considered to be a risk factor for infection of the infant, especially when complicated by chorioamnionitis. Not knowing the exact time of membrane rupture, however, we classified the corresponding group as 'unknown'.

Following standard definitions, neonatal sepsis was classified into early (≤72 h) and late onset (>72 h–<4 weeks) based on postnatal age at onset.[1] Early-onset sepsis is generally considered to originate from vertical transmission. The progression of late-onset neonatal sepsis is relatively slow, usually occurs in the nursery, and is associated with skin and soft-tissue lesions and focal infections as well as nosocomial and health-care-associated infections. Because focal infections, such as meningitis, pneumonia, urinary tract infection, otitis media, conjunctivitis, omphalitis, cellulitis or osteomyelitis, may precede or accompany neonatal sepsis, we also investigated diseases associated with neonatal sepsis and positive culture results from blood, CSF, urine or other sterile sites. The associated diseases were grouped using the International Classification of Disease, Tenth Revision (ICD-10).

Data collection

We reviewed medical records for perinatal characteristics and risk factors for sepsis such as sex, gestational age, birthweight, 1 and 5 min Apgar scores, delivery methods, birth hospitals (study hospitals vs other hospitals), and prolonged ROM. Trained medical students entered medical record data on mothers and on newborn infants onto a computer using Excel software, which was confirmed by a researcher. The researcher classified the outcome of sepsis either as survival or death. This study was approved by the Institutional Review Board (IRB) of the University of Michigan on 14 November 2003.

Data analysis

The incidence of sepsis was estimated by dividing the number of inborn infants with sepsis by the total number of live births from all four centers. The confidence interval of the incidence rate was calculated using Poisson distribution. The case fatality rate was estimated by dividing the number of deaths from sepsis by the total number of sepsis cases. We used the χ^2 test, log likelihood test and Fisher's exact test to assess the associations between known and hypothesized risk factors of sepsis. Simple and multiple logistic regression models were used to assess associations between case fatality of sepsis and maternal or neonatal characteristics. Analyses of clustered data were performed using SPSS 12.0 (SPSS Inc., Chicago, IL, USA).

Results

Incidence of neonatal sepsis

The incidence of early-onset neonatal sepsis confirmed on culture was 4.5 (95% confidence interval [CI]: 3.1–6.3) per 1000 live births in 1997, 6.6 (95%CI: 5.0–8.7) in 1998, and 1.7 (95%CI: 1.0–2.9) in 1999, with a 3 year annual average incidence rate of 4.3 (95%CI: 3.5–5.2). The incidence rates of late-onset neonatal sepsis from 1997 to 1999 were lower: 1.4, 2.6 and 1.2 per 1000 live births, respectively. Clinical sepsis rates, however, for both early and late onset were significantly higher: 34.1 (1997), 24.5 (1998), and 16.7 (1999) per 1000 live births for early-onset sepsis and 5.4 (1997), 4.9 (1998), and 6.0 (1999) per 1000 live births for late-onset sepsis. The incidence of early-onset neonatal sepsis tended to decrease every year for both culture-confirmed sepsis ($P = 0.007$) and clinical sepsis ($P < 0.001$). There was no significant decline, however, in the rate of late-onset neonatal sepsis ($P = 0.79$, confirmed sepsis; $P = 0.61$, clinical sepsis; Table 1).

The majority of sepsis cases were not confirmed by culture: among inborn patients, 14.6% of early-onset sepsis (102/697) and 24.4% of late-onset sepsis (42/171) were culture confirmed. Among outborn patients the confirmation rate was much lower: only 6.2% of early-onset sepsis (16/257) and 12.3% of late-onset sepsis (19/155) were culture confirmed. The differences

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Table 1 Incidence rates per 1000 live births of neonatal sepsis vs year of diagnosis, Korea, 1997–1999

	Year	No. live births†	Culture-confirmed sepsis		Clinically diagnosed sepsis		Total	
			n‡	Incidence	*n*‡	Incidence	*n*	Incidence
Early onset	1997	7770	35	4.5	265	34.1	300	38.6
(≤72 h)	1998	7986	53	6.6	196	24.5	249	31.2
	1999	8012	14	1.7	134	16.7	148	18.5
	Total	23 768	102	4.3	595	25.1	697	29.3
Late onset	1997	7770	11	1.4	42	5.4	53	6.8
(>72 h–	1998	7986	21	2.6	39	4.9	60	7.5
<4 weeks)	1999	8012	10	1.2	48	6.0	58	7.2
	Total	23 768	42	1.8	129	5.4	171	7.2
Total	1997	7770	46	5.9	307	39.5	353	45.4
	1998	7986	74	9.3	235	29.4	309	38.7
	1999	8012	24	3.0	182	22.7	206	25.7
	Total	23 768	144	6.1	724	30.5	868	36.5

†Sum of the number of live births in four study hospitals.
‡Only infants born at and treated for sepsis at a study hospital (inborn) are included in calculation of incidence rates.

in confirmation rate between inborn cases and outborn cases ($P < 0.001$), and early- and late-onset neonatal sepsis ($P = 0.006$) were statistically significant.

Microbiology of neonatal sepsis

A total of 185 pathogens were isolated from 179 infants confirmed by culture. The most frequently isolated organisms were *Staphylococcus aureus* (44.5%), followed by other staphylococcus (31.3%), *Escherichia coli* (9.3%), streptococcal species excluding *Streptococcus agalacteae* (7.7%), candida species (6.0%), and other pathogens (1.6%, one pseudomonas species, one proteus and one pheomycosis). *Streptococcus agalacteae* was isolated from two patients (1.1%, two of 185 positive cultures; Table 2).

Risk factors for early-onset neonatal sepsis among culture-confirmed and clinical sepsis

More male than female infants developed both early-onset and late-onset sepsis; gender differences were more pronounced in culture-confirmed cases but the differences by onset were not statistically significant ($P = 0.14$, confirmed-sepsis; $P = 0.85$, clinical sepsis). Prolonged ROM ≥18 h occurred more frequently among early- than late-onset cases ($P = 0.005$, confirmed sepsis; $P < 0.001$, clinical sepsis). Infants born in study centers (inborn infants) with sepsis were more common in early-onset sepsis than in late-onset sepsis ($P = 0.005$, confirmed sepsis; $P < 0.001$, clinical sepsis). There were no significant differences, however, in delivery method in both culture-confirmed and clinical neonatal sepsis ($P = 0.30$, confirmed sepsis; $P = 0.08$, clinical sepsis; Table 3).

The median birthweight of infants with culture-confirmed and clinically diagnosed sepsis was 3240 g and 2960 g, respectively. The birthweight for early-onset sepsis was lower than that for late-onset sepsis, the difference being statistically significant for clinically diagnosed sepsis ($P < 0.001$). Younger gestational age also occurred significantly more frequently among early-onset sepsis compared with late-onset sepsis in both culture-confirmed and clinically diagnosed sepsis ($P = 0.01$, $P < 0.001$, respectively). The proportion of 5 min Apgar scores ≤7 was higher in early-onset sepsis than in late-onset sepsis in both culture-confirmed and clinically diagnosed sepsis, with the difference being statistically significant in clinically diagnosed sepsis ($P < 0.001$). There were 22 patients who had 0–3 Apgar score of 5 min, among these, 21 had 'clinically diagnosed early-onset sepsis' and one had 'confirmed early-onset sepsis'. The duration of hospitalization for early-onset sepsis was longer than that for late-onset sepsis, with the difference being significant in both confirmed ($P = 0.003$) and clinical sepsis ($P < 0.001$; Table 3).

Table 2 Causative organisms of culture-confirmed neonatal sepsis vs time of onset, Korea, 1997–1999

Organisms	Early onset (no. deaths)	Late onset (no. deaths)	Total (no. deaths)	% total
Staphylococcus aureus	58	23 (1)	81 (1)	44.5
Other staphylococcus	33	24	57	31.3
Escherichia coli	12 (2)	5	17 (2)	9.3
Streptococcus agalacteae	2 (1)	0	2 (1)	1.1
Other streptococcus	9	5	14	7.7
Candida spp.	4	7	11	6.0
Others†	3	0	3	1.6
Total	121 (3)	64 (1)	185 (4)	101.6

†Proteus one case, Pseudomonas one case, and pheomycotic brain abscess one case.
Early onset, ≤72 h; late onset, >72 h–<4 weeks. Six patients had two different microorganisms.

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Table 3 Sepsis patient characteristics vs time of onset, Korea, 1997–1999

	Culture-confirmed sepsis							Clinically diagnosed sepsis						
	Early onset		Late onset		Total		$P^{\dagger}$	Early onset		Late onset		Total		$P^{\dagger}$
	No.	%	No.	%	No.	%		No.	%	No.	%	No.	%	
Sex														
Boys	72	61.0	44	72.1	116	64.8	0.1	463	55.4	145	54.7	608	55.2	0.8
Girls	46	39.0	18	27.9	63	35.2		373	44.6	120	45.3	493	44.8	
Delivery method														
Vaginal delivery	61	51.7	24	39.3	85	47.5	0.3	389	46.5	123	46.4	512	46.5	0.08
Cesarean section	52	44.1	29	47.5	81	45.3		390	46.7	94	35.5	484	44.0	
Others	5	4.2	8	13.1	13	7.3		57	6.8	48	18.1	105	9.5	
Prolonged ROM (h)														
≥18	13	11.0	0	0	13	7.3	0.005[§]	116	13.9	3	1.1	119	10.8	<0.001
<18	91	77.1	51	83.6	142	79.3		657	78.6	212	80.0	869	78.9	
Unknown	14	11.9	10	16.4	24	13.4		63	7.5	50	18.9	113	10.3	
Birth hospital														
Study hospital (inborn)	102	86.4	42	68.9	144	80.4	0.005	595	71.2	129	48.7	724	65.8	<0.001
Non-study hospital (outborn)	16	13.6	19	31.1	35	19.6		241	28.8	136	51.3	377	34.2	
Gestational age (weeks)														
≥37	88	74.6	49	80.3	137	76.5	0.03	537	64.2	212	80.0	749	68.0	<0.001
33–36	23	19.5	4	6.6	27	15.1		172	20.6	11	4.2	183	16.6	
≤32	5	4.2	0	0	5	2.8		109	13.0	2	0.8	111	10.1	
Unknown	2	1.7	8	13.1	10	5.6		18	2.2	40	15.1	58	5.3	
Birthweight (g)														
>2500	100	84.7	53	86.9	153	85.5	0.1[‡]	535	64.0	216	81.5	751	68.2	<0.001
1501–2500	15	12.7	3	4.9	18	10.1		216	25.8	10	3.8	226	20.5	
≤1500	2	1.7	0	0	2	1.1		71	8.5	1	0.4	72	6.5	
Unknown	1	0.8	5	8.2	6	3.4		14	1.7	38	14.3	52	4.7	
Apgar score at 5 min														
≥8	89	75.4	33	54.1	122	68.2	0.2[§]	446	53.3	108	40.8	554	50.3	<0.001
≤7	12	10.2	1	1.6	13	7.3		179	21.4	4	1.5	183	16.6	
Unknown	17	14.4	27	44.3	44	24.6		211	25.2	153	57.7	364	33.1	
Duration of hospitalization (days)														
≤4	10	8.5	19	31.1	27	15.1	0.003	151	18.1	94	35.5	245	22.3	<0.001
5–9	65	55.1	25	41.0	90	50.3		343	41.1	117	44.2	460	41.8	
≥10	43	36.4	17	27.9	62	34.6		341	40.8	54	20.4	395	35.9	
Prognosis														
Survival	114	96.6	56	91.8	170	95.0	1.00[§]	771	92.2	226	85.3	997	90.6	<0.001
Death	3	2.5	1	1.6	4	2.2		51	6.1	1	0.4	52	4.7	
Unknown	1	0.8	4	6.6	5	2.8		14	1.7	38	14.3	52	4.7	
Total	118	100.0	61	100.0	179	100.0		836	100.0	265	100.0	1101	100.1	

[†]χ^2 test; [‡]log likelihood test; and [§]Fisher's exact test between early-onset and late-onset sepsis. Data for unknown or others were excluded for calculation of statistics.
Early onset, ≤72 h; late onset, >72 h–<4 weeks; ROM, rupture of membrane.

For early onset sepsis, more cases of <37 weeks ($P = 0.02$), ≤2500 g ($P < 0.001$), and ≤7 Apgar score ($P < 0.001$) were included in clinical sepsis, than in culture-confirmed sepsis, which implies that more severe cases were included using the clinical definition. The duration of hospitalization was significantly longer for early-onset sepsis than late-onset sepsis for both clinically diagnosed and confirmed cases; and the duration was longer for clinical than confirmed cases ($P = 0.004$). In late-onset sepsis the proportion of boys in confirmed cases was significantly higher than that of clinical sepsis ($P = 0.01$). More inborn cases were culture confirmed than outborn cases in both early- ($P < 0.001$) and late-onset sepsis ($P = 0.02$).

Focal infections associated with neonatal sepsis

Out of the 179 infants with culture-confirmed neonatal sepsis, 50 infants (27.9%) had focal infections, with 52 infections occurring among the 50 infants. Of these, 32 infections were related to early-onset sepsis and 20 infections were related to late-onset sepsis. Urinary tract infection was the most common focal infection for both early-onset and late-onset sepsis (46.9%, 15/32; 45.0%, 9/20).

Of the 1101 infants with clinical sepsis, 118 (10.7%) had focal infections, with 122 infections occurring among the 118 infections. Of these, 64 infections were related to early-onset sepsis and 58 infections of were related to late-onset sepsis. Among the 64 infections of early-onset neonatal sepsis patients, pneumonia (43.8%) was the most common focal infection, followed by urinary tract infection (20.3%), conjunctivitis (18.8%), omphalitis (10.9%), and meningitis (4.7%). Among the 58 infections of late-onset neonatal sepsis patients, meningitis (46.6%) was the most frequent focal infection, followed by urinary tract infection (17.2%), conjunctivitis (12.1%), and pneumonia (12.1%; Table 4).

Risk factors associated with the case fatality rate in early-onset neonatal sepsis

The case fatality rate of neonatal sepsis, clinical or culture-confirmed, was 4.4%. The fatality rate, however, was significantly higher in early-onset sepsis than in late-onset sepsis (5.7%, 54/954 vs 0.6%, 2/326, $P < 0.001$; Table 3). Of 179 infants with culture-confirmed sepsis, four died (2.2%, 4/179). The case fatality rate of clinical cases was higher than confirmed cases (4.7% vs 2.2%), but not statistically significant ($P = 0.12$). Among culture-confirmed cases, the fatality rate appeared to be higher in early-onset sepsis than in late-onset sepsis (2.5% vs 1.6%), this difference also was not statistically significant ($P = 1.00$, Fisher's exact test). Organisms causing mortality were *Streptococcus agalacteae* (one infant) and *E. coli* (two infants) in early-onset sepsis and *Staphylococcus aureus* (one infant) in late-onset sepsis.

Among early-onset clinical sepsis, the fatality rate in 1998 decreased from that of 1997 but, overall, there was no statistically significant difference year to year. Infants who were outborn had a significantly lower mortality rate, 3.2%, compared to 7.2% of inborn infants. Factors such as sex, mode of delivery, and prolonged ROM lasting 18 h were not significantly associated with mortality. Very low birthweight (≤1500 g; VLBW) compared to higher birthweight (2500 g) was associated with an increased risk of mortality (relative risk [RR], 29.4; 95%CI: 14.24–60.62). Short gestational periods (≤32 weeks) compared to term births were also associated with an increased risk of mortality (RR, 16.9; 95%CI: 8.69–33.02). Low (≤7) compared to higher Apgar scores (≥8) at 5 min after birth was associated with an increased risk of mortality (RR, 17.5; 95%CI: 7.64–39.93; Table 5).

To identify the joint effects of the risk factors individually associated with case fatality in early-onset clinical sepsis, we fitted a multiple logistic regression model. We excluded the gestational age from the model because gestational age is closely related to birthweight and Apgar score. After adjustment for gender, birthweight, and Apgar score, the case fatality rate in early-onset clinical sepsis was higher in male infants than in female infants (RR, 2.5; 95%CI: 1.21–5.06). In addition, ≤1500 g birthweight was associated with increased fatality rate (RR, 11.3; 95%CI: 4.55–28.21). An Apgar score 5 min after birth of ≤7 score also was associated with increased fatality rate (RR, 6.8; 95%CI: 2.62–17.55; Table 5).

The small number of culture-confirmed cases of early-onset sepsis precluded identifying risk factors for fatality in that group.

Discussion

Among Korean infants born at one of four neonatal centers located in Seoul, Gyeonggi province, and Daejeon between 1997 and 1999, the incidence rate of culture-confirmed sepsis was 6.1 per 1000 live births (4.3 for early onset and 1.8 for late onset). We found no more recent incidence estimates in the literature. The incidence rate is

Table 4 Site of focal infections in neonatal sepsis vs time of onset, Korea, 1997–1999

	Culture-confirmed sepsis				Clinically diagnosed sepsis			
	Early onset ($n = 118$)	Late onset ($n = 61$)	Total ($n = 179$)	% total	Early onset ($n = 836$)	Late onset ($n = 265$)	Total ($n = 1101$)	% total
Urinary tract infection	15	9	24	46.0	13	10	23	18.9
Meningitis	8	2	10	19.2	3	27	30	24.6
Pneumonia	4	3	7	13.5	28	7	35	28.7
Conjunctivitis	2	3	5	9.6	12	7	19	15.6
Skin infection	2	3	5	9.6	1	4	5	4.1
Omphalitis	1	0	1	1.9	7	3	10	8.2
Total	32	20	52	100.0	64	58	122	100.0

Early onset, ≤72 h; late onset, >72 h–<4 weeks. Six patients (confirmed sepsis, $n = 2$; clinical sepsis, $n = 4$) had two different localized infections.

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Table 5 Case-fatality rate and RR of death for neonatal sepsis, Korea, 1997–1999

	Early-onset clinical sepsis	No. deaths	Case-fatality rate (%)	RR (95%CI)	Adjusted RR (95%CI)†
Hospitalization year					
1997	319	28	8.8	1.0	
1998	287	12	4.2	0.5 (0.23–0.91)	
1999	216	11	5.1	0.6 (0.27–1.15)	
Birth hospital					
Study hospital (inborn)	595	43	7.2	1.0	
Non-study hospital (outborn)	227	8	3.2	0.5 (0.22–1.01)	
Sex					
Girls	366	18	4.9	1.0	1.0
Boys	456	33	7.2	1.5 (0.84–2.73)	2.5 (1.21–5.06)
Delivery method					
Vaginal delivery	389	22	5.7	1.0	
Cesarean section	390	25	6.4	1.1 (0.63–2.06)	
Others	43	4	9.3	1.7 (0.56–5.22)	
Prolonged ROM (h)					
≥18	116	5	4.3	1.0	
<18	657	41	6.2	1.5 (0.57–3.82)	
Unknown	49	5	10.2	2.5 (0.70–9.15)	
Birthweight (g)					
>2500	535	13	2.4	1.0	1.0
1501–2500	216	8	3.7	1.5 (0.63–3.78)	1.0 (0.37–2.60)
≤1500	71	30	42.3	29.4 (14.24–60.62)	11.3 (4.55–28.21)
Gestational age (weeks)					
≥37	537	14	2.6	1.0	
33–36	172	3	1.7	0.7 (0.19–2.34)	
≤32	109	34	31.2	16.9 (8.69–33.02)	
Unknown	4	0	–	–	
Apgar score, 5 min					
≥8	446	7	1.6	1.0	1.0
≤7	179	39	21.8	17.5 (7.64–39.93)	6.8 (2.62–17.55)
Unknown	197	5	2.5	1.63 (0.51–5.21)	1.64 (0.50–5.35)
Total	822	51	6.2		

†Adjusted relative risks were obtained on multiple logistic analysis; sex, birthweight and Apgar score were included in the model. All variables are adjusted for all others.

Patients with unknown prognosis ($n = 14$) were excluded from this analysis.

CI, confidence interval; early onset, ≤72 h; ROM, rupture of membrane; RR, relative risk.

similar to the rate reported in 1997 for Korea of 6.6 per 1000 live births,[3] and to that reported for Malaysia,[16] Africa, South America and the Caribbean, and considerably lower than that for China,[9] with slightly higher rates of early-onset sepsis but lower rates of late-onset sepsis than reported for the USA and Australia.[4,17–19]

The incidence rate, however, of clinically diagnosed sepsis, 30.5 per 1000 live births (724 of 23 768), was considerably higher than similar reports from other countries, as was the ratio of 5 for clinically diagnosed to culture-confirmed cases. In Spain the incidence of clinical sepsis was 3.6 per 1000 live births,[15] with a ratio of clinically diagnosed to culture-confirmed of 1.4. In the USA, in a study conducted in a health-care maintenance organization population, the incidence of clinical sepsis was 2 per 1000 live births; they did not report any culture-confirmed cases.[20] At least in the present data, however, the case-fatality rates was higher for clinically diagnosed than culture-confirmed sepsis. Because antimicrobial treatment is commonly given in Korea to babies with sepsis-like symptoms, without waiting for culture confirmation (Hye Sun Yoon, pers. comm., 2007), bacteria often cannot be cultured from clinically diagnosed sepsis cases. This would increase the numbers of clinically diagnosed sepsis cases. There also may be differences in assignment of diagnostic category, which would account for some of the large variation in rates of clinical diagnoses between countries.

A variety of microorganisms cause neonatal sepsis, with local variations in organism type. Prior to the implementation of group B *Streptococcus* screening followed by intrapartum prophylaxis, group B *Streptococcus* was the most common cause of neonatal sepsis in the USA followed by Gram-negative enteric bacilli, predominantly *E. coli*.[1] Many other pathogens, however, including *Staphylococcus aureus*, coagulase-negative staphylococcal species, *Viridans* streptococci, *E. coli*, *Klebsiella* and Enterobacter spp. have recently emerged as significant pathogens for neonatal sepsis in the USA.[12,21] Among the culture-confirmed cases in the present study, *Staphylococcus* spp. including *S. aureus* were the most frequent pathogens, followed by *Streptococcus* and *E. coli* for early-onset sepsis, and by *E. coli*, *Streptococcus* and *Candida* spp. for late-onset sepsis. The low rate of group B *Streptococcus*, which is susceptible to many antibiotics, might reflect the extravagant

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use of antibiotics: intrapartum antimicrobial prophylaxis is commonly given in Korea in all cases of ROM, rather than waiting for 18 h as is recommended in the USA.

The present observed incidence of late-onset sepsis due to *Candida* spp., 0.46 per 1000 live births, is lower than that in reports from Israel of 0.4–2 per 1000 live births.[22] Candida is especially a problem for infants cared for in intensive care units, where rates are considerably higher, ranging from 3.8% to 12.9% for VLBW infants,[22] accounting for 0.5–2.0% of neonatal intensive care unit admissions. Consistent with the literature, many of the infants' mothers experienced prolonged ROM, and the proportions were higher among those with early-onset disease for both clinically diagnosed and culture-confirmed cases.[17] Also consistent with the literature, vaginal delivery was more common among early-onset sepsis than in late-onset sepsis cases in both proven and clinical sepsis.[23]

In the present study urinary tract infection (46.0% in culture-confirmed, 18.9% in clinical) was the most common focal infection followed by meningitis, pneumonia, conjunctivitis, skin infection and omphalitis. Excluding pneumonia and meningitis, we found no difference in the distribution of focal infection type between late- and early-onset cases. The percent of focal infection (excluding pneumonia or meningitis), however, in late-onset sepsis was higher than that of early-onset sepsis in both culture-confirmed (24.6% vs 16.9%) and clinical sepsis (9.1% vs 3.9%). This is similar to previous studies that suggest that focal infection involving any organ (excluding pneumonia or meningitis), occurs most frequently in neonates with late-onset rather than early-onset disease.[1]

Previous studies of culture-confirmed sepsis in Korea have reported higher case-fatality rates for neonatal sepsis than the 2.2% reported here: 24.3% in the 1960s,[8] 15.2% in the 1970s,[24] 21.9%[25]–27.8% in the 1980s[26], and 17.1% in the 1990s.[10] Changes in case-fatality rates over time may reflect differences in patient populations or changes in environmental factors or medical practice. The estimated fatality rate for culture-confirmed sepsis, 2.2% (4/179), was lower than that reported for 1995–1997 in Spain, 8.7%,[15] and for 2002–2005 in Iran, 19.8%,[27] but for clinical sepsis the fatality rate of 4.7% (52/1100) is similar to the 4.3%[15] of the 1995–1997 Spain study. Differences among countries may reflect differences in host and environmental factors and medical practice.

Although birthweight and Apgar score have been associated previously with risk of early onset neonatal sepsis, we found no earlier reports suggesting that they predict mortality. Gestational age is associated with birthweight and has been previously associated with mortality. We cannot rule out, however, that the infection led to premature labor and delivery, and hence the VLBW and young gestational age. Because the present study was retrospective we could not validate the exact cause for preterm delivery for all cases, nor if there were other conditions present in premature infants that might have increases risk of mortality such as hyaline membrane disease and intraventricular hemorrhage. Nonetheless, VLBW (≤1500 g) and a lower Apgar scores 5 min after birth (≤7) increased the fatality rate, by RR = 11.3 and RR = 6.8 respectively, thus it seems prudent to take rapid and decisive steps toward better management of this group whether the sepsis is clinically diagnosed or culture-confirmed.

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