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Aetiologies and risk factors for neonatal sepsis and pneumonia mortality among Alaskan infants

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SUMMARY

We evaluated all fatal neonatal sepsis and pneumonia cases occurring in Alaska during 1992–2000. Risk factors were evaluated using a database of all births occurring during the study period. Of 32 cases, group B streptococcus (GBS) was isolated from 21% (all <7 days of age), *Candida* spp. from 19% (all >7 days of age), non-GBS Gram-positive bacteria from 50% (53% <7 days of age), and Gram-negative infections from 38% (58% <7 days of age). Infants born at <37 weeks gestation accounted for 72% of cases and had an increased risk of GBS [rate ratio (RR) 9·1, 95% confidence interval (CI) 2·0–41] and non-GBS (RR 40, 95% CI 16–101) disease. Neonatal sepsis mortality has become an outcome concentrated among pre-term infants. Aetiologies include GBS during the early neonatal period, *Candida* spp. during the late neonatal period, and other bacteria during both periods.

INTRODUCTION

Recent work on neonatal sepsis has focused on group B streptococcal (GBS) disease occurring during the first week of life, primarily because of debate over the appropriate peripartum antibiotic strategy [1–4]. When multiple neonatal sepsis pathogens have been considered, most previous studies have been restricted to sterile site isolates [5–8], thereby underestimating the significance of sepsis by an unknown amount [9]. Moreover, few studies have focused on fatal cases, even though these cases should form one of the primary bases for interventions. We present an evaluation of neonatal sepsis and pneumonia deaths that occurred to Alaska residents during 1992–2000. Our goal was to determine sterile-site and overall sepsis and pneumonia mortality rates, quantify the contribution of specific organisms, and identify risk factors for illness.

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METHODS

The data for the current evaluation came from records gathered as part of the Alaska Maternal–Infant Mortality Review (AMIMR) process during 1992–2000, the first 9 years of the surveillance system's existence. Guidelines to prevent perinatal GBS disease changed during the study period [1], with guidelines released during 1996–1997 recommending either a risk-based approach or a culture-based screening method. Guidelines were not updated until 2001, after the end of the study period.

AMIMR included all resident infant deaths. Data sources included maternal prenatal and infant medical records, birth and death certificates, and autopsy reports. AMIMR staff also obtained medical records from out-of-state hospitals if the infant was transferred for care. Each death was reviewed by a group

of experts who assigned consensus underlying and contributory causes of death.

In addition to the standard database maintained for routine AMIMR purposes, for the current study an additional form was developed to abstract data relevant to sepsis and pneumonia mortality. This included maternal, placental, and infant culture results and dates as well as antibiotic resistance patterns. To identify potential cases of sepsis or pneumonia, we used this form to abstract data for all infants for whom the AMIMR committee or the death certificate identified sepsis or pneumonia as an underlying or contributory cause of death.

To evaluate population-based incidence rates and the contribution of birth weight and gestation, a database of Alaska resident births was obtained from the Alaska Bureau of Vital Statistics. This database was linked to the database of cases using an exact match of date of birth and infant last and first names. One Alaska resident infant who was born and died in Seattle could not be matched to birth certificates.

A confirmed case was defined as an infant that died before 28 days of life during 1992–2000, who had medical chart documentation of physician-diagnosed sepsis or pneumonia and from whom a plausible neonatal pathogen was isolated from blood, cerebrospinal fluid, or another sterile site [5, 8, 10, 11]. For the current study, isolation sites included blood ($n=18$), multiple organs post-mortem ($n=2$), and amniotic fluid or placenta ($n=2$). Probable cases included those that met the definition for being a confirmed case except that isolates came from non-sterile rather than sterile sites [9]. Cases with positive cultures for coagulase-negative staphylococci were included if two specimens collected at the same time were positive. Early-onset disease included cases with a positive specimen collected at <7 days of life while late-onset cases were those occurring from 7 to <28 days.

AMIMR is prohibited from communicating information about specific individuals outside of the review process and from using results for any purpose other than generating population-based recommendations. As part of routine public health surveillance, no institutional review board oversees the project and informed consent is not sought.

Rate ratios and their 95% confidence intervals were determined with SPSS version 11.0 statistical software (SPSS Inc., Chicago, IL, USA). Cause-specific neonatal mortality rates are presented as outcomes per 1000 live births.

RESULTS

During 1992–2000, there were 93 695 live births and 32 infant deaths that met the case definition of probable sepsis ($n=23$), pneumonia ($n=3$), or both ($n=6$). The incidences of total and confirmed sepsis/pneumonia mortality were 0·34 and 0·24/1000 live births respectively. The incidences of total and confirmed early-onset GBS mortality were 0·075 and 0·032/1000 live births respectively, compared to 0·15 and 0·12/1000 live births for early onset non-GBS mortality and 0·15 and 0·11/1000 live births for late onset non-GBS mortality (there were no late-onset GBS cases).

Of the 32 total cases, 13 occurred during 1992–1994, 12 during 1995–1997, and seven during 1998–2000. The incidence of total non-GBS sepsis/pneumonia decreased from 0·33/1000 live births during 1992–1994 to 0·30 and 0·20/1000 live births during 1995–1997 and 1998–2000 respectively (χ^2 for trend 0·97, $P=0·61$). For GBS, rates during the same three time periods were 0·060, 0·13, and 0·034/1000 live births.

Among the 32 deaths, 47 organisms were identified and 31% of cases involved more than one organism (Table 1). For four cases, an initial non-fatal episode of sepsis was followed at least a week later by a secondary infection and death. The most common category of organism identified was non-GBS Gram-positive bacteria followed by Gram-negative bacteria, GBS, and *Candida* spp. (three *C. albicans*, one *C. parapsilosis*, and two not further speciated). All GBS cases were early-onset, all *Candida* spp. cases were late-onset (and 55% of late-onset cases were *Candida*-associated), and other cases occurred during both periods. GBS cases occurred primarily among term or near-term infants while other cases occurred primarily among pre-term or low-birth-weight infants.

When examined on a population basis, infants born pre-term (<37 weeks gestation) and with low (<2500 g) or very-low (<1500 g) birth weight were at greatly increased risk of sepsis or pneumonia mortality (Table 2). Although prematurity and low birth weight were risk factors for both GBS- and non-GBS-associated deaths, they were greater risk factors for non-GBS deaths. The percent population attributable risk provides a measure of the proportion of an outcome in a population associated with a particular risk factor and is defined as

$$[f*(\text{rate ratio}-1)]/[1+f*(\text{rate ratio}-1)],$$

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Table 1. *Organisms isolated from 32 neonates diagnosed with sepsis or pneumonia, Alaska 1992–2001*

Organism	No. of neonates affected	Median gestation, weeks (range)	Median birth weight, grams (range)	Median age at isolation (range)	Median age at death, weeks (range)	Sources (some neonates had the same organism isolated from multiple sources)
Group B streptococcus						
Sterile site	3	39 (24–41)	2935 (709–3486)	0 (0–0)	1 (0–2)	Blood (3), trachea (1), gastric (1)
Non-sterile site	4	35 (28–37)	2164 (1500–2835)	0 (0–1)	7·5 (1–24)	Urine antigen (4), trachea (3), gastric (2)
Other Gram-positive bacteria*						
Sterile site	6	25 (23–36)	770 (540–2540)	0 (0–16)	4 (0–28)	Blood (3), trachea (2), gastric (2), placenta (1), catheter tip pus (1), amniotic fluid (1)
Non-sterile site	11	26 (23–42)	907 (595–4451)	9 (0–23)	15 (1–27)	Trachea (10), gastric (2)
Gram-negative bacteria†						
Sterile site	9	27 (25–40)	936 (550–3034)	8·5 (0–18)	6 (0–21)	Blood (7), trachea (6), gastric (3), multiple organs post-mortem (2)
Non-sterile site	4	31 (25–37)	1703 (652–2608)	19 (0–25)	16 (1–24)	Trachea (3), gastric (2)
Candida spp.						
Sterile site	4	27 (23–37)	983 (595–2608)	11 (8–18)	23 (15–25)	Blood (4), trachea (3) urine (1)
Non-sterile site	2	31 (25–36)	1511 (907–2115)	13 (11–14)	21 (15–27)	Trachea (2)
Other organisms‡						
Sterile site	1	27	1200	17	25	Blood (1)
Non-sterile site	3	25 (25–38)	936 (880–2721)	7 (0–18)	8 (3–21)	Trachea (2), gastric (1), skin (1)

* Coagulase-negative staphylococci (5), *Staphylococcus aureus* (4), *Streptococcus viridans* (2), group G streptococcus (1), *Corynebacterium* (1), *Listeria monocytogenes* (1), *Streptococcus pneumoniae* (1), *Enterococcus* (1), Gram-positive cocci on Gram stain (1).

† *Escherichia coli* (3), *Enterobacter cloacae* (3), *Pseudomonas aeruginosa* (3), *Haemophilus influenzae* (2), *Klebsiella pneumoniae* (1), Gram-negative bacilli on Gram stain (1).

‡ Herpes simplex (2), *Gardnerella vaginalis* (1), *Ureaplasma urealyticum* (1).

where f is the percent of the population with the risk factor. For pre-term birth, low birth weight, and very-low birth weight, 7·6, 5·4 and 1·0% respectively, of the total birth cohort had the risk factor in question providing attributable risks for sepsis/pneumonia deaths of 70, 67 and 56%.

Among confirmed cases, 17 out of 19 non-GBS cases occurred among pre-term infants, while 16 and 15 occurred to low and very low-birth-weight infants respectively. While 16 of the 18 cases (83%) involving very low-birth-weight infants were confirmed, this was true for only six (43%) of the 14 cases involving heavier infants.

Among the Gram-negative isolates, antibiotic sensitivity patterns were known for six. Two *Enterobacter cloacae*, one *Escherichia coli*, and the *Klebsiella pneumoniae* isolates were ampicillin-resistant while one *E. coli* was ampicillin-sensitive and one *Pseudomonas aeruginosa* was susceptible to a variety of aminoglycosides. Although antibiotic sensitivities were not performed for the two *Haemophilus influenzae* isolates, one was β-lactamase-positive. One of two *Staphylococcus aureus* isolates tested was methicillin-resistant and the single enterococcus was ampicillin-sensitive. Overall, six (55%) of these 11 isolates had evidence of antibiotic resistance, of which four were associated with cases occurring during 1997–2000.

Among GBS cases, the mothers of two infants, both of whom delivered during 1993, had no documentation that a prenatal GBS culture had been

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Table 2. *Combined sterile site and non-sterile site neonatal sepsis or pneumonia mortality rates (per 1000 live births), by risk group, Alaska 1992–2000*

	All sepsis causes			Group B streptococcus*			Other organisms*		
Risk group	*n*	Mortality rate	Rate ratio (95% CI)	*n*	Mortality rate	Rate ratio (95% CI)	*n*	Mortality rate	Rate ratio (95% CI)
Gestation <37 weeks									
Yes	23	3·2	31 (14–67)	3	0·42	9·1 (2·0–41)	20	2·8	40 (16–101)
No	9	0·10	—	4	0·047	—	6	0·070	—
Birth weight <2500 g									
Yes	22	4·3	38 (18–81)	3	0·59	13 (2·9–58)	19	3·7	47 (20–112)
No	10	0·11	—	4	0·045	—	7	0·079	—
Birth weight <1500 g									
Yes	18	19·2	127 (63–255)	1	1·1	16 (2·0–137)	17	18	187 (84–418)
No	14	0·15	—	6	0·064	—	9	0·097	—

* One case involved group B streptococcus and an organism other than group B streptococcus.

performed. One mother who delivered during 1998 had a single negative culture 6 weeks before delivery and one who delivered during 1995 had a single positive culture 24 weeks before delivery. The remaining three delivered during 1995–1997 and had positive prenatal cultures within 1 day of delivery; two of these three mothers received peripartum antibiotics.

DISCUSSION

In Alaska, neonatal sepsis/pneumonia mortality was largely an outcome of pre-term and low birth weight. Previous studies have identified pre-term and low birth weight as risk factors for GBS [10–13] and other [5, 8, 14] neonatal sepsis; however, because few population-based risk-factor studies have been conducted, few have appreciated the extent to which neonatal sepsis mortality has become an outcome concentrated among pre-term infants.

Neonatal sepsis/pneumonia mortality had four broad aetiologies: GBS during the first 7 days of life, *Candida* spp. during the subsequent 21 days, and Gram-negative and non-GBS Gram-positive organisms during both periods. Studies of non-fatal early-onset disease have almost universally found GBS and *E. coli* to be the most common pathogens, with some authors reporting a shift from GBS to *E. coli* coincident with the institution of prenatal antibiotic prophylaxis [5–7, 14–18]. *Candida* spp. have also been recognized as increasingly important causes of neonatal sepsis, the more so because of their high case-fatality rate and epidemic potential [19–21].

Similar to a study in Great Britain of early-onset GBS disease [9], we found that approximately one third of neonatal sepsis/pneumonia deaths were missed if the definition relied solely on sterile-site isolates. Although a definition relying on sterile-site isolates would have missed few cases among the smallest infants, it would have missed over half of cases among infants born at >1500 g. Thus, while reliance on sterile-site isolates may allow for consistency between studies and has the advantage of including only definite cases, it may also underestimate the importance of neonatal sepsis, particularly among heavier infants.

The primary limitations of our study were a small sample size (despite the comprehensiveness of our study for Alaska) and lack of access to records for children who did not die. This prevented us from determining if temporal trends in mortality were related to random fluctuations associated with a small sample size, decreased incidence of disease, or decreased case-fatality ratio. Similarly, no conclusive statements could be made regarding trends in antibiotic resistance. Because the study was retrospective, we could not definitively determine if a particular infection formed part of the causal chain of events leading to an infant's death. Finally, even though we included infections involving non-sterile site isolates, it is likely that we missed numerous instances where an infection contributed to infant death, for example through pre-term birth, congenital anomalies, or undiagnosed postpartum illness.

Efforts to decrease neonatal sepsis mortality should focus on pre-term and low-birth-weight infants.

Providers should recognize the importance of GBS during the early neonatal period, *Candida* spp. during the later neonatal period, and other bacteria during both periods. Overall trends in sepsis-related mortality and antibiotic-resistance patterns should be monitored. Surveillance efforts used to determine disease burden should not be limited to cases meeting the definition of confirmed sepsis.

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