Etiologies and Risk Factors for Neonatal Sepsis and Pneumonia Mortality Among Alaskan Infants

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Summary

Few studies have focused on fatal sepsis cases occurring throughout the neonatal period. 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* species from 19% (all 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 to 41) and non-GBS (RR, 40; 95% CI, 16 to 101) disease. Neonatal sepsis mortality has become an outcome concentrated among preterm infants. Etiologies include GBS during the early neonatal period, *Candida* species during the late neonatal period, and gram-negative organisms during both periods.

Introduction

The majority of previous 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). Similarly, most previous studies of neonatal sepsis – including disease burden 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 the primary basis 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.

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. 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 contributing 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 contributing cause of death.

To evaluate population-based incidence rates and risk factors, 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. To eliminate a potential source of bias, we did not use the medical record abstraction form to collect or verify risk factor information for cases; rather, all risk factor information was derived from the birth certificate.

A definite 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). Total cases included definite cases and probable cases, i.e., those that met the definition for being a definite case except that isolates came from non-sterile rather than sterile sites (9). Cases with positive cultures for coagulase negative staphylococcus 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- <28 days.

Rate ratios and their 95% confidence intervals were determined with SPSS version 11.0 statistical software. Cause-specific neonatal mortality rates are presented as outcomes per 1,000 live births.

Results

Case characteristics

We identified 32 infant deaths that met the case definition of probable sepsis (n=23), pneumonia (n=3), or both (n=6) of which 18 also met the definition of definite sepsis. Twenty-one infants (66%) had at least one organism identified from a collection at <7 days postnatally (i.e., early onset). Twenty-five (78%) had associated severe medical conditions - usually preterm birth – identified as causes of death by the death certificate or the AMIMR committee. More than one potential organism was identified for 31% of cases. For four cases, an initial non-fatal episode of sepsis was followed at least a week later by a secondary infection and death. Thirteen cases occurred during 1992-4, 12 during 1995-7, and seven during 1998-2000.

The most commonly identified organism was GBS (21%), isolated from blood in three infants and from urine antigen plus gastric or tracheal aspirate for four additional infants. All GBS-related deaths occurred during 1998 or earlier and all involved early-onset. The mothers of two infants diagnosed with GBS disease, both of whom delivered during 1993, had no documentation that a prenatal GBS culture had been performed. One mother had a single negative culture 6 weeks before delivery and one had a single positive culture 24 weeks before delivery. The remaining three had positive prenatal cultures within one day of delivery two of whom received peripartum antibiotics.

Candida species (three *C. albicans*, one *C. parapsilosis*, and two not further speciated) occurred in 19% of cases making them the second most commonly identified agent after GBS. All *Candida*-associated deaths were late-onset and 55% of late-onset cases were *Candida*-associated. Gram-negative organisms were implicated in 12 (38%) deaths including *Escherichia coli* (9%), *Enterobacter cloacae* (9%), *Pseudomonas aeruginosa* (9%), non-typable *Haemophilus influenzae* (6%), *Klebsiella pneumoniae* (3%), and one unidentified species (3%). Seven of these 12 deaths were early-onset. Other organisms associated with multiple deaths included coagulase negative staphylococcus (16%) and *Staphylococcus aureus* (13%).

Among the gram-negative isolates, antibiotic sensitivity patterns were known for six. Two *E. cloacae*, one *E. coli*, and the *K. pneumoniae* isolates were ampicillin-resistant while one *E. coli* was ampicillin-sensitive and one *P. aeruginosa* was susceptible to a variety of aminoglycosides. Although antibiotic sensitivities were not performed for the two *H. influenzae* isolates, one was β-lactamase positive and one was negative. One of two *S. 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 occurred during 1997-2000.

Incidence, trends, and risk factors

During 1992-2000, there were 93,695 live births. The incidences of total and definite sepsis/pneumonia mortality were 0.34 and 0.19 per 1,000 live births, respectively. For all identified cases, the incidences of GBS and non-GBS sepsis/pneumonia mortality were 0.075 and 0.28 per 1,000 live births, respectively (one case involved GBS and non-GBS). Early-onset cases contributed the most to total and definite sepsis/pneumonia mortality rates (three cases involved both early and late onset disease) (Table 1).

The neonatal mortality rate for total non-GBS sepsis/pneumonia decreased from 0.33 per 1,000 live births during 1992-94 to 0.30 and 0.20 per 1,000 live births during 1995-97 and 1998-2000, respectively. For GBS, rates during the same three time periods were 0.060, 0.13, and 0.034 per 1,000 live births.

Compared to other infants, infants born preterm (<37 weeks gestation) and with low (<2500 g) or very low (<1500 g) birth weight were at greatly increased risk of total sepsis/pneumonia deaths (Table 2). Although preterm and low birth weight birth were risk factors for both GBS and non-GBS associated deaths, they were greater risk factors for non-GBS deaths. While most (72%) of the 18 cases involving very low birth weight infants were definite (i.e., had a sterile site isolate), this was true for only 36% of the 14 cases involving heavier infants.

Following adjustment for gestational age and birth weight, the following birth certificate-derived risk factors were not associated with total sepsis/pneumonia (at the 95% confidence level): infant gender, and maternal education, rural residence, race, marital status, age, prenatal alcohol or tobacco use, and history of previous child death.

Discussion

In Alaska, neonatal sepsis/pneumonia mortality was largely an outcome of preterm and low birth weight birth and had three broad etiologies: GBS during the first 7 days of life, *Candida* species during the subsequent 21 days, and gram negative organisms during both periods. Few previous studies have focused only on fatal neonatal sepsis. Studies of 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 (5-7,12-16). *Candida* species have also been recognized as increasingly important causes of neonatal sepsis, the more so because of their high case fatality rate and epidemic potential (17-19).

Previous studies have identified preterm and low birth weight birth as risk factors for GBS (10,11,20,21) and other (5,8,15) 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 preterm infants. Multiple mechanisms may account for this association. Prenatal infection may precipitate preterm labor (22,23). Alternatively, preterm infants may have impaired immunological function or may develop iatrogenic and nosocomial infections. Regardless, our results indicate that efforts to reduce neonatal sepsis mortality must be focused on infants born or at high risk of being born prematurely.

Similar to a study in Great Britain of early-onset GBS disease (9), we found that approximately half 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, it may do so at the cost of substantially underestimating the public health importance of neonatal sepsis.

Neonatal mortality rates in our study were roughly similar to those reported previously (7,8,11,12,20). Some studies have found that overall or *E. coli* sepsis incidences have increased even while GBS incidence has decreased (7,11,24,25). Our study had a sample size too small to make definitive statements about temporal trends. However, we observed that non-GBS sepsis/pneumonia mortality rates decreased over the study period.

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, if real, the trend in antibiotic resistance may have occurred because of increasing resistance or increasing mortality among those with resistant organisms. An additional limitation was our inability to know whether the infections suffered by infants in our study were part of the causal chain leading to their deaths. While this is true of all studies of neonatal sepsis, it becomes more problematic when including cases involving non-sterile site isolates.

Efforts to decrease neonatal sepsis mortality should focus on preterm and low birth weight infants. Providers should recognize the importance of GBS during the early neonatal period, *Candida* species during the later neonatal period, and gram-negative infections 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 definite sepsis.

Acknowledgements

Table 1. Definite (i.e., sterile-site) and total neonatal sepsis and pneumonia mortality rates, divided by early (<7 days) and late (7 to <28 days) onset*; Alaska, 1992-2000.

Category	Cases	Incidence per 1,000 live births
Early onset group B streptococcus		
Sterile site[†]	3	0.032
Total	7	0.075
Early onset non-group B streptococcus		
Sterile site[†]	8	0.085
Total	14	0.15
Late onset non-group B streptococcus[‡]		
Sterile site[†]	9	0.096
Total	14	0.15

*Three cases involved both early and late onset disease.

† Sterile site includes only blood as no culture-positive cerebrospinal fluid specimens were identified during the study period

‡ No cases of late-onset group B streptococcal sepsis or pneumonia death were identified.

Table 2.   Combined sterile site and non-sterile site neonatal sepsis or pneumonia mortality rates (per 1,000 live births), by risk group; Alaska, 1992-2000.

	All 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 to 67)	3	0.42	9.1 (2.0 to 41)	20	2.8	40 (16 to 101)
No	9	0.10	---	4	0.047	---	6	0.070	---
Birth weight <2500 g									
Yes	22	4.3	38 (18 to 81)	3	0.59	13 (2.9 to 58)	19	3.7	47 (20 to 112)
No	10	0.11	---	4	0.045	---	7	0.079	---
Birth weight <1500 g									
Yes	18	19.2	127 (63 to 255)	1	1.1	16 (2.0 to 137)	17	18	187 (84 to 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.

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