Neonatal Sepsis 2004-2013: The Rise and Fall of Coagulase-Negative Staphylococci

Matthew J. Bizzarro, MD[1], Veronika Shabanova, MPH[2], Robert S. Baltimore, MD[1,2,3], Louise-Marie Dembry, MD[3,4], Richard A. Ehrenkranz, MD[1], and Patrick G. Gallagher, MD[1]

Objectives To evaluate data for the period 2004-2013 to identify changes in demographics, pathogens, and outcomes in a single, level IV neonatal intensive care unit.

Study design Sepsis episodes were identified prospectively and additional information obtained retrospectively from infants with sepsis while in the neonatal intensive care unit from 2004 to 2013. Demographics, hospital course, and outcome data were collected and analyzed. Sepsis was categorized as early (≤3 days of life) or late-onset (>3 days of life).

Results Four hundred fifty-two organisms were identified from 410 episodes of sepsis in 340 infants. Ninety percent of cases were late-onset. Rates of early-onset sepsis remained relatively static throughout the study period (0.9 per 1000 live births). For the first time in decades, most (60%) infants with early-onset sepsis were very low birth weight and *Escherichia coli* (45%) replaced group B *streptococcus* (36%) as the most common organism associated with early-onset sepsis. Rates of late-onset sepsis, particularly due to coagulase-negative staphylococci, decreased significantly after implementation of several infection-prevention initiatives. Coagulase-negative staphylococci were responsible for 31% of all cases from 2004 to 2009 but accounted for no cases of late-onset sepsis after 2011.

Conclusions The epidemiology and microbiology of early- and late-onset sepsis continue to change, impacted by targeted infection prevention efforts. We believe the decrease in sepsis indicates that these interventions have been successful, but additional surveillance and strategies based on evolving trends are necessary. *(J Pediatr 2015;166:1193-9)*.

Yale-New Haven Hospital (YNHH) has maintained a continuously running, single-center database of neonatal bloodstream infections (BSIs), beginning with Ethel Dunham's case series from 1928 to 1933.[1] Since that time, documentation and analyses of evolving center-specific data have assisted greatly in the formulation of strategies to treat and prevent sepsis in the neonatal intensive care unit (NICU) population and have allowed tracking of the emergence and disappearance of certain pathogenic organisms from the NICU landscape.[2-6]

One example is the increase[2-4] and subsequent decrease[6] of group B *streptococcus* (GBS)-related early-onset sepsis. The identification and tracking of high rates of GBS early-onset sepsis and its significant associated morbidity and mortality resulted in the implementation of maternal screening and intrapartum antibiotic prophylaxis in the 1990s.[6,7] In our NICU,[6] in Connecticut,[8] and across the US,[7] the results of that effort exemplified how a targeted intervention could impact neonatal morbidity and mortality dramatically. Although cases of early-onset sepsis declined, late-onset sepsis was increasing at an alarming rate.[5,6] From 1989 to 2003, 27% of all very low birth weight (VLBW) infants in our NICU suffered at least one episode of sepsis, and coagulase-negative staphylococci (CoNS) emerged as the predominant organisms responsible for late-onset sepsis.[6,9] A similar trend was observed by Stoll et al,[9] on behalf of the Neonatal Research Network, who commented "strategies to reduce late infections…are urgently needed" and "successful interventions should improve survival, shorten mechanical ventilation and hospital stay, decrease antibiotic usage, and reduce the high cost of caring for VLBW infants." Several infection-prevention strategies were implemented in our NICU during the 2004-2013 study period with these goals in mind.

BSI	Bloodstream infection
BW	Birth weight
CLABSI	Central line–associated bloodstream infection
CoNS	Coagulase-negative staphylococci
GA	Gestational age
GBS	Group B *streptococcus*
NICU	Neonatal intensive care unit
VLBW	Very low birth weight
YNHH	Yale-New Haven Hospital

From the Departments of [1]Pediatrics and [2]Epidemiology and Public Health, Yale University School of Medicine; [3]Department of Quality Improvement Support Services, Yale-New Haven Hospital; and [4]Department of Internal Medicine, Yale University School of Medicine, New Haven, CT

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This report details changes in the epidemiology of early- and late-onset sepsis at YNHH from 2004 to 2013 and compares these findings with those observed at our institution from the previous 75 years. We also assess the impact of a series of interventions, including an effort to reduce central line–associated BSIs (CLABSIs),[10] on the microbiology, rates, and outcomes associated with late-onset sepsis in a single, level IV NICU.

Methods

The 54-bed level IV NICU at YNHH supports a high-risk obstetrical service and is a major referral center for fetuses and newborns with complex medical and surgical conditions. Positive blood cultures from our NICU were identified prospectively via frequent review of medical records and by direct communication with the microbiology lab and infection control providers. This study was approved by the Human Investigation Committee of the Yale University School of Medicine.

Any positive blood culture yielding a traditional neonatal pathogen met criteria for inclusion as a case of neonatal sepsis. Cultures that yielded commensal species (eg, CoNS) were reviewed with criteria modified from the Centers for Disease Control and Prevention.[6,11] Before 2008, the surveillance definition stated that, in addition to the presence of signs and symptoms of infection, CoNS had to be retrieved from at least 2 blood cultures or from 1 blood culture after which appropriate antimicrobial therapy was administered.[11] As of January 2008, the definition was made more stringent to specify that a minimum of 2 positive blood cultures are required to fulfill criteria for a CoNS-related BSI.[12] To maintain consistency in reporting and to allow for comparisons with previous study periods, we chose to follow the previous definition. Blood cultures that did not fulfill these criteria or that yielded organisms believed to be contaminants, including *Corynebacterium* and nonspeciated Gram-positive bacilli, were excluded. Multiple positive blood cultures from a single infant yielding the same species with identical antibiotic susceptibility patterns were considered a single episode of sepsis if the time between positive cultures was ≤7 days.

Cases of sepsis were classified according to the infant's age at the time of the positive blood culture as follows: early-onset (≤3 days of life) and late-onset (>3 days) infection. Two modifications were made from previous cases series. The category late, late-onset sepsis (>30 days), was eliminated, and the dividing line between early and late-onset was chosen at 3 instead of 4 days to coincide with current reporting.[9,13]

Additional data were collected retrospectively from the medical records of infants with a positive blood culture(s) obtained as inpatients in the YNHH NICU from January 1, 2004, through December 31, 2013. Demographics, information related to the hospital course, and outcomes were collected and reviewed.

The majority of variables were defined as previously described.[6] Sepsis-related death was defined as death occurring within 7 days of a positive blood culture(s) or when clinical signs and symptoms of sepsis were believed to be, and documented as, the direct cause of death. Sepsis-related death was calculated with the numerator representing the number of episodes of sepsis resulting in death and the denominator as the total number of episodes of sepsis. In the case in which an infant had multiple episodes of sepsis, only the last one was included in the calculation of mortality and previous episodes were recorded as sepsis with survival. Blood cultures were assessed with a fluorescent-detection system for the presence of carbon dioxide (Bactec II or 9240, Becton Dickinson, Franklin Lakes, New Jersey).

Statistical Analyses

Univariate comparisons were made using the independent samples Student *t* test for continuous data and χ^2 or Fisher exact test, if any cell in the analysis contained <5, for dichotomous data. A *P* value of <.05 based on 2-sided tests was considered statistically significant (SPSS Inc, Chicago, Illinois).

Trends in infection rates were assessed from 1979 (the first year with complete data available on live births and NICU admissions at YNHH) through 2013 and independently from 2004 through 2013. The number of infections during a specified year-interval was assumed to be Poisson-distributed; therefore, the change in rates of infections over time was analyzed with Poisson regression with the number of live births (for early-onset sepsis) or total NICU admissions (for late-onset sepsis) in a given year used as an offset variable (SAS 9.3, Cary, North Carolina). The time effect was not assumed to be linear, and polynomial time effects such as quadratic, cubic, and quartic were tested in the regression models. To supplement the parametric modeling of the infection rates with Poisson regression, the primary goal of which was to investigate the effect of time, a nonparametric method was used to estimate infection rates in a more dynamic manner using smoothing spline Poisson regression, with approximate Bayesian CIs for the smoothed rates.[14] Statistical significance was established with $\alpha = 0.05$.

Results

Early-Onset Sepsis

Forty-two episodes of early-onset sepsis yielding 44 organisms were identified in 42 infants during the 10-year study period. *Escherichia coli* was the most common organism isolated from blood culture (45%), followed by GBS (36%), *Haemophilus influenzae* (7%), and *Staphylococcus aureus* (7%) (**Table I**). In infants with *E coli* early-onset sepsis, 13 of 19 (68%) were exposed to intrapartum antibiotics, but in only 55% of cases was the *E coli* strain susceptible to the antimicrobial regimen administered to the mother. Ampicillin resistance was observed in 63% of available *E coli* isolates. Fifteen infants had GBS early-onset sepsis. In 11 of