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Contribution of Concurrent Comorbidities to Sepsis-Related Mortality in Preterm Infants ≤ 32 Weeks of Gestation at an Academic Neonatal Intensive Care Network

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Abstract

Objective: This study sought to identify concurrent major comorbidities in preterm infants ≤ 32 weeks of gestation that may have contributed to sepsis-related mortality following a diagnosis of bacteremia or blood culture-negative sepsis within the neonatal period (≤28 days of life).

Study Design: This is a retrospective chart review of infants ≤ 32 weeks of gestation, who were admitted to a single academic network of multiple neonatal intensive care units between

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Acquisition of data: Barnette, Lazar, and Richardson.

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January 1, 2012 and December 31, 2015, to determine the primary cause(s) and timing of death in those diagnosed with bacteremia or blood culture-negative sepsis. Direct comparisons between early-onset sepsis (EOS; ≤ 72 hours) and late-onset sepsis (LOS; > 72 hours) were made.

Results: In our study cohort of 939 total patients ≤ 32 weeks of gestation, 182 infants were diagnosed with 198 episodes of sepsis and 7.7% (14/182) died. Mortality rates did not significantly differ between neonates with bacteremia or blood culture-negative sepsis (7/14 each group), and those diagnosed with EOS compared with LOS (6/14 vs. 8/14). Nearly 80% (11/14) of infants were transitioned to comfort care prior to their death secondary to a coinciding diagnosis of severe grade 3 or 4 intraventricular hemorrhage, periventricular leukomalacia, necrotizing enterocolitis, and/or intestinal perforation.

Conclusion: Pre-existing comorbidities commonly associated with extreme preterm birth contributed to sepsis-related mortality in our patient cohort.

Keywords

Neonatal sepsis; sepsis-related mortality; prematurity; bacteremia; blood culture negative sepsis; comorbidities; comfort care

Introduction

Neonates are at considerable risk for developing life-threatening infections with aggressive, virulent organisms due to gestational age-related functional deficiencies of their innate and adaptive immune responses [1–3]. Worldwide, an estimated 13-15% of all neonatal deaths is attributed to sepsis. Nearly 42% of these losses, however, are experienced within the first week of life due to complications associated with early-onset sepsis (EOS; sepsis occurring ≤ 72 h of life) [4, 5]. In the United States, sepsis is the fifth leading cause of neonatal mortality and is surpassed only by complications related to pregnancy, preterm birth, and congenital anomalies [6].

While the incidence of neonatal sepsis in the US is reported to be 0.9-1.5 per 1000 live births for EOS and 3.0-3.7 per 1000 live births for late-onset sepsis (LOS; > 72 hours of life) [6], the diagnosis of infection is inversely proportional to gestational age and weight at birth [2]. Thus, the least mature, smallest, and most critically-ill premature infants have the highest incidence of neonatal sepsis [2]. Supportive intensive care for developmental immaturity that follows being born months too soon, including prolonged placement of indwelling central lines, frequent laboratory tests, increased likelihood for mechanical ventilation, and protracted hospital stays, contributes to sepsis-related morbidity and mortality during the neonatal period, particularly in very low birth weight (VLBW; birth weight < 1500 grams) infants [7–10]. Consequently, the mortality rate for VLBW infants compared with their term counterparts is significantly greater (30%-35% for EOS and 18% for LOS compared to an upper limit of 3% overall mortality for term infants) [11, 12, 2, 13].

Although the direct association between increased sepsis-related mortality and decreased gestational age is well documented, the contribution of coexisting comorbidities that commonly accompany extreme preterm birth has not been well described. Ascertaining this information through data extraction (without concurrent chart review) may be challenging in

large, multicenter studies due to differences in electronic medical record networks between study sites and limitations of individual hospital computer systems. The purpose of this study, therefore, is to determine how concurrent comorbidities may contribute to death in infants born ≤ 32 weeks of gestation and admitted to the University California, San Diego, (UCSD) or the Rady Children's Hospital of San Diego's (RCHSD) network of regional neonatal intensive care units (NICUs), following a diagnosis of bacteremia or culture negative sepsis. We additionally characterize pathogens associated with positive blood culture results in our patient cohort.

Methods:

Study Population

A retrospective chart review of infants born ≤ 32 weeks of gestation between January 1, 2012 and December 31, 2015 and admitted to the following hospitals were included: UCSD Hillcrest Medical Center, Rady Children's Hospital of San Diego, and Rady Children's Hospital satellite NICUs at Scripps Memorial Hospital (La Jolla), Scripps Mercy Hospital (Hillcrest), Scripps Chula Vista, Scripps Memorial Hospital (Encinitas), Palomar Medical Center (Escondido), and Rancho Springs Medical Center. Infants were included for analysis if they had a positive blood culture(s), ICD codes corresponding to culture negative sepsis (A41.89, A41.9, P36.8, P36.9, R65.20, R65.21, R68.89, Z05.1, and Z91.89), or treatment with antibiotics ≥ 5 days (or death prior to 5 days with intention to treat).

Patient Protection

Our research plan (#170992) was approved by the Rady/UCSD Institutional Review Board and determined to present no greater than minimal risk, in accordance with research guidelines involving children (45 CFR 46.404). A waiver of assent was also approved, as set forth in HHS regulations at 45 CFR 46.408 and specified in 45 CFR 46.116(d).

Definition of Sepsis, Blood Culture Negative Sepsis, and Sepsis-Related Mortality

There is currently no consensus definition for neonatal sepsis [14–17].—We defined sepsis as either the laboratory finding of bacteremia (positive blood culture) or as *blood "culture negative sepsis"*, if the blood culture result remained negative but the physician believed the patient to have bacterial sepsis with antibiotic administration for ≥5 days and a diagnosis of culture negative sepsis reported in the patient's electronic medical record. Sepsis was further defined as early, if onset occurred within the first 72 hours of life, or late if diagnosed > 72 hours. Positive blood cultures were considered contaminated if the resulting organism was a known contaminant [i.e., coagulase-negative *Staphylococcus* (CoNS) or *S. epidermidis*], the infant received < 5 days of antibiotics, and/or the attending physician documented the isolate to be a suspected contaminant. While all patient deaths were recorded and correlated to their proximity to their sepsis episode, *sepsis-related mortality* was defined as mortality within 14 days of a sepsis diagnosis (either blood culture positive or negative), death beyond 14 days of a sepsis diagnosis if the infant remained on a prolonged antibiotic course, and documentation that the sepsis event was clinically relevant. Transition to comfort care and documented contributors to death were also noted.

Outcome Measures

The electronic health records of these infants were reviewed to ascertain and document: (a) date and time of the infectious workup, including blood culture collection, (b) date and time of blood culture positivity, if applicable, with pathogen identification, and (c) antibiotics use with their duration. If the patient died, then the date and time, interval from evaluation, and circumstances of the patient's death were recorded and analyzed, including transition to comfort measures. Additionally, nSOFA (neonatal sequential organ failure assessment) scores were calculated around the neonate's sepsis workup and time of death [18, 19].

Statistical Analysis

A descriptive analysis was conducted using R Studio 3.6.3 (RStudio, Inc., Boston, MA). Infants who had unique cases of both early-onset and late-onset sepsis were included in early-onset and late-onset groups based on the timing for each episode. Data are presented as means and standard deviations (SD) for numeric data and as frequencies and percentages for nominal data. Chi-square tests were used to compare counts across strata if all expected cell sizes were ≥ 5, otherwise Fisher's exact test was used. Additionally, after visual confirmation of normality from Q-Q plots for all relevant covariates, t-tests were used to compare means across strata. A *p*-value less than 0.05 was considered statistically significant.

Results:

Patient Demographics

Between January 1, 2012 and December 31, 2015, a total of 939 infants ≤ 32 weeks of gestation were admitted to a NICU within our hospital network, of which 183 patients were found to have either ≥ 1 positive blood culture result(s) or medical coding concerning for culture negative sepsis for a total of 198 sepsis-related episodes (Table 1). One patient coded for culture-negative sepsis was excluded, however, as this patient had no documented positive cultures, no indication of physician concerns regarding sepsis, and discontinuation of antibiotics at 48 hours after birth with no further antibiotic exposure during their hospital course. A total of 182 patients with a total of 198 sepsis episodes were, therefore, used for analysis, including 109 positive blood culture results and 89 diagnoses of blood culture-negative sepsis. Four patients had separate episodes of early-onset and late-onset sepsis, which were classified accordingly. No statistical differences were observed in regard to sex, ethnicity, or mode of delivery between bacteremic and blood culture-negative infants. As expected, neonates born at lower birth weights and gestational ages exhibited a higher incidence of LOS than EOS (946 gm vs. 1241 gm and 27 weeks vs. 29 weeks of gestation; $p<0.001$). The diagnosis of EOS was 5.8-times more likely to be classified as blood culture-negative than -positive sepsis, and bacteremia was nearly 4-times more likely to be identified in infants diagnosed with LOS.

Cause of Death

Of the 182 patients reviewed, a total of fourteen patients died (Table 2 and 3). Mortality was not significantly different between EOS and LOS groups [24.4% (6/14) vs. 17.1% (8/14)],

nor for blood culture -positive vs. negative sepsis [50% (7/14) each group]. The majority of infants (80% or 11/14) in this cohort died at ≤ 14 days of life. Two infants, born at 24 weeks of gestation, died within 24 hours of life. The first (Patient 8) died following a diagnosis of blood culture negative sepsis, spontaneous intestinal perforation, and severe metabolic acidosis. The second, diagnosed with *Escherichia coli* bacteremia, had a clinical course complicated by grade 4 IVH and bilateral pneumothoraces (Patient 14).

In our cohort (Table 3), seven patients very likely died as a direct result of infection, irrespective of transition to comfort care: (a) Patient 5 was newly diagnosed with high-stage NEC and severe metabolic acidosis, (b) Patient 10 with *S. aureus* bacteremia, CDH, and intestinal perforation on DOL 14, (c) Patient 14 discussed above, and (d) four infants who succumbed following acute intestinal perforation, with or without fungemia/bacteremia and/or severe IVH (Patients 8, 11, 12, and 13). Conversely, two other infants died following a positive blood culture for CoNS while receiving antibiotics. The first infant (Patient 2) was born at 25 weeks of gestation with complex congenital anomalies, including congenital heart disease and CDH, experienced progressive deterioration in their clinical course with death occurring on DOL 117 from pulseless ventricular tachycardia. The second infant (Patient 9) died of severe pulmonary hemorrhage and bilateral grade 3 IVH on the third DOL after preterm birth at 24 weeks of gestation. Although blood cultures isolated CoNS in both of these cases, the attending physicians' documentation clearly defined each as a contaminant and death was attributed to noninfectious-related causes. The accurate determination of blood culture contamination, however, can be challenging in this patient population if multiple cultures are not obtained and mortality occurred while the patient was still receiving antibiotics.

Five patients diagnosed with culture-negative sepsis highlight the importance of concurrent comorbidities in relation to sepsis mortality in this patient cohort. The first (Patient 3) died following failure of full resuscitative measures from a pulmonary hemorrhage associated with severe coagulopathy following a traumatic hepatic injury sustained at the time of birth. The other four (Patients 1, 4, 6, and 7) were transitioned to comfort care measures due to severe IVH and/or PVL, with two infants each at 31 weeks' gestational age also having concurrent congenital anomalies, including hypoplastic left heart syndrome (Patient 6) and TEF (Patient 7).

Two deaths were classified as "not sepsis related" after careful review of their medical records. Patient 1, born at 23 weeks of gestation, died after initiation of comfort care measures on day of life (DOL) 103 due to worsening seizure activity associated with post-hemorrhagic IVH and evolving PVL with previous history of intestinal perforation. The other infant, Patient 2 discussed above, was born extremely preterm at 25 weeks' CGA and succumbed after full resuscitative measures failed on DOL 117 from complications related to congenital heart disease (coarctation with Ebstein's anomaly) and congenital diaphragmatic hernia (CDH).

In our patient cohort the transition to comfort care procedures was associated with the majority of sepsis-related deaths. We determined that 80% (11/14) of infants with either bacteremia or blood culture negative sepsis died following transition to comfort measures.

In this subgroup, nearly three-fourths (8/11) of patients had a corresponding diagnosis of severe grade 3/4 IVH or PVL, an equal number (8/11) had developed NEC or suffered from an intestinal perforation (IP), and almost half (5/11) had a concurrent diagnosis of IVH/PVL and NEC/IP.

nSOFA Scores of Infants Who Died

The nSOFA score incorporates a patient's respiratory dysfunction (need for ventilatory support, supplemental oxygen provided in the context of transcutaneous oxygen saturations), cardiovascular dysfunction (pharmacologic blood pressure support including inotropes, vasopressors, and steroids), and hematologic dysfunction (platelet counts) to determine an overall risk of mortality following a diagnosis of neonatal sepsis [18, 19]. The score ranges from a minimum of 0 (best score) to a maximum of 15 (worst score). Patients with late-onset infection with a nSOFA score of >4 at evaluation were five-times more likely to die compared with those who score ≤4 [18]. Among the patients that experienced mortality, the mean nSOFA at evaluation was 4.5 [standard deviation (SD) 3.4], and the mean maximum nSOFA during the episode of 8.8 (SD 4.0) (Table 3). Five infants in our study had nSOFA scores at evaluation <4, including three with concurrent congenital anomalies (hypoplastic left heart syndrome, TEF, and CDH with Epstein's anomaly and coarctation), one with evolving PVL and severely abnormal electroencephalogram, and one died of an acute pulmonary hemorrhage with bilateral grade 3 IVH. Three of these five infants died following transition to comfort care protocols.

Distribution of Bacterial Pathogens Isolated from Blood Culture Analysis

A total of 162 positive blood culture results were identified (Table 4). *E.coli* was prominent in infants with EOS (46.2% or 6/13 blood cultures), while 80% of LOS infections were caused by gram-positive organisms including CoNS, *Enterococcus cloacae*, and *S. aureus*. Similar to published studies concerning LOS, CoNS was the primary organism isolated in blood culture tests in more than half of cases (56%). Fungal pathogens were exclusively found in the evaluation and diagnosis of LOS.

Discussion:

Infection remains an important clinical entity in neonatology. In the United States, an estimated six of ten VLBW infants admitted to neonatal intensive care units will be diagnosed with bacteremia or blood culture negative sepsis, and nearly one-third may die from complications related to their infection [20, 13]. Although multiple factors contribute to the heightened risk for infection in VLBW infants, multi-organ immaturity and other natural, gestational age-appropriate physiologic processes may closely resemble infectious processes. A primary fear of missing or misdiagnosing an infection, therefore, may lead clinicians to administer prolonged antibiotic courses, even if presented with a negative blood culture result, contributing to the overuse of antibiotics in our smallest and youngest gestational age neonates [6]. This concern is elevated by the potential development of substantial long-term health issues and neurodevelopmental disabilities in sepsis survivors due to infection-mediated inflammatory stressors that lead to permutations of developing organ systems, including the brain [periventricular leukomalacia (PVL),

intraventricular hemorrhage (IVH), cerebral palsy, retinopathy of prematurity (ROP), and hearing impairments], lung (respiratory distress syndrome and bronchopulmonary dysplasia), gastrointestinal tract [necrotizing enterocolitis (NEC) or spontaneous intestinal perforation (SIP)], and heart (patent ductus arteriosus) [7, 21].

Case-fatality within a given time interval is typically employed in clinical studies to detail neonatal sepsis-related mortality. The time interval, generally defined as the period between culture procurement and time of death, normally transpires within 72 hours, between 4-7 days, > 7 days, within 30 days, or during the infant's initial hospital course [7, 22, 11, 23, 24, 13]. While half of all EOS deaths will occur within the first three days of life [13], an estimated 40% of neonates with LOS died more than 7 days from their last blood culture [7]. As expected, death associated with LOS was primarily attributable to infection when mortality occurred within three days of a positive culture, while death ≥ 4 days was more likely to be caused by deleterious, non-infectious, but chronic etiologies [7]. Similar results were obtained in this study, where the classical pro-inflammatory sepsis pathways and multi-organ dysfunction did not directly lead to mortality of two patients who died >14 days from their last sepsis evaluation (Patients 1 and 2), but may have contributed to neurologic or cardiac injury and dysfunction that contributed to their deaths.

Apart from physiologic differences, the risk of developing sepsis also varies greatly between preterm versus term infants, as recently reported in a study regarding culture-positive EOS by *Stoll and colleagues* [13]. Using the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development Neonatal Research Network, these authors determined the rate of EOS to be 30-fold higher in preterm infants born between 22 to 28 weeks of gestation compared to their term counterparts. While all term infants survived their infection, nearly three in ten bacteremic preterm infants born between 22 to 36 weeks of gestation died from sepsis-related complications. The median gestational age of infants who died was 25.5 (IQR, 24-28) weeks with a median birth weight of 850 (IQR, 680-1370) grams, with half of these deaths occurring within the first 3 days of life. While concurrent comorbidities and transition to comfort care measures where not reported in this study, all infants ≤32 weeks of gestation demonstrated clinical symptoms within 72 hours of life, including respiratory compromise and hypotension, which the authors suggests may be compatible with sepsis but are also common in preterm neonates who are not infected.

Our findings are similar to those reported by *Jacobs and colleagues* [25], who employed a large Mednax database to determine the primary cause of death of 641 preterm and term infants. In this prospectively-defined patient population, the leading causes of mortality were attributable to complications associated with extreme birth, including intraventricular hemorrhage, necrotizing enterocolitis, sepsis, and respiratory failure resulting from progressive respiratory distress. The etiology of mortality, however, shifted with increasing gestational age to include hypoxic-ischemic encephalopathy and genetic and structural anomalies in infants born closer to term gestation.

In conclusion, inherent difficulties remain in our ability to accurately assess sepsis-related mortality in preterm neonates. Potentially life-threatening co-morbidities, common to infants born extremely preterm, may substantially contribute to neonatal mortality and artificially

inflate sepsis-related case-fatality rates [16]. Future studies should, therefore, incorporate data regarding confounding factors and/or comorbidities that contribute to neonatal sepsis-related mortality, including the transition to comfort care protocols. Because current published definitions of neonatal sepsis are heterogenous (bacteremia +/− culture negative sepsis) and without considerations for new onset organ dysfunction, the establishment of a consensus definition is critical. As emerging therapeutics and technologies are being engineered to remedy sepsis-mediated pathophysiologic processes, an accurate assessment of the incidence of sepsis is vital to determine study feasibility, calculate sample size, and validate outcome measures.

In our study, sepsis-related mortality largely resulted from the transition of intensive care clinical management to comfort care protocols. This conversion was primarily guided by pre-existing serious comorbidities, including severe grade 3-4 IVH, respiratory failure or lung hypoplasia, and/or congenital anomalies, suggesting a baseline increased risk for poor survivability and/or substantial long-term neurodevelopmental impairments. Because infection-associated pro-inflammatory immune responses may exacerbate or worsen baseline neonatal outcomes [20, 26, 27], the additional diagnosis of sepsis may have further facilitated discussions of initiation of comfort protocols with the patient's parents and family. Development of a consensus definition for neonatal sepsis could improve clarity and promote opportunities to consider how sepsis-related deaths should be regarded in terms of neonatal statistics, research, and education, thereby aligning clinicians, researchers, and epidemiologists to potentially improve patient outcomes [14–17].

In this study, mortality data demonstrates a lower rate of death than historically described, with an overall case-fatality rate of 7.7%. The inclusion of both bacteremia and blood culture-negative sepsis in this study cohort may have contributed to this discrepancy, as many neonatal studies only include bacteremic patients. No significant differences in mortality caused by Gram -positive compared with -negative sepsis were demonstrated, which could be related to low sample size. Other limitations of this study include its retrospective nature and decision to define neonatal sepsis based on blood culture results only. The analysis of a small sample size and failure to capture infants with positive viral studies (culture or quantitative nucleic acid testing) are additional weaknesses. Even though this is a multicenter study, it encompasses a single academic neonatal-perinatal medicine practice group with approximately twenty-two neonatologists, so findings may not be applicable to other neonatal centers. Transitions to comfort care, as embraced by our institution, may also not be acceptable to other neonatal providers.

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Table 1.

Patient Demographics and Infection Evaluations, 2012-2015

Characteristic[†]	Total	Early Onset	Late Onset	*P*-value[a]
Gestational Age at Birth, Mean (SD) [*]	28 W (3 W)	29 W (3 W)	27 W (3 W)	**<0.001**
Birth Weight (Grams), Mean (SD) [*]	1066 (452)	1241 (459)	946 (407)	**<0.001**
Race/Ethnicity, n (%) [*]				0.29
Hispanic	101 (54.0)	37 (48.7)	64 (57.7)	
Non-Hispanic	86 (46.0)	39 (51.3)	47 (42.3)	
Sex, n (%) [*]				0.40
Male	121 (64.7)	46 (60.5)	75 (67.6)	
Female	66 (35.3)	30 (39.5)	36 (32.4)	
Mode of Delivery, n (%) [*]				0.71
Caesarean Section	132 (70.6)	52 (68.4)	80 (72.1)	
Vaginal	55 (29.4)	24 (31.6)	31 (27.9)	
Culture Status, n (%) [**]				**<0.001**
Culture Positive	109 (55.1)	11 (14.7)	98 (79.7)	
Culture Negative	89 (44.9)	64 (85.3)	25 (20.3)	

[†] Out of 182 unique patients, unless otherwise noted. (n = 198 sepsis episodes)

[a] *P*-value from the *t*-test for continuous variables and Chi-Sq. goodness of fit test for categorical variables across sepsis onset categories.

[*] Four (4) patients had separate episodes of early and late onset sepsis were classified as both early and late onset; thus, for time-fixed variables, the sample size will be 4 patients larger than the reported sample size.

[**] Out of 198 sepsis episodes; the 4 patients with early and late onset (8 episodes) were not recategorized at all.

Bold indicates significance at the $P < 0.05$ level.

Table 2.

Survival and Cause of Death by Sepsis Onset, 2012-2015

		Culture Positive		Culture Negative		
Characteristic[†]	**Total (n = 198)**	**Early Onset (n = 11)**	**Late Onset (n = 98)**	**Early Onset (n = 64)**	**Late Onset (n = 25)**	***P*-value**[*]
Survival to Discharge, n (%)						0.20
Yes	184 (92.9)	9 (81.8)	93 (94.9)	60 (93.8)	22 (88.0)	
No	14 (7.1)	2 (18.2)	5 (5.1)	4 (6.2)	3 (12.0)	
Sepsis-Related Death[**]						0.78
No	2 (14.3)	0 (0.0)	1 (20.0)	0 (0.0)	1 (33.3)	
Yes	12 (85.7)	2 (100.0)	4 (80.0)	4 (100.0)	2 (66.7)	
Yes, Withdrawal	10 (71.4)	2 (100.0)	3 (60.0)	3 (75.0)	2 (66.7)	

[†] Out of 198 episodes, unless otherwise noted. (n = 182 patients)

[*] *P*-value for Fisher's exact test across the four categories of sepsis and its onset.

[**] Out of 14 deaths.

Sepsis-related death is defined as death ≤ 14 days of sepsis onset or death while on antibiotic treatment.

Bold indicates significance at the $P < 0.05$ level.

Table 3:

Patient-Specific Clinical Conditions Attributable to Cause of Death

GA at Birth	Birth Weight (gm)	Age at Death (days)	Organism	Sepsis-Related Death	nSOFA Score	Transition to Comfort Care	Associated Clinical Conditions
23	575	103	Culture Negative Sepsis	No	5	Yes	Worsening post-hemorrhagic changes resulting from right grade 4 and severely abnormal electroencephalogram; previous h/o intestinal perforation
25	610	117	*Staphylococcus epidermitis*	No	1	No	Died from pulseless ventricular tachycardia associated with CHD (coarctation, left ventricular outflow tract obstruction, and Ebstein's anomaly); Blood culture felt to be contaminant; BC drawn 10/6/12 and baby died 12/11/12
26	940	2	Culture Negative Sepsis	Yes	6	No	Hepatic hemorrhage with intrabdominal bleeding; metabolic acidosis; coagulopathy; acute severe pulmonary hemorrhage
26	790	8	Culture Negative Sepsis	Yes	4	Yes	New onset right grade 3 and left grade 4
24	605	10	Culture Negative Sepsis	Yes	10	Yes	NEC; severe metabolic acidosis
31	1528	33	Culture Negative Sepsis	Yes	6	Yes	Hypoplastic left heart syndrome; NEC s/p laparotomy; IVH with evolving PVL
31	1800	9	Culture Negative Sepsis	Yes	3	Yes	Acute onset bilateral grade 4 IVH, TEF with esophageal atresia, duodenal atresia, and double outlet right ventricle
24	620	0	Culture Negative Sepsis	Yes	9	Yes	Intestinal perforation, profound metabolic acidosis, bleeding, and hypotension
24	610	3	*Staphylococcus epidermitis*	Yes	11	No	Severe pulmonary hemorrhage, bilateral grade 3 IVH
31	1380	14	*Staphylococcus aureus*	Yes	12	Yes	Patient also had a left-sided CDH, severe pulmonary hypertension, and pneumoperitoneum
25	791	8	*Escherichia coli*	Yes	3	Yes	Recovering from *E. coli* sepsis (6 days into treatment); acute intestinal perforation on day of death with pre-existing right grade 3; left grade 4 IVH
23	646	6	*Candida albicans*	Yes	4	Yes	Intestinal perforation with right grade 4; left grade 3 IVH
23	561	7	*Enterobacter cloacae*	Yes	5	Yes	Intestinal perforation with right grade 4; left grade 3 IVH
24	709	0	*Escherichia coli*	Yes	12	Yes	Severe metabolic acidosis; coagulopathic and anemic with poor cardiac function; bilateral pneumothoraces; bilateral IVH; severe perinatal infection

CHD: congenital heart disease; **TEF:** tracheoesophageal fistula; **CDH:** congenital diaphragmatic hernia; **IVH:** intraventricular hemorrhage; **NEC:** necrotizing enterocolitis; **PVL:** periventricular leukomalacia

Table 4.

Blood Culture Pathogens, 2012-2015

Characteristic	Total (n = 162)	Cultures Isolates Early (n = 13)	Late (n = 149)	*P*-value*
Pathogen, n (%)				**<0.001**
CoNS	86 (53.1)	2 (15.4)	84 (56.4)	
Enterococcus spp.	18 (11.1)	1 (7.7)	17 (11.4)	
Staphylococcus aureus	17 (10.5)	0 (0.0)	17 (11.4)	
Escherichia coli	9 (5.6)	6 (46.2)	3 (2.0)	
Candida spp.	7 (4.3)	0 (0.0)	7 (4.7)	
Group B *Streptococcus*	5 (3.1)	1 (7.7)	4 (2.7)	
Klebsiella pneumoniae	5 (3.1)	1 (7.7)	4 (2.7)	
Enterobacter spp.	4 (2.5)	0 (0.0)	4 (2.7)	
Pseudomonas spp.	3 (1.9)	1 (7.7)	2 (1.3)	
Acinetobacter spp.	1 (0.6)	0 (0.0)	1 (0.7)	
Bacillus spp.	1 (0.6)	0 (0.0)	1 (0.7)	
Citrobacter koseri	1 (0.6)	1 (7.7)	0 (0.0)	
Micrococcus spp.	1 (0.6)	0 (0.0)	1 (0.7)	
Paenibacillus spp.	1 (0.6)	0 (0.0)	1 (0.7)	
Salmonella spp.	1 (0.6)	0 (0.0)	1 (0.7)	
Serratia spp.	1 (0.6)	0 (0.0)	1 (0.7)	
Other *Streptococcus* spp.	1 (0.6)	0 (0.0)	1 (0.7)	

n = 162 true positive blood culture results

*P-value for Fisher's exact test across the categories of sepsis onset.

Bold indicates significance at the $P < 0.05$ level.