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: The lack of a consensus definition for neonatal sepsis may complicate the accurate calculation of sepsis-related mortality in infants ≤ 32 weeks of gestation. This study evaluates whether concurrent major comorbidities influenced neonatal sepsis-related mortality in this patient population following a diagnosis of bacteremia or blood culture-negative sepsis.

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 January 1, 2012 and December 31, 2015, to determine if concurrent co-morbidities contributed to bacteremia or blood culture-negative sepsis-related mortality. 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: Those with sepsis-related mortality had pre-existing comorbidities that are commonly associated with extreme preterm birth. The contribution of comorbidities to sepsis-related mortality should be considered in future investigations designed to evaluate the efficacy of therapeutics and/or technologies that target sepsis-mediated pathways.

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Conclusion: Those with sepsis-related mortality had pre-existing comorbidities that are commonly associated with extreme preterm birth. The contribution of comorbidities to sepsis-related mortality should be considered in future investigations designed to evaluate the efficacy of therapeutics and/or technologies that target sepsis-mediated pathways.
Key Points:

A. Concurrent co-morbidities significantly contribute to, and may artificially inflate, sepsis-related mortality in preterm infants.

B. The absence of a consensus definition for neonatal sepsis complicates the investigation of infection and the precise determination of sepsis-related mortality.

C. Accurate assessment of the incidence of sepsis in very low birth weight infants is vital for future investigations of therapeutics and/or technologies that target sepsis-mediated pathways.
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 are attributed to sepsis and 42% of losses 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\(^6\).

To date, no consensus definition for neonatal sepsis has been established. Historically, bacteremia has been considered the “Gold Standard” for the diagnosis of neonatal sepsis (sepsis diagnosed ≤28 days of life), but up to 14% of newborns with unequivocal infection documented at autopsy reported negative premortem blood cultures\(^7\). Blood culture-negative neonatal sepsis leading to life-threatening organ dysfunction may occur when the primary site of infection includes meningitis, soft-tissue (omphalitis), osteomyelitis, pneumonia, and perforated bowel [e.g., spontaneous intestinal perforation (SIP) or necrotizing enterocolitis (NEC)]\(^8\)-\(^11\). In addition, blood culture-negative sepsis is diagnosed in more than half of adult and pediatric patients presenting with clinical signs and symptoms of septic shock\(^11\)-\(^13\).

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\(^1\). Thus, the least mature, smallest, and most critically-ill infants have the highest incidence of neonatal sepsis\(^1\). Infection risks are heightened in very low birth weight (VLBW; birth weight < 1500 grams) infants.
because of the need for specialized intensive care supportive measures. Common interventions and procedures that are vital for sustaining developmentally immature organ systems, including prolonged placement of indwelling central lines, frequent laboratory tests, and non-invasive respiratory support or mechanical ventilation, may also promote sepsis-related morbidity and lead to protracted hospital stays. 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 overall upper limit of 3% mortality for term infants).

The development of neonatal co-morbidities, such as severe intraventricular hemorrhage (IVH), periventricular leukomalacia (PVL), retinopathy of prematurity (ROP), patent ductus arteriosus (PDA), and neonatal death, have been reported as complications resulting from placental chorioamnionitis and funisitis in multiple studies. The direct association between increased sepsis-related mortality and decreased gestational age is also well documented, but 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 \( \leq 32 \) 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 – other specified sepsis, A41.9 – sepsis, unspecified organism, P36.8 – other bacterial sepsis of newborn, P36.9 – Bacterial sepsis of newborn, unspecified, R65.20 – severe sepsis without septic shock, R65.21 - severe sepsis with septic shock, R68.89 – other general symptoms and signs, Z05.1 – observation and evaluation of newborn for suspected infectious condition ruled out, and Z91.89 – other specified personal risk factor, not elsewhere classified), or treatment with antibiotics \( \geq 5 \) 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\textsuperscript{26-29}. 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 \( \geq 5 \) 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. Determination of contaminating blood isolates were made at the discretion of the attending neonatologist, if the organism was known to be a possible contaminant [i.e., coagulase-negative \textit{Staphylococcus} (CoNS) or \textit{S. epidermidis}] or if the infant received < 5 days of antimicrobial therapy. Infants routinely completed blood culture analysis using a single 1.0 mL peripheral blood volume sample, unless a central line was in place for which a 1.0 mL peripheral and central blood volume sample were simultaneously tested.

While all patient deaths were recorded and correlated to their proximity to their sepsis episode, \textit{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. Acute clinical deterioration, including increased apnea/bradycardia/desaturation events, respiratory decompensation requiring increased support or intubation with mechanical ventilation, or demonstration of acute onset end-organ damage or failure, may lead a clinician to determine the event as clinically relevant. Institution prescribing guidelines for antimicrobial therapeutics were similar among hospital systems. Decisions to prolong antibiotics beyond fourteen days were attending neonatologist-dependent and typically based on the source of the primary infection.
and/or clinical course in conjunction with a pediatric infectious disease consultation. 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\textsuperscript{30, 31}.

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 $\geq 5$, 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, as this patient had a single documented negative culture, 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 (intraventricular hemorrhage) 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). In our cohort, all infants except for one had a diagnosis of NEC or SIP that preceded their diagnosis of bacteremia. Patients 10, 12, and 13 had their blood cultures obtained after the intestinal perforation was diagnosed (positive for *S. aureus*, *Candida albicans*, *Enterobacter cloacae*, respectively), while Patient 11 was convalescing from *E. coli* EOS when they developed a SIP six days into antimicrobial therapy, with a negative blood culture obtained at the time of their SIP diagnosis.

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 blood culture-negative sepsis highlight the importance of
concurrent comorbidities in relation to sepsis mortality in this patient cohort and the need to
develop a consensus definition for neonatal sepsis. 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 periventricular
leukomalacia (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).
While each of these patients fulfilled our *a priori* definition of sepsis-related death and had culture-
negative sepsis listed as a contributing factor to mortality in their medical records, it remains most
plausible that non-infectious comorbidities and congenital anomalies were primarily involved in
their deaths.

Two deaths were classified as “not sepsis related” after careful review of their medical
records and failure to meet our *a priori* definition. 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. 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. 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\(^\text{20, 32}\). 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 may, therefore, lead clinicians to administer prolonged antibiotic courses, even if presented with a negative blood culture result\(^\text{6}\).

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\(^\text{14, 18, 20, 33-35}\). While half of all EOS deaths will occur within the first three days of life\(^\text{20}\), an estimated 40% of neonates with LOS
died more than 7 days from their last blood culture. 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. 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. 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, 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 IVH, NEC, 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 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, the additional diagnosis of sepsis may have further facilitated discussions of initiation of comfort protocols with the patient’s parents and family.

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, excluding other important sources of infection such as cerebrospinal fluid or urine. 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.

In conclusion, inherent difficulties remain in our ability to accurately assess sepsis-related mortality in preterm neonates. Because current published definitions of neonatal sepsis are heterogeneous (bacteremia +/- culture negative sepsis) and without considerations for new onset organ dysfunction, the establishment of a consensus definition is critical. The primary use of bacteremia to diagnose neonatal sepsis falsely assumes only bacteremic patients can experience life-threatening organ dysfunction resulting in sepsis-related mortality. 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 improve patient outcomes.  

A higher number of severe comorbidities were observed in our VLBW infant cohort who died following a diagnosis of sepsis compared to our historic baseline NICU data of approximately 40%. Future research should examine the number and type of comorbidities and their role in sepsis related mortality, as these common conditions may artificially inflate sepsis-related case-fatality rates. As emerging therapeutics and technologies are engineered to remedy sepsis-mediated pathophysiologic processes, an accurate assessment of the incidence of sepsis will be vital to determine study feasibility, calculate sample size, and validate outcome measures. Future studies should incorporate data regarding confounding factors and/or comorbidities that contribute to neonatal sepsis-related mortality, including the transition to comfort care protocols.
Table 1. Patient Demographics and Infection Evaluations, 2012-2015

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

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

*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

<table>
<thead>
<tr>
<th>Characteristic†</th>
<th>Total (n = 198)</th>
<th>Early Onset (n = 11)</th>
<th>Late Onset (n = 98)</th>
<th>Early Onset (n = 64)</th>
<th>Late Onset (n = 25)</th>
<th>P-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Survival to Discharge, n (%)</td>
<td>184</td>
<td>9 (81.8)</td>
<td>93 (94.9)</td>
<td>60 (93.8)</td>
<td>22 (88.0)</td>
<td>0.20</td>
</tr>
<tr>
<td>Yes</td>
<td>(92.9)</td>
<td>9 (81.8)</td>
<td>93 (94.9)</td>
<td>60 (93.8)</td>
<td>22 (88.0)</td>
<td>0.20</td>
</tr>
<tr>
<td>No</td>
<td>14 (7.1)</td>
<td>2 (18.2)</td>
<td>5 (5.1)</td>
<td>4 (6.2)</td>
<td>3 (12.0)</td>
<td>0.20</td>
</tr>
<tr>
<td>Sepsis-Related Death**</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.78</td>
</tr>
<tr>
<td>Yes</td>
<td>12 (85.7)</td>
<td>2 (100.0)</td>
<td>4 (80.0)</td>
<td>4 (100.0)</td>
<td>2 (66.7)</td>
<td>0.78</td>
</tr>
<tr>
<td>No</td>
<td>2 (14.3)</td>
<td>0 (0.0)</td>
<td>1 (20.0)</td>
<td>0 (0.0)</td>
<td>1 (33.3)</td>
<td>0.78</td>
</tr>
<tr>
<td>Transition of Care</td>
<td>10 (71.4)</td>
<td>2 (100.0)</td>
<td>3 (60.0)</td>
<td>3 (75.0)</td>
<td>2 (66.7)</td>
<td>0.78</td>
</tr>
</tbody>
</table>

†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

<table>
<thead>
<tr>
<th>Patient</th>
<th>GA at Birth</th>
<th>Birth Weight (gm)</th>
<th>Age at Last Blood Culture (days)</th>
<th>Age at Death (days)</th>
<th>Max nSOFA score</th>
<th>Organism</th>
<th>Sepsis-Related Death</th>
<th>Transition to Comfort Care</th>
<th>Associated Clinical Conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>23</td>
<td>575</td>
<td>44</td>
<td>103</td>
<td>7</td>
<td>Culture Negative Sepsis</td>
<td>No</td>
<td>Yes</td>
<td>Worsening post-hemorrhagic changes from grade 4 IVH with severely abnormal EEG; previous h/o intestinal perforation</td>
</tr>
<tr>
<td>2</td>
<td>25</td>
<td>610</td>
<td>52</td>
<td>117</td>
<td>1</td>
<td><em>Staphylococcus epidermitis</em></td>
<td>No</td>
<td>No</td>
<td>Pulseless ventricular tachycardia associated with CDH and CHD</td>
</tr>
<tr>
<td>3</td>
<td>26</td>
<td>940</td>
<td>0</td>
<td>2</td>
<td>12</td>
<td>Culture Negative Sepsis</td>
<td>Yes</td>
<td>No</td>
<td>Hepatic hemorrhage with intrabdominal bleeding; metabolic acidosis; coagulopathy; acute severe pulmonary hemorrhage</td>
</tr>
<tr>
<td>4</td>
<td>26</td>
<td>790</td>
<td>6</td>
<td>8</td>
<td>7</td>
<td>Culture Negative Sepsis</td>
<td>Yes</td>
<td>Yes</td>
<td>New onset right grade 3 and left grade 4</td>
</tr>
<tr>
<td>5</td>
<td>24</td>
<td>605</td>
<td>10</td>
<td>10</td>
<td>12</td>
<td>Culture Negative Sepsis</td>
<td>Yes</td>
<td>Yes</td>
<td>NEC; severe metabolic acidosis</td>
</tr>
<tr>
<td>6</td>
<td>31</td>
<td>1528</td>
<td>30</td>
<td>33</td>
<td>14</td>
<td>Culture Negative Sepsis</td>
<td>Yes</td>
<td>Yes</td>
<td>Hypoplastic left heart syndrome; NEC s/p laparotomy; IVH with evolving PVL</td>
</tr>
<tr>
<td>7</td>
<td>31</td>
<td>1800</td>
<td>2</td>
<td>9</td>
<td>6</td>
<td>Culture Negative Sepsis</td>
<td>Yes</td>
<td>Yes</td>
<td>Acute onset bilateral grade 4 IVH, TEF with esophageal atresia, duodenal atresia, and double outlet right ventricle</td>
</tr>
<tr>
<td>8</td>
<td>24</td>
<td>620</td>
<td>0</td>
<td>0</td>
<td>8</td>
<td>Culture Negative Sepsis</td>
<td>Yes</td>
<td>Yes</td>
<td>Intestinal perforation, profound metabolic acidosis, bleeding, and hypotension</td>
</tr>
<tr>
<td>9</td>
<td>24</td>
<td>610</td>
<td>4</td>
<td>4</td>
<td>11</td>
<td><em>Staphylococcus epidermitis</em></td>
<td>Yes</td>
<td>No</td>
<td>Severe pulmonary hemorrhage, bilateral grade 3 IVH</td>
</tr>
<tr>
<td>10</td>
<td>31</td>
<td>1380</td>
<td>11</td>
<td>14</td>
<td>15</td>
<td><em>Staphylococcus aureus</em></td>
<td>Yes</td>
<td>Yes</td>
<td>Left-sided CDH, severe pulmonary hypertension, and intestinal perforation</td>
</tr>
<tr>
<td>11</td>
<td>25</td>
<td>791</td>
<td>2</td>
<td>8</td>
<td>8</td>
<td>Escherichia coli</td>
<td>Yes</td>
<td>Yes</td>
<td>Recovering from <em>E. coli</em> sepsis (6 days into treatment) with acute intestinal perforation; pre-existing right grade 3; left grade 4 IVH</td>
</tr>
<tr>
<td>12</td>
<td>23</td>
<td>646</td>
<td>6</td>
<td>6</td>
<td>4</td>
<td><em>Candida albicans</em></td>
<td>Yes</td>
<td>Yes</td>
<td>Intestinal perforation with right grade 4; left grade 3 IVH</td>
</tr>
<tr>
<td>13</td>
<td>23</td>
<td>561</td>
<td>7</td>
<td>7</td>
<td>6</td>
<td><em>Enterobacter cloacae</em></td>
<td>Yes</td>
<td>Yes</td>
<td>Intestinal perforation with right grade 4; left grade 3 IVH</td>
</tr>
<tr>
<td>14</td>
<td>24</td>
<td>709</td>
<td>0</td>
<td>0</td>
<td>12</td>
<td>Escherichia coli</td>
<td>Yes</td>
<td>Yes</td>
<td>Severe metabolic acidosis; coagulopathy, anemia, poor cardiac function; bilateral pneumonia; bilateral IVH</td>
</tr>
</tbody>
</table>

EEG: electroencephalogram; CHD: congenital heart disease; TEF: tracheoesophageal fistula; CDH: congenital diaphragmatic hernia; IVH: intraventricular hemorrhage; NEC: necrotizing enterocolitis; PVL: periventricular leukomalacia
<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Total (n = 162)</th>
<th>Early (n = 13)</th>
<th>Late (n = 149)</th>
<th>P-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pathogen, n (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Gram-Positive</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Coagulase-negative <em>Staphylococcus</em></td>
<td>86 (53.1)</td>
<td>2 (15.4)</td>
<td>84 (56.4)</td>
<td></td>
</tr>
<tr>
<td><em>Enterococcus</em> spp.</td>
<td>18 (11.1)</td>
<td>1 (7.7)</td>
<td>17 (11.4)</td>
<td></td>
</tr>
<tr>
<td><em>Staphylococcus aureus</em></td>
<td>17 (10.5)</td>
<td>0 (0.0)</td>
<td>17 (11.4)</td>
<td></td>
</tr>
<tr>
<td>Group B <em>Streptococcus</em></td>
<td>5 (3.1)</td>
<td>1 (7.7)</td>
<td>4 (2.7)</td>
<td></td>
</tr>
<tr>
<td><em>Enterobacter</em> spp.</td>
<td>4 (2.5)</td>
<td>0 (0.0)</td>
<td>4 (2.7)</td>
<td></td>
</tr>
<tr>
<td>Other <em>Streptococcus</em> spp.</td>
<td>1 (0.6)</td>
<td>0 (0.0)</td>
<td>1 (0.7)</td>
<td></td>
</tr>
<tr>
<td><em>Bacillus</em> spp.</td>
<td>1 (0.6)</td>
<td>0 (0.0)</td>
<td>1 (0.7)</td>
<td></td>
</tr>
<tr>
<td><em>Micrococcus</em> spp.</td>
<td>1 (0.6)</td>
<td>0 (0.0)</td>
<td>1 (0.7)</td>
<td></td>
</tr>
<tr>
<td><strong>Gram-Negative</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Escherichia coli</em></td>
<td>9 (5.6)</td>
<td>6 (46.2)</td>
<td>3 (2.0)</td>
<td></td>
</tr>
<tr>
<td><em>Klebsiella pneumoniae</em></td>
<td>5 (3.1)</td>
<td>1 (7.7)</td>
<td>4 (2.7)</td>
<td></td>
</tr>
<tr>
<td><em>Pseudomonas</em> spp.</td>
<td>3 (1.9)</td>
<td>1 (7.7)</td>
<td>2 (1.3)</td>
<td></td>
</tr>
<tr>
<td><em>Acinetobacter</em> spp.</td>
<td>1 (0.6)</td>
<td>0 (0.0)</td>
<td>1 (0.7)</td>
<td></td>
</tr>
<tr>
<td><em>Citrobacter koseri</em></td>
<td>1 (0.6)</td>
<td>1 (7.7)</td>
<td>0 (0.0)</td>
<td></td>
</tr>
<tr>
<td><em>Salmonella</em> spp.</td>
<td>1 (0.6)</td>
<td>0 (0.0)</td>
<td>1 (0.7)</td>
<td></td>
</tr>
<tr>
<td><em>Serratia</em> spp.</td>
<td>1 (0.6)</td>
<td>0 (0.0)</td>
<td>1 (0.7)</td>
<td></td>
</tr>
<tr>
<td><strong>Fungal</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Candida</em> spp.</td>
<td>7 (4.3)</td>
<td>0 (0.0)</td>
<td>7 (4.7)</td>
<td></td>
</tr>
<tr>
<td><strong>Other</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Paenibacillus</em> spp.</td>
<td>1 (0.6)</td>
<td>0 (0.0)</td>
<td>1 (0.7)</td>
<td></td>
</tr>
</tbody>
</table>

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.
Acknowledgements:

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Author’s Contribution:

Study Concept and design: Barnette, Wynn, and Lawrence

Acquisition of data: Barnette, Lazar, and Richardson.

Analysis and interpretation of data: Barnette, Schumacher, Armenta, and Lawrence.

Drafting of Manuscript: Barnette and Lawrence

Critical Revision: All authors
References:


