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Late-Onset Sepsis in Extremely Premature Infants: 2000–2011

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Abstract

Background—Late-onset sepsis (LOS) is an important cause of death and neurodevelopmental impairment in premature infants. The purpose of this study was to assess overall incidence of

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LOS, distribution of LOS-causative organisms, and center variation in incidence of LOS for extremely premature infants over time.

Methods—In a retrospective analysis of infants 401–1000 g birth weight and 22–28 6/7 weeks' gestational age born at 12 NICHD Neonatal Research Network centers in the years 2000–2005 (Era 1) or 2006–2011 (Era 2) who survived >72 hours, we compared the incidence of LOS and pathogen distribution in the 2 eras using the chi-square test. We also examined the effect of birth year on the incidence of LOS using multivariable regression to adjust for non-modifiable risk factors and for center. To assess whether the incidence of LOS was different among centers in Era 2, we used a multivariable regression model to adjust for non-modifiable risk factors.

Results—10,131 infants were studied. LOS occurred in 2083/5031 (41%) infants in Era 1 and 1728/5100 (34%) infants in Era 2 (*P*<.001). Birth year was a significant predictor of LOS on adjusted analysis, with birth years 2000–2009 having a significantly higher odds of LOS than the reference year 2011. Pathogens did not differ, with the exception of decreased fungal infection (P<.001). In Era 2, nine centers had significantly higher odds of LOS compared with the center with the lowest incidence.

Conclusions—The incidence of LOS decreased over time. Further investigation is warranted to determine which interventions have the greatest impact on infection rates.

Keywords

late-onset sepsis; extremely premature infants; neonatal intensive care unit

Late-onset sepsis (LOS, occurring after 3 postnatal days) is associated with increased mortality and morbidity among infants hospitalized in the neonatal intensive care unit (NICU).[1] Extremely low birth weight (ELBW) infants are at particularly high risk for infection due to multiple factors including immaturity of the immune system, prolonged hospitalization, and frequent invasive procedures such as endotracheal intubation and intravascular catheterization. LOS is associated with poor outcomes, including 18% mortality and prolonged hospital stay.[1] Among surviving ELBW infants, 65% have at least one suspected or culture-proven infection episode during their hospitalization after birth, and 35–37% have culture-proven LOS.[1,2] ELBW infants with LOS, even without meningitis, also have significantly increased rates of neurodevelopmental impairment compared to those not infected.[2]

Given the morbidity and mortality associated with LOS, strategies have been implemented in NICUs worldwide to decrease the incidence of infection. Interventions include maternal chemoprophylaxis for prevention of early-onset group B streptococcal infection, rigorous hand hygiene procedures, improved central line care with central line bundles, antifungal prophylaxis, and careful attention to NICU design and staffing.[3–10] Several studies have suggested a decreased incidence of LOS over time,[5,6,11] but others have shown a stable to slightly increased incidence.[3,12,13] The purpose of this study was to assess: 1) the incidence of LOS over time, 2) the distribution of LOS-associated pathogens over time, and 3) center variation in incidence of LOS among extremely premature infants cared for at the academic centers of the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) Neonatal Research Network (NRN).

METHODS

Subjects

This was a retrospective analysis of a prospective cohort study of infants entered into the Generic Database of the NRN who were born between January 1, 2000, and December 31, 2011, and survived >72 hours after birth. This study period was selected to coincide with NRN funding periods in order to minimize variability among centers present in the NRN. Data from the 12 centers that participated in the NRN for the entire study period (Brown University, Case Western Reserve University, Cincinnati Children's Hospital Medical Center, Duke University, Emory University, Indiana University, Stanford University, University of Alabama at Birmingham, University of Texas Southwestern Medical Center, University of Texas Health Science Center at Houston, Wayne State University, and Yale University) were included. Infants studied had a birth weight of 401–1000 g and gestational age of 22 0/7 – 28 6/7 weeks. Clinical data for these infants were recorded and processed as described previously.[14] The institutional review board at each center approved the NRN Generic Database.

Definitions

To assess trends in LOS over time, data were divided into 2 eras: 2000–2005 (Era 1) or 2006–2011 (Era 2). The cutoff between eras was selected *a priori* to achieve an equal length of time for each era (and thus roughly equal numbers of infants in each group). The primary outcome of the study was LOS. LOS was defined as the first episode of a positive blood culture for a bacterial or fungal organism that was obtained after 72 hours of life. We included positive blood cultures for potential contaminants, such as coagulase-negative staphylococci (CoNS), if the infants were treated with antimicrobials for ≥5 days.[1] As a sensitivity analysis to determine whether this more inclusive definition of LOS could have affected the results, we repeated our primary analysis using a definition of LOS that excluded episodes caused by CoNS and other possible contaminants. Secondary outcomes included death (all-cause mortality) prior to discharge, death associated with infection prior to discharge, length of hospital stay (including infants who died), and postmenstrual age at discharge. Death was determined to be associated with infection if the attending physician noted that, based on clinical evidence and autopsy findings, infection was the underlying, proximate disease that initiated the series of events leading to death. There was no specified timing between LOS and death that limited physicians from choosing infection as a contributory cause of death.

We evaluated the distribution of organisms causing the first episode of LOS in our cohort of infants. Due to differences in database entry practices over time (in 2000 and 2001, causative organisms were not assigned to a particular episode of sepsis), we could not identify the causative organism for 189 episodes of LOS occurring in Era 1. These episodes were excluded from analysis of organism types but included in the overall analyses.

Statistical Analysis

Assessment of LOS incidence over time—We evaluated the change in LOS over time using 2 methods. First, a direct comparison between eras allowed us to illustrate differences

in demographics, pathogens, and clinical characteristics that could explain potential differences. We compared the incidence of the primary and secondary outcomes in the 2 eras using the chi-square test (categorical variables) and the Wilcoxon rank sum test (continuous variables). We repeated this analysis of secondary outcomes among just infants with LOS and also generated logistic or linear regression models with gestational age as an additional covariate. For our second approach to assessing incidence of LOS over time, we performed an additional multivariable regression analysis that included the above covariates (including center) in addition to birth year.

Assessment of organ distribution over time—We compared the distribution of LOS pathogens between Eras 1 and 2 using the chi-square test.

Assessment of center variation—To assess whether the incidence of LOS was different among centers in Era 1 and Era 2, we used a logistic regression model with center as a fixed effect to adjust for known risk factors including gestational age (using 28 weeks as a reference), birth weight, small for gestational age (SGA), race, sex, antenatal steroids, and multiple births. The center with the lowest incidence of LOS in each Era was used as the reference center.

All *P*-values were 2-tailed and were considered to be significant for values <.05. Analyses were conducted using SAS 9.3.

RESULTS

A total of 10,131 infants were included in the study (5031 in Era 1 and 5100 in Era 2). Overall median birth weight was 760 g (interquartile range [IQR]: 646–875), and the median gestational age was 25 weeks (24–27). Infants in the 2 eras were similar in gestational age, birth weight, SGA status, sex, and multiple births (Table 1). In Era 2, a significantly higher proportion of infants were exposed to antenatal steroids and were delivered by cesarean section (*P*<.001).

Overall, LOS occurred in 3811/10,131 infants (38%). The overall incidence of LOS declined from 41% to 34% between Era 1 and Era 2 (Table 2; *P*<.001). In the longitudinal analysis of incidence of LOS, birth year was a significant predictor of LOS on adjusted analysis, with all birth years 2000–2009 having a significantly higher odds of LOS than the reference year 2011 (Figure 1). The difference in incidence of LOS between Eras 1 and 2 remained significant even when fungal organisms were excluded (Era 1: 38% vs. Era 2: 32%; *P*<.001) and when episodes of CoNS and other possible contaminants were excluded (Era 1: 24% vs. Era 2: 17%; *P*<.001). Among all patients, length of hospital stay was 5 days longer and infants were discharged at a slightly later postmenstrual age in Era 2 compared to Era 1 (*P*<.001). After adjustment for gestational age, these differences remained significant in the overall population, but the differences among the subset of infants with LOS were no longer significant. There was no difference in the overall incidence of death or death associated with infection between the 2 eras. Of the infants with LOS, a higher proportion with gram-positive organisms died in Era 2 (297/1340, 22%) compared to Era 1 (253/1430, 18%; *P*<.01). There was no difference among organism types in death associated with infection (Table

2). In both eras, a higher proportion of infants with LOS died compared to infants without LOS (Era 1: 482/2076 [23%] vs. 549/2940 [19%] without LOS, $P<.001$; Era 2: 447/1727 [26%] vs. 579/3367 [17%], $P<.001$).

Among episodes for which organism data were available, 2657/3624 (73%) were caused by gram-positive organisms only, 603/3624 (17%) were caused by gram-negative organisms only, 241/3624 (7%) were caused by fungal organisms only, and 123/3624 (3%) were polymicrobial, with multiple types of organisms (Table 3). The proportion of episodes of LOS caused by gram-positive organisms and gram-negative organisms did not change between the 2 study periods, but the proportion of episodes caused by fungal organisms was lower in Era 2 (111/1728, 6% vs. 188/1896, 10%; $P<.001$). The proportion of polymicrobial infections was significantly lower in Era 2 compared to Era 1 (44/1728, 2.6% vs. 79/1896, 4.2%; $P=.007$).

Of the 12 centers, 7 showed a significantly lower incidence of LOS in Era 2 compared to Era 1 (Figure 2A). On multivariable regression, 9 out of 11 centers had significantly higher odds of LOS in Era 2 than the reference center, which had the lowest incidence ($P<.05$; Figure 2B). Gestational age of 23, 24, 25, and 26 weeks (compared to reference, 28 weeks), birth weight, and male sex were significant predictors of LOS ($P<.05$). Multiple birth, SGA, race, and exposure to antenatal steroids were not significant covariates in the model. Similar center variation was also noted in Era 1, with all centers showing significantly higher odds of LOS than the reference center (data not shown).

DISCUSSION

This study demonstrates a decline in LOS over time among extremely preterm infants cared for at 12 academic centers that participated in the NICHD NRN over a 12-year period, 2000–2011. A reduced incidence of infection was found in 7 of 12 study centers, with no centers showing significantly higher incidence of LOS in Era 2 compared to Era 1. The decrease in LOS associated with increasing birth year remained significant after adjustment for center and other risk factors. The 7% absolute change (17% relative change) in incidence of LOS represents a clinically significant finding and validates the efforts that NICUs across the United States and other countries have made to reduce infection. The relative decrease in incidence of LOS was even higher (29%) when CoNS and other potential contaminants were excluded. Our findings are consistent with other studies that have suggested a decrease in LOS over time. A single-center study showed an improvement in LOS incidence in premature infants 1 year after relocation of a nursery to a different facility.[5] Another single-center study reported decreased rates of nosocomial infection of 26–29% in the first 3 years after several catheter care interventions, including improved training and education in addition to implementation of a specialty nursing team for catheter care.[15] Twenty-four NICUs in Ohio instituted a quality improvement collaborative to improve catheter care and demonstrated a 20% reduction in incidence of LOS over 16 months,[6] while another study of 2 hospitals in Minnesota achieved 50% reduction in nosocomial infection after the institution of quality improvement efforts.[9] Quality-improvement interventions were also associated with decreased rates of nosocomial infection between 1994–1996 in 6 NICUs in the Vermont Oxford Network, between 2007–2013 among 330 NICUs in the Pediatrix

network, and between 2004–2013 at Yale-New Haven Children's Hospital's NICU.[10,16,17] These studies demonstrate that quality improvement interventions can lead to decreased incidence of infection.

Several older studies failed to demonstrate a reduction in LOS over time, suggesting that more recent interventions have been more beneficial. An older report from Yale-New Haven Children's Hospital showed that from 1989–2003, the number of LOS episodes increased significantly.[3] Two previous studies from the NRN have evaluated the incidence of LOS in infants <1500 g and <25 weeks' gestational age at birth.[13,18] The incidence was increased in 2002–2004 (59%) compared to 1991–2001 (50%). These proportions are both increased from 1991–1994 (45%) and 1995–1998 (44%). The incidence of LOS in the most recent era (2006–2011) of the current study was 38%, which is lower than these previous reports from the NRN. However, it should be noted that the current study represents a slightly different population of infants (those <1000 g and <28 weeks gestational age at birth). Of note, older NRN studies were performed prior to the introduction of central line bundles, antibiotic stewardship, and antifungal prophylaxis. Lack of antibiotic stewardship (i.e., broad spectrum antibiotics and longer initial empiric antibiotic courses) has been associated with increased risk of sepsis.[19–21] The most recent NRN Generic Database report confirmed an increased incidence of LOS through 2004 and a decreasing incidence from 2005 to 2012, although this report did not quantify center differences or examine pathogens.[16]

We found that despite the association of LOS with adverse outcomes in ELBW infants, the decrease in LOS over time was not accompanied by a decrease in mortality or length of hospital stay. The explanation for this finding is unclear. A slightly higher percentage of infants with LOS died in Era 2 compared to Era 1. While more infants with gram-positive infections died in Era 2, there was no difference in infection-associated death among infants with gram-positive infections between Eras 1 and 2. It is possible that the episodes of LOS prevented in the more recent era would have been milder episodes, and thus the elimination of these episodes had no impact on overall mortality or length of stay. Infants with gram-positive infections may also represent a group of infants at higher risk of death with a longer exposure to invasive devices, such as catheters, and the gram-positive organisms were not the cause of death. In addition, although the difference was not significant, the median gestational age was 1 week lower in Era 2 than Era 1, which may account for the lack of impact on mortality and the longer length of stay. When we adjusted for gestational age, there was no significant difference in length of hospital stay or postmenstrual age at discharge among infants with LOS.

Multiple previous studies have shown variation in the risk of infection across NICUs.[19,22] The incidence of LOS in Era 2 of our study varied markedly across centers, with a maximum odds ratio of 4.8 compared to the reference center. We elected to use the low incidence center as the reference center rather than comparing all sites to a central tendency because we thought that after risk adjustment, if there were truly no significant differences or potential for a best practice to be identified, no center would be statistically different from the low center. We found the odds of LOS at nine out of 11 sites to be statistically significantly higher than the reference center after risk adjustment; we believe this strengthens the case that "best practices" could be identified and that LOS may be

preventable in many cases. The reason why some centers were able to demonstrate a more robust improvement in infection risk over time remains unclear. We postulate that multiple factors contribute to infection risk at a given center, including hand hygiene policies, differences in central line bundle practices and staff training, antibiotic regimens typically used at a particular center (type and duration), nursery design and staffing, use of antifungal prophylaxis, and underlying differences in genetic risk of infection. Previous studies on human milk in low birth weight infants have also shown a dose-related impact on neonatal outcomes.[23,24] Unfortunately, our study was limited in that our database contains no information about the timing and duration of quality improvement projects. In addition, information across the entire study period about centers' antimicrobial use practices and details about human milk feeding were not available, which represents an additional limitation. Given the growing body of literature on the role of lactoferrin and probiotics in infection prevention, further study is warranted on the effect of varying feeding and medication practices across institutions.[25,26]

The strengths of our study include the large sample size of extremely preterm infants, uniform definitions and data collection over time, and ability to observe the incidence of LOS across time and across centers in multiple regions in the United States. Our study was limited by its design in that it was a retrospective analysis of a prospective observational study cohort. Regression models in retrospective cohort studies may omit variables that could influence outcomes. Because death associated with infection was defined according to clinician diagnosis, this variable could have been subject to reporting bias. In addition, data on some organisms were not available in Era 1, which may have affected our analysis of the organism distribution. The number of positive cultures for CoNS in each episode was also not available, and therefore we relied on a clinical definition for infection that has been used previously within our network.[1] Use of this definition may have overestimated the true incidence of LOS in our cohort. We also did not collect information on one of the most significant risk factors for LOS, the presence of central catheters. Knowledge of a change in the use or duration of central catheters in this population could impact our understanding of the change in incidence of LOS over time. We observed a lower incidence of fungal infections in Era 2, but we cannot speculate on the cause for this change, as we did not have data on the use of antifungal prophylaxis at participating centers. We also did not have data regarding timing of infection prevention processes or programs that may have been associated with the variation in the incidence of LOS across different centers. Finally, although the NRN overall mortality among ELBW infants has been dropping over time,[16] we did not note a difference in death associated with infection.

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Appendix

The following investigators, in addition to those listed as authors, participated in this study: NRN Steering Committee Chairs: Alan H. Jobe, MD, PhD, University of Cincinnati (2003–2006), and Michael S. Caplan, MD, University of Chicago, Pritzker School of Medicine (2006–2011); Alpert Medical School of Brown University and Women & Infants Hospital of Rhode Island (U10 HD27904) – William Oh, MD, Angelita M. Hensman, RN, BSN, Kristin Basso, RN, MaT; Case Western Reserve University, Rainbow Babies & Children's Hospital (U10 HD21364, M01 RR80) – Avroy A. Fanaroff, MD; Cincinnati Children's Hospital Medical Center, University Hospital, and Good Samaritan Hospital (U10 HD27853, M01 RR8084) – Kurt Schibler, MD, Edward F. Donovan, MD, Barbara Alexander, RN, Kate Bridges, MD, Cathy Grisby, BSN, CCRC, Marcia Worley Mersmann, RN, Holly L. Mincey, RN, BSN, Jody Hessling, RN, Lenora Jackson, Kristin Kirker, Estelle E. Fischer, MHSA, MBA, Greg Muthig, BS; Duke University School of Medicine, University Hospital, Alamance Regional Medical Center, and Durham Regional Hospital (U10 HD40492, M01 RR30) – Ronald N. Goldberg, MD, C. Michael Cotten, MD, MHS, Kathy J. Auten, MSHS, Kimberley A. Fisher, PhD, FNP-BC, IBCLC, Melody B. Lohmeyer, RN, MSN, Sandra Grimes, RN, BSN, BSN, Katherine A. Foy, RN; Emory University, Children's Healthcare of Atlanta, Grady Memorial Hospital, and Emory University Hospital Midtown (U10 HD27851, M01 RR39) – David P. Carlton, MD; NICHD – Linda L. Wright, MD, Elizabeth M. McClure, MEd, Stephanie Wilson Archer, MA; Indiana University, University Hospital, Methodist Hospital, Riley Hospital for Children, and Wishard Health Services (U10 HD27856, M01 RR750) – Brenda B. Poindexter, MD, MS, James A. Lemons, MD, Dianne E. Herron, RN, Lucy C. Miller, RN, BSN, CCRC, Leslie Dawn Wilson, BSN CCRC; RTI International (U10 HD36790) – W. Kenneth Poole, PhD, Dennis Wallace, PhD, Jeanette O'Donnell Auman, BS, Margaret Crawford, BS, CCRP, Betty K. Hastings, Carolyn M. Petrie Huitema, MS, CCRP, Kristin M. Zaterka-Baxter, RN, BSN, CCRP; Stanford University, California Pacific Medical Center, Dominican Hospital, El Camino Hospital, and Lucile Packard Children's Hospital (U10 HD27880, M01 RR70) – David K. Stevenson, MD, Marian M. Adams, MD, Charles E. Ahlfors, MD, Andrew W. Palmquist, RN, Melinda S. Proud, RCP, Robert D. Stebbins, MD; University of Alabama at Birmingham Health System and Children's Hospital of Alabama (U10 HD34216, M01 RR32) – Namasivayam Ambalavanan, MD, Monica V. Collins, RN, BSN, MaEd, Shirley S. Cosby, RN BSN; University of Iowa and Mercy Medical Center (U10 HD53109, M01 RR59) – Karen J. Johnson, RN, BSN, Donia B. Campbell, RNC-NIC, John A. Widness, MD, Dan L. Ellsbury, MD, Tarah T. Colaizy, MD, MPH; University of Texas Southwestern Medical Center at Dallas, Parkland Health & Hospital System and Children's Medical Center Dallas (U10 HD40689, M01 RR633) – Charles R. Rosenfeld, MD, Walid A. Salhab, MD, Luc P. Brion, MD, P. Jeannette Burchfield, RN, BSN, Alicia Guzman, Gaynelle Hensley, RN, Melissa H.

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References

1. Stoll BJ, Hansen N, Fanaroff AA, et al. Late-onset sepsis in very low birth weight neonates: the experience of the NICHD Neonatal Research Network. Pediatrics. 2002; 110(2 Pt 1):285–291. [PubMed: 12165580]
2. Stoll BJ, Hansen NI, Adams-Chapman I, et al. Neurodevelopmental and growth impairment among extremely low-birth-weight infants with neonatal infection. JAMA. 2004; 292(19):2357–2365. [PubMed: 15547163]
3. Bizzarro MJ, Raskind C, Baltimore RS, Gallagher PG. Seventy-five years of neonatal sepsis at Yale: 1928–2003. Pediatrics. 2005; 116(3):595–602. [PubMed: 16140698]
4. Bizzarro MJ, Dembry LM, Baltimore RS, Gallagher PG. Changing patterns in neonatal Escherichia coli sepsis and ampicillin resistance in the era of intrapartum antibiotic prophylaxis. Pediatrics. 2008; 121(4):689–696. [PubMed: 18381532]
5. Jones AR, Kuschel C, Jacobs S, Doyle LW. Reduction in late-onset sepsis on relocating a neonatal intensive care nursery. J Paediatr Child Health. 2012; 48(10):891–895. [PubMed: 22897216]
6. Kaplan HC, Lannon C, Walsh MC, Donovan EF. Ohio statewide quality-improvement collaborative to reduce late-onset sepsis in preterm infants. Pediatrics. 2011; 127(3):427–435. [PubMed: 21339274]
7. Trijbels-Smeulders M, de Jonge GA, Pasker-de Jong PC, et al. Epidemiology of neonatal group B streptococcal disease in the Netherlands before and after introduction of guidelines for prevention. Arch Dis Child Fetal Neonatal Ed. 2007; 92(4):F271–276. [PubMed: 17227807]
8. van den Hoogen A, Gerards LJ, Verboon-Maciolek MA, Fleer A, Krediet TG. Long-term trends in the epidemiology of neonatal sepsis and antibiotic susceptibility of causative agents. Neonatology. 2010; 97(1):22–28. [PubMed: 19571584]
9. Payne NR, Barry J, Berg W, et al. Sustained reduction in neonatal nosocomial infections through quality improvement efforts. Pediatrics. 2012; 129(1):e165–173. [PubMed: 22144702]
10. Horbar JD, Rogowski J, Plsek PE, et al. Collaborative quality improvement for neonatal intensive care. NIC/Q Project Investigators of the Vermont Oxford Network. Pediatrics. 2001; 107(1):14–22. [PubMed: 11134428]
11. Wilson-Costello D, Friedman H, Minich N, et al. Improved neurodevelopmental outcomes for extremely low birth weight infants in 2000–2002. Pediatrics. 2007; 119(1):37–45. [PubMed: 17200269]
12. Hintz SR, Kendrick DE, Vohr BR, Poole WK, Higgins RD. Changes in neurodevelopmental outcomes at 18 to 22 months' corrected age among infants of less than 25 weeks' gestational age born in 1993–1999. Pediatrics. 2005; 115(6):1645–1651. [PubMed: 15930228]

13. Hintz SR, Kendrick DE, Wilson-Costello DE, et al. Early-childhood neurodevelopmental outcomes are not improving for infants born at <25 weeks' gestational age. Pediatrics. 2011; 127(1):62–70. [PubMed: 21187312]
14. Stoll BJ, Hansen NI, Bell EF, et al. Neonatal outcomes of extremely preterm infants from the NICHD Neonatal Research Network. Pediatrics. 2010; 126(3):443–456. [PubMed: 20732945]
15. Schelonka RL, Scruggs S, Nichols K, Dimmitt RA, Carlo WA. Sustained reductions in neonatal nosocomial infection rates following a comprehensive infection control intervention. J Perinatol. 2006; 26(3):176–179. [PubMed: 16341027]
16. Stoll BJ, Hansen NI, Bell EF, et al. Trends in care practices, morbidity, and mortality of extremely preterm neonates, 1993–2012. JAMA. 2015; 314(10):1039–1051. [PubMed: 26348753]
17. Bizzarro MJ, Shabanova V, Baltimore RS, Dembry LM, Ehrenkranz RA, Gallagher PG. Neonatal sepsis 2004–2013: the rise and fall of coagulase-negative staphylococci. J Pediatr. 2015; 166(5): 1193–1199. [PubMed: 25919728]
18. Hintz SR, Poole WK, Wright LL, et al. Changes in mortality and morbidities among infants born at less than 25 weeks during the post-surfactant era. Arch Dis Child Fetal Neonatal Ed. 2005; 90(2):F128–133. [PubMed: 15724036]
19. Benjamin DK Jr, Stoll BJ, Gantz MG, et al. Neonatal candidiasis: epidemiology, risk factors, and clinical judgment. Pediatrics. 2010; 126(4):e865–873. [PubMed: 20876174]
20. Cotten CM, Taylor S, Stoll B, et al. Prolonged duration of initial empirical antibiotic treatment is associated with increased rates of necrotizing enterocolitis and death for extremely low birth weight infants. Pediatrics. 2009; 123(1):58–66. [PubMed: 19117861]
21. Cotten CM, McDonald S, Stoll B, et al. The association of third-generation cephalosporin use and invasive candidiasis in extremely low birth-weight infants. Pediatrics. 2006; 118(2):717–22. [PubMed: 16882828]
22. Chien LY, Macnab Y, Aziz K, et al. Variations in central venous catheter-related infection risks among Canadian neonatal intensive care units. Pediatr Infect Dis J. 2002; 21(6):505–511. [PubMed: 12182373]
23. Meinzen-Derr J, Poindexter B, Wrage L, Morrow AL, Stoll B, Donovan EF. Role of human milk in extremely low birth weight infants' risk of necrotizing enterocolitis or death. J Perinatol. 2009; 29(1):57–62. [PubMed: 18716628]
24. Patel AL, Johnson TJ, Engstrom JL, et al. Impact of early human milk on sepsis and health-care costs in very low birth weight infants. J Perinatol. 2013; 33(7):514–519. [PubMed: 23370606]
25. Rao SC, Athalye-Jape GK, Deshpande GC, Simmer KN, Patole SK. Probiotic supplementation and late-onset sepsis in preterm infants: a meta-analysis. Pediatrics. 2016; 137(3):e20153684. [PubMed: 26908700]
26. Pammi M, Abrams SA. Oral lactoferrin for the prevention of sepsis and necrotizing enterocolitis in preterm infants. Cochrane Database Syst Rev. 2015:CD007137. [PubMed: 25699678]

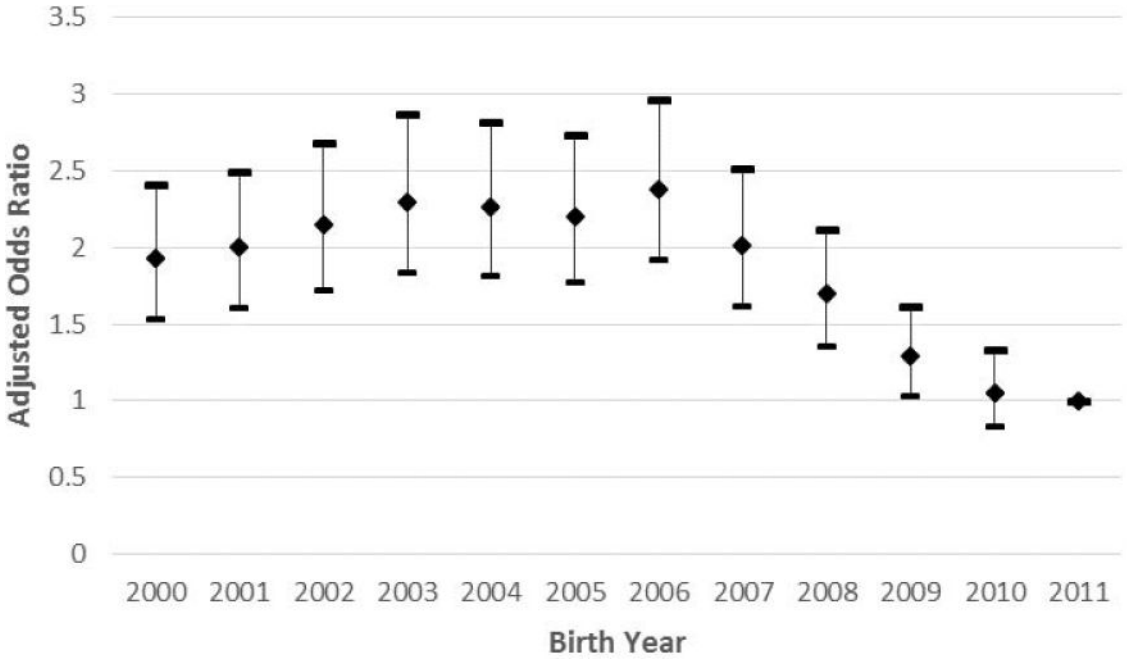

Figure 1.
Adjusted Odds Ratio for Late-Onset Sepsis by Birth Year (Reference: 2011)

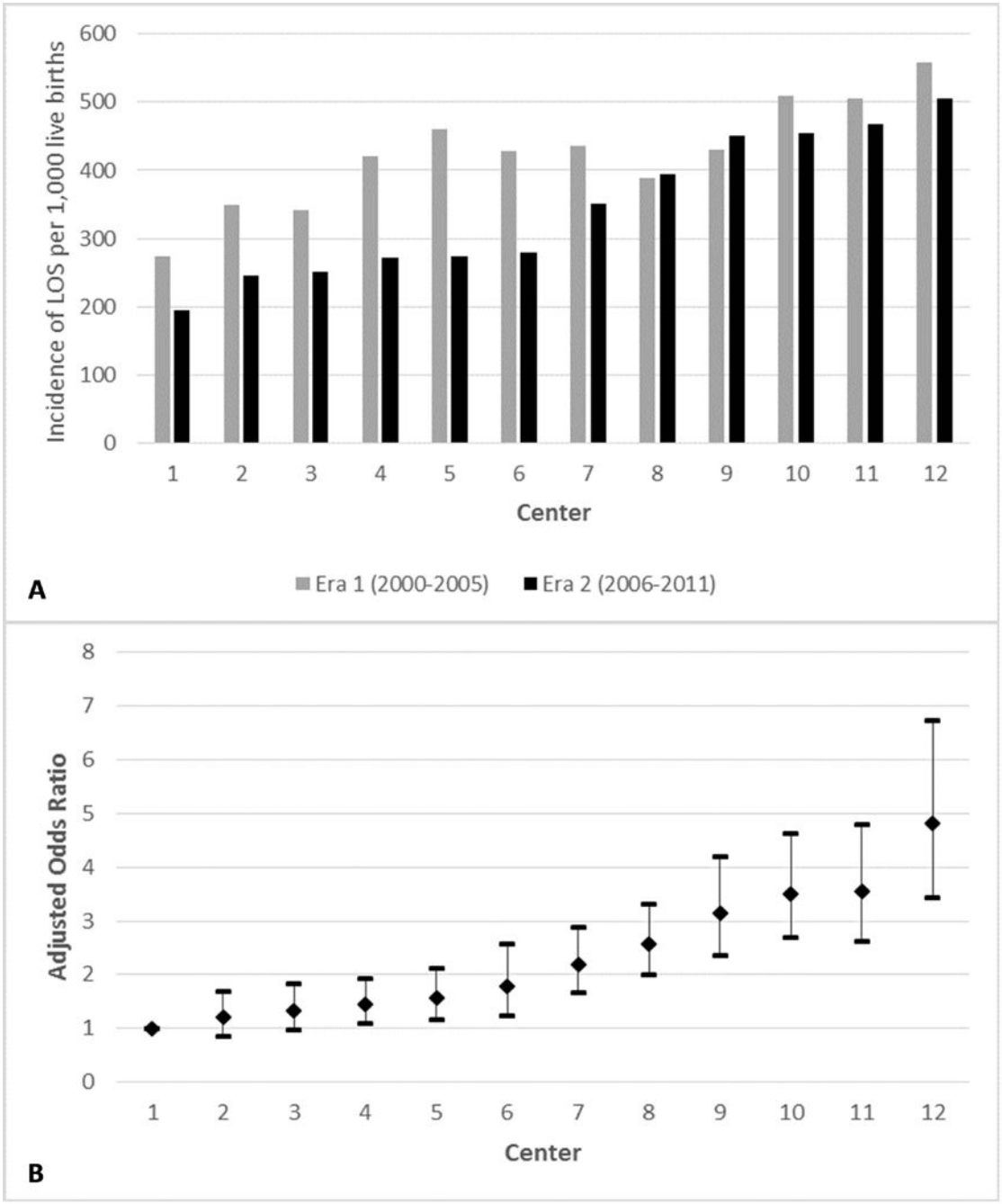

Figure 2.

A) Incidence of Late-Onset Sepsis (LOS) by Center and B) Adjusted Odds Ratio for LOS in Era 2 by Center (Reference: Center 1)

Table 1

Demographics

	Era 1 (2000–05) (N = 5031)	Era 2 (2006–11) (N = 5100)	*P*-value
Birth weight, median (IQR), g	760 (645–876)	760 (650–875)	.60
Gestational age, median (IQR), weeks	26 (24–27)	25 (24–27)	.10
SGA, N (%)	515 (10)	521 (10)	.97
Male, N (%)	2470 (49)	2440 (48)	.21
Race, N (%)			<.001
Black	2387 (47)	2434 (48)	.33
White	2508 (50)	2380 (47)	.01
Other	136 (3)	213 (4)	<.01
Hispanic ethnicity, N (%)	685 (14)	745 (15)	.08
Multiple birth, N (%)	1185 (24)	1239 (24)	.38
Antenatal steroids, N (%)	4173 (83)	4461 (88)	<.001
Cesarean section, N (%)	3098 (62)	3444 (68)	<.001

Abbreviations: IQR, interquartile range; SGA, small for gestational age.

Table 2

Outcomes for Entire Study Cohort and Infants With Late-Onset Sepsis

	Era 1 (2000–05)	Era 2 (2006–11)	Unadjusted *P*-value	Adjusted *P*-value*
All infants	**N=5031**	**N=5100**		
LOS, N (%)	2083 (41)	1728 (34)	<.001	<.001
Death, N (%)	1031 (21)	1026 (20)	.61	.32
Death associated with infection, n/N† (%)	118/1031 (11)	124/1026 (12)	.63	.64
Length of hospital stay, median (IQR), days	87 (65–112)	92 (67–117)	<.001	<.01
Postmenstrual age at discharge, median (IQR), weeks	39 (37–42)	40 (37–42)	<.001	<.01
Infants with LOS	**N=2083**	**N=1728**		
Death, n/N†,‡ (%)	482/2076 (23)	447/1727 (26)	.06	.18
Gram-positive	249/1432 (17)	282/1300 (22)	.01	.02
Gram-negative	119/316 (38)	112/290 (39)	.81	.99
Fungal	62/151 (41)	36/93 (39)	.72	.35
Polymicrobial	52/177 (29)	17/44 (39)	.24	.22
Death associated with infection, n/N† (%)	85/482 (18)	81/447 (18)	.82	.84
Gram-positive	35/249 (14)	42/282 (15)	.76	.75
Gram-negative	26/119 (22)	20/112 (18)	.45	.53
Fungal	16/62 (26)	14/36 (39)	.18	.16
Polymicrobial	8/52 (15)	5/17 (29)	.28	.28
Length of hospital stay, median (IQR), days	98 (73–125)	104 (74–131)	.04	.43
Postmenstrual age at discharge, median (IQR), weeks	40 (38–44)	41 (39–44)	<.001	.43

Abbreviations: LOS, late-onset sepsis; IQR, interquartile range.

*Adjusted for gestational age.

†A separate N is reported when the denominator for the outcome differs from the overall denominator.

‡Excludes 7 infants in Era 1 and 1 infant in Era 2 with missing death information.

Table 3

Organisms Isolated in First Episode of Late-Onset Sepsis

	Era 1 (2000–05) (N = 1896)	Era 2 (2006–11) (N = 1728)	*P*-value
Gram-positive, N (%)	1504 (78%)	1386 (79%)	.55
CoNS	973 (50%)	1007 (57%)	
Staphylococcus aureus	217 (11%)	212 (12%)	
Staphylococcus spp. (unspecified)	136 (7%)	0 (0%)	
Enterococcus spp.	61 (3%)	92 (5%)	
Streptococcus spp. (unspecified)	52 (3%)	0 (0%)	
Group B *Streptococcus*	30 (2%)	45 (3%)	
Streptococcus pneumoniae	1 (0.1%)	1 (0.1%)	
Group A *Streptococcus*	0 (0%)	6 (0.3%)	
Clostridia spp.	0 (0%)	1 (0.1%)	
Possible contaminants[a]	34 (2%)	22 (1%)	
Gram-negative, N (%)	371 (19%)	329 (19%)	.74
Escherichia coli	103 (5%)	117 (7%)	
Klebsiella spp.	92 (5%)	90 (5%)	
Enterobacter spp.	74 (4%)	45 (3%)	
Pseudomonas spp.	58 (3%)	30 (2%)	
Serratia spp.	30 (2%)	24 (1%)	
Citrobacter spp.	7 (0.4%)	10 (0.6%)	
Proteus spp.	4 (0.2%)	6 (0.3%)	
Acinetobacter spp.	2 (0.1%)	6 (0.3%)	
Stenotrophomonas maltophilia	0 (0%)	1 (0.1%)	
Possible contaminants[a]	1 (0.1%)	0 (0%)	
Fungus, N (%)	188 (10%)	111 (6%)	<.001
Candida spp.[b]	182 (9%)	96 (6%)	
Other fungi[c]	6 (0.3%)	15 (0.9%)	

If first episode was associated with multiple organisms, all organisms are included in table.

Abbreviation: CoNS, coagulase-negative staphylococci.

[a]Possible gram-positive contaminants include *Bacillus* spp., *Streptococcus viridans*, *Micrococcus* spp., and *Corynebacterium* spp. Possible gram-negative contaminants include *Bacteroides* spp.

[b]Includes the following *Candida* species: *albicans, parapsilosis, tropicalis, glabrata, guilliermondi*, and *lusitaniae.*

[c]Includes *Saccharomyces* species, *Malassezia furfur*, and other unspecified fungal organisms.