HHS Public Access

Author manuscript

J Perinatol. Author manuscript; available in PMC 2021 February 18.

Published in final edited form as:

J Perinatol. 2021 February ; 41(2): 255–262. doi:10.1038/s41372-020-00784-y.

Delivery Based Criteria for Empiric Antibiotic Administration among Preterm Infants

Samuel J. Garber, MD[1,2], **Miren B. Dhudasia, MBBS, MPH**[1,3], **Dustin D. Flannery, DO, MSCE**[1,2,3], **Molly R. Passarella, MS**[1], **Karen M. Puopolo, MD, PhD**[1,2,3], **Sagori Mukhopadhyay, MD, MMSc**[1,2,3]

[1]Division of Neonatology, Department of Pediatrics, Children's Hospital of Philadelphia, Philadelphia, PA, United States

[2]Department of Pediatrics, University of Pennsylvania Perelman School of Medicine, Philadelphia, PA, United States

[3]Center for Pediatric Clinical Effectiveness, Children's Hospital of Philadelphia, Philadelphia, PA, United States

Abstract

Objective: Determine impact of using delivery criteria to initiate antibiotics among very low birth weight (VLBW) and extremely low birth weight (ELBW) infants.

Design: Single site cohort study from 01/01/2009 to 01/31/2020. After 04/2017, infants delivered by Cesarean section, without labor or membrane rupture were categorized as low-risk for early-onset infection and managed without empiric antibiotics. We determined effect of this guideline by pre-post, and interrupted time series analyses.

Result: After 04/2017, antibiotic initiation ≤3 days decreased among low-risk VLBW (62% vs. 13%, p<0.001) and low-risk ELBW (88% vs. 21%, p<0.001) infants. In time series analysis, guideline was associated with decreased initiation among low-risk ELBW infants. In contrast, low-risk VLBW infants demonstrated decreased antibiotic initiation throughout study period. Incidence of confirmed infection, death or transfer ≤7 days age was unchanged.

Conclusion: Delivery criteria may be used to optimize early antibiotic initiation among preterm infants without short-term increase in adverse outcomes.

Corresponding Author: Sagori Mukhopadhyay, MD, MMSc, **Address:** The Roberts Center for Pediatric Research, Children's Hospital of Philadelphia, 2716 South Street, Office 19-322, Philadelphia, PA 19146, United States. MUKHOPADHS@EMAIL.CHOP.EDU. Phone: (215) 829-3603. Fax: (215) 829-7211.

AUTHOR CONTRIBUTIONS

SJG contributed to study design and analytic plan, data collection, reviewed and revised the manuscript. MBD contributed to data collection and management, data analysis and interpretation, reviewed and revised the manuscript. DDF contributed to study design and analytic plan, data collection, reviewed and revised the manuscript. MRP contributed to data analysis and interpretation, reviewed and revised the manuscript. KMP contributed to study design and analytic plan, reviewed and revised the manuscript. SM conceptualized and designed the study, contributed to data collection and analysis, and drafted the first manuscript. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

CONFLICT OF INTEREST

The authors have no conflicts of interest relevant to this article to disclose.

Supplementary information is available at JPER's website.

INTRODUCTION

Antibiotic administration to preterm infants in the days after birth has side effects that range from concomitant drug toxicity and microbiome disruption to potential long-term health consequences.(1–5) More discriminatory antibiotic use is especially needed among very low birth weight infants (VLBW, birth weight <1,500 grams) and extremely low birth weight infants (ELBW, birth weight <1,000 grams). An estimated 80% of VLBW infants and 87–95% of ELBW infants are administered empiric antibiotics shortly after birth as part of early-onset sepsis (EOS) evaluation, and large proportions of such infants are administered prolonged periods of antibiotics despite sterile cultures.(3,6–8)

The pathogenesis of EOS is primarily ascending colonization of the uterine compartment with maternal gastrointestinal and genitourinary flora, and subsequent transition to invasive fetal and neonatal infection.(9) We have previously demonstrated that preterm infants delivered by Cesarean section due to maternal non-infectious illness in the absence of labor or attempts to induce labor, and rupture of membranes at delivery are at significantly lower risk of EOS compared to infants born in the absence of such criteria.(7,10) Updated guidance from the American Academy of Pediatrics (AAP) suggests that such infants (referred to as “low-risk infants”) may be managed without evaluation for EOS and without routine empiric antibiotic administration.(11) Concerns with this approach may include reluctance not to administer antibiotics in the presence of neutropenia, the potential shift of antibiotic use later in the first week after birth, and inadvertent delay in the diagnosis and antibiotic initiation in culture confirmed EOS cases. These concerns are accentuated among the ELBW infants given the higher rates of proven infection and mortality compared to more mature infants.(12)

In 2017, our center adopted a clinical guideline that is aligned with the current AAP recommendations for identifying and empirically treating preterm infants at risk for EOS based on delivery criteria.(11,13) The primary objective of this study was to quantify the impact on antibiotic exposure among low-risk VLBW and ELBW infants, and monitor for adverse outcomes in the first week after birth.

METHODS

Study Design:

Prospective observational cohort study with retrospective controls.

Setting and study population:

The study was set in the Pennsylvania Hospital neonatal intensive care unit (NICU), a 50-bed, Level 3 center in Philadelphia, Pennsylvania with a high risk, primarily inborn population. All inborn VLBW infants that survived to NICU admission were included. Period 1: No written protocol for VLBW infant EOS management (01/01/2009-03/31/2017). Period 2: Written guideline for empiric antibiotic initiation among VLBW infants based on delivery criteria (04/01/2017 to 01/31/2020). The study was approved with waiver of consent by Institutional Review Board at the University of Pennsylvania.

Data sources:

Demographic and clinical information, and pharmacy and laboratory data were abstracted from a curated data warehouse for data from 2009-2014 and by manual medical record review thereafter. Guideline compliance was prospectively monitored in Period 2 and information on clinical decision making collected in real-time.

Clinical guideline:

EOS was defined as growth of a pathogen from blood or cerebrospinal fluid culture obtained ≤3 days after birth. Details of the clinical guideline for VLBW EOS risk assessment have been described previously.(13) In brief, low-risk infants were defined as infants born with all of the following: (a) delivery by Cesarean section; (b) absence of labor documented in delivery reports; and (c) rupture of membranes at time of delivery (recorded as <6 minutes prior to delivery). Deliveries complicated by placental abruption, attempts to induce labor (regardless of duration) and unexplained isolated fetal distress were excluded from the low-risk definition. Blood culture and routine empiric antibiotics for risk of EOS were not recommended for low-risk infants. Need for respiratory support after birth was not a criterion for initiating antibiotics in an infant categorized as 'low-risk' for EOS by delivery criteria. At the discretion of the care team, administration of empiric antibiotics to low-risk infants would be considered if significant hemodynamic instability was present. Conversely, any well appearing VLBW infants without need for hemodynamic or respiratory support could be cared for as a low-risk infant. Empiric antibiotics were discontinued if cultures were sterile at 48 hours of incubation. A clinical guideline based on these principles was adopted by the site as the standard of care in 04/2017. At the time the guideline was adopted, pre-specified safety assessments for VLBW infants included: time from birth to collection of blood culture and antibiotic initiation among infants with culture confirmed infection diagnosed at ≤7 days after birth; proportion of infants for whom antibiotics were initiated at 4–7 days after birth; proportion diagnosed with culture confirmed infection and proportion who died or were transferred to higher level unit ≤7 days after birth.

Outcomes:

The primary outcome was the proportion of all VLBW infants and of low-risk VLBW infants for whom antibiotics were initiated at ≤3 days after birth. Secondary outcomes included: (a) proportion of infants with antibiotic initiation in ≤3 days after birth and continued for >3 days in the absence of culture confirmed infection, necrotizing enterocolitis (≥Stage II), spontaneous intestinal perforation, death or transfer ≤7 days after birth (14); (b) proportion of low-risk ELBW infants for whom antibiotics were initiated at ≤3 days after birth; and (c) pre-specified adverse outcomes ≤7 days after birth. Our primary concern was missed or delayed detection of infants with EOS and therefore a duration of ≤7 days after birth was chosen for monitoring adverse outcomes. We also conducted a sub-analysis of antibiotic use among VLBW infants with leukopenia defined as a white blood cell count <5,000 cells/microliter or neutropenia defined as absolute neutrophil count <1,000 cells/microliter.

Analysis:

The impact of guideline implementation on antibiotic initiation was assessed using χ^2 test, interrupted time series (ITS) analysis, and statistical process control methods. The ITS analysis used segmented regression to account for change over time. Periods 1 and 2 formed the two segments in the model. Antibiotic initiation was measured quarterly for low-risk VLBW infants, but 6-month intervals for low-risk ELBW infants due to no low-risk ELBW infant admission in some quarters. The model included the baseline trend of antibiotic initiation and change in level and trend after guideline implementation. Statistical process control methods were used to visualize antibiotic use over the study period and were presented as quarterly data for both VLBW and ELBW infants. We considered special cause variation for over four consecutive measures (equal to change over a year) above or below prior mean. Pre-specified adverse outcome measures were compared using univariable tests (χ^2, Student's *t*-test and Kruskal-Wallis test) as appropriate. Analyses were conducted using Stata 14 (StataCorp, College Station, TX). The ITS model was generated using a SAS macro(15) in SAS 9.4 (Cary, NC). Autocorrelation up to six-orders was assessed and accounted for in the model by using Newey-West autocorrelation adjusted standard errors. (15) Control charts were generated using QI Macros version 2109.05 (KnowWare International, Denver, CO) for Microsoft Excel.

RESULTS

The study included 918 VLBW infants, 727 in Period 1 and 191 in Period 2 (Table 1). Overall, 381 (41.5%) infants were categorized as low-risk for EOS. Period 1 infants were more likely to be of multiple gestation, born to a mother after onset of labor and rupture of membrane. However, a similar proportion of infants were born with low-risk delivery criteria during the two study periods (41.0% vs. 43.5%, p = 0.54). Compliance with the guideline was high. Reason for antibiotic initiation in ≤3 days after birth among low-risk infants is shown in Supplementary Table 1.

Antibiotic initiation:

Overall, empiric antibiotics administration ≤3 days after birth was lower in all VLBW and ELBW infants in Period 2 (Table 2). Among low-risk infants, there was a 48.8% reduction (95% CI 39.7, 58.0) in administration of empiric antibiotics among VLBW infants, and 65.3% reduction (95% CI 50.5, 80.1) among ELBW infants in Period 2. Prolonged antibiotic use >48 hours also decreased among all VLBW infants and among low-risk infants. In the ITS model, the proportion of low-risk VLBW infants administered empiric antibiotics after birth decreased with time (−2.3%, 95% CI −3.0% to −1.5%, p <0.001) but no significant change was observed with guideline implementation either in level or in trend (Table 3). In contrast, among low-risk ELBW infants the effect of time (−1.7%, 95% CI −2.7% to −0.7%, p = 0.003) and the effect of guideline implementation in level change (−39.5%, 95% CI −72.7% to −6.4%, p = 0.03) were significant without an effect in the post-implementation trend. This can be interpreted as 1.7% reduction every 6 months over the study period among low-risk ELBW infants (with confidence limits from 0.7% to 2.7%) and a 39.5% reduction with guideline implementation (with confidence limits from 6.4% to 72.7%). Statistical process control charts (Figure 1, Panel A) for low-risk VLBW infants shows a

decrease in mean proportion of infants with antibiotic initiation first at the end of 2012, followed by a decrease in the second quarter of 2016, a year prior to when the written guidelines were implemented, and finally a smaller decrease in 2019. Among low-risk ELBW infants, the antibiotic initiation decreased consistently after guideline implementation with the exception of the first three quarters of 2018 (Figure 1, Panel B), where antibiotic initiation for changing status or laboratory findings were clustered.

Adverse outcome assessments:

Occurrence of pre-specified adverse outcome measures between the study periods were similar (Table 2 and Table 4). These measures included incidence of culture confirmed infection at ≤3 days or 4–7 days after birth, timing of blood culture and antibiotic initiation among culture confirmed cases, proportion of infants started on empiric antibiotics in 4–7 days after birth and proportion of infants who died or were transferred out in the first week after birth. In Period 2, all cases where death/transfer occurred in the first week after birth had a blood culture obtained and antibiotics initiated ≤3 days after birth in all except one. This last patient had a blood culture obtained, but antibiotics were not initiated. The blood culture was sterile, and the infant was transferred at 7 days after birth for management of congenital nephrotic syndrome. Thus, none of these adverse outcomes were attributed to delayed or missed early infection.

Antibiotic use in low-risk infants with neutropenia:

All low-risk VLBW infants had complete blood counts (CBC) obtained ≤3 days after birth in both periods but fewer infants had a repeat CBC at 4-7 days after birth in Period 2 (74.8% vs. 60.2%, p = 0.009, Supplementary Table 2). Overall, 44.1% low-risk VLBW infants had leukopenia or neutropenia at ≤3 days after birth, with a similar proportion in both study periods (42.6% vs. 49.4%, p = 0.27). During Period 1, 98/127 (77.2%) infants with leukopenia/neutropenia were administered empiric antibiotics compared to 11/41 (26.8%) in Period 2 (p <0.001). A similar proportion of infants with leukopenia/neutropenia had a repeat CBC obtained 4-7 days after birth in both periods (87.4% vs. 87.8%, p = 0.95). Resolution of leukopenia and neutropenia occurred in a similar proportion of infants (52.3% vs. 63.9%, p = 0.22) despite differential antibiotic management.

DISCUSSION

In a single-center experience over 10 plus years, we found decreasing rates of antibiotic initiation for EOS evaluations among VLBW infants categorized as low-risk based on delivery criteria. A written guideline was associated with decreased empiric early antibiotic initiation in ELBW infants. No cases of culture confirmed EOS occurred among infants categorized as low-risk for EOS either before or after guideline adoption. Comparing outcomes before and after guideline use, we found no increase in use of antibiotics at 4-7 days after birth, nor in adverse events that could be associated with a delay in diagnosis or management of infection such as later age for obtaining blood cultures or antibiotics initiated among confirmed bacteremia, increase in transfer to a quaternary level of care or death before 7 days after birth. The decrease in early antibiotic use among low-risk VLBW infants led to a decrease in overall early antibiotic use in all VLBW infants and were

associated with lower rates of prolonged early antibiotic administration in the absence of culture confirmed infection, necrotizing enterocolitis or spontaneous intestinal perforation.

Prior studies have reported that a large proportion of infants with low-risk delivery criteria are started on antibiotics and many are continued on antibiotics despite negative cultures.(3,6,8) In 2018, the AAP endorsed approaching EOS evaluation and antibiotic use in preterm infants based on delivery criteria.(11) Evidence for these recommendations was based on large retrospective studies.(7,10) In our prospective implementation of practice aligned with these recommendations, we monitored for two possible outcomes that can be difficult to predict in a retrospective analysis. First, infants categorized as low-risk for EOS are not low-risk for other prematurity-associated characteristics and outcomes such as physiological lability, hypotension, necrotizing enterocolitis, or spontaneous intestinal perforation. It was unclear whether such occurrences would result in antibiotic use for indications other than empiric EOS evaluation and negate the net effect on antibiotic utilization. In our study, we observed an increase in antibiotic use during second, third and fourth quarters of 2018 (Figure 1) for such indications but overall only 11 low-risk infants required antibiotic initiation in ≤3 days after birth for any indications (Supplementary Table 1). Second, while these infants may be at low risk for vertical transmission of infection from mother, they may not be at low risk for early nosocomial infection. Clinicians worry that with exposure to intensive care such as central catheters, combined with the leukopenia and/or neutropenia noted in many of these infants, the absence of early antibiotic therapies may lead to a rising incidence of acquired infections after 24 hours after birth. However, we did not find an increase in infection in the first week with decreased antibiotic initiation at ≤3 days after birth.

In the time series analysis, we did not find a significant effect of guideline implementation on antibiotic initiation among all VLBW infants. Both ITS and statistical process control analysis found that antibiotic initiation in low-risk VLBW infants had been decreasing over the study time period (Figure 1, Panel A). We do not see this as a failure of the guideline: we recognized the drift in our center practice in the preceding years based on emerging literature about delivery criteria-based risk stratification and awareness raised by local neonatal antibiotic stewardship efforts.(4,7,10,16) Among low-risk ELBW infants, however, the trend over time was less pronounced and standardized guidelines were associated with a significant decrease in antibiotic use among these infants (Table 3 and Figure 1, Panel B). We interpret this as a reluctance to extend evidence into practice among these less mature, more unstable infants that was overcome with the use of a formal practice guideline.

Leukopenia and neutropenia are associated with bacterial infection.(17) Low-risk infants are often delivered to women with preeclampsia or with growth restriction. These *in utero* conditions are associated with fetal bone marrow suppression and newborn leukopenia and neutropenia, but their association with infection is less well-established.(18–20) As part of the guideline implementation, clinicians were discouraged from basing EOS antibiotic decisions on isolated non-microbiological laboratory values. Low-risk infants with moderate to severe leukopenia/neutropenia were managed more frequently without antibiotics post guideline implementation, and we found no difference in bone marrow recovery or adverse outcomes. Animal studies have shown that antibiotic exposure early in life can suppress

granulopoiesis by altering microbiome formation and subsequently increase risk of mortality from later infection.(21) In the absence of demonstrable benefit, and with the possibility of harm we propose that antibiotic use among low-risk infants soon after birth solely based on leukopenia and/or neutropenia in the setting of a maternal *in utero* etiology for bone marrow suppression, is not best practice. As our center moved away from using early laboratory values for antibiotic decisions, we observed a significant decrease in the frequency of repeated CBC measures (Supplementary Table 2).

We assessed multiple adverse outcomes expected to occur if true EOS was missed. In not obtaining blood cultures at birth for low-risk infants, it was possible that delayed recognition of bacteremia could occur. We tracked time from birth to when blood culture was obtained, and first antibiotics were ordered, in all cases of confirmed infection or death in the first week after birth. Among all infants who died, cultures had been obtained and antibiotics initiated at ≤3 days. Similarly, we found no difference in time to culture and antibiotic initiation before and after guideline implementation in culture confirmed cases in the first week after birth.

The primary limitation of our study is that this is a single center experience with a small number of time-points and a limited number of adverse outcomes to gauge occurrence of rare events. What we know of the natural history of preterm gestation is a reflection of existing standard interventions. As early antibiotic use is reduced among infants that nearly universally received this treatment in the past, we remain cautious to unexpected outcomes and adverse events. It should be noted that we chose a conservative definition of “low-risk” delivery, and categorized any labor or breach of the intrauterine environment, such as may occur during placental abruption, as not low-risk. Despite this we categorized over 40% of the VLBW infants admitted to our unit as low-risk, suggesting that these recommendations can impact overall antibiotic use in the NICU based on center-specific maternal demographics.

CONCLUSION

We found that guidelines aligned with the current AAP recommendation for management for preterm infants support optimized antibiotic use in the VLBW population without increase in short-term adverse outcomes. Formal guidelines informing clinical care may be especially impactful among ELBW infants who frequently suffer from clinical instability inherent to their gestational age at birth.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

FUNDING INFORMATION

The study was partly supported by *Eunice Kennedy Shriver* National Institute of Child Health and Human Development of the National Institutes of Health Grants (Number – K23HD088753 and T32HD060550).

Funding source: SM was supported by *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) of the National Institutes of Health (NIH) grant (K23HD088753) and DDF by NICHD/NIH grant (T32HD060550).

Abbreviations:

AAP	American Academy of Pediatrics
CBC	complete blood count
ELBW	extremely low birth weight
EOS	early onset sepsis
ITS	interrupted time series
NICU	neonatal intensive care unit
VLBW	very low birth weight

REFERENCES

(1). Fouhy F, Guinane CM, Hussey S, Wall R, Ryan CA, Dempsey EM, et al. High-throughput sequencing reveals the incomplete, short-term recovery of infant gut microbiota following parenteral antibiotic treatment with ampicillin and gentamicin. Antimicrob Agents Chemother 2012 Nov;56(11):5811–5820. [PubMed: 22948872]

(2). Le J, Nguyen T, Okamoto M, McKamy S, Lieberman JM. Impact of empiric antibiotic use on development of infections caused by extended-spectrum beta-lactamase bacteria in a neonatal intensive care unit. Pediatr Infect Dis J 2008 Apr;27(4):314–318. [PubMed: 18316990]

(3). Ting JY, Roberts A, Sherlock R, Ojah C, Cieslak Z, Dunn M, et al. Duration of Initial Empirical Antibiotic Therapy and Outcomes in Very Low Birth Weight Infants. Pediatrics 2019 Mar;143(3):10.1542/peds.2018-2286.

(4). Kuppala VS, Meinzen-Derr J, Morrow AL, Schibler KR. Prolonged initial empirical antibiotic treatment is associated with adverse outcomes in premature infants. J Pediatr 2011 Nov;159(5):720–725. [PubMed: 21784435]

(5). Ting JY, Synnes A, Roberts A, Deshpandey AC, Dow K, Yang J, et al. Association of Antibiotic Utilization and Neurodevelopmental Outcomes among Extremely Low Gestational Age Neonates without Proven Sepsis or Necrotizing Enterocolitis. Am J Perinatol 2018 Aug;35(10):972–978. [PubMed: 29475201]

(6). Flannery DD, Ross RK, Mukhopadhyay S, Tribble AC, Puopolo KM, Gerber JS. Temporal Trends and Center Variation in Early Antibiotic Use Among Premature Infants. JAMA Network Open 2018;1(1):e180164–e180164. [PubMed: 30646054]

(7). Puopolo KM, Mukhopadhyay S, Hansen NI, Cotten CM, Stoll BJ, Sanchez PJ, et al. Identification of Extremely Premature Infants at Low Risk for Early-Onset Sepsis. Pediatrics 2017 11;140(5):10.1542/peds.2017-0925. Epub 2017 Oct 5.

(8). Greenberg RG, Chowdhury D, Hansen NI, Smith PB, Stoll BJ, Sanchez PJ, et al. Prolonged duration of early antibiotic therapy in extremely premature infants. Pediatr Res 2019 Jun;85(7):994–1000. [PubMed: 30737489]

(9). BENIRSCHKE K. Routes and types of infection in the fetus and the newborn. AMA J Dis Child 1960 6;99:714–721. [PubMed: 13798887]

(10). Mukhopadhyay S, Puopolo K. Clinical and Microbiologic Characteristics of Early-Onset Sepsis Among VLBW Infants: Opportunities for Antibiotic Stewardship [in press]. PIDJ 2016.

(11). Puopolo KM, Benitz WE, Zaoutis TE, COMMITTEE ON FETUS AND NEWBORN, COMMITTEE ON INFECTIOUS DISEASES. Management of Neonates Born at less than or

equal to 34 6/7 Weeks' Gestation With Suspected or Proven Early-Onset Bacterial Sepsis. Pediatrics 2018 12;142(6):10.1542/peds.2018-2896.

(12). Stoll BJ, Hansen NI, Sanchez PJ, Faix RG, Poindexter BB, Van Meurs KP, et al. Early onset neonatal sepsis: the burden of group B Streptococcal and E. coli disease continues. Pediatrics 2011 May;127(5):817–826. [PubMed: 21518717]

(13). Mukhopadhyay S, Sengupta S, Puopolo KM. Challenges and opportunities for antibiotic stewardship among preterm infants. Arch Dis Child Fetal Neonatal Ed 2019 5;104(3):F327–F332. [PubMed: 30425110]

(14). Bell MJ. Neonatal necrotizing enterocolitis. N Engl J Med 1978 2 2;298(5):281–282.

(15). Caswell JM. Interrupted Time Series Analysis for Single Series and Comparative Designs: A Guide for Beginners with SAS Macro. 2019; Available at: https://www.academia.edu/35275583/Interrupted_Time_Series_Analysis_for_Single_Series_and_Comparative_Designs_A_Guide_for_Beginners_with_SAS_Macro?sm=b.

(16). Ting JY, Synnes A, Roberts A, Deshpandey A, Dow K, Yoon EW, et al. Association Between Antibiotic Use and Neonatal Mortality and Morbidities in Very Low-Birth-Weight Infants Without Culture-Proven Sepsis or Necrotizing Enterocolitis. JAMA Pediatr 2016 12 1;170(12):1181–1187. [PubMed: 27775765]

(17). Newman TB, Puopolo KM, Wi S, Draper D, Escobar GJ. Interpreting complete blood counts soon after birth in newborns at risk for sepsis. Pediatrics 2010 11;126(5):903–909. [PubMed: 20974782]

(18). Christensen RD, Yoder BA, Baer VL, Snow GL, Butler A. Early-Onset Neutropenia in Small-for-Gestational-Age Infants. Pediatrics 2015 11;136(5):e1259–67. [PubMed: 26459642]

(19). Doron MW, Makhlouf RA, Katz VL, Lawson EE, Stiles AD. Increased incidence of sepsis at birth in neutropenic infants of mothers with preeclampsia. J Pediatr 1994 9;125(3):452–458. [PubMed: 8071757]

(20). Teng RJ, Wu TJ, Garrison RD, Sharma R, Hudak ML. Early neutropenia is not associated with an increased rate of nosocomial infection in very low-birth-weight infants. J Perinatol 2009 3;29(3):219–224. [PubMed: 19078971]

(21). Deshmukh HS, Liu Y, Menkiti OR, Mei J, Dai N, O'Leary CE, et al. The microbiota regulates neutrophil homeostasis and host resistance to Escherichia coli K1 sepsis in neonatal mice. Nat Med 2014 5;20(5):524–530. [PubMed: 24747744]

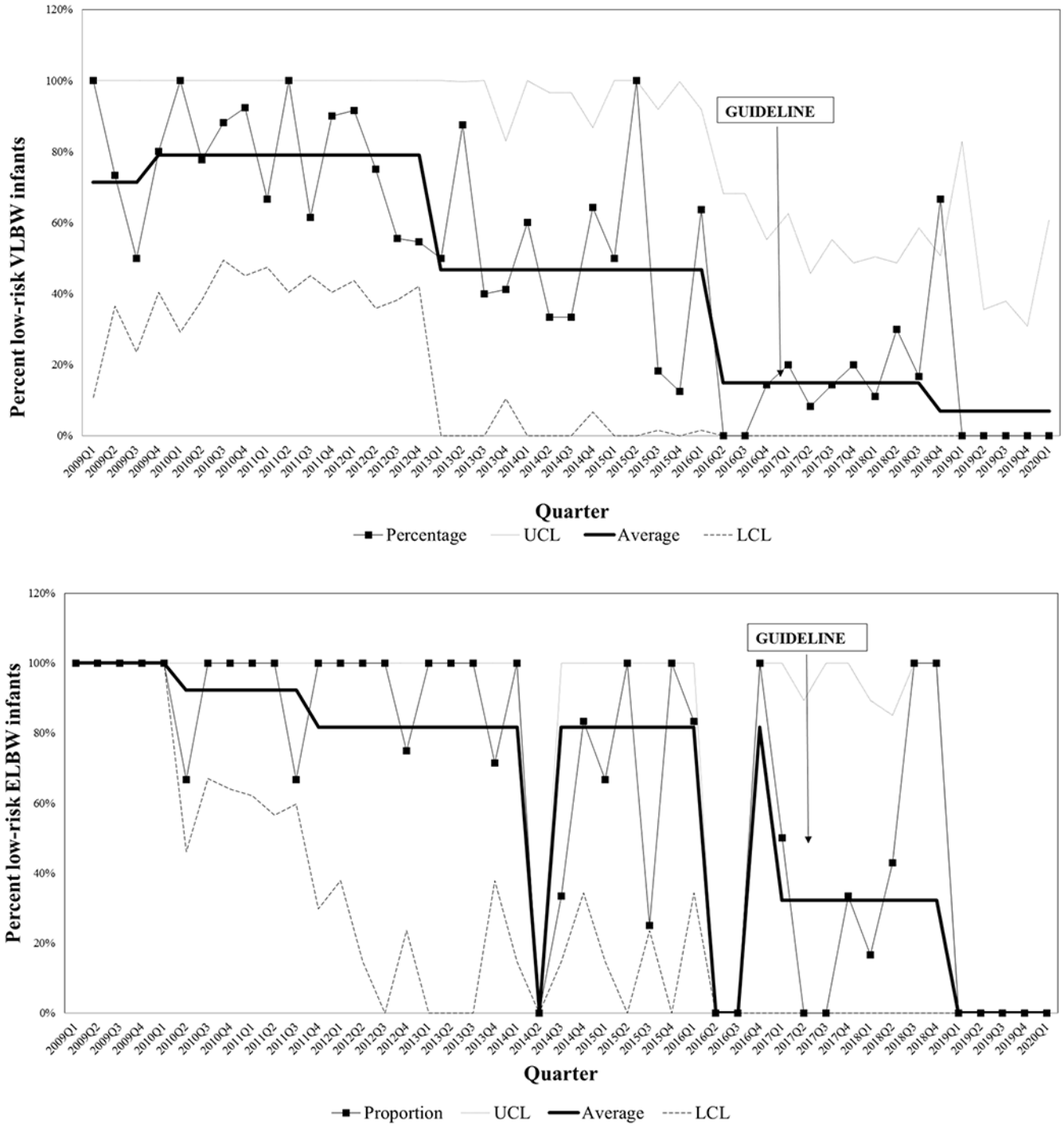

Figure 1:

Change in proportion of infants initiated on antibiotics ≤3 days after birth during study period.

Panel A shows the changing average proportion of low-risk VLBW infants started on antibiotics over time and with guideline implementation.

Panel B shows the changing average proportion of low-risk ELBW infants started on antibiotics over time and with guideline implementation.

ELBW, extremely low birth weight (birth weight <1,000 grams); LCL, lower confidence limit; UCL, upper confidence limit; VLBW, very low birth weight (birth weight <1,500 grams).

Table 1.

Clinical characteristics of study cohort

	Period 1 n = 727	Period 2 n = 191	p-value
Birth weight (grams), mean (SD)	1,056 (298)	1,046 (312)	0.70
ELBW infants, n (%)	297 (40.9)	85 (44.5)	0.36
Gestational age (weeks), median (IQR)	28 4/7 (26 3/7, 30 4/7)	28 5/7 (26 3/7, 30 4/7)	0.98
Females, n (%)	365 (50.2)	107 (56.0)	0.15
Multiple gestation, n (%)	233 (32.1)	41 (21.5)	0.004
Cesarean delivery, n (%)	564 (77.6)	137 (71.7)	0.09
Rupture of membranes at the time of delivery, n (%)	419 (57.6)	128 (67.0)	0.02
Any labor (spontaneous or induced) prior to delivery, n (%)	425 (58.5)	92 (48.2)	0.01
Infants meeting low-risk criteria, n (%)	298 (41.0)	83 (43.5)	0.54
ELBW infants meeting low-risk criteria, n (%)	120 (16.5)	38 (19.9)	0.27

ELBW, extremely low birth weight (birth weight <1,000 grams); SD, standard deviation; IQR, interquartile range.

Table 2.

Study outcomes

	All VLBW Infants[a]			Low-Risk VLBW Infants		
	Period 1 n = 727	Period 2 n = 191	p-value	Period 1 n = 298	Period 2 n = 83	p-value[b]
Day 0-3 after birth, n (%)						
Blood culture obtained, n (%)	643 (88.5)	117 (61.3)	<0.001	225 (75.5)	14 (16.9)	<0.001
Antibiotic initiation, n (%)	590 (81.2)	113 (59.2)	<0.001	185 (62.1)	11 (13.3)	<0.001
Antibiotic initiation among ELBW infants	281/297 (94.6)	56/85 (65.9)	<0.001	105/120 (87.5)	8/36 (22.2)	<0.001
Blood culture positive for a pathogen, n (%)	9 (1.2)	2 (1.1)	0.83	0	0	-
Infants initiated on antibiotics and survived 7 days without culture-confirmed infection, NEC or SIP[c]	539	99		172	9	
Antibiotic duration >3 days, n (%)	175/539 (32.5)	2/99 (2.0)	<0.001	55/172 (32.0)	0/9	-
4-5 days	12/539 (2.2)	1/99 (1.0)	0.43	6/172 (3.5)	0/9	-
6-7 days	86/539 (16.0)	1/99 (1.0)	<0.001	26/172 (15.1)	0/9	-
>7 days	77/539 (14.3)	0/99	<0.001	23/172 (13.4)	0/9	-
Day 4-7 after birth, n (%)						
Blood culture obtained, n (%)	130 (17.9)	25 (13.1)	0.12	61 (20.5)	9 (10.8)	0.045
Antibiotic initiation, n (%)	67 (9.2)	22 (11.5)	0.34	34 (11.4)	9 (10.8)	0.89
Blood culture positive for a pathogen, n (%)	15 (2.1)	3 (1.6)	0.66	6 (2.0)	1 (1.2)	0.63
Deceased or transferred by 7 days age, n (%)	36 (5.0)	10 (5.2)	0.87	11 (3.7)	2 (2.4)	0.57

[a] Includes low-risk infants.

[b] χ^2 analysis not done when cell value is zero.

[c] Excluded from the denominator are infants not started on antibiotics in ≤3 days after birth, infants with culture confirmed infection, NEC/SIP ≤7 days after birth, or infants admitted for ≤7 days after birth. In Period 1 reasons for exclusion were early culture confirmed infection (9), late-onset infection (14), NEC/SIP (4), death (16), and transfer (8); in Period 2, early culture confirmed infection (2), late-onset

infection (3), NEC/SIP (4), death (4) and transfer (1). ELBW, extremely low birth weight (birth weight <1,000 grams); NEC, necrotizing enterocolitis; SIP, spontaneous intestinal perforation; VLBW, very low birth weight (birth weight <1,500 grams).

Table 3.

Estimate of percent change in antibiotic initiation by interrupted time series analysis

Parameter	Estimate	CI upper limit	CI lower limit	p-value
Low-risk VLBW infants[a]				
Time (every quarter)	−2.3%	−3.0%	−1.5%	<0.001
Level change with guideline	1.5%	−14.6%	17.6%	0.86
Trend change with guideline	0.7%	−1.7%	3.1%	0.59
Combined change in trend before and after guideline adoption	−1.6%	−3.7%	0.5%	0.13
Low-risk ELBW infants[b]				
Time (every 6 months)	−1.7%	−2.7%	−0.7%	0.003
Level change with guideline	−39.5%	−72.7%	−6.4%	0.03
Trend change with guideline	−0.26%	−9.1%	8.6%	0.95
Combined change in trend before and after guideline adoption	−1.95%	−10.9%	7.0%	0.67

[a]Time expressed in quarter year with guideline adoption in second quarter of 2017.

[b]Time expressed bi-annually with guideline adoption in first half of 2017. CI, 95% confidence interval; ELBW, extremely low birth weight (birth weight <1,000 grams); VLBW, very low birth weight (birth weight <1,500 grams).

Table 4.

Adverse outcomes in all VLBW infants

	Period 1 n = 727	Period 2 n = 191	p-value[a]
EOS (Culture confirmed infection at 0-3 days after birth), n (%)	9 (1.2)	2 (1.1)	0.83
Hours from birth when culture obtained[b], Median (IQR)	0.6 (0.5-1.0)	1.1 (1.0-1.1)	0.41
Hours from birth when first dose of antibiotic given, Median (IQR)	1.8 (1.4-2.1)	1.8 (1.6-2.0)	0.81
Organisms, n			-
Escherichia coli	7	2	
Klebsiella pneumoniae	1	0	
Candida albicans	1	0	
Culture confirmed infection at 4-7 days after birth, n (%)	15 (2.1)	3 (1.6)	0.66
Hours from birth when culture obtained, Median (IQR)	138.2 (115.5-152.3)	137.1 (121.3-139.7)	0.59
Hours from drawing culture and start of antibiotics[c], Median (IQR)	0.8 (0.2-6.8)	1.0 (0.8-2.1)	0.77
Organisms, n			–
Coagulase-negative staphylococci	9	2[d]	
Escherichia coli	1	1	
Klebsiella pneumoniae	3	0	
Staphylococcus aureus	1	1	
Enterobacter cloacae	1	0	
NEC/SIP ≤7 days after birth, n (%)	7 (1.0)	5 (2.6)	0.07
Indication for transfer ≤7 days[e], n (%)	17 (2.3)	6 (3.1)	0.53
Anomalies	9	2	
NEC/SIP	7	4	
Respiratory management	1	0	

	Period 1 n = 727	Period 2 n = 191	p-value[a]
Cause of death ≤7 days[f], n (%)	19 (2.6)	4 (2.1)	0.68
Extreme prematurity and respiratory failure	12	3	
EOS	3	0	
Intracranial hemorrhage	3	0	
Other	1	1	

[a] χ^2 analysis not done when cell value is zero.

[b] One EOS infant in Period 1 had culture drawn at 65 hours for onset of SIP (excluded from median).

[c] Two infants in Period 1 were being treated with antibiotics when blood culture was obtained: in the first case, for cellulitis, and blood culture grew same the bacteria as wound culture; and in the second case, the blood culture was for test of cure in the setting of prior bacteremia.

[d] This infant also grew *Staphylococcus aureus* from blood culture has been counted in both.

[e] All infants who were transferred at ≤7 days after birth had a blood culture obtained, and all except 1 infant in Period 2 (negative blood culture after birth) had empiric antibiotics initiated ≤3 days after birth.

[f] All infants who died at ≤7 days after birth had a blood culture obtained and empiric antibiotics initiated ≤3 days after birth. EOS, early-onset sepsis; IQR, interquartile range; NEC, necrotizing enterocolitis; SIP, spontaneous intestinal perforation; VLBW, very low birth weight (birth weight <1,500 grams).