Title: Sustainability and Safety of an Early-Onset Sepsis Risk-Stratification Guideline for Very-low Birth Weight Infants

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Purpose: To evaluate sustainability and ongoing safety of a very-low birth weight infants (VLBW, >1500g) early-onset sepsis (EOS) risk-stratification guideline.

Background/Significance: Approximately 80% of very-low birth weight infants in the US receive empiric antibiotics at birth due to the risk of EOS. We previously reported (Garber et al. J Perinatol 2021) that implementing a guideline specifying the use of delivery criteria to determine VLBW EOS risk was associated with lower rates of early antibiotic initiation without short-term increases in adverse outcomes.

Design: Retrospective cohort study of VLBWs admitted to a Level 3 III NICU, 01/2009-09/2024. EOS was defined as pathogen isolation from blood or CSF culture ≤3 days after birth. VLBWs were considered at low-risk for EOS if born for maternal non-infection indications, by cesarean delivery without labor, and with rupture of membranes at delivery.

Methods: Primary outcomes were the proportion of all VLBWs and of low-risk VLBWs administered antibiotics ≤3 days after birth, comparing the post-implementation period (4/2017-1/2020) to a sustainability time period (02/2020-09/2024). Safety outcomes included: proportion of VLBWs with antibiotics initiated at days 4-7 after birth; positive blood or CSF culture at days 4-7; death or transfer by day 7. Data were extracted from the electronic medical record. Descriptive statistics were used to compare characteristics and outcomes between cohorts. Statistical process control analysis was done using p-charts with 3-month intervals.

Results: Analysis included 1195 total VLBWs: 727 in pre-implementation, 191 in post-implementation, and 277 in sustainability period. Of these, the proportions deemed low-risk were 41%, 44%, and 37%, respectively. Baseline characteristics did not differ. There were no significant differences in antibiotic initiation ≤3 days among all VLBWs or low-risk VLBWs. There were no differences in infection, death, or transfer on days 4-7, but antibiotic initiation on days 4-7 was significantly lower during the sustainability period **(Table 1).** The quarterly rate of antibiotic initiation at ≤3 days after birth for low-risk VLBWs decreased from 77.6% (period 1) to 43.2% (period 2) and was maintained at 16.9% in the sustainability period (period 3).

Discussion: In a single-center experience over 15 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 and sustained over the 4-year sustainability period. No cases of culture confirmed EOS occurred among infants categorized as low-risk for EOS either before or after guideline adoption including the 4-year sustainability period.

Conclusion: The use of a VLBW EOS risk-stratification guideline was sustained over 7 years without safety concerns, resulting in a lower proportion of VLBW infants administered empiric

antibiotics from birth. A lower rate of antibiotic initiation at 4-7 days in the sustainability period may suggest greater confidence in the guideline over time.

Table 1: Study Outcomes

	All VLBW infants			p-value		Low-Risk VLBW Infants			p-value	
	Pre-implementation Period 1 n=727	Post-implementation Period 2 n=191	Sustainability Period 3 n=277	Period 1 vs. 2[&]	Period 2 vs. 3	Pre-implementation Period 1 n=298	Post-implementation Period 2 n=83	Sustainability Period 3 n=102	Period 1 vs. 2[&]	Period 2 vs. 3
Day 0-3 after birth, n (%)										
Blood culture obtained, n (%)	643 (88.4)	117 (61.3)	185 (66.8)	<0.001	0.22	225 (75.5)	14 (16.9)	20 (19.6)	<0.001	0.63
Antibiotic initiation, n (%)	590 (81.2)	113 (59.2)	185 (66.8)	<0.001	0.09	185 (62.1)	11 (13.3)	20 (19.6)	<0.001	0.25
Antibiotic initiation among ELBW[#] infants, (%)	281/297 (94.6)	56/85 (65.9)	93/124 (75.0)	<0.001	0.15	105/120 (87.5)	8/36 (22.2)	16/45 (35.6)	<0.001	0.19
Blood culture positive for a pathogen, n (%)	9 (1.2)	2 (1.1)	7 (2.5)	1.0*	0.32*	0	0	0	-	-
Day 4-7 after birth, n (%)										
Blood culture obtained, n (%)	130 (17.9)	25 (13.1)	17 (6.1)	0.12	0.01	61 (20.5)	9 (10.8)	6 (5.9)	0.05	0.22
Antibiotic initiation, n (%)	67 (9.2)	22 (11.5)	16 (5.8)	0.34	0.03	34 (11.4)	9 (10.8)	6 (5.9)	0.89	0.22
Blood culture positive for a pathogen, n (%)	15 (2.1)	3 (1.6)	3 (1.1)	1.0*	0.69*	6 (2.0)	1 (1.2)	0	1.0 *	0.45*
Deceased/Transferred by 7 days age, n (%)	36 (5.0)	10 (5.2)	14 (5.1)	0.87	0.93	11 (3.7)	2 (2.4)	2 (2.0)	0.74*	1.00*

Footnote: [&]Data from Garber, et al. *J Perinatol* 2021. [#]ELBW, extremely low birth weight (birth weight < 1000 grams)

[*] P-values were calculated using Fisher's exact test to ensure accuracy with small sample sizes and low expected frequencies

References

Coggins SA, Willis Z, Benjamin DK, Mukhopadhyay S, Laughon M, Greenberg RG, Clark RH, Puopolo K. Early antibiotic exposure in very-low birth weight infants and infection risk at 3-7 days after birth. J Perinatol. 2023;43(9):1158-1165.

Flannery DD, Puopolo KM. Neonatal Early-Onset Sepsis. Neoreviews, American Academy of Pediatrics. 2022 Nov 1;23(11):756-770. doi: 10.1542/neo.23-10-e756. PubMed PMID: 36316253.

Flannery DD, Mukhopadhyay S, Morales KH, Dhudasia MB, Passarella M, Gerber JS, Puopolo KM. Delivery Characteristics and the Risk of Early-Onset Neonatal Sepsis. Pediatrics. 2022;149(2):e2021052900. PubMed PMID: 35022750; PubMed Central PMCID: pending doi: 10.1542/peds.2021-052900.

Flannery DD, Edwards EM, Puopolo KM, Horbar JH. Early-Onset Sepsis Among Very Preterm Infants. Pediatrics. 2021 Oct;148(4):e2021052456. PubMed PMID: 34493539.

Garber SJ, Dhudasia MB, Flannery DD, Passarella MR, Puopolo KM, Mukhopadhyay S. Delivery-based criteria for empiric antibiotic administration among preterm infants. J Perinatol. 2021 Feb;41(2):255-262. PubMed PMID: 32792629; PubMed Central PMCID: PMC7881045.

Puopolo KM, Benitz WE, Zaoutis TE; Committee on Fetus and Newborn; Committee on Infectious Diseases. Management of Neonates Born at ≤34 6/7 Weeks' Gestation With Suspected or Proven Early-Onset Bacterial Sepsis. Pediatrics. 2018 Dec;142(6). pii: e20182896. doi: 10.1542/peds.2018-2896. PMID: 30455344.