Published in final edited form as:

Arch Dis Child Fetal Neonatal Ed. 2019 May ; 104(3): F327–F332. doi:10.1136/archdischild-2018-315412.

Challenges and Opportunities for Antibiotic Stewardship Among Preterm Infants

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Abstract

Antibiotic stewardship programs aim to optimize antimicrobial use to prevent the emergence of resistance species and protect patients from the side effects of unnecessary medication. The high incidence of systemic infection and associated mortality from these infections leads neonatal providers to frequently initiate antibiotic therapy and make empiric antibiotic courses one of the main contributors of antibiotic use in the neonatal units. Yet, premature infants are also at risk for acute life-threatening complications associated with antibiotic use such as necrotizing enterocolitis and for long-term morbidities such as asthma. In this review, we discuss specific aspects of antibiotic use in the very-low birth weight preterm infants, with a focus on empiric use, that provide opportunities for stewardship practice. We discuss strategies to risk-stratify antibiotic initiation for the risk of early-onset sepsis, optimize empiric therapy duration and antibiotic choice in late onset sepsis, standardize decisions for stopping empiric therapy. Lastly review the evolving role of biomarkers in antibiotic stewardship.

Keywords

very-low birth weight; prematurity; antibiotic stewardship

RISKS AND BENEFITS OF ANTIBIOTICS FOR PRETERM INFANTS

Antibiotics are the most commonly used drugs in the NICU¹. More than 75% of very-low birth weight infants (birth weight <1500 grams, VLBW) and over 80% of extremely-low birth weight infants (birth weight <1000 grams, ELBW) receive antibiotics for the risk of early-onset sepsis (EOS, infection occurring < 72 hours of age)^{2,3}. Two-thirds of VLBW infants cared for in the NICHD Neonatal Research Network (NRN) centers are evaluated at least once for late-onset sepsis (LOS, infection occurring ≥ 72 hours of age)⁴. Neonatal antibiotic use is as variable as it is prevalent. Among 22 centers participating in the NRN the proportion of preterm infants administered prolonged antibiotics in the first week after birth varied from 16–77% across sites, while the incidence of culture-confirmed EOS ranged from

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0–7%⁵. Similarly, overall antibiotic use varied 40-fold in a study of 127 NICUs; variation that was unexplained by differences in rates of proven infection, necrotizing enterocolitis (NEC) surgical volume or mortality⁶. Such variation strongly suggests a contribution of antibiotic prescriber preferences beyond biological drivers of antibiotic usage.

Clinicians administer antibiotics to ensure the safety of preterm infants, but antibiotic administration is not without risk. The risk/benefit analysis that drives the common practice of administering antibiotics in the absence of culture-confirmed infection is based on two assumptions: (1) the risk associated with antibiotic use is predictable and manageable, and (2) antibiotic use, even in absence of known organism or antibiotic susceptibility data, has significant benefit. In recent years both these assumptions have been questioned.

The predictable risks of antibiotics exposure include issues such as acute drug toxicities, the need for intravenous access, and the costs and potential unintended consequences of escalated monitoring. An evolving understanding of the role of microbiome in human health has added new, potentially more pervasive, and currently unpredictable risks to neonatal antibiotic exposure. Newborn antibiotic exposure via maternal antibiotic administration just prior to delivery^{7,8} and neonatal administration after birth⁹, both alter the neonate's microbiome composition well into infancy. Observational studies find an association of early life antibiotics in premature infants with increased risks of NEC, fungal infection and death^{2,10,11}. Multiple preclinical studies provide insight into the mechanistic pathways by which altered microbiota can influence the host immune state and overall health^{12–14}. Finally, the emergence of multi-drug resistant organisms remains an underappreciated but increasingly reported threat in neonatal units across the world^{15,16}. The extent to which any individual infant will suffer from one or more of the adverse outcomes associated with antibiotic use is difficult to predict. However, it is clear that antibiotic use is associated with a cumulative risk that is neither entirely predictable nor immediately manageable.

The benefits of antibiotic administration are clear for infected infants, and infection is prevalent among preterm infants. Culture-confirmed EOS occurs in ~1% of VLBW infants, an incidence that is 20-fold higher than that in infants born with birth weight >2500 grams¹⁷. Culture-confirmed LOS is reported in ~20% of ELBW infants¹⁸. Additionally, 5% of overall mortality in the ELBW population is attributable to infection and NEC¹⁹. Antibiotic therapy is potentially life-saving. However, extrapolating the efficacy of antibiotics to infants without culture-confirmed infection or NEC generally requires three assumptions: (1) microbiological cultures lack sufficient sensitivity for detecting existing infection; (2) clinical exam and non-microbiological tests serve as reasonable surrogates for identifying infection; and (3) clinical decompensation observed on examination or the inflammatory state captured in the test, is not only bacterial in origin but also from a susceptible bacterium that will respond to the chosen antibiotic type and duration. No clinical trials have tested these assumptions. Indeed, most observational studies challenge these assumptions, finding increased mortality and morbidity in infants treated with prolonged antibiotics in the absence of culture-confirmed infection compared to infants with similar clinical characteristics managed without antibiotics^{2,10,11,20,21}. One explanation could be residual confounding in these studies. However, additional concerns should be that the worse

outcome is related to negative effects of antibiotics or due to inadequate treatment of the true cause of decompensation.

DRIVERS OF ANTIBIOTIC USE AND OPPORTUNITIES FOR ANTIBIOTIC STEWARDSHIP AMONG PREMATURE INFANTS

The increased understanding of risk and limited evidence for benefit of antibiotic therapy in the absence of culture-confirmed infection demands that neonatal providers examine current practice. Specific drivers of neonatal antibiotic use inform the opportunities for antibiotic stewardship. Canteley et al quantified indications for antibiotic use among all infants cared for at a single center over 14 months²². Most antibiotic initiation (79%) occurred within 72 hours after birth. Sixty-three percent of antibiotic use was for “rule-out sepsis,” targeting both EOS and LOS, which ended when cultures were reported as sterile. For the remaining 31%, ~7% was for the combined indication of culture confirmed infection (5%), NEC (2%), or cellulitis (<1%), and the rest was for presumed and culture-negative infection (CNI) or pneumonia. Patel et al¹⁴ reported on indications for antibiotic use for LOS in 4 neonatal centers. Empiric initiation again accounted for the majority of initiation (66%); and presumed, CNI treatment accounted for ~1/3 of the continued use. Empiric initiation and antibiotic use for CNI is driven by the non-specific nature of VLBW instability. Indications for LOS antibiotic initiation at a perinatal center and a referral center with surgical cases, included feeding intolerance (25–35%), increased need for respiratory support (15–25%), increased apnea and bradycardia (10–15%) and ill-appearance (5–10%), with few evaluation for specific indications such as cellulitis, seizures or recent surgery²³.

The general goals of hospital-based antibiotic stewardship are described by the Centers for Disease Control and Prevention²⁴. These guidelines focus on the elements of initiating and discontinuing antibiotics, optimizing infection and biomarker testing, choosing empiric and definitive antibiotic therapy, and limiting duration of empiric therapy. Decreases in overall neonatal antibiotic utilization are reported in conjunction with multiple antimicrobial stewardship interventions^{25–27} and among term infants with use of multivariate risk models for EOS risk assessment^{28,29}. Schulman et al recently reported a significant decrease in antibiotic use rate of 21.9% in ~130 NICUs across California from 2013 to 2016³⁰. They found a greater reduction in centers participating in study-defined antibiotic stewardship efforts compared with centers without such participation (28.7% vs. 16.2%) underscoring the importance of stewardship efforts. However, NICUs utilizing antimicrobial stewardship committees report less impact specifically among VLBW infants^{31,32}. A possible reason for this is that the major contributor of antibiotic use in the VLBW population is the empiric ‘rule out’. A labile clinical status, high incidence of infection and an extended turn-around time for culture results limits the scope for safely reducing empiric initiation. While factors such as the infection rate maybe modifiable, clinical lability is unlikely to change. Thus a focus on the choice and duration of empiric therapy and risk-stratification to minimize empiric early initiation are likely to have the most immediate impact on VLBW antibiotic use. Here we will discuss aspects of empiric antibiotic use that provide opportunities for stewardship practice among VLBW preterm infants.

EMPIRIC INITIATION FOR SUSPECTED EARLY ONSET SEPSIS

EOS pathogenesis predominantly involves colonization and invasion of the fetus or newborn by maternal genitourinary flora. A breach in the gravid uterine environment with onset of spontaneous or induced labor and/or membrane rupture provides opportunity for ascending infection. However, a substantial proportion of preterm infants are delivered for maternal indication by cesarean section (CS), without labor and with membrane rupture at delivery. We have reported the significantly different risk of EOS based on delivery characteristics. In a study of 15,433 infants born 22–28 weeks gestation, 5759 (37%) infants were delivered by CS, with rupture at delivery and without a diagnosis of chorioamnionitis⁵. The composite outcome of death at <12 hours or EOS was 64% lower in infants delivered with these criteria (2.6% vs 15.1%; aRR [95% CI] 0.36 [0.30–0.43]). Yet, among infants with low-risk delivery criteria, 66 infants were treated for presumed CNI for each case of confirmed EOS, compared with 19 infants per case in the comparison group ($p<.001$). In a 25-year single-center study, where detailed chart review for the presence of labor was feasible, only 3/109 cases of culture confirmed EOS were found among infants delivered by CS without labor or rupture³³. As empiric antibiotic initiation for EOS is a major driver of NICU antibiotic use, restricting initiation in infants based on delivery characteristics can have a substantial impact on overall antibiotic use in preterm infants. A written policy and auditing may be necessary to establish practice, ensure compliance and determine balance measures. An example of such a policy is shown in Figure 1. Of note, the goal of the algorithm is to provide clarity for situations where antibiotic can be withheld, not to mandate management approach in all other situations which should continue to be informed by local practices.

DURATION OF EMPIRIC ANTIBIOTIC THERAPY

Optimal duration for empiric therapy balances the provision of antibiotic therapy to infants whose blood culture will grow a pathogen with minimized antibiotic exposure in those where the blood culture will remain sterile. Traditional 48- and 72-hour “rule out” periods are based on data from Pichichero et al³⁴, in which positive cultures were identified by daily examination of broth culture for visual turbidity and 12-hourly review of plate subcultures. Current blood culture techniques rely on production of CO₂ or change in gas pressure for continuous detection of bacterial growth and are optimized to detect very low levels of bacteremia. Reports of modern blood culture performance rarely focus on the VLBW population (Table 1). We reviewed 84 cases of VLBW EOS detected in aerobic culture at a single center over 25 years and found a cut-off of 36 hours would have detected ~90% of the infections³³. Had we stopped antibiotics at 36 hours, 4/8 cases detected after 36 hours would have had an ampicillin dose delayed by 3 hours, 2/8 by 9 hours and the remaining 10 hours. During this time period 5313 VLBW infants were admitted to the NICU and ~85% underwent empiric EOS therapy. We estimate that using a cut-off of 36 hours of incubation to discontinue antibiotics would have reduced ~4400 doses of ampicillin in uninfected preterm infants. Given that EOS risk is the primary indication for empiric antibiotic use among VLBW infants, as well as the prolonged half-life of antibiotics such as ampicillin and gentamicin in premature infants in the first week after birth^{35,36} limiting duration of empiric therapy could be a meaningful component of VLBW antimicrobial stewardship.

Implementation of standard cut-off periods to rule out sepsis regardless of duration is best implemented by hard stops in order-sets^{26,37}.

EMPIRIC ANTIBIOTIC CHOICE

Ampicillin, gentamicin and vancomycin are among the top medications used in NICU's across the U.S.¹ The most common empiric antibiotic choice for EOS is ampicillin and gentamicin¹. Recent national surveillance demonstrates ~70% VLBW EOS is due to GBS or *E. coli*, and >90% of these isolates were sensitive to one of these antibiotics⁴². There is less clarity in empiric antibiotic choice for LOS, which may provide an opportunity for VLBW stewardship. Stoll et al reported that 62% of 6215 VLBW infants were evaluated for risk of LOS at least once⁴. Vancomycin was prescribed to ~40% of the infants including 30% of infants without proven infection. The choice for vancomycin in LOS empiric therapy is driven by the predominance of coagulase-negative staphylococcus (CONS) as a cause of LOS and concern for methicillin-resistant *Staphylococcus aureus* (MRSA) infection. However, there are several arguments against use of vancomycin as first line empiric therapy for LOS. The discrepancy between the frequency of "rule-out LOS" and the actual incidence of LOS means a substantial proportion of uninfected infants are exposed to this medication which should be reserved for clinical situations in which its use is mandated by culture data^{43,44}. Ototoxicity, renal failure and development of resistant organisms have all been reported with vancomycin use^{37,42}. Among infants with CONS infection, the adjusted odds of mortality before hospital discharge when empiric vancomycin was administered immediately after blood culture was obtained (n= 2848) was similar to infants (n=1516) where vancomycin was initiated 1 day after culture (1.06, 95% CI 0.81– 1.39)⁴⁵. Possible misclassification of CONS that are contaminants as pathogens and the non-fulminant nature of CONS sepsis provide further arguments for not basing empiric regimen on this organism. A concern for MRSA infection is a justified indication for vancomycin empiric therapy with reported mortality benefit⁴⁶. However, the reported incidence of MRSA LOS among VLBW infants is significantly lower (~1%) compared to incidence of methicillin-sensitive *Staphylococcus aureus* (MSSA) sepsis (2.7%) with comparable mortality⁴⁷. Beta-lactam medications such as oxacillin are more quickly bactericidal compared to vancomycin and may provide benefit as the empiric choice in cases of MSSA infection. MRSA screening in NICUs may provide an opportunity to restrict vancomycin empiric therapy to patients known to be colonized. Multiple studies have demonstrated the success of reducing unnecessary vancomycin use in neonates without increasing adverse events^{23,48}. Thus a review of local pathogen distribution and screening policies may provide an opportunity to reduce empiric vancomycin use in VLBW infants.

STOPPING EMPIRIC ANTIBIOTIC THERAPY

Continuation of antibiotics in the absence of evidence for infection such as bacteremia or cellulitis contributes significantly to overall antibiotic use in the NICU⁴⁹. There are no standard clinical algorithms to inform such decisions, likely adding to the wide center-specific variation in CNI treatment⁴. The potential of biomarkers to inform antibiotic decisions is discussed below. In Table 2, we summarize strategies to support decision making when considering CNI treatment.

BIOMARKERS OF INFLAMMATION

The use of biomarkers, specifically acute phase reactants, to guide antibiotic therapy in the NICU has long been proposed among neonates⁵⁰. An obvious drawback is that these biomarkers reflect systemic inflammation that can be caused by other conditions besides bacterial infection. The scope for biomarker-guided antibiotic use includes: determining initiation, determining continuation when an infection is suspected but not confirmed and determining duration in diseases with an unambiguous need for antibiotics such as bacteremic sepsis.

The sensitivity of biomarkers, even in combination, is not high enough to be the sole determinant in withholding antibiotic initiation in the extremely preterm population^{51–53}. Biomarker-guided antibiotic initiation is likely to perform best in scenarios with a low prior probability of true infection, high antibiotic use rates and among populations with low risk of morbidity if therapy is delayed. Consequently, most studies of biomarker-guided initiation have been conducted in outpatient settings^{54–56}. In ICU, two trials in adult patients have studied antibiotic initiation based on procalcitonin (PCT)-guided algorithms. One study found no effect, and although the other found a significant reduction in antibiotic use⁵⁷, a 53% non-compliance in the PCT arm raised concerns about generalizability of the study^{55,57,58}. One trial in neonates found the addition of IL8 (> 70 pg/ml) to standard management (clinical signs and CRP >10 mg/L) among 1291 NICU admissions resulted in a reduction of antibiotic initiation for suspected EOS from 49.6% to 36.1% (p <0.001) without any ‘missed’ infections⁵⁹. The study however was not focused on preterm infants and included only 13 cases of culture-confirmed infection. Multiple studies report significant reductions in antibiotic duration using biomarker-guided decision tools (particularly PCT) without changes in mortality or re-infection⁵⁵. Most of these studies include patients with a known focus of infection such as community-acquired pneumonia and exclude immunosuppressed patients or patients with an unknown infection source⁵⁵. In contrast, biomarkers have been used in neonates to determine duration of therapy for CNI with variable impact⁵². The NeoPINS trial randomized infants born < 34 weeks gestation with suspected EOS to antibiotic therapy guided by PCT measurements⁶⁰. Antibiotic duration was decreased by 9.9 hours (55.1 vs 65 hours, p <0.001) and length of stay by 3.5 hours (123 vs. 126.5 hours, P=0.002) in the PCT arm. The recommended antibiotic regimens of 5–7 days for culture-negative infants in the standard arm classified as intermediate risk is greater than that reported at other centers²⁸ suggesting that the efficacy of this intervention will vary depending on local practice. The opposite effect, of significantly increased antibiotic use, has been reported with CRP use and argues against incorporation of using biomarkers to guide antibiotic durations in CNI without evidence for improved outcomes with such practice^{61,62}.

A final use of biomarkers may be to determine length of therapy for conditions in which antibiotic use is mandated. Hemels et al, observed that most CONS bacteremia at their center resolved within 72 hours of initiation antibiotic initiation when the infants demonstrated clinical improvement, CRP levels decreased and central catheters were removed³⁰. This group later reported an observational experience of treating infants meeting such criteria with 3 or 7 days of antibiotics, and found no difference in resolution of

bacteremia or clinical outcome⁶³. Cuoto et al conducted a pre-post study utilizing CRP measurements to determine length of antibiotic treatment among infants with culture-confirmed sepsis (77 vs 122 infants)⁶⁴. A significant reduction (16 to 9 medians days) was observed in the post-implementation period when antibiotics were stopped if CRP declined to <12 mg/L⁶⁴. Whether resolution of a host inflammatory marker consistently reflects resolution of tissue level bacteremia with negligible recurrent bacteremia requires larger studies.

Overall, the role of biomarkers in determining antibiotic prescription among preterm infants remains promising but unclear. Studies reporting antibiotic use reduction with biomarker-guided therapy have high baseline antibiotic use rates that will impact the anticipated effect size when translated to a different setting. While we await definitive studies perhaps the best first step would be to optimize blood culture collection technique and considering discontinuation of antibiotics in culture negative infants⁶⁵.

CONCLUSION

Despite the challenges of implementing antibiotic stewardship in the premature infant, promising strategies that specifically target this population exist. Incorporating these strategies require a re-adjustment of our risk-benefit mind-set such that we acknowledge and account for the risk of unnecessary antibiotic use. Much of the focus in antibiotic use among premature infants has been to protect the child from infection – while undoubtedly a relevant focus, that protection should not happen at the risk of injury to the uninfected child. Achieving this balance requires standardization of care, measurement of antibiotic use, strong balance measures and continuous evaluation of practices and outcomes. An urgent need of the field lies in building the “equipoise” around the current approach to antibiotic use that will enable systematic examination of the risk and benefits.

Acknowledgments

Funding Source: 1K23HD088753-01A1 NICHD; 1K08HL132053-01A1 NHLBI

Financial disclosure and conflict of interest: The authors have no financial relationships or conflicts of interest relevant to this article to disclose.

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What is known about this topic:

Empiric antibiotic use for “rule-outs” is a major contributor of overall antibiotic use in neonatal units. In the presence of high incidence of infection, labile clinical status and long turn-around time for cultures, finding strategies that allow safe antibiotic restriction can be challenging.

What this study adds:

This review focuses on aspects of empiric therapy commonly prescribed in the very low birth weight infant. We describe strategies that are likely to have the most immediate impact on optimizing antibiotic use in his population.

Guidelines for EOS Evaluation in Infants <34 Weeks Gestation

Maternal Indications : Pregnancy induced hypertension, pre-eclampsia, other maternal medical condition, long standing intrauterine growth restriction

Respiratory support: need for supplemental oxygen (>1hr after birth), CPAP, mechanical ventilation

Hemodynamic support: Inotrope administration for poor perfusion/low blood pressure for gestational age in absence of other explanation (i.e. anemia)

Rule out EOS : blood culture, CBC/diff, antibiotics

Routine care: No culture. CBC for non-infectious concerns (e.g. anemia, PEC induced neutropenia/thrombocytopenia)

--Adapted from the consensus guideline of Pennsylvania Hospital Intensive Care Nursery

Figure 1:

Guidelines for Evaluation of EOS in Infants Born <34 weeks

Table 1.

Blood culture time-to-positivity among neonates

Reference	Study Cohort	Culture Timing [†]	Culture n [*]	Culture positive by hours of incubation (%)			
				24	>24–36	>36–48	>48–72
Pichiero et al, 1979 ³⁴	24–41 weeks	n/a	105	67.6	n/a	96.2	98.1
Mukhopadhyay et al, 2017 ³³	Birth weight <1500 g	72 hours of age	84	74.4	90.2	97.6	100.0
Garcia-Prats et al, 2000 ³⁸	All gestations (including CONS)	~84% at >72 hours of age	248	81.5	92.7	94.8	97.2
Garcia-Prats et al, 2000 ³⁸	All gestations (excluding CONS)	n/a	113	91.2	93.8	94.7	96.5
Kumar et al, 2001 ³⁹	All gestations	Majority >48 hours of age	366	51.9	88.3	95.9	98.9
Guerti et al, 2010 ⁴⁰	All gestations	~80% at >72 hours	358	59.5	n/a	91.1	97.5
Guerti et al, 2010 ⁴⁰	All gestations (excluding CONS)	n/a	144	86.8	n/a	93.8	95.8
Biondi, 2014 ⁴¹	Infants in non-ICU setting	<90 days of age	392	91	96	99	100

Footnotes:

* Number of culture shown exclude contaminants (*micrococcus*, *Bacillus sp.*, *Corynebacterium sp.*); yeast isolates; and cultures obtained after start of antimicrobials, except Biondi et al⁴¹, where contaminants could not be excluded in time to positivity results. n/a-not reported.

[†]Timing shown for all positive cultures reported in the study including those classified as contaminants. ref 34 specifies subjects were neonates but does not clarify infant age at time of cultures. CONS-coagulase negative staphylococcus

Table 2.

Strategies to Optimize Use of Antibiotics for Culture-negative sepsis among VLBW Infants

Sepsis Evaluation	
Blood culture	<ol style="list-style-type: none"> 1. Obtain minimum 1 mL blood per pediatric blood culture bottle 2. Consider 2 separate cultures to optimize identification of contaminant species after 72 hours of life
CSF culture	Strongly consider obtaining CSF culture prior to initiation of antibiotics for evaluations after 72 hours of life
Urine culture	<ol style="list-style-type: none"> 1. Strongly consider urine culture in older VLBW infants without central lines 2. Obtain culture by sterile catheter or supra-pubic aspirate to minimize isolation of contaminant species
Non-bacterial cultures	<ol style="list-style-type: none"> 1. Consider urine CMV testing for infants with BW <1000 grams fed mother's own milk 2. Consider additional respiratory and gastrointestinal viral testing in site-specific appropriate seasons
Antibiotic Choice and Duration	
Conduct annual review of unit-specific culture isolates and antibiotic susceptibility data to inform empiric antibiotic choice	
Discontinue antibiotics when blood cultures are sterile by 36–48 hours incubation	
<p>If decision is made to empirically administer antibiotics for presumed and culture-negative infection (CNI):</p> <ol style="list-style-type: none"> 1. Use patient-specific colonizing data to choose least broad-spectrum antibiotic 2. Set local guidelines for antibiotic duration for presumed and CNI 3. Ensure that the rationale, risks and benefits of antibiotic administration for presumed and CNI are discussed with all members of the clinical care team and with the infant's parent(s) or guardians 4. Involve the stewardship team in decision making 	