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Adverse Consequences of Neonatal Antibiotic Exposure

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Abstract

Purpose of the review—Antibiotics have saved lives and improved outcomes, but they also influence the evolving microbiome. This review 1) summarizes reports on neonatal infections and variation in antibiotic utilization, 2) discusses the emergence of resistant organisms, and 3) presents data from human neonates and animal models demonstrating impact of antibiotics on the microbiome, and how microbiome alterations impact health. The importance of antibiotic stewardship is also discussed.

Recent findings—Infections increase neonatal morbidity and mortality. Furthermore, the clinical presentation of infections can be subtle, prompting clinicians to empirically start antibiotics when infection is a possibility. Antibiotic-resistant infections are a growing problem. Cohort studies have identified extensive center variations in antibiotic usage and associations between antibiotic exposures and outcomes. Studies of antibiotic-induced microbiome alterations and downstream effects on the developing immune system have increased our understanding of the mechanisms underlying the associations between antibiotics and adverse outcomes. The emergence of resistant microorganisms and recent evidence linking antibiotic practice variations with health outcomes has led to initiation of antibiotic stewardship programs.

Summary—This review encourages practitioners to assess local antibiotic use with regard to local microbiology, and to adopt steps to reduce infections and use antibiotics wisely.

Keywords

Antibiotics; neonate; microbiome; antibiotic resistance; antibiotic stewardship

Introduction

Humans are colonized with microorganisms with which we co-exist in a mutualistic relationship. Microbes contribute to mechanisms that protect against colonization by pathogens, participate in maturation of the immune system, and provide key metabolic functions. [1*–4] On the other hand, microbes also cause infections in neonates that result in significant mortality and neurodevelopmental impairment among survivors.[5–6] Clinicians have used antibiotics to prevent and treat infections resulting in millions of lives saved;

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Conflicts of Interest

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however, with benefits come risks. Microorganisms develop mechanisms of resistance against antibiotics and transfer them to other microorganisms.[7, 8**] Genes conferring antibiotic resistance are present in the microbes inhabiting the intestine of preterm infants cared for in a NICU environment as well as healthy term infants [9, 10*, 11*, 12] Antibiotic-resistant pathogenic microorganisms can cause serious, difficult to treat infections in neonates.[8] Because of the impact of infections and the subtle clinical presentation of infection in neonates, exposure to antibiotics is unavoidable for many neonates, particularly those born prematurely. Epidemiologic evidence suggests associations between neonatal antibiotic exposures and short and long term health outcomes. Through neonatal animal studies we are gaining an understanding of how antibiotic exposures influence acquisition of microbial diversity in the neonatal period, and how these antibiotic-influenced alterations could impact microbiome-linked short and long-term health. [1*, 13, 14*, 15**]

This review will: 1) describe the extent and variation in antibiotic practice in NICUs; 2) update information on infections caused by resistant organisms in neonates, and 3) present evidence identifying associations between antimicrobial practice and short and long term clinical outcomes. Because the biologic plausibility for these associations is based in part on expanding knowledge of how antimicrobials influence the developing microbiome, we will summarize recent animal studies linking neonatal antibiotic exposure, microbiome variation, immune system development, and disease. Finally, because efforts to optimize antibiotic use in neonatal intensive care units are underway, we will review emerging evidence of their effectiveness.

Rationale for preventive and empirical therapeutic use of antibiotics in neonates

In the modern era of antibiotics, which arguably began in September 1928 in the staphylococcal plate contaminated with *Penicillium notatum* in Alexander Fleming's laboratory [16], clinicians have used antibiotics therapeutically and prophylactically to save millions of lives. Particularly noteworthy for neonates, the incidence of early-onset Group B streptococcus (GBS; *Streptococci agalactiae*) sepsis has decreased 10-fold since 1996 when a risk-factor based preventive approach inclusive of antenatal and postnatal antibiotics was introduced. However, with this approach approximately 30% of mothers in the U.S. are exposed to intrapartum antibiotics. [17–22]

Early onset sepsis, even with GBS prophylaxis, affects a higher percentage of prematurely born infants than term infants. [20] Preterm infants, who stay for weeks in the NICU, remain at risk for late onset sepsis (LOS).[23] The prematurely born neonatal population presents challenges due to imperfect skin and mucosal barriers, invasive procedures, and a partially effective immune system which relies largely on innate immunity and neutrophil function for defense against infection. [24, 25**]

Infections occurring after the first postnatal days, which affect 20–40% of extremely preterm infants, are due predominantly to gram-positive bacteria (approximately 70–80%). Coagulase negative staphylococcus (CONS), an oxacillin resistant organism, is the most commonly isolated organism. Methicillin resistant staphylococcal (MRSA) infections are

also on the rise. Gram negative infections, particularly from enteric gram negative bacilli, account for 10–20% of infections, and fungal species account for the remainder (approximately 10%).[5, 8**, 23**, 26]

As a consequence of the GBS prevention guidelines, approximately 10% of the total neonatal population are exposed to antibiotics in the first postnatal days, and almost 100% of the extremely preterm population are exposed to ampicillin and an aminoglycoside.[27, 28*, 29, 30, 31 32**] The presentation of neonatal infections can be subtle, leading clinicians to empirically use antibiotics to avoid delay in treating true infections. [27, 31] In a sample of over 200 NICUs, ampicillin, gentamicin and vancomycin were the first, second and fourth most commonly prescribed medications.[32**] While empirical antibiotic use is frequent, a review of over 1500 patients in one NICU revealed that only 5% of all neonatal antibiotic use was for culture proven infections.[33]

Variations in antimicrobial practice

Centers vary widely in use of antibiotics for neonates, [28*, 34, 35, 36]. In a recent survey of guidelines for use of 41 antimicrobials in French NICUs, 1 to 32 different dosing regimens per drug were identified.[37*] A forty-fold variation in NICU antibiotic prescribing practice was observed in a review of over 50,000 NICU patients in 127 California NICUs with similar burdens of proven infection, NEC, surgical volume, and mortality.[38**] A review of antibiotic use in 89 NICUs participating in the European Study of Neonatal Exposure to Excipients identified variation in antibiotic dosing among the most commonly used antibiotics, with significant under- and over-dosing of antibiotics (based on dosing guidelines produced by the British National Formulary for Children). [39*] Under-dosing of antibiotics leads to low concentrations of antibiotics, particularly at sites of heavy microbial concentrations such as mucosal surfaces and biofilms surrounding central lines, and increases the likelihood of developing resistant microbes.[8**, 40]

Antibiotic Resistance: emerging problem for neonatal infections

Mechanisms to develop antibiotic resistance include: 1) acquisition of enzymes that alter antibiotic structure and function; 2) mutations in bacterial targets such as penicillin-binding proteins, and 3) changes in efflux pumps allowing removal of antibiotics from bacteria or porins which prevent antibiotics from entering bacteria. [8**] With awareness of resistance mechanisms, Harold Neu warned of complacency with regard to the threat of antimicrobial resistance. In 1992 he warned that bacteria had become resistant to antimicrobial agents as a result of chromosomal changes or the exchange of genetic material via plasmids and transposons. By 1992, Gram positive and Gram negative pathogens had become resistant to virtually all of the original generations of antibiotics. He hypothesized that extensive community and hospital-based use of antibiotics had fueled the problem. Furthermore, he suggested that antibiotic control programs, better hand washing and other infection control practices, as well as more potent antibiotics would need to be adopted and developed to limit resistance.[7] Neu’s warnings and advice must be acknowledged by clinicians caring for neonates.

Dr. Roger Soll responded to the California NICUs report on variations in antibiotic practice by identifying increases in antibiotic resistant microorganisms as a major threat and direct result of our overuse of antibiotics.[41] Dr. Using data from the World Health Organization (WHO), he found the proportion of *Escherichia coli*, Klebsiella *pneumoniae* and *Staphylococcus* aureus resistant to commonly used antibacterial drugs exceeded 50% in many settings.[42] The U.S. Centers for Disease Control (CDC) estimated that greater than 2 million people in the U.S. become ill annually, and over 23,000 die as a result of resistant bacteria.[43] Continued and widespread use of antibiotics has generated strong selective pressure on microorganisms, favoring the emergence of resistant strains.[44] This is problematic as prevalence of microbes with antibiotic resistance has reached critically high levels and antibiotic discovery efforts have reached critically low levels. Federal funding of antibacterial research is dwarfed by that of other disease areas.[45]

Among Gram positive pathogens, the emergence of strains of GBS that are resistant to erythromycin and clindamycin have caused problems, especially for women who are penicillin allergic.[19] Later NICU infections caused by staphylococcal species have been more problematic. Coagulase negative staphylococcus (CONS) and MRSA are common NICU pathogens. CONS usually requires treatment with vancomycin, as does MRSA.[46] However, widespread use of vancomycin can lead to development of vancomycin resistance, particularly with vancomycin-resistant enterococci, or VRE. VRE has been linked with higher mortality than vancomycin susceptible enterococci.[47*] Unfortunately, extended spectrum β-lactamase (ESBL)-producing gram negative pathogens that are resistant to cephalosporins have also emerged, as have gram negative organisms resistant to piperacillin-tazobactam, aminoglycosides and Klebsiella resistant to carbepenems such as meropenem. [8**, 44, 48]

Antibiotic Practice Linked to NICU outcomes

In the last decade, single and multi-center reports have linked use of broad spectrum antibiotics, particularly cephalosporins, with subsequent mortality and candida infections. [35, 49*] Studies have linked the number of days exposed to antibiotics with subsequent mortality, necrotizing enterocolitis and non-CONS infections.[28*, 50, 51] As noted, highly prevalent use of vancomycin in NICUs and other hospital areas has been associated with high colonization rates and outbreaks of infections with VRE.[47*] Infections may emanate from the intestine, the site of development of resistant strains and transfer of resistance genes among microorganisms. [52] In one cohort of infants longitudinally followed through their NICU stay, sequencing identified detectable levels of the sepsis-causative organism in stool samples prior to disease onset for 82% of LOS cases.[53]

Antibiotic Practice influences the microbiome

The diversity of the microbiome is contributes to normal growth and development, including normal maturation of the immune system.[2] Before the associations between antimicrobial selection, duration and outcomes were known, investigators had ascribed the decreased intestinal microbial diversity in neonates with increased exposure to antibiotics in the first postnatal days.[54–56] More recently, using molecular sequencing approaches, early

postnatal as well as prenatal antibiotic exposure for GBS prophylaxis has been associated with significant alterations of the microbial inhabitants on the intestine.[57*, 58*] A higher percentage of Enterobacter colonization and lower bacterial diversity were noted in preterm infants who received 5–7 days of empirical antibiotics compared with those not exposed or exposed to shorter courses.[59] Small longitudinal studies also point to increased colonization with proteobacteria, inclusive of *Enterobacter* spp, comprising the microbiota in infants who subsequently develop NEC.[60, 61] Enterobacter species are often resistant to beta-lactam antibiotics. The resistance genes against beta-lactams are often carried in plasmids, which are easily transmitted between bacteria, so if there are more resistance-mechanism carrying bacteria in the intestine, the risk for an accumulation of resistance plasmids is increased. This phenomenon of development of resistance gene 'clusters' has been identified in swine that are routinely treated with antimicrobials. [59**, 62]

Of some consolation, recent reports suggest microbiome diversity recovers over time after relatively short antibiotic courses in the first postnatal days. Shorter courses of antibiotics (1–3 days vs. 5–7 days), were associated with suppression and alteration of the microbiome for several weeks, but recovery occurred after the third postnatal week. [59**, 63, 65]

Antibiotics, the microbiome and longer-term effects

As information has emerged about associations between microbiome diversity and health, investigators have studied links between antibiotic exposures in the neonatal period and development of immune-related diseases such as asthma. In a U.S. cohort of 1401 children association between neonatal antibiotic exposure and asthma was strongest for those with no asthma family history. [65] Such associations are compelling and biologically plausible and fit with the hygiene hypothesis.[66] A systematic review of 20 studies identified the potential for bias, but concluded that early antibiotics, and even prenatal antibiotic exposures "seemed to slightly increase the risk of childhood asthma."[67] A subsequent meta-analysis of over 40 studies concluded that "truly indicated antibiotics should not be withheld from infants or young children for fears they might develop asthma." [68] Subsequent studies of large population-based cohorts continue to indicate that there may be associations, but evidence is not overwhelming. Swedish investigators have reported a positive association between antibiotic exposure in fetal life or childhood and subsequent asthma in a National Birth cohort; however, in sibling control analyses, associations disappeared or decreased, indicating that factors shared by the families may be influencing the association.[69]

More recent cohort studies have assessed associations between early antibiotic exposure and other long-term health outcomes. One study examining the association between antibiotic exposures in the first postnatal year and subsequent asthma (n = 79,946) demonstrated that more antibiotic exposure was associated with subsequent higher body mass index in boys. [70] In population-based studies in Denmark and the U.S., accumulating antibiotic exposures, particularly anti-anaerobic medications, throughout the early years (not limited to neonatal exposures) were associated with subsequent inflammatory bowel disease and celiac disease.[71–73] These associations are of interest; however, cause and effect cannot be inferred as the antibiotic courses could be a marker of clinicians' responses to the natural history of the disease.[73]

A recent animal model study suggests an association between antibiotic alterations of microbial colonization and type 1 diabetes. In this experiment, a combination of broad-spectrum antibiotics or vancomycin alone was given to neonatal non-obese diabetic (NOD) mice that spontaneously develop autoimmune type 1 diabetes. The antibiotic-treated male animals developed higher rates of diabetes. The microbiome was ablated in the combination treated group, and was significantly altered by vancomycin. Among the changes in microbiome that occurred with Vancomycin were increased Escherichia and Lactobacillus genera and decreased members of the Clostridiales order compared to controls. Along with the microbiome alterations, a major reduction of IL-17-producing cells was observed in the lamina propria of the ileum and the colon of vancomycin-treated mice. [14*]

The mechanism linking antimicrobials, microbiome and disease could be via the disruption of the interactions of specific microbiome microorganisms, and ‘first responder’ immune cells in the ileal lamina propria.[14*] Discovery of a connection between antibiotics and suppression of IL-17 producing T cells (Th17) led to discovery of the importance of segmented filamentous bacterium (SFB) on the differentiation of the Th17 cells. SFB are non-culturable Clostridia-related species. In studies of germ-free mice, colonization with SFB alone could recapitulate coordinated maturation of a wide range of both pro and regulatory T cell responses induced by the whole mouse microbiota. This led investigators to hypothesize that SFB, already known as a potent inducer of mucosal IgA, likely play a unique role in the postnatal maturation of gut immune functions. The low level production of IL-17 stimulated by SFB may optimize local protective bactericidal mechanisms and reduce infection risk in immunocompetent hosts by inducing production of anti-infective compounds (such as IgA) and helping to maintain a sufficient number of neutrophils to contain potential invading pathogens. In addition, SFB, in contrast to most culturable intestinal flora, develop tight junctions with the luminal surface of the small intestine. The tight adherence may strengthen barrier function.[74, 75] While the data linking antibiotic use with T cell subset suppression, and the importance of SFBs in maturation of intestinal immunity is of interest, these theories have yet to be validated in human neonates.

Microbiome Alterations and Developing Immune System

For neonates, particularly those born extremely prematurely, immune cell synthesized antibiotic proteins and neutrophils are key aspects of neonatal immune system defense. [24, 25**] In a piglet model, treatment with antibiotics reduced diversity of gut microbiota and reduced the expression of a large number of immune-related genes.[76] Recent investigations have identified links between the developing gut microbiome in the neonatal period and increases in circulating protective neutrophils postnatally.[15**, 77] In a neonatal rodent model, treatment with postnatal antibiotics decreased the quantity and diversity of microbes in the newborn animal’s intestine, which may be beneficial if further pathogen exposure could be avoided. However, when normal colonization by gamma-proteobacteria and subsequent granulocytosis were inhibited, the likelihood of sepsis after exposure to E coli and Klebsiella administered after the microbiome-altering antimicrobial course was increased. The mechanism appears to be related to decreased TLR4 receptor stimulation following microbiome alteration which led to downstream decreases in IL-17A and G-CSF production.[15**] This suggests an antibiotic-linked mechanism which places infants at

higher risk of infection via intestinal translocation to a neutrophil-depleted environment after antibiotic exposure. Thus, like the earlier description of the interactions between segmented filamentous bacteria and T cell development, it is of interest that the intestinal microbiome may be a source of both immune protection, and organisms responsible for late onset sepsis. [78]

Antibiotic practice modifications/stewardship efforts

While investigations of mechanisms of how the microbiome influences neonatal health are ongoing, clinicians make daily antibiotic decisions for thousands of infants. Clinicians choose which infants to treat, what to treat with, and how long to treat.

Who to treat?

Efforts to improve the accuracy of which neonates to empirically treat with antibiotics include development of an on-line tool to quantify risk of early onset sepsis among term and near term infants. [29, 79**, 80] The online tool includes consideration of population prevalence of early onset sepsis, maternal clinical signs and GBS colonization status, and the neonate's clinical signs. Application of such a guideline could result in decreased antibiotic treatment in 80,000 to 240,000 US newborns each year.[79**]

Biomarkers from blood testing including cytokines and cell surface markers, are promising, but are most helpful for their negative predictive value. [81] Two recent reports suggest that gene expression patterns may distinguish infected from uninfected neonates. These efforts may eventually aid in detection of truly infected neonates, but in the shorter term will help us better understand variations and mechanisms of the neonatal immune response. [82, 83*] For these blood sampling-based approaches, clinical suspicion must exceed a threshold that drives clinicians to order the test.

For neonates in the NICU, use of heart rate characteristics to help determine who to empirically treat for sepsis appears to be helpful. [84, 85*] In the multicenter randomized trial of visible results from heart rate characteristic monitoring vs. blinded data collection, 30 day mortality among infected infants was 10% among those with displayed heart rate characteristics, and 16% among controls ($p = 0.01$). Investigators also found that the number of sepsis work-ups and days of antibiotics total in both groups were similar.[86]

What to use?

Some clinicians choose oxacillin or other similar antibiotics for for empirical therapy of late onset sepsis and reserve vancomycin when cultures are positive, while others may chose vancomycin for empirical therapy the prevalence of CONS. The choice for Gram negative coverage is frequently an aminoglycoside, but some clinicians can be driven by concerns that these organisms can cause meningitis, leading to use of cephalosporins. [27, 32]

While debate surrounds the choice for empirical coverage for early and late onset sepsis in NICUs, a cohort study of infants with positive cultures for E. coli (n =267) revealed that when empirical therapy did not include an antimicrobial agent against the infecting E. coli strain, it was not associated with increased 30 day mortality. This suggests that initial

empirical treatment with aminoglycosides, and later treatment with more potent, broader spectrum antibiotics may be safe.[87] Similar results were observed with studies of infants with CONS, where mortality outcomes were not improved with empirical vancomycin started before culture results were available.[88] A similar look suggested benefit for empirical vancomycin when MRSA caused the infection, but screening strategies may identify infants at risk for MRSA and allow for selective use of empirical vancomycin.[89]

How to dose?

Gentamicin dosing is frequently guided by assessment of peak and trough levels. While over 80% of empirically selected doses result in effective and non-toxic levels, preterm infants exhibit variation in pharmacokinetics.[90] Only in the last year have we had dosing guidance for ampicillin derived from pharmacokinetics (pK) studied in a NICU cohort.[91] Vancomycin pK has also recently been examined, and modifications in dosing based on individual variations may result in more infants reaching targeted trough levels.[92*, 93] Work by the Pediatric Trials Network has identified dosing regimens based on gestational and postnatal age for piperacillin tazobactam, metronidazole, meropenem, and antifungals.[94*, 95–97, 98*]

How long to treat?

Benitz and colleagues have provided an approach for preterm and term infants at risk for early onset sepsis.[99] Among the key recommendations which could limit antibiotic use and is concordant with the latest recommendation by members of the AAP Committee on Fetus and Newborn, is that isolated abnormal hematological or acute-phase-reactant measurements should not justify continuation of empiric antibiotics for more than 48 hours in well-appearing infants with negative culture results. [99, 100] We await similar evidence to support guidance for late onset sepsis in NICUs.

Impact of stewardship

While antibiotic stewardship continues to be a priority [101], use of antibiotics is likely to remain high among the neonatal population. As the Vermont Oxford Network's 'Choosing Antibiotics Wisely' program begins, we can be heartened by reduction in candidiasis which is correlated to both increases in fluconazole prophylaxis and decreased empirical use of broad spectrum antibiotics, particularly cephalosporins.[102, 103] In the single center report on VRE mentioned earlier, colonization with vancomycin resistant organisms decreased over a period of strict use guidelines for vancomycin. Vancomycin resistance increased as adherence to guidelines waned.[47]

In addition to choice of antibiotics, another recommendation by Neu was to pay closer attention to hand hygiene.[7] Single and multicenter center efforts have reduced the incidence of central line associated blood stream infections, which should lead to decreased antibiotic exposures, but better diagnostic methodologies may be needed before clinicians will significantly reduce empirical treatment, particularly for preterm infants.[104–108] The CDC has provided four core principles (TABLE) to put in place to reduce development of

resistant organisms, inclusive of considerations for improved hygiene.[7, 43] To this list, we would add improvement in diagnostic test sensitivity and optimizing dosing information.

Conclusion

Antibiotics are an unavoidable fact of neonatal life. However, antibiotics are most often used in infants who are not infected. Their use has wide variations and neonatal-specific pharmacokinetic data on many antimicrobials is increasing, but for most antimicrobials, is lacking. Evidence from animal studies linking antibiotic use in the neonatal period to variation in the evolving microbiome which impacts immune development and subsequent health is emerging, but associations between antibiotic use early in postnatal life in humans and later complex common diseases such as asthma have not been strengthened (or refuted) by epidemiologic studies. More acutely, organisms responsible for late onset sepsis in neonates may be more likely to emerge and invade via selection influenced at least in part by early antimicrobial practice variations (choice of antibiotic, dose used, duration used), and possibly by effects on the local immune and barrier defenses in the intestine. Increasing knowledge of antimicrobial pharmacokinetics will help avoid under-dosing that contributes to development of resistant microorganisms. Selective use of antibiotics through evidence-based antibiotic stewardship programs is also likely to help, as will clinical approaches that appear to be effective at reducing occurrence of any infections.

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Key points

1. Antibiotics are an often unavoidable, and sometimes life-saving part of neonatal clinical care.
2. Antibiotic use by clinicians has been accompanied by bacterial development and sharing of antibiotic resistance
3. Prevalent empirical antibiotic use has been linked with subsequent risk of infections, necrotizing enterocolitis and death
4. Understanding of mechanisms linking the evolving microbiome, the developing immune system, and subsequent health in animal models is increasing
5. Antibiotic stewardship efforts, including increasing knowledge of pharmacokinetics of antimicrobials, to optimize antimicrobial use have been successful.

Table 1

CDC 2013 core principles

■ preventing infections and preventing the spread of resistance
■ tracking resistant bacteria
■ improving the use of today’s antibiotics
■ promoting the development of new antibiotics and developing new diagnostic tests for resistant bacteria