Abuse of Antibiotics in Perinatology: Negative Impact for Health and the Economy

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Education Gaps

1. The highest abuse rate of antibiotics occurs during the perinatal period and before the infant is 1 year of age.
2. Antibiotics affect the microbiome, which leads to consequences.
3. Short- and long-term negative effects of antibiotic use during pregnancy and the neonatal period are underestimated.

Abstract

To use medications appropriately, patients need to be treated based on their clinical conditions, in doses that are based on their individual requirements, for an adequate amount of time, and at the lowest expense. The perinatal period is characterized by an excessive use of antibiotics. This antibiotic abuse can lead to antibiotic resistance, microbiome alterations, and dysbiosis, which have been associated with serious complications such as infections, abnormal brain development, allergies, autoimmune disorders, obesity, and an increase in mortality as well as an increase in health care expenditures. The need to optimize antibiotic utilization in perinatal medicine has never been more urgent; there is not much more time to wait.

Objectives After completing this article, readers should be able to:

1. Identify potential adverse effects of antibiotic misuse.
2. Recognize the responsibilities of clinicians to prevent antibiotic abuse.
3. Apply clinical measures to modify current practices and improve outcomes and costs.

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ABBREVIATIONS

CI	confidence interval
GBS	group B *Streptococcus*
HR	hazard ratio
ICU	intensive care unit
RR	relative risk
WHO	World Health Organization

INTRODUCTION

Antibiotics do save lives but, unfortunately, they are abused and misused in perinatal medicine. The Conference of Experts on the Rational Use of Drugs, convened by the World Health Organization (WHO) in Nairobi in 1985, defined the rational use of medications as follows: "The rational use of drugs requires that

patients receive medications appropriate to their clinical needs, in doses that meet their individual requirements, for an adequate period of time, and at the lowest cost to them and their community." (1) The irrational use of medications is a major problem worldwide. WHO estimates that "more than half of all medicines are prescribed, dispensed or sold inappropriately" and the 2 most important issues may be the prescription of too many medications per patient (ie, polypharmacy) and the improper use of antimicrobials. (2)

In this article, I will focus on issues surrounding irrational uses of antibiotics in perinatal medicine, because it is apparent that the highest abuse rate of antibiotics occurs during this period and before the infant is 1 year of age. It is likely that at least 50% of pregnant women receive antibiotics during their hospitalizations, though the specific data have not been documented. In some NICUs, more than 70% of neonates are prescribed antibiotics. (3)(4) A similar situation occurs in pediatric outpatient departments and intensive care units (ICUs) but these will not be reviewed in this article. Antibiotic abuse is associated with antibiotic resistance, microbiome alterations, and dysbiosis. This has been linked to greater length of hospital stay, increased mortality, and greater risk of various disease states later in life such as infections, asthma, obesity, diabetes, atherosclerosis, and autoimmune disorders, among others. To minimize antibiotic abuse in ICUs, a multidisciplinary team can work to develop and implement interventions to decrease the inappropriate use of antibiotics. Indeed, antimicrobial stewardship programs have been shown to decrease or avoid misutilization and improve outcomes. Optimizing antibiotic utilization in perinatal medicine is a challenge but the rewards are extraordinary.

ANTIBIOTIC ABUSE DURING PREGNANCY

During pregnancy, most women receive at least 1 medication, with antibiotics being among the more frequently prescribed. (5) It has been estimated that antibiotics account for 80% of the medications prescribed during pregnancy (6) and more than 40% of pregnant women receive an antibiotic immediately before delivery. (7) Although most obstetric studies have examined the benefits of antibiotics from the perspective of short-term maternal and neonatal complications, very few publications have addressed the risks and long-term consequences.

Antibiotic use in pregnancy is aimed at preventing neonatal group B *Streptococcus* (GBS) sepsis, cesarean prophylaxis, chorioamnionitis, preterm labor with intact or ruptured membranes, screening and treatment of asymptomatic bacteriuria or bacterial vaginosis, and documented infections such as endometritis and urinary tract infections. Therefore, the vast majority of infants are being exposed to antibiotics before delivery. Although indications for maternal antibiotics are sometimes justified, there are potential risks linked to their overuse and misuse that may surpass the benefits. In the United States, the proportion of women receiving unindicated antibiotics has been shown to be approximately 40% to 45%. (8)

The following is a summary of the main conditions that are frequently associated with obstetric antibiotic abuse or misuse.

Prevention of Neonatal GBS Sepsis

Intrapartum antibiotic prophylaxis to decrease the risk of neonatal early-onset GBS infection has coincided with a significant decrease in incidence. In some countries, up to 30% of pregnant women are treated with intrapartum antibiotics. However, universal GBS screening has some limitations and recent evidence suggests a link between intrapartum antibiotic prophylaxis and adverse short- and long-term neonatal outcomes. One review found that intrapartum antibiotic prophylaxis was effective but high-quality evidence of the effectiveness of such a practice was limited. (9) In addition, the studies included did not consider the potential risks of antibiotics. (9) A retrospective cohort study in Australia showed that 7 of 10 term neonates with early-onset GBS infection were born to women who had negative results on screening. (10) Also, the authors did not find any difference in rates of infection between screened and unscreened pregnancies. (10) However, the American Academy of Pediatrics and the American College of Obstetricians and Gynecologists currently recommend the use of universal antenatal microbiologic-based testing for the detection of maternal GBS colonization to determine which women should receive intrapartum antibiotic prophylaxis. (11) Authors of a meta-analysis estimated that globally, GBS colonization occurs in approximately 18% of pregnant women, with regional variation of 11% to 35%. Without intrapartum antibiotics prophylaxis, approximately 50% of neonates born to GBS-positive mothers become colonized with GBS, and of those, 1% to 2% will develop GBS infection. Current clinical practices are focused on identifying women at highest risk of colonization and/or intrapartum transmission to target antibiotic prophylaxis for GBS.

Prophylaxis in Cesarean Sections and Operative Vaginal Deliveries

Cesarean delivery is the most significant cause of infections in women during the postpartum period. Women

undergoing cesarean section have a 5- to 20-fold greater chance of getting an infection compared with women who give birth vaginally. Approximately 20% to 25% of women who have a cesarean delivery develop a wound infection, endometritis, or urinary tract infection. (12) Prophylactic antibiotics given to women who deliver via cesarean section have been shown to reduce the incidence of wound infection, endometritis, and serious infection-related complications by 60% to 70%. (12)(13) However, there are very few data about the adverse effects of this practice and there is no information about the effect on the neonate, which makes it difficult to determine the risk-benefit ratio. The simplest and shortest antibiotic regimen should be used (ie, single intravenous dose regimen). This has been shown to be as effective as multiple-dose regimens, which sometimes are unfortunately extended to the postoperative period. (12)(13)

The medical literature does not support the use of routine antibiotic prophylaxis after normal vaginal birth. (14) Instrumental vaginal delivery with forceps or vacuum assistance is also associated with an increased risk of a postpartum infection (0.7%–16%). (15) Although this approach has declined in the United States, it is still used with some frequency in various areas of the world. For example, approximately 13% of women in the United Kingdom have an assisted vaginal delivery. (16) In cases of operative vaginal birth, however, there is benefit of a single dose of prophylactic antibiotic after delivery (co-amoxiclav, 1 mg of amoxicillin with 200 mg of clavulanic acid) but there are no data to support more than 1 dose or the administration of antibiotics before delivery. (15)(16)

Risk of Preterm Birth

Inflammation and infection are clearly linked to preterm birth, but it is not known whether antibiotic therapy can prevent early delivery. A systematic review found that antibiotics administered during the second and third trimester to prevent preterm labor with intact membranes are ineffective at reducing adverse pregnancy outcomes, preterm birth, or neonatal morbidity. (17)

Chorioamnionitis

A diagnosis of intrapartum chorioamnionitis requires prompt treatment with antibiotics to prevent at least maternal complications. However, using a fever during labor and delivery as a proxy for chorioamnionitis is not ideal, because the most frequent reason for a maternal fever is usually prolonged labor not chorioamnionitis. Therefore, careful assessment of maternal and fetal clinical signs and symptoms, maternal white blood cell counts, and other laboratory tests should be performed before initiating intravenous intrapartum antibiotics. If a woman does receive antibiotics, the duration of the antibiotics should be as short as possible. Data suggest that for women treated with an initial dose of intrapartum antibiotics for chorioamnionitis, 1 additional dose of antibiotics after delivery is just as effective as a longer duration of treatment. (18)

Urinary Tract Infection

A urinary tract infection is another relatively frequent infection that occurs during pregnancy. Approximately 60% of pregnant women have leukocytes in their urine without any infectious complication; thus, the presence of leukocytes should not be used to diagnose an asymptomatic urinary tract infection in pregnant women. (19) Unfortunately, some clinicians prescribe antibiotics to women if they suspect a possible urinary tract infection. However, there is no valid reason to expose the woman and fetus to potential side effects of these antibiotics. A recent Cochrane review found that antibiotics for asymptomatic bacteriuria in pregnant women may decrease the risk of bacteriuria at the time of delivery (average relative risk [RR], 0.30; 95% confidence interval [CI], 0.18–0.53; 4 studies; 596 women); however, the results were inconclusive for serious adverse neonatal outcomes (average RR, 0.64; 95% CI, 0.23–1.79; 3 studies; 549 neonates). (20) In the studies included, maternal adverse effects were rarely described and 14 of the 15 studies were assessed as having high or unclear risk of bias. GRADE software analysis showed low-certainty evidence for pyelonephritis, preterm birth, and birthweight less than 2,500 g. In summary, there is no evidence that low-risk pregnant women benefit from antibiotic treatment for asymptomatic bacteriuria. (20)

Genital Infections

Screening and treating genital infections such as *Trichomonas vaginalis* or bacterial vaginosis for the prevention of preterm birth also adds risk without confirmed benefit. Metronidazole treatment was found to actually increase the risk of preterm delivery (19% vs 10.7% in the placebo group). The probability of having a positive vaginal culture during screening of asymptomatic women is very high (20%–50% for various organisms), which does not necessarily mean that there is a pathogenic infection. Unfortunately, a large number of women receive antibiotics for their normal vaginal flora.

In summary, clinical antibiotic use during pregnancy continues to be excessive, despite the potential for short- and long-term negative effects, as discussed in the next section.

SHORT- AND LONG-TERM NEGATIVE EFFECTS OF MATERNAL ANTIBIOTICS DURING PREGNANCY

Administration of antibiotics during pregnancy may be lifesaving but at other times, antibiotic use may be unnecessary and lead to negative consequences. Studies have found that antibiotics alter the composition of the maternal and neonatal intestinal microbiota, which can play an important role in maternal and child health outcomes, such as immune and metabolic function later in life. (21)(22)(23)(24)(25)(26) The effect of the perinatal microbiome on immunity early in life is thought to affect neurodevelopment, potentially altering the risk of childhood atopy, asthma, allergy, obesity, and neurologic disorders. (23) Concerns have been raised that extensive antepartum and intrapartum antibiotic use can potentially disrupt the infant's intestinal microbiota and alter maturation to the adult microbiome. However, current research studies on this possible connection have not sufficiently addressed potential confounding variables. In addition, these studies have not consistently controlled for the frequency, dose, timing, type (narrow range vs broad spectrum), and indication of antibiotic usage. (24)

Even 1 antibiotic course during pregnancy has been found to disrupt the bacterial intestinal community of the maternal and fetoplacental microbiomes, which has not been found to return completely to baseline after treatment. Antibiotics administered during labor and delivery can also alter the developmental trajectory of the infant's intestinal microbiota, potentially altering the organism type and proportion, as characterized using 16S rRNA sequencing and metagenomics analysis in fecal samples collected at 6 weeks and 1 year of age. (25) The class of intrapartum antibiotics was associated with lower bacterial diversity and a distinct community of organisms at both time points. Infants in the penicillin-only group had significantly lower diversity scores than infants not exposed to intrapartum antibiotics and, in contrast to the penicillin group, the use of cephalosporins was significantly associated with higher levels of *Bacteroides* fragilis and a significantly lower rise over time in *Bifidobacterium*. (25) Women receiving 2 or more drugs under the category of penicillin, cephalosporin, vancomycin, clindamycin, and/or gentamicin experienced a significantly higher increase in *Veillonella dispar*. Intrapartum antibiotic administration also affects the vaginal microbiome before delivery, which has been shown to influence the early microbial colonization in the neonate. (26)

In the following paragraphs, I review the associations of antibiotic exposure during pregnancy with risks for neurologic disorders, obesity, asthma, allergy, anaphylaxis, infections during childhood, and antibiotic resistance.

GBS Prophylaxis

Intrapartum antibiotic prophylaxis for GBS-positive women is common practice in obstetrics and is administered in up to 40% of deliveries. One study examined 502 stool samples collected up to 3 months of age in 272 infants who had been exposed to intrapartum antibiotic prophylaxis because of GBS colonization. (21) Those infants who were exposed to antibiotics had a lower bacterial diversity; decreased amount of *Actinobacteria*, especially *Bifidobacteriaceae*; and a greater relative amount of *Proteobacteria* in their gut microbiota compared with nonexposed infants. (21) Such alterations during the "critical window" in infants when the intestinal microbiota and the immune response develop concurrently may play an important role in immune development. The potential long-term negative impact of these alterations on the health of children requires further investigation. (21)(22)

Preterm Birth

It is possible that maternal antibiotic administration to prevent preterm birth might have harmful long-term effects. (27) One study found an associated increased risk of cerebral palsy and function impairment at age 7 years in children of women who received antibiotics for spontaneous preterm labor with intact membranes. (28) Unfortunately, despite the lack of effectiveness of antibiotics for preterm labor with intact membranes and the potential long-term risks to the infant, antibiotics are still being regularly prescribed in this scenario.

Impact on the Fetal Brain

Prenatal exposure to antibiotics has also been associated with an increased risk of epilepsy in childhood. Among children exposed prenatally, the incidence rate was 117 per 100,000 person-years, with an adjusted ratio of 1.40 (95% CI, 1.22–1.61), compared with unexposed children. (29) This association was not altered by the timing of the exposure, type of antibiotic, or antibiotic dose. (29)

In an analysis of febrile seizure risk in a large cohort of children in Denmark, a slightly increased hazard ratio (HR) was found among the groups most exposed to different antibiotics during pregnancy compared with the unexposed group (HR, 1.08; 95% CI, 1.05–1.11). (30) This may indicate that the use of antibiotics during pregnancy could have an impact on the fetal brain and increase an infant's susceptibility to febrile seizures.

Gut Microbiome, Obesity, and Immunity

For over a decade, obesity has been linked to alterations of the microbiome. (31) Prenatal antibiotic exposure during the

second or third trimester has been found to be associated with an altered composition of the intestinal microbiome of the infant and a higher risk of obesity during childhood (after multivariable adjustment, 84% increased obesity risk with range between 33% and 154%). (32)(33) Antibiotic exposure during the second or third trimester was also positively associated with body mass index z-scores, waist circumference, and percentage of body fat. (32). In a subsequent study, antibiotic exposure during the second trimester was associated with an altered composition of the intestinal microbiome at 3 and 12 months of age and with higher infant sex-specific weight-for-length z score and subscapular skinfold thickness at 12 months. (34)

Early postnatal innate immune development is driven by maternal microbiota during pregnancy. (35)(36) Interfering with this may delay or even obstruct the natural process of prenatal immune priming. Illnesses such as autoimmune and allergic disorders, including childhood asthma, may be imprinted during infancy, only to manifest later in life. (35)(36)(37)

Asthma

The Copenhagen Prospective Study on Asthma in Childhood followed a cohort of children born to women who received antibiotics during the last trimester of pregnancy and found them to have an increased risk of asthma. (38) In another study, prenatal systemic antibiotic use was a significant predictor of asthma by age 3 years after controlling for confounders. (39)

Maternal Anaphylaxis

The widespread use of antibiotics has also been associated with maternal anaphylaxis during both pregnancy and the peripartum period. (40)(41) Maternal anaphylaxis followed by maternal hypotension affects fetal oxygenation with a risk of hypoxic-ischemic encephalopathy and permanent central nervous system injury. (42)(43) This risk was found to occur after a few minutes of maternal anaphylaxis. (40)(41)

Childhood Infections

In addition to the aforementioned issues, antibiotic exposure during pregnancy has been associated with an increased risk of childhood infection–related hospitalizations during the first 6 years of age (HR, 1.18; 95% CI, 1.17–1.19). (44) Greater risks of infection-related hospitalization were found when intrapartum antibiotics were prescribed closer to birth and in women receiving a greater number of antibiotics during pregnancy.

Multiresistant Bacteria

Development of multiresistant bacteria is a major complication of antibiotic overuse, discussed later in some detail. Bacterial resistance can lead to increased morbidity and mortality of affected individuals, burdens on health care systems, and unnecessary expenditures that affect not only individual maternity services but also national health expenditures. These are overwhelming and can and should be reduced.

Negative Effects of Cumulative Exposure to Antibiotics During Development

There are still many unknowns about the negative effects of cumulative exposure to antibiotics during the most vulnerable periods of human development. The Fetal Antibiotic EXposure (FAX) study examines the association between intrauterine antibiotic exposure and adverse childhood outcomes such as body weight, atopic diseases, and autism spectrum disorders. (45) The study cohort includes 223,431 children born in Southern California between January 1, 2007, and December 31, 2015, with 65.7% being exposed to antibiotics in utero. The 5-year retention of children in the cohort was greater than 80% and the population studied had multiple medical visits over time. (45) The analysis and results of the long-term sequelae of intrauterine exposure to antibiotics is in progress. Regardless of the findings of this research, antibiotics should only be prescribed during pregnancy when indicated. If a maternal infection is proven, narrow-spectrum antibiotics should be used to decrease the effects of antibiotics on the microbiome of the infant.

The necessity to treat most cases of symptomatic bacterial infections is clear, but it is also clear that during the last 20 years there has been an inappropriate overuse of antibiotics in obstetrics. Are we doing more harm than good? Based on what is known to date, one can only wonder about the potential negative impact of prolonged cumulative exposure to antibiotics during development, before birth, during labor, and then subsequently during the neonatal period, for days or weeks after birth, without any clear documentation of infection.

ANTIBIOTIC ABUSE DURING THE NEONATAL PERIOD

Antibiotic administration to neonates can be life-saving but this medication can be used unnecessarily as well. The identification of neonates with sepsis, particularly early-onset sepsis, is extremely inefficient. Despite the infrequency of positive cultures in the NICU, antibiotics are the most frequently used medications in the NICU and there is significant variability in antibiotic utilization. In a

cross-sectional study published in 2019 of 326,845 live births in California hospitals, the percentage of newborns with antibiotic exposure varied considerably from 1.6% to 42.5%. (46) This was not explained by proven bloodstream infection and it was not correlated to the percentage of patient-days of antibiotic exposure. (46)

If one could influence the abuse and misuse of antibiotics in newborns, it would be useful to know the answer to 2 questions. The first one is: "Why do neonatologists initiate antibiotic treatment?" and the second one, "Why do neonatologists not discontinue antibiotic treatment in an opportune manner?" The first question has had a long-lasting influence in my own practice and in my approach in all the neonatal centers that I had the responsibility to direct. When I was pediatric chief resident in 1976 and decided to train in neonatal-perinatal medicine, the Chairman, Dr. James B. Hanshaw, a well-known expert in pediatric infectious diseases and virology, asked me that very same question. When I started to provide a long list of medical reasons (as a "knowledgeable chief resident"), he told me to mention only the 2 main reasons why neonatologists start antibiotics in newborns. I could not identify them. He said: "One is because they have apneic spells and do not breathe. The other one is … because they breathe."

Today, neonatologists use countless reasons to start or continue antibiotics but, as I discuss herein, they are mistaken in the great majority of cases. Unfortunately, many of my colleagues use the word "fear" many times to justify their use of antibiotics—fears of making a mistake and that their patients will be hurt by something they failed to do. This leads to the prescription of antibiotics when they are not indicated or necessary and to the fact that antibiotics are not discontinued despite the clinical evidence. Ideally, the use of antibiotics in NICUs should be so precise that only newborns with a proven infection would receive antibiotics and even then, receive those antibiotics with the narrowest effective spectrum for the shortest period. (47)

Suspected early-onset neonatal bacterial sepsis is one of the most common diagnoses in the NICU. However, few neonates (1%–3%) with a suspected early-onset neonatal bacterial infection will be proven to have sepsis. Considering many newborns as infected when they are not leads to antibiotic abuse and misuse. Puopolo et al described the issue of management of newborns with suspected or proven early-onset bacterial sepsis, both for preterm infants at less than 34 6/7 weeks' gestation and for newborns born at 35 weeks' gestation or later. (48) The authors addressed extremely essential themes and topics, (46) several of which are highlighted as follows:

- Risk assessment should be based on a newborn's clinical condition.
- Decisions to start antibiotics in suspected early-onset bacterial sepsis should be based on the clinical condition of the newborn.
- Inflammatory markers should not be measured in asymptomatic newborns.
- Physicians should consider the risk-benefit balance of an early-onset bacterial sepsis evaluation and empirical antibiotic therapy.
- Preterm infants born via cesarean delivery as a result of a noninfectious maternal etiology in the absence of labor or if rupture of membranes occurs close to delivery are at a relatively low risk for early-onset bacterial sepsis.
- When cultures are sterile, discontinue antibiotics in 36 to 48 hours (unless there is clear evidence of a site-specific infection).
- Laboratory test abnormalities rarely justify prolonged empirical antibiotic administration, particularly for preterm infants at lower risk of suspected early-onset bacterial sepsis
- Persistent cardiorespiratory instability is common in preterm infants weighing less than 1,500 g but is not an indication by itself to use prolonged empirical antibiotics.

For many years clinicians have been aware that prolonged antibiotic therapy for "culture-negative" sepsis is not good clinical practice. (49) However, recent reports of neonatal networks show that they are still widely used and that there are significant practice differences among NICUs related to the initiation of antibiotics in suspected sepsis and also in the duration of antibiotics for more than 3 days. For example, in Canada, the rate for the whole network for initiation of antibiotics was just above 40%, but it varied considerably from about 20% to 70%. (3) In the network of the Ibero American Society of Neonatology (SIBEN), with 40 NICUs from 10 Latin-American countries, we explored the administration of antibiotics for more than 3 days in infants with negative blood cultures during 2018. (4) The variability among NICUs was surprising and ranged from 10% to 92%. In 5 NICUs, more than 60% of neonates received such management, whereas in 4 NICUs, this was done in fewer than 20% of infants. In infants with negative blood cultures, an association was found between excessive prolonged antibiotics and mortality. (4)

When early-onset sepsis is "suspected," proven sepsis is extremely rare, particularly in the great majority of newborns who are asymptomatic. The risk of early-onset sepsis is low in well-appearing, asymptomatic newborns (approximately 0.21 in 1,000 live births). (50)(51)(52) In this

situation, it is safe to avoid the unnecessary use of antibiotics if serial observations demonstrate that the newborn remains asymptomatic. On the other hand, when there are clinically evident signs in the first 12 hours after birth, the risk of early-onset sepsis is about 11 in 1,000 live births. In these cases, a blood culture and empirical antibiotics should be started immediately without delay, with admission to the NICU. In cases of equivocal clinical presentation, the risk is about 2.6 in 1,000 live births; in this case, a blood culture specimen can be obtained and vital signs carefully monitored every 4 hours for at least 24 hours. Treatment with antibiotics will be based on the culture results or persistence of suggestive symptoms.

The objective of this review is not to elaborate on the impact that nonspecific inflammatory markers (C-reactive protein, procalcitonin, and others) had on antibiotic abuse in neonatology worldwide; however, we need to keep in mind the inaccuracy of these tests. (53)(54)(55) For example, for procalcitonin, it was found to be best if it was measured at 12 hours of age, but even at that time it is still not helpful for clinical decision-making (sensitivity 83%, specificity 56%, positive predictive value 32%, negative predictive value 93%). Procalcitonin levels, similar to C-reactive protein, have more clinical value when they are normal, meaning that the likelihood of infection is very low. However, even when the results are normal, clinicians sometimes still start antibiotics or continue them for a longer period. Accordingly, if antibiotics are started and inflammatory markers are normal and blood cultures are negative, it is imperative to discontinue antibiotics.

In pregnant women with clinical chorioamnionitis, the incidence of early sepsis in neonates has been reported as low as 1 in 1,000 to about 4 to 7 in 1,000 live births. Therefore, there is no medical value or need to treat all asymptomatic newborns delivered after a diagnosis of chorioamnionitis. (55)(56)(57)(58) When antibiotics are started in asymptomatic infants born to mothers with chorioamnionitis, there would be hundreds, maybe thousands, of admissions for every case of culture-confirmed sepsis because of the extremely high number needed to treat to identify 1 infant with confirmed early-onset sepsis. Even in symptomatic infants born to mothers with chorioamnionitis, the number needed to treat to identify 1 infant with early-onset sepsis is high, 23 or greater. It has become clear that the systematic, immediate use of antibiotics in asymptomatic neonates is not justified. (59) By holding off on antibiotics and instead, performing repeated and detail clinical examinations, we will not interfere with mother-infant bonding and at the same time, we will be able to quickly determine the need to intervene. (60)

In summary, the use of systematic, immediate antibiotics is not justified in most asymptomatic neonates. There is an imperative need for more cautious use of antibiotics in neonates, discouraging systematic empirical antibiotic use if sepsis is only a remote possibility. Neonatal clinicians must try to counteract traditional approaches to antibiotic usage and support practice improvements to ensure that better practices are adopted and sustained over time across all NICUs.

Short- and Long-Term Negative Effects of Antibiotics During the Neonatal Period

Prolonged (often unnecessary) exposure to antibiotics during the neonatal period has been associated with significant morbidities such as systemic candidiasis, necrotizing enterocolitis, late-onset sepsis, bronchopulmonary dysplasia, retinopathy of prematurity, emergence of multiresistant microorganisms, and alterations of the intestinal microbiome. Publications in this field have been numerous in the last few years. (3)(61)(62)(63) Several of these articles report an increase in mortality. In SIBEN's network, an association was also found between excessive prolonged antibiotics and mortality in infants with negative blood cultures. (4)

Antibiotics during the first and second year of age increase the risk for childhood obesity by 10% to 15% (64)(65) and for early childhood asthma and other allergic conditions, (66) celiac disease, (67) Crohn disease (7 times higher risk), (68)(69)(70) juvenile idiopathic arthritis, (71) and, maybe intestinal cancer. (72)

Antibiotic Resistance

The introduction of antibiotics in clinical use was among the greatest medical breakthroughs of the 20th century. In addition to treating infections, antibiotic use made many modern medical options possible, including cancer treatment, organ transplantations, and open-heart surgery. However, misuse of these valuable medications has led to the rapid rise of antimicrobial resistance, with some infections now being very difficult to treat or untreatable. Every year, drug-resistant infections—exacerbated by antibiotic overuse in humans—kill 700,000 people in the world. According to a report from the United Nations and another one from the United Kingdom, if substantial modifications are not made in antibiotic prescribing practices by all clinicians, 10 million people per year will die worldwide from drug-resistant infections after 2050. (73)(74) There is not much time to wait.

What can be Done to Decrease the Abuse of Antibiotics in Neonatal Medicine?

Studies that examined the impact of antimicrobial stewardship programs and prospective audits and feedback in the

NICU setting have reported different rates of effectiveness in improving antibiotic prescribing practices. (50)(51)(52)(53)(75)(76)(77)(78)(79)(80)(81)(82)(83)(84)(85)

The most frequently used antibiotics in neonatal medicine are ampicillin and gentamicin. Initiation of both of these medications is recommended for suspected early-onset sepsis, with discontinuation in 36 to 72 hours if blood cultures are negative. However, a recent study found that this is not always followed, reporting a mean duration of antibiotic course of 10.8±7.3 days; carbapenems and vancomycin were the most commonly used antibiotics. (86) This and similar practices must be modified.

In newborns at high risk with clinical signs of sepsis, antibiotics must be started immediately because the beneficial impact of antibiotics for newborns with sepsis decreases with longer intervals to their initiation.

Quality improvement to ensure the appropriateness of antibiotic use in the neonatal population is necessary and needs to take into account the clinical status of the infant, diagnostic tools, antibiotic choice, and length of treatment. Effective interventions to reduce antibiotic utilization can be designed and implemented in NICUs in a collaborative manner by a multidisciplinary team to decrease or avoid prolonged misuse. The main quality improvement goals are to decrease the number of infants who are started on antibiotics and the days of therapy (the sum of the days of therapy accounting for each antibiotic) per 1,000 patient-days, maintaining or even improving safety outcomes.

Antimicrobial stewardship programs with interdisciplinary collaboration and creation of a team are very useful but not identical in every NICU. A thorough assessment of antibiotic use in each NICU is necessary to identify and implement high-yield stewardship targets tailored to the individual center. For example, an automatic discontinuation of antibiotics policy was effective in reducing the mean total number of antibiotic days per patient and the mean number of excess days of antibiotics at 1 center. (78) Such automatic discontinuation authorizes the antimicrobial stewardship program team to automatically stop antibiotics when there is inappropriate duplicate antimicrobial coverage or inappropriate length of therapy. Such automatic discontinuation of antibiotics improves the efficiency of the antimicrobial stewardship program. Programs that use this approach have also reported important successes, with a significant decrease in antibiotic days per 1,000 patient-days, blood cultures performed, and percentage of infants who are started on antibiotic therapy, without any difference in safety outcomes. (79)(80)

The neonatal early-onset sepsis calculator is an effective tool for antibiotic stewardship in newborns, shown to reduce the use of empirical antibiotic treatment for neonates with suspected early-onset sepsis. (53)(79)(80)(81)(82)(83)(84) In newborns at risk for early-onset sepsis, implementation of the calculator was associated with a significant reduction in laboratory testing and significantly shorter length of stay in those newborns. (84) In addition, this practice was associated with a mean reduction in costs of US $225 per admitted newborn. (84) Daily prospective audit and feedback produced an overall decrease in antibiotic consumption of 14% among extremely preterm and near-term neonates. (85) However, this approach had no impact on the number of neonates who continued to receive antibiotics despite negative culture results and it did not change the duration of antibiotic therapy. (85)

Finally, several reviews and meta-analyses have shown the benefits of hospital antimicrobial stewardship and interventions in improving antibiotics prescribing practices for hospital inpatients. (76)(87)

Economic Impact of Antibiotic Abuse

There are direct and indirect cost savings by decreasing antibiotic abuse and misuse. Significant savings have occurred as a result of decreasing unnecessary practices such as a:

- Shift from more expensive broad-spectrum antibiotics to less expensive first-line narrow-spectrum antibiotics
- Decrease in the number of patients in whom antibiotics are initiated
- Discontinuation of antibiotics to eliminate their prolonged duration
- Decrease in laboratory testing

These practices have also led to a reduction in the incidence of antibiotic-resistant infections, a decrease in antibiotic-associated adverse events, and shorter length of stay.

An evaluation of antibiotic expenditures in different health care settings in the United States revealed that total antibiotic expenditures were approximately $10.7 billion, with $6.2 billion attributed to ambulatory care and $3.5 billion spent during hospitalizations and, for the 6-year period 2010 to 2015, the total expenditures were $56 billion. (88)(89)

Several examples can be used to describe the impact of antibiotic stewardship. If we extrapolate the cost reduction in using the sepsis calculator of US $225 per admitted newborn (described above) (84) to 2 or 3 NICUs with a total of 1,000 admissions per year, the cost savings would be about US $ 230,000 dollars (€207,000) per year. In one pediatric ICU with 1,815 antibiotic exposure days, 512 (28%) were prescribed as prophylaxis for postoperative care after

cardiac surgery, major pediatric surgery, and severe trauma, and 1,303 for suspected pneumonia. (90) By limiting the unnecessary use of antibiotics for suspected pneumonia and "extended" prophylaxis, there was an estimated potential savings of more than US $26,000. (90)

CONCLUSION

It has been estimated that without implementing restrictions and local programs in developed nations and in low- and medium-income countries, the use of global antibiotics will increase 3 times in 2030. The projections, assuming no policy changes, are up to 200% higher than the 42 billion defined daily doses estimated in 2015. (91) What could the perinatal health care team do to prevent this from happening?

A germane focus in antibiotic use in perinatal medicine has been to protect the mother and child from infection. No doubt this improves outcomes. Nevertheless, such protection should not happen at the risk of injury to the uninfected mother and/or child. In the United States, data from 297 centers (92) showed that the majority of premature infants had early antibiotic initiation, with 78.6% of infants being less than 1,500 g and 87% of those greater than 1,000 g. Many of these infants had subsequent prolonged antibiotic administration for more than 5 days. Early antibiotic exposures and the proportion of infants administered prolonged antibiotics varied across centers. It is therefore imperative that we modify our attitude to our risk-benefit assessment and that we are mindful and accept the increased risk and potential injury we are causing with unnecessary antibiotic use, abuse, or misuse. Achieving this balance requires being sensible and thoughtful, and of course, standardization of care, with continuous evaluation of practices and outcomes. Constructing "equipoise" around the current approach to antibiotic use will enable systematic examination of the risk and benefits (93) and decrease antibiotic abuse.

Stewardship is defined by the Merriam-Webster dictionary as "the careful and responsible management of something entrusted to one's care." Antimicrobial stewardship is 1 of the 3 "pillars" of an integrated approach to strengthen health systems. The Centers for Disease Control and Prevention undertook a nationwide effort to improve antibiotic use in inpatient and outpatient settings (94) and has described the core elements of antibiotic stewardship, recognizing that there is no "one size fits all" approach to improve antibiotic use for all settings. The primary goal of antibiotic stewardship is to improve patient care, prescribing antibiotics only when necessary, using the appropriate medication(s), at the correct dosage, and for the proper amount of time. Sometimes, better patient care involves starting broad-spectrum antibiotics, an action that also falls under antibiotic stewardship, because infection is an important cause of neonatal morbidity and mortality and of maternal morbidity, with pregnancy-related sepsis accounting for 11% of maternal deaths. (95) Frequency of maternal infection was recently described in the first systematic review and meta-analysis ever published. (95) The incidence of chorioamnionitis was 3.9%, endometritis 1.6%, wound infection 1.2%, maternal peripartum infection 1.1%, and sepsis 0.05%. This study shows that prevention of maternal infection should be a priority and that the number of women treated with antibiotics is excessive.

The need to improve the use of antibiotics in perinatal medicine in developed and low- and middle-income countries has never been more urgent. (96) It is our responsibility in NICUs and obstetric facilities to improve our approach to the use of antibiotics.

American Board of Pediatrics Neonatal-Perinatal Content Specification

- Know the effective techniques for control of healthcare-associated infection in the nursery, neonatal intensive care unit, and obstetrical unit.

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Abuse of Antibiotics in Perinatology: Negative Impact for Health and the Economy

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