Seminars in Fetal & Neonatal Medicine 22 (2017) 278–283

Contents lists available at ScienceDirect

Seminars in Fetal & Neonatal Medicine

journal homepage: www.elsevier.com/locate/siny

Antibiotic stewardship in perinatal and neonatal care

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Keywords:
Antibiotics
Stewardship
Newborn
Neonatal intensive care
Sepsis

A B S T R A C T

The spread of antibiotic resistance due to the use and misuse of antibiotics around the world is now a major health crisis. Neonates are exposed to antibiotics both before and after birth, often empirically because of risk factors for infection, or for non-specific signs which may or may not indicate sepsis. There is increasing evidence that, apart from antibiotic resistance, the use of antibiotics in pregnancy and in the neonatal period alters the microbiome in the fetus and neonate with an increased risk of immediate and long-term adverse effects. Antibiotic stewardship is a co-ordinated program that promotes the appropriate use of antibiotics, improves patient outcomes, reduces microbial resistance, and decreases the spread of infections caused by multidrug-resistant organisms. This review addresses some of the controversies in antibiotic use in the perinatal period, examines opportunities for reduction of unnecessary antibiotic exposure in neonates, and provides a framework for antibiotic stewardship in neonatal care.

1. Introduction

When considering the use and misuse of drugs in perinatal care, the topic of antibiotic stewardship is of prime importance. Antimicrobial resistance has emerged as one of the most serious health threats in the world, generating calls for action from the World Health Organization [1] and the Centers for Disease Control and Prevention [2]. Antimicrobial resistance has been postulated to be responsible for about 30% of deaths from neonatal sepsis worldwide, primarily-in low and middle-income countries [3], but there is growing realization that developed countries are not immune from this crisis [2]. When standard antibiotics are no longer effective, second- and third-line antibiotics are required, with potential delays in effective therapy, increased morbidity and mortality, adverse effects and costs.

Antimicrobial stewardship is a co-ordinated program that promotes the appropriate use of antimicrobials (including antibiotics), improves patient outcomes, reduces microbial resistance, and decreases the spread of infections caused by multidrug-resistant organisms [4]. The Infectious Diseases Society of America, the Pediatric Infectious Disease Society, and the Society for Healthcare Epidemiology of America published guidelines in 2007 for developing an institutional program to enhance antimicrobial stewardship, endorsed by the American Academy of Pediatrics [4]. A small number of studies evaluating formal antibiotic stewardship programs (ASPs) in pediatric patients have demonstrated reductions in antibiotic utilization, cost, and prescribing errors [5]. Even though antibiotics are among the most widely prescribed medications in hospitalized neonates in industrialized nations [6,7], there is little published data on formal ASPs specifically addressing the neonatal population [8]. Many pregnant women are also exposed to antibiotics [9]. Evidence is mounting that antibiotic treatment of mothers in pregnancy may have immediate and long-term consequences for neonates.

This article reviews some of the controversies and opportunities for antibiotic stewardship in the neonatal–perinatal period and suggests a framework for setting up neonate-specific ASPs. This review does not address antibiotic stewardship related to neonatal sepsis in resource-constrained nations, which is also critical, but the epidemiology, resistance patterns and clinical conditions pose a very different set of challenges [3].

2. Antibiotic use in pregnancy

It is estimated that 40% of pregnant women in the USA receive antibiotics prior to delivery to prevent infectious complications in both the mother and fetus [9]. Given the 10–30% incidence of maternal colonization with group B streptococcus (GBS) and with

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http://dx.doi.org/10.1016/j.siny.2017.07.001
1744-165X/

33% of women undergoing cesarean delivery, between 1.5 and 2.0 million women and their infants are exposed to antibiotics annually in the USA. In addition, antibiotics are prescribed for the treatment of asymptomatic bacteriuria, which complicates 2–10% of pregnancies, pyelonephritis, in the context of preterm premature rupture of membranes (PPROM) [10], and for the treatment of chorioamnionitis in labor [11].

The Centers for Disease Control and Prevention (CDC) 2010 revised guidelines recommend universal screening for GBS between 35 and 37 weeks gestation [12]. Intrapartum antibiotic prophylaxis is indicated when culture-based screening is positive for GBS, with a history of a previous infant with invasive GBS disease, maternal GBS bacteriuria ($\geq 10^4$ colony-forming units), or other clinical factors such as preterm delivery (<37 weeks gestation), rupture of membranes ≥18 h, intrapartum fever (temperature ≥38.0 °C), and intrapartum nucleic acid amplification test positive for GBS. Implementation of national guidelines for intrapartum antibiotic prophylaxis in the early 1990s has resulted in an 80% reduction of early-onset GBS neonatal sepsis, from 1.7 cases to fewer than 0.4 cases per 1000 live births in the early 2000s [12].

Penicillin is the agent of choice for intrapartum prophylaxis, though ampicillin is an acceptable alternative. Specific antibiotic recommendations have been made for patients with penicillin allergies, depending on the severity of the allergy and isolate susceptibility, but the alternative agents given to penicillin-allergic women often do not comply with CDC recommendations [13]. Unfortunately, the use of medications other than penicillin, ampicillin or cefazolin is not considered to be adequate prophylaxis, and this may in turn lead to additional evaluation and intervention in the newborn.

Women who have cesarean deliveries, particularly those who have been in labor, or after membrane rupture, are at increased risk of postpartum infection, including wound infection and endometritis, compared to women delivering vaginally. Antibiotic prophylaxis given after cord clamping, to avoid neonatal exposure to antibiotics has been supplanted by pre-incision prophylaxis, similar to prophylaxis for other surgical procedures, again increasing the exposure to antibiotics to the neonate, albeit briefly [14].

Chorioamnionitis or acute inflammation of the chorion and amnion layers of the membranes is estimated to occur in 3–10% of deliveries at term but clinical diagnosis is subjective and variable, leading to antibiotic treatment in the mother, and, invariably, evaluation and antibiotic treatment of the newborn [11].

3. Antibiotic use in neonates

Suspected sepsis is the most usual working diagnosis for infants admitted to neonatal intensive care units (NICUs) [15]. Ampicillin and gentamicin have led the list of 10 drugs most widely used in neonatal units in the USA since 1996 [6,7]. Symptoms of neonatal sepsis range from subtle to severe, but are non-specific and may overlap with many non-infectious clinical conditions in neonates. Given the high risk of morbidity and mortality with neonatal sepsis, and the poor positive predictive value of ancillary laboratory tests [16,17], empirical antibiotic treatment is often initiated, targeting the most likely micro-organisms, based on the clinical situation, but antibiotic use is extremely variable across institutions. A recent retrospective cohort study of more than 50,000 infants in 127 NICUs across California in 2013 showed that overall antibiotic use varied 40-fold, from 2.4% to 97.1% of patient days [18]. Antibiotic use was independent of rates of proven infection, surgical volume, necrotizing enterocolitis or mortality. Most of the intermediate-level NICUs reported zero rates of culture-proven infection, and yet 50% were in the highest antibiotic use quartile.

4. Adverse effects of antibiotics in neonates

Whereas the benefits of antibiotics cannot be denied, there are real and potential risks of the prevalent exposure of the maternal–fetal dyad to antibiotics. The rate of GBS sepsis has decreased from 1.7 to 0.4 per 1000 births with universal screening and GBS prophylaxis, but this results in almost 700 women (and their unborn infants) being exposed to antibiotics to prevent one case of early onset GBS disease. Concerns have been raised about the potential for development of antibiotic-resistant neonatal sepsis with widespread maternal GBS prophylaxis, but in the absence of an effective vaccine to prevent GBS disease or a rapid, sensitive diagnostic test to detect GBS colonization when women are admitted in labor or with rupture of membranes, antibiotic prophylaxis is likely to be continued. No increase has been noted so far in rates of ampicillin-resistant infections in term infants, but in very low birth weight infants (VLBW, birth weight <1500 g), some studies have noted an increase in rates of *E. coli* infections [19], whereas others have shown no change in the rate [20]. However, an association has been noted between intrapartum ampicillin exposure and ampicillin-resistant *E. coli* infection at birth, ranging from 55% to 85% [19,20].

Antibiotics are used to prolong latency and reduce infectious complications in women with PPROM, and a combination of intravenous ampicillin and erythromycin is usually recommended, in order to cover GBS, Gram-negative infections, mycoplasma, and ureaplasma [10]. In the ORACLE 1 study, exposure to co-amoxiclav (a combination of amoxicillin and clavulinic acid) during pregnancy was associated with a four-fold risk of necrotizing enterocolitis in the newborn compared to placebo (relative risk: 4.72; 95% confidence interval: 1.57–14.23) [10]; the pathogenesis of this is uncertain but could be related to abnormal colonization of the intestinal tract.

There is now evidence that the intrauterine environment is not sterile, and there is an active maternal–fetal exchange of commensal micro-organisms, establishing the fetal intestinal microbiome well before delivery [21,22]. Antibiotics administered before delivery may disrupt the normal colonization of the developing fetal intestinal microbiome with long-lasting effects. Exposure of mothers to antibiotics in the second and third trimester has been associated with increases in childhood obesity [23], and in asthma [24]. Although transfer of macrolides across the placenta is estimated to be small, Cho et al. showed that administration of subtherapeutic antibiotic therapy increased adiposity in young mice with changes in the microbiome and increased hormones related to metabolism, which may explain some of these associations [25].

Perinatal and early empiric antibiotic use has been associated with lower bacterial diversity in the developing microbiome of the neonate, and an increase in colonization with potentially pathogenic Enterobacteriaceae, which may precede bloodstream infection in preterm infants [26]. Prolonged initial antibiotic therapy in VLBW infants has been associated with increased risks of necrotizing enterocolitis (NEC) and death [27,28], with each additional empirical day of treatment associated with measurable increase in risk [27]. In a large study of 11,669 VLBW infants without culture-proven sepsis or NEC in the Canadian Neonatal network, a 10% increase in antibiotic use rate (AUR) was associated with increased odds of mortality, and major morbidity (chronic lung disease, persistent periventricular echogenicity or echolucency, or stage 3