Antibiotics in the prevention of neonatal group B streptococcal infections: the evidence.

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Abstract

To prevent group B streptococcal early-onset disease (GBS-EOD) in the neonate, many pregnant women are treated with antibiotics during labor and/or delivery. During the last years several countries implemented the screening-based strategy to prevent GBS-EOD, resulting in an increase in the use of antibiotics during delivery. Overall, most incidence figures of culture-proven GBS-EOD decreased in the last decades. Because incidence figures are influenced by multiple factors, a decrease cannot be considered as exclusive evidence for efficacy of antibiotics. Despite limited knowledge on the efficacy of the antibiotics prescribed, they are used worldwide as preventive measure in up to 35% of pregnant women shortly before and during delivery. In this paper, we review the available evidence, from pharmacokinetics of antibiotics used as intrapartum prophylaxis to infection parameters and GBS-EOD incidence figures to evaluate the efficacy and safety of currently advised prophylaxis.
Introduction

In the 1970s group B streptococcus (GBS) infection emerged as a major cause of neonatal morbidity and mortality in the industrialized world. This led the Centers for Disease Control and Prevention (CDC) and other organizations to issue guidelines in the 1990s for prevention of neonatal GBS disease by intrapartum prophylaxis with antibiotics (IPA)\(^1\). CDC guidelines discuss a wide variety of issues associated with GBS disease, such as transmission of infection and selection of patients eligible for prophylaxis, and highlight a steady decline in incidence of GBS disease since introduction of IPA. However, the guidelines recommend regimens for IPA, but give no arguments for dose, dosing interval and duration of treatment\(^1\)\(^2\).

The decline in incidence of GBS early-onset disease (GBS-EOD), i.e. onset of symptoms within 7 days after birth, has generally been considered as evidence for effectiveness of IPA. However, because other factors may have influenced incidence figures as well, it is arguable whether this is conclusive proof. In a recent review it was discussed why time-trend analyses have their drawbacks in this respect\(^3\). The question remains how else efficacy should be judged and whether available evidence justifies widespread IPA.

This paper reviews the available evidence for efficacy of IPA used in the prevention of neonatal GBS disease. We will first describe the clinical presentation of GBS-EOD, etiology and the working mechanisms of the recommended antibiotics. Pharmacokinetic-pharmacodynamic measures generally used to predict efficacy of antibiotic therapy, as well as the available data during pregnancy and delivery are described. Clinical studies were also reviewed to determine the likeliness for efficacy of IPA from this point of view. Finally, unintended consequences for mother and neonate are discussed.

Search strategy and selection criteria

Data for this review were identified by searches of PubMed, MEDLINE, Current Contents, the Cochrane Library, and references from relevant articles. Search terms included combinations of “Streptococcus agalactiae”, “group B streptococcus”, “pharmacokinetics”, “pharmacodynamics”, “elimination”, “half life”, “incidence”, “epidemiology”, “vertical transmission”, “neonatal”, “fetal”, “amniotic fluid”, “colonisation”, “anaphylaxis”, “adverse reactions”, “immune system”, and terms for the specific antibiotics (eg, “penicillin”). No date or language restrictions were set in these searches, but only English, Dutch, German, French and Spanish manuscripts were selected afterwards. No studies were excluded based on study design.
Etiology and clinical presentation of neonatal GBS disease

In figure 1 it is illustrated how GBS-EOD is usually acquired during labor or delivery. Of neonates born from GBS colonized mothers 1-2% develop GBS-EOD. Mortality has decreased in the few last decades, but survivors may suffer from severe disability (e.g., hearing or visual loss, uncontrolled seizures, impaired psychomotor development and/ or mental retardation).

Figure 1: Hypothesized pathogenesis of GBS-EOD.

1 Colonization in the rectovaginal compartment; 2 Rupture of the membranes; 3 GBS enters the amniotic fluid; 3a GBS colonization of skin and mucocutaneous areas; 4 Aspiration of infected amniotic fluid; 5 Infected amniotic fluid causes pneumonia (if the bacterial load is high enough); 6 Entry of GBS in the bloodstream (sepsis or bacteremia); 7 Entry in cerebrospinal fluid after hematogenous spread (meningitis). (See color inlay for a full color version of this figure.)
GBS meningitis results in children with disabilities in 34.8% of cases, and in an earlier study 33% of the surviving children showed abnormalities related to GBS septicemia or meningitis.

GBS-EOD may present in different ways. GBS-EOD is diagnosed as culture-proven when streptococci are isolated from blood and/or cerebrospinal fluid and when physical signs and laboratory results are clear. The diagnosis probable GBS-EOD is used for cases of serious neonatal disease when GBS is detected at various sites, but not in blood and/or cerebrospinal fluid. Finally, culture-proven GBS-EOD may also present as “asymptomatic” bacteremia. Asymptomatic bacteremia was defined as positive blood cultures for GBS in neonates without clinical signs of infection. Such cases may be discovered by accident when blood cultures are taken shortly after birth in neonates when only maternal risk factors were present during delivery. In this way, culture-proven GBS-EOD was found to be asymptomatic in 4-20%. Weisman et al found that 15% of 149 term neonates with bacteremia were asymptomatic, whereas all 96 preterm neonates had clinical or laboratory signs of infection. It is unclear for how long bacteremia persists. Prolonged bacteremia for >24 hours has been described. The possibility of developing a life-threatening illness and poorly understood pathogenesis of late-onset GBS disease (GBS-LOD, i.e. 7-90 days of life), justifies treatment of asymptomatic GBS bacteremia in neonates.

Both host related factors and bacterial properties may increase the risk on GBS-EOD. Host related factors include >18 hours of ruptured membranes, fever during delivery, GBS bacteriuria in current pregnancy, having a neonate with GBS disease in obstetrical history and preterm delivery. These factors are associated with an increased risk on GBS-EOD and were incorporated in guidelines to prevent GBS-EOD. At least one of the risk factors preterm delivery, intrapartum fever and membrane rupture of at least 18 hours is found in 49% of GBS-EOD cases. On the other hand, bacterial virulence properties might also influence this risk. But, unfortunately little is known about specific virulent GBS subtypes. Furthermore, there are some other risk factors for GBS-EOD known, such as low levels of maternal antcapsular antibodies, increased number of vaginal exams and intrauterine fetal monitoring.

Intrapartum prophylaxis with antibiotics

The primary aim of IPA is to prevent fetal infection by lowering the bacterial load sufficiently. Optimal IPA requires an antibiotic that preferably selectively kills GBS. The ideal dosing regimen should be designed in a way to achieve prompt, effective concentrations at the site of infection for sufficient time to lower the bacterial load to a harmless level. At the same time toxicity for both mother and fetus should be avoided.
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Different strategies have been used to select candidates for IPA\textsuperscript{1,2}. For instance, current CDC guidelines\textsuperscript{2} advise the administration of intrapartum antibiotics to all GBS carriers during delivery (2-35% of all pregnant women\textsuperscript{20-27}). Dosing schedules are shown in table 1. Women with unknown GBS carriage during delivery, are treated with IPA when host related risk factors are present\textsuperscript{2}.

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Initial dose</th>
<th>Subsequent dose</th>
<th>Dosing interval</th>
<th>Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benzyl-penicillin</td>
<td>5 million Units *</td>
<td>2.5 million Units *</td>
<td>4 h</td>
<td>Not penicillin allergic</td>
</tr>
<tr>
<td>Ampicillin</td>
<td>2g</td>
<td>1g</td>
<td>4 h</td>
<td>Not penicillin allergic</td>
</tr>
<tr>
<td>Cefazolin</td>
<td>2g</td>
<td>1g</td>
<td>8 h</td>
<td>Allergic to penicillin; low risk of anaphylaxis</td>
</tr>
<tr>
<td>Clindamycin</td>
<td>-</td>
<td>900 mg</td>
<td>8 h</td>
<td>Allergic to penicillin; high risk of anaphylaxis; susceptibility to clindamycin proven</td>
</tr>
<tr>
<td>Erythromycin</td>
<td>-</td>
<td>600 mg</td>
<td>6 h</td>
<td>Allergic to penicillin; high risk of anaphylaxis; susceptibility to erythromycin proven</td>
</tr>
<tr>
<td>Vancomycin</td>
<td>-</td>
<td>1g</td>
<td>12 h</td>
<td>Allergic to penicillin; high risk of anaphylaxis; resistant to clindamycin and erythromycin</td>
</tr>
</tbody>
</table>

* Dutch and Australian guidelines deviate without an explanation from these guidelines, advising a initial dose of 2 million Units and subsequent doses of 1 million Units\textsuperscript{115}.

Table 1: Dosing regimen as recommended by CDC\textsuperscript{2}
The evidence of *GBS* prophylaxis

The choice of the antibiotics
Antibiotics as recommended by CDC are active against *GBS*. Beta-lactam antibiotics, such as the penicillins and cephalosporins, are active against *GBS* by disrupting the synthesis of the cell wall. Both erythromycin and clindamycin show a growth-inhibiting action by interfering with protein synthesis. Vancomycin resembles the penicillins with regard to the mechanism of action in that it interferes with cell wall synthesis and thereby increases cell wall permeability.

According to the guidelines, penicillin G is the antibiotic of first choice because of its narrow spectrum and lack of resistance of *GBS* to penicillin G, with ampicillin as alternative. Although not mentioned in the CDC guidelines, amoxicillin could be used as well. *GBS* may or may not be cross resistant to erythromycin and clindamycin, depending on the mechanism of resistance, and this is becoming an increasing problem. Vancomycin is the last resort, and is not optimal because of its low intrinsic killing activity.

Adequate concentrations
Considering the infection pathway (figure 1), adequate levels in both fetal serum and amniotic fluid (AF) are required. Measures to evaluate efficacy should ideally concern fetal serum and amniotic fluid levels. Maternal levels are a prerequisite for adequate fetal serum levels and equilibrium between fetal and maternal levels is reached within limited amount of time. Therefore, maternal concentration-time profiles might be used as well. Before reviewing and evaluating available data, we will discuss general criteria for effective concentrations and issues related to pregnancy which might influence pharmacokinetics and pharmacodynamics.

General pharmacokinetic-pharmacodynamic measures for efficacy
In the simplest approach antibiotics are divided into agents that display time-dependent killing and agents with a concentration-dependent action. While this concept is still valid, it should be noted that several more refined measures have been developed in pre-clinical studies which are predictive for efficacy in humans as well.

Antibiotics mentioned in the CDC guidelines, except clindamycin and vancomycin, display time-dependent killing. For beta-lactam agents the time the free fraction of the drug, i.e. the fraction not bound to proteins (f), above the minimum inhibitory concentration (MIC) is the best predictor for efficacy (fT>MIC). In general, a fT>MIC for 30-50% of the dosing-interval is considered adequate for optimal treatment in non-neutropenic patients. Clindamycin also has a time-dependent action in vitro, but clinical efficacy is more closely related to the area under the concentration curve over MIC for 24 hours (AUCo-24h/MIC). Similarly, although vancomycin displays time-dependent action in vitro studies, animal and clinical studies suggest that the effect of vancomycin is better related to the fAUCo-24h/MIC ratio. Furthermore, vancomycin seems to display some concentration-
dependency. For this drug studies indicate that the $fAUC_{0-24h}/MIC$ ratio needs to be at least 25-30 to be effective\textsuperscript{34,37}, but may be much higher for optimal effect.

Development of invasive disease is also dependent on interaction of GBS with the neonatal immune system. Three basic mechanisms are required for effective elimination of invasive GBS: chemotaxis, phagocytosis and intracellular as well as extracellular bacterial killing. Deficiencies on all levels have been identified in neonates, particularly in those born prematurily\textsuperscript{39-41}. Infants are protected in part by active transplacental acquisition of maternal antibodies that significantly occurs in the third trimester of pregnancy\textsuperscript{42}. The neonatal adaptive immune system is still poorly developed due to low synthesis of IgG, especially of prematures\textsuperscript{42}. Deficiencies in both innate and adaptive immune system make neonates vulnerable for GBS-EOD. Therefore (premature) neonates have to be regarded as immunocompromised patients and consequently the $fT>MIC$ should be larger (40-60\%) than in immunocompetent patients\textsuperscript{38}.

**Pharmacokinetics in the maternal-fetal unit**

Since antibiotics reach the fetus after transplacental transfer, adequate maternal serum levels are the first requirement to reach fetal serum concentrations. Secondly, antibiotics should reach the AF. Transplacental passage of antibiotics occurs primarily by simple diffusion of the free fraction\textsuperscript{43}. Therefore, the rate of transfer is related to the maternal-fetal concentration gradient and is inversely proportional to the thickness of the placental membrane\textsuperscript{44}. The thickness decreases with gestational age and in various disease states, like diabetes and hypertensive disorders complicating pregnancy\textsuperscript{45}. In the third trimester AF levels of antibiotics eliminated by the kidneys largely depend on fetal renal excretion\textsuperscript{46,47} and are influenced by maturation of the fetal kidneys\textsuperscript{48}.

The continuously changing physiological adaptations to advancing pregnancy are likely to modify the pharmacokinetics. Therefore, to determine whether the recommended dosing regimens are indeed adequate to achieve the desired concentration profiles it is essential to focus on pharmacokinetic information obtained shortly before and during labor. Unfortunately, most studies reviewed in Table 2 present data that are far from optimal to make a sound judgement. Essential data are often missing (e.g. fetal concentrations, protein binding) and presented pharmacokinetic data or observed concentrations do not allow proper estimation of $fT>MIC$ or other indices. Also, the numbers of patients included per study were limited and exhibited a wide range in gestational ages. Furthermore, most studies included patients without uterine contractions, a factor which might further influence pharmacokinetics\textsuperscript{49,50}.

CDC guidelines call for at least 4h of IPA prior to delivery to be adequate\textsuperscript{2}. From a pharmacokinetic point of view there is no rationale for this interval of 4 hours. Antibiotics reach fetal serum within several minutes after the administration to the
Voigt et al. found the pharmacokinetics in pregnant women to be similar to non-pregnant women. But being in labor affected the pharmacokinetics significantly.\(^49\)

** Data derived from one patient in the second trimester of pregnancy.

**Table 2**: Pharmacokinetic data of the antibiotics recommended in CDC-guidelines.

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Maternal serum levels</th>
<th>Total body clearance</th>
<th>Terminal half life</th>
<th>Cord blood levels</th>
<th>Amniotic fluid levels</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benzylpenicillin</td>
<td>Adequate</td>
<td>Increased</td>
<td>Decreased</td>
<td>-</td>
<td>-</td>
<td>116</td>
</tr>
<tr>
<td>Ampicillin</td>
<td>Decreased*</td>
<td>Increased*</td>
<td>Decreased*</td>
<td>Detectable after 3-10 min; equal to maternal serum after 2h. Above MIC for GBS 27min-8h after iv injection (1g).</td>
<td>Below MIC for GBS within the first 30-67 min</td>
<td>48-50,62,117-123</td>
</tr>
<tr>
<td>Cefazolin</td>
<td>Decreased</td>
<td>Increased</td>
<td>Decreased</td>
<td>Above MIC for GBS 0.5-6h after iv injection</td>
<td>Above MIC for GBS 0.5-6h after iv injection</td>
<td>124,125</td>
</tr>
<tr>
<td>Erythromycin</td>
<td>Decreased</td>
<td>-</td>
<td>-</td>
<td>2-10% of maternal levels (one study 5-20%)</td>
<td>-</td>
<td>126-132</td>
</tr>
<tr>
<td>Clindamycin</td>
<td>Unchanged</td>
<td>-</td>
<td>Slightly decreased</td>
<td>50% of maternal levels</td>
<td>First 30-60 min after iv injection to the mother not detectable</td>
<td>121,126,128,132,133</td>
</tr>
<tr>
<td>Vancomycin</td>
<td>-</td>
<td>-</td>
<td>Similar**</td>
<td>Feto-maternal ratio 0.76**</td>
<td>-</td>
<td>134</td>
</tr>
</tbody>
</table>
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mother\textsuperscript{48}. Afterwards the concentration will decrease both in fetal and in neonatal serum. Antibiotics in neonatal serum will continue to eliminate bacteria with the same rate as before birth. Therefore, a short time interval between administration of antibiotics and delivery does not reduce adequacy of IPA.

In conclusion, these data, especially data in relation to pharmacodynamic indices, are insufficient to judge efficacy of IPA. Most information is based on concentrations in maternal serum, but antibiotics reach fetal serum after transfer across the placental barrier, what might influence the T>MIC. Pharmacokinetic-pharmacodynamic measures found for other infections in non-pregnant individuals or animal models are not necessary valid in fetal serum and amniotic fluid.

Clinical evidence in favor of the efficacy of IPA

In addition to pharmacokinetic data other studies may contribute to the evaluation of efficacy of GBS-IPA. The most direct indicator for efficacy is the bacterial load in neonatal blood cultures. Also the number of colonized mucocutaneous areas in the neonate has been shown to be a determinant of GBS-EOD\textsuperscript{51}. Neonates with GBS-EOD had significantly more GBS positive surface areas than infants without GBS-EOD\textsuperscript{51}. Obviously, effective prophylaxis should be reflected in decreased incidence figures. However other factors may influence these figures as well and blood cultures are taken from a selection of the neonates. Therefore, it is important to separate the contribution of IPA from the contribution of other factors whenever possible.

Blood cultures

Prospective studies comparing antibiotic treatment with no treatment provide the strongest evidence for effectiveness. In a randomized prospective study Boyer and Gotoff\textsuperscript{52} observed a lower incidence of positive blood cultures in neonates of GBS carriers treated with ampicillin intrapartum compared to neonates of patients not treated with ampicillin\textsuperscript{52}. In contrast to the present guidelines\textsuperscript{2}, neonates in the study of Boyer received antibiotics after maternal IPA as well\textsuperscript{52}. The reduced number of positive blood cultures suggests that IPA decreases the incidence of GBS-EOD\textsuperscript{52}, but since clinical neonatal outcome was not reported, it cannot be concluded that current IPA is optimal.

Another issue is apparent IPA failure. Six studies report that 6-19% of neonates with invasive GBS disease were born from mothers with IPA\textsuperscript{12,14,53-57}. Obviously, antibiotic treatment was not optimal in these cases. Maternal fever is associated with the presence of positive neonatal blood cultures after IPA (referred to as prophylaxis-failure)\textsuperscript{12,54,58}. Most likely adequate fetal serum levels are achieved within the first hour, but apparently more time is needed to eradicate GBS, as is
The evidence of GBS prophylaxis

Figure 2: The effect of antibiotic prophylaxis on the bacterial load of GBS.

ROM = Rupture of membranes, tR = time between ROM and start of antibiotics, AB = start of administration of antibiotic, MIC = minimum inhibitory concentration, t[F] = time the fetal concentration exceeds the MIC; 1 changes in bacterial load. 2 enhanced bacterial load in patients in maternal fever or prolonged ROM. (See color inlay for a full color version of this figure.)
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illustrated in figure 2. The amount of time needed to eradicate GBS depends on the bacterial load. The bacterial load is believed to be increased in cases with maternal fever and prolonged rupture of the membranes. Consequently, a short time span between administration of IPA and delivery will result in a higher number of positive blood cultures taken immediately after birth. This is consistent with the fact that within cases of prophylaxis-failures duration of IPA <1-2 hour prior to delivery is indicated as risk factor for failure\textsuperscript{53,56,59}. This indicates that IPA is insufficient when an overwhelming infection might have been established in utero before initiation of antibiotics, because the antibiotic concentration was maintained for insufficient time to eradicate all bacteria at the time the blood culture was taken.

Reduction in neonatal colonisation

As explained above, observational studies suggested that vertical transmission of GBS might be interrupted by IPA. Most often neonatal colonization is determined by the use of cultures taken from three mucocutaneous areas (pharynx, umbilicus, and external auditory canal) to serve as a measure of effectiveness. In the absence of IPA in vaginal deliveries, neonates born from GBS colonized mothers were colonized in 43\% to 53\% at one or more surface areas\textsuperscript{60-64}. Transmission from mother to child after caesarean section in patients with ruptured membranes or active labor was 25.9\%\textsuperscript{61}. After administration of IPA with ampicillin a lower neonatal colonization rate has been seen after vaginal delivery, varying from 0\% to 10\%\textsuperscript{52,60,62,64-66}.

The time interval between administration of IPA and delivery is an important determinant in interrupting mother-to-child transmission (figure 2)\textsuperscript{63, 65}. Adequate AF antibiotic concentrations are likely to be involved in eradication of GBS from surface areas. Since there is some time needed to achieve adequate AF concentrations and eradicate GBS from these areas, the bacterial load will decrease after an increased time interval between IPA and delivery. De Cueto et al. found for ampicillin that when this interval is at least 2 hours, vertical transmission of GBS was minimized to 1.5\%\textsuperscript{63}.

Unfortunately, data on vertical transmission after IPA with clindamycin, erythromycin or vancomycin are scarce. One study in 7 patients receiving intramuscular erythromycin for an unknown period demonstrated that none of the neonates carried GBS when cultured within 24 hours after birth\textsuperscript{67}. Since adequate AF antibiotic levels, rather that adequate fetal serum concentrations are likely to be involved in eradication of GBS from mucocutaneous areas of the fetus, the effect of IPA with erythromycin and clindamycin might be limited or delayed.
Changes in incidence figures and case fatality

Most trends in incidence rates of culture-proven GBS-EOD decreased within a geographical area after implementation of IPA, suggesting a causal relation. Before the implementation of prophylaxis in the US the incidence of GBS-EOD fell from 2-3/1000 live births in the 1970s-1980s to 1.4-1.8/1000 live births in 1990 with a constant prevalence of maternal GBS colonisation of 20-25%\textsuperscript{68}. While it is likely that IPA is in part responsible for the decrease in incidence and low mortality rate, other factors may contribute as well, among which are early recognition of infection and improved neonatal care\textsuperscript{3,56}. Furthermore, natural fluctuations in incidence figures of GBS-EOD as large as 2.85 to 0.45 per 1000 live births from year to year\textsuperscript{69} may occur within regional populations and may therefore erroneously be interpreted as being caused by IPA. Such fluctuations may be due to changes in prevalence of maternal colonisation as well as variation in GBS subtype distribution.

There are other issues to be considered as well. Many studies on incidence are difficult to compare because of methodological diversity\textsuperscript{56,70,71}. Since there is an extremely low risk for full-term infants born by elective caesarean section without rupture of the membranes or onset of labor on GBS-EOD\textsuperscript{2,72}, an increased application of this procedure will decrease the incidence. Incidence figures should therefore be corrected for this aspect.

The substantial decline in incidence figures is based on data of culture-proven GBS-EOD. Since suboptimal IPA may lead to negative blood cultures in clinically ill neonates (see above), studies can be interpreted with confidence only when incidence figures of culture-proven as well as probable EOD are reported\textsuperscript{57,73}. With suboptimal IPA the incidence of culture-proven EOD will be decreased, while the incidence of probable EOD might be increased. Estimates of the incidence of probable GBS-EOD are higher than culture-proven incidence rates, indicating a greater disease burden than suggested by studies based on only culture-proven GBS-EOD\textsuperscript{57,74,75}. Comparing incidence rates after correction for underreporting before and after the introduction of IPA showed that the incidence of probable GBS-EOD was constant in the Netherlands (1.3-1.4/1000 live births). There was only a limited decrease in the culture-proven GBS-EOD from 0.54/1000 live births before introduction of IPA to 0.36/1000 live births afterwards\textsuperscript{75}. Because asymptomatic bacteremic neonates are often included the culture-proven incidence rates, local protocols on neonatal blood cultures can also influence incidence figures.

Finally, incidence figures do not always decline. Noteworthy is the unchanged incidence of GBS-EOD in a hospital where the intrapartum use of antibiotics increased from 13% to 44% of all deliveries between 1989 and 2002\textsuperscript{76}. As reviewed by Gilbert\textsuperscript{3} earlier, it appears from these findings that incidence rates provide only moderate evidence for efficacy of the GBS prophylaxis.

In the last 40 years the case fatality rate of culture-proven cases of GBS-EOD has decreased from 55% in the 1970s to <10% in 2000-2005\textsuperscript{2,53,57,77}. An important
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factor in this decline is likely to be the improved neonatal care. IPA may have contributed to this decline by advancing the antibiotic effect on the child and decreasing the severity of the disease. However, recently Norway reported an yet unexplained, marked increase in case fatality from an average of 5.8% in 2000-2005 to 33% in the first 6 months of 2006 and a slightly increased incidence of invasive GBS disease in neonates in the first 90 days of life using a risk factor based strategy. Such changes in case fatality rates without alterations in antibiotic policy, might be explained by changes in the virulence characteristics of circulating GBS strains.

From these clinical studies we can conclude that the intrapartum administration of antibiotics to prevent GBS-EOD is likely to have clinical effect. However, it is unclear to what extent the decrease in GBS-EOD can be attributed to the administration of antibiotics and whether the currently used dosing schedules are optimal. After reviewing the positive effects of IPA, it is also important to discuss the unintended consequences of IPA, as will be described in the following.

Unintended consequences of IPA

To justify the administration of antibiotics as prophylaxis against GBS-EOD in up to 35% of women in labor, apart from being effective, prophylaxis should have minimal risks for both mother and child. The risk for the mother is limited to the risk on anaphylactic reactions on administered antibiotics. The (long-term) unintended consequences for neonates are still under debate. An increase use of (suboptimal) IPA may also affect the susceptibility of GBS.

Maternal risks

An increased use of antibiotics will result in more adverse reactions. The most serious reaction is an anaphylactic shock with consequences for both mother and fetus. Many pregnant women have a history of penicillin “allergy”, often described as a rash. In spite of the fact that most antibiotic-associated rashes are not IgE-mediated, the risk of anaphylaxis can not be ignored. In general, the incidence of anaphylaxis among inpatients has been reported to be three to five per 10,000. The incidence of anaphylaxis after administration of penicillin is estimated to be 0.01% with a mortality rate of 9%. Anaphylaxis occurs more often after parenteral administration than after oral administration. In pregnant patients with anaphylactic shock there will be fetal distress due to maternal hypoxia and hypotension. On the other hand parenteral antibiotics used for GBS prophylaxis have rarely been noted to cause severe reactions in pregnant women without a history of penicillin allergy. Penicillin skin testing can be performed in advance in pregnant women and penicillin can be administered safely if the result is negative.
Neonatal risks
Several possible unintended consequences of IPA have raised concern for the neonate. Firstly, some investigators have reported an increase in incidence of non-GBS-EOD. These increases appear to be limited to preterm or low-birth-weight infants and ampicillin-resistant pathogens. Among cases of sepsis, non-GBS sepsis in infants was caused more frequently by ampicillin-resistant pathogens in the era of IPA. Especially rates of ampicillin-resistant Escherichia coli sepsis have increased among preterm neonates. Is was suggested that the increase of ampicillin-resistant pathogens might be partially attributable to maternal antibiotic exposure before delivery. But, as reviewed by Moore et al., there are some confounders in the interpretation of these studies. None of the studies was designed to estimate the efficacy of IPA against susceptible infections. Duration and indication of IPA as well as the presence of other known risk factors for EOD, like prematurity, and natural fluctuations in incidence numbers should be taken into account in the analysis. Simultaneously, the proportion of community-acquired E. coli infections that are ampicillin-resistant has been increasing suggesting that trends in antimicrobial resistance should not be attributed to GBS prophylaxis alone. To summarize, trend analyses do not allow a direct assessment of causality between IPA and risk of non-GBS sepsis.

Secondly, one study reported an association between the use of IPA and LOD. GBS-LOD has usually been considered community-acquired. The incidence of GBS-LOD did not change after implementation of the prophylaxis. Glasgow et al. compared the frequency of LOD in infants exposed to IPA and non-exposed infants. Exposure to IPA was strongly associated with the occurrence of LOD. Pathogens causing LOD were more likely to be ampicillin-resistant in infants exposed to IPA. Both findings seemed to be associated to the use of broad-spectrum antibiotics, rather than benzylpenicillin.

There is also some evidence from basic animal and human studies that peripartum antibiotics may have long-term consequences for the neonate. The use of antibiotics during delivery influences the maternal vaginal and fecal flora, which provide the first natural sources of colonizing organisms in the neonatal gut. Acquired abnormalities in early-life bacterial colonization may affect the development of the immune system and a change in pattern of initial colonization of the gut in the first days of life may be linked to later development of allergic disease. Unlike broad-spectrum antibiotics, benzylpenicillin does not perturb normal gastrointestinal flora and for intrapartum amoxicillin the influence was shown to be limited to a reduced initial colonization by Clostridium in infants exposed to antibiotics. Apart from IPA it has also been found in infants with an age of one month that the intestinal flora was influenced by such factors as mode of delivery, breast-feeding, hospitalization after birth, prematurity and the presence of older siblings.
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Notwithstanding the fact that several confounders complicate the interpretation of the relation between IPA and non-GBS sepsis, and that many factors may be involved in the development of the neonatal immune system, the association with IPA may not be ignored. Based on current data, the estimated number of prevented infections from IPA still outweighs the possible neonatal unintended consequences. Concerning the choice of the antibiotic, available data suggest that the risk on neonatal unintended consequences is minimal with the use of benzylpenicillin, compared to broad-spectrum antibiotics, like ampicillin.

Risk on emergence of resistance
Besides aspects of efficacy, dosing schedules should also be designed to minimize the chance of bacterial resistance. Appropriate exposure to antibiotics achieved by adequate dosing is important to limit resistance development\textsuperscript{102}. The potential for resistance development can be defined as the ability of a bacterial strain to survive killing and regrow. Thus, there is an inverse relationship between the efficacy of an antibiotic and the resistance induction potential of an antibiotic\textsuperscript{103}. For several micro-organisms and antimicrobials the area under the curve of the unbound fraction over MIC ($f_{\text{AUC}}/\text{MIC}$) has been investigated in the prediction of selecting resistant organisms\textsuperscript{104-107}. However, since there are no data on prevention of resistance in GBS, dosing regimens used in the prevention of GBS-EOD can not be judged on their potential to select resistant organisms. Studies in pre-clinical infection models could be very useful for designing dosing regimens that avoid resistance development\textsuperscript{32}.

Conclusions

Having reviewed data on efficacy of IPA, the question whether IPA is truly preventing GBS infection of the fetus, can not be answered with certainty. Limited available data suggest that IPA to some extent prevents GBS-EOD, but other factors are likely to contribute to lowering of the incidence. Apart from these studies, concerns on unintended consequences for mother and neonate are rising and are still under debate.

It is surprising that discussions on effectiveness of IPA only have concerned proper identification of patients at risk, implementation of the prophylaxis and circumstantial aspects affecting incidence, but have not questioned practice itself. Dosing regimens are based on tradition\textsuperscript{108}, rather than on pharmacokinetic data during pregnancy. Physiological changes due to complications of pregnancy, such as severe preeclampsia, might also have an additional effect on pharmacokinetics. CDC guidelines call for at least 4h of IPA prior to delivery to be adequate\textsuperscript{2}. But neither studies on the decrease of transmission of GBS nor pharmacokinetic data provide a rationale for this 4 hour threshold\textsuperscript{109}. Even if a short time interval is
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expected between administration of antibiotic and delivery, this is no reason to omit IPA. Of the antibiotics advised for the prevention of GBS-EOD, the penicillins have been studied most extensively. But even their efficacy can not be guaranteed.

The optimal timing in labor to initiate antibiotics is difficult to assess. The presence of risk factors for development of GBS-EOD influences the initiation of prophylaxis. These factors might all be related to an increase in bacterial load in the AF (figure 3). The current practice in GBS prophylaxis is based on the idea that the risk on GBS-EOD primarily exists after rupture of the membranes. Indeed, the bacterial load increases with the duration of ruptured membranes and subsequently the attack rate increases with a marked rise after 18 hours. However penetration of GBS through intact membranes can also occur, leading to severe cases of intra-amniotic infection or abortion. The ability of GBS to attach and invade the chorioamniotic membranes has been demonstrated in vitro, but might be limited to a specific GBS subtype. In this scenario it might be appropriate to start antibiotic therapy earlier than is advised now.

Nowadays, many pregnant women are candidates for IPA and this, in conjunction with the lack of high quality studies and concerns on the unintended consequences of IPA, should be the motivation to continue research. Although some data are available for the penicillins, additional studies including patients with uterine contractions as representatives for IPA-candidates are needed to clarify efficacy. For erythromycin, clindamycin and vancomycin maternal pharmacokinetics and transplacental transfer need to be further investigated in this special patient group. The increase in IPA due to change in strategy to the screening-based approach, adds to the general increase in antibiotic use. Widespread use of antibiotics generally contributes to the increase in resistance. As an alternative preventive strategy interference with the neonatal immune system has been mentioned. Especially the development of a universal maternal vaccine may benefit from the application of genomic/proteomic technologies. However, implication of the current prevention strategy may interfere with clinical vaccine efficacy trials. Furthermore, research on virulence factors within the different GBS types may lead to early detection of virulent GBS strains and thereby narrow the use of IPA to carriers of virulent GBS strains in the future.

Reviewing the evidence for efficacy and unintended consequences, the use of IPA should be limited to patients at risk for GBS-EOD. The unintended consequences of IPA indicate that administration of IPA to all GBS carrying patients is not desirable. Until new information becomes available, the dosing regimen should be continued as recommended by the CDC. Benzylpenicillin is still the antibiotic of first choice. Firstly, because most data are available for this antibiotic, suggesting efficacy. And secondly because the risk on neonatal unintended consequences is limited. Skin testing should be performed in patients suspect for penicillin allergy in history. Clindamycin, and not erythromycin is the
Figure 3: Hypothetic interrelationship between risk factors to increased risk of GBS-EOD.
alternative for penicillin allergic patients. In patients with a negative skin test the administration of benzylpenicillin is recommended. Since fever during delivery is the most important factor for development of GBS-EOD after IPA, neonates from mothers with intrapartum fever should always be admitted to the neonatal care unit.

References


Chapter 2


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