

Parenteral Antibiotics for the Treatment of Serious Neonatal Bacterial Infections in Developing Country Settings

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Background: A number of special issues must be considered when selecting simple, safe, inexpensive, and effective antimicrobial regimens for treatment of neonatal sepsis in developing country community settings.

Methods: We reviewed available data regarding pharmacologic profiles of parenteral antibiotics with specific attention to properties relevant to their use in the treatment of neonatal infections in developing country communities.

Results: For community-based management of neonatal infections, particularly attractive properties include efficacy and safety of extended-interval, intramuscular dosing regimens. The penicillins and cephalosporins have relatively favorable efficacy and safety profiles. Although the aminoglycosides have narrow therapeutic indices, when used appropriately, they are safe and effective. Although inexpensive and effective, the potential for significant life-threatening toxicity among neonates associated with chloramphenicol makes it the least preferred of the parenteral agents for empiric therapy.

Conclusions: The preferred parenteral regimens for community and first-level facility use are a combination of procaine penicillin G and gentamicin, or ceftriaxone given alone, which are safe and retain efficacy when dosed at extended intervals (≥ 24 hours) by intramuscular administration.

Key Words: antibiotic resistance, community, developing country, neonatal sepsis, pharmacokinetics, serious bacterial infections

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Choosing simple, safe, inexpensive, and effective antimicrobial regimens for treatment of neonatal sepsis in community settings poses many challenges. Adequate data are lacking on identification of pathogens and antimicrobial susceptibilities, efficacy, pharmacokinetics, and safety in neonates. Antibiotics with good safety profiles may be too expensive or impractical for developing countries to use, and legitimate concerns exist about further promoting the emergence of antibiotic resistance, a growing problem in many developing country health facilities.

In this review, we focus primarily on pharmacologic considerations in selecting parenteral antimicrobial regimens for use in developing country settings. A number of special issues must be taken into account when devising antibiotic treatment strategies for neonatal infections in these settings (Tables 1, 2).¹ In general, these factors mandate that studies be performed specifically in neonates to understand and predict reliably the pharmacokinetics and ultimately the efficacy and potential toxicity of antibiotics given for management of infections. However, data from studies among neonates are not uniformly available for many of the antimicrobials currently in

use, or for potentially useful agents in the treatment of serious infections.

Antibiotics Choices for Community Settings in Developing Countries

Antibiotics of potential use in community-based strategies in developing country settings are discussed in detail below.

Ampicillin and Penicillin G

Ampicillin has been widely used in neonatal medicine as empiric therapy for early-onset neonatal sepsis and meningitis, in combination with gentamicin for synergistic activity against Group B *Streptococcus* (GBS), enterococci, *Listeria monocytogenes*, and some Enterobacteriaceae (eg, *Enterobacter* spp., *Proteus* spp., *Escherichia coli*).² Ampicillin and gentamicin (see later in the text) continue to be the first-line, standard-of-care antibiotics for treatment of neonatal sepsis in developing as well as developed countries.^{2–4} Although ampicillin remains the first-line antibiotic of choice for use in health-facilities, use in community-based settings is not feasible because of the need to administer doses more frequently than once daily. Furthermore, increasing ampicillin resistance among Gram-negative rods has developed worldwide.^{2,5,6} *Klebsiella* spp. are intrinsically resistant to ampicillin, and most strains of *Staphylococcus aureus* are now also resistant.⁷

The half-life of ampicillin is 5 to 6 hours in neonates <7 days old and 2 hours in older neonates.⁸ Thus, neonates <1 week old can maintain adequate levels with twice daily dosing, but older neonates should be given 3 to 4 doses per day. The low penetration of ampicillin into cerebrospinal fluid (CSF) increases with meningeal inflammation, but higher doses (eg, 200–300 mg/kg/d) should be used to achieve adequate mean inhibitory concentrations (MICs) against many organisms in the CSF.⁹

In general, ampicillin is preferred to penicillin G due to activity against some Gram-negative pathogens such as *Haemophilus influenzae*, *E. coli*, *Proteus* spp., *Salmonella* spp., *Shigella* spp.; significantly increased activity against *Listeria*; slightly increased activity against enterococci; and equivalent activity against *Neisseria meningitidis*. However, it should be noted that ampicillin is slightly less active against group A and B streptococci and pneumococci than penicillin G. Penicillin G remains the preferred antimicrobial for treatment of *Treponema pallidum* and for meningococcal infections. The half-life of aqueous penicillin G is inversely correlated with birthweight and postnatal age, with ranges reported from 1.5 to 10 hours in the first week of life.¹⁰ The half-life for infants older than 7 days ranges from 1.5 to 4 hours.¹⁰ Even in the setting of inflammation of the meninges, penicillin G does not penetrate the CSF well; however, sufficient CSF concentrations can be attained for treatment of *Treponema pallidum*.¹⁰

Procaine Penicillin

There is substantial experience in using longer-acting procaine penicillin G administered intramuscularly (IM) to neonates with sepsis and congenital syphilis.^{2,11,12} Procaine penicillin provides excellent coverage against GBS, Group A streptococci, meningococci, *Treponema pallidum*, *L. monocytogenes*, and most

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TABLE 1. Special Pharmacological Considerations in the Treatment of Serious Neonatal Infections

	Mode of Drug Administration		
	Parenteral (IV or IM)	Intramuscular (IM)	Oral
Physiologic immaturity of metabolic enzymes [eg, hepatic glucuronyl transferase, pancreatic lipase (de-esterification)]		Primary determinant of absorption is regional blood flow	Alkaline gastric pH Slow gastric emptying
Large extracellular fluid volume (lower peak aminoglycoside levels, prolonged elimination)		Reduced absorption in hypoxic, hypotensive infants	High ratio GI tract: whole body surface area Increased permeability of gastric mucosa Irregular peristalsis
Protein-binding affinities of antibiotic, especially relative to bilirubin			Prolonged interstitial transport time Immature de-conjugational activity of β -glucuronidase and other enzymes of drug metabolism
Decreased protein binding of nafcillin, ceftriaxone, increased drug available; significance not well defined			Unpredictable absorption and bioavailability especially in seriously ill neonates
Displacement of bilirubin by sulfonamides; also by ceftriaxone, weakly by ampicillin			
Impaired, highly dynamic renal function (GFR 30%–60% of adult values, varies with gestational age and chronological age)—Maturation of metabolic enzyme systems and renal function, decreasing extracellular fluid volume leads to dynamic changes in drug levels over time			

TABLE 2. Special considerations for Selection of Parenteral Antibiotic Regimens for Treatment of Serious Neonatal Infections in Developing Country Settings

Pharmacologic Considerations
Availability of extended interval dosing (>24-hr dosing)
Safety/efficacy of intramuscular dosing, for use in community settings
Wide therapeutic index, given limited precision of weight-based dosing in community settings and limited availability of serum drug level measurements
Mode of clearance, given challenges in management of fluid status and measurement of serum electrolytes
Target population
Broad spectrum, given limited capacity for identification and antimicrobial susceptibility testing
Promotion of antimicrobial resistance, given use of broad spectrum regimens, and potentially accentuated adverse effects of missed, extended interval doses
Local/regional antimicrobial resistance patterns
Need for availability of laboratory measurements of renal function and serum electrolytes
Practical considerations
Cost
Availability
Supply logistics
Storage
Mode of administration
Ease of dilution, administration
Stability of drug, lyophilized and reconstituted
Multiple-dosage vs. single use vials available

strains of *Streptococcus pneumoniae*. Procaine penicillin combined with an aminoglycoside, administered IM, is used as empiric first-line treatment of neonatal sepsis in some developing countries, especially in areas where difficulty in establishing venous access precludes use of intravenous (IV) ampicillin. This regimen is also used in neonatal IMCI protocols in some countries. The penicillin agents exhibit synergy with aminoglycosides against GBS as well as *S. aureus*, enterococci, and *Listeria*. However, ampicillin is preferred over penicillin when venous access and multiple daily dosing are not problematic because of its wider spectrum of activity with an equivalent safety profile and better CSF penetration.

Procaine penicillin is relatively inexpensive and well tolerated. A dose of 50,000 units/kg IM produces peak levels 4 to 6 hours

after administration, mean serum levels of 7 to 9 $\mu\text{g/mL}$ for up to 12 hours, and 1.5 $\mu\text{g/mL}$ at 24 hours after the dose in infants <7 days of age, making once-daily dosing possible.¹³ Procaine penicillin G administered once-daily IM along with gentamicin once daily has been shown recently to be feasible and effective for treatment of serious neonatal infections in the community in Bangladesh and Pakistan.^{14,15}

Serum levels decrease more rapidly in older neonates because of greater renal system maturity, with levels of 0.4 $\mu\text{g/mL}$ at 24 hours.¹³ Nevertheless, this is above the MIC for streptococci and most pneumococci, which have MICs for penicillin between 0.005 and 0.1 $\mu\text{g/mL}$.² CSF penetration is variable.^{11,13,16}

Procaine penicillin has been used successfully in the management of congenital neurosyphilis, although some have expressed concern that adequate spirocheticidal concentrations may not always be achieved.¹⁷ The chief disadvantages of procaine penicillin for treatment of neonatal sepsis are lack of coverage against staphylococci, rising resistance among pneumococci, lack of activity against Gram-negative rods, and uncertain CSF penetration.

Antistaphylococcal Penicillins

The combination of parenteral oxacillin (or nafcillin) and gentamicin is widely recommended for empirical treatment of suspected serious staphylococcal infections, for example when umbilical or skin infection, or a consolidated pneumonia suspicious for *S. aureus*, is identified as the potential source for invasive disease, in addition to some late-onset neonatal infections.² These antimicrobials can also be used to treat infections caused by streptococci, including Group B streptococcal and pneumococcal infections; however, the natural penicillins are preferred.¹⁰ The antistaphylococcal penicillin alone, however, lack activity against enterococci or Gram-negative bacilli. Nafcillin is preferred for central nervous system (CNS) infections. Antistaphylococcal penicillins are safe and well tolerated in neonates, although occasional cases of nephrotoxicity (due to large doses of methicillin) and hepatotoxicity (due to oxacillin) have been described.² Moreover, repeated IM dosing of these agents may result in muscle damage. Half-life is prolonged in neonates <7 days old and dosing intervals of 12 hours are adequate.¹⁸ Oral cloxacillin is commonly used for the treatment of superficial skin and umbilical cord infections in developing countries; however, there is no experience with using oral cloxacillin in the treatment of invasive neonatal infections. Frequent dosing, lack

of CSF penetration, and narrow spectrum of activity (eg, not active against enterococci or Gram-negative bacilli) are limitations for home-based therapy. Methicillin resistant *S. aureus* is reported as a significant pathogen in hospital-based studies in India and elsewhere in low resource settings^{6,19,20}; however, it is unclear if methicillin resistant *S. aureus* is a problem in the community, although limited data suggest this may be so (Darmstadt GL, unpublished data).

Chloramphenicol

Chloramphenicol was used extensively in the treatment of neonatal infections worldwide before the advent of the third generation cephalosporins.² Today, because of safer alternatives, use of chloramphenicol is largely restricted to developing countries where third generation cephalosporins are used infrequently because of their expense. Chloramphenicol is cheap, has broad-spectrum activity, and excellent CNS penetration.² It is bactericidal against *H. influenzae* and *S. pneumoniae*, but bacteriostatic against GBS and most Gram-negative enteric rods.² Large variability in serum concentrations and half-lives after both oral and IV administration has been reported by many investigators.^{21–29} Therefore, monitoring of serum levels to guide dosage is necessary to avoid subtherapeutic or potentially toxic levels.^{2,30,31} Concentrations in CSF are 35% to 90% of those in the serum, regardless of meningeal inflammation.^{29,32} Oral administration of chloramphenicol in neonates results in much lower serum concentrations than those observed after IV or IM administration, and wide fluctuations in levels have been observed in neonates given the same dosage, perhaps because of immaturity of the neonatal gastrointestinal tract and resultant erratic absorption.^{21,25,26}

Chloramphenicol toxicity, especially in preterm and low birth weight babies is well documented, and is the major limitation to its use.^{2,25,33} A cardiovascular collapse reaction, “gray baby syndrome,” which presents with vomiting, refusal to suck, respiratory distress, metabolic acidosis, abdominal distention, and diarrhea, has been described in many infants.^{2,25,33} The syndrome is especially common in preterm babies and is related to high serum levels of chloramphenicol, immaturity of the hepatic glucuronyl transferase system, and diminished renal clearance.² Thus, chloramphenicol is contraindicated in premature or low birth weight babies and should be used with extreme caution in the neonatal period.

IM or IV administration of chloramphenicol is currently recommended in WHO protocols for neonates beyond the first week of life and young infants hospitalized with very severe pneumonia as a first-line agent, and for sepsis as a second-line agent if no improvement occurs after 48 hours of a penicillin and aminoglycoside.³

Cephalosporins

There is extensive experience on use of cephalosporins in neonates, as parenteral administration of penicillin/ampicillin with third generation cephalosporins, particularly cefotaxime, is standard therapy, albeit second-line, for neonatal sepsis. The cephalosporins tend to be relatively expensive, however, and there is more concern over emergence of resistance with their use than with the penicillins and aminoglycosides.^{2,34,35} The first generation cephalosporins (eg, cephalexin, cefazolin) lack sufficient activity against Gram-negative pathogens, whereas the third generation agents provide excellent coverage against Gram-negative organisms but activity against *S. aureus* and *Streptococcus pyogenes* may be compromised. For example, cefixime, a third generation cephalosporin, entirely lacks activity against *S. aureus*.

The second generation cephalosporins, such as cefuroxime, have a very favorable side effect profile and good spectrum of activity against most isolates of the principal agents thought to cause

serious bacterial infections in neonates in the community, namely *S. aureus*, *S. pneumoniae*, *S. pyogenes*, *E. coli*, *Salmonella* spp., *Enterobacter* spp., and *Klebsiella* spp. They are relatively expensive, however, costing approximately \$1 for a course of treatment. Intravenous cefuroxime, which has equivalent pharmacokinetics as IM administration, has been used in neonates for the treatment of sepsis, meningitis and pneumonia, as well as for *Salmonella* infections, including meningitis.^{36–41} However, with the availability of third generation cephalosporins, IV cefuroxime is no longer used in neonates in industrialized countries, since a delayed sterilization (>24 hours) was reported in 10% of cases of meningitis, particularly due to *H. influenzae*, treated with cefuroxime.^{5,42}

The parenteral third generation cephalosporins are highly active against the major pathogens of neonates and young infants, including GBS, pneumococci, Gram-negative rods, and *H. influenzae*. They also have some activity against methicillin-susceptible *S. aureus*, although less compared with first and second generation cephalosporins. They do not have activity against *L. monocytogenes* and enterococci, but *Listeria* has not been described as a major pathogen of neonates in developing countries. The cephalosporins also lack synergism with aminoglycosides, although use in combination with aminoglycosides helps to limit risk for emergence of resistance. Two third generation cephalosporins, cefotaxime and ceftriaxone, have been widely used in the treatment of neonatal infections in developed and developing countries.^{2,5,43–45} Both drugs have excellent CSF penetration and safety profiles, making them drugs of choice for the treatment of Gram-negative meningitis in neonates and young infants.^{2,46–48} Cefotaxime has been preferred for neonatal therapy because of concern about aggravation of hyperbilirubinemia with ceftriaxone.^{2,5} Ceftriaxone has high protein-binding capacity and can cause displacement of bilirubin from albumin, and has significant excretion via the biliary system, which may be immature in neonates and low-birth weight infants.^{49–54} However, attractive features of ceftriaxone include its long serum half-life, which makes once-daily dosing possible—a significant advantage which has popularized its outpatient use; and wide therapeutic index which obviates the need for monitoring drug levels.^{2,44} Although ceftriaxone has been used successfully, even in low-birth weight babies without significant worsening of jaundice,^{2,55,56} more experience is needed in the neonatal period. In a recent community-based, randomized controlled trial, ceftriaxone given once daily IM was equally effective and as safe as once daily procaine penicillin plus gentamicin IM.¹⁵ Ceftriaxone should not be used alone to treat meningitis due to enterococci, staphylococci or *Pseudomonas* spp., due to insufficient activity and risk for emergence of resistant strains. The dosage of ceftriaxone is 50 mg/kg once daily for all newborns except those older than 1 week who weigh more than 2 kg, in whom it is increased to 75 mg/kg once daily.²

Aminoglycosides

Aminoglycosides, including gentamicin, have been widely used as first-line therapy for neonatal infections, primarily because of their excellent spectrum of activity against Gram-negative rods, and because of synergy with penicillin agents against GBS as well as *S. aureus*, enterococci, and *Listeria*. *S. aureus* exhibits in vitro susceptibility but break-through colonies appear within 24 to 48 hours—therefore, gentamicin by itself has little activity against staphylococci and has to be combined synergistically with a beta-lactam agent. Hospital data from developing countries indicate that Gram-negative rods are increasingly resistant to gentamicin, but this needs to be confirmed in community settings.⁵⁷

Several features of gentamicin make it an attractive antibiotic from the point of view of community-based management of sepsis.⁵⁸ Gentamicin pharmacokinetics are essentially identical whether ad-

TABLE 3. Preferred Parenteral Regimens for Treatment of Neonatal Sepsis in Developing Country Community Settings

	Dose	Route	Interval	Reference
First line regimen				
Procaine Penicillin G AND Gentamicin	50,000 units/kg 13.5 mg (for ≥ 2500 g) 10 mg (for 2000–2499 g) 10 mg (for < 2000 g)	IM IV, IM IV, IM IV, IM	24 h 24 h 24 h 48 h	10 58
Alternative regimen				
Ceftriaxone	50 mg/kg (for ≤ 2000 g or ≤ 7 d old) 75 mg/kg (for > 2000 g and > 7 d old)	IV, IM IV, IM	24 h 24 h	10

TABLE 4. Advantages and Limitations of Parenteral Antibiotics Relevant to Use in Developing Country Settings

Antibiotic	Advantages	Limitations
Ampicillin	Extensive prior use among neonates Synergy with aminoglycosides Penetration into cerebrospinal fluid (CSF) is increased with meningeal inflammation Improved activity against gram negative rods compared with penicillin	Multiple daily administration (2–4 doses per d) Increasing resistance worldwide Reduced activity against gram positive pathogens compared to penicillin
Procaine Penicillin G	Extensive prior use among neonates Synergy with aminoglycosides Once daily dosing Proven efficacy in treatment of congenital syphilis	Reduced CSF penetration as compared with ampicillin Minimal activity against staphylococci Increasing resistance worldwide No activity against gram negative rods
Antistaphylococcal Penicillins	Extensive prior use among neonates Preferred for staphylococcal infections Nafcillin has good CSF penetration Twice daily dosing effective among neonates < 7 d old	No activity against gram negative organisms, and enterococci Occasional renal (methicillin) and hepatic (oxacillin) toxicity Repeated IM dosing may cause muscle damage at the injection site
Chloramphenicol	Extensive prior use among neonates Excellent CSF penetration	Serum level monitoring recommended due to variations in serum concentrations and half-life Well-documented severe and life-threatening adverse reactions among neonates, especially premature and low birth weight infants IM dosing well-tolerated, once daily dosing available Recommended as first line agent for severe pneumonia after the first week of life
Cephalosporins	Extensive prior use among neonates Once daily dosing available with ceftriaxone Excellent CSF penetration Wide therapeutic index	Relatively expensive May promote more rapid resistance than penicillins First generation cephalosporins lack gram negative activity and require 2–4 doses per d Third generation cephalosporins have reduced gram positive activity Theoretical risk of increased bilirubin toxicity with ceftriaxone
Aminoglycosides	Extensive prior use among neonates (gentamicin) Extended interval dosing (> 24 h) is effective Pharmacokinetics identical with IM dosing Synergy with penicillins	No synergy with aminoglycosides Rising resistance among hospitalized patients in developing countries Narrow therapeutic index, potential for nephro- and ototoxicities Pharmacodynamics are variable among neonates and dependent on fluid status Serum concentration monitoring recommended

ministered by IM or IV routes. The drug exhibits a concentration-dependent bactericidal effect in which a linear relationship exists between higher peak:MIC ratio and improved clinical response. Moreover, the postantibiotic effect of gentamicin, or the ability of the drug to continue to suppress bacterial growth even after antibiotic concentrations have fallen below the MIC for the organism, is also concentration-dependent.^{2,5} These 2 features (concentration-dependent killing and postantibiotic effect) mean that gentamicin exerts a significant antibacterial effect even with extended-interval dosing such as once-daily administration. Multiple studies have shown that once-daily dosing of gentamicin produces higher peak drug concentrations than more frequent dosing intervals, and several studies in neonates have confirmed these findings.^{59–72} Doses used have ranged from 4 to 5 mg/kg given once daily.^{59–72}

A limitation of aminoglycoside therapy is the relatively narrow therapeutic index, and potential for nephrotoxicity and ototoxicity, particularly with prolonged periods during which trough serum levels exceed 2 µg/mL. Moreover, pharmacokinetics are particularly variable in preterm young neonates because of dynamic changes in renal function and fluid status. The serum half-life may also be prolonged in asphyxiated newborns. Thus, monitoring of serum levels is standard-of-care for treatment of serious neonatal infections. A recent developing country study, however, demonstrated that extended interval gentamicin dosing for neonates based on weight category could be administered safely.⁷³ Thus, when guidelines for serum levels are adhered to, aminoglycosides are safe and effective first-line agents for empiric treatment of early and late onset neonatal sepsis and early-onset meningitis (ie, gentamicin in combination with ampicillin). Gentamicin (or amikacin), in combination with ampicillin and possibly also cefotaxime, is also considered by many experts as first-line therapy for late-onset neonatal meningitis; and gentamicin/amikacin plus ampicillin and clindamycin is standard therapy for sepsis of presumed gastrointestinal tract origin.

SUMMARY

No data comparing oral and parenteral antibiotic treatment regimens in the community have been reported, and the incremental benefit of injectable over oral antibiotics is not known. Among parenteral agents, there is considerable experience with the use of penicillins, cephalosporins, aminoglycosides, and chloramphenicol in both developed and developing country health-facility settings for the treatment of neonatal infections. For community-based management of neonatal infections, particularly attractive properties include efficacy and safety of extended-interval, IM dosing regimens. The penicillins and cephalosporins have relatively favorable efficacy and safety profiles. Although the aminoglycosides have narrow therapeutic indices, when used appropriately they are safe and effective. Although inexpensive and effective, the potential for significant life-threatening toxicity among neonates associated with chloramphenicol makes it the least preferred of the parenteral agents for empiric therapy.

The preferred parenteral antibiotic regimen for community and first-level facility use is a combination of procaine penicillin G given once daily and gentamicin given at intervals of ≥24 hours, depending on category of body weight (Table 3).^{58,73} Both agents can be given IM or IV. Ceftriaxone is much more expensive and promotion of resistance in community settings is a major concern; however, it offers an excellent alternative as a single agent given once daily (Table 3). The complexity of the issues involved in antibiotic selection are summarized in Table 4 and are further considered by Bhutta et al in analyzing community-based antibiotic treatment strategies for serious neonatal infections in developing country settings.⁷⁴

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