

Oral Antibiotics in the Management of Serious Neonatal Bacterial Infections in Developing Country Communities

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Background: Parenteral antibiotic therapy is the standard of care for treatment of serious neonatal infections. This may not be possible, however, in some developing country settings with limited health systems capacity.

Methods: We reviewed the evidence for treatment of neonatal infections in developing countries with oral antibiotics, evaluated properties of oral agents that could be considered, and identified priority research questions.

Results: Case management of pneumonia in developing country community settings suggests that this strategy has resulted in substantial reductions in neonatal mortality. However, limited available data indicate that injectable antibiotic therapy is superior to oral regimens.

Conclusions: Parenteral therapy should be used for treatment of serious neonatal infections whenever possible. In settings in which this is not possible, however, oral antibiotic therapy is superior to no antibiotic therapy. Further research is needed to define subgroups of patients and settings in which therapy with oral agents is ethical and effective.

Key Words: neonatal sepsis, serious bacterial infections, home-based treatment, oral antibiotics, developing country

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Case fatality rates for severe bacterial infections in developing countries are high, in part because of late or inadequate administration of necessary antibiotics.^{1,2} Overall, case fatality rate due to neonatal sepsis in developing countries is estimated at about 40%, based largely on data for infants treated in hospitals.^{3,4} When neonatal infections occur, many deaths can be avoided if the signs are recognized early and the disease is treated promptly and adequately.^{5–9}

The World Health Organization (WHO) recommends parenteral antibiotic therapy (eg, benzylpenicillin or ampicillin plus an aminoglycoside such as gentamicin) in a health facility as the standard treatment for serious neonatal infections (ie, septicemia, pneumonia, and meningitis) in developing countries.^{10,11} In resource poor countries, however, the majority of births and neonatal deaths still take place at home, and families often are reluctant to seek care outside the home for neonatal illness for a variety of reasons, including cultural (eg, confinement after birth), economic, logistical (eg, lack of transportation), and health care availability (eg, lack of quality referral-level care).^{9,12–15} Thus, facility-based care that includes a complete course of parenteral antibiotics is not feasible for

many neonates in developing countries, and alternative management strategies are needed.

Home-Based Treatment of Neonatal Sepsis

Little information is available on treatment of serious neonatal infections in the community in developing countries. A study of domiciliary newborn care in Gadchiroli, India^{9,16} demonstrated that trained and supervised community health workers were capable of identifying and successfully treating neonatal infections using a combination of oral and injectable antibiotics. Introduction of a package of interventions that included administration of oral cotrimoxazole (10 mg trimethoprim twice daily for 7 days) and intramuscular gentamicin (5 mg twice daily for 10 days in preterm infants and 7.5 mg twice daily for 7 days in term infants) for treatment of suspected “sepsis” based on use of a clinical algorithm to identify newborns with suspected sepsis resulted in a 76% reduction in the cause-specific neonatal mortality rate attributed to sepsis. This decrease in deaths among neonates with signs of sepsis was credited for three-fourths of the 59% total reduction in neonatal mortality.^{9,16} Overall, the study reported a reduction of neonatal sepsis mortality from 27.5 to 6.6 per 1000 live births. Case fatality attributed to sepsis was reduced in the intervention area from 16.6% before to 9.6% after introduction of the home-based package of neonatal care. Case fatality among neonates treated for suspected sepsis in the community was 6.9% compared with 22% among those not treated.¹⁶ Of note, neonatal case fatality was 13% in the same area in a previous study when village health workers focused on recognition of pneumonia and treated suspected cases with oral cotrimoxazole alone.¹⁷

The precise contribution that the addition of injectable gentamicin made to mortality reduction above that due to oral cotrimoxazole alone cannot be determined, however, as many other aspects of neonatal care were introduced simultaneously with injectable antibiotic therapy. Nevertheless, antibiotic susceptibility testing of vaginal isolates from women in the community showed that 93% of isolates were susceptible to cotrimoxazole alone, and all isolates were susceptible to the combination of cotrimoxazole and gentamicin.^{16,18,19} Since the agents of early neonatal sepsis and pneumonia during the first week of life come in large part from the birth canal, these data suggest that on the basis of antibiotic susceptibility patterns in isolation, oral cotrimoxazole alone would have been expected to provide adequate coverage against the majority of neonatal bacterial pathogens. However, a number of other factors must be considered that may influence effectiveness of antibiotics when given orally (Table 1).²⁰ A primary factor is the erratic absorption of antibiotics from the gastrointestinal tract of newborns, especially when seriously ill.²¹

Other community-based studies in Guatemala,²² Bangladesh,^{7,8} and in urban slums in New Delhi, India,²³ have reported low neonatal case fatality (0%–4%) with use of injectable antibiotics to treat neonates with suspected sepsis. In the Indian study, oral cephalixin was given in combination with injectable amikacin.²³

More recently, in semi-urban squatter settlements of Karachi, Pakistan, a randomized controlled trial demonstrated that among

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TABLE 1. Considerations in Selection of an Oral Antibiotic

Ethical considerations
Cost considerations
Per-dose cost
Number of doses (ie, duration and frequency of treatment)
Indirect costs
Compliance
Frequency and length of therapy
Palatability
Incidence of treatment failure
Incidence of adverse drug reactions, including drug interactions
Pharmacologic considerations
Pharmacodynamic considerations
Bactericidal
Intrinsic activity against pathogens
β -lactamase stability
Little potential for resistance development
Pharmaceutical considerations
Available in concentrated suspension
No direct gastrointestinal irritation
Food (ie, breast milk) does not interfere with absorption
Pharmacokinetic considerations
High bioavailability
Rapid intestinal absorption
Good tissue penetration
Long elimination half-life

neonates with suspected sepsis who refused to go to the hospital for treatment and were offered treatment at community clinics, treatment failure and mortality were significantly lower in the infants treated with injectable procaine penicillin and gentamicin compared with oral cotrimoxazole and injectable gentamicin.²⁴ This confirms that in neonates deemed sick enough to require treatment in the hospital, injectable therapy as recommended by WHO is superior. However, this study also highlights the fact that not all families will accept or can access hospital therapy and demonstrates that outpatient therapy is feasible in some settings.

Home-Based Treatment of Neonatal Pneumonia

To gain further understanding of the potential impact of oral antibiotic treatment on serious neonatal infections in the community in developing countries, it is instructive to examine data on management of neonates with suspected pneumonia using oral antibiotics. Data have been summarized in a meta-analysis of all published and unpublished community-based intervention trials on case management of pneumonia in neonates, infants, and children ≤ 5 years of age in developing countries.^{25,26} The analysis aimed to determine the impact of pneumonia case management on total neonatal mortality and pneumonia-specific neonatal mortality. Of the 6 studies included in the original meta-analysis that compared neonatal mortality in concurrent control and treatment groups,^{27–33} one lacked data on pneumonia-specific mortality.^{27,28} In 4 of the studies, neonates with suspected pneumonia were treated with oral cotrimoxazole^{27,28,30–32}; injectable penicillin was used in 1 study,²⁹ and another used both injectable penicillin and oral ampicillin.³³ Uncorrected analysis showed a 13% to 30% reduction in all-cause neonatal mortality. After correction for perceived biases that may have affected the study results, the estimated reduction in total and pneumonia-specific neonatal mortality was 27% (95% CI: 18% to 35%) and 42% (95% CI: 22% to 57%), respectively. Similar results were found when additional studies were evaluated, which had a longitudinal, prepost intervention design.

This meta-analysis did not specifically address the issue of impact of oral compared with injectable antibiotics in the management of neonatal pneumonia. Moreover, the effects on neonatal

mortality seen in the meta-analysis of pneumonia case management trials cannot be attributed solely to antibiotic effects, because a variety of other interventions accompanied case management. However, the diversity of the interventions included in the various packages, the variety of developing country settings, and the consistency of the impact in the various studies suggests that antibiotic treatment, which was common to all the trials, likely played an important role in mortality reduction in patients identified through case management as having pneumonia. Moreover, the reduction in neonatal mortality found in the meta-analysis was comparable with estimates of the proportion of neonatal mortality due to serious infections,^{34,35} suggesting that a substantial proportion of these potential deaths due to infections were averted through case management that included oral antibiotic therapy in the home.

Other data not included in the meta-analysis are available in which oral antibiotics have been used to treat neonatal infections, particularly pneumonia, in the community. In Indonesia, use of ampicillin plus supportive care (eg, continued breast-feeding, clearing of the nose, fever control) in neonates with pneumonia had no measurable impact on cure rates of mild disease at 1-week follow-up, and did not halt progression to moderate disease at 1-week compared with the use of supportive care alone in the control group.³⁶ In Nepal, pneumonia case management using oral ampicillin (along with health education and immunizations) significantly reduced infant mortality in a prepost treatment design, although data specific to the neonate was not presented.³⁷

Overall, oral antibiotics have been used with some success to treat serious neonatal bacterial infections in the community; these antibiotics include cotrimoxazole,^{9,17,19,27,28,30–32} cephalixin,²³ penicillin,^{7,8,12} and ampicillin.^{33,37} Supportive evidence is most extensive for cotrimoxazole, which is the agent recommended by the WHO for community management of infant and childhood pneumonia, and for most situations in which facility-based treatment of neonates with parenteral antibiotics is not feasible.³⁸ However, further examination of the merits of various oral agents for treatment of serious neonatal infections is warranted.

Choice of Oral Antibiotic for Home Use

A large number of oral antibiotics could be considered for treatment of infections in neonates. Principal factors to consider in choosing an oral antibiotic are outlined in Table 1, and we have briefly reviewed pharmacological considerations in the treatment of serious neonatal infections elsewhere.²⁰ Ethical considerations, of paramount importance, are addressed separately below. We have previously presented consideration of these factors and made detailed comparisons among available oral antibiotics.^{39,40} Salient features of oral antibiotics available in most developing country settings that could be considered for use in treating neonatal sepsis are summarized in Table 2. The macrolides, such as erythromycin, were not included in the current comparison because of insufficient spectrum of activity, significant gastrointestinal side effects including a possible association with hypertrophic pyloric stenosis in neonates,⁴¹ and association with emergence of antibiotic resistance.

The cephalosporins and penicillins both have favorable side effect profiles. There is extensive experience on use of cephalosporins and penicillins in neonates, as parenteral administration of penicillin/ampicillin or third generation cephalosporins (eg, cefotaxime) is standard therapy for neonatal sepsis in many centers around the world. The cephalosporins tend to be relatively expensive, however, and there are concerns regarding emergence of resistance. The first generation cephalosporins (eg, cephalixin, cefadroxil) lack sufficient activity against Gram-negative pathogens, whereas the third generation agents provide excellent coverage against most Gram-negative organisms but have more limited activity against *Staphylococcus aureus* and *Streptococcus pyogenes*,²

TABLE 2. Comparison of Oral Antibiotics

Antibiotic	Cost*	Activity			Prior Use in Neonates [†]	Tissue Penetration	CNS Penetration	Absorption [‡]	Dosing
		<i>S. aureus</i>	<i>S. pneumoniae</i>	Gram-bacilli					
Cotrimoxazole	\$0.13	++	Rising resistance in some areas	++	Yes, most extensive	+++	++	+++	10 mg/kg b.i.d
Amoxicillin	\$0.27	-	++	+	Yes	++	+	+++	30 mg/kg b.i.d
Amoxicillin-Clavulanate	\$0.59	+++	+++	+++	Yes	++	+	+++	15 mg/kg b.i.d
Cephalexin	\$0.14	+++	++	+	Yes	++	+	++	25 mg/kg q.i.d
Cefadroxil	\$0.37	+++	++	+	Yes	++	+	++	15 mg/kg b.i.d
Cefuroxime	\$2.81	+++	+++	++	Yes	++	+	++	15 mg/kg b.i.d
Cefixime	\$0.64	-	++	+++	No	++	++	+++	16 mg/kg q.i.d
Ciprofloxacin [§]	\$0.06	++	+	+++	No	+++	+++	+++	15 mg/kg b.i.d

*Cost for a 10-day course of treatment in a 2-kg neonate (based on 2005 estimates from Management Sciences for Health. International drug price indicator guide. Boston: Management Sciences for Health, 2005).

[†]Refers to prior use in trials in developing countries.

[‡]Considering bioavailability and impact of food on absorption.

[§]Based on tablet pricing, suspension pricing not available.

of the most important agents of serious bacterial infections in young infants.⁴² Cefixime, a third generation cephalosporin, entirely lacks activity against *S. aureus*.

Overall, the most promising oral agents for treatment of neonatal infections in the community are cotrimoxazole, the second generation cephalosporins (eg, cefprozil and cefuroxime, which can be considered interchangeable), ciprofloxacin, amoxicillin, and amoxicillin-clavulanate. As noted above, cotrimoxazole has been used most extensively and successfully in neonates in the community and is the least expensive among these agents. Although it is not approved for use in neonates, it seems to have had a favorable safety record, and Bang et al found no increase in jaundice among treated neonates.⁹ However, a primary concern with use of cotrimoxazole, suppression of the bone marrow, has not been monitored systematically in neonates and it is also unclear whether surveillance has been adequate to monitor the incidence of hypersensitivity reactions. The primary obstacle to use of cotrimoxazole, however, is rising resistance among pneumococcal isolates over the past decade, such that the majority are now resistant and use of cotrimoxazole for treatment of community-acquired pneumonia in children is falling out of favor in Bangladesh, for example.⁴³ This is tempered, however, by some data which suggests that in vitro resistance does not consistently predict in vivo response, although this relationship requires further investigation.^{44,45}

Ciprofloxacin, a fluoroquinolone antimicrobial agent, has not been approved for use in pediatric patients or neonates in large part because of evidence in animal studies of irreversible damage caused by ciprofloxacin to the cartilage in weight-bearing joints.⁴⁶ However, because of the emergence of multiple drug-resistant strains of Gram-negative organisms, ciprofloxacin is being used with increasing frequency in the treatment of serious infections among pediatric patients and neonates. Ciprofloxacin is a relatively broad spectrum agent (with the exception of some Gram-positive organisms such as streptococci), has good oral bioavailability, is relatively inexpensive, and penetrates the cerebrospinal fluid readily, making it a potentially useful agent for the treatment of neonatal infections (Table 2). In a recent study from Dhaka Shishu Hospital in Bangladesh, 48 preterm (<33-week gestation) neonates with serious bacterial infections that did not respond to other antimicrobials were treated with parenteral ciprofloxacin.⁴⁷ Sixty-six gestational age, birth weight, and gender-matched patients in whom serious bacterial infections were successfully treated with other antibiotics were used for comparison. Patients were monitored closely during treatment and for approximately 2 years at regular intervals. The authors reported no signif-

icant differences between the 2 groups with respect to growth and development and there were no reported joint deformities or osteo-articular problems noted in the ciprofloxacin-treated patients.

Similarly, a study from Northern India reported no growth impairment among 61 preterm (<37 weeks) infants with birth weight <1500 g who were treated with ciprofloxacin as compared with control patients treated with other antibiotics.⁴⁸ Similar results have been reported from a study among hospitalized neonates in Greece.⁴⁹ In another study from India in which serial ultrasonography of the knee joint was performed at 1 and 6 months after 14 days of parenteral antibiotic treatment for neonatal serious bacterial infections (n = 30 for ciprofloxacin treated, n = 30 for other antibiotic treated), there was no differences in femoral and tibial cartilage quantification between the 2 groups, further suggesting that ciprofloxacin seems to be safe in human neonates.⁵⁰ At this time there are no published reports of oral ciprofloxacin treatment among neonates; however, future studies are warranted.

The second generation cephalosporins such as cefprozil and cefuroxime have a very favorable side effect profile and good spectrum of activity against most isolates of the principal agents presumed to cause serious bacterial infections in neonates in the community, namely *S. aureus*, *Streptococcus pneumoniae*, *S. pyogenes*, *Escherichia coli*, *Salmonella*, *Enterobacter*, and *Klebsiella*. However, they are relatively expensive, costing approximately \$0.67 for a course of treatment (2 kg infant, treated for 10 days).

Amoxicillin has a similar spectrum and degree of antimicrobial activity as ampicillin, an agent of choice for treatment of neonatal group B streptococcal infections. Antimicrobial activity includes most streptococci, including *S. pneumoniae*, β -lactamase-negative *Haemophilus influenzae*, and a limited number of Gram-negative enteric bacilli. In general, bioavailability of orally administered amoxicillin is high, about 80%.⁵¹ A recent study demonstrated that in 222 full-term neonates with definite or possible group B streptococcal infection who were clinically asymptomatic after 48 hours of intravenous ampicillin therapy, a switch to oral amoxicillin at dosages of 200 or 300 mg/kg/d in 4 divided doses produced median serum amoxicillin concentrations of 25.80 and 31.15 mg/L, respectively, well above the target trough level of ≥ 5 mg/L.⁵² All patients tolerated oral dosing without apparent side effects, all remained disease free during the 3-month follow-up period, and the median length of hospital stay was reduced by 5 days. Thus, a switch to oral therapy after 48 hours of intravenous ampicillin in stable-term neonates with early-onset group B streptococcal infection appears to be feasible and effective. Initiation of

therapy with oral amoxicillin is not recommended, however, because of the potential for erratic and delayed intestinal absorption in the first few postnatal hours^{21,51} and lack of established equivalence of oral amoxicillin and IV ampicillin.

Amoxicillin-clavulanate is approved for use in neonates by the US Food and Drug Administration, and because of the extended spectrum afforded by competitive inhibition of β -lactamases by clavulanic acid, is also active against most pathogens of serious neonatal infections. The spectrum of activity of amoxicillin-clavulanate, cefuroxime, and ceftazidime are essentially identical, and in clinical practice these agents are interchangeable.³⁹ Amoxicillin-clavulanate generally costs about the same (approximately \$0.59 for a 10-day course of treatment for a neonate weighing 2 kg) as the cephalosporin class of antibiotics, with less concern about induction of resistance.

Recent studies showing an association between use of amoxicillin-clavulanate among women in labor and increased risk of necrotizing enterocolitis (NEC) in their newborns raise questions about the safety of this antimicrobial combination for the newborn.^{53,54} There was no significant increase among the newborns, however, in neonatal mortality or in a composite of neonatal death, chronic lung disease or major cerebral abnormality. Thus, although there is no direct data to suggest that treatment of newborns would result in a similar risk of NEC as when exposure occurs in utero, caution in use of amoxicillin-clavulanate in the treatment of newborn infections may be prudent, particularly because other antibiotics with a comparable spectrum of activity but fewer safety concerns are available, such as second generation cephalosporins, including ceftazidime and cefuroxime.

Ethics of Use of Oral Antibiotics

As noted above, current recommendations for the treatment of serious bacterial infections among neonates call for treatment with parenteral antibiotics. Moreover, a randomized trial has demonstrated that combination oral (cotrimoxazole) and injectable (gentamicin) antibiotic therapy was inferior to 2-drug injectable therapy (procaine penicillin plus gentamicin).²⁴ Implicit in such recommendations, however, is the availability of a health care infrastructure to ensure access to health facilities where parenteral antibiotics may be administered safely to neonates. In settings with evolving health system infrastructures that are yet insufficient to ensure such access, an unmet need for improving the treatment of neonatal infections exists. These settings include areas where effective facility-based case management strategies do not currently exist. Approximately half to nearly two-thirds of babies in developing countries are delivered at home and only half of those births are assisted by a trained traditional birth attendant or midwife.³⁵ Because signs of illness due to infections are most likely to manifest while the infant is at home, and families in many societies are reluctant to take newborns outside the home, even when ill,^{12-15,55} an important strategy for reducing neonatal mortality is to improve the ability of first-line health workers to prevent, recognize, and provide initial management of infectious diseases in the home or at health facilities.^{7-9,14,56,57} By treating uncomplicated cases of presumed neonatal sepsis in the home or at community-based clinics, the potential burden to the family of accessing hospital care, and the costs associated with hospitalization could also be alleviated. Although parenteral antibiotic therapy is preferable, oral antibiotic therapy may provide an acceptable alternative approach to addressing the needs of neonates in such developing country settings where alternatives to the gold standard for care are unavailable or impractical. In settings with limited health infrastructures, community-based management of childhood infections, such as childhood pneumonia, with oral antibiotic therapy has proven effective in reducing mortality.²⁵ Therefore, among subgroups of neonates who do not have

access to facility-based management of infections and in settings where community-based health care providers may be trained in recognizing signs of infection and in assessing response to therapy,⁶⁻⁹ oral antibiotic therapy may demonstrate practical advantages in treating neonatal infections and may be used to reduce mortality. Further research is needed to evaluate such an alternative strategy. Oral antibiotics could be used promptly after recognition of the early signs of illness, until facility-based management can be accessed, such as in the first 24 hours of illness. Alternatively, in settings where ready access exists to health facilities where parenteral therapy is available, it is possible that oral antibiotic therapy may be used after initial stabilization and treatment with parenteral antibiotics. This could shorten hospital stay, burden of hospitalization to the family, risk for nosocomial acquisition of infection, particularly with multidrug resistant isolates, and cost of therapy incurred by families, potentially alleviating some of the barriers to accessing care in these communities.⁵¹ Additional subgroups of patients for whom oral antibiotic therapy for serious neonatal bacterial infections may be acceptable and perhaps preferable include patients with late-onset disease such as after the first 4 weeks of life, and patients who do not appear to be systemically ill but have localized skin or umbilical stump infections; however, this requires further research.

Future studies of oral antibiotic therapy in such settings are warranted, although simultaneous improvement in access to facility-based care is paramount for assessing efficacy of oral antibiotic therapy as compared with parenteral therapy. Critical to the design and implementation of ethically acceptable studies of oral antibiotic therapy in resource-limited settings is defining a study population with a favorable risk-benefit ratio, where improving the treatment of neonatal infections represents a social priority. At the same time, it is important to design scientifically rigorous and feasible intervention strategies that not only benefit the study population but may be generalizable to other similar populations.^{58,59}

Conclusions on Use of Oral Antibiotics for Treatment of Neonatal Infections

Data from developed countries suggests that serious neonatal bacterial infections are best managed using parenteral antibiotics, and this standard of care should be provided whenever feasible in

TABLE 3. Research Priorities Regarding Potential Uses of Oral Antibiotics for Treatment of Serious Neonatal Infections in Developing Countries

Are there sub-groups of neonates for whom oral antibiotic therapy could be considered?
Are certain clinical signs associated with less severe forms of illness potentially treatable with oral antibiotics?
Is oral antibiotic therapy feasible for young infants beyond the neonatal period, eg, second month of life?
What characterizes the health system capability of settings in which oral antibiotic therapy could be considered?
What is the efficacy of switch therapy [eg shorter-course (eg, 3-4 d) parenteral therapy followed by oral therapy]?
In settings in which delays are likely in reaching a health facility of providing definitive parenteral therapy, what is the benefit of treating with oral agents during transit to the health facility?
What are the safety profiles of cotrimoxazole, amoxicillin-clavulanate, ciprofloxacin, and other potential oral agents for neonatal use?
Improved understanding of pharmacokinetics of oral agents in sick newborns
Are there alternative antibiotic delivery strategies that could supplant the need for injectable therapy, eg, transcutaneous delivery?

developing countries. For many families, however, facility-based care or injectable antibiotic therapy is not within their reach. Thus, alternative strategies are needed for managing serious bacterial infections in many developing country communities. Available data indicate that a case management approach that emphasizes essential newborn care along with prompt recognition of serious bacterial infections and treatment with oral antibiotics is superior to no case management.

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, although available evidence corroborates the recommendation that injectable therapy be provided when feasible. In situations in which facility-based care and use of parenteral antibiotics are not feasible, however, clean delivery and healthful newborn care practices along with prompt recognition of and oral antibiotic therapy for potentially serious bacterial infections is likely to be of substantial benefit.

Among oral agents, cotrimoxazole has the most extensive evidence base for community-based treatment of serious neonatal bacterial infections, although emergence of resistance threatens the utility of this agent. Although amoxicillin-clavulanate has been approved for use in neonates by the US Food and Drug Administration, the possible association of maternal puerperal use and NEC in the infant may warrant caution in its use among a large population of neonates. The second generation cephalosporins have an excellent safety profile, a spectrum of activity similar to cotrimoxazole, and may be more effective given the rising resistance of pneumococcal isolates to cotrimoxazole. Ciprofloxacin also is increasingly accepted as safe in neonates and warrants further investigation for treatment of infections in newborns. Of note, however, the increased cost of these agents limits their availability for widespread use.

Many ethical and technical questions remain that must be addressed before widespread implementation of oral antibiotic therapy for treatment of serious neonatal infections could be considered (Table 3).

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