

# **Empiric treatment of neonatal sepsis in developing countries**

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## **Abstract**

Infections are among the leading causes of neonatal mortality, and about 75% of the burden occurs in developing countries. Diagnosis of neonatal sepsis in these countries is dependent on the recognition of a set of non-specific clinical signs that aim to maximise sensitivity since staff making initial assessments may not have specialist paediatric training. Accurate diagnosis is usually limited by the unavailability of reliable microbiological investigation. The World Health Organization recommends ampicillin (or penicillin; cloxacillin if Staphylococcal infection is suspected) plus gentamicin for empiric treatment of neonates with suspected clinical sepsis or meningitis. However, there is a lack of data on the causes and antimicrobial susceptibility in developing countries to support these recommendations, especially in rural settings. Bacterial pathogens (predominantly Gram negative) with reduced susceptibility to empiric medication have been reported, with variations both between and within regions. Improving local surveillance data using standardised antimicrobial susceptibility testing methods and validation of diagnostic algorithms against microbial findings are essential. Standardised monitoring of treatment outcomes is also required to evaluate existing practice, provide guidance on second-line regimes, and to conduct studies of new approaches such as simplified community-based regimens and to determine the appropriate duration of empiric treatment for apparently low-risk neonates with early resolution of clinical signs, or where available, negative blood cultures. Thus a multifaceted approach, with attention to microbiological quality-assurance, is needed to better guide antimicrobial use, and thus reduce mortality and long term impairment.

**Key words:** neonatal sepsis, neonatal infections, empiric treatment, antibiotics, developing countries.

**Abbreviations:** pSBI (possible Severe Bacterial Infection), WHO (World Health Organization), IMCI (Integrated Management of Childhood Illnesses), AST (Antimicrobial Susceptibility Testing), EONS (Early Onset Neonatal Sepsis), LONS (Late Onset Neonatal Sepsis), ESBL (Extended Spectrum Beta-Lactamase), MRSA (Methicillin resistant *Staphylococcus aureus*), IAP (Intrapartum Antibiotic Prophylaxis), RR (Relative Risk), CI (Confidence Interval).

## **Introduction**

Neonatal deaths account for 44% of all deaths under the age of five years and three quarters of these neonatal deaths occur in developing countries (1). A recent analysis of the burden of clinically-defined neonatal infection in sub-Saharan Africa, South Asia and Latin America estimated that 6.8 million (uncertainty range 5.4-8.2) neonates had 'possible severe bacterial infection' (pSBI) (2). Infections are thought to account for around one third of neonatal deaths (1), but the consequences of neonatal infection extend beyond mortality, to long term neurodevelopmental impairment in survivors (3). Improving recognition of neonatal sepsis and rapid provision of effective treatment is key to reducing this burden. This review aims to provide an overview of the management of neonatal sepsis in developing countries, consider emerging issues and what is needed for more effective empiric treatment.

## **Diagnosis of neonatal sepsis**

Diagnosis of neonatal sepsis in developing countries is usually based on the presence of clinical signs, using the World Health Organization (WHO) Integrated Management of Childhood Illness (IMCI) clinical algorithms. IMCI defines danger signs (not feeding well, convulsions, drowsiness or unconsciousness, movement only when stimulated or no movement at all, fast breathing  $\geq 60$  breaths/minute, grunting, severe chest in-drawing, raised temperature  $>38^{\circ}\text{C}$ , hypothermia  $<35.5^{\circ}\text{C}$  or central cyanosis) and priority signs (severe jaundice, severe abdominal distension or localising signs of infection). These signs are non-specific (4) and often overlap with clinical features present in other conditions, such as respiratory distress syndrome or neonatal encephalopathy (5). IMCI clinical signs focus on sensitivity rather than specificity because untreated cases of neonatal infection have a very high case fatality risk and health workers implementing the algorithms may not have specialist paediatric training. Blood culture is the gold standard for the diagnosis of neonatal sepsis but cultures are rarely available,

usually only in research settings. Blood cultures have high specificity but low sensitivity for invasive infections (6) and currently there is no reliable alternative biomarker.

### **Aetiology of neonatal sepsis**

There is a paucity of data on bacterial causes of neonatal sepsis and antimicrobial susceptibility in developing countries, especially from community settings. The available data suggest that *Klebsiella* species, *Escherichia coli*, *Staphylococcus aureus*, and Group B Streptococci (GBS) predominate in early onset neonatal sepsis (EONS). Late onset neonatal sepsis (LONS) is predominantly caused by Gram-positive pathogens (*Streptococcus pneumoniae*, *Streptococcus pyogenes*, *S. aureus*, and GBS). In addition, non-typhoidal *Salmonella* species are commonly isolated (7, 8).

The available susceptibility data suggest that common neonatal pathogens are often resistant to WHO-recommended empiric antibiotics. 68% (34/50) of *K. pneumoniae* and (15/22) *E. coli* isolated from 149 neonates in Tanzania were resistant to gentamicin and 100% resistant to ampicillin. In this study, mortality was significantly higher among neonates with positive blood cultures, Gram-negative sepsis, or infection with either extended spectrum beta-lactamase (ESBL) or methicillin resistant *S. aureus* (MRSA). Neonates infected with bacteria sensitive to empiric antibiotic agents had a better response to treatment than those infected with resistant strains (80.8% versus 2.2% showing improvement within 72 hours of treatment [p=0.0001]) (9). Another study done in Tanzania reported that >80% *S. aureus* and >90% *Klebsiella* species were resistant to ampicillin and cloxacillin, while >50% *S. aureus* and >60% *Klebsiella* species were resistant to gentamicin (10). In rural India, where Gram-negative bacteria were the main causes of sepsis, 100% resistance to ampicillin and gentamicin has been reported (11). A recent review of community-acquired neonatal sepsis in developing countries reported high levels of resistance predominantly among Gram-negative

isolates, with 57% of isolates susceptible to the combination of penicillin and gentamicin (8). Resistance to third-generation cephalosporins in developing countries has also been reported (8-12).

### **Currently recommended empiric treatment**

Ampicillin (or penicillin) plus gentamicin are currently recommended by WHO as first-line antimicrobials (13). Neonates with signs of Staphylococcal infection (extensive skin pustules, abscess or omphalitis) are recommended to receive cloxacillin rather than ampicillin. Third-generation cephalosporins such as ceftriaxone are suggested as second-line antimicrobials. Recommended treatment duration is 7-10 days, with those not responding within 2-3 days having their treatment regimen adjusted and being referred to high level care, if required. Intrapartum antibiotic prophylaxis (IAP) is not currently recommended by WHO; there are substantial resource and infrastructure constraints (14), but empiric treatment with ampicillin and gentamicin in neonates with documented clinical risk factors at delivery is recommended, with review at 48 hours. None of these recommendations are based on strong evidence of efficacy.

### **Emerging issues and recommendations**

Improving diagnosis is essential. Further research is needed to validate clinical signs that predict severe infection in community and hospital settings for both EONS and LONS (9). Current clinical algorithms are likely to over-diagnose infections resulting in inappropriate treatment, and may increase risks: invasive fungal infection, drug-resistant infection, necrotising enterocolitis, and death (15-17). Although viruses (such as Enterovirus) are known to cause severe neonatal sepsis-like illnesses (18), they are often overlooked as potential pathogens in developing countries. Results of a recent population-based study of the incidence and aetiology of neonatal infections in south Asia (the ANISA study) will provide vital

evidence of the common causes of sepsis and inform treatment policies (19). However, although modern molecular diagnostic techniques can be more sensitive than traditional culture methods in detecting a wider range organisms and conventional culture, interpretation of results may be complicated by false positive or false negative tests. The analysis of these kinds of studies is often challenged by lack of suitable samples from control infants resulting in difficulties in making causal inferences.

Better understanding of local antimicrobial susceptibilities is an urgent issue; this may have an impact on the success of interventions such as community-based treatment of sepsis with amoxicillin and gentamicin, currently under evaluation in Bangladesh (20). Data are limited in developing countries, but antimicrobial susceptibility to first line agents appear to be decreasing, especially in *Klebsiella* sp. (8). Changes to empiric treatment guidelines must depend on well-defined benefits and risks. Improving infrastructures for surveillance of aetiology, antimicrobial susceptibility and clinical outcomes is essential to inform guidelines on antimicrobial choices at all levels, locally, regionally, and internationally (see Figure 1). Alternative empiric antibiotics (either penicillin/gentamicin or ceftriaxone) are currently under evaluation in Malawi, with case fatality and neurological impairment as outcomes (21). Antimicrobials such as amikacin, fluoroquinolones, carbapenems, and extended-spectrum penicillins (e.g. ticarcillin-clavulinate) are alternative therapeutic agents, but are expensive, not readily available in most developing countries, and will require strong stewardship measures to be in place to avoid development of resistance (8, 12, 22).

Recommendations for the duration of antimicrobial therapy are important and should provide adequate treatment for neonatal sepsis, but not to prolong treatment unnecessarily (increasing hospital stays and costs and possibility of hospital acquired infection (23)). The optimal duration of treatment of neonatal sepsis in settings of very limited laboratory support is unknown. A trial investigating the safety of a shortened duration of therapy among neonates

$\geq 32$  weeks gestation and/or  $\geq 1,500$ g admitted to a neonatal unit in Northern India with culture-proven sepsis reported that 7 days of antibiotic therapy after remission of clinical signs was associated with more cases of treatment failure than 14 days, especially among those with Staphylococcal sepsis (24). Duration of antibiotic treatment may be influenced by clinical status and blood culture positivity and pathogen isolated. No difference in treatment failure rate was found between short course (antibiotics stopped after sterile 48-hour culture) and 7 days' treatment among Indian neonates  $>30$  weeks and  $>1,000$ g with culture-negative sepsis and early remission of clinical signs (25).

Empiric treatment of neonatal sepsis in community settings in developing countries is essential, as health care facilities may be inaccessible or parents may decline hospital admission because of cost. Management of neonatal sepsis in primary care clinics with 7 days' penicillin/gentamicin (superior to trimethoprim-sulfamethoxazole with gentamicin [relative risk [RR] of treatment failure 2.0, 95% confidence interval [CI] 1.1-3.8]) was found to be effective among young infants whose parents declined inpatient care in Pakistan (26). Home-based packages for neonatal care that included 7-10 day treatment of infections with injectable penicillin and gentamicin have been shown to reduce mortality by 34% (27). Results are awaited from studies of simplified empiric antibiotic regimens for outpatient management of clinically diagnosed neonatal sepsis in south Asia and sub-Saharan Africa (28-30).

In addition to empiric treatment of neonatal sepsis with antimicrobials, certain inexpensive interventions have been shown to reduce the risk of neonatal infection. Community-based studies conducted in south Asia reported a 23% reduction in mortality (RR 0.77, 95% CI: 0.63-0.94) and 27-56% reduction in omphalitis with umbilical cord antisepsis using chlorhexidine compared to dry cord care (31, 32). Studies investigating chlorhexidine use in African community settings are underway (33, 34) and results will inform WHO guidelines (which currently recommends dry cord care) (13). Topical emollient therapy has been shown to reduce



neonatal mortality by 27% (RR 0.73, 95% CI: 0.56-0.94) and nosocomial infection by 50% (RR 0.50, 95% CI: 0.36-0.71) among preterm neonates in developing countries (35) and large trials and, if appropriate, subsequent scale-up is required. Maternal vaccines are development, including for GBS using both conventional and advanced (reverse vaccinology) techniques (36). Safety and efficacy studies have been conducted in South Africa (37).

## **Conclusions**

Reducing neonatal mortality and morbidity depends on more effective diagnosis and improved empiric treatment of neonatal sepsis. To achieve this, we need a much better understanding of pathogens, their antimicrobial susceptibilities and for how long treatment should be given where laboratory support is inadequate. Without improving evidence base, the choice of empiric antimicrobial treatment for neonatal sepsis will remain uninformed at local, regional, national and international levels.

Figure 1: Strengthening of activities and provision of data required for optimal development of empiric treatment guidelines and improved patient care.

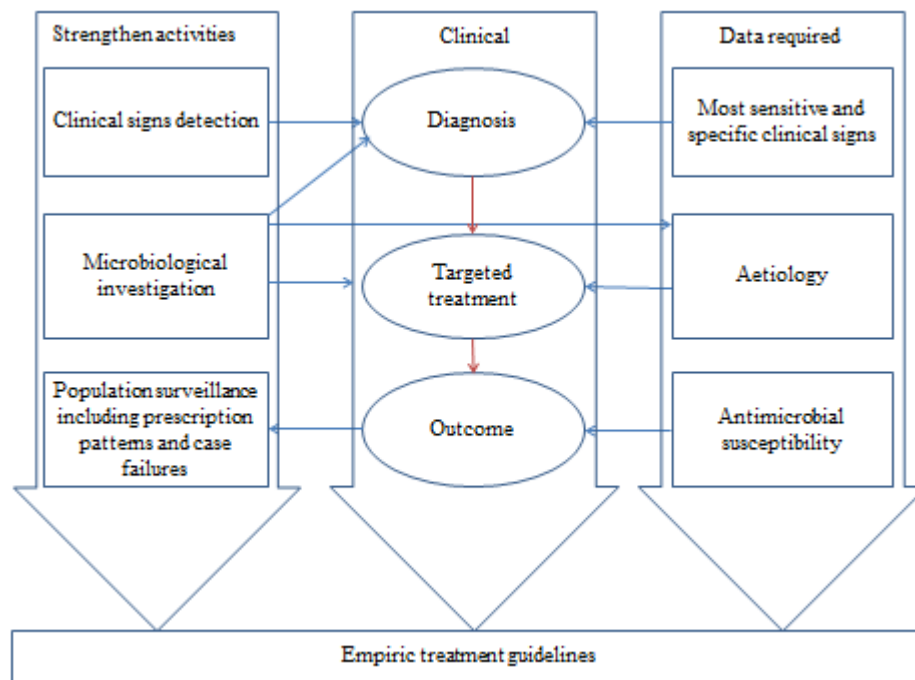


Table 1: Current<sup>a</sup> clinical trials of empiric treatment of neonatal sepsis in developing countries.

Study	Methods	Participants	Intervention	Outcomes
<a href="#">Evaluation of community-based management of neonatal sepsis, Bangladesh</a>	Single blind, cluster randomised study	Neonates with danger signs of sepsis	Training of health workers on managing sepsis (amoxicillin and gentamicin), in addition to essential neonatal care	Coverage of intervention, provider performance, referral compliance
<a href="#">Infant Severe Sepsis and Bacterial Meningitis in Malawi</a>	Open label randomized trial	Infants <2mo with severe sepsis or meningitis	Ceftriaxone vs penicillin and gentamicin	Recovery vs death or severe neurological sequelae
<a href="#">Simplified Antibiotic Therapy for Sepsis in Young Infants, Karachi</a>	Three-arm open label equivalence randomized controlled trial	Infants <60 days old with pSBI	Procaine penicillin+gentamicin, or amoxicillin+gentamicin, or procaine penicillin+gentamicin then amoxicillin	Treatment failure within seven days of enrolment
<a href="#">Simplified Antibiotic Regimens for Outpatient Treatment of Suspected Sepsis in Bangladesh</a>	Three-arm open label randomized trial	Infants <60 days old with pSBI	Procaine penicillin+gentamicin, or amoxicillin+gentamicin, or penicillin+gentamicin then amoxicillin	Treatment failure
<a href="#">7 vs 10d Antibiotics for Neonatal Sepsis, India</a>	Open label randomized trial	Neonates ≥32 weeks and ≥1,500g with culture-positive sepsis	7d vs 10d of ceftriaxone, or amikacin, or vancomycin, or meropenem	Treatment failure
<a href="#">Antibiotic Combinations for Infection in Newborn Babies, India</a>	Randomized parallel group trial	Neonates 3-28d old with clinical and laboratory evidence of LONS	Cloxacillin+amikacin vs cefotaxime+gentamicin for 7-10d	Mortality, treatment failure, fungal infections, cost analysis
<a href="#">Short Course Treatment of Early Onset Neonatal Sepsis, Iran</a>	Single-blind, randomized trial	Neonates >1,500g and/or >34 weeks with clinical sepsis within 7 postnatal days	3d vs 5d of ampicillin+amikacin	C-reactive protein level at end of treatment course, post-discharge cure rates
<a href="#">Children's Antibiotic Resistant Infections in Low Income Countries, Madagascar</a>	Prospective cohort study	Neonates with features of infection	No intervention. Samples collected prior to initiation of empiric antibiotics	Bacterial aetiology of infections, incidence of infections with resistant bacteria
<a href="#">Efficacy Study of Community-Based Treatment of Serious Bacterial Infections in Young Infants, Karachi</a>	Three-arm open label equivalence randomized controlled trial	Infants <60 days old with clinically-diagnosed pSBI	Procaine penicillin+gentamicin, or ceftriaxone, or trimethoprim/sulfamethoxazole +gentamicin	Treatment success/cure rates, completion rates, adverse events, relapse rates
<a href="#">Zambia Chlorhexidine Application Trial</a>	Cluster-randomized controlled trial	Neonates born of women recruited during 2 <sup>nd</sup> or 3 <sup>rd</sup> trimesters	4% chlorhexidine vs dry cord care	Neonatal mortality, omphalitis
<a href="#">Chlorhexidine Cordcare for Reduction in Neonatal Mortality and Omphalitis, Zanzibar</a>	Double-blind, community-based randomized controlled trial	Neonates with first contact with health workers within 48h of delivery	4% chlorhexidine vs a control cord cleaning solution without chlorhexidine, then vs dry cord care	Neonatal mortality, omphalitis
<a href="#">Chlorhexidine Skin Application for Prevention of Infection, India</a>	Double-blind, randomized controlled trial	Neonates weighing <1500g at birth	0.25% chlorhexidine vs sterile water wipes	Sepsis, readmission and mortality rates, skin colonization rates
<a href="#">Chlorhexidine Vaginal and Infant Wash in Pakistan</a>	Double-blind randomized controlled trial	Gravid women and their neonates	0.6% chlorhexidine vaginal and infant wash vs sterile physiologic saline solution	Neonatal death or sepsis, maternal infection or death

<sup>a</sup> As of September 2014

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