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 nonspecific clinical signs that maximize sensitivity because staff making initial assessments may not have specialist pediatric 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 comprehensive data on the causes of infection 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. Nosocomial infections with resistant organisms and high case fatality challenge the first-line use of cephalosporins. Improving local surveillance data using standardized antimicrobial susceptibility testing methods and validation of diagnostic algorithms against microbial findings are essential. Standardized reporting of treatment outcomes is required to evaluate practice, provide guidance on second-line regimes and for 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 reduce mortality and long-term impairments.

Key Words: neonatal sepsis, neonatal infections, empiric treatment, antibiotics, developing countries

Neonatal deaths account for 44% of all deaths under the age of 5 years, and three-quarters of these neonatal deaths occur in developing countries.1 Infections are thought to account for around one-third of neonatal deaths,2 but the consequences of neonatal infection extend beyond mortality, to long-term neurodevelopmental impairment in survivors.2 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.

ETIOLOGY 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 (after the first week of life) 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.43 The available susceptibility data suggest that common neonatal pathogens
are often resistant to WHO-recommended empiric antibiotics. Sixty-eight percent (34 of 50) of *Klebsiella pneumoniae* and (15 of 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 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% vs. 2.2% showing improvement within 72 hours of treatment (*P* = 0.0001)].

In rural India, where Gram-negative bacteria were the main causes of sepsis, 100% resistance to ampicillin and gentamicin has been reported. 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. Resistance to third-generation cephalosporins in developing countries has also been reported.5–7

**CURRENTLY RECOMMENDED EMPIRIC TREATMENT**

Ampicillin (or penicillin) plus gentamicin is currently recommended by WHO as first-line antimicrobials for both EONS and LONS.9 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 is not currently recommended by WHO, 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 is 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 for both EONS and LONS.6 Current clinical algorithms are likely to overdiagnose infections resulting in inappropriate treatment and may increase risks: drug-resistant infection, invasive fungal infection, necrotizing enterocolitis and death.9 Viruses may cause severe sepsis-like illnesses in neonates but are often overlooked as potential pathogens. Results of a recent population-based study of the incidence and aetiology of neonatal infections in south Asia will provide vital evidence of the common causes of sepsis and inform treatment policies.9 However, although modern molecular diagnostic techniques are more sensitive than traditional culture methods in detecting a wider range of organisms, interpretation of results may be complicated by false-positive or false-negative tests. Lack of suitable samples from control groups in such studies may also result in difficulties in making causal inferences.

Better understanding of local antimicrobial susceptibilities is an urgent issue; studies evaluating effectiveness of both hospital and community-based empiric treatment of neonatal sepsis are currently underway in developing countries (see Table, Supplemental Digital Content 1, http://links.lww.com/INF/C82). Data are limited in developing countries, but antimicrobial susceptibility to first line agents appear to be decreasing, especially in *Klebsiella* sp.5 Changes to empiric treatment guidelines must depend on well-defined benefits and risks. Improving infrastructures for surveillance of etiology, antimicrobial susceptibility and clinical outcomes is essential to inform guidelines on antimicrobial choices at all levels, locally, regionally and internationally (Fig. 1). Alternative therapeutic...
CONCLUSIONS

Reducing neonatal mortality and morbidity depends on better 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.

REFERENCES

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