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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

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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.

Keywords

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,[1] 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.

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 ≥60 breaths/min, grunting, severe chest in-drawing, raised temperature >38°C, hypothermia <35.5°C or central cyanosis) and priority signs (severe jaundice, severe abdominal distension or localizing signs of infection). 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 pediatric training. Blood culture is the standard for the diagnosis of neonatal sepsis, but cultures are rarely available in resource-poor settings. Blood cultures have high specificity but low sensitivity for invasive infections,[3] and currently there is no reliable alternative biomarker.

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, nontyphoidal *Salmonella* species are commonly isolated.[4,5]

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

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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 ($P = 0.0001$)].[6] In rural India, where Gram-negative bacteria were the main causes of sepsis, 100% resistance to ampicillin and gentamicin has been reported.[7] 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.[5] 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.[8] 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.[10] 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 antimicrobials, such as amikacin, fluoroquinolones, carbapenems and extended-spectrum penicillins (eg, ticarcillin–clavulanate) are expensive, not readily available in most developing countries and require strong stewardship measures to be in place to avoid development of resistance.[5]

Recommendations for the duration of antimicrobial therapy are important and should provide adequate treatment for neonatal sepsis but not to prolong treatment unnecessarily. The optimal duration of treatment of neonatal sepsis in settings of very limited laboratory support for microbiology or acute-phase markers (C-reactive protein, procalcitonin, etc.) is unknown. A trial investigating the safety of a shortened duration of therapy among neonates ≥32 weeks gestation and/or ≥1500 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.[11] Duration of antibiotic treatment may be influenced by clinical status, blood culture positivity and pathogens 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 >1000g with culture-negative sepsis and early remission of clinical signs.[12]

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.[13] 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 (see Table, Supplemental Digital Content 1, http://links.lww.com/INF/C82).

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 with dry cord care.[14] Studies investigating chlorhexidine use in African community settings are underway (see Table, Supplemental Digital Content 1, http://links.lww.com/INF/C82), and results will inform WHO guidelines (which currently recommends dry cord care).[8] 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[15] and large trials and, if appropriate, subsequent scale-up is required. Development and efficacy studies of maternal vaccines, including GBS vaccine, are currently underway.

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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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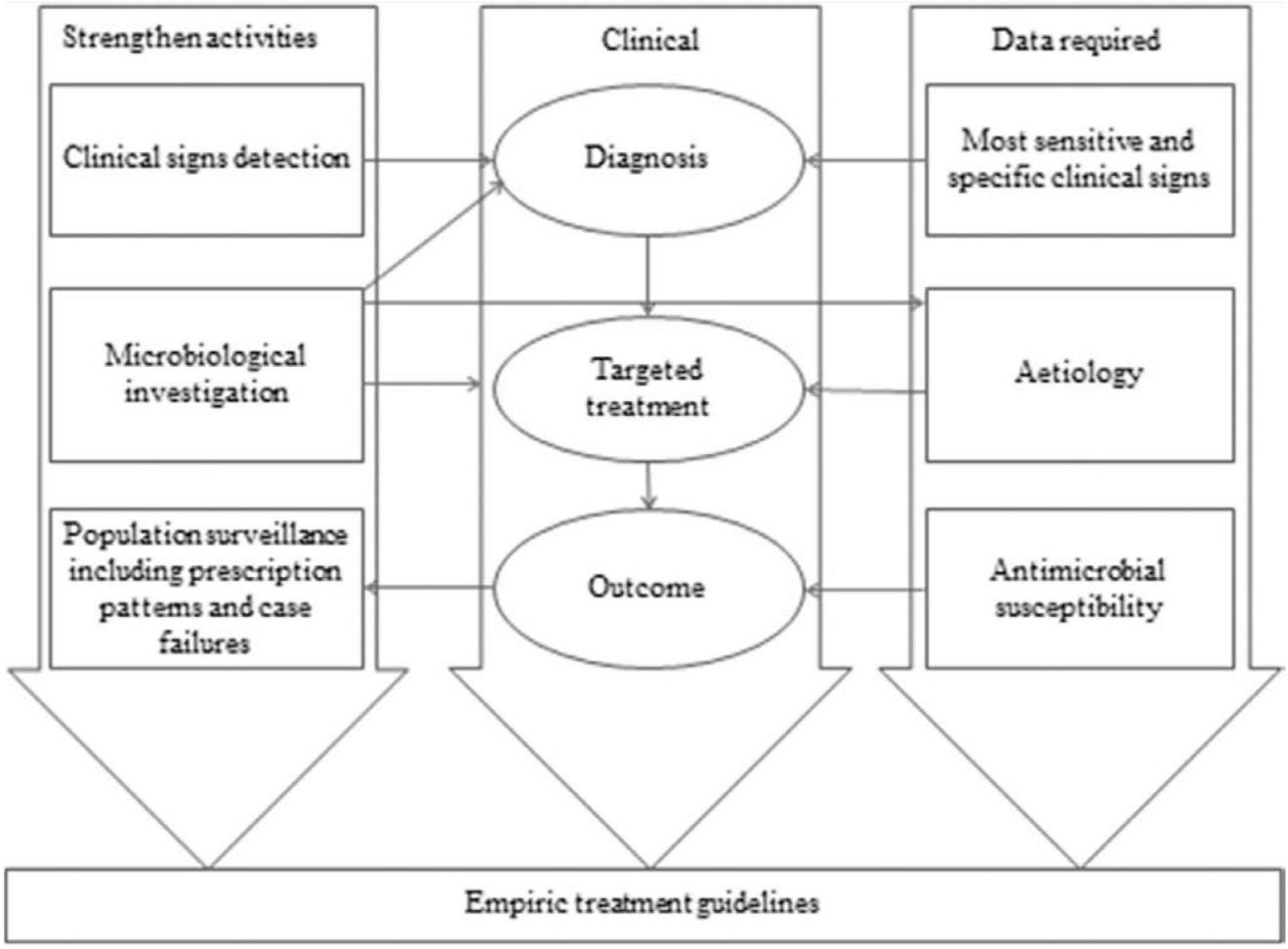

Figure 1.
Strengthening of activities and provision of data required for optimal development of empiric treatment guidelines and improved patient care.

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