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EXPLORE SIMPLIFIED ANTIMICROBIAL REGIMENS FOR THE TREATMENT OF NEONATAL SEPSIS

Geneva, 30th September – 1st October 2002

MEETING REPORT

Department of Child and Adolescent Health and Development
World Health Organization

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Background and objectives of the meeting

It is estimated that approximately 4 million deaths occur annually in developing countries in the neonatal period, attributable mostly to infection, birth asphyxia, and consequences of premature birth and low birth weight. Most sick newborns present with signs and symptoms related to more than one condition. A large number (up to 20% of all live births) develop an infection (sepsis, pneumonia, meningitis etc.) during the neonatal period. The identification and treatment of newborns with infection is unsatisfactory in such settings. Some estimates put half of newborn deaths in the community as being due to bacterial infections.

The Department of Child and Adolescent Health and Development (CAH) recently commissioned a review of published and unpublished data on the management of neonatal sepsis in developing countries. The objective of the review was to scientifically and systematically evaluate existing therapeutic strategies for the management of serious bacterial infections (pneumonia, sepsis, and meningitis) among newborn infants in developing countries. The outcomes evaluated were success rates of therapy, ease of use of regimen, cost-effectiveness and methodological or other potential problems. Researchers at Aga Khan University, Karachi conducted the review with assistance from the Johns Hopkins University, Baltimore. At the same time researchers at Johns Hopkins University also completed a meta-analysis of available data on effectiveness of oral and parenteral therapy for treatment of neonatal pneumonia in the community in developing countries.

Objectives

- Review the results of the commissioned literature review and meta-analysis on strategies for management of neonatal bacterial infections in developing countries; and
- Identify effective therapeutic regimens that are more practical for implementation at community or first level facility for the management of neonatal sepsis in developing countries.

Expected outcomes

- Identify potentially effective therapeutic regimens for treatment of neonatal sepsis.
- Plan for testing clinical efficacy and effectiveness of the above mentioned regimens.

The agenda of the meeting and the list of participants are provided in Annexes I and II.

Dr Mathuram Santosham was nominated as the chairperson of the meeting.

In the opening discussion, the following remarks were made:

- Upcoming studies on community-based newborn health interventions in different countries provide a timely opportunity to test the effectiveness of candidate antimicrobial regimens for newborn sepsis;
- Accuracy of dose of antibiotics administered to neonates in community-based research/programme should be assured and monitored;
- Cost effectiveness of antimicrobial therapy with different regimens in the community should be evaluated; and
- Ethical issues in treating neonates in the community/home settings should be carefully examined.

This meeting probably will not be able to cover the special problems of neonates born to HIV positive mothers.

Review of etiology and management of serious bacterial neonatal infections in developing countries

WHO/HQ and Saving Newborn Lives/Save the Children (US) had commissioned a review of etiology and management of serious bacterial infections in developing countries. The review was undertaken by a team from the Aga Khan University comprising of Drs Anita Zaidi, Syed Asad Ali, and Zulfiqar Bhutta, with contributions from Dr Gary Darmstadt (Johns Hopkins University) Dr Zaidi presented the summary of the methodology and the findings.

Methodology

An extensive literature search on studies reporting etiology of neonatal and post-neonatal infections and studies reporting management in community-settings in developing countries was conducted via the PubMed and other database and bibliographies of key references. Countries in the low to middle income group as defined by the World Bank, as well as those in the Middle East, were considered "developing". Neonatal and post-neonatal sepsis was defined as septicemia, pneumonia, or meningitis in the 0-30 day and 31-90 day periods, respectively.

Studies reporting exclusively or predominantly nosocomial (hospital-acquired) infections were excluded from the analysis (e.g. studies from neonatal intensive care units with sepsis developing in pre-term or low-birth-weight babies beyond 7 days of life). The remaining data were categorized as either non-nosocomial (where the authors excluded hospital-acquired infections) or "undifferentiated" where infections were predominantly early-onset (within 7 days of life) and/or authors discussed maternal risk factors for neonatal infection and did not report nosocomial infections as being a problem in their nursery. Studies reporting community-based management of infants or children were reviewed for inclusion of neonates and presentation of disaggregated neonatal or post-neonatal data.

Conclusions on etiological agents

No community-based studies of etiology of neonatal sepsis were identified and limited data were available from first-level health facilities and home-delivered babies. Because of the selection criteria used and the attempts to exclude hospital-acquired neonatal infections, data reported in this study predominantly reflects early-onset sepsis. However, most hospital-based studies do not distinguish between maternally acquired, community-acquired, or hospital-acquired infections. Moreover, these distinctions may not hold much value in situations where clean delivery and baby handling practices are lacking and both home and hospital environments are contaminated.

All the data available (studies reporting very-early-onset sepsis, those that have excluded hospital-acquired infections, that are from rural hospitals, and on causes of sepsis in home-delivered infants) indicate that gram-negative rods, especially *Klebsiella* organisms are the most important cause of neonatal sepsis, followed by *Staphylococcus*, and *Escherichia* (Figure 1 and Figure 2).

Figure 1 Neonatal pathogens in different settings

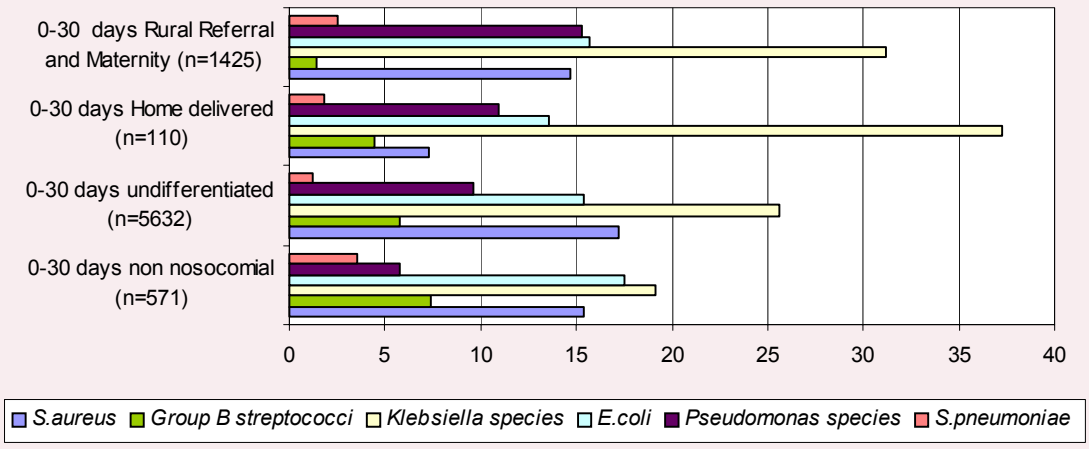
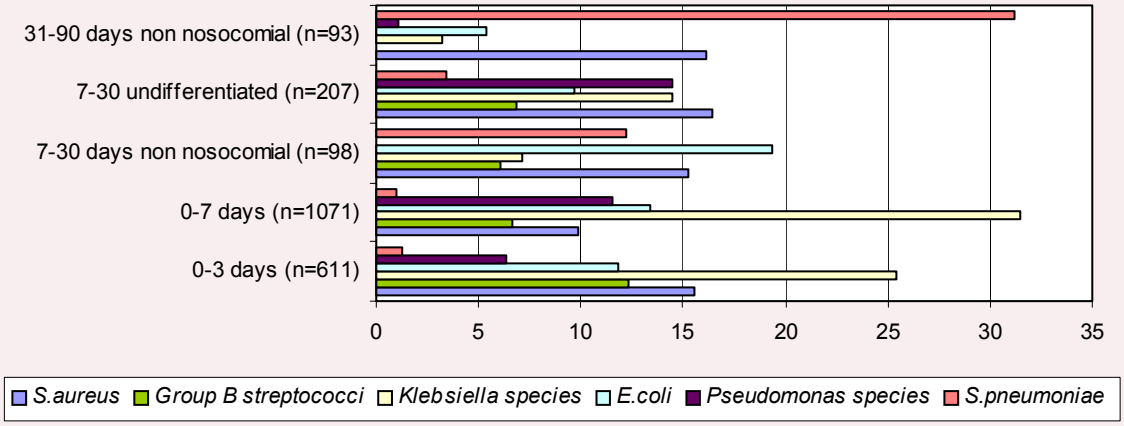


Figure 2 Changing spectrum of pathogens in early-onset neonatal sepsis, late-onset neonatal sepsis and sepsis in young infants



No conclusions can be drawn about causes of late-onset (community-acquired) neonatal sepsis from hospital-based studies because these invariably include many hospital-acquired infections. Limited data from the WHO Young Infant Study[1] indicate that *Streptococcus pneumoniae, Staphylococcus aureus, Escherichia coli, Streptococcus pyogenes*, and *Salmonella* species are important pathogens beyond the first week of life in Africa and Papua New Guinea. This study, however, included only those neonates who reached the hospital and may not represent the true bacteriological spectrum in the community. No data on causes of late-onset neonatal sepsis in babies presenting from the community are available from South Asia, which is home to a major burden of neonatal mortality. Notably, the pathogens in the WHO supported Young Infant Study were mainly gram-positive, whereas hospital data indicate gram-negative organisms to be predominant. This is most likely due to the fact that hospital-based data included in this study mainly represented early-onset sepsis, whereas 85% of babies with sepsis in the Young Infant Study were older than 7 days. In the few babies who developed early-onset sepsis, gram-negative rods accounted for 56% of all invasive disease.

There are sinificant regional differences in pathogens of importance in neonatal sepsis, especially in the proportion of infections caused by Group B streptococci (GBS), *S. aureus*, and *Acinetobacter/Pseudomonas.* GBS is an important pathogen in some African countries (but absent in others), Middle-eastern countries, and the Caribbean Islands, but is less important in South Asia. However, intra-country differences also occur and isolated studies in India and Pakistan have reported GBS to be an important cause of early-onset sepsis. *S. aureus* is the most common pathogen in African countries and a peculiar trend of *Acinetobacter/Pseudomonas* infections was noted in Asia Pacific, even in early-onset sepsis and in the Young Infant Study.

Antimicrobial resistance patterns of neonatal pathogens

There is insufficient information on antimicrobial resistance patterns in community settings on the three most common pathogens (*E. coli, Klebsiella species*, and *S. aureus*) causing early-onset neonatal sepsis. Available data indicate that India and Pakistan may have significant antimicrobial resistance among *E. coli, Klebsiella species*, and *S. aureus* which, if confirmed by future studies, will make devising inexpensive but effective empiric regimens for treatment of neonatal sepsis difficult. Resistance among these three pathogens appears to be less common in Africa, but data are insufficient. There are important regional differences in susceptibility patterns of *Haemophilus influenzae* and pneumococci in Africa, with some countries (South Africa, Malawi) reporting high resistance rates to penicillin, chloramphenicol and cotrimoxazole; other African countries have intermediate (Kenya, Senegal), or low resistance rates (Gambia, Central African Republic, Ghana). There is a substantial resistance among respiratory pathogens to cotrimoxazole in South Asia.

[1] The WHO young infant study group.Bacterial etiology of serious infections in young infants in developing countries. PIDJ;1999:S17-22

Conclusions of the review

Etiology data

- No data from community settings
- Hospital data included in this review predominantly reflect early-onset sepsis since late-onset sepsis reported from hospital settings include significant proportions of hospital-acquired sepsis and were excluded from the review.
- Gram-negative rods, especially *Klebsiella* species are major pathogens in early-onset sepsis (hospital data), in home-born neonates, in rural hospitals, and in non-nosocomial data from hospitals.
- Limited data on late-onset sepsis; cannot use hospital data to assess spectrum
- No data on late-onset or post-neonatal community-acquired sepsis from South Asia.
- Data from Young Infant Study show *S. aureus, S. pyogenes, E. coli*, pneumococci, and *Salmonella* species to be important pathogens but insufficient numbers of 0-7 day old neonates were studied.
- *S. aureus* is important in all periods of young infancy, and in all regions except Asia-Pacific.
- Pneumococci proportion increases with age.
- GBS importance varies with country and even within country

Antimicrobial resistance

- Serious lack of data from community settings
- Alarming resistance in hospital-based studies in gram-negative rods and *S. aureus*
- GBS and *S. pyogenes* have predictable susceptibility to penicillin, and are "tolerant" to cotrimoxazole

Following points were made during the discussion:

- The definition of young infant should be reviewed. WHO uses infant of up to 59 days as the young infant, but it is not a universally accepted definition.
- It was clarified that omphalitis was included in sepsis in the review because many babies had positive blood cultures.
- It was suggested that a review of PUBMED and EXTRAMED alone was not enough for a comprehensive search of the subject area. Other databases including WHO databases should be included in future revisions and expansion.
- It was a matter of concern that no data was available from China.
- Low maternal group B streptococcus colonization rates in South Asia may be due to genetic factors or menstrual hygiene practices.
- In order to complete the picture of etiology of early onset sepsis, it is crucial to review the data on maternal genital colonization
- Etiology of neonatal sepsis may be birth weight specific; data from hospitals would have disproportionate representation of organisms causing sepsis among the very low birth weight infants.
- No study has attempted to characterize strains of *Klebsiella* species grown from neonates.
- The alarmingly high incidence of antimicrobial resistance among common pathogens of neonatal sepsis (*Klebsiella* species, *E. coli, S. aureus, Enterobacter* species) in hospitals in South Asia is a cause of extreme concern. Urgent steps are required to mobilize concerted action to control this menace.

Meta-analysis of community-based trials of case-