

Neonatal sepsis: an international perspective

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Neonatal infections currently cause about 1.6 million deaths annually in developing countries. Sepsis and meningitis are responsible for most of these deaths. Resistance to commonly used antibiotics is emerging and constitutes an important problem world wide. To reduce global neonatal mortality, strategies of proven efficacy, such as hand washing, barrier nursing, restriction of antibiotic use, and rationalisation of admission to neonatal units, need to be implemented. Different approaches require further research.

According to World Health Organisation (WHO) estimates, there are about 5 million neonatal deaths a year, 98% occurring in developing countries.^{1,2} Infection, prematurity, and birth asphyxia are the main causes.

The purpose of this article is to give an overview of the burden of bacterial sepsis and meningitis in the newborn population in developing countries. The focus will be on the pathogens mostly implicated, their antibiotic susceptibility patterns, and management. Other infections of interest in the neonatal period, such as HIV and other sexually transmitted diseases, malaria, tetanus, and tuberculosis, are not subjects of the review.

METHODS

We searched Pubmed, Ovid Medline, Embase, and Popline (2004) using as key words neonatal sepsis, neonatal meningitis, developing countries, Africa, Asia, and Latin America. We consulted the relevant WHO and Save the Children US web pages. We expanded our search by following the references of the identified papers and manually searching the most recent issues of some relevant journals (*Lancet*, *BMJ*, *Archives of Diseases in Childhood*, *Pediatric Infectious Diseases Journal*). We found 150 articles and subsequently included 39 published papers from sub-Saharan Africa, South East Asia, the Middle East, Latin America, and the Caribbean. We searched for both hospital and community based studies in the attempt to represent most geographical areas. All the community studies identified were included.^{3–5} Among the hospital based series, where possible, we incorporated only prospective surveys. A few larger retrospective studies conducted over several years were also considered.^{6–10} The data presented in this review are directly derived from the papers selected and have not been subjected to further statistical analysis.

EPIDEMIOLOGY

In developing countries, neonatal mortality (deaths in the first 28 days of life per 1000 live births) from all causes is about 34; most of these deaths occur in the first week of life, most on the first day¹¹ (WHO 2001 Estimates). In contrast, neonatal mortality for developed countries is in the region of five.¹¹ Neonatal mortality in Asia is about 34, in Africa about 42, and in Latin America and the Caribbean about 17, although there are wide variations between different countries in these regions as well as within the countries themselves. For example, neonatal mortality for different African countries ranges from 68 in Liberia to 11 in South Africa.¹¹ Discrepancies will often be due to under-reporting: in some countries, babies, in particular those born preterm and small for dates, are not registered, because of registration fees, ignorance, or logistical difficulties. In some traditions, babies do not become part of the family until they are a few days or weeks old, therefore early deaths are not acknowledged.³ It is generally assumed that neonatal mortality in developing countries is under-reported by at least 20%.¹

CAUSES OF NEONATAL DEATHS

The most common causes of death in the neonatal period are infections, including septicaemia, meningitis, respiratory infections, diarrhoea, and neonatal tetanus (32%), followed by birth asphyxia and injuries (29%), and prematurity (24%).¹¹ The data available are a mixture of official sources and hospital and community based studies. In developing countries, the rate of home deliveries is high, and the percentage of deliveries assisted by a skilled attendant is low: in Africa it ranges from 37% in sub-Saharan Africa to 69% in North Africa, in Asia from 29% in South Asia to 66% in East Asia and the Pacific region. In South America and the Caribbean, it is about 83%.¹¹ Establishing the numbers and causes of neonatal deaths is therefore difficult because a high percentage of babies are delivered and die at home without ever being in contact with trained healthcare workers and therefore without ever reaching the statistics.

Neonatal care settings and practices are very different in different countries. In most African studies, the neonatal population includes mainly term babies looked after in high dependency units, with scarce supportive and monitoring equipment, overcrowding, poor staffing levels, and difficulty in providing even basic supportive treatment.¹² In contrast, many of the Indian,

Abbreviations: CONS, coagulase negative staphylococci; EOS, early onset; GBS, group B streptococcus; LOS, late onset

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Table 1 Clinical criteria for the diagnosis of sepsis

	IMCI criteria for severe bacterial infection*	WHO young infant study group†
Convulsions	X	X
Respiratory rate >60 breaths/min	X	X (divided by age group)
Severe chest indrawing	X	X
Nasal flaring	X	
Grunting	X	
Bulging fontanelle	X	
Pus draining from the ear	X	
Redness around umbilicus extending to the skin	X	
Temperature >37.7°C (or feels hot) or <35.5°C (or feels cold)	X	X
Lethargic or unconscious	X	X (not aroused by minimal stimulus)
Reduced movements	X	X (change in activity)
Not able to feed	X	X (not able to sustain suck)
Not attaching to the breast	X	
No suckling at all	X	
Crepitations		X
Cyanosis		X
Reduced digital capillary refill time		

*Any of the signs listed implies high suspicion of serious bacterial infection.

†Each symptom or sign is associated with a score. The score indicates the probability of disease.^{14 15}
IMCI, Integrated Management of Childhood Illness.

South East Asian, Middle Eastern, and Latin American studies are carried out in level 3 nurseries, have a population of mainly premature and low birthweight babies, and may have facilities similar to those of neonatal units in developed countries.^{7 13} These geographical differences are likely to be reflected in different patterns of neonatal sepsis.

DEFINITION OF SEPSIS

Neonatal sepsis may be defined both clinically¹⁴⁻¹⁶ (table 1) and/or microbiologically, by positive blood and/or cerebrospinal fluid cultures. In this review, only microbiologically proven cases are included.

Neonatal sepsis may be classified according to the time of onset of the disease: early onset (EOS) and late onset (LOS).

The distinction has clinical relevance, as EOS disease is mainly due to bacteria acquired before and during delivery, and LOS disease to bacteria acquired after delivery (nosocomial or community sources). In the literature, however, there is little consensus as to what age limits apply, with EOS ranging from 48 hours to 6 days after delivery. This makes it difficult to compare studies where cases are grouped into EOS and LOS without further details. Those studies using longer definitions will incorporate a larger proportion of cases where the organism is acquired horizontally, from nosocomial or community sources, rather than as a result of vertical transmission. Different practices of care can therefore impact on these rates—for example, hospitals with early discharge policies may expose infants to community infections, and

Table 2 Studies of neonatal sepsis in developing countries

Country	Type of study	Duration of study (months)	Total No of positive blood cultures	Early onset		Late onset		Most common isolates
				EOS %	Mortality %	LOS %	Mortality %	
Malaysia ¹³	Prospective surveillance	9 (1991)	136	26 (35/136)	12	74(20/69)	18	<i>Acinetobacter</i> , <i>Klebsiella</i>
Kenya ¹²	Prospective and retrospective survey	6 (1997-8)	121	30 (21/69) (72 h)	4	30 (>72 h)	10	<i>Klebsiella</i> , <i>Citrobacter</i>
Nigeria ³⁹	Prospective surveillance	11 (1994-5)	62	47	8	53	5	<i>Staph aureus</i> , <i>Pseudomonas</i>
India ²⁵	Prospective Surveillance	6 (1997)	96	50	9	50	4	<i>Staph aureus</i> , <i>Klebsiella</i>
Panama ⁹	Surveillance, retrospective	216 (1975-92)	577	47 (<5 days)	44	53 (>5 days)	22	<i>Klebsiella</i> , <i>Staph aureus</i>
India ¹⁷	Surveillance	15 (1996-7)	157	86 (6 days)	49	14 (>6 days)	68	<i>Klebsiella</i> , <i>Pseudomonas</i>
Saudi Arabia ⁴⁰	Case control study	60 (1983-8)	61	39	21	61	24	<i>Staphylococci</i> , <i>Klebsiella</i> , <i>Enterobacter</i> , <i>Serratia</i>
India ³⁶	Prospective surveillance	24 (1995-6)	131	23	4	77	10	<i>Klebsiella</i> , <i>Enterobacter fecalis</i>
The Gambia, Papua New Guinea, Philippines, Ethiopia ⁴¹	Multicentre study (4 prospective surveillance studies)	Each study conducted over 24 months (1990-1993)	167 (84 in the neonatal period)	30% (7 days)	n/a	70%	n/a	<i>Staph aureus</i> , <i>Streptococcus pyogenes</i> , <i>E coli</i>

Percentage of cases by age of onset and most common isolates. If not otherwise stated, early onset (EOS) is defined as first 48 hours, and late onset (LOS) as more than 48 hours.

*The data in the table refer to the blood culture results of the newborn (0-1 months old) of the four studies. In The Gambia the most common pathogen was *Staph aureus*, in Papua New Guinea *S pyogenes*, in the Philippines *Salmonella*, and in Ethiopia *S pyogenes* and *E coli*. GBS, Group B streptococcus. All the data refer to blood cultures only. EOS %, EOS/all positive blood cultures × 100; LOS %, LOS/all positive blood cultures × 100. Mortality %, EOS/all positive blood cultures × 100 and LOS/all positive blood cultures × 100; n/a, not available.

those with late discharge policies to nosocomial infections. Studies based in hospitals with early discharge will probably report lower rates of late-early or LOS infection, especially if infants presenting from the community are not incorporated into analyses. A few papers distinguish between very early onset (within 24 hours), EOS (24 hours to six days), and LOS (more than six days) sepsis.^{17 18}

INCIDENCE OF NEONATAL SEPSIS

The reported incidence of neonatal sepsis varies from 7.1¹³ to 38¹⁷ per 1000 live births in Asia, from 6.5¹⁹ to 23¹⁵ per 1000 live births in Africa, and from 3.5⁹ to 8.9¹⁰ per 1000 live births in South America and the Caribbean. By comparison, rates reported in the United States and Australasia range from 1.5 to 3.5 per 1000 for EOS sepsis and up to 6 per 1000 live births for LOS sepsis, a total of 6–9 per 1000 for neonatal sepsis.^{21–24}

ORGANISMS CAUSING NEONATAL SEPSIS

The pathogens most often implicated in neonatal sepsis in developing countries differ from those seen in developed countries. Overall, Gram negative organisms are more common and are mainly represented by *Klebsiella*, *Escherichia coli*, *Pseudomonas*, and *Salmonella*.^{9 17 18 25 26} Of the Gram positive organisms, *Staphylococcus aureus*,^{18 25 27 28} coagulase negative staphylococci (CONS),²⁹ *Streptococcus pneumoniae*,³⁰ and *Streptococcus pyogenes*^{30 31} are most commonly isolated.

Group B streptococcus (GBS) is generally rare^{8 26 32} or not seen at all,³³ although maternal rectovaginal carriage rates of GBS may be similar to those recorded in developed countries.³⁴ In most of the African studies,^{27 30} the incidence is low, with the exception of South Africa.³⁵ In Asia^{6 7 32 33 36 37} GBS is also reported to be extremely rare. In South America¹⁰ GBS incidence is comparable to the West. It is not known whether these differences reflect true differences in pathogens across the world, reflecting an epidemiological transition in some countries, or whether it reflects an epidemiological bias linked to the fact that most EOS babies die at home before reaching the health facilities and they do not appear in the statistics.

Neonatal surveillance in developed countries generally identifies GBS and *E coli* as the dominant EOS pathogens and CONS the dominant LOS pathogen followed by GBS and *Staph aureus*.^{21 22 24 38}

In developed countries, EOS disease is often more severe and case fatality rate is higher than it is for LOS disease. As the latter is usually caused by CONS, the associated morbidity and mortality are low.³⁸ In developing countries, this may not be the case; in some series, LOS disease has a

higher case fatality rate, particularly when Gram negative bacteria are involved. Table 2 shows the proportion of EOS and LOS disease in developing countries and their case fatality rates in different studies. *E coli*, GBS, *Enterobacter*, *Enterococcus*, and *Listeria* are mostly associated with EOS disease. *Klebsiella*, *Acinetobacter*, and *Staph aureus* are associated with both. *Pseudomonas* spp, *Salmonella*, and *Serratia* are more often associated with LOS disease. CONS are found in both.

There appears to be a wide variety of bacteria causing EOS and LOS sepsis in developing countries. This variation may be true, but important confounders may include different definitions of EOS and LOS, different inclusion criteria for studies (including population sampled), inability to culture certain organisms, small numbers, and/or short periods of surveillance. The latter may be particularly important, as surveillance may be occurring during, or indeed may have been initiated because of, an outbreak of a specific pathogen and may not therefore be representative.

ORGANISMS CAUSING NEONATAL MENINGITIS

Neonatal meningitis in developing countries is a serious problem, with a mortality of 33–48%.⁶ The pathogens involved are similar to those associated with sepsis, mainly Gram negative organisms such as *Klebsiella*, *E coli*, *Serratia marscesens*, *Pseudomonas*, and *Salmonella*, and among the Gram positive organisms *Staph aureus* and CONS. A multicentre WHO study on serious infections in young infants involving four centres in the Gambia, Ethiopia, the Philippines, and Papua New Guinea found that the organisms causing meningitis in babies under 1 week were mainly Gram negative. In babies older than 1 week *Streptococcus pneumoniae* becomes very common, accounting for 50% of all bacterial meningitis occurring between 7 and 90 days of age, with a case fatality rate of 53%. Of the *S pneumoniae*, isolated serotype 2 was responsible for 26% of cases.⁴¹ GBS, *E coli*, *S pneumoniae*, and *Listeria* account for nearly all cases of neonatal meningitis in developed countries.³⁸

ANTIBIOTIC RESISTANCE

Antibiotic resistance is now a global problem. Reports of multiresistant bacteria causing neonatal sepsis in developing countries are increasing, particularly in intensive care (see tables 3 and 4).^{6 17 25 39 42} *Klebsiella* and *Enterobacter* species are often reported in this context.¹⁸ At major risk are unwell or premature babies, those needing additional support such as ventilation, intravenous fluids, or blood products, and those babies who stay in hospital for more than 48 hours.⁴³ Spread of resistant organisms in hospitals is a recognised problem, although babies admitted from the community may also carry resistant pathogens.⁴⁴ The wide availability of over the counter antibiotics and the inappropriate use of broad spectrum antibiotics in the community may explain this. More studies are needed to compare patterns of resistance in babies born in and out of hospital.^{4 5}

It is difficult to compare antibiotic resistance between countries because the epidemiology of neonatal sepsis is extremely variable. Few studies compare antibiotic susceptibility over time in the same unit, but where data are available they show increasing resistance to commonly used antibiotics.²⁸ The antibiotic combination prescribed in most units is a penicillin (benzylpenicillin, ampicillin, or cloxacillin) together with an aminoglycoside, most commonly gentamicin. Most Gram negative bacteria are now resistant to ampicillin and cloxacillin, and many are becoming resistant to gentamicin (table 4). In some units, antibiotic policies have changed to include a third generation cephalosporin.^{6 13} However, reduced susceptibility to third generation cephalosporins¹² and even to quinolones is emerging.⁴² In some countries, *Staph aureus* is the most common cause of

Table 3 Pattern of resistance of Gram positive bacteria to the most commonly used antibiotics in developing countries^{13 17 20 25 33}

	<i>Staph aureus</i>	<i>Streptococci</i>
Penicillin	63–93	0–100
Cloxacillin	64–90	
Ampicillin	40–98	0–100
3rd generation cephalosporin		
Cefotaxime	50–67	
Ceftazidime	8–63	
Ceftriaxone	5–59	
Erythromycin	12 to >90	0–30
Gentamicin	4–76	
Amikacin	13–62	
Coltrimoxazole	30–83	0–58
Ciprofloxacin	3–45	
Chloramphenicol	30–60	0–33
Methicillin	64–85	

Values are percentages.

Table 4 Pattern of resistance of Gram negative bacteria to the most commonly used antibiotics in developing countries^{13 17 20 25 33}

	<i>Klebsiella</i> spp	<i>Pseudomonas</i> spp	<i>Acinetobacter</i>	<i>Citrobacter</i>	<i>E coli</i>
Penicillin				100	100
Ampicillin	65–100	75–100	88–100	100	69–100
3rd generation cephalosporin					
Cefotaxime	0–86	10–100	4–84	0	0–75
Ceftazidime	66–95	56–90			0–67
Ceftriaxone	6–96	12–100		0	0–56
Erythromycin	87	100		100	
Gentamicin	16–85	0–79	3–73	0–40	30–93
Amikacin	0–74	23–100	14–79	0	0–67
Cotrimoxazole	22–97	33–67	30–65	17	12–62
Ciprofloxacin	0–36	0–49	0–7	5	15–56
Chloramphenicol	49–100	40–93	87–96	50	23–100
Imipenem	0–6	0–48			0

Values are percentages.

neonatal sepsis, and methicillin resistant strains (methicillin resistant *Staph aureus* (MRSA)) are widespread (see table 3). Vancomycin is often not affordable.²⁵ The experience in the western world suggests that this may change in the future.

MANAGEMENT

Newborn infants are especially vulnerable to nosocomial infections because of their intrinsic susceptibility to infection as well as the invasive procedures to which they are subjected. This is particularly so for those born prematurely or of low birth weight. To plan effective strategies to reduce the burden of neonatal sepsis, it is essential to define the sources of infection. Therefore continuous surveillance is essential.⁴⁵

Preventive measures need to be implemented. Hand washing has been shown to be effective ever since the 19th century, and several guidelines are available.⁴⁶ Unfortunately, across the world, implementation of correct hand washing protocols has been difficult, even in optimal conditions. Health personnel require education, continuous reminding, and feedback if compliance is to be maintained.⁴⁷ In developing countries, further obstacles to the implementation of hand washing include the lack of water, soap, and sinks in the nurseries, low level of staffing and consequently low morale and overcrowding. Bedside dust is ubiquitous and difficult to deal with. Studies looking at early discharge policies for the low risk newborns as a means of reducing staff workload and exposure to nosocomial infection need to be undertaken.

Minimising invasive procedures has also shown an impact in reducing nosocomial infections. Fewer venepunctures and intravenous catheters minimise the risk of infection. As gentamicin is part of the first line antibiotics in most neonatal units across the world, a number of studies have emphasised that it can be safely and effectively administered once a day to newborns.⁴⁸ This results in fewer procedures to the newborn and reduces the workload of nursing staff.

Skin preparation before procedures has been shown to be effective, but studies are needed on the exact procedures and antiseptic to be used. The importance of appropriate sterilisation procedures for the equipment used in neonatal units also needs to be emphasised.⁴⁵

The impact of using antiseptic solution to disinfect the birth canal⁴⁹ on the incidence of neonatal sepsis needs to be further explored.

Possible advantages deriving from changes in neonatal unit practice such as implementation of strict antibiotic policy and restriction of admissions to neonatal units also need to be investigated.

CONCLUSIONS AND FURTHER RESEARCH

This review highlights several important features of neonatal sepsis in the developing world. In general, it is more common than in developed countries, the pathogen distribution is different with a predominance of Gram negative bacteria and *Staph aureus*, and the mortality is higher. In keeping with developed countries, resistance to commonly used antibiotics is an increasing problem. In resource poor countries, however, the availability of alternative antibiotics is limited.

There are a number of important gaps in our knowledge, and there is an urgent need for studies looking at simple and sustainable interventions to reduce the burden of neonatal infection. Longitudinal surveillance to describe the varied pathogens causing neonatal sepsis as well as their changing antibiotic susceptibility profile is important. Without such a platform, the introduction of new methods of prevention is difficult. Possible strategies to be considered might include intrapartum antibiotic prophylaxis, the use of antiseptic solution to disinfect the birth canal, and implementation of simple infection control methods of proven efficacy such as hand washing and barrier nursing, promotion of clean deliveries, exclusive breast feeding, restriction of antibiotic use, and rationalisation of admissions to and discharges from neonatal units.

Studies on the impact of HIV infection on the incidence of neonatal sepsis, the pathogens involved, and their resistance patterns are needed to inform the decision on the best management for infants born to HIV positive mothers.

Neonatal infections currently cause about 1 600 000 deaths per year in developing countries. The introduction of effective interventions therefore has great potential to decrease neonatal mortality.

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