MALAWI MEDICAL JOURNAL;17(3):92-96
September 2005

Aetiology of neonatal sepsis at QECH, Blantyre: 1996-2001

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Summary

Neonatal sepsis is common and often fatal in Malawi. The aim of this retrospective study was to report causes, antibiotic resistance and outcome of sepsis in Malawian neonates. We reviewed all blood and cerebrospinal fluid isolates collected between January, 1996, and December, 2001, from inpatients aged 0-30 days with suspected sepsis at the Queen Elizabeth Central Hospital, Blantyre. *In vitro* resistance to antibiotics commonly used in Malawi was assessed. Case-fatality rate was analysed with respect to age, bacterial pathogen and infection site. A total of 801 bacteria were isolated from 784 neonates over six years – 599 isolates from blood and 202 from cerebrospinal fluid. Overall, 54% of bacteria were Gram positive and 46% were Gram negative. The commonest causes of neonatal sepsis were Group B *Streptococcus* (17%) and non-typhoidal *Salmonella* (14%). In vitro antibiotic susceptibility to the first-line antibiotic combination of penicillin and gentamicin was 78% for all isolates, but *in vitro* sensitivity to gentamicin for *Klebsiella* spp. and non-typhoidal *Salmonella* was 33% and 53% respectively. In-hospital case-fatality rate was known for only 301 cases and was high at 48%. Group B *Streptococcus* was associated with the best outcome. Mortality was significantly higher if presentation was in the first week of life or if sepsis was due to Gram-negative bacteria.

Introduction

Neonatal infection is common in developing countries and a major cause of neonatal deaths.[1,2]. The incidence and case-fatality rate of neonatal sepsis is much higher than in developed countries, but aetiology has not been as widely reported and in some regions there is a different spectrum of causative bacterial pathogens.[3-5] In the developed world, group B *Streptococcus* (GBS) is usually the commonest single cause of neonatal sepsis followed by Gram negative bacteria such as *Escherichia coli, Klebsiella pneumoniae* or *Pseudomonas aeruginosa.* In contrast, studies from some developing countries have reported that GBS was a rare cause of neonatal sepsis, that Gram-negative bacteria were the commonest isolates and that *Staphylococcus aureus* was the commonest Gram-positive agent.[3-5]

Aetiologic data are important for guiding choice of antibiotic therapy – first-line therapy for suspected neonatal sepsis in Malawi is penicillin and gentamicin. There is also a need for data on antibiotic susceptibility patterns of the common causes of neonatal sepsis, as multi-drug resistant bacteria become increasingly prevalent. We report aetiology, pattern of antibiotic resistance and outcome for Malawian neonates with confirmed sepsis over a six-year period.

Patients and methods

Study setting

We reviewed retrospectively all bacterial isolates from cerebrospinal fluid (CSF) and blood culture from neonates (aged 0-30 days) hospitalised with suspected sepsis at Queen Elizabeth Central Hospital (QECH), Blantyre, between January 1st, 1996, and December 31st, 2001. The neonates reported in this study were admitted to either the Special Care Nursery (SCN) or to the Paediatric Nursery Ward (PNW). A recent audit provides useful background data of admission patterns to SCN (unpublished data, D. Drejer). From November 2003 until November 2004, there were 13,574 deliveries at QECH and 2,730 (20%) of these were low-birth-weight (LBW<2500 grams). There were 2,584 (19% of all deliveries) admissions to SCN after delivery - usually from the labour ward but also from the post-natal wards - and 1,255 were LBW (48% of admissions). Many births take place at home or at peripheral health centres and sick neonates are also admitted to the SCN if referred from health centres immediately after birth (6% of admissions in 2003/4). Case-fatality rate for neonates admitted to SCN was 23% and 73% (433/590) of these deaths were in LBW babies.

All other sick neonates (0-30 days of age) presenting to QECH, including those born at QECH but discharged after post-natal assessment, are admitted to the Paediatric Nursery Ward that admits sick infants between 0 and 6 months of age. No data are available on whether mothers were given antenatal or peri-natal antibiotics for fever or prolonged rupture of membranes. HIV infection is a problem in this population but there are no data available of prevalence of HIV infection among sick neonates at QECH or the impact of HIV on sepsis and case-fatality rate.

Study Population

Clinical data, including birth weight and gestational age, were not collected prospectively. If septicaemia or meningitis is suspected in a neonate, the attending clinician usually performs a blood culture (a single bottle only) or lumbar puncture respectively before administering parenteral penicillin (50,000 units/kg three or four times daily) and gentamicin (6mg/kg daily). However, this does not always happen (e.g. if the neonate is considered too unstable on clinical grounds for lumbar puncture) and practice has varied over time. The MLW Clinical Research Programme was established in 1996 and provides a microbiological service to QECH outside of the research context. The availability and utilisation of this service, particularly of blood cultures, has increased over subsequent years. Therefore, the numbers of isolates identified do not include all cases of neonatal sepsis at the hospital during the reported six-year period, especially for those admitted to PNW. For the purposes of this retrospective study, neonatal sepsis is defined as isolation of a bacterial pathogen from blood or CSF taken from a neonate (0-30 days of age) with suspected sepsis. The main clinical features that lead to a presumptive diagnosis of suspected sepsis are the presence of fever, poor feeding, lethargy, respiratory distress or seizures.

Clinical care includes regular administration of intramuscular antibiotics, correction of hypoglycaemia, hypothermia and hypoxia (oxygen via nasal cannulae), nutritional support (expressed breast milk by cup and spoon if unable to suck or by nasogastric tube if unable to suck and swallow). Quality of nursing care is limited by low staffing numbers – on average one per 15-30 patients. Details of clinical observation, investigation, drug administration, and progress are recorded on standard "Critical care pathway" forms developed after consultation within the department.[6] Positive-pressure ventilation is not available for respiratory failure. Outcome was recorded simply as "died" or "home" in the database and there was no follow-up after discharge from hospital.

Laboratory Methods

Blood and CSF were taken by standard methods and investigated in the microbiology laboratory of the MLW Clinical Research Programme in Blantyre, as previously described.[7,8] Venous blood to a maximum of 2 mL blood was added to 20 mL Brain Heart Infusion Broth containing sodium polyanethol sulphonate (E&O Laboratories, Bonnybridge, UK). Bottles were incubated upon receipt in the laboratory and then processed by a conventional manual technique. Cultures were examined macroscopically every day, and Gram stained if turbid or haemolysed. Subcultures and direct susceptibility testing were done as directed by the Gram-stain findings. All bottles were subcultured on to sheep blood agar for all bottles after 18–24 h, 36–48 h, and after 7 days. All plates were incubated in a candle jar, and examined after 24 h and 48 h of incubation. CSF was examined microscopically for total cell count and white cell differential. A Gram stain was done on all samples that were cloudy or had more than 8 white blood cells/mL. After centrifugation, 5mL Brain Heart Infusion Broth with 1% Vitox (Oxoid, Basingstoke, UK) was added to the deposit for enrichment culture. This broth was incubated for 48 h, and the centrifuged deposit was then cultured. Contaminants were classified on the basis of organism alone. Mixed growths or growth of micrococci, *Bacillus* species or coagulase-negative staphylococci were considered contaminants and not included in the analysis.

All media (Oxoid, Basingstoke, UK) were prepared in-house; sheep blood agar (using blood obtained from our own flock) was quality controlled using local wild strains of *S. pneumoniae* and *Streptococcus pyogenes.* Isolates were identified according to standard techniques[9], including seroagglutination (Pro-Lab Diagnostics, Merseyside, UK and Murex Biotech, Dartford UK) and biochemical tests (API strips, bioMerieux UK Ltd, Basingstoke, UK). Antibiotic susceptibilities were determined by disc diffusion on Mueller-Hinton agar, interpreted with the National Committee for Clinical Laboratory Standards guidelines[10] and quality controlled using *Escherichia coli* ATCC 25922 and *Staphylococcus aureus* ATCC 25923. For pneumococci, penicillin susceptibility was assessed with a screening technique using a 1mg oxacillin disc. For these organisms, Mueller-Hinton agar with 5% sheep blood was used, which was initially quality controlled with S. pneumoniae ATCC 49619 and thereafter with wild pneumococcal strains. Minimum inhibitory concentrations were not performed for any isolate.

Data Analysis

Data were entered and analyzed with a statistical program (Epi-Info 6). Associations between categorical variables such as case fatality rate were assessed with Pearson's Chi-square test.

Results

Causative Organisms

A total of 801 bacteria were isolated over the 6-year period from 784 neonates. There were 17 neonates with bacteria cultured from both CSF and blood and these were recorded as cases of neonatal meningitis (Table 1). The common causes of neonatal meningitis were GBS, *S. pneumoniae* and non-typhoidal *Salmonella* (NTS). The common causes of neonatal bacteraemia were *S. aureus,* GBS and NTS, followed by *E. coli, Klebsiella* spp., Group A *Streptococcus* and *S. pneumoniae.* The most prevalent causes of all neonatal sepsis were GBS (17%) and NTS (14%). Overall, 54% of isolates were Gram positive and 46% were Gram negative. The prevalence of causative bacteria varied between cases of neonatal sepsis that presented in the first week of life and those that presented after day 7 (Figure).

TABLE 1. Aetiology of neonatal sepsis at QECH, Blantyre: Jan 1996- Dec 2001

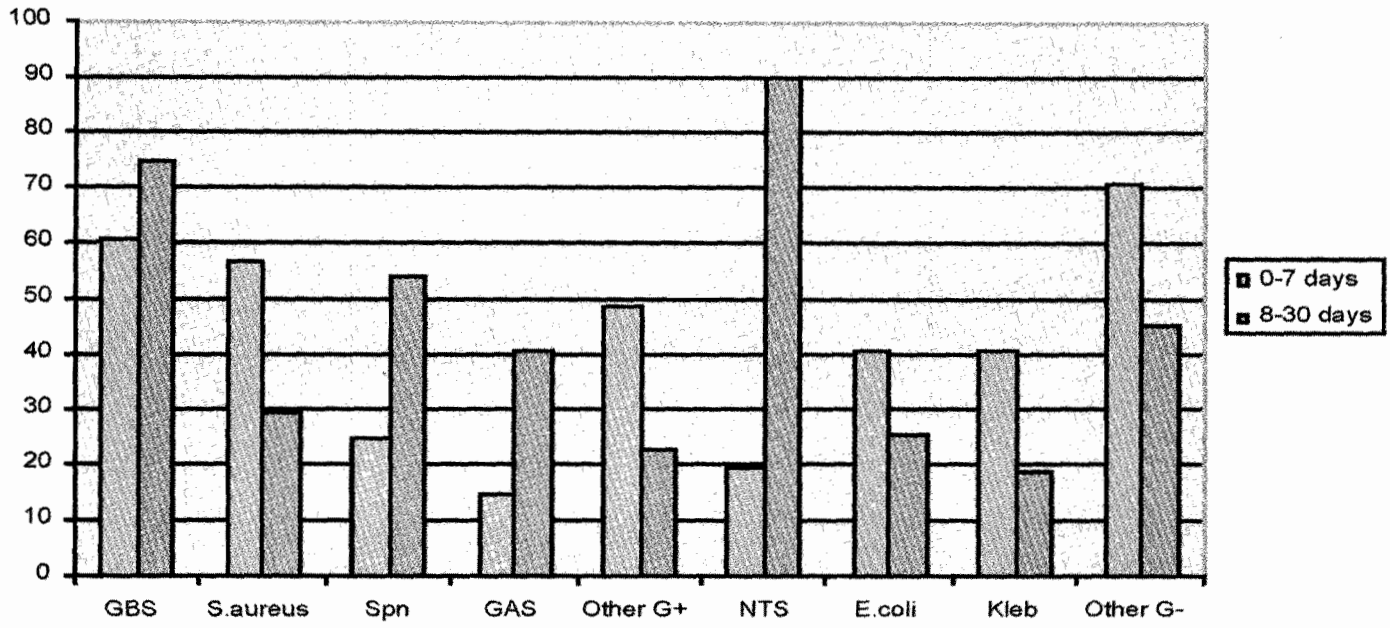
Bacterial isolates	Neonatal sepsis N (%)	Neonatal meningitis N (%)	Neonatal bacteraemia N (%)	Neonatal sepsis 0-7 days (%)	Neonatal sepsis 8-30 days (%)
Gram positive					
Group B *streptococcus*	136 (17)	60 (30)	76 (13)	61 (16)	75 (19)
Staphylococcus aureus	87 (11)	2 (1)	85 (15)	57 (15)	30 (7)
Streptococcus pneumoniae	79 (10)	47 (23)	32 (6)	25 (6)	54 (13)
Group A *streptococcus*	56 (7)	7 (4)	49 (8)	15 (4)	41 (10)
Others	72 (9)	11 (5)	61 (10)	49 (13)	23 (6)
Gram negative					
Non-typhoidal *Salmonella*	110 (14)	33 (16)	77 (13)	20 (5)	90 (22)
Escherichia coli	67 (9)	10 (5)	57 (10)	41 (11)	26 (7)
Klebsiella spp.	60 (8)	6 (3)	54 (9)	41 (11)	19 (5)
Others	117 (15)	26 (13)	91 (16)	71 (19)	46 (11)
Total (% total)	784	202 (26)	582 (74)	380 (48)	404 (52)

Age-related data were analyzed for all blood and CSF samples cultured between May 1st, 1999 and December 31st 2001. During this period, there were a total of 483 CSF samples processed for neonates (0-30 days) of which 81(17%) were positive on culture, 396 (82%) were negative and 6 (1%) grew contaminants. Over the same period there were 2,442 blood samples cultured of which 448 (18%) were positive, 1,213 (50%) were negative and 781 (32%) grew contaminants. The commonest contaminants were coagulase-negative Staphylococci, accounting for 80% of all contaminants, and other "skin flora" organisms comprised 20%.

In addition to the 202 cases with confirmed bacterial meningitis over the study period, there were a further 140 cases with a diagnosis of meningitis on the basis of a positive Gram stain and/or a raised white cell count (more than 20 white blood cells/mL) in the CSF but with no growth on culture. One reason for lack of positive culture may be that lumbar puncture was performed after antibiotics were commenced. In those whose outcomes were recorded, the mortality associated with growing an organism from the CSF was 43% (n=119). Mortality in the group that was positive for leucocytes but grew no organism was 21% (n=67). The difference was significant with an odds ratio of 2.89 (95% CI 1.4 to 6.1).

Our data showed a seasonal variation for NTS bacteraemia with the peak incidence in May at the end of the wet season and the lowest incidence during February, usually the wettest month.

FIGURE. 3 Frequency of causative organism comparing early onset (0–7 days) to late onset (8–30 days) neonatal sepsis



GBS = Group B Streptococcus, S aureus = Staphylococcus aureus, Spn = Streptococcus pneumoniae, GAS = Group A Streptococcus, Other G+ = other Gram positive bacteria, NTS = Non-typhoidal Salmonella, E.coli = Escherichia coli, Kleb = Klebsiella spp., Other G- = other Gram negative bacteria

Antibiotic Resistance

The patterns of antibiotic susceptibility for different isolates are listed in Table 2. Overall, 78% of all isolates showed *in vitro* susceptibility to penicillin or gentamicin. The Gram-positive organisms and *E. coli* were usually sensitive to one or other of the recommended first-line combination of penicillin and gentamicin. However, a large proportion of *Klebsiella* spp. and NTS showed *in vitro* resistance to gentamicin which is the antibiotic used to treat Gram-negative sepsis. There was no difference in susceptibility between blood and CSF isolates (data not shown).

TABLE 2. Proportion of antibiotic susceptible isolates from cases of neonatal sepsis

Organism (no. of organism)	Pen (no. tested)	Eryth (no. tested)	Amp (no. tested)	C'col (no. tested)	Gent (no. tested)	Cipro (no. tested)	Cefriaxone (no. tested)	Pen or Gent (no. tested)
Gp B strep (136)	100%(136)	98%(135)	NT	86%(135)	1%(136)	NT	NT	100%(136)
Staph. aureus(87)	4%(84)	86%(85)	NT	60%(85)	86%(86)	NT	NT	89%(87)
S. pneumoniae (79)	96%(79)	100%(78)	NT	93%(76)	0%(75)	NT	NT	96%(79)
Gp A strep (56)	100%(56)	100%(56)	NT	98%(56)	8%(52)	NT	NT	98%(56)
Other Gram Positive (72)	56%(66)	56%(66)	77%(13)	69%(67)	20%(66)	NT	NT	59%(69)
NTS (110)	NT	NT	4%(108)	70%(108)	53%(106)	100%(29)	100(28)	53%(106)
E.coli (67)	NT	NT	25%(67)	57%(67)	93%(67)	100%(8)	100%(8)	93%(56)
Klebsiella spp. (60)	NT	NT	0%(60)	22%(60)	33%(60)	100%(9)	100%(4)	33%(60)
Other Gram Negative (117)	NT	NT	22%(100)	41%(108)	68%(108)	100%(19)	78%(18)	71%(109)

NT = Not tested or tested on less than 10 isolates except for sensitivities to ciprofloxacin and ceftriaxone. Ciprofloxacin sensitivity was only determined for blood isolates, Ceftriaxone sensitivity was only determined for CSF isolates.
Pen= Penicillin; Eryth= Erythromycin; Amp= Ampicillin;
C'col= Chloramphenicol; Gent= Gentamicin; Cipro= Ciprofloxacin

Mortality

Case-fatality data were only available for 301 out of 784 patients. Overall case-fatality rate was 48%, and was 42% for meningitis and 52% for septicemia. The outcome for the two commonest isolates was markedly different. Of neonates with GBS septicemia, 21% died compared with 62% for NTS septicemia. Meningitis due to GBS had a significantly lower case fatality rate at 26% (OR 0.37; 95% CI 0.14-0.91) compared with 49% for all other causes, while meningitis due to NTS had a case fatality rate of 64%, significantly higher than the rate for all other groups (37%) (OR 2.97; 95% CI 1.04-8.66).

A fatal outcome was more common in sepsis caused by Gram-negative bacteria (66%) than in sepsis due to Gram-positive bacteria (30%)(OR 4.59; 95% CI 2.75-7.70). The case fatality rate was 65% in the patients presenting in the first week of life compared with 38% for those presenting after day 7 (OR 3.14; 95% CI 1.86-5.30). This difference was more pronounced for neonatal bacteraemia than for meningitis.

Discussion

The most remarkable finding is that GBS was the commonest isolate. Large studies from other regions of the developing world[3-5,11,12] including The Gambia and Ethiopia found that *S. aureus* was the commonest Gram-positive pathogen with GBS being rare. In contrast, however, a smaller study from a coastal region of Kenya reported a pattern of etiology more similar to ours with GBS accounting for 23% of 52 isolates from neonates, followed by *Klebsiella* (19%), *E. coli* (17%) and *S. pneumoniae* (13%).[13] GBS was also reported as the most frequent cause of neonatal sepsis or meningitis in Zimbabwe, South Africa and the West Indies.[14-17] The reasons for such differences in the reported prevalence of neonatal sepsis due to GBS is not certain. Studies of mothers in populations where GBS infection is rare in neonates have found levels of ante-natal carriage of GBS to be as high as in developed country populations.[18-20] Differences in reported rates may also reflect different laboratory practices.[2,18] Recognition of GBS as a common neonatal pathogen is particularly important because of the potential of preventative interventions such as intrapartum chemoprophylaxis for high-risk mothers and maternal immunization.[21]

The other important difference in aetiology from studies elsewhere in the developing world is that NTS were the commonest Gram-negative bacteria isolated. Other studies, including the study from Kenya, reported that *Klebsiella* and *E. coli* were the usual Gram negatives with NTS being uncommon.[3,5,11-13] The multi-centre study found that NTS were the cause in 11% (9/84) of neonates with septicemia from the Gambia, Ethiopia and The Philippines.[4] NTS are increasingly common as a cause of meningitis in Malawian infants and children presenting to QECH.[7,22] NTS are well recognized as a frequent cause of invasive disease in children living in tropical Africa, especially in the rainy season, and associated risk factors include malaria, anaemia, young age and malnutrition.[23] Invasive NTS disease is now also common and often fatal in Malawian adults, usually in association with HIV infection.[24]

Despite this, very little is known of the modes of acquisition, carriage or transmission of NTS in the region. A better understanding of epidemiology and transmission could facilitate prevention strategies, but without such knowledge we can only speculate on the possible mechanisms. The peak prevalence for NTS sepsis in our study was in the second week of life and it was most common at the end of the rainy season when carriage rates in the community are likely to be high.[25] This suggests that infection was post-natal or horizontally acquired, such as for *S. pneumoniae,* rather than perinatally or vertically acquired as it is for other common causes such as GBS or *E. coli* (Figure). The risk of transmission from chronically or recently infected mothers to neonates and infants is quite high.[25] HIV infection may also be an important risk factor for carriage and transmission but we have no data on the impact of HIV in this study group. Nosocomial transmission in the hospital nursery is another possible source of infection.[23,26]

The finding that *S. pneumoniae* and Group A *Streptococcus* are major neonatal pathogens, particularly after the first week of life, has been noted elsewhere in developing countries.[4] Nasopharyngeal colonization with *S. pneumoniae* is likely to occur early in Malawian infants - a study at the same institution isolated pneumococcus from the nasopharynx of 34% of well infants less than 2 months of age.[27] Group A *Streptococcus* was a common cause of puerperal sepsis and of neonatal sepsis in developed countries in the past but is now unusual.[28] Similarly, *Staphylococcus aureus* is consistently an important cause of neonatal sepsis in developing countries.[3-5] The majority of cases in our study presented in the first week of life but we do not have data on the frequency of skin or umbilical sepsis in this group. Cloxacillin should be routine in the initial therapy of suspected septicemia in neonates with skin sepsis.[4]

We report a high contamination rate among blood cultures that is likely to be due to the difficulties of ensuring aseptic technique when taking blood samples from neonates at QECH, a procedure usually performed by nursing staff. It is possible that the culture of contaminants masks the growth of a genuine pathogen, particularly a more fastidious or slow growing organism, and so a lower contamination rate could have meant a higher rate of isolation of pathogens. The commonest contaminant was coagulase-negative Staphylococcus, which is a common neonatal pathogen in industrialized countries in the setting of very low-birth-weight neonates requiring intensive care over long periods.[29] That scenario is very different from the setting in which the neonates we report were managed.

Increasing antibiotic resistance among the common neonatal pathogens has been recognized in large studies from a number of sites[3,11,12,17,30] and may be associated with poorer outcome. *In vitro* testing showed that 78% of organisms causing neonatal sepsis in our institution were susceptible to our first line antibiotic combination of penicillin and gentamicin. The susceptibility of *Klebsiella* spp. and NTS to gentamicin was only 33% and 53% respectively (Table 2) but they were susceptible to ceftriaxone and ciprofloxacin. Oral ciprofloxacin was recently included on the Essential Drugs list in Malawi. The use of ciprofloxacin in neonates is increasingly acceptable as follow-up studies have shown no adverse effects.[31] However, we would not advocate change to antibiotic policy for suspected neonatal sepsis on the basis of our data. Prospective studies are required to determine the potential benefit of newer antibiotics before they can be adopted as first-line therapy especially as widespread use of third-generation cefalosporins or quinolones is likely to lead to further emergence of resistance.[3]

The major short-comings of this report are the lack of clinical and outcome data. Case-fatality rates in our study rate were very high but data were available for only 40% of cases, and only

recorded for neonates that died in hospital. Certainly our data are biased towards early and in-hospital mortality. Earlier studies from the region also reported high mortality for neonatal sepsis.[1,4,14,32] While the case-fatality rate for cases with Gram-negative sepsis was significantly higher than for Gram-positive sepsis and *in vitro* resistance to first-line antibiotics was higher for Gram negatives, there were not sufficient mortality data to determine whether antibiotic resistance was a factor determining poorer outcome. Other risk factors for poor outcome are likely to be low-birth-weight[14,32,33], HIV infection and late presentation. These factors are common in our setting but such data were not known in this series. The finding of higher mortality associated with early-onset sepsis (0-7 days) is in agreement with earlier studies.[5,30] In Lahore, Pakistan, the mortality rate in the first week of life was 47% versus 12% in the later 3 weeks of the neonatal period.[30] Also consistent with other studies is the finding that outcome is better for neonatal sepsis due to GBS is better than for other bacteria.[14,33]

Acknowledgment

Particular thanks to the nursing staff of Chatinkha SCN ward and the Paediatric Nursery Ward at QECH who strive to provide optimal care for these sick newborns with limited resources under difficult circumstances.

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