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Invasive Bacterial Infections in Neonates and Young Infants Born Outside Hospital Admitted to a Rural Hospital in Kenya

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Abstract

Background—Bacterial sepsis is thought to be a major cause of young infant deaths in low income countries, but there are few precise estimates of its burden or causes. We studied invasive bacterial infections (IBI) in young infants, born at home or in first level health units ("outborn") who were admitted to a Kenyan rural district hospital during an 8-year period.

Methods—Clinical and microbiologic data from admission blood cultures and cerebrospinal fluid cultures on all outborn infants aged less than 60 days admitted from 2001 through 2009, were examined to determine etiology of IBI and antimicrobial susceptibilities.

Results—Of the 4,467 outborn young infants admitted, 748 (17%) died. Five hundred and five (11%) had IBI (10% bacteremia,3% bacterial meningitis), with a case fatality of 33%. The commonest organisms were *Klebsiella* spp., *Staphylococcus aureus, Streptococcus pneumoniae,* Group B *Streptococcus, Acinetobacter* spp., *Escherichia coli* and Group A *Streptococcus.* Notably, some blood culture isolates were seen in outborn neonates in the first week of life, but not in inborns: *Salmonella, Aeromonas* and *Vibrio* spp. Eighty-one percent of isolates were susceptible to penicillin and/or gentamicin and 84% to ampicillin and/or gentamicin. There was a trend to increasing *in vitro* antimicrobial resistance to these combinations from 2008 but without a worse outcome.

Conclusions—IBI is common in outborn young infants admitted to rural African hospitals with a high mortality. Presumptive antimicrobial use is justified for all young infants admitted to hospital.

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Keywords

neonatal sepsis; bacteremia; meningitis; antibiotic resistance; Africa

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Background

Millennium Development Goal 4 is to reduce the number of child deaths by two thirds of the 1990 level to 31 per 1,000 live births by 2015[1]. However, neonatal mortality has fallen at a slower rate than early child mortality[2]. Consequently, about half of all childhood deaths in developing countries occur in the neonatal period. Global neonatal mortality is estimated at 30 per 1,000 live births[3]. Bacterial infections are thought to be the second most important cause worldwide accounting for 26% of the deaths, but in countries with the highest neonatal mortality rates, infection may account for a greater proportion[4]. Furthermore, because these countries lack microbiology laboratory facilities, there are few data on the causative organisms.

Most studies in these countries have been conducted in tertiary centers in urban areas[5-12], but the majority of children are born in the community in rural areas[13], often outside hospital. A review of 14 studies of the bacterial etiology of young infant sepsis noted that the setting influences the pattern of causative agents and antimicrobial susceptibility[14]. In many published reports it is not possible to tell whether the infection occurred following delivery at home or in hospital, or was a nosocomial infection.

One important study of community-acquired young infant sepsis was the World Health Organization (WHO) Young Infant Study, carried out in 1990-1993 in 4 countries (Papua New Guinea, Philippines, The Gambia and Ethiopia)[15-17]. Among infants with proven bacterial infection, Gram positive organisms were more common than Gram negative but this study had only 31 isolates from the first week of life[15]. A retrospective study of 801 isolates from 784 neonates in a tertiary referral hospital in Malawi also found that Gram positive organisms predominated[18]. Neither of these studies differentiated between those born in hospital or at home. A previous study in Kilifi, Kenya of community acquired bacteremia in pediatric admissions from August 1998 to July 2002 found a prevalence of 12.8% in young infants less than 60 days [19]. The most common isolates were *Escherichia coli* (14%) and Group B *Streptococcus* (11%). A recent review highlighted the paucity of antimicrobial resistance data for infections in young infants from community-based studies and the need for further data from different developing countries to determine prevalence of resistant strains and time trends[20]

We examined prospectively collected data on all pediatric admissions to Kilifi District Hospital from 2001. We aimed to study the etiology, antimicrobial sensitivity and outcome of invasive bacterial infections in neonates and young infants born outside hospital aged less than 60 days, to provide data on the burden of disease in a rural area.

Methods

Kilifi District Hospital is situated in a rural area on the Kenyan coast. It is a government district hospital, providing first referral level care for a population of approximately 250,000 who are mainly subsistence farmers. Primary care facilities in the district are limited. Immunization with conjugate *Haemophilus influenzae* type b vaccine was introduced in November 2001. There is no routine immunization with conjugate pneumococcal vaccine. A Kenya Medical Research Institute (KEMRI) research center is located at the hospital. Government-employed clinical officers in the outpatient department, working independently

of the inpatient research team, referred children for admission. Sick neonates were also admitted directly from the maternity department.

There is a 35-bed pediatric ward and a 7-bed pediatric high dependency unit and over 5,000 children are admitted each year. In the maternity unit up to 3,500 deliveries occur each year. In 2000, 9.8 percent of women attending the hospital antenatal clinic were infected with HIV, declining to 6.6% by 2009.

Clinical methods

Clinical officers and junior doctors were trained in the recognition of standardized clinical signs and recorded their findings directly on a computer database before any results from blood tests or lumbar puncture (LP) were known. Weight was measured using an electronic scale (Weylux, London, UK), which was checked for accuracy and consistency weekly. Routine HIV antibody testing of all pediatric admissions was commenced in late 2006.

We defined invasive bacterial infection (IBI) as bacteremia (the presence of a positive blood culture) and/or acute bacterial meningitis (a positive cerebrospinal fluid (CSF) culture or a positive CSF latex agglutination test, or bacteria seen on Gram stain, or a CSF total leukocyte count ≥ 50 cells/μl[19]).

Clinical research staff provided 24-hour clinical care, supervised by consultant pediatricians. Interventions available included oxygen, intravenous fluids, antibiotics, phototherapy, exchange transfusion and nasogastric tube feeding, but not parenteral nutrition, mechanical ventilation or umbilical arterial catheterization. Central venous cannulation was only used for exchange transfusion. Neonates and young infants with suspected IBI were treated with benzylpenicillin (50,000 units/kg every 6 to 12 hours, depending on age), plus gentamicin (3 to 7.5 mg/kg once daily depending on age and weight) until June 2008 when new hospital guidelines were introduced and ampicillin (50mg/kg every 8-12 hours, depending on age) and gentamicin were used. Alteration to the antimicrobial therapy, including increased dosing with penicillin for meningitis, was subsequently guided by microbiologic findings and the response to treatment.

Lumbar puncture policy

The indications for LP were: any suspicion of meningitis or sepsis; impaired consciousness; inability to breastfeed or convulsions. The LP was delayed if the infant had hemodynamic instability or severe respiratory distress. Admissions were reviewed at least daily and an LP was subsequently performed if meningitis was suspected.

Sampling and labs

On admission, blood was drawn from the child and inoculated aseptically into a BACTEC® PedsPlus culture bottle (Becton Dickinson, New Jersey, USA). Blood culture samples were processed by a BACTEC® 9050 instrument (Becton Dickinson, New Jersey, USA). Positive blood and CSF samples were cultured on 5% horse blood agar and chocolate agar. API® biochemical galleries (Biomerieux, Louvres, France) and/or serology were used to confirm suspected pathogens. The CSF leukocyte count was determined manually with a modified Neubauer counting chamber. Gram stain and latex agglutination antigen testing for *Haemophilus influenzae* type b and *Streptococcus pneumoniae* (Murex Diagnostics, UK) were performed if the CSF leukocyte count was >10 cells/μl. Antibiotic sensitivity tests were performed using the British Society for Antimicrobial Chemotherapy (BSAC) method. Antimicrobial susceptibility patterns were determined using breakpoints for zone sizes; these guidelines were updated each year. All laboratory procedures were internally

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controlled and external quality monitoring was achieved through the UK National External Quality Assessment Service (Colindale, UK).

Analysis

We analyzed data from all young infants (age <60 days at admission) from January 1st 2001 to December 31st 2009. Data from admission blood cultures, or CSF culture at any time (since LP was delayed if contraindicated at admission) were used. Proportions were compared using the χ^2 test with Fishers exact test or χ^2 test for trend where appropriate. Neonates less than 7 days old at admission were analyzed separately to look for differences in bacterial etiologies in early and late onset sepsis. Analysis was performed using STATA® 9.2 (Stata Corp, College Station, TX).

Results

General

There were 58,414 pediatric admissions during the study period, of whom, exactly 7,000 were young infants less than 60 days old. From 2007 through 2009, one hundred and eighteen (4.7%) of young infants admitted had antibodies to HIV. Blood cultures were not performed in 188 (3%) young infants (case fatality 26%), and these infants were excluded from further analysis. The remaining 6,812 young infants accounted for 12% of all admissions and 27% of deaths on the pediatric ward during the period of study. Forty two percent were female. Overall 1,148 (17%) young infants died, the mortality was highest in the youngest age groups: 24% days 0-6, 8% days 7-28, 6% days 29-59 (χ^2 for trend p<0.001).

Place of birth was recorded in 98% of these young infants; 32% were born in hospital, including 53% of those admitted on the first day and 44% in the first week. The proportion of young infants born in hospital increased from 24% in 2001 to 47% in 2009 (χ^2 for trend p<0.001).

Characteristics of young infants born outside hospital

The 4,467 outborn young infants had a similar prognosis to those born in hospital: 17% in each group died during admission. (χ^2 p=0.8) Outborn infants admitted in the first week of life had the highest case fatality: 26% compared with 9% in the late neonatal period and 6% in the second month of life. Despite the same overall case fatality, inborns had lower mortalities in each of the respective age groups: 21%, 4% and 5% because fewer outborn young infant admissions were admitted in the first week of life (48%) compared with 77% of the outborns (χ^2 p <0.001).

Invasive bacterial infection in outborns

Out of the total 4,849 blood cultures performed on outborns, 1,118 (23%) grew organisms regarded as contaminants: coagulase negative *Staphylococci* (n=710), *Bacillus* spp (n=389), *Micrococcus* spp (n=15) and *Coryneforms* (n=4). Young infants with these organisms had a mortality of 15% compared to 14% mortality in those with no bacterial growth from blood cultures (3,250 cultures) χ^2 p=0.69.

Invasive bacterial infection was found in 505 (11%) of outborn neonates and infants younger than 60 days. There was a statistically non-significant trend of decreasing Invasive bacterial infection with age (χ^2 trend p=0.06). IBI was detected in 165 (22%) of all deaths in outborn neonates and young infants. The overall case fatality for IBI was 33%, and was highest among neonates admitted in the first week of life: 44% day 0-6, 20% day 7-28 and 23% day 29-59 (χ^2 for trend p<0.001). Invasive bacterial infection was more common amongst

outborn (11%) compared to inborn young infants (5%) χ^2 p<0.001. There was no discernible seasonal pattern of admission with IBI.

Bacteremia

In the outborn young infants, 449 (10%) had a positive blood culture and the frequency decreased with age: (table 1) (χ^2 for trend p=0.02). The case fatality was 37% accounting for 22% of all young infant deaths. The case fatality decreased with age (χ^2 for trend p<0.001).

In the young infants with a positive blood culture, 474 organisms were cultured. Twenty five infants had two different organisms. Gram negative organisms were found in 56% of positive blood cultures. Gram negative organisms were more common than Gram positive in the first week of life, thereafter Gram positive organisms were more common.

Of the *Acinetobacter* isolates identified, 8 were of the *Acinetobacter baumannii/ calcoaceticus* complex which is potentially more likely to include clinically significant pathogens. The case fatality in these infants was 38% (3/8) compared with 18% (7/40) (Fisher's exact test p= 0.3) in infants with bacteremia with other *Acinetobacter* species.

There was a significant increase in bacteremia in infants born at home (10%) compared with those born in hospital (6%) χ^2 p<0.001. Some organisms isolated from blood cultures from outborn infants were not seen in hospital born infants (Table 2).

Meningitis

Among 2,140 (48%) young infants who had lumbar punctures performed, 152 (7% of those who had an LP, 3% of young infants) had meningitis (3% for day 0-6, 5% day 7-28 and 4% for day 29-59 (χ^2 for trend p=0.03)). There were 86 positive CSF cultures (4% of LPs), 1 infant had 2 organisms on CSF culture. A further 7 infants had positive CSF antigen tests or organisms seen on Gram stain. In 60 infants, the CSF WBC was ≥50 cells/μl, but no organisms were seen on Gram stain nor grown on CSF culture and CSF antigen tests were negative. None of these infants died. Bacterial meningitis was found in 16% of infants with a positive blood culture and 15% of those with positive blood cultures also had a positive CSF culture.

Table 3 describes the organisms isolated on CSF culture in outborns. Among all infants with meningitis, 45% had positive blood cultures and among those with positive CSF cultures, 78% had positive blood cultures. The overall case fatality of those with meningitis was 19%.

Antimicrobial resistance in outborns

Antimicrobial susceptibilities to six common organisms are shown in SDC Table 1 Supplemental Digital Content 1, http://links.lww.com/INF/A470. All *Staphylococcus aureus* blood culture isolates were susceptible to methicillin.

The sensitivities of all isolates tested to antibotic combinations penicillin/gentamicin (Kenyan Ministry of Health policy[20]) and ampicillin/gentamicin (WHO guidelines[21]) were compared and found to be similar: 81% versus 84%. There was a reduction in sensitivity of isolates to the ampicillin/ gentamicin combination during the study period: only 66% of blood culture isolates tested in 2009 were susceptible compared with 88% in 2001 (χ^2 for trend p<0.001) There was no discernible change in resistance to gentamicin in *E.coli* isolates over time, but from 2007 over 50% of *Klebsiella* spp. isolates were resistant rising to 73% in 2009.

There was no significant association of antimicrobial resistance with fatal outcome (Odds Ratio for death associated with penicillin/gentamicin resistance was 1.12, (95% CI 0.69, 1.84) and for ampicillin/gentamicin resistance was 1.19, (95% CI 0.72, 1.98). When the effect of ampicillin/ gentamicin resistance on deaths occurring more than 48 hours after treatment was calculated there was no significant difference (OR for death =1.16 (95% CI 0.68, 1.96 p=0.59). There was no significant difference in resistance before and after the first week for either ampicillin/gentamicin (early 17%, late 11% Fisher's exact test p= 0.16) or penicillin/gentamicin (early 23%, late 16% Fisher's exact test p=0.17).

Discussion

Bacterial infection is an important cause of admission to hospital and death among outborn young infants. Confirmed IBI accounted for 11% of admissions and 22% of deaths.

This is the largest series of blood and CSF cultures from young infants admitted to an African hospital, with 4,849 blood cultures and 2,140 CSF cultures performed in outborns. The culture rate was high, and the microbiologic techniques were reliable.

One limitation of our data collection was that we did not have information on whether those born outside hospital were home births or were delivered in dispensaries or health centers. It is unlikely that dispensaries would harbor multi-drug resistant strains.

The most common organisms isolated on blood culture were: *Escherichia coli*, *Staphylococcus aureus*, *Acinetobacter* and *Streptococcus pneumoniae*. Gram negative organisms comprised 56% of those cultured from blood. This differs from the WHO Young Infant[16] and the Malawian[18] studies where Gram positive organisms predominated. This may be because our study had a much higher proportion of subjects presenting in the first week: 48% compared with 8% in the WHO study[15]. In the first week of life Gram negative organisms were more common than Gram positive.

Aquatic gram negative organisms *Aeromonas* spp. and *Vibrio* spp. were isolated from blood and CSF in those admitted in the first week of life from those born at home; neither of these found in isolates from hospital born neonates. These systemic infections may be related to poor drinking water quality and the practice of giving pre-lacteal feeds but further research is required to elicit the risk factors. An Australian study reported that the seasonal pattern of clinical isolates showed a correlation with the level of *Aeromonas* contamination of the metropolitan water supply[21].

Salmonella was another important genus only isolated from blood cultures of outborn infants which suggested that environmental hygiene may play a part in determining the etiology of invasive bacterial infections in this group. In a study of non-typhoid multi-drug resistant *Salmonella* infections in children in an urban environment in Nairobi which genotyped organisms from infected children, their families and their immediate environment the authors did not find a major reservoir in animals or food from their homes and concluded that human-to-human transmission was a possible mechanism[22].

The most important Gram positive organisms in our study were *Staphylococcus aureus, Streptococcus* Group A, *Streptococcus pneumoniae* and *Streptococcus* Group B. *Streptococcus* Group B was much more common than in the WHO study[16], but less common than in the Malawian[18] study. Prevalence in different settings is important for evaluating possible infection prevention strategies.

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Antimicrobial resistance

The WHO recommended first line antibiotics for empiric treatment of neonatal sepsis are ampicillin and gentamicin and second line are cefotaxime and gentamicin unless there is infection of the skin or umbilicus, when cloxacillin is substituted for ampicillin[23]. Two Cochrane reviews of treatment of early (EONS) and late onset neonatal sepsis (LONS) concluded that there were few randomized clinical trials of antibiotics in this age group and that there was no evidence which is the best regime[24, 25]. We found that the WHO regimen of ampicillin and gentamicin covered 84% of the organisms isolated in the young infants in our study but that since 2008 the susceptibilities appear to be decreasing.

Penicillin and gentamicin together cover 81% of isolates from young infants in Kilifi. The study in Malawi [18] found a similar coverage: 78% of all isolates tested, but they noted a much lower sensitivity of *Klebsiella* spp. to gentamicin: 33% compared with 51% in our study. A population based study of community acquired neonatal bacteremia in Bangladesh found similar levels of sensitivity to trimethoprim-sulfamethoxazole (52%. 14/27) as ours (56%), but lower sensitivity to the ampicillin and gentamicin combination (21/30 isolates 70%)[26].

We found that antimicrobial resistance to ampicillin/gentamicin was not associated with worse outcomes. Our situation differs from other parts of the world where reports of studies, which included hospital acquired infections, have concluded that increasing antimicrobial resistance means that the combination of beta-lactam antibiotics and gentamicin is no longer appropriate to treat the organisms associated with neonatal sepsis. Ongoing surveillance is required to monitor the consequences of changes in antimicrobial resistance.

Conclusion

Our district hospital based study of 4,467 outborn young infants with blood culture results confirms that invasive bacterial infection is a significant cause of morbidity and mortality in outborn young infants. The burden of long term sequelae is not known. We believe that the presumptive use of antibiotics is justified for all admissions in this age group.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Isolates from blood cultures in young infants born outside hospital under 60 days

	Day 0-6	Day 7-28	Day 29-59	TOTAL
Staphylococcus aureus	21	23	11	55
Streptococcus Group A	6	24	9	39
Streptococcus pneumoniae	14	8	11	33
Streptococcus Group B	15	14	3	32
Streptococcus Group D	18	6	3	27
Viridans streptococcus	9	6	1	16
Streptococcus Group G	4	0	0	4
Streptococcus Group C	1	0	0	1
Subtotal Gram Positive	**88**	**81**	**38**	**207**
Klebsiella spp	35	11	11	57
Acinetobacter spp	28	10	10	48
Escherichia coli	25	11	5	41
Enterobacter spp	20	11	1	32
Salmonella spp	6	14	2	22
Aeromonas spp	21	0	0	21
Haemophilus influenzae	2	0	12	14
Pseudomonas aeruginosa	5	4	0	9
Vibrio spp	8	0	0	8
Proteus spp	5	0	0	5
Neisseria meningitidis	0	1	0	1
Other species	7	2	0	9
Subtotal	**162**	**64**	**41**	**267**
Total	**250**	**145**	**79**	**474**

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Table 2

Comparison of blood culture isolates from young infants born in and out of hospital

	Hospital born n= 2,189		Outborn n= 4,467		Difference in percentages
Organism	**No. of isolates**	**Percentage (95% C.I)**	**No. of isolates**	**Percentage (95% C.I)**	**p value**
S. aureus	18	0.8 (0.5, 1.3)	55	1.2 (0.9,1.6)	0.17
Streptococcus Group A	4	0.2 (0.05, 0.5)	39	0.9 (0.6,1.2)	<0.01
Streptococcus Group B	20	0.9 (0.6, 1.4)	32	0.7 (0.5, 1)	0.38
Streptococcus pneumoniae	5	0.2 (0.1, 0.5)	33	0.7 (0.5, 1)	<0.01
Other Gram positive	24	1.1 (0.7, 1.6)	48	1.1 (0.8, 1.4)	0.9
All Gram positive	**71**	**3.2 (2.5, 4.1)**	**207**	**4.6 (4.0, 5.3)**	**0.08**
Acinetobacter spp	17	0.8 (0.5, 1.2)	48	1.1 (0.8, 1.4)	0.29
Aeromonas spp	-	-	21	0.5 (0.3, 0.7)	<0.001
Enterobacter spp	8	0.4 (0.2, 0.7)	32	0.7 (0.5, 1.0)	0.09
E. coli	17	0.8 (0.5, 1.2)	41	0.9 (0.7, 1.2)	0.67
Klebsiella spp.	12	0.5 (0.3, 1.0)	57	1.3 (1, 1.7)	<0.01
Pseudomonas aeruginosa	8	0.4 (0.2, 0.7)	9	0.2 (0.1, 0.4)	0.3
H. influenzae	1	0.05 (0.01, 0.3)	14	0.3 (0.2, 0.5)	0.03
Salmonella spp	-	-	22	0.5 (0.3, 0.7)	<0.001
Vibrio spp.	-	-	8	0.2 (0.1, 0.4)	0.05
Other Gram negative	1	0.05 (0.01, 0.3)	15	0.3 (0.2, 0.6)	0.03
All Gram negative	**64**	**3 (2.3, 3.7)**	**267**	**6 (5.3, 6.7)**	**<0.001**
Total	**135**	**6.2 (5.2, 7.3)**	**474**	**10.6 (9.7, 11.6)**	**<0.001**

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Table 3

Organisms identified in CSF samples in outborn young infants less than 60 days

Age group	Day 0-6	Day 7-28	Day 29-59	Total
S. pneumoniae	5	7	5	17
Streptococcus Group B	3	11	2	16
Streptococcus Group A	2	3	2	7
Streptococcus Group D	1	0	0	1
Viridans streptococcus	1	0	0	1
Gram positive cocci[a]	2	4	1	7
Subtotal Gram positive	**14**	**25**	**10**	**49**
Salmonella spp.	3	5	2	10
H. influenzae[c]	0	0	9	9
Enterobacter spp.	3	3	0	6
E. coli	5	1	0	6
Klebsiella spp.	2	2	1	5
Vibrio spp.	4	0	0	4
P. mirabilis	1	0	0	1
N. meningitidis	0	1	0	1
Aeromonas sobria	1	0	0	1
Pseudomonas cepacia	0	0	1	1
Gram negative rods [b]	1	1	0	2
Subtotal Gram negative	**20**	**13**	**13**	**46**
Total	**34**	**38**	**23**	**95**

[a] seen on Gram stain but blood and CSF cultures and antigen tests were negative