

Clinical and Bacteriological Profile of Neonatal Septicaemia at A Community Level Medical College Hospital

ASMNU AHMED^a, MI PERVEZ^b, BK PAUL^c, KK BISHWAS^d

Summary:

Septicaemia is a significant cause of morbidity and mortality in neonates. Meningitis is a serious problem in newborns with high mortality and frequent neurological sequelae. In neonates, signs and symptoms of infections are often obscure and clinical examination cannot distinguish septicaemic babies with or without meningitis. Therefore, lumbar puncture is often not done in time and thus diagnosis of meningitis is missed. Our aim was to see the association of bacterial meningitis in neonatal septicaemia and their clinical and bacteriological profile. This study was performed at the neonatal ward of Kumudini Women's Medical College Hospital from August 2007 to July 2009. All admitted newborns diagnosed as septicaemia clinically were enrolled prospectively. Detailed history was taken, thorough clinical examination performed, and blood culture, CSF study and other relevant investigations were done. Patients received standard medical care and followed-up daily till discharge/death. Among 86 suspected cases, 30 (34.9%) had positive blood culture. Common clinical presentations of culture-positive cases were poor feeding (86.7%), lethargy (70%), respiratory distress (56.7%), fever

(46.7%), jaundice (33.3%), seizure (26.7%) and cyanosis (20%). Male child outnumbered the baby girls (1.7:1). Other risk factors were maternal fever during delivery, prolonged rupture of membranes, birth asphyxia and poor socio-economic status. Majority (63.3%) of the cultures isolated gram-negative bacilli, most commonly Klebsiella pneumonia (16.7%), Pseudomonas sp. (16.7%), and Acinetobacter (10%). Staphylococcus aureus (20%) was most common among gram-positive organisms, followed by Streptococcus pneumoniae (10%); no Group B streptococcus was isolated. Associated meningitis was present in two cases (6.7%) and nine out of 30 culture-positive cases (30%) died. This study confirms that neonatal septicaemia is a major problem in perinatology with high case fatality. As associated meningitis is difficult to distinguish clinically, CSF study needs to be included in septicaemia screening. An alarming finding of the study is that high proportion of the organisms are resistant to most of the commonly used antibiotics, again emphasize the importance of judicious antibiotic use.

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Introduction:

The World Health Organization (WHO) estimates that 4 million neonatal deaths occur around the world every year¹. Approximately 98% of these deaths occur in developing countries, and are attributable to infections, asphyxia, and consequences of prematurity and low birth

weight². Overall, neonatal mortality accounts for nearly two-thirds of infant mortality and one-third of under-five childhood mortality worldwide³⁻⁵. Serious bacterial infections are major contributors to newborn morbidity and mortality. An estimated 20% of all children born in developing countries, or 30 million annually develop an infection during the neonatal period, and infectious diseases account for an estimated one-third of all neonatal deaths^{1,6}.

Meningitis is a serious problem in newborn infants with a high mortality and frequent neurological sequelae in survived patients. About 20-30% of neonatal septicaemia, whether early or late, is complicated by bacterial meningitis^{7,8}. One study from Saudi Arabia showed 21 per 1000 admission at NICU had bacterial meningitis⁹. In a two-year (1985-87) prospective study of acute meningitis in England and Wales in infants; the incidence of neonatal meningitis was 0.32 per 1000 live

- Dr. A.S.M. Nawshad Uddin Ahmed, FCPS, Associate Professor, Bangladesh Institute of Child Health, Dhaka Shishu Hospital
- Dr. Md. Imtiaz Pervez, DCH, Registrar of Paediatrics, Kumudini Women's Medical College, Mirzapur, Tangail
- Dr. Bijoy Kumar Paul, MBBS, Medical Officer, Kumudini Hospital, Mirzapur, Tangail
- Dr. Kishore Kumar Bishwas, MBBS, Medical Officer, Kumudini Hospital, Mirzapur, Tangail

Address of Correspondence: Dr. A.S.M. Nawshad Uddin Ahmed, FCPS, Associate Professor, Bangladesh Institute of Child Health, Dhaka Shishu Hospital, Sher-e-Bangla Nagar, Dhaka-1207, Cell: 01552-372200, E-mail: dr_nawshad@yahoo.com

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births¹⁰, another study done in Oxford showed 0.38 per 1000 live births¹¹. Reviews from USA,^{7,12} Europe^{10,13} and Australia¹⁴ have shown 0.2 – 0.5 cases of bacterial meningitis per 1000 live births. In our country we do not have much data, but two prospective studies done at Dhaka Shishu Hospital have shown that 13-27% of neonates with septicaemia had concurrent meningitis^{15,16}.

Several studies report that prematurity, low birth weight, prolonged rupture of membranes and maternal infections are most common perinatal factors associated with septicaemia and meningitis in the newborn period^{7,8,12,13,17}. Clinical examination cannot distinguish septicaemic babies with meningitis from those without meningitis. Blood culture may also be negative in meningitis. One study showed 13% of bacterial meningitis with positive CSF culture had negative blood culture¹³, another study showed 15% case of meningitis with negative blood culture¹⁸.

The causative agents of neonatal septicaemia and meningitis vary between geographical areas and with time in any particular locality. To our knowledge, there has been no documented survey on causative agents of neonatal septicaemia and meningitis at community level from our country. During 1975-91, the leading causes of neonatal bacterial meningitis were Group B streptococcus (34.1%) and *Escherichia coli* (28.5%), which accords with the patterns of causative organisms reported from UK¹⁰, USA¹⁹ and Australia.¹⁴ Another study done at Saudi Arabia shows *Klebsiella pneumoniae* and *Serratia marcescens* as the important organisms of neonatal meningitis⁹. In North America and Europe, the prevalent bacterial agents of late-onset septicaemia include coagulase negative staphylococcus, *Klebsiella* sp. and *Escherichia coli*.²⁰ The two studies done at Dhaka Shishu Hospital showed *Escherichia coli*, *Klebsiella pneumoniae* and *Pseudomonas aeruginosa* as the common organisms of neonatal septicaemia and meningitis^{15,16}.

Materials and methods:

Study site: This hospital based prospective study was conducted at the neonatal ward of Kumudini Hospital in a cohort neonates admitted between August 2007 and July 2009. Kumudini Hospital is a 70 years old, 750-bedded non-profit private hospital, with laboratory and radiology facilities in Mirzapur, a rural sub-district

(Thana) of Bangladesh, located 60 km north of Dhaka. Mirzapur has an estimated total population of 400,000, distributed in 13 unions and 219 villages. The hospital is staffed by specialists of all disciplines. A medical college, Kumudini Women's Medical College, is affiliated to the hospital. As the major referral hospital, Kumudini Hospital serves most patients throughout the Mirzapur sub-district.

Study Population: All admitted newborns diagnosed as septicaemia clinically on admission or at any stage of hospitalization were considered for enrolment. Septicaemia was suspected based on the presence of one or more clinical sign consistent with possible serious bacterial infection including lethargy, refusal of feeds, abdominal distension, vomiting, groaning, grunting, facial grimace, respiratory distress, hypothermia, hyperthermia or sclerema with or without supporting evidence of risk factors such as prematurity, low birth weight (LBW), birth asphyxia, maternal chorioamnionitis (maternal fever and/or foul smelling vaginal discharge) and prolonged rupture of membranes. Meningitis was suspected from a history of irritability, convulsions, high-pitched cry and full, tense anterior fontanel along with other features of septicaemia. We excluded babies in moribund condition and those who had active bleeding for which lumbar puncture could not be done.

Babies were categorized according to the following risk factors for septicaemia: birth weight (<1500 g, 1500 – 2500 g, >2500 g), gestational age (<37 weeks, 37 – 42 weeks, >42 weeks), birth-place (home, hospital/clinic), and mode of delivery (normal, forceps-assisted, Caesarean section). Study patients were also categorized as having early- or late-onset septicaemia depending upon whether the onset of symptoms was within 7 days (early-onset) or 8 to 28 days of life (late-onset).

After enrolment, patients underwent the following diagnostic procedures: complete blood count, blood culture, CSF study (cytology, biochemistry and culture) and other relevant investigations as necessary. A diagnosis of definitive septicaemia was made when the clinical suspicion was confirmed by a positive blood culture. Similarly bacterial meningitis was diagnosed depending on clinical suspicion and positive CSF culture. Of the total 86 cases evaluated during the study period, 30 had a positive blood culture; 2 of them also

had positive CSF culture. The presenting symptoms and signs, agents of infection and outcome of the 30 culture positive cases are described here.

Culture methods: A blood sample was taken from each patient with suspected septicaemia after careful preparation of the skin site with 70% isopropyl alcohol. The site chosen was a peripheral vein, preferably the antecubital vein. Blood (~2 ml) was withdrawn using a sterile disposable syringe and transferred using sterile technique to 5 ml of Trypticase Soy broth. In the laboratory, subculture was done on days 1, 2, 3 and 5 of incubation onto blood agar, chocolate agar and MacConkey's media. Cerebrospinal fluid was plated on the same media as the blood. Antimicrobial sensitivity testing of all isolates was performed on Muller Hinton Agar (MHA) plates by the Kirby Bauer diffusion method.

Patient management: All patients received the standard treatment for neonatal septicaemia followed in the hospital. Cefotaxime and gentamicin were started at enrolment and changed later, if needed, depending on the culture sensitivity report as well as the clinical condition. Other supportive therapy such as correction of acidosis, maintenance of fluid and electrolyte balance, ventilatory assistance, phototherapy and blood transfusion was given as required. Infants enrolled in the study were evaluated on a daily basis while hospitalized.

Data collection: At enrolment a detailed history was taken and thorough physical examination was performed and recorded on standard forms. The parents of the

neonates were explained about the study and then witnessed verbal consent was taken.

Statistical analysis: The data were subjected to statistical analysis according to standard procedure. SPSS version 12.0 for Windows (SPSS Inc, Chicago, IL, USA) software was used for data recording and analysis. Results of the findings were verified by conducting standard tests for significance, including unpaired student T-test and Chi-square (χ^2) tests, as appropriate. A p-value of <0.05 was considered as statistically significant.

Results:

Among 86 cases of clinically suspected neonatal septicaemia, 30 (34.9%) had a positive blood culture; 12 (40%) had early- and 18 (60%) late-onset infection. Blood culture positivity was significantly lower in those with early- (25.5%, 12/47) compared to late-onset (46.1%, 18/39) disease ($p<0.05$). Although males with positive blood cultures (63.3%, 19/30) outnumbered females (36.7%, 11/30), there were no gender differences in culture positivity rate (males 32.7%, 19/58; females 39.3%, 11/28) or proportion of early- (males 42.1%, 8/19; females 36.4%, 4/11) and late-onset (males 57.9%, 11/19; females 63.6%, 7/11) disease. Forty percent of neonatal septicaemia cases were pre-term and 18 (60%) were term babies. Blood culture positivity rate was equivalent, however, for preterm (30.0%, 12/40) and term (39.1%, 18/46) infants; and for very LBW (30.8%, 4/13), LBW (36.8%, 14/38) and normal birth weight (34.3%, 12/35) infants. (Table I).

Table-I

Blood culture-positivity and mortality rates of sub-categories of neonates with suspected sepsis (n=30)

Category		Number enrolled cultures (n)	Positive blood positivity (%)	Blood culture	Mortality (n)	Mortality (% of blood culture positive cases)
Onset	Early	47	12	25.5	3	25.0
	Late	39	18	46.1	6	33.3
Gender	Male	58	19	32.7	6	31.6
	Female	28	11	39.3	3	27.3
Gestational age	Pre-term	40	12	30.0	4	33.3
	Term	46	18	39.1	5	27.8
Birth weight (g)	<1,500	13	4	30.8	2	50.0
	1,500 – 2,500	38	14	36.8	4	28.6
	>2,500	35	12	34.3	3	25.0
Monthly income (Tk.)	<5,000	50	16	32.0	5	31.2
	5,000 – 10,000	25	9	36.0	3	22.2
	>10,000	11	5	45.4	1	20.0

Majority of the deliveries of septicaemic neonates in this study were conducted at home (70%, 21/30) and 9 (30%) took place in a hospital or clinic. Five culture positive cases (16.7%) were delivered by caesarean section, and 11 (36.7%) had a history of birth asphyxia. Neonates with septicaemia more often were from low socio-economic classes (family income < 5,000 Taka per month) (53.3%, 16/30) than middle (5,000 to 10,000 Taka) (30%, 9/30) or higher income (> 10,000 Taka) (16.7%, 5/30) groups. There was a trend for the culture positivity rate to be lower in the low (32%, 16/50) than the middle (36%, 9/25) or high (45.4%, 5/11) income groups, although the difference was not significant statistically. (Table I) Prolonged rupture of membranes for more than 18 hours was present in 20% (6/30) cases and maternal fever during delivery in 10% (3/30), one of them had both (4%).

The most frequent clinical presentations of patients with culture-proven serious neonatal bacterial infection were poor feeding (86.7%, 26/30), lethargy (70%, 21/30), respiratory distress (56.7%, 17/30), fever (46.7%, 14/30), jaundice (33.3%, 10/30), seizure (26.7%, 8/30) and cyanosis (20%, 6/30). Jaundice and convulsion were more common in early-onset and fever was more common in late-onset disease, though not statistically significant ($p>0.05$); other presenting signs were almost similar in both groups. (Table II) Meningitis cases were presented with features of septicaemia; there were no specific symptoms or signs related to meningitis.

Of the 30 organisms isolated, about two-thirds (63.3%, 19/30) were gram-negative bacilli; 11 (36.7%) were gram-positive. Among the gram-negative bacilli, *Klebsiella pneumonia* (16.7%, 5/30), *Pseudomonas* sp. (16.7%, 5/30), and *Acinetobacter* (10%, 3/30) was the most common and *Staphylococcus aureus* (20%, 6/30) and *Streptococcus pneumoniae* (10%, 3/30) was most common among gram-positive organisms, The pattern of organisms isolated was similar, regardless of time of onset of disease, birth weight or gestational age. (Table III) A large number of the organisms are resistant to all of the commonly used antibiotics. Ampicillin virtually has no effect except against *Streptococcus pneumoniae* and *H. influenza*. Gentamicin, third generation cephalosporins and ciprofloxacin showed mixed sensitivity pattern. Imipenem and netilmicin are found most effective against majority of the organisms. (Table IV).

Of the 30 culture-positive cases, 9 (30%) died. The case fatality rate was inversely related to birth weight (<1500 g: 50%, 2/4; 1500-2500 g: 28.6%, 4/14; >2500 g: 25%, 3/12), and was highest in neonates infected with *E. coli* (50%), followed by *Klebsiella pneumoniae* and *Pseudomonas* sp. (40%) and no mortality in neonates infected with *H. influenza*, *Streptococcus* sp, *Enterobacter* and *Salmonella* sp. (Fig. I) Case fatality was not influenced by time of onset (early-onset: 25%, 3/12; late-onset: 33.3%, 6/18) or gender (males: 31.6%, 6/19, females: 27.3%, 3/11). (Table I).

Table-II

Common Clinical Manifestations of the Blood Culture Positive Cases of Neonatal Septicaemia (n=30)

Clinical features	Prevalence (%)			p-value
	All	Early-onset	Late-onset	
Poor feeding	86.7	91.7	83.3	NS
Lethargy	70.0	66.7	72.2	NS
Respiratory distress	56.7	66.7	50.0	NS
Fever	46.7	33.3	55.6	NS
Jaundice	33.3	41.7	27.8	NS
Seizure	26.7	41.7	16.7	NS
Cyanosis	20.0	16.7	22.2	NS
Vomiting	13.3	16.7	11.1	NS
Hypothermia	10.0	16.7	5.6	NS
Apnoea	10.0	16.7	5.6	NS

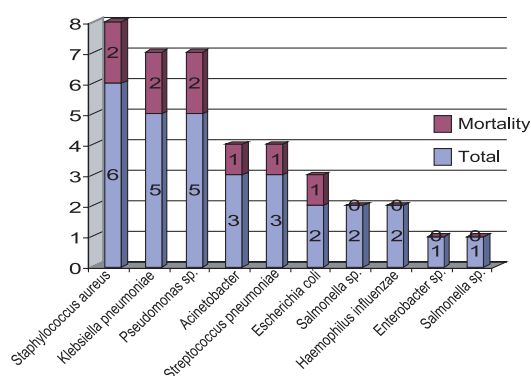
NS=Non-significant

Table-III*Organisms Isolated in Relation to Onset of Disease, Birth Weight and Gestational Age (n=30)*

Organisms	Total (percentage)	Age of onset		Birth weight (g)			Gestational age	
		Early	Late	<1500	1500 -2500	>2500	Pre-term	Term
<i>Staphylococcus aureus</i>	6 (20.0)	2	4	1	2	3	3	3
<i>Klebsiella pneumoniae</i>	5 (16.7)	2	3	-	3	2	1	4
<i>Pseudomonas sp.</i>	5 (16.7)	1	4	1	2	2	1	4
Acinetobacter	3 (10.0)	1	2	1	1	1	2	1
<i>Streptococcus pneumoniae</i>	3 (10.0)	2	1	-	2	1	1	2
Streptococcus sp.	2 (6.7)	-	2	-	1	1	1	1
<i>Haemophilus influenzae</i>	2 (6.7)	1	1	-	1	1	1	1
<i>Escherichia coli</i>	2 (6.7)	1	1	-	1	1	1	1
Enterobacter sp.	1 (3.3)	1	-	1	-	-	1	-
Salmonella sp.	1 (3.3)	1	-	-	1	-	-	1
Total	30 (100)	12	18	4	14	12	12	18

Table-IV*Antibiotic Resistance (%) of Organisms Isolated (n=30)*

Antibiotic	<i>Staph. aureus</i>	<i>Kl. pneumoniae</i> (n=6)	Pseudo- monassp. (n=5)	Acineto- bacter (n=5)	<i>Str. pneumoniae</i> (n=3)	<i>Streptococcus</i> (n=3)	<i>H. influenzae</i> sp. (n=2)	<i>E. coli</i> (n=2)	Entero- bacter sp. (n=1)	Salmo- nella sp. (n=1)
Ampicillin	83.3	100	100	100	0	50	0	50	100	100
Gentamicin	16.7	60	80	66.7	0	0	0	0	0	0
Cefotaxime	16.7	60	80	33.3	0	0	0	0	0	100
Ceftriaxone	16.7	60	60	33.3	0	50	0	0	0	100
Ceftazidime	33.3	20	40	33.3	0	0	0	0	0	100
Ciprofloxacin	16.7	40	40	33.3	0	0	0	0	0	100
Imipenem	0	0	20	0	0	0	0	0	0	0
Netilmicin	0	0	60	0	0	0	0	0	0	0

**Fig.-1.** Mortality of the 30 Blood Culture Positive Cases of Neonatal Septicaemia in Relation to Bacterial pathogens. (Total no of deaths n=9)

Of the 30 culture-positive cases, 2 also had meningitis with culture-positive CSF; among them, 1 patient (50%) died. *Streptococcus pneumoniae* caused meningitis in early-onset and *Klebsiella pneumoniae* in late-onset disease.

Discussion:

In this study, at a community level medical college hospital in Bangladesh, we found that late-onset neonatal septicaemia was more common than early-onset disease; in contrast to other reports in which early-onset septicaemia generally has been more common^{21,22}. Perhaps this discrepancy is due to the fact that mortality in early-onset cases is relatively high²³, and thus, some

neonates in the catchment area of our hospital, which largely serves a low socioeconomic status community with poor communication facilities, might have died prior to arrival at the hospital. Although males have been reported to be 2- to 6-fold more likely than females to develop septicaemia^{23,24}, the 1.7:1 ratio of male-to-female infants in our study, while seemingly consistent with this data, could also reflect a gender bias in presentation to the hospital for care. Population-based studies would be needed to address this important question. The clinical features, culture positivity rates, and case fatality rates, however, were equivalent across gender, suggesting that the males and females in the study overall had a similar degree of illness.

The majority of the study population was poor, and delivered at home, largely in the hands of untrained birth attendants. Home deliveries are common in Bangladesh²⁵, and typically are conducted in poor standards of asepsis²⁶. History of unclean vaginal examination was associated with a 10% incidence of deep infection in one study²⁷. Home deliveries also are significantly related to birth asphyxia²⁸, which was highly prevalent in our study population, and which, in turn, is associated with an increased risk of serious neonatal infection²⁹.

The clinical features of neonatal septicaemia seen in this series are similar to those previously reported in other studies^{30,31}. In majority of cases early clinical presentation was nonspecific simulating other common neonatal problems. Poor feeding was present in majority of the cases (86.7%). Other common presentations were lethargy (70%), respiratory distress (56.7%), fever (46.7%), jaundice (33.3%), seizure (26.7%) and cyanosis (20%). Jaundice and convulsion were more common in early-onset and fever in late-onset disease, though the difference was not statistically significant ($p>0.05$); other presenting signs were almost similar in two groups. Apnoea and hypothermia was mostly seen in preterm babies. The more non-specific symptomatology of disease and the relatively greater tendency to over-diagnose illness in the younger age group may have contributed to the lower percentage of positive cultures in neonates with early- compared to late-onset disease. Nonetheless, negative blood culture does not rule out septicaemia. Squire et al³² reported 7 cases with negative culture, fatal outcome and post-mortem evidence of infection. The possibility of

infection with anaerobes also cannot be ruled-out as anaerobic culture was not performed in this series. Chow et al³³ reported that 26% of all neonatal septicaemia was caused by anaerobes.

Of the organisms isolated 19 (63.3%) were gram negative and the rest (11,36.7%) gram positive. Increasing prevalence of gram negative septicaemia has been reported from other studies in India^{34,35} and Pakistan^{23,36} as well as previous studies in our country^{15,16,37}. Earlier study showed prevalence of *E. coli*, followed by *Klebsiella pneumonia* and *Pseudomonas* sp.,¹⁵ later studies showed preponderance of *Klebsiella*, followed by *Pseudomonas* sp. and *Acinetobacter*^{16,37}. In the present study, *Klebsiella pneumonia* was also the most prevalent organism (16.7%), followed by *Pseudomonas* sp. (16.7%) and *Acinetobacter* (10%) and only 2 (6.7%) *E. coli*. This supports the changing trend of bacterial etiology in neonatal septicaemia³⁸. Group B *Streptococcus* was not isolated in this study, unlike western, developed countries where it is the major agent of neonatal septicaemia^{21,22,39}. The insignificance of GBS as a pathogen in many developing countries is supported by a number of other studies^{34,40-46}. This may be attributable to low prevalence of GBS colonization of pregnant mothers in this area, or, possibly, to the presence of strains with low virulence⁴⁷.

An alarming finding in this study is the high proportion of the organisms are resistant to all of the commonly used antibiotics. Imipenem and netilmicin are found most effective against majority of the organisms. Gentamicin, third generation cephalosporins and ciprofloxacin, which previously had good sensitivity, also becoming resistant. This observation shows that the problem of antibiotic resistance is a serious threat for treating serious bacterial infections in neonates and to control antibiotic resistance, practice of prudent or judicious use of antibiotics is very important.

The present survey confirms the high case fatality rate in neonatal septicaemia, despite care in a medical college hospital and use of appropriate antimicrobial therapy. The death rate was higher in preterm LBW, highlighting the importance of anticipatory guidance for parents at home, particularly those with a LBW infant, and early clinical suspicion on the part of practitioners. The survey also showed epidemiological features of neonatal

septicaemia that may have direct future preventive measures. But due to small sample size the study identified the need for continuing evaluation at different levels of local patterns and antibiotic sensitivities of pathogens of neonatal septicaemia to formulate rational antibiotic policy. There also is a need for community-based case-control studies with larger sample sizes to identify risk factors and preventive measures for neonatal septicaemia.

Conclusion:

The present survey confirms that neonatal septicaemia is a major problem in perinatology and paediatric infectious disease with high case fatality. To identify risk factors for adverse outcome and preventive measures, case-control studies with representative sample size is recommended. High incidence of antibiotic resistance amongst the various organisms again emphasizes the importance of judicious antibiotic use.

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