

A Study of the Clinico-Bacteriological Profile of Infants Aged 29-59 Days Suffering from Very Severe Disease According to WHO IMCI Guideline

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ABSTRACT

INTRODUCTION: According to the IMCI guidelines young infants below 2 months are considered a special group because these infants have special characteristics, that they can become sick and die very quickly from serious bacterial infections. This descriptive cross-sectional study was carried out to assess clinical characteristics of very severe disease according to WHO IMCI guideline among young infants of 29-59 days age and to determine whether clinically severe infections are associated with culture-positive bacteremia as well as to find out common etiological factors including organisms involved. The rationale behind conducting such research was that, although young infants of 29-59 days were equally vulnerable to severe infections as are the neonates; similar research addressing the condition in the young infants of the mentioned age is generally lacking. **METHODS AND MATERIALS:** This was a descriptive cross-sectional study conducted in the Department of Pediatrics, Chittagong Medical College Hospital, from March 2016 to September 2016. Young infants aged between 29-59 days presenting with signs of very severe disease were enrolled. Exclusion criteria were young infants with a congenital anomaly and very sick infants. **RESULTS:** In this study, it was observed that the majority (43.8%) of patients belonged to age 31-40 days and the mean age was 42.2 ± 7.4 days, ranged from 30 to 57 days. Regarding the sign of severe infection, the majority (97.7%) of patients had a fever, followed by 81.6% fast breathing, 65.5% history of unable to feed, 29.9% convulsion, 27.6% movement when stimulated, 18.4% grunting, and 2.3% had low body temperature. Eleven patients were found in blood culture positive. *Klebsiella spp.* was the most prevalent pathogens, comprising 6(54.5%) of the isolates, followed by coliform 2(18.2%), *staphylococcus aureus* 2(18.2%), and coagulase -ve staphylococcus was 1 (9.1%). **CONCLUSION:** Fever, fast breathing, and unable to feed were more common signs of very severe disease in the patients and positive blood culture was found in 12.6% of the cases. *Klebsiella* was found to be the commonest pathogen.

KEYWORDS: antimicrobial susceptibility, mortality, young infant sepsis.

INTRODUCTION

Neonatal period is defined by the age of infants at 0 days to 28 days. It is the time when the infants are particularly vulnerable to serious infections.^{1,2,10} First week of life has the highest vulnerability to acquire serious infections

which are called “early-onset neonatal sepsis”, with very high mortality.^{7,14} As for the neonates, the infants at the second month are also at a higher risk of mortality from infections than at later ages.^{2,20} It has been suggested that immunologically naive neonates and young infants are particularly susceptible to bacterial infections because the immune system requires the first two to three months of infantile life to steadily mature up.^{9,11,12,20} The Integrated Management of Childhood Illness (IMCI), formulated by WHO since 1992 has divided the under 5 children into two separate groups for the management of childhood illnesses, that is

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children aged 2 months up to 5 years and that of young infants below 2 months of age.¹⁸ According to this guideline, this stratification is because of the very idea that the young infants below 2 months have the same special characteristics, that they can become sick and die very quickly from serious bacterial infections.¹⁹ It is necessary to develop research priorities to understand the critical aspects of the clinico-bacteriological presentations of “very severe disease” in this age group, for the prevention of similar infections in the future.

Neonates are vulnerable to serious infections as are infants of 29-59 days of age. Considering the fact, an ample amount of research has been done on neonatal infections both in the developed as well as in the developing countries. But little or no such research has been found on serious infections in infants of 29-59 days of age. Furthermore, such studies on “very severe disease” according to IMCI guidelines in infants of 29-59 days are ever more deficient in Bangladesh. This study was conducted to understand the clinico-bacteriological profile of “very severe disease” according to IMCI guidelines in the vulnerable age group of 29-59 days, in Bangladeshi patients.

METHODS AND MATERIALS

This was a descriptive cross-sectional study conducted in the Department of Pediatrics, Chittagong Medical College Hospital (CMCH), from March 2016 to September 2016. Informed written consent was obtained from a parent or legal guardian of each patient who enrolled in the study. Young infants aged between 29-59 days presenting with signs of very severe disease defined as having either “convulsion, not feeding well/ unable to feed, grunting, fast breathing, fever > 99.5°F (37.22°C) or feels hot, low body temperature <95°F (35°C) or feels cold, movement when stimulated or no movement at all” were enrolled consecutively as the study population. Exclusion criteria were young infants with a congenital anomaly and very sick infants. According to the present inclusion and exclusion criteria, this study included 87 infants. History and clinical examination findings were noted in a case record form. Blood was collected with all aseptic precautions for doing blood culture. Blood culture was done in chocolate, blood, and McConkey agar media by lysis direct plating method under strict quality control. The

results of blood culture were included in the appropriate sections of the case record form.

DATA ANALYSIS

Statistical analyses were carried out by using the Statistical Package for Social Sciences version 20.0 for Windows (SPSS Inc., Chicago, Illinois, USA). The mean values were calculated for continuous variables. The quantitative observations were indicated by frequencies and percentages. Chi-Square test with Yates correction was used to analyze the categorical variables, shown with cross-tabulation. Student t-test was used for continuous variables. A p-value of <0.05 was considered statistically significant.

ETHICAL IMPLICATIONS

Informed written consent was obtained from each parent before enrolment into the study. Ethical clearance for the study was taken from the Ethical Committee of Chittagong Medical College.

RESULTS

Distribution of the study population by demographic variables

It was observed that the majority (43.8%) of patients belonged to age 31-40 days. The mean age of the study population was found to be 42.2 ± 7.4 days with a range from 30 to 57 days. 55.2% of patients were male and 39 (44.8%) were female. 79.3% of the mothers were housewives and 18 (20.7%) were service holders. 82.8% of the patients were rural and 15 (17.2%) were from the urban area. The majority (80.5%) of the patients were delivered at home and 17 (19.5%) had had institutional delivery. 96% of the study population received appropriate umbilical care.

Signs of very severe disease according to IMCI guideline in the study population

The majority (97.7%) of the patients had a fever, 71 (81.6%) had fast breathing, 57 (65.5%) had unable to feed, 26 (29.9%) had a convulsion, 24 (27.6%) had

movement when stimulated, 16 (18.4%) had grunting and 2 (2.3%) had low body temperature. majority (97.7%) patients had a fever, 71 (81.6%) had fast breathing, 57 (65.5%) had unable to feed, 26 (29.9%) had a convulsion, 24 (27.6%) had movement when stimulated, 16 (18.4%) had grunting and 2 (2.3%) had low body temperature (Please refer Table I).

Table I : Signs of austere disease in the study population (n=87)

Sign of Severe Infection	Number of patients	Percentage
Fever	85	97.7
Fast breathing	71	81.6
Unable to feed	57	65.5
Convulsion	26	29.9
Movement when stimulated	24	27.6
Grunting	16	18.4
Low body temperature	2	2.3

Distribution of the study patients by blood culture

11 (12.6%) patients had positive blood culture and 76 (87.4%) were negative for blood culture (Please refer Table II).

Table II: Distribution of the study patients by blood culture (n=87)

Blood culture	Number of patients	Percentage
Positive	11	12.6
Negative	76	87.4

Organisms found in culture-positive cases

Eleven patients were found in blood culture positive. Among them 6 (54.5%) were *Klebsiella spp.*, 2 (18.2%) were Coliform, 2 (18.2%) were *Staphylococcus aureus* and 1 (9.1%) was coagulase -ve staphylococcus (Please refer Table III).

Antibiotic sensitivity status

Highest sensitivity was with Ciprofloxacin and Amikacin in 8 (72.2%) cases, followed by Cotrimoxazole which was sensitive in 7 (63.6%) patients. Gentamycin was found sensitive in 4 (36.3%) cases. Cefixime had the highest resistance (100%), followed by Amoxicillin-

Clavulanic acid 8(72.7%), Azithromycin 7(63.6%), and Ceftriaxone 6(54.5%) (Please refer Table IV).

Table III: Organisms found in culture-positive cases (n=11)

Culture result	Number of patients	Percentage
<i>Klebsiella</i>	6	54.5
<i>Coliform</i>	2	18.2
<i>Staphylococcus aureus</i>	2	18.2
Coagulase -ve staphylococcus	1	9.1

Association between blood culture with demographic variable

A majority (45.5%) of the patients belonged to age 41-50 days in the blood culture-positive cases. The mean age was found to be 39.1 ± 7.2 days in positive blood culture and 42.5 ± 7.5 days in negative groups, respectively. Almost two-thirds (63.6%) of the patients were female in the positive blood culture group and one-third (42.1%) in the negative group. Almost two-thirds of the mothers were housewives in both blood culture positive and negative cases. Blood culture positive cases were all (100.0%) from the rural area, wherein the negative group, this was in 80.3% cases. Most of the patients were delivered at home in both positive (81.8%) and negative 61(80.3%) cases. Overall, the variables the differences were not statistically significant among blood culture positive and negative cases. (Table V)

Correlation between blood culture positivity with the sign of very severe disease

Convulsion was found in three of the eleven (27.3%) culture-positive cases and 23 (30.3%) of the negative patients. Eight (72.7%) patients had unable to feed in positive blood culture cases and 49 (64.5%) in negative cases. Two (18.2%) patients had grunting in positive blood culture and 14 (18.4%) in the negative group. Seventy-one (93.4%) patients had fast breathing in negative blood culture and not found in positive blood culture. All (100.0%) patients had a fever in positive blood culture and 74 (97.4%) in the negative cases. Two (2.6%) patients had low body temperature in negative blood culture and were not found in the positive blood culture group. Two (18.2%) patients had movement when stimulated in positive blood culture and 22

Table IV: Distribution of the study patients by antibiotic sensitivity status (n=11)

Antibiotic	Sensitive (n=11)		Intermediate sensitive (n=11)		Resistant (n=11)	
	n	%	n	%	N	%
Amoxicillin + Clavulanic Acid	0	0	3	27.2	8	72.72
Amikacin	8	72.72	0	0	3	27.2
Azithromycin	3	27.2	0	0	7	63.6
Cefixime	0	0	0	0	11	100
Ceftazidime	1	9.09	0	0	5	45.4
Ceftriaxone	0	0	0	0	6	54.5
Cefuroxime	0	0	0	0	1	9.09
Co-Trimoxazole	7	63.6	0	0	2	18.1
Ciprofloxacin	8	72.7	3	27.2	0	0
Gentamycin	3	27.2	4	36.3	2	18.1
Imipenem	3	27.2	1	9.1	1	9.1
Levofloxacin	2	18.1	0	0	2	18.1
Lomefloxacin	2	18.2	0	0	2	18.1
Meropenem	1	9.1	0	0	1	9.1
Netilmicin	1	9.1	0	0	0	0
Piperacillin Tazobactam	3	27.2	0	0	1	9.1
Vancomycin	0	0	0	0	2	18.1

(28.9%) in negative blood culture cases. Signs of very severe disease were not statistically significant concerning blood culture yield (Please refer Table VI).

DISCUSSION

This descriptive cross-sectional study was carried out to assess clinical characteristics of very severe disease according to WHO IMCI guideline among young infants of 29-59 days age and to determine whether clinically severe infections are associated with culture-positive bacteremia, and to find out common etiological factors including organisms involved.

A total of 87 infants of 29-59 days presenting with the features of very severe disease (according to the IMCI guideline), admitted in the pediatrics department of Chittagong Medical College were enrolled in the study. Infants with a congenital anomaly and those who were very sick were excluded from the study. The present study findings were discussed and compared with previously published relevant studies.

In this study, it was observed that the majority (43.8%) of the patients belonged to age 31-40 days and the mean age was 42.2 ± 7.4 days, ranging from 30 to 57 days. No

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study was found to compare the situation, for the inadequacy of research done on the target population. In a study done in Bangladesh, Darmstadt et al. took infants aged 1 week to 2 months presenting at the outpatient or emergency department of a tertiary care hospital with very severe disease, and the mean age of young infants was 32 days (range, 7-59 days); 72% were male.³

In this current study, it was observed that the majority (55.2%) of patients were male and 44.8% were female. Kalter et al.⁸ also found most (72%) of their study population to be male. Similarly, Darmstadt et al.³ found 42.0% of their <60 days study patients to be female.

In this series, it was observed that the majority (79.3%) of the mothers were housewives and 82.8% came from the rural area. 80.5% of the study infants were home delivered. Almost all (96.6%) of the patients in our study were found to have received appropriate care of the umbilicus.

The WHO young infants clinical signs study group has identified in their large multicenter study (n = 8889) that, the seven signs of very severe disease have 74% sensitivity and 79% specificity in clinically predicting

Table V: Association between blood culture with demographic variable (n=87)

Demographic variable	Blood culture				p value
	Positive (n=11)		Negative (n=76)		
	n	%	n	%	
Age (in days)					
29-38	4	36.4	25	32.9	
39-48	6	54.5	36	47.4	
49-58	1	9.1	15	19.7	
Mean ± SD	39.1±7.2		42.5±7.5		*0.162 ^{ns}
Range (min, max)	30, 54		30, 57		
Gender					
Male	4	36.4	44	57.9	^b 0.155 ^{ns}
Female	7	63.6	32	42.1	
Mother's occupation					
Housewife	7	63.6	62	81.6	^b 0.163 ^{ns}
Service holder	4	36.4	14	18.4	
Residence					
Urban	0	0.0	15	19.7	^b 0.108 ^{ns}
Rural	11	100.0	61	80.3	
Place of delivery					
Home	9	81.8	61	80.3	^b 0.634 ^{ns}
Institutional	2	18.2	15	19.7	

sepsis in neonates and young infants.¹⁶ Signs of severe Infection as found in our study was that the majority (97.7%) of the patients had a fever, followed by fast breathing (81.6%), history of unable to feed (65.5%), convulsion (29.9%), movement when stimulated (27.6%), as well as 18.4% had grunting and only 2.3% had low body temperature. In the review by Opiyo & English, that reviewed five large prospective observational studies (n = 17,506 infants) and it was shown that fever, fast breathing, and history of unable to feed were the commonest signs of very severe disease among 0-59 days infants and had the highest predictive value in diagnosing very severe disease or severe infection in these children.¹¹ English et al. had a similar finding in their study.⁶ The above findings are consistent with the present study.

In this study, it was observed that blood culture was positive in 12.6% of cases. It was shown by Downie et al.⁴ in their meta-analysis that, when it was reported, the range of prevalence of bacteremia in infants for whom a blood culture was performed was 3-16%. In the large six countries multi-center study by Hamer et al. 10.9% of infants 7-59 days of age infants had blood culture positivity. Similarly, Talbert et al.¹³ found in the out-born young infants, 10.0% had a positive blood culture, which is consistent with the present study.

Eleven patients were found in blood culture positive. Among them, *Klebsiella* was the most prevalent pathogen, comprising 6 (54.5%) of the isolates, followed by coliform 2 (18.2%), *Staphylococcus Aureus* 2(18.2%), and coagulase -ve staphylococcus was 1(9.1%). In the meta-analysis by Downie et al.⁴ among infants of 29-90 days, the most prevalent pathogens were *S aureus*, *E Coli*, *Klebsiella spp.*, *Salmonella spp.* and *Streptococcus Pneumoniae*, accounting for 59% (26–92%) of positive sepsis cases. Another study from a resource-poor country also demonstrated *Klebsiella sp.* to be the most common pathogen in severe young infant sepsis as in our study.²⁰

Among the 11 patients with whom the blood culture was positive, the most sensitive drugs were Ciprofloxacin and Amikacin (72.2%), followed by Cotrimoxazole (63.6%). Cefixime was found resistant in all (100%) cases. Other resistant drugs were Amoxicillin -Clavulanic acid 8 (72.7%), Azithromycin 7 (63.6%), and Ceftriaxone 6 (54.5%).

In this series, it was observed that the majority (45.5%) patients belonged to age 41-50 days in positive blood culture and 23 (30.3%) in negative blood culture. The mean age was found 39.1 ± 7.2 days in blood culture-positive cases and 42.5 ± 7.5 days in blood culture-negative cases. Almost two-thirds (63.6%) patients were

Table VI: Correlations between blood culture positivity with signs of austere disease (n=87)

Sign of severe infection	Blood culture				p value
	Positive (n=11)		Negative (n=76)		
	n	%	n	%	
Convulsion					
Yes	3	27.3	23	30.3	0.573 ^{ns}
No	8	72.7	53	69.7	
Unable to feed					
Yes	8	72.7	49	64.5	0.432 ^{ns}
No	3	27.3	27	35.5	
Grunting					
Yes	2	18.2	14	18.4	0.674 ^{ns}
No	9	81.8	62	81.6	
Fast breathing					
Yes	0	0.0	71	93.4	0.001 ^s
No	11	100.0	5	6.6	
Fever					
Yes	11	100.0	74	97.4	0.762 ^{ns}
No	0	0.0	2	2.6	
Low body temperature					
Yes	0	0.0	2	2.6	0.762 ^{ns}
No	11	100.0	74	97.4	
Movement when stimulated					
Yes	2	18.2	22	28.9	0.365 ^{ns}
No	9	81.8	54	71.1	

female in positive blood culture and 32 (42.1%) in negative blood culture cases. The majority (63.6%) of the mother were housewives in positive blood culture and 62 (81.6%) in negative blood culture. All (100.0%) patients were from the rural area in positive blood culture and 61 (80.3%) in negative blood culture. Most (81.8%) patients were delivered at home in positive blood culture cases and 61 (80.3%) in negative cases. No statistically significant association was found for any of the demographic variables between the blood culture positive and negative cases. Culture positivity rates varied significantly, with reported rates as high as 65.0% obtained by Tallur et al.¹⁴ and as low as 5.0% reported by Hamer et al.⁷

In this series it was found that in blood culture-positive cases, all (100%) had a fever, 72.7% had a history of unable to feed, 27.3% had convulsions and 18.2% had movement only when stimulated, whereas in blood culture-negative cases fever was also present in almost all (97.4%) of the cases, history of unable to feed was present in 64.5%, fast breathing in 93.4%, grunting in 18.4% and 2.6% had low body temperature. No statistically significant association was found between blood culture positivity and the presence of one or the other sign of austere diseases in the patients. There was no study found that evaluated the association of

presence or absence of any of the signs of very severe disease with that of the blood culture yield.

CONCLUSION

Very severe disease according to the WHO IMCI guideline is rather a clinical diagnosis because the diagnostic yield of blood culture positivity is very low in these patients. The study has shown this very result. Fever, fast breathing, unable to feed were found to be the predictors of very severe disease in this age group. The patients with positive blood culture had *Klebsiella spp.* as the commonest bacteria causing the illness, and the antibiotic sensitivity pattern has been changing over the years. To establish a bacteriological diagnosis and show the antibiotic sensitivity pattern a PCR or molecular-based study could be undertaken in the future.

LIMITATIONS OF THE STUDY

The main limitations of the study were that the study population was relatively smaller and was done over a shorter period. The patient population may not also be fully representative of the country, as they were selected from a selected hospital in Chittagong city.

RECOMMENDATION

Further studies are needed to be done by including a larger number of patients.

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