Food and Nutrition Sciences, **2013, 4, 709-714**
http://dx.doi.org/10.4236/fns.2013.47090 Published Online July 2013 (http://www.scirp.org/journal/fns)

Predictors of Death in Under-Five Children with Sepsis Attending an Urban Diarrheal Treatment Centre in Bangladesh

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Received May 10th, 2013; revised June 10th, 2013; accepted June 18th, 2013

ABSTRACT

SETTING: Special Care Ward (SCW) of the Dhaka Hospital of icddr,b, Bangladesh. **OBJECTIVE**: To evaluate the clinical and laboratory predictors of death in under-five children with clinically defined sepsis presenting with diarrhea. **METHODS:** We prospectively enrolled all the diarrheal children (n = 151) aged 0 to 59 months with clinical sepsis admitted in the SCW during September'2007 through December'2007. Comparison was made between deaths (n = 23) and survivors (n = 128). Sepsis is defined as presence of inflammation [abnormal WBC count (>11 × 10^9/L or, <4 × 10^9/L or, band and neutrophil ratio ≤0.10] plus presence or presumed presence of infection with thermo-instability [hypo (≤35.0˚C) or hyperthermia (≥38.5˚C)], tachycardia, tachypnea, and/or the indications of altered organ function (altered mental status and bounding pulse) in the absence of clinical dehydration or after correction of dehydration. **RESULTS:** The median (inter-quartile range) age (months) of the children who survived and died was comparable [4.0 (2.0, 12.0) vs. 1.5 (0.8, 10.0); p = 0.703]. In the logistic regression analysis, after adjusting for potential confounders, such as abnormal WBC count, use of intravenous fluid, patient with fatal outcome more often presented with hypernatremia (odds ratio = 16.48, 95% confidence interval = 2.21 - 123.12; p = 0.006), lobar consolidation (odds ratio = 19.9, 95% confidence interval = 2.99 - 132.80; p = 0.002), hypoxemia (odds ratio = 14.78, 95% confidence interval = 1.38 - 157.90; p = 0.026) and severe under-nutrition (odds ratio = 7.57, 95% confidence interval = 1.24 - 46.11; p = 0.028). **CONCLUSIONS:** Our data suggest that children under-five with clinical sepsis who present with lobar pneumonia, hypoxaemia, severe acute malnutrition and hyperntaemia are at higher risk of death and identification of these simple factors may help clinicians to take prompt initiative for the aggressive management of such children especially in a resource-limited setting like Bangladesh.

Keywords: Bangladesh; Diarrhea; Hypoxemia; Sepsis; Severe Malnutrition

1. Introduction

Sepsis is one of the most important causes of death in under-five children in developing countries [1,2]. The largest part of the global sepsis burden occurs in middle- and low-income countries. Around 70% of the 7.6 million global deaths in neonates and infants are attributable to sepsis, with the majority of cases occurring in Asia and sub-Saharan Africa [3]. There are between 77 to 240 new cases of sepsis per 100,000 population each year [4,5] and the incidence may continue to increase by approximately 1.5% in every year, resulting in an additional 1 million cases per year by 2020 [4,6,7]. As sepsis is the final common pathway in most of the pediatric diseases and presence of sepsis in children with diarrhea is often associated with high case-fatality [8], sepsis may be considered the number one killer of children worldwide [9]. Thus, clinicians as well as health workers in resource limited settings should have understanding on simple associated factors that may predict fatal outcome

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in diarrheal children with sepsis. However, data are very limited on the predicting factors of death in such population.

In the Dhaka Hospital of icddr,b, a number of children used to be admitted on a daily basis with diarrheal diseases along with other co-morbidities such as severe acute malnutrition, severe and very severe pneumonia, with the consequence of sepsis, and often with fatal outcome. The aim of our study was to identify the factors that predict deaths in under-five children with sepsis admitted to urban diarrheal treatment centre.

2. Materials and Methods

2.1. Patient Enrollment

All the diarrheal children of either sex, aged 0 - 59 months, with clinical sepsis who required admission and care to the Special Care Ward (SCW) of the Dhaka Hospital of icddr,b from September, 2007 to December, 2007 were enrolled in this study. The hospital provides care and treatment to around 110,000 patients of all ages each year. The majority of the patients is residents of Dhaka city or its suburbs and come from poor socio-economic backgrounds. Nearly all patients attend the hospital with diarrheal diseases, whether associated with complications or other associated health problems. On arrival to the hospital triage, nurses obtain the medical history and perform a rapid assessment of the patients, focusing on the nature and severity of diarrhea, including the magnitude of dehydration and any complications. Features of any other health problems are also sought at presentation. Following triage, patients are also examined and assess by the attending physician for consultation or admission for an appropriate ward of the hospital. Patients with severe illnesses, including those with altered mental status, convulsions, severe or very severe pneumonia, hypoxemia, cyanosis and suspected sepsis, are admitted directly to the SCW. On admission at SCW the attending physician again perform a thorough assessment of the patients, organize any investigation necessary and determine the management plan including drug and other supportive therapies. Our study patients were admitted to SCW having diarrhea and sepsis with or without other associated problems such as electrolytes imbalance, severe acute malnutrition, features of severe/very severe pneumonia and hypoxemia.

2.2. Study Design

In this prospective cohort study, comparison of the clinical and laboratory features of under-five diarrheal children with sepsis was made who had and who did not have fatal outcome. Consent was obtained from respective parents or the attending family members before children were enrolled in the study and relevant clinical information were collected. Clinical management of all children for the sepsis was done according to the standard management guidelines of the hospital based on the surviving sepsis guideline [10]. These include management by restoration of circulation, respiration, maintenance of temperature and blood glucose level, appropriate antimicrobial therapy to cover the possible causative organism, appropriate feeding; and provision of micronutrients, viatamins and minerals as required. The hospital follows the protocolized guidelines for the management of children with severe protein-energy malnutrition [11,12].

2.3. Recognizing the Septic Patient

2.3.1. Definition

Sepsis

Sepsis is defined as presence of inflammation [abnormal WBC count (>11 × 10^9/L or, <4 × 10^9/L or, band and neutrophil ratio ≤0.10) plus presence or presumed presence of infection with thermo-instability [hypothermia (≤ 35.0˚C) or hyperthermia (≥38.5˚C)], tachycardia, tachypnea, and/or the indications of altered organ function (altered mental status and bounding pulse) in the absence of clinical dehydration or after correction of dehydration [1].

2.3.2. Statistical Methods

We used pretested case report forms (CRF) for data acquisition. All CRFs were manually verified for completeness and errors, edited where necessary, and then data entered onto a personal computer (PC). Data were entered and analyzed using SPSS for Windows (version 17.0; SPSS Inc, Chicago, IL, USA) and Epi Info (version 6.0; USD, Stone Mountain, GA, USA). The differences in proportions were compared by the chi-square test and differences of means by Student's t-test or Mann-Whitney test, as appropriate. A probability of <0.05 was considered statistically significant.

Strength of association was determined by estimating the odds ratio (OR) and the 95% confidence intervals (CI). Univariate analysis and logistic regression were both performed in identifying risk factors. The analyses of socio-demographic data included age, sex, gestational age, residence (in Dhaka or not), maternal and paternal education, mothers' occupation, breastfeeding status, not use high-potency vitamin A capsule within 6 months prior to admission, and use of antibiotics before admission. The analyses of clinical data included presence or absence of dehydration, cyanosis, hypoxemia, fever, hypothermia, severe malnutrition and requirement of IV fluid after admission. The laboratory data analyses included total peripheral white blood cell (WBC) count, presence of immature neutrophils in blood such as band,

serum electrolytes, blood glucose, radiological pneumonia. Initially, univariate analyses of these factors were performed to evaluate their association with fatal outcome, and then logistic regression analysis was performed to identify the independent predictors of death where death was the dependent variable and the factors that were significantly associated with deaths in the univariate analysis acted as independent variables.

3. Results

Among the 151 under-five diarrheal children with sepsis admitted to the SCW of the Dhaka hospital of icddr,b 23 (15%) had fatal outcome. In univariate analyses, children who died more often had hypoxemia, severe under-nutrition, higher total leucocyte count, and lobar consolidation compared to those who survived (**Tables 1** and **2**). Proportionately higher children with fatal outcome presented with edematous malnutrition and immature poly on admission compared to those who survived, but it was not statistically significant (**Tables 1** and **2)**. In logistic regression analysis, after adjusting for potential confounders such as use of I/V fluid after admission and total WBC count, severe under nutrition, hypoxemia, lobar consolidation and hypernatremia were remained as independent predictors of death in sepsis (**Table 3**). Other parameters in **Tables 1** and **2** were comparable among the groups.

Table 1. Clinical characteristics of the under-five children with clinical sepsis who died (cases) and survived (controls).

Variables	Deaths (n = 23)	Survivors (n = 128)	OR	95% CI	p
Male gender	13 (57)	75 (59)	0.92	0.34 - 2.46	0.865
Age in months (Median, IQR)	1.5 (0.8, 10.0)	4.0 (2.0, 12.0)	-	-	0.703
Gestational age (weeks) (mean ± standard deviation)	38.0 ± 2.9	38.0 ± 3.7	-	-	0.974
Not use of capsule vitamin-A within last 6 months	11 (50)	72 (56)	0.78	0.29 - 2.10	0.755
History of measles within last 6 months	2 (9)	20 (16)	0.52	0.08 - 2.59	0.530
Use of antibiotic before admission	13 (59)	52 (43)	1.92	0.70 - 5.32	0.245
Clinical dehydration (some/severe)	15 (65)	68 (53)	1.65	0.60 - 4.62	0.398
Cyanosis	4 (17)	14 (11)	1.71	0.42 - 6.4	0.481
Fever (≥38˚C)	19 (83)	111 (87)	0.73	0.20 - 2.88	0.530
Hypothermia on or after admission (Temp ≤ 35˚C)	2 (9)	5 (4)	2.34	0.29 - 15.08	0.289
Hypoxaemia (SpO_2 < 90%)	19 (83)	52 (41)	6.94	2.06 - 25.73	<0.001
Oedematous malnutrition	5 (22)	10 (8)	3.28	0.86 - 12.16	0.055
HAZ (< −3 z score)	10 (44)	38 (30)	1.82	0.67 - 4.93	0.287
WAZ (< −3 z score)	16 (70)	48 (38)	3.81	1.35 - 11.10	0.008
WHZ (< −3 z score)	6 (26)	35 (27)	0.94	0.30 - 2.80	0.897
User of IV fluid	17 (74)	75 (59)	2.00	0.68 - 6.13	0.248

Figures represent n (%), unless specified. OR: odds ratio; CI: confidence interval; IQR: inter-quartile range; HAZ: height for age z score; WAZ: weight for age z score; WHZ: weight for height z score; SpO_2 = transcutaneously measured blood oxygen concentration.

Table 2. Laboratory characteristics of the under-five children with clinical sepsis who died (cases) and survived (controls).

Variables	Cases (n = 23)	Controls (n = 128)	p
Total WBC count (number/cu. mm) (Median, IQR)	11,000 (8900, 25,350)	14,500 (9300, 20,000)	0.046
Immature Poly (number/cu. mm) (Median, IQR)	00 (00, 1.00)	00 (00, 00)	0.087
Hyponatraemia (mmol/L)	5 (22)	33 (26)	0.880 0.80 (0.24 - 2.54)*
Hypernatraemia (mmol/L)	5 (22)	11 (9)	0.072 2.95 (0.78 - 10.74)*
Hypokalaemia (mmol/L)	8 (35)	34 (27)	0.577 1.47 (0.52 - 4.13)*
Hyperkalaemia (mmol/L)	3 (13)	9 (7)	0.395 1.98 (0.39 - 9.05)*
Lobar consolidation	9 (56)	6 (7)	<0.001 16.93 (3.99 - 76.96)*
Hypoglycemia (RBS < 3 mmol/L)	3 (13)	17 (14)	1.00 0.96 (0.20 - 3.96)*
Growth on blood culture	1/15 (7)	12/111 (11)	1.00 0.57 (0.03 - 4.86)*

Figures represent n (%), unless specified. IQR: interquartile range; *OR (95% CI); RBS: Random blood sugar.

Table 3. Results of logistic regression to explore the independent predictors of death in under-five children with sepsis.

Characteristics	OR	95% CI	p
Severe under nutrition	7.57	1.24 - 46.11	0.028
Hypoxemia	14.78	1.38 - 157.90	0.026
Lobar consolidation	19.9	2.99 - 132.80	0.002
Hypernatraemia	16.48	2.21 - 123.12	0.006
Total WBC count	1.00	1.00 - 1.00	0.156
User of IV fluid after admission	0.54	0.09 - 3.08	0.484

4. Discussion

Our finding of the association of severe malnutrition, lobar pneumonia and hypoxemia as predictors of death in SCW is similar to earlier reports [13,14]. Severely malnourished children have depressed cell mediated as well as humoral immune responses, and they are more susceptible to infection often with serious ramification such as fatal outcome [15].

We observed that lobar consolidation in septic children was one of the predictors of death. Lobar consolidation is usually associated with bacterial pneumonia which is often associated with fatal outcome especially in children under five in developing countries like Bangladesh [13], mostly due to overwhelming hypoxemia resulting from ventilation perfusion mismatch from para-pneumonic shunting. [14,16,17]. Sepsis may be the consequences of lobar pneumonia, as observed in our cases, frequently associated with high case-fatality rate [14].

Our observation of hypernatraemia as a predictor of death is also understandable. Hypernatraemic dehydration is usually associated with high case fatality either because of intracranial hemorrhage resulting from intracellular dehydration or because of cerebral oedema as a result of aggressive correction [18]. The observation of high case fatality in children with hypernatraemia has been reported earlier from Bangladesh [19]. The management of hypernatremic dehydration in diarrheal children remains a challenge, and more works need to be carried out into the treatment of this condition.

We observed that a higher proportion of children with fatal outcome had a leucocytosis and immature neutrophils. Increased number of immature neutrophils in the peripheral blood smears of children is an expression of severe illness common in bacterial sepsis [1]. An earlier study from Bangladesh reported that children with leukocytosis and immature neutrophils in their peripheral blood are more likely to be bacteremic and to have a higher risk of death [1]. Thus, the presence of immature neutrophils in peripheral blood in diarrheal children should alert clinicians to look for sepsis in order to reduce morbidity and deaths in such population.

The number of children with fatal outcome in our study was much smaller compared with the control children. This might have reduced the power to identify factors that could actually have an independent association with fatal outcome. Further studies using adequate number of cases could provide better insight.

In conclusion, our data suggest that under-five diarrheal children with clinical sepsis admitted to a special care ward of a resource-limited setting in a developing country, who present with severe malnutrition, hypernatraemia, lobar pneumonia and hypoxaemia are more likely to have a fatal outcome. Thus, efforts should be taken to specifically look for the presence of these features in all hospitalized diarrheal children with clinical sepsis to identify those with higher risk of death for the institution of energetic and efficient antimicrobial and other supportive therapy with the prospect of achieving a better outcome.

5. Acknowledgements

We gratefully acknowledge the donors for their support and commitment to icddr,b's research efforts which currently provide unrestricted support to the centre's research efforts: Government of the People's Republic of Bangladesh, Canadian International Development Agency (CIDA), Embassy of the Kingdom of the Netherlands (EKN), Swedish International Development Cooperation Agency (Sida) and the Department for International Development, UK (DFID). We offer our sincere gratitude to all physicians including clinical fellows, nurses, members of the feeding team and cleaners of SCW for their invaluable contribution during patient enrollment and data collection.

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Elaboration of Abbreviations:

CI: Confidence interval
CIDA: Canadian International Development Agency
CRF: Case report form
EKN: Embassy of the Kingdom of the Netherlands
HAZ: Height for age z score
IQR: Inter-quartile range
IV: Intra-venous
mmol/L: Milimol/Liter
OR: Odds ratio
RBS: Random blood sugar
SCW: Special care ward
Sida: Swedish International Development Cooperation Agency
SpO_2: Transcutaneously measured blood oxygen concentration
DFID: Department for International Development
WAZ: Weight for age z score
WBC: White blood count
WHZ: Weight for height/length z score

