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Original Article

Progression of severe sepsis to septic shock in under-five diarrheal children in an urban critical care ward in Bangladesh: Identifiable risks, blood isolates and outcome

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Abstract:

Background: *Both severe sepsis and septic shock are the terminal events of all infectious diseases including diarrhea and often associated with fatal outcome. However, death is highest in septic shock even in high resource centre in developed countries. Thus, identification of factors associated with septic shock from severe sepsis is critically important. Nevertheless, data are scarce on the clinical predictors of septic shock in under-five children presenting with severe sepsis especially in resource poor settings. We evaluated the factors associated with septic shock and their outcome in such population.*

Methods: *This study involved the analysis of retrospective data in diarrheal children which had been extracted from the hospital management system (SHEBA), an online data base of the Dhaka Hospital of icddr,b. All under-five diarrheal children, admitted to the Dhaka Hospital of the International Canter for Diarrhoeal Diseases Research, Bangladesh (icddr,b) having severe sepsis between October`2010 and September`2011 were studied. Severe sepsis defined as tachycardia plus hypo (≤35.0° C) or hyperthermia (≥38.5° C), or abnormal WBC count plus presence of infection with poor peripheral perfusion (age specific hypotension and/or absent peripheral pulses or delayed capillary refilling time (CRT) in absence of dehydration. Patient unresponsive to fluid (normal saline/cholera saline) boluses (20 ml/kg; maximum 60 ml/kg and 40 ml/kg in well nourished and malnourished children respectively) and required inotrop(s) categorized as septic shock. Children with (cases=88) and without septic shock (controls=116) wee compared.*

Results: *Median (inter-quartile range) age (months) was comparable among the cases and the controls [5.3 (3.2, 12.0) vs. 5.6 (2.7, 10.0); p = 0.515). Case-fatality-rate was significantly higher among the cases than the controls (67% vs. 14%; p<0.001). In logistic regression analysis after adjusting for potential confounders such as severe under-weight, nutritional edema, respiratory difficulty and pneumonia, cases more frequently had drowsiness on admission (OR = 4.2, 95% CI = 1.3-14.2, p = 0.017), received blood transfusion (OR = 5.8, 95% CI = 2.7-12.2, p <0.001), and required mechanical ventilation (OR = 13.7, 95% CI = 4.8-39.5, p <0.001). Bacterial isolates were equally distributed among the groups but more than three-fourths were gram negatives.*

Conclusion: *The results of our data suggest that darrheal children under five years of age with severe sepsis presenting with drowsiness on admission are vulnerable to develop septic shock and may often require blood transfusion and mechanical ventilation. Thus, clinicians may consider inotrop(s) in such children presenting with the co-morbidity of severe sepsis and drowsiness which may help to prevent mechanical ventilation and death.*

Key Words: *Bangladesh; children; diarrhea; severe sepsis; septic shock*

Introduction:

Progression of severe sepsis to septic shock is one of the major health care problems, not only in developing countries but also in developed countries, and often associated with high number of deaths.[1-3] This event in critically ill children with infectious diseases, including diarrhoea, is the terminal event.[4-7] Developing countries face the largest global sepsis burden.[8] Almost two third of the 7.6 million worldwide deaths in

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neonates and infants are due to sepsis and the bulk of cases occurring in Asia and Sub-Saharan Africa.[9,10] Judicious recognition of septic shock with early on administration of antibiotic therapy can reduce deaths in children.[11,12] Early fluid resuscitation in children with severe sepsis prevents irreversible septic shock, and reduces deaths.[5] Identification and treatment of severe sepsis and septic shock in diarrheal children is very really captivating. In diarrheal children shock may resulting from severe dehydration as well as severe sepsis, overlapping the clinical signs. However, identification of severe sepsis in diarrheal children becomes little bit easier in absence of dehydration or after correction of dehydration.[13,14] Additionally, diarrheal children with hypovolemic shock used to respond in fluid resuscitation whereas diarrheal children with septic shock might not respond to fluid resuscitation.[15] Nevertheless, both severe dehydration and sever sepsis may present in a same patient, other clinical signs of severe sepsis in diarrheal children such as thermo-instability, delayed CRT are very important for the diagnosis of severe sepsis in this population. On the other hand, clinical signs of severe sepsis in severely malnourished children are invariably absent[16] even in sick children and aggressive fluid management may have an undesirable effect.[17]

Fluid resuscitation in severely malnourished children is always very intriguing. World Health Organization (WHO) recommends blood transfusion for the management of severely malnourished children having septic shock in order to reduce mortality[18]. Inotrope support is needed for patient not responding to fluid resuscitation and several studies have shown improvement in hemodynamic and urine output in septic shock treated with dopamine[19,20]. Intensive Care Unit of the Dhaka Hospital of the International Centre for Diarrhoeal Diseases Research, Bangladesh (icddr,b) treats a number of diarrheal children with severe sepsis and septic shock following survival sepsis guideline[3] and still encounters high burden of mortality. However, data on the risks and outcome of the progression of severe sepsis to septic shock especially in diarrheal children are lack. Our aim was to evaluate the risks and outcome of the progression of severe sepsis to septic shock in diarrheal children.

Materials & methods:

Ethical statement:

In this chart review, data were analyzed anonymously, thus, no parental or ethical consent was required.

Study design:

This study involved the analysis of retrospective data in diarrheal children which had been extracted from the hospital management system (SHEBA), an online data base of the Dhaka Hospital of icddr,b. All under-five diarrheal children, admitted to the Dhaka Hospital of the International Canter for Diarrhoeal Diseases Research, Bangladesh (icddr,b) having severe sepsis between October`2010 and September`2011 were studied. Sepsis was defined as tachycardia plus hypo (≤ 35.0° C) or hyperthermia (≥38.5° C), or abnormal WBC count plus presence or presumed presence of infection. Severe sepsis was defined as the presence of sepsis plus poor peripheral perfusion (age specific hypotension and/ or absent peripheral pulses and/or delayed capillary refilling time (CRT) in absence of dehydration. Patient unresponsive to fluid (normal saline/cholera saline) boluses [20 ml/kg (maximum 40 ml/kg for severely malnourished children over 2 hours and 60 ml/kg over 10-15 minutes for the children without severe malnutrition)], and required support of inotrop(s) categorized as septic shock. Comparison of clinical characteristics of diarrheal children who progressed from severe sepsis to septic shock (cases) was made with those without septic shock (controls).

Study site:

Dhaka Hospital of icddr,b, Dhaka, Bangladesh was the study site which provides care and treatment to around 140,000 patients of all ages and both sexes with diarrhea, with or without associated complications and with or without other health problems each year. Diarrhea is the entry point for admission to the hospital. After admission, the hospital triage nurses obtain brief medical history and make a quick assessment of the patients, focusing on the severity and complication of diarrhea and dehydration status but also look for associated health problems. Following this, patients are referred either to the emergency physician for re-assessment or are admitted to an appropriate ward of the hospital. Patients with complications of diarrhea, or those with respiratory distress, cyanosis, apnea, hypothermia, sepsis, severe sepsis, septic shock, impaired consciousness, convulsion, severe pneumonia with hypoxemia or respiratory failure are admitted to the ICU. The vast majority of the patients at icddr,b have poor socio-economic backgrounds and live in urban and peri-urban Dhaka, the capital city of Bangladesh.

Patient management:

On arrival in the ICU, attending physicians re-evaluate the patients, commence required work up and prescribe a management plan according to standard management guidelines of the hospital. Arterial oxygen saturation (SpO2) was measured using a portable pulse oximeter (OxiMaxN-600, Nellcor, Boulder, Co) and blood glucose was estimated using a Gluco-check machine (STADA, Bad Vilbel, Germany). Children with hypoxemia received oxygen supplementation through nasal prongs (2L/min) or mask (5L/min). Antibiotic therapy was provided for children with pneumonia, sepsis, severe cholera, dysentery, severe malnutrition, and other bacterial infections following standard management guideline in our hospital.[21,22] Dehydration was corrected using oral (for those with some dehydration) or intravenous fluids (for those with severe dehydration and also those who were unable to drink due to any reason); appropriate feeding, micronutrients, vitamins and minerals as and when required.[23]After correction of dehydration (defined by "Dhaka methods" of assessment of dehydration that is almost similar to WHO method and approved by WHO),[24,25] patients were assessed for features of severe sepsis, and IV fluid was administered to patient with severe sepsis according to surviving sepsis guideline.[26] Patient with septic shock received blood transfusion.[23] In resource poor setting, like Bangladesh it is difficult to arrange safe blood promptly. So, inotrope(s) were started in patients not responding to fluid without waiting for blood transfusion. However, as soon as the blood was

arranged, transfusion was given immediately. Our treatment goal was to achieve good peripheral perfusion [mean arterial pressure (MAP) >50 mm Hg, and/or urine output (U/O) >1 ml/kg/hour, and capillary refilling time (CRT) <3 sec]. Mechanical ventilation was used for management of children admitted to ICU with respiratory failure.

Measurements and data collection:

Data acquisition was done after development of case report forms (CRF) which were pretested before finalization. Characteristics analyzed include demographic (age, gender,), clinical signs [nutritional status, drowsiness, abdominal distension and convulsion at admission, respiratory rate, temperature, lower chest wall in-drawing (inward movement of the bony structures of the lower chest wall with inspiration), crackles and rhonchi in lungs (by auscultation), dehydration, systolic and diastolic blood pressure, level of haemoglobin, blood transfusion, mechanical ventilation, hospital stay, clinical diagnosis (severe sepsis, septic shock) and outcome. Data were retrospectively collected from "SHEBA", a computer based system for keeping documents of patients management. After admission at Dhaka Hospital of icddr,b, every patient got a unique identifying number. All the data including history, clinical examination findings, laboratory reports, treatments provided, dietary management, daily follow up and clinical outcome (improved, or discharged or referred to other hospital for necessary management or fatal outcome) were recorded against this number. To avoid potential error these data were also re-checked manually.

Analysis:

Data of all the study children were entered into a personal computer and edited before analysis using SPSS for Windows (version15.0; SPSS Inc, Chicago) and Epi Info (version 6.0, USD, Stone Mountain, GA). Differences in proportions were compared by the Chi-square test. In normally distributed data differences of means were compared by Student's t-test and Mann-Whitney test was used for comparison of data that were not normally distributed. A probability of less than 0.05 was considered statistically significant. Strength of association was determined by calculating odds ratio (OR) and their 95% confidence intervals (CIs). In identifying predictors associated with septic shock, variables were initially analyzed in a uni-variate model, then after adjusting with potential confounders, multiple logistic regression models were used to identify the independent predictors of the progession.

Results:

We were able to identify 88 cases and 116 controls. The progression of severe sepsis to septic shock at Dhaka Hospital of icddr,b during the study period was estimated at 43% (88/204) . The case-fatality-rate was significantly higher among the cases compared to the controls (Table 1).

Table 1. Clinical and laboratory parameters of under-five diarrheal children who progressed septic shock (cases) from severe sepsis (controls) at the ICU of Dhaka Hospital of icddr,b.

Parameters	Cases n=88 n (%)	Controls n=116 n (%)	OR (95% CI)	p value
Age (median, IQR)	5.3 (3.2, 12.0)	5.6 (2.7, 10.0)	-	0.515
Nutritional edema	15 (17%)	8 (7%)	287 (1.03 - 7.9)	0.041
Abdominal distension	13 (15)	6 (5)	3.2 (1.1 - 10.6)	0.036
Poor Intake	7 (8)	2 (2)	4.9 (0.9 - 49.4)	0.071
Respiratory difficulty	53 (60)	50 (43)	1.9 (1. 1 -3.7)	0.022
Drowsiness	22 (25)	5 (4)	7.4 (2.6 - 25.9)	<0.001
Vomiting	25 (28)	21 (18)	1.79 (0.9 - 3.7)	0.115
Dehydration (some/severe)	26 (31)	34 (29)	0.4 (0.1 - 0.8)	0.014
Pneumonia	66 (75)	69 (57)	2.04 (1.1 - 3.9)	0.029
Respiratory rate(mean± SD)	48.4 ± 16.7	53.2 ± 16.9	-4.8 (-9.5 - 0.1)*	0.047
Temperature(mean± SD)	37.2 ± 1.4	37.6±1.5	-0.4(-0.8 - 0.01)*	0.052
Pulse (mean± SD)	130.8 ± 51.1	128±59.9	2.0 (-13.6 - 17.6)*	0.097
Systolic Blood Pressure (mean± SD)	41.6 ± 30.0	47.66±36.3	-6.1 (-20.3 - 8.2)*	0.398
Diastolic Blood Pressure(mean± SD)	19.6 ± 18.15	23.8±20.5	-4.1 (-12.5 - 4.2)*	0.323
Delayed CRT	20 (23)	39 (34)	0.58 (0.3-1.1)	0.123
Rales in lung	39 (44)	52 (45)	0.9 (0.5-1.8)	0.944
Rhonchi in lung	4 (5)	5 (4)	1.1 (0.2-5.1)	0.792
Supra-sternal resection	4 (5)	8 (7)	0.6 (0.1 - 2.5)	0.680
Lower chest wall in-drawing	25 (28)	40 (35)	0.8 (0.4 - 1.4)	0.441

Mechanical ventilation	36 (41)	6 (5.0)	12.7 (4.8 -38.7)	<0.001
Blood transfusion	50 (57)	21 (18)	5.9 (3.0 - 11.8)	<0.001
Haemoglobin (mean± SD)	10.0 ± 3.5	10.4±2.5	-0.4 (-1.3 - 0.4)*	0.340
Neutrophil (mean± SD)	55 ± 16.4	91.5±381.2	-36.5 (-7.7 - 44.6)*	0.367
Band (mean± SD)	4.2 ± 5.4	3.1 ± 5.8	1.1 (-0.5 - 2.7)*	0.166
Bacterial isolates from blood	22 (25)	28 (24)	1.1 (0.5 - 2.1)	0.982
Severe wasting	22 (36%)	25 (33)	1.2 (0.6 - 2.5)	0.680
Severe under-weight	59 (67)	60 (52)	1.9 (1.03-3.5)	0.040
Hospital stay in hours (median, IQR)	92.5 (34.3,184.0)	137.5 (74.8, 242.0)	-	0.011
Deaths	59 (67)	16 (14)	12.71 (6.07-27.64	<0.001

OR = Odds ratio; CI = Confidence interval; IQR = Inter-quartile range; SD = Standard deviation; *MD (95% confidence interval); Severe wasting = weight for length/height z score <-3; Severe under-weight = weight for age z score <-3

The cases more frequently presented with nutritional edema, abdominal distension, respiratory difficulty, pneumonia (Table 1), higher respiratory rate, and required lesser hospital stay (Table 2) compared to the controls.

Table 2: Results of logistic regression analysis by enter method to disclose the independent clinical predictors of progression of severe sepsis to septic shock

Characteristics	OR	95% CI	p value
Mechanical ventilation	13.7	4.8-39.5	<0.001
Blood transfusion	5.8	2.7-12.2	<0.001
Drowsiness	4.2	1.3-14.2	0.017
Pneumonia	1.7	0.7-4.0	0.210
Nutritional edema	1.5	0.5-4.7	0.468
Severe underweight	1.4	0.7-3.0	0.341
Respiratory difficulty	1.0	0.4-2.2	0.950

In logistic regression analysis, after adjusting for potential confounders such as pneumonia, nutritional edema, severe underweight, and respiratory difficulty, cases more often had drowsiness on admission, received blood transfusion and required mechanical ventilation (Table 3).

Table 3. Bacterial isolates from blood of the study children

Bacterial isolates	Cases n = 22 (%)	Controls n = 28 (%)
Acinetobacter	1 (4)	2 (7)
Aeromonas	0	1 (4)
Candida	1 (4)	1 (4)
Enterobacter Species	1 (4)	2 (7)
Escherichia Coli	5 (23)	6 (22)
Enterococcus Species	2 (9)	4 (14)
H inflenzae	0	1 (4)
Klebsiella Species	1 (5)	3 (10)
Pseudomonas Species	7 (33)	4 (14)
Salmonella typhi	1 (4)	0
Staphylococcus aureus	0	2 (7)
streptococcus Species	3 (14)	2 (7)

The distribution of other variables in table 1 and 2 were comparable among the cases and the controls. Among the isolated organisms from blood 41 (82%) were gram negatives which were equally distributed among the groups (Table 3).

Discussion:

Our study revealed a number of important observations for clinicians in developing countries: first- progression of septic was strongly associated with high case-fatality rate; two-severe sepsis and septic shock is similarly associated with gram negative bacteremia; third- strong association of drowsiness with progression to septic shock from severe sepsis. Our observation of very high case-fatality-rate from septic shock is understandable and consistent with earlier observation.[26, 27] The observation of predominant Gram negatives in blood isolates in children with severe sepsis with or without the progression of septic shock is an important observation for the clinicians as well as policy makers in developing countries. This observation indicates that diarrheal children with severe sepsis, with or without the progression to septic shock should receive extended spectrum antibiotics to provide adequate coverage against the wide range of gram negative bacteremia in order to evade potential deleterious effect of gram negative bacteremia.[28] Our observation of drowsiness as an independent predictor of the progression to septic shock from severe sepsis in under-five diarrheal children is also understandable and could be used as a startling sign for the potential early initiation of aggressive therapy. Our study children comprised of severe sepsis and/or septic shock and both the groups needed aggressive management. However, survival rate in under-five children with severe sepsis who did not develop septic shock was higher which accentuates the significance of timely recognition of these diarrheal children in order to initiate any potential additional therapy such as inotrope(s) simultaneously with fluid resuscitation. Aggressive fluid therapy in children with septic shock found to be associated with higher deaths in study from Kenya.[29] Nonetheless, our study population were comparatively more sick than the Kenyan study population and we were essentially not aware of any potential deleterious effect of rapid fluid therapy that contributed higher case fatality in our study population.

The observation of repeated requirement of blood transfusion

and mechanical ventilation in diarrheal children with septic shock is also comprehensible as nearly all diarrheal children who had progression to septic shock from severe sepsis received blood transfusion. A recent published data from Bangladesh also observed similar events.[16] The diarrheal children with progression to septic shock from severe sepsis having respiratory failure required respiratory support by mechanical ventilation.

Diarrheal children who had progression of septic shock from severe sepsis more often had nutritional edema, severe underweight, and pneumonia compared to their counterpart and co-morbidity of severe malnutrition and pneumonia is often associated with high mortality.[30-32]

These children more often presented with respiratory difficulty, higher respiratory rate, pneumonia, abdominal distension and severe underweight by uni-variate analysis, but logistic regression analysis revealed that these variables were no longer significant. This phenomenon designates the subsistence of solemn illness of the diarrheal children in both the groups and emphasizes the requirement of aggressive treatment in both the groups.

The overwhelming evidence from our data concludes that the case-fatality-rate was significantly higher among the under-five diarrheal children who had the progression to septic shock from severe sepsis. Diarrheal children under the age of five years presenting with severe sepsis having drowsiness on admission were at risk of developing septic shock and often entailed blood transfusion as well as mechanical ventilation. From this point of view, the intensivists in developing countries with less resource may consider early initiation of inotrope(s) in such children.

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