PREDICTORS OF SEVERE ILLNESS IN CHILDREN UNDER AGE FIVE WITH CONCOMITANT INFECTION WITH PNEUMONIA AND DIARRHEA AT A LARGE HOSPITAL IN DHAKA, BANGLADESH

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Abstract. We compared the socio-demographic and clinical outcomes as predictors in severely ill hospitalized under-five diarrheal children with and without pneumonia. We studied 496 under-five children with diarrhea admitted to the Special Care Ward (SCW) of Dhaka Hospital of International Center for Diarrheal Disease Research, Bangladesh from 1999 to 2004. Children with pneumonia, in addition to their diarrhea, constituted the study group (cases), and those who did not have pneumonia constituted the comparison (control) group. The individual predictors of pneumonia in children were a history of cough (OR 2.19, 95% CI 1.30-3.72, p=0.002), fever (OR 1.73, 95% CI 1.19-2.53, p=0.003), and rapid breathing (OR 2.45, 95% CI 1.49-4.03, p<0.001). Hypothermia (6% *vs* 2%; p=0.02), hyponatremia (41% *vs* 27%; p=0.003) and dehydrating diarrhea (81% *vs* 69%, p=0.003) were more frequent in control children. On logistic regression analyses, the case fatality among children with pneumonia was nearly two times (OR, 1.88 CI, 1.12-3.15, p= 0.02) than that of controls. Formulation of guidelines and implementation of a more comprehensive approach to managing pneumonia among severely ill diarrheal children is necessary to reduce childhood deaths in Bangladesh.

INTRODUCTION

Pneumonia is currently the leading cause of morbidity, hospitalization, and death in children under-five in Bangladesh and many other developing countries (Chretien *et al*, 1984; Kirkwood *et al*, 1995; Monica and Alicemaria, 2004). Globally, it accounts for 25 - 33% of the 15 million deaths yearly in this population (Leowski, 1986; Graham, 1990; Berman, 1991; WHO, 1998; Straliotto *et al*, 2001). It accounts for 40% of deaths among children seeking medical care in South Africa. Several studies have identified a number of predictors for pneumonia, including severe malnutrition, lack of exclusive breast-feeding, inappropriate immunization, and parental illiteracy (Denny and Loda, 1986; Berman, 1991; Garenne *et al*, 1992; Murtagh *et al*, 1993; Shah *et al*, 1994; Suwanjuth *et al*, 1994; Agrawal *et al*, 1995; Dharmage *et al*, 1996; Hamid *et al*, 1996; Banajeh, 1998; Broor *et al*, 2001).

A recent study in Dhaka, Bangladesh observed pneumonia as a co-morbidity in 61% of severely malnourished children hospitalized for diarrheal illness. Pneumonia was the reason for hospitalization of 63% of severely malnourished children who had a fatal outcome

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(Tahmeed *et al*, 1999). Other studies also reported similar findings (Zaman *et al*, 1997; Rahman and Rahman, 1997). Case fatality was much higher when pneumonia was associated with other illnesses, particularly diarrhea, the second leading cause of morbidity and mortality in this population. Considering the high disease burden due to pneumonia and diarrhea it is important to understand the characteristics of young children presenting to health care facilities with both of these illnesses, and more importantly identify the predictors for their early identification, and define effective case management for reducing morbidity and mortality, as well as reduce hospitalization and costs. The aims of our study were to identify the predictors of pneumonia and the clinical features of severely ill young children admitted to a hospital in Bangladesh with diarrhea and pneumonia.

MATERIALS AND METHODS

Study population and site

This study was conducted at Dhaka Hospital of the International Center for Diarrheal Disease Research, Bangladesh (ICDDR, B), Dhaka, Bangladesh. This hospital provides care and treatment to over 100,000 patients with diarrheal illnesses each year. Children under age 5 constitute the majority of the patients. They are often malnourished and have other health problems, such as acute respiratory tract infection and severe malnutrition. Upon arrival to the hospital, experienced triage nurses obtain a medical history and make a quick assessment of the patients, and refer them to appropriate wards of the hospital based on the severity of diarrhea and dehydration, and the presence of complications of diarrheal disease as well as other health problems. Those with severe illnesses with higher risk for death, such as marked lethargy, irritability, convulsions, severe pneumonia, sepsis, cyanosis, or hypoxia are admitted to the Special Care Ward (SCW) of the hospital for closer monitoring, appropriate workups, and appropriate drug and supportive therapy. Nearly all patients admitted to the SCW need antimicrobial therapy and other supportive measures, such as oxygen therapy and naso- or oropharyngeal suctioning. Blood glucose and arterial oxygen saturation are determined using a portable glucose meter (ACCU-CHEK Active, Ireland) and pulse oximeter (Mallinckrodt N-20E, USA). For this prospective study, we studied 10% of patients directly admitted to the SCW between January 1999 and December 2004.

Study design

During the study period, 10,187 severely ill patients of both sexes, age 3 days to 80 years, were admitted to the SCW. Systematic sampling of 10% of the patients identified 967 patients, of whom 496 (51%) were children under age 5 years who constituted our study population. Two hundred one (41%) of these children with pneumonia, diagnosed on the basis of the presence of adventitious sounds in their lungs on auscultation, were regarded as cases and the remaining 295 children served as the control group.

Data analysis

We extracted relevant data from the patient records. The nutritional status of the child was based on the age, sex, weight, and admission length/height and discharge weight, except for those who died in the hospital for whom weight on their last hospital day was used in the assessment.

Data were analyzed using SPSS for Windows (version 10.2; SPSS, Chicago) and Epi Info (version 6.0, USD, Stone Mountain, GA). Differences in proportions were compared using a chi-square test, and a probability of less than 0.05 was considered statistically significant. Strength of association was determined by estimating the odds ratio (OR) and the 95% confidence interval (CI). All charac-

teristics, including the child's age, sex, breastfeeding and immunization status, maternal education, history of measles, nutritional status, monthly family income, degree of dehydration (some or severe), history of cough, fever, hypothermia, cyanosis, age-specific fast breathing (≥60/minute in <2 months of age; # ≥50/minute in 2-11 months of age, and ≥40/minute in 12-59 months of age), nutritional edema and anion gap # (≥20 mmol/l) were analyzed on a univariate model. To explore the predictors of pneumonia, logistic regression analysis was performed using a model comprised of independent variables, such as fever (> 38ºC), rapid breathing (respiratory rate >60/min), severe underweight (WAZ <-3), cough, male gender, dehydrating diarrhea (some or severe) and pneumonia as the dependent variable. On this multivariate analysis the independent predictors of pneumonia were male gender, severe underweight, history of cough, fever, and elevated respiratory rate, and dehydrating diarrhea was negatively associated with pneumonia. Since most of these predictors were well known as features of pneumonia we fitted another model with male gender, fatality, age of the child, lack of formal schooling of mother, and severe underweight as the independent variables, while pneumonia served as the dependent variable as before. We had missing values in less than one percent of cases and controls, these patients were not included in our analysis and did not have an impact on the outcome of the study.

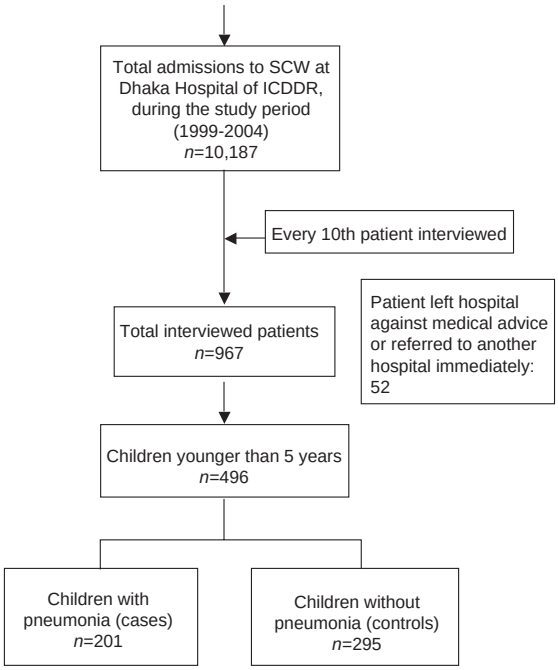

Fig 1–Flow diagram of patient selection for the study.

RESULTS

Of 496 children evaluated, 201 (41%) had abnormal findings on auscultation of the lungs (adventitious sounds) defined as pneumonia (Fig 1), 148 (74%) of them were infants. Hospitalization for pneumonia peaked during early spring (March-April). The admission characteristics of the children are presented in Table 1. A significantly higher proportion of children with pneumonia were male (62% *vs* 52%, p=0.05), and a higher proportion of them had a history of cough (88% *vs* 76%, p=0.002), fever (58% *vs* 44%, p=0.003) rapid breathing (25% *vs* 12%, p<0.001), and more frequently presented with severe underweight (46% *vs* 37%, p=0.039) than those without pneumonia. However, a significantly higher proportion of non-pneumonic children had hypothermia (6% *vs* 2%, p=0.02), hyponatremia (41% *vs* 27%, p=0.003) and more frequently presented with dehydrating diarrhea (81% *vs* 69%, p=0.003) compared to children with pneumonia. Other predictors, such as breastfeeding and immunization status, history of measles in the previous 6 months, presence of cyanosis, hypernatremia, and the socio-economic characteristics and literacy of the parents were not different between the two groups (Table 1). A higher proportion of children with pneumonia had severe growth delay, but the proportion of children with nutritional edema or severe

Table 1
Admission socio-economic and clinical characteristics of the study children.

Characteristic	Pneumonia children *n* = 201 (%)	Non-pneumonia children *n* = 295 (%)	OR (95% CI)	p-value
Male	124 (62)	155 (52)	1.45 (1.00-2.13)	0.05
Age 0-23 months	182 (91)	256 (87)	1.46 (0.79-2.72)	0.25
24-59 months	19 (9)	39 (13)		
Cough	176 (88)	225 (76)	2.19 (1.30-3.72)	0.002
Fever (Temp ≥ 38ºC)	116 (58)	130 (44)	1.73 (1.19-2.53)	0.003
Tachypnea (≥ 60/min)	51 (25)	31 (12)	2.45 (1.49-4.03)	<0.001
Non-breastfed	64 (32)	110 (37)	0.22 (0.53-1.17)	0.25
Illiterate mother	119 (59)	167 (57)	1.11 (0.76-1.63)	0.63
Monthly income <5,000 Taka	158 (79)	221 (75)	1.23 (0.79-1.93)	0.40
H/o of measles in last 6 months	19 (10)	15 (5)	1.95 (0.92-4.16)	0.09
Not immunized against measles	32/70 (46)	30/78 (39)	1.35 (0.66-2.74)	0.46
Cyanosis	9 (5)	11 (4)	1.21 (0.45-3.21)	0.85
Nutritional edema	28 (14)	27 (9)	1.61 (0.88-2.92)	0.13
Dehydrating (some/severe) diarrhea	138 (69)	238 (81)	0.52 (0.34-0.81)	0.003
Hypothermia (Temp ≤ 36ºC)	3 (2)	18 (6)	0.23 (0.05-0.85)	0.02
Hyponatremia (serum sodium <130mmol/l)	55 (27)	120 (41)	0.55 (0.37-0.82)	0.003
Hypernatremia (serum sodium ≥ 150 mmol/l)	31 (15)	31 (11)	1.55 (0.88-2.74)	0.14
Anion gap (≥ 20 mmol/l)	67 (34)	82 (28)	1.30 (0.86-1.95)	0.22
Severe under nutrition (Weight for age <-3 Z-score)	93 (46)	108 (37)	1.49 (1.02-2.18)	0.039
Severe stunting (Height for age<-3 Z score)	68 (34)	75 (25)	1.5 (0.99-2.26)	0.054
Severe wasting (Weight for height<-3 Z score)	13 (7)	25 (9)	0.75 (0.35-1.57)	0.51
Fatality	39 (19)	30 (10)	2.13 (1.23-3.67)	0.005

Table 2
Results of logistic regression analysis of children admitted to the Special Care Ward with pneumonia.

Variable	OR	95% CI	p-value
Male	0.85	0.59-1.22	0.38
Fatality	1.88	1.12-3.15	0.02
Age (0-23 months)	1.51	0.84-2.74	0.17
Illiteracy	1.00	0.69-1.45	0.99
Severe underweight	1.02	0.70-1.48	0.93

wasting was not different between the two groups. On multivariate analysis after adjusting for covariates (Table 2) children severely ill with pneumonia and diarrhea (19%) were two times more likely to die than their non-pneumonia counterparts (10%; p = 0.02).

DISCUSSION

The World Health Organization guidelines for the diagnosis of pneumonia are based on age specific respiratory rate cut-offs (≥60/minute for infants <2 months of age; ≥50/

minute for infants aged 2-11 months; ≥40/ minute for children aged 12-59 months) and the presence of lower chest wall in-drawing (WHO, 1990a,b,1991). We did not use the WHO guidelines in our study because 43% of our study children were severely malnourished, a population in which the reported sensitivity of respiratory rate cut-off values and chest wall in-drawing is low, found to be 61% in a recent Gambian study (Falade *et al*, 1995). The authors of the Gambian study suggested reduction in the WHO respiratory rate cut-offs by 5 breaths/minute to improve the sensitivity in diagnosing pneumonia in severely malnourished children (Falade *et al*, 1995). Severe malnutrition is associated with a blunted inflammatory response, and thus the markers of acute inflammation, such as fever, may also be absent or subtle in such a population (WHO, 1999). A recent study at Dhaka Hospital documented dehydration and acidosis in diarrheal children, both of which elevate the respiratory rate, leading to an over-diagnosis of pneumonia (false-positives) when the diagnosis is based on age-adjusted respiratory rate cut-offs alone (Salam *et al*, 2002, unpublished). In our study, 76% of children had clinical (some or severe) dehydration. WHO guidelines do not have a provision for adjustment of respiratory rates in the diagnosis of pneumonia in children with dehydrating diarrhea. We did not include chest X-ray in diagnosing pneumonia in our study. A recent study in Pakistan reported that chest X-ray was not essential (Hamid *et al*, 1996). Instead, we based our diagnosis on the presence of adventitious sounds in the lungs on auscultation, which has been reported to have a high sensitivity and specificity, and excellent correlation with radiological features (Gupta *et al*, 1996). It has also been reported that in the absence of clinical signs, radiological features are less likely to be noted (Shamo`on *et al*, 2004). Pulse oximetry provides a good estimate of arterial oxygen saturation and the magnitude of hypoxia serves as a good prognostic indicator in the management of pneumonia (Linda *et al*, 2006), however, its value in diagnosing pneumonia has not been reported. We, therefore, based our diagnosis of pneumonia on abnormal findings on lungs auscultation.

In our study, infants constituted 74% of children under-five with pneumonia. They have less acquired immunity than older children and are thus more vulnerable to severe infections. Our findings are similar to those of a number of recent studies (Broor *et al*, 2001; Dharmage *et al*, 1996; Nathon *et al*, 1993; Mtango *et al*, 1989). We observed higher number of admissions due to pneumonia in children between March and April when the season in Bangladesh changes from cooler to dusty and hotter in the early spring. This is known as the influenza season, and in many cases it precedes bacterial respiratory infections; earlier studies reported similar findings (Wang *et al*, 1994; Zhu *et al*, 2005).

We observed patients with a history of cough, fever, and tachypnea (≥60/minute), individual predictors of pneumonia; these are common features of pneumonia and have been used in other studies (WHO, 1990a,b, 1991; Nathon *et al*, 1993; Zaman *et al*, 1997; Broor *et al*, 2001; Monica and Alicemaria, 2001). However, proportion of children with pneumonia and fever in our study was lower than would be expected. This could be explained by the fact that many of the children were severely malnourished and might not mount a febrile response to infection (WHO, 1999). Hyponatremia was less frequent in children with pneumonia than in the control children, and they had less severe diarrhea as evidenced by a lower proportion of them having clinical dehydration. Thus, fecal loss of sodium can be assumed to be less. Fever and tachypnea are both associated with increased insensible water loss that not only prevents a fall in serum sodium (Von Schirnding *et al*, 1991) but also are recognized risk factors for

hypernatremia. Hyponatremia may rarely occur in pneumonia when there is association with the syndrome of inappropriate antidiuretic hormone (SIADH) (Saldias *et al*, 2002). At the Dhaka Hospital of ICDDR, B hypernatremia is usually noted in healthier, non-breastfed children with acute watery diarrhea, particularly those with pneumonia (Samadi *et al*, 1983). The higher anion gap of ≥20 mmol/l in severely pneumonic children may have resulted from increased levels of serum lactate due to metabolic derangements, particularly in association with sepsis (Bowling and Morgan, 2005; Corley *et al*, 2005).

In our study, children without pneumonia were more often (9% *vs* 7%) severely wasted. Such children had a higher proportion of body weight as water, which is often reflected in a lower plasma sodium (dilutional hyponatremia), despite the fact that their total body sodium may be normal or even high. They are also at higher risk for developing sepsis, which may contribute to the development of hyponatremia by causing SIADH. Hypothermia is common in severely malnourished children, which may reflect their compromised immune status, poor inflammatory response, and inability to mount a febrile response, as reported by earlier studies (Van den Broek *et al*, 2005; Carcillo, 2006).

In our study, predictors, such as non-breastfeeding, lack of immunization against measles and a history of measles in last 6 months, cyanosis, nutritional edema, severe wasting or stunting, hypernatremia, an anion gap ≥20 mmol/l, maternal illiteracy and low family income were not significantly different between the cases and the controls. Previous studies reported most of these factors to be significantly associated with pneumonia; however, unlike in our study, the control groups in those studies did not include seriously ill patients without pneumonia (Broor *et al*, 2001; Deb, 1998). Thus, these factors might reflect common features in severely ill young children. A previous study also found similar distribution of illiterate mothers in both groups (Broor *et al*, 2001). Diarrhea was the feature common to cases and controls in our study, many patients were hypovolemic on arriving at the hospital.

Male sex was a predictor for pneumonia in our study. This may reflect a gender bias in this society, and is reflected by the sex distribution of the general patient population at our hospital (males *vs* females 5:4), which has been reported earlier (Dharmage *et al*, 1996; Broor *et al*, 2001). More males are reported to visit community health facilities (Al-Ghizawi, 2007). Severe underweight was another predictor of pneumonia, which is not surprising since severely malnourished children are often immuno-compromised, and their respiratory tract mucosa lack an adequate protective ability against pathogenic microbes and opportunistic pathogens that commonly cause pneumonia (Mtango *et al*, 1989; Garenne *et al*, 1992; Nathon *et al*, 1993; Dharmage *et al*, 1996; Carcillo, 2006). Dehydrating diarrhea was significantly less common in severely ill children with both diarrhea and pneumonia; however, we did not evaluate predictors of dehydrating diarrhea, such as infection due to *V. cholerae*, severe malnutrition, or vomiting. Pneumonia has been reported to be associated with "parenteral diarrhea" (Capano and Guandalini, 2004), which is generally milder and may not lead to severe dehydration (Sibal *et al*, 1996). It is possible that parenteral diarrhea in association with pneumonia prompted the parents to bring their children for diarrhea treatment at the hospital.

Only patients with severe illness are admitted to the Special Care Ward (SCW) at Dhaka Hospital; both the cases and controls were selected from this general population. Our findings may not be generalized for the under-five population with only pneumonia, though high case fatality in pneumonia in earlier studies in the community where controls

were not so severely ill has been reported (Leowski, 1986; Graham, 1990; Berman, 1991; Von Schirnding *et al*, 1991; Garenne *et al*, 1992).

About 50% of deaths in our SCW occur within a few hours of admission, which reflects a general failure to understand the seriousness of illness or reluctance to take children to a hospital that is associated with cost or due to other reasons. A high case fatality rate among children who have the two leading causes of death, pneumonia and diarrhea, has been reported previously (Tahmeed *et al*, 1999; Salam *et al*, 2002, unpublished).

The results of our study support the theory that adventitious sounds on lung auscultation are an effective method in diagnosing pneumonia in children who have diarrhea. This is not influenced by an increased respiratory rate due to dehydrating diarrhea or decreased respiratory rate due to severe malnutrition, and may be considered as reliable diagnostic criteria in children with dehydrating dairrhea.

The findings of our study clearly indicate that case fatality from severely ill young diarrheal children with pneumonia is substantially higher than those with severe illness requiring admission to the SCW but without pneumonia. This finding underscores the importance of formulating an effective management guideline for severely ill patients with pneumonia/ acute respiratory infection. More importantly, this highlights the need for education of parents to improve their health seeking behavior favoring early referral to an appropriate health facility.

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