COMMUNITY ACQUIRED PNEUMONIA AMONG ADULT BANGLADESHI PATIENTS HOSPITALIZED FOR DIARRHEA

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Abstract. Community acquired pneumonia (CAP) in adults is a major cause of death among patients admitted to Dhaka Hospital of the International Centre for Diarrheal Disease Research, Bangladesh (ICDDR,B). Since the majority of diarrheal patients treated at our hospital are not given antibiotics and since the majority of CAP patients treated at our hospital do require antibiotics, it is important to recognize the CAP patients among our diarrheal patients. We aimed to determine the risk factors, etiology and outcome of CAP among adults, hospitalized for diarrhea at our hospital but also have concomitant pneumonia on admission. We retrospectively reviewed the charts of diarrheal patients aged ≥ 16 years admitted from January 2010 to December 2013 at our hospital. Of the 5,980 diarrheal patients admitted during the study period, 372 (6%) had CAP. We reviewed the charts of these patients retrospectively and compared them to the charts of 372 randomly selected diarrheal patients without pneumonia. At admission, 372 diarrheal patients who had CAP were identified by using the following criteria: symptoms of cough, breathing difficulty, fever, pleuritic chest pain and signs of hypo or hyperthermia, abnormal breath sounds and/or increased/decreased vocal resonance on auscultation consistent with an acute lower respiratory tract infection and the findings of a new radiographic abnormality showing lobar consolidation, para-pneumonic infiltrate or pleural effusion. The mortality rate among study subjects with diarrheal disease and CAP (4%) was significantly greater (p=0.006) than among diarrheal study subjects without CAP (1%). On logistic regression analysis, after adjusting for potential confounders, we found chronic lung disease, hypoxemia and hypomagnesemia to be independently significantly associated with CAP (p<0.05 for all 3 factors). Therefore, recognition of CAP on admission in adults hospitalized for diarrhea is critically important to reduce pneumonia related deaths. Patients with history of chronic lung disease, hypoxemia and hypomagnesemia need to be monitored carefully for signs and symptoms of CAP and treated promptly.

Keywords: diarrhea, community acquired pneumonia, chronic lung disease, hypomagnesemia

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INTRODUCTION

Community acquired pneumonia (CAP) is a common serious illness in Bangladesh (Saibal *et al*, 2012), in spite of effective anti-microbials and promising vaccines (Shah *et al*, 2010). The annual incidence of CAP in Europe is 1.6-10.6/1,000 adults (Walden *et al*, 2014). In Asia, CAP causes an estimated one million adult deaths per year (160,000 cases per year among those aged 15-59 years) (Peto *et al*, 2014). Diarrhea is also common in adults and can lead to death, especially in developing countries. Diarrhea and pneumonia can occur in conjunction (Song *et al*, 2011) and might increase the fatality rate of either disease individually. Adults with the pneumonia often have the following: productive cough, respiratory difficulty, fever, pleuritic chest pain and with opacity on chest radiography (Morgan and Glossop, 2015). Diarrheal patients with pneumonia may not have the same sign and symptoms (Morgan and Glossop, 2015), and may have more extra-pulmonary signs and symptoms (Bascir *et al*, 2014), their symptoms may be assumed to be due to diarrhea, such as rapid breathing caused by pneumonia may be assumed to be due to metabolic acidosis or dehydration caused by diarrhea. Most adult patients have acute diarrhea and only need to be treated with hydration and correction of electrolyte abnormalities (Andrews *et al*, 2017). Oral rehydration solution (ORS) or intravenous fluids are used to treat the dehydration (WHO, 2005). However, those with pneumonia usually require timely use of appropriate antimicrobials. The common causes of CAP include *Streptococcus pneumoniae*, atypical bacteria and gram-negative enteric bacilli (GNEB) (Arnold *et al*, 2007; Cilloniz *et al*, 2011; Marrie and File, 2016). One study among children with diarrhea and pneumonia found gram-negative bacilli to be the most common organism isolated from the lungs (Chisti *et al*, 2015b). We need to better understand the risk factors, etiologies and outcome of diarrheal patients with CAP. However, we found no published data on adult diarrheal patients with CAP admitted to the hospitals.

Dhaka Hospital treats a large number of adult diarrheal patients, where diarrhea is the primary admitting diagnosis in all patients (Chisti *et al*, 2016). We aimed to assess the etiology, associated clinical features, management and outcomes of adults hospitalized for diarrhea were also diagnosed with pneumonia.

MATERIALS AND METHODS

Study design

We conducted a retrospective review of patients treated at Dhaka Hospital of ICDDR,B among adults aged ≥ 16 years who were hospitalized for diarrhea from January 2010 to December 2013 with a diagnosis of diarrheal illness and CAP (cases) and compared them with patients hospitalized for diarrhea who did not have CAP (controls).

CAP was defined using the following criteria: symptoms of cough, breathing difficulty, fever, pleuritic chest pain and signs of fever (temperature ≥38°C) or hypothermia (temperature ≤36°C), abnormal breath sounds and/or increased/decreased vocal resonance on auscultation (Macfarlane, 1999; Lim *et al*, 2009), radiographic abnormality showing lobar consolidation, a para-pneumonic infiltrate or a pleural effusion (Lim *et al*, 2009), and the diagnosis made within 24 hours of admission.

Consolidation on a radiograph was defined as a dense homogeneous opacity with lobar/segmental involvement (often

containing air bronchograms). Other infiltrates were defined as linear or patchy alveolar or interstitial densities. A pleural effusion was defined as evidence of fluid collection in the pleural space on radiograph (Cherian *et al*, 2005; Nelson *et al*, 2008; Watt *et al*, 2010).

Patients who were hospitalized during the previous 10 days were excluded from the study. Others excluded were those with HIV infection, chronic diarrhea and pulmonary tuberculosis.

After identification of the total number of cases, the same numbers of controls were chosen for comparison at random using statistical package for the social sciences (SPSS), version 15.0 (SPSS, Chicago, IL).

Patient management

Antibiotics were prescribed for patients with CAP, sepsis, cholera, dysentery and other bacterial infections. Dehydration was corrected using oral rehydration salt (ORS) orally or via a nasogastric tube and with intravenous fluid when severely dehydrated.

Both ceftriaxone and levofloxacin were given intravenously if they had a CURB-65 score ≥ 3 and levofloxacin if they had a CURB-65 score ≤ 2. The CURB-65 score was defined by giving 1 point for each of the following: confusion, a blood urea nitrogen > 7 mmol/l, a respiratory rate ≥ 30, a systolic blood pressure < 90 mmHg, a diastolic blood pressure ≤ 60 mm Hg and the age of the patients ≥ 65 years (Lim *et al*, 2009). Patients were discharged from the hospital when their temperature was ≤ 38ºC, their heart rate was ≤ 100/min, their systolic blood pressure was ≥ 90 mmHg, the oxygen saturation level was ≥ 90%), they were able to take food and fluid adequately and their mental status was normal (Lim *et al*, 2009).

Measurements

Data collected from the medical chart included patient demographic data (age, gender), clinical data (abnormal auscultatory findings in the lungs, sepsis, and history of chronic lung disease), laboratory data (total leukocyte count, serum electrolytes, serum creatinine and blood, stool and urine cultures) and radiograph results. Laboratory data were recorded if serum creatinine was 1.5 times the upper limit of normal (*ie*, > 159 μmol/l in men and > 146 μmol/l in women), if there was hypokalemia (serum potassium < 3.5 mmol/l) or hyperkalemia (serum potassium > 5.3 mmol/l), hyponatremia (serum sodium < 135 mmol/l), hypocalcemia (serum calcium < 2.12 mmol/l), hypomagnesemia (serum magnesium < 0.65 mmol/l), metabolic acidosis (serum TCO_2 < 24 mmol/l) and leukocytosis (WBC count > 10,000/l). Other data included the number of days in the hospital, the hospital course and outcome.

Data analysis

All the data were entered into SPSS for Windows (Version 20.0; IBM, Armonk, NY) and Epi Info (version 7.0, Epi Info™ software; Center for Disease Control and Prevention, Atlanta, GA). Clinical data were summarized using descriptive statistics. Continuous variables were presented as means, standard deviations, medians and interquartile ranges (IQRs); categorical data, as numbers and percentages. We calculated the 95% confidence intervals (CIs) where appropriate. The Student's *t*-test was used to compare means of normally distributed data and the Mann-Whitney *U* test was used to compare non-normally distributed data. A *p*-value < 0.05 was considered statistically significant. Strength of association was estimated by evaluating the odds ratio (OR)

and their 95% confidence intervals (CIs). If a variable was significant, but one cell value was zero, we did not include it in the regression model. Variables independently associated with CAP in diarrheal patients were analyzed with univariate model first and then with multivariate logistic regression analysis, adjusting for relevant confounding variables.

Ethical considerations

Since this was a retrospective study and patients' identification was removed from the evaluation, no informed consent was obtained from study subjects. However, ethical approval for this study was obtained from the Institutional Review Board and Ethics Committee of ICDDR,B.

RESULTS

Of 5,980 diarrheal patients admitted to the hospital during the study period, 372 had CAP. We randomly selected the same number of controls who did not have CAP. The cases had a higher mean age, were more likely to have hypoxemia, severe sepsis, abdominal complaints (ileus), a higher creatinine, hypomagnesemia, hypoglycemia, and hypocalcemia on admission, and required more days to recover compared to controls (Table 1). During hospitalization, 91 cases (24%) and 28 controls (8%) developed sepsis; of these, 83 cases (22%) and 20 controls (5%) developed septic shock requiring inotropes. The cases were more likely to require mechanical ventilation and more likely to die than controls (Tables 1, 2).

On logistic regression analysis, after adjusting for potential confounders such as age, vomiting, severe sepsis, high serum creatinine and hypocalcemia, we found chronic lung disease, hypoxemia and hypomagnesemia were significantly independently associated with CAP (all $p<0.05$) (Table 3).

The blood culture isolates among cases and controls are shown in Table 4 and their sensitivities are shown in Table 5. The most common pathogen identified in CAP patients was *Streptococcus pneumoniae* (36%). All isolates were sensitive to beta-lactam antibiotics.

DISCUSSION

Six percent of patients admitted to the hospital for diarrhea had CAP. All the patients were admitted for diarrhea; and CAP was found as an associated problem after admission for diarrhea. In our study 3 parameters were independently associated with CAP: chronic lung disease, hypoxemia and hypomagnesemia. Hospitalized adults with CAP having any comorbidity were evaluated in different studies and demonstrated a higher mortality (Kaplan *et al*, 2003; Niederman, 2007). The most common cause of sepsis requiring escalation of treatment is severe CAP (Morgan and Glossop, 2015). In our study, cases were more likely to have sepsis than controls. Sepsis results in poor peripheral microcirculation, hypotension and higher risk of dying (Annane *et al*, 2005; Ebrahim, 2011).

Our study findings of hypoxemia as independently associated with CAP since pneumonia interfere with pulmonary gas exchange (Chisti *et al*, 2013) and the level of hypoxemia reflects the severity of lung impairment (Levin *et al*, 2001). This finding in our study is consistent with previous observations (Buising *et al*, 2007; Bewick *et al*, 2010).

The risk of CAP is higher among patients with a history of chronic respiratory diseases, such as with chronic bronchitis, emphysema, and asthma (Jackson *et al*, 2009; Flory *et al*, 2009; Vinogradova *et al*,

Table 1
Characteristics of study diarrheal patients with and without community acquired pneumonia.

Characteristics	Pneumonia (*n*=372) No. (%)	No pneumonia (*n*=372) No. (%)	OR (95%CI) (Unadjusted)	*p*-value
Male sex	207 (56)	195 (52)	1.14 (0.8-1.53)	0.418
Mean age in years (±SD)	49.2 (±20.1)	44.4 (±19.5)		0.001
Presence of watery stool	325 (90)	300 (80.6)	1.14 (0.71-1.83)	0.671
Presence of vomiting	95 (26)	65 (17)	1.56 (1.09-2.24)	0.016
History of chronic lung disease	60 (16)	30 (8)	2.19 (1.38-3.48)	0.001
Hypoxemia (SpO_2 < 90% on room air)	96 (26)	5 (1)	23.67 (9.54-58.98)	<0.001
Dehydration due to diarrhea	127 (34)	129 (44)	0.91 (0.64-1.28)	0.658
Mean temperature in °C (±SD)	38.0 (±2.2)	38.0 (±1.3)	-	0.421
Severe sepsis	91 (24)	28 (8)	3.97 (2.53-6.25)	<0.001
Hypoglycemia (RBS < 3.0 mmol/l)	13 (3)	0	Undefined	<0.001
Positive blood culture	36 (10)	36 (10)	0.64 (0.39-1.05)	0.102
Positive stool culture	28 (8)	28 (8)	1.05 (0.59-1.87)	0.97
Elevated serum creatinine	144 (43)	76 (31)	1.66 (1.76-2.35)	0.005
Hypomagnesemia	137 (37)	38 (10)	1.94 (1.15-3.28)	0.017
Hypokalemia	36 (10)	41 (11)	0.64 (0.39-1.03)	0.089
Hypocalcemia	179 (48)	53 (14)	2.62 (1.55-4.41)	<0.001
Hyponatremia	89 (24)	87 (23)	0.73 (0.51-1.04)	0.096
Hyperkalemia	14 (4)	10 (3)	1.08 (0.47-2.48)	0.99
Metabolic acidosis	253 (73)	192 (72)	1.06 (0.74-1.52)	0.821

No. (%), unless specified; OR, odds ratio; CI, confidence interval; SD, standard deviation; SpO_2, transcutaneously measured blood oxygen concentration; RBS, random blood sugar.

2009; Juthani-Mehta *et al*, 2013; Shea *et al*, 2014). Our findings also support this association. Magnesium deficiency can occur in a number of diseases *eg*, bronchopneumonia and urinary tract infection (Velissaris *et al*, 2015). Up to 65% of critically ill patients develop hypomagnesemia (Deheinzelin *et al*, 2000). In our study, 37% of cases and 10% of control had hypomegnesemia (p =0.002). Hypomagnesemic patients are at higher risk of developing sepsis syndrome originating from bronchopneumonia than those with normal magnesium level (Chen *et al*, 2015; Velissaris *et al*, 2015).

In our study, more cases than controls had hypoglycemia on admission, which is not surprising since hypoglycemia is more common in critically ill severe sepsis patients (Chisti *et al*, 2015a).

Identification of the causative agent in CAP was challenging in our study where in only 10% CAP cases an organism found on blood culture, however, the isolation from blood culture was found to be even lower (5.66%) in a previous study (Campbell *et al*, 2003). Our findings of *S. pneumoniae* being the most common organism among study cases is similar to studies from South and Southeast Asia (Wattanathum *et al*, 2003; Bansal *et al*, 2004).

Table 2
Complications and deaths in the study patients.

Characteristics	Pneumonia (*n*=372) No. (%)	No pneumonia (*n*=372) No. (%)	OR (95%CI) (Unadjusted)	*p*-value
Required inotropes	83 (22)	20 (5)	5.05 (3.02-8.4)	<0.001
Intubation and mechanical ventilation	12 (3)	0	Undefined	<0.001
Cardiac complications	32 (9)	2 (0.5)	17.42 (4.14-73.2)	<0.001
Death	13 (3)	2 (0.53)	6.69 (1.5-29.9)	0.006

Cardiac complications include: atrial fibrillation, ischemic heart diseases, unstable angina, myocardial infarction, cardiogenic shock and other arrythmias.

Table 3
Factors associated with community acquired pneumonia on logistic regression analysis.

Parameters	Adjusted OR	95% CI	*p*-value
Age	1.0	0.98 - 1.01	0.376
Vomiting	1.8	0.90 - 3.62	0.095
Chronic lung disease	2.61	1.0 - 6.79	0.05
Hypoxemia	11.53	3.44 - 38.63	<0.001
Severe sepsis	1.06	0.54 - 2.08	0.856
Elevated serum creatinine	0.94	0.48 - 1.84	0.854
Hypocalcemia	1.7	0.86 - 3.36	0.130
Hypomagnesemia	2.53	1.40 - 4.56	0.002

Table 4
Bacterial isolates from blood culture among study patients.

Isolates	Pneumonia *n*=36, No. (%)	No pneumonia *n*=36, No. (%)
S. pneumoniae	13 (36)	0
Salmonella Typhi	5 (14)	22 (61)
Salmonella Paratyphi	1 (2.8)	4 (11)
Pseudomonas spp	3 (8.3)	4 (11)
Escherichia coli	4 (11)	2 (5.6)
Enterobacter spp	7 (19.4)	1 (2.8)
Klebsiella spp	1 (2.8)	1 (2.8)
Enterococcus spp	0	1 (2.8)
Acinetobacter spp	1 (2.8)	0
Staphylococcus aureus	1 (2.8)	0

Table 5
Antimicrobial sensitivities of blood culture of bacterial isolates among study patients.

Isolates	*n*=72 No. (%)	Sensitivities of antibiotics (%)														
		AMP	AMX	AMK	AZM	CFX	CTX	CZD	STX	CIP	ERM	GEN	IMP	LFX	MRP	NLM
Aeromonas	1 (1.4)	-	-	-	-	-	-	-	0/1 (1)	1/1 (100)	0/1 (0)	1/1 (100)	-	-	-	-
Acinetobacter spp	1 (1.4)	-	-	1/1 (100)	-	-	1/1 (100)	1/1 (100)	-	1/1 (100)	-	1/1 (100)	1/1 (100)	-	1/1 (100)	1/1 (100)
Enterobacter spp	8 (11)	-	-	-	7/8 (87.5)	6/8 (75)	7/8 (87.5)	-	-	6/8 (75)	-	7/7 (100)	8/8 (100)	-	8/8 (100)	-
Enterococcus spp	1 (1.4)	-	1/1 (100)	-	-	-	-	-	-	0/1 (0)	-	1/1 (100)	-	-	-	-
Escherichi coli	6 (8)	0/3 (0)	0/2 (0)	6/6 (100)	1/1 (100)	4/6 (67)	4/6 (67)	4/6 (67)	3/6 (50)	3/6 (50)	-	5/6 (83)	5/6 (83)	-	6/6 (100)	6/6 (100)
Klebsiella spp	2 (3)	-	0/1 (0)		0/1 (0)	2/2 (100)	2/2 (100)		-	1/2 (50)	-	2/2 (100)	1/1 (100)	-	1/1 (100)	
Pseudomonas spp	7 (10)	-	-	5/7 (71)	-	-	-	7/7 (100)	-	6/7 (86)	-	5/7 (71)	7/7 (100)	-	7/7 (100)	4/7 (57)
Salmonella Typhi	27 (37.5)	9/12 (75)	7/15 (47)	-	25/25 (100)	27/27 (100)	27/27 (100)	-	17/27 (63)	2/27 (7)	-	2/2 (100)	-	-	-	-
Salmonella Paratyphi	5 (7)	3/3 (100)	2/2 (100)	-	3/5 (60)	5/5 (100)	5/5 (100)	-	5/5 (100)	1/5 (20)	-	-	-	-	-	-
Streptococcus pneumoniae	13 (18)	8/8 (100)	3/3 (100)	-	9/11 (82)	10/10 (100)	12/12 (100)	-	1/2 (8)	3/4 (75)	8/10 (80)	0/5 (0)	-	9/9 (100)	-	-
Staphylococcus aureus	1 (1.4)	-	-	0/1 (0)	0/1 (0)	0/1 (0)	0/1 (0)	-	0/1 (0)	0/1 (0)	0/1 (0)	1/1 (100)	-		-	-

AMP, Ampicillin; AMX, Amoxycillin; AMK, Amikacin; AZM, Azythromycin; CFX, Cefixime; CTX, Ceftriaxone; CZD, Ceftazidime; STX, Trimethoprim-sulfametoxazole; GEN, Gentamicin; CIP, Ciprofloxacin; IMP, Imipenam; MRP, Meropenam; ERM, Erythromycin; NLM, Natilmycin; LFX, Levofloxacin.

A limitation of our study is its retrospective design where we used the registry data. The patients` signs and symptoms were incomplete in medical records, making evaluation of this data inaccurate. Standard diagnostic testing for CAP was not adequately performed in our patients. No sputum samples were obtained. The etiology of CAP in our study was based only on the blood culture result which has a low sensitivity.

In our study, CAP among diarrheal patients was infrequent but the mortality rate was higher among cases than controls. CAP in diarrheal adults was independently associated with a history of chronic lung disease, presence of hypoxemia and hypomagnesemia at presentation. Standard treatments for diarrhea are unlikely to treat CAP. Therefore, it is important to recognize the signs and symptoms of CAP and conduct adequate evaluation to correctly diagnose and begin treatment of CAP. Further studies of these diarrheal patients with CAP are needed to clarify the clinical data in this group.

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