Concurrent Pneumonia in Children under 5 Years of Age Presenting to a Diarrheal Hospital in Dhaka, Bangladesh

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Abstract. Respiratory and gastrointestinal infections are the top killers of children worldwide, and their co-occurrence is reported but not well understood. Our aim was to determine the risk factors for concurrent presentation of diarrhea and pneumonia (DP) in a resource-limited setting in Bangladesh. We used data from the Diarrheal Disease Surveillance System of the icddr,b Dhaka Hospital to identify children < 60 months of age with diarrhea and concurrent pneumonia, defined as a history of cough, an abnormal lung examination, and tachypnea. For the years 1996–2007, out of total 14,628 diarrheal patients surveyed, there were 607 (4%) patients who satisfied criteria for pneumonia. Those with DP had a higher mortality rate (4% versus 0.05%, odds ratio [OR] = 86, 95% confidence interval [CI] = 26–286) and a longer hospital stay (mean 84 versus 26 hours, difference 58 hours, 95% CI = 52–64 hours) than those with diarrhea (D) only. In multivariable logistic regression comparing cases ($N = 607$) with controls matched for month and year of admission at a ratio of 1:3 ($N = 1,808$), we found that DP was associated with younger age, male gender, severe acute malnutrition (SAM), less maternal education, lower family income, and lack of current breast-feeding history.

INTRODUCTION

Globally, diarrhea and respiratory infections cause significant morbidity and mortality in children under 5 years of age. Pneumonia and diarrhea account for over 2 million deaths a year worldwide, most of which occur in low-income countries.¹ Although the two diseases usually occur separately, we have previously demonstrated that in children with diarrhea, the presence of concomitant pneumonia increases risk of death.^{2,3} A recent study showed that diarrhea and acute lower respiratory tract infections occurring in the same week happen more often than chance alone,⁴ and studies of young children in Pakistan⁵ and Ghana⁶ have demonstrated recent diarrheal illness to be associated with an increased risk of subsequent pneumonia. Studies in animals have shown that gut microbiota composition regulates immunity in the lung mucosa through inflammasome activation⁷ and that intestinal *Shigella* infection influences respiratory epithelial antimicrobial peptide expression.⁸

Clinical and epidemiological studies looking at interactions between diarrhea and pneumonia are limited, and risk factors have not been well described. Furthermore, no studies have examined the contributions of specific enteric pathogens and the risk of concurrent pneumonia. Thus, the objective of this study was to determine the incidence, outcome, and risk factors for concurrent diarrhea and pneumonia in young children presenting to an urban hospital in Dhaka, Bangladesh.

METHODS

Hospital surveillance system. The Dhaka hospital of the icddr,b is a diarrheal treatment center that provides free care to over 140,000 patients yearly. The 2% Diarrheal Disease

Surveillance System of the hospital prospectively collects demographic, clinical, and enteric pathogen data from every 50th patient.⁹ As part of this surveillance, a health assistant administers a questionnaire to an adult guardian that includes sociodemographic, medical history, and behavioral questions. A physician performs a physical examination that includes the dehydration status, a lung exam, and respiratory rate.

For this study, we used data collected from 1996 to 2007. This period was chosen because in the period after 2007, there were changes in the method of recording physical examination parameters, including those used for our definition of pneumonia (below). Severe acute malnutrition (SAM) was defined as a weight-for-height z score of ≤ -3 .

Microbiological methods. Stool samples from each patient enrolled in the surveillance system were analyzed for presence of 1) Bacterial enteric pathogens, including *Vibrio*, *Salmonella*, *Shigella*, *Aeromonas*, and *Campylobacter* spp., by conventional culture methods; 2) rotavirus by enzyme-linked immunosorbent assay; and 3) parasites, including *Entamoeba*, *Giardia*, *Ascaris*, *Trichuris* spp., and hookworms by direct microscopy, except for *Cryptosporidium*, which was detected with a modified acid-fast stain. Data for respiratory pathogens were not included in the surveillance system.

Pneumonia definition. We used the data from the surveillance system to identify children < 60 months of age who presented with signs and symptoms of pneumonia concurrent with diarrhea, defined as a patient who satisfied all three criteria: 1) history of cough with diarrhea, 2) an abnormal lung examination on admission, and 3) tachypnea (age appropriate) on admission. This definition was determined on the basis of World Health Organization (WHO) guidelines,¹⁰ as well as a previous study demonstrating that tachypnea and lung exam to be predictive of radiological pneumonia.¹¹

Study design. We compared the characteristics of those with concurrent diarrhea and pneumonia (DP) against a control group who had diarrhea but did not satisfy any of the pneumonia criteria (D), matched for month and year of admission at a ratio of 1:3. Because of the large number of patients with

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multiple pathogens identified in stool, we compared the pathogens identified as separate variables.

Statistical analysis. We used χ^2 test with Yates correction to compare differences in categorical variables and Student's *t* test to compare differences in continuous variables. We entered potential risk factors for pneumonia into a multivariable logistic regression model. We entered age, sex, SAM, and all pathogen categories into a separate multivariable logistic regression model. Statistical analyses were performed using Stata version 13.1 (Stata Corp, College Station, TX). Statistical significance was defined as a two-tailed *P* value < 0.05. The figure was generated using GraphPad Prism (GraphPad Software, Inc., La Jolla, CA).

RESULTS

For the years 1996–2007, a total of 14,628 diarrheal patients < 60 months of age were enrolled in the surveillance system. Out of these, 607 (4%) met all the three criteria for pneumonia, 8,227 (56%) satisfied one or two criteria (indeterminate), and 5,794 (40%) did not satisfy any of the criteria for pneumonia. Figure 1 shows total numbers surveyed and proportion with pneumonia by month of admission.

Of those with concurrent diarrhea and pneumonia (DP), 26 (4%) died, whereas only three (0.05%) of the diarrhea only (D) group died (odds ratio [OR] = 86, 95% confidence interval [CI] = 26–286, *P* < 0.0001). Patients with DP also had a longer hospital stay (mean 84 ± 4 hours) than non-pneumonia (D) patients (26 ± 0.5 hours, *P* < 0.001, difference 58 hours, 95% CI = 52–64 hours, *P* < 0.0001). A pathogen was detected in the stool of 353 (58%) of those with pneumonia and 4,536 (78%) of non-pneumonia patients. We examined the seasonality of DP and found that the majority of months had a DP rate of 3.3–4.6%, with the exception of April (5.3%), November (5.9%), and December (2.2%).

Given the seasonal nature of many diarrheal and respiratory pathogens, we conducted a case-control analysis where we compared demographic and clinical characteristics of those with pneumonia (DP) with non-pneumonia controls (D), matched for month and year of admission at a ratio of 1:3. Thus, we matched the 607 patients with DP with 1,808 D controls (there were three pneumonia patients who only had two matching controls). A pathogen was identified in 353 (58%) cases and 1,300 (72%) controls.

FIGURE 1. Numbers of diarrheal patients surveyed, and % with pneumonia by month, Dhaka Hospital, 1996–2007.

Table 1 shows the unadjusted and adjusted odds ratio (aOR) comparing the sociodemographic, behavioral, clinical, and microbiological variables between pneumonia patients and a control group of non-pneumonia patients matched for month and year of admission. We found that children with pneumonia were more likely to be younger, male, have less educated parents, come from a poorer family, have more children under 5 years of age in the home, and cooked in bedroom or in single-roomed homes. They were less likely to be female, have piped water, boil drinking water, have electricity, sleep on a cement floor, use gas for cooking, to have received BCG vaccination, and to have received a vitamin A capsule. In a multivariable logistic regression, we found that younger age, lower maternal education, lower family income, not currently being breast-fed, and SAM, to associate with an increased risk of concurrent pneumonia.

In a multivariable regression including age, sex, malnutrition status, and presence of individual pathogens, we found that those with DP were more likely to have *Cryptosporidium*, *Giardia*, or *Aeromonas* infections or no pathogen identified in stool (Table 2).

To determine if the increased risk of mortality and duration of hospitalization could be explained by severity of illness on presentation rather than the presence of pneumonia, we performed a separate multivariable logistic regression with death as primary outcome and presence of pneumonia, SAM, severe dehydration, fever, and feeble pulse as independent variables. We found that the presence of pneumonia had the highest OR (OR = 17, 95% CI = 4–75, *P* < 0.001). Similarly, using duration of hospitalization greater than 48 hours as primary outcome in a similar multivariable regression, presence of pneumonia had the highest OR (OR = 6.4, 95% CI = 5.2–7.9, *P* < 0.001).

DISCUSSION

Gastrointestinal and respiratory infections are the two leading causes of death of children under 5 years of age worldwide, together accounting for over 2 million deaths annually. Concurrent diarrhea and pneumonia has been reported earlier, but studies to date on this phenomenon have been limited. In this study, we used a large database of children with diarrhea to identify those with concurrent diarrhea and pneumonia, and in comparing the characteristics of those with diarrhea only, characterized the outcomes and risk factors associated with this comorbidity.

We found that children presenting with DP have a > 80 times higher risk of death and a three times longer length of stay compared with those with D alone. Our findings are consistent with that of a smaller study focused on children admitted to an intermediate care unit at the icddr,b, where those with pneumonia coinfection were found to have a two times higher mortality rate than those without pneumonia.² More recently, we have shown that children admitted with severe malnutrition and pneumonia to our diarrheal hospital have a 9% in-hospital death rate,¹² with an additional 9% children dying within 3 months of hospital discharge, even after inpatient nutritional rehabilitation was given. All of these data underline the potentially severe consequences of respiratory and gastrointestinal coinfection. Early identification of those with concurrent pneumonia is likely important in preventing poor outcomes, though

TABLE 1
Multivariable regression of risk factors associated with concurrent pneumonia

Risk factor	Diarrhea only (N = 1,808)	Concurrent pneumonia (N = 607)	OR (95% CI)	P value	aOR (95% CI)	P value
Demographic						
Age, months, mean (SD)	14 (11)	11 (9)	0.96 (0.95–0.97)	< 0.001	0.94 (0.93–0.95)	< 0.001
Sex, female (%)	738 (41)	218 (36)	0.81 (0.67–0.98)	0.03	0.86 (0.69–1.06)	0.16
Mother's education, ≥ 6 years (%)	844 (47)	118 (19)	0.28 (0.22–0.34)	< 0.001	0.34 (0.26–0.44)	< 0.001
Family income, > 5,000 Tk/month (%)	822 (45)	148 (24)	0.67 (0.61–0.73)	< 0.001	0.80 (0.72–0.90)	< 0.001
Housing						
No. of children < 5 years in home, mean (SD)	1.3 (0.5)	1.4 (0.5)	1.4 (1.2–1.6)	< 0.001	1.3 (1.1–1.6)	0.003
Drinking water source, tap (%)	1,065 (59)	296 (49)	0.66 (0.55–0.80)	< 0.001	0.97 (0.75–1.24)	0.78
Boils drinking water (%)	565 (31)	111 (18)	0.49 (0.39–0.62)	< 0.001	0.90 (0.66–1.22)	0.48
Has electricity (%)	1,628 (90)	496 (82)	0.49 (0.38–0.64)	< 0.001	0.82 (0.60–1.13)	0.23
Floor, cement (%)	1,135 (63)	265 (44)	0.46 (0.38–0.55)	< 0.001	0.89 (0.68–1.17)	0.41
Uses gas for cooking (%)	1,057 (58)	271 (45)	1.7 (1.5–2.1)	< 0.001	1.05 (0.79–1.40)	0.74
Behavior						
Received BCG (%)	1,678 (93)	520 (86)	0.46 (0.35–0.62)	< 0.001	0.84 (0.60–1.18)	0.32
Currently breast-fed (%)	1,439 (75)	467 (77)	0.86 (0.69–1.08)	0.19	0.48 (0.37–0.63)	< 0.001
Father smokes (%)	684 (38)	235 (39)	1.03 (0.85–1.25)	0.35	1.05 (0.85–1.30)	0.63
Received vitamin A in past 3 months (%)	849 (47)	236 (39)	0.72 (0.60–0.87)	0.001	1.05 (0.85–1.32)	0.62
Cook in bedroom (%)	69 (4)	36 (6)	1.59 (1.05–2.40)	0.03	1.05 (0.65–1.69)	0.84
Clinical presentation						
Persistent diarrhea, ≥ 15 days (%)	49 (3)	24 (4)	1.5 (0.9–2.4)	0.12	1.2 (0.7–2.1)	0.52
Severe acute malnutrition (%)	125 (7)	130 (21)	3.7 (2.8–4.8)	< 0.001	3.0 (2.2–4.0)	< 0.001

aOR = adjusted odds ratio; BCG = Bacillus Calmette–Guérin vaccine; CI = confidence interval; SD = standard deviation; Tk = Taka (Bangladesh currency).

further studies are needed to determine optimal management of children with concurrent illnesses.

We have previously shown in a smaller group of children admitted to an intermediate care unit at icddr,b that those with concurrent pneumonia and diarrhea were more likely to have slept on a bare wooden-slatted or bamboo bed, and whose guardians had a poor knowledge of pneumonia.¹³ In this study, we found that housing variables were not independently associated with pneumonia; rather, we found that broader socioeconomic indicators such as higher education status of the mother and a higher family income were protective for coinfection, which is consistent with previous studies showing that such risk factors are associated with childhood pneumonia in resource-limited settings, including Egypt,¹⁴ Brazil,¹⁵ and India.¹⁶ We also demonstrate that for those under 12 months of age, breast-feeding was associated with a lower risk of concurrent pneumonia. Our finding adds to the large body of evidence suggesting that breast-feeding is protective against both the incidence of hospitalization¹⁷ and death due to¹⁸ pneumonia in young children.

Studies have demonstrated that the presence of SAM in children with pneumonia increases the risk of death,¹⁹ and that approximately 60% of children with diarrhea and malnutrition also had clinical signs of pneumonia on admission.²⁰ In our study, SAM was an independent predictor of concurrent pneumonia, and of the DP patients who died, approximately half had SAM. Furthermore, given that WHO-recommended clinical signs of pneumonia are less sensitive in children with SAM,¹⁹ the burden of respiratory disease is likely underestimated.

We found that April and November had the highest rates of DP, while December had the lowest. The reasons for these outlier months are unclear. In Bangladesh, influenza and influenza-like illnesses occur mostly during the rainy season of June–September.²¹ Thus, the high rates of concurrent pneumonia in November, and the low rates seen in December, are unexpected and likely unrelated to seasonality of respiratory viruses. Nevertheless, given the seasonality of various diarrheal and respiratory pathogens in Bangladesh, we selected controls matched for month of admission.

TABLE 2
Multivariable regression of pathogens associated with concurrent pneumonia

Pathogen	Diarrhea only (N = 1,808)	Concurrent pneumonia (N = 607)	OR (95% CI)	P value	aOR* (95% CI)	P value
<i>Salmonella</i> spp.	23 (1)	12 (2)	1.6 (0.8–3.2)	0.21	1.5 (0.5–4.5)	0.46
<i>Shigella</i> spp.	124 (7)	39 (6)	0.93 (0.64–1.35)	0.71	1.2 (0.6–2.2)	0.59
<i>Vibrio</i> spp.	183 (10)	53 (9)	0.85 (0.62–1.17)	0.32	1.4 (0.8–2.4)	0.21
<i>Aeromonas</i> spp.	93 (5)	36 (6)	1.16 (0.78–1.73)	0.46	1.8 (1.1–2.9)	0.03
<i>Campylobacter</i> spp.	113 (6)	46 (8)	1.23 (0.86–1.76)	0.25	1.3 (0.8–2.2)	0.35
Other bacteria	26 (1)	8 (1)	0.92 (0.41–2.03)	0.83	0.9 (0.3–2.2)	0.78
Rotavirus	712 (39)	176 (29)	0.62 (0.51–0.76)	< 0.001	0.9 (0.6–1.4)	0.72
Geohelminth	223 (12)	52 (9)	0.67 (0.49–0.91)	0.01	0.8 (0.4–1.6)	0.48
<i>Cryptosporidium parvum</i>	11 (0.6)	9 (1.5)	2.5 (1.01–6.0)	0.04	2.7 (1.04–7.2)	0.04
<i>Giardia lamblia</i>	14 (0.8)	5 (0.8)	1.06 (0.38–3.0)	0.91	3.7 (1.1–12.3)	0.03
Multiple pathogens	240 (13)	74 (12)	1.4 (0.9–2.2)	0.53	1.2 (0.5–2.5)	0.70
No pathogen	508 (28)	254 (42)	1.8 (1.5–2.2)	< 0.001	2.0 (1.3–3.1)	0.002

aOR = adjusted odds ratio; CI = confidence interval.

*Adjusted for age, sex, and severe acute malnutrition.

We found that concurrent pneumonia was associated with the lack of diarrheal pathogens identified in stool. We suspect that some of those with no pathogens identified in stool are cases of respiratory tract infection that present with diarrhea as an accompanying symptom, as approximately 10% of pneumococcal pneumonia cases have been reported to present with gastrointestinal symptoms.^{22,23} Notably, *Cryptosporidium* isolation was more often associated with concurrent pneumonia. This is consistent with studies showing that respiratory symptoms can be seen in almost half of children with cryptosporidiosis, more than that of diarrhea of other etiologies,²⁴ and that 35% of HIV-negative Ugandan children with evidence of intestinal cryptosporidiosis also had *Cryptosporidium* spp. detected in their sputum,²⁵ possibly due to vomiting and aspiration of oocysts. *Aeromonas* infection has been shown to cause both respiratory and gastrointestinal symptoms, though the mechanisms behind concurrent symptoms are not well understood.²⁶ These findings do not exclude the possibility that some diarrheal pathogens may be associated with subsequent development of pneumonia. Studies to date linking recent diarrheal illness to subsequent respiratory infections have lacked microbiological analysis,⁴⁻⁶ and further studies are needed to determine if certain diarrheal pathogens are more predisposed to concurrent or subsequent respiratory disease.

Our study had several limitations. First, we used data from a hospital-based surveillance system, and thus our findings are limited to the population who present for medical care in an urban setting. Second, our definition of pneumonia was limited to history (cough) and physical examination findings (rapid breathing, abnormal lung exam), and did not include radiological findings. Third, we did not exclude children who had severe dehydration as these children potentially had tachypnea because of metabolic acidosis; however, we recently showed that tachypnea associated with metabolic acidosis in young children with diarrhea has no impact on the diagnostic clinical features of radiological pneumonia,²⁷ and thus our definition is consistent with the WHO definition of pneumonia. Fourth, we used conventional culture- and microscopy-based assays to detect bacterial and parasitic pathogens, respectively. We lack data on known pathogens such as diarrheagenic *Escherichia coli*, norovirus, and adenovirus, among others. Fifth, the lack of a pneumonia-only comparison group limits our ability to discern whether the risk factors are specific to coinfection or to pneumonia. Sixth, we do not have any data on respiratory pathogens and cannot confirm that respiratory symptoms were due to pulmonary infection. We also do not have data on the number of children who received immunizations against respiratory pathogens; of note, the expanded program on immunization in Bangladesh includes vaccination against *Haemophilus influenzae*, but not *Streptococcus pneumoniae* or influenza virus. Finally, the interpretation of this retrospective analysis may be limited by confounding, although we have attempted to minimize this by including possible confounders in the multivariable regression analysis.

Nevertheless, in the largest analysis of children with concurrent pneumonia and diarrhea in a resource-limited setting to date, we have shown concurrent pneumonia to be associated with higher rates of death and longer duration of hospitalization, and identified several risk factors associated with concurrent illness. A prospective study with more detailed

characterization of both respiratory and gastrointestinal pathogens is needed.

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