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MAJOR ARTICLE

Antibiotic-Resistant Bacteremia in Young Children Hospitalized With Pneumonia in Bangladesh Is Associated With a High Mortality Rate

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Background. Pneumonia is a leading cause of sepsis and mortality in children under 5 years. However, our understanding of the causes of bacteremia in children with pneumonia is limited.

Methods. We characterized risk factors for bacteremia and death in a cohort of children admitted to the Dhaka Hospital of the International Centre for Diarrhoeal Disease Research, Bangladesh (icddr,b) between 2014 and 2017 with radiographically confirmed pneumonia.

Results. A total of 4007 young children were hospitalized with pneumonia over the study period. A total of 1814 (45%) had blood cultures obtained. Of those, 108 (6%) were positive. Gram-negative pathogens predominated, accounting for 83 (77%) of positive cultures. These included *Pseudomonas* (N = 22), *Escherichia coli* (N = 17), *Salmonella enterica* (N = 14, including 11 *Salmonella* Typhi), and *Klebsiella pneumoniae* (N = 11). Gram-positive pathogens included Pneumococcus (N = 7) and *Staphylococcus aureus* (N = 6). Resistance to all routinely used empiric antibiotics (ampicillin, gentamicin, ciprofloxacin, and ceftriaxone) for children with pneumonia at the icddr,b was observed in 20 of the 108 isolates. Thirty-one of 108 (29%) children with bacteremia died, compared to 124 of 1706 (7%) who underwent culture without bacteremia (odds ratio [OR], 5.1; 95% confidence interval [CI], 3.3–8.1; $P < .001$). Children infected with bacteria resistant to all routinely used empiric antibiotics were at greater risk of death compared to children without bacteremia (OR, 17.3; 95% CI, 7.0–43.1; $P < .001$).

Conclusions. Antibiotic-resistant Gram-negative bacteremia in young children with pneumonia in Dhaka, Bangladesh was associated with a high mortality rate. The pandemic of antibiotic resistance is shortening the lives of young children in Bangladesh, and new approaches to prevent and treat these infections are desperately needed.

Keywords. antibiotic-resistant; bacteremia; Bangladesh; children; pneumonia.

Pneumonia is the most common cause of death in young children beyond the immediate neonatal period, accounting for over 800 000 deaths in children under 5 annually [1]. Pneumonia is also the third leading cause of sepsis in this age group [2].

The introduction of vaccines for *Haemophilus influenza* type B and *Streptococcus pneumoniae* has contributed to a decline in pneumonia-related mortality over the past 2 decades [3]. The World Health Organization's (WHO) Integrated Global Action Plan for the Prevention and Control of Pneumonia and Diarrhoea (GAPPD) aims to further reduce deaths from pneumonia to less than 3 children per 1000 live births by 2025. Among 30 high pneumonia-burden countries according to the GAPPD, Bangladesh is 1 of only 3 countries on track to achieve the GAPPD 2025 milestones [4]. However, pneumonia still accounts for 12% of all deaths in children under 5 in Bangladesh [4], and the country needs to continue to achieve an 8% average annual rate of reduction in pneumonia-related deaths to meet the GAPPD target [4].

A major obstacle to further reducing childhood pneumonia-associated mortality in Bangladesh and elsewhere is the lack of data regarding its infectious causes; this knowledge gap is due to the lack of accurate diagnostic tests and is amplified by variability in the microbial etiologies of pneumonia across populations. This variation is indicated by findings from the Pneumonia Etiology Research for Child Health (PERCH) study, a large multicountry case-control

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study performed in 7 countries between 2011 and 2014, which evaluated viral and bacterial causes in young children hospitalized for pneumonia. The study found that blood cultures were positive in only 56 (3%) of 1749 cases, and that *S pneumoniae* was the most common pathogen isolated (33.9% of 56) [5]. However, among the 211 children with pneumonia and a blood culture enrolled in the Dhaka site of the PERCH study, only 2 had a positive blood culture and both were positive for *Enterobacteriaceae*. This variation across populations and geographic locations underscores the need to expand laboratory diagnostic and surveillance activities. This is especially true in South Asia, where the aggregate levels of antibiotic resistance are very high and have increased rapidly [6].

Our study sought to address these knowledge gaps by defining the pathogens associated with bacteremia in a large cohort of young children with radiographically confirmed pneumonia in Dhaka, Bangladesh. We describe the antibiotic resistance of these bacteria to the standard empiric antibiotics given to young children with pneumonia at our institution, and we compare the risk of death in children with bacteremia, investigating the impact of the type of organism isolated and antibiotic resistance.

METHODS

Study Site

The study was performed at the Dhaka Hospital of the International Centre for Diarrhoeal Disease Research, Bangladesh (icddr,b), a tertiary facility that serves the Dhaka metropolitan area and provides care for diarrheal illness, childhood respiratory illness, and undernutrition [7]. The intensive care unit (ICU) of the icddr,b Dhaka Hospital manages over 600 children with pneumonia annually.

Study Population and Design

All children under 5 years of age who met the WHO criteria for both clinically defined pneumonia [8] and radiographic pneumonia [9] admitted to the Dhaka Hospital of icddr,b between January 2014 and December 2017 were included in this retrospective cohort study. Standardized radiographic criteria included end-point consolidation, defined as a dense or fluffy opacity that may occupy a portion, or a whole lobe, or the entire lung, as well as pleural effusion [9]. Clinical criteria included cough or respiratory difficulty plus either age-specific tachypnea or lower chest wall in-drawing for nonsevere pneumonia, and in the case of severe pneumonia, hypoxemia, cyanosis, inability to breastfeed or drink, or, grunting, and general danger signs including lethargy, reduced consciousness, and seizures [8]. All study children were managed using standard treatment according to our institutional guidelines, which have been described in detail previously [7]. First-line antibiotic therapy was ampicillin plus gentamicin, and second-line antibiotic therapy (for those who failed to respond to first-line treatment after 48 hours) was ceftriaxone plus levofloxacin.

Demographic, clinical, and laboratory data were extracted from the electronic database of the Dhaka hospital of the icddr,b using a case report form designed for this study. Clinical data included respiratory findings and markers of pneumonia severity. Respiratory failure was clinically defined if the patient presented without adequate respiratory drive, such as gasping respiration or required cardiopulmonary resuscitation on admission in the ICU. Unconsciousness was defined as a lack of response during the examination after AVPU (alert, voice, pain, unresponsive). Congenital heart disease was defined by the presence of an obvious pathological murmur upon chest auscultation on admission or echocardiographically proven heart disease. Additional clinical information included the presence and type of diarrhoea, the presence and severity of dehydration, and the presence of severe malnutrition, as well other clinical features of illness identified upon admission according to standard WHO definitions [8]. Extracted laboratory measures included the presence or absence of hypoglycemia (bedside blood glucose <3 mmol/L) on admission by bedside testing, the white blood cell count, hemoglobin, and serum bicarbonate level (HCO_3) level upon admission. A total carbon dioxide (TCO_2) of ≤17 meq/L was defined as metabolic acidosis.

Microbiologic Testing

Blood cultures were collected on hospital admission, processed, and resulted on site at the Dhaka Hospital of the icddr,b as part for routine clinical care as described previously [10]. Blood (1–3 mL) was collected and inoculated into a single pediatric FAN blood culture bottle. Bottles were incubated in the BACT/Alert machine for up to 5 days, and positive culture samples were directly inoculated onto MacConkey (MC), chocolate and blood agar plates. The MC plates were then incubated at 35°C in aerobic conditions. Chocolate and blood agar plates were incubated at 35°C in microaerophilic conditions (containing 5% CO_2). Suspected bacterial colonies were identified using standard bacteriological procedures. API identification strips (bioMérieux, Lyon, France) were used as supportive tests for further identification. Coagulase-negative Staphylococci and *Corynebacterium* species were considered presumed skin contaminants and were treated as negative cultures in subsequent analyses. Antimicrobial susceptibility tests were performed by using the disk diffusion method, and susceptibility patterns were determined following Clinical and Laboratory Standards Institute (CLSI) guidelines.

Analysis

We analyzed data on all children under 5 years with a clinically and radiographically confirmed diagnosis of pneumonia and a blood culture within the enrollment period. We performed a bivariate analysis on characteristics and

outcomes of children with bacteremia versus without bacteremia using logistic regression models for categorical variables and linear regression models for continuous variables. We also performed a bivariate analysis on characteristics of children who died versus those who survived. A multivariate logistic regression model was run including age, sex, and significant covariates. We elected not to include serum bicarbonate (because of a high rate of missing data), severe pneumonia (because of redundancy with hypoxemia, convulsion, and respiratory failure, which are included in the definition of severe pneumonia), and hospital length of stay (confounded by death). We performed all analyses using Stata version 14.0 (StataCorp, College Station, TX). A *P* value of <.05 was considered statistically significant. Strength of association was determined by calculating odds ratios (ORs) and their 95% confidence intervals (CIs).

Ethical Standards

The study was approved by the Institutional Review Board (IRB) of icddr,b. The RB of icddr,b comprises 2 bodies, ie, Research Review Committee and Ethical Review Committee, and the study has been approved by both of the committees.

Patient Consent Statement

The study involved a retrospective review of electronic medical records and no intervention or alterations in patient care. The study was approved by the Research and Ethical Review Committees of the icddr,b and not deemed to require consent.

RESULTS

Characteristics of Young Children With Clinical as Well as Radiographic Pneumonia and Bacteremia

A total of 4007 young children were admitted with clinical and radiographic pneumonia during the study period. As shown in Table 1, 1814 children (45%) were evaluated with blood culture upon admission. Compared to those in whom no blood culture was obtained, children who were cultured were more likely to have clinical signs of severe pneumonia, hypoxemia, or sepsis. Although increasing age was associated with a slightly higher likelihood of having a culture obtained, biological sex was not associated with the likelihood of having blood cultures.

Of the1814 children who were evaluated with blood culture, 108 (6%) had a positive blood culture. As shown in Table 2, among those who had a blood culture performed, children who were severely underweight (≤3 standard deviation by weight-for-age) were more likely to have a positive blood culture (OR,

Table 1. Characteristics of Young Children Whose Blood Culture Was Obtained Versus Those Who Did Not Have Blood Culture Obtained

		Children With:		Univariate Analysis			Multivariate Regression		
	Characteristics	Blood Culture Obtained (n = 1814) (%)	No Blood Culture (n = 2193) (%)	OR	95% CI	*P*	aOR	95% CI	*P*
Demographic	Male gender	**1166 (64)**	**1478 (67)**	**0.87**	**0.76–0.99**	**.038**[a]	1.05	0.90–1.23	.535
	Age in months (median, IQR)	7.9 (4.8–11.6)	8.0 (5.0–12.0)	-	-	.720	**1.02**	**1.01–1.03**	**.001**[a]
Clinical Features	**Severe underweight**	**663 (37)**	**574 (26)**	**1.62**	**1.42–1.86**	**<.001**[a]	1.05	0.88–1.26	.595
	Severe acute malnutrition	**846 (47)**	**818 (37)**	**1.47**	**1.29–1.67**	**<.001**[a]	1.01	0.84–1.22	.891
	Severe pneumonia	**1502 (83)**	**1254 (57)**	**3.60**	**3.11–4.18**	**<.001**[a]	**1.71**	**1.37–2.13**	**<.001**[a]
	Presence of Diarrhea	**1575 (87)**	**1727 (79)**	**1.78**	**1.50–2.11**	**<.001**[a]	1.50	0.99–2.28	.055
	Acute watery	**1405 (77)**	**1570 (72)**	**1.363**	**1.18–1.57**	**<.001**[a]	0.96	0.66–1.41	.836
	Invasive	81 (4)	78 (4)	1.267	0.92–1.74	.143			
	Persistent	**89 (5)**	**79 (4)**	**1.38**	**1.01–1.88**	**.041**[a]	**1.70**	**1.02–2.84**	**.040**[a]
	Dehydration (some/severe)	**560 (31)**	**337 (15)**	**2.46**	**2.11–2.87**	**<.001**[a]	**1.83**	**1.51–2.22**	**<.001**[a]
	Ileus	**139 (8)**	**69 (3)**	**2.55**	**1.90–3.43**	**<.001**[a]	1.37	0.97–1.95	.076
	Hypoxemia	**817 (45)**	**310 (14)**	**4.98**	**4.28–5.79**	**<.001**[a]	**2.62**	**2.14–3.21**	**<.001**[a]
	Respiratory failure	**159 (9)**	**29 (1)**	**7.168**	**4.80–10.70**	**<.001**[a]	1.39	0.86–2.25	.184
	Severe sepsis	**313 (17)**	**54 (2)**	**8.26**	**6.14–11.11**	**<.001**[a]	**3.89**	**2.67–5.67**	**<.001**[a]
	Congenital heart disease	**133 (7)**	**124 (6)**	**1.32**	**1.03–1.70**	**.031**	1.20	0.89–1.62	.242
	Convulsions	**358 (20)**	**131 (6)**	**3.87**	**3.13–4.78**	**<.001**[a]	**1.50**	**1.16–1.95**	**.002**[a]
	Fever	**1147 (63)**	**1189 (54)**	**1.45**	**1.28–1.65**	**<.001**[a]	**1.51**	**1.29–1.77**	**<.001**[a]
Laboratory Findings	**WBC count (median, IQR)**	**14 940 (10 650–20 550)**	**13 640 (10 090–18 210)**	**-**	**-**	**<.001**[a]			
	Serum bicarbonate (median, IQR)	15.7 (11.9–19.8)	16.5 (12.6–20.2)	-	-	.064			
	Hemoglobin (median, IQR)	**10.2 (9.1–11.5)**	**11.0 (9.7–12.1)**	**-**	**-**	**<.001**[a]	**0.87**	**0.83–0.90**	**<.001**[a]
Outcomes[b]	**Duration hospitalization (median, IQR)**[a]	**8 (5–12)**	**5 (3–7)**	-	-	**<.001**[a]			
	Death	**155 (9)**	**31 (1)**	**6.52**	**4.41–9.63**	**<.001**[a]			

Bold text indicates significant finding.

Abbreviations: aOR, adjusted odds ratio; CI, confidence interval; IQR, interquartile range; OR, odds ratio; WBC, white blood cells.

[a]Hospital stay not including those transferred, left against medical advice, or died in hospital.

[b]Outcomes excluded from multivariate analysis.

Table 2. Characteristics of Young Children with Pneumonia: With Versus Without Bacteremia

	Characteristics	Children With:		Univariate Analysis			Multivariate Regression		
		Bacteremia (n = 108) (%)	No Bacteremia (n = 1706) (%)	OR	95% CI	*P*	aOR	95% CI	*P*
Demographic	Male gender	65 (60)	1101 (65)	0.83	0.56–1.24	.361	0.89	0.58–1.35	.574
	Age in months (median, IQR)	6.98 (3.18–11.34)	8.0 (4.89–11.63)	-	-	.963	1.01	0.98–1.03	.604
Clinical Features	**Severe underweight**	**54 (50)**	**1097 (64)**	**1.80**	**1.22–2.66**	**.003**[a]	**1.57**	**1.02–2.41**	**.039**[a]
	Severe acute malnutrition	49 (45)	797 (47)	0.95	0.64–1.40	.786			
	Severe pneumonia	94 (87)	1408 (83)	1.42	0.80–2.53	.231			
	Presence of Diarrhea	98 (91)	1477 (87)	1.52	0.78–2.96	.218			
	Acute watery	86 (80)	1319 (77)	1.15	0.71–1.86	.577			
	Invasive	5 (5)	76 (4)	1.04	0.41–2.63	.932			
	Persistent	7 (6)	82 (5)	1.37	0.62–3.05	.436			
	Dehydration (some/severe)	34 (31)	526 (31)	1.03	0.68–1.57	.887			
	Ileus	8 (7)	131 (8)	0.10	0.46–2.02	.918			
	Hypoxemia	**63 (58)**	**754 (44)**	**1.77**	**1.19–2.62**	**.005**[a]	1.30	0.83–2.04	.258
	Respiratory failure	**25 (23)**	**134 (8)**	**3.53**	**2.19–5.71**	**<.001**[a]	**2.03**	**1.13–3.63**	**.017**[a]
	Severe sepsis	**38 (35)**	**275 (16)**	**2.82**	**1.86–4.28**	**<.001**[a]	**1.87**	**1.13–3.09**	**.015**[a]
	Congenital heart disease	5 (5)	128 (8)	0.60	0.24–1.50	.272			
	Convulsions	19 (18)	339 (20)	0.86	0.52–1.43	.564			
	Fever	65 (60)	1082 (63)	0.50	0.59–1.30	.872			
Laboratory Findings	WBC count (median, IQR)	16 615 (7550–26 430)	14 890 (10 775–20 365)	-	-	.157			
	Serum bicarbonate (median, IQR)	15.2 (10.3–19.0)	15.6 (12–19.9)	-	-	.108			
	Hemoglobin (median, IQR)	**9.8 (8.5–10.9)**	**10.3 (9.1–11.5)**	**-**	**-**	**.001**[a]	**0.88**	**0.80–0.97**	**.009**[a]
Outcomes[b]	Duration hospitalization (med, IQR)[a]	8 (5.5–12.5)	8 (5.0–12.0)			.668			
	Death	**31 (29)**	**124 (7)**	**5.14**	**3.26–8.10**	**<.001**[a]			

Bold text indicates significant finding.

Abbreviations: aOR, adjusted odds ratio; CI, confidence interval; IQR, interquartile range; OR, odds ratio; WBC, white blood cells.

[a]Hospital stay not including those transferred, left against medical advice, or died in hospital.

[b]Outcomes excluded from multivariate analysis.

1.8; 95% CI, 1.2–2.7; *P* = .003). Children with bacteremia also had a significantly lower mean hemoglobin level (9.8 g/dL) compared to nonbacteremic children (10.3 g/dL, *P* = .001). Children with bacteremia were more likely to meet the WHO clinical criteria for severe sepsis and respiratory failure compared to nonbacteremic children. There was no significant difference in the median white blood cell count in children with and without bacteremia. Concomitant diarrheal illness was common in this cohort but was not predictive of bacteremia. In a multivariate analysis, severe malnourishment, lower hemoglobin levels, and clinical findings meeting the criteria for severe sepsis and respiratory failure remained associated with bacteremia.

Distribution of Pathogens Associated With Bacteremia in Young Children With Pneumonia

The distribution of pathogens identified in blood cultures obtained from this cohort of children is shown in Table 3. Gram-negative bacteria were predominant pathogens (N = 83, 77% of 108 isolates), and *Pseudomonas* was the most common isolate (N = 22). *Enterobacteriaceae* accounted for 46 of 108 isolates (43%) overall, with *Escherichia coli*, *Klebsiella pneumoniae*, and *Salmonella enterica* predominating. Although Gram-positive bacteria were less commonly observed than the Gram-negative bacteria, they still accounted for 25 of the 108 isolates (23%) overall. The most common Gram-positive bacteria identified were *Pneumococcus* (N = 7) and *Staphylococcus aureus* (N = 7).

Antibiotic Resistance

Antibiotic resistance data are shown in Table 3, according to bacterial class or species. Multidrug resistance was common among the *Enterobacteriaceae*. Of 30 *E coli*, *K pneumoniae*, and *Enterobacter* isolates, 12 (40%) were resistant to all routinely used empiric antibiotics (using ciprofloxacin resistance as a proxy for levofloxacin resistance, because the latter was not tested routinely). Most *Enterococcus* isolates (4 of 5) were ampicillin and ciprofloxacin resistant. In contrast, most other bacteria, including many *Pseudomonas* and *Acinetobacter* isolates, were not multidrug resistant. Among the *Pseudomonas* isolates that were tested for resistance against ceftazidime, only 2 of the 20 tested demonstrated resistance.

Mortality Among Young Children With Pneumonia and Bacteremia

Of the 4007 children hospitalized with pneumonia, 186 died during the course of their hospitalization. Death occurred a median of 3 days (interquartile range [IQR], 2–5) from the time of hospitalization. A total of 3333 (83%) children were discharged after a median hospital stay of 6 days (IQR, 4–9). Another 280 (7%) were transferred to another hospital, whereas 208 (5%) left the hospital

Table 3. Antibiotic Resistance and Bacterial Isolates From Blood in Children Less Than Five Years of Age Hospitalized for Pneumonia

				Resistant to 1st Line (Resistant/Tested)			Resistant to 2nd Line (Resistant/Tested)			
Classification of Bacterial Type/ Species (N = 108)	Bacteremic (N [%])	Severe Sepsis (N)	Died (N)	Ampicillin, N = 77	Gentamicin, N = 34	Both, N = 31	Ceftriaxone N = 59	Ciprofloxacin N = 60	Both N = 34	Resistant to all 1st and 2nd line Resistant/tested N = 20
Enterobacteriaceae	**46 (43)**									
Escherichia coli	17	10	9	16/17	8/17	8/17	14/17	13/17	13/17	7/17
Klebsiella pneumoniae	11	5	4	*R**	7/11	7/11	8/10	7/11	5/10	4/11
Enterobacter	2	2	0	2/2	1/2	1/2	1/2	1/2	1/2	1/2
Salmonella enterica										
Typhi	11	3	1	4/11	1/2	0/7	0/11	11/11	0/11	0/11
Non-Typhi	3	1	1	1/3	-	0/2	0/3	2/3	0/3	0/3
Shigella	2	1	0	0/2	-	0/2	0/2	1/2	0/2	0/2
Gram-Negative, Non-*Enterobacteriaceae*	**37 (34)**									
Pseudomonas sp[a]	22	5	5	*R**	4/21	4/21	*R**	3/22	3/22	2/22
Acinetobacter sp	7	0	2	7/7	1/7	1/7	5/7	6/7	5/7	1/7
Hemophilus sp										
Haemophilus *influenzae*	1	1	1	0/1	-	0/1	0/1	-	0/1	0/1
Haemophilus *parainfluenzae*	1	0	0	0/1	-	0/1	0/1	-	0/1	0/1
Moraxella catarrhalis	1			-	-	-	0/1	-	0/1	0/1
Campylobacter	5	0	0	4/5	-	0/1	1/1	4/5	1/2	0/1
Gram-Positive Bacteria	**25 (23)**									
Streptococcus sp										
Pneumococcus	7	3	2	0/4	-	0/4	0/7	-	0/7	0/7
Other	6	2	0	0/3	-	0/3	2/5	1/1	0/3	0/4
Enterococcus	5	2	2	4/5	*R**	4/5	*R**	5/5	5/5	4/5
Staphylococcus										
MSSA	6	2	2	5/6	*R**	5/6	*S**	5/6	0/6	0/6
MRSA	1	1	1	*R**	*R**	1/1	*R**	1/1	1/1	1/1

Bold text indicates bacteremia sub-categories.

Abbreviations: MRSA, methicillin-resistant *S aureus*; MSSA, methicillin-sensitive *S aureus*; *R**, denotes that intrinsic resistance is assumed for this combination OR that the agent does not constitute an acceptable treatment regimen (eg, gentamicin is used only as an adjunctive therapy for *S aureus* infection, not primary therapy); *S**, denotes assumed susceptibility (MSSA implies susceptibility to ceftriaxone); -, denotes not tested.

[a]Two of 20 *Pseudomonas* species tested were found to be susceptible to ceftazidime; however, this was not used routinely nor was it used as part of an empiric regimen.

Table 4. Characteristics of Children Who Died Compared to Those Who Survived

Characteristics		Children Who:		Univariate Analysis			Multivariate Regression		
		Died (n = 186) (%)	Survived (n = 3821) (%)	OR	95% CI	*P*	aOR	95% CI	*P*
Demographic	**Male gender**	**101 (54)**	**2543 (67)**	**0.60**	**0.44–0.80**	**.001***	0.86	0.53–1.40	.544
	Age in months (median, IQR)	7.6 (4.0–11.0)	7.95 (4.9–18.1)	-	-	.139	0.98	0.95–1.02	.363
Clinical Features	**Severe underweight**	**117 (63)**	**1120 (29)**	**4.09**	**3.013–5.55**	**<.001***	1.64	0.96–2.80	.071
	Severe acute malnutrition	**101(54)**	**1563 (41)**	**1.72**	**1.28–2.31**	**<.001***	1.70	0.98–2.97	.060
	Severe pneumonia	**181 (97)**	**2575 (67)**	**17.52**	**7.19–42.70**	**<.001***	0.81	0.24–2.68	.726
	Presence of Diarrhea	**167 (90)**	**3135 (82)**	**1.92**	**1.19–3.11**	**.008***	0.73	0.24–2.68	.624
	Acute watery	**158 (85)**	**2817 (74)**	**2.01**	**1.34–3.03**	**.001***	1.89	0.65–5.48	.122
	Invasive	5 (3)	154 (4)	.6577	0.27–1.62	.363			
	Persistent	4 (2)	164 (4)	.490	0.18–1.34	.163			
	Dehydration (some/severe)	**67 (36)**	**830 (22)**	**2.03**	**1.50–2.76**	**<.001***	0.65	0.38–1.12	.122
	Ileus	15 (8)	193 (5)	1.65	.95-2.85	.073			
	Hypoxemia	**153 (82)**	**974 (25)**	**13.55**	**9.24–19.88**	**<.001***	**3.13**	**1.72–5.71**	**<.001***
	Respiratory failure	**133 (72)**	**55 (1)**	**171.83**	**113.46–260.21**	**<.001***	**76.2**	**43.21–134.37**	**<.001***
	Severe sepsis	**119 (64)**	**248 (6)**	**25.59**	**18.47–35.45**	**<.001***	**5.01**	**3.04–8.50**	**<.001***
	Congenital heart disease	14 (8)	243 (6)	1.20	0.68–2.10	.526			
	Convulsions	**59 (32)**	**430 (11)**	**3.66**	**2.65–5.07**	**<.001***	0.58	0.32- 1.05	.071
	Fever	1089 (58)	2228 (58)	0.99	0.73–1.33	.947			
	Blood culture								
	No blood culture obtained			Ref					
	Negative blood culture	**124 (67)**	**1582 (40)**	**5.47**	**3.67–8.15**	**<.001***	1.82	0.96–3.48	.068
	Positive blood culture	**31 (17)**	**77 (2)**	**28.08**	**16.24–48.53**	**<.001***	**6.25**	**2.33–16.75**	**<.001***
Laboratory Findings	**WBC count (median, IQR)**	**16 100 (10 960–28 040)**	**14 350 (10 320–19 090)**	**-**	**-**	**<.001***	1.00	0.99–1.00	.206
	Serum bicarbonate (median, IQR)	**14.4 (10.1–19.4)**	**16.1 (12.3–19.9)**	**-**	**-**	**.035***			
	Hemoglobin (median, IQR)	**10 (8.3–11.2)**	**10.6 (9.5–11.9)**	**-**	**-**	**<.001***	0.98	0.82–1.02	.098

Asterisks indicate significant *P* values.

Abbreviations: aOR, adjusted odds ratio; CI, confidence interval; IQR, interquartile range; OR, odds ratio; Ref, indicates the reference group for the Odds Ratio. "No blood culture obtained" is the reference group for the comparison to "negative blood culture" and "positive blood culture; WBC, white blood cells.

before discharge against medical advice. Risk factors for death are shown in Table 4. Female sex was associated with an increased risk of death in the univariate analysis but was not an independent predictor of mortality after adjusting for other factors also associated with death. In a univariate analysis, having a blood culture obtained was a risk factor for death (OR, 5.5; 95% CI, 3.7–8.2; $P < .0001$), but this was no longer significant after adjusting for age, sex, and other risk factors associated with mortality (aOR, 1.8; 95% CI, 0.96–3.48; $P = .068$). Having a positive blood culture was also associated with an increased risk of mortality (OR, 28.1; 95% CI, 16.2–48.5; $P < .0001$). This remained significant even after adjusting for malnutrition and other clinical and laboratory characteristics associated with death (aOR, 6.3; 95% CI, 2.3–16.8; $P < .0001$).

Increased Likelihood of Death Is Associated With Antibiotic Resistance

Figure 1 shows the OR of death in young children with pneumonia classified by the type of bacteria isolated in their blood cultures. Both Gram-negative and Gram-positive bacteremia were associated with a similarly increased risk of death relative to nonbacteremic children (OR = 5.2, $P < .001$ for Gram-negative and an OR = 5.0, $P < .001$ for Gram-positive). Resistance to antibiotics conferred an increasing likelihood of death (Figure 1). For example, bacteremia resistant to both first-line antibiotics (resistant to ampicillin and gentamicin) was associated with a 9.6-fold increased odds of death compared to no-bacteremia ($P < .001$), whereas resistance to all first- and second-line therapies was associated with a 17.3-fold increased odds of death ($P < .001$). Children with a positive blood culture for bacteria that demonstrated resistance to all first- and second-line therapies (pan-resistant) had an increased risk of death compared to children with bacteremia due to a nonpan-resistant organism (sensitive to at least 1 antibiotic). In particular, 8 of the 12 children (67%) with a pan-resistant *E coli*, *K pneumoniae*, or *Enterobacter* died compared to 5 of 18 (28%) children infected for whom a blood culture grew an isolate that was susceptible to any one of the first- or second-line antibiotics (OR, 5.2; 95% CI, 1.1–25.3; $P = .041$).

DISCUSSION

To effectively prevent and treat childhood pneumonia, it is necessary to identify the infectious causes. This requires investment in global laboratory infrastructure as the causes of pneumonia, and their associated antimicrobial resistance patterns differ across populations, geographic locations, and over time.

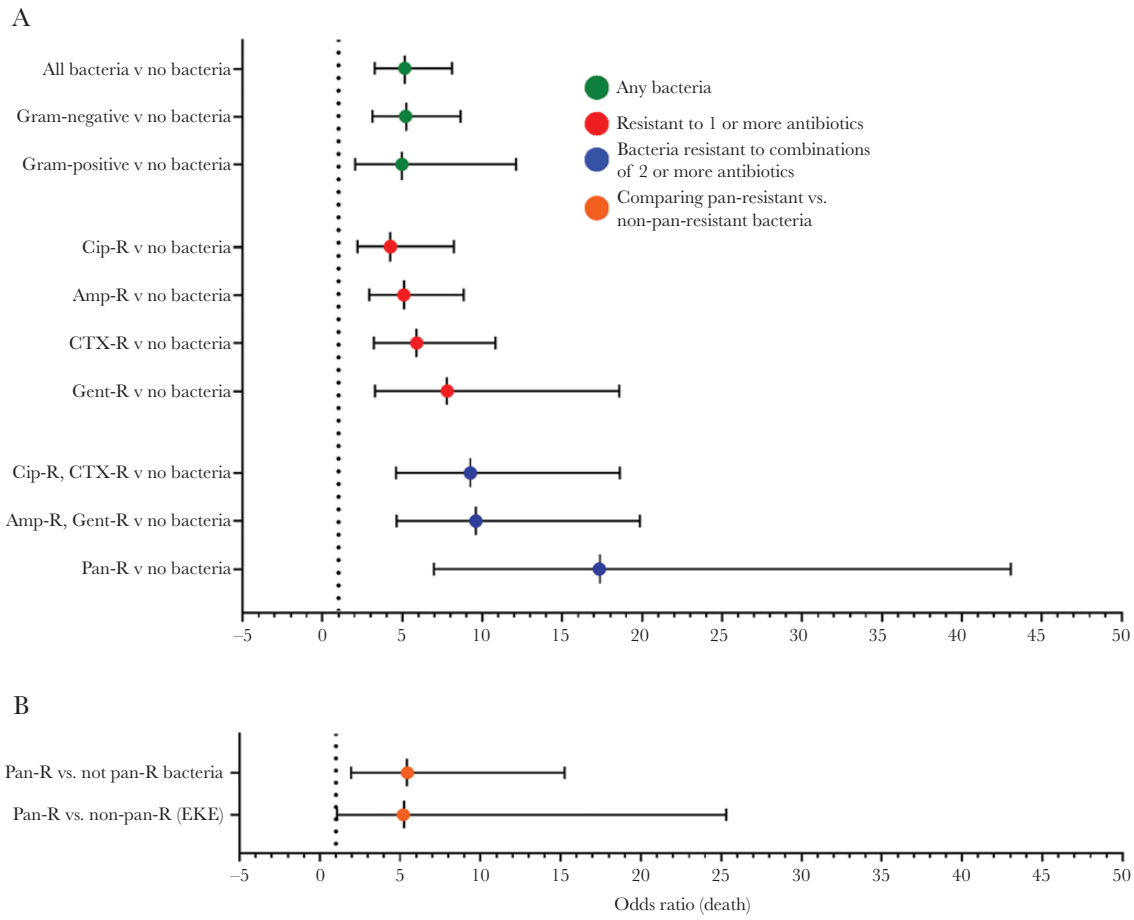

Figure 1. Odds ratio of death by antibiotic resistance.

This study, conducted in a cohort of young children hospitalized with pneumonia in urban Bangladesh, had several key findings. First, despite care in a tertiary setting with expertise in the treatment of critically ill malnourished children [11], 9% of children admitted with pneumonia who had a blood culture obtained died before discharge from the hospital, including 30% of children with bacteremia and pneumonia. Second, among children with pneumonia who were bacteremic, Gram-negative pathogens accounted for an unexpectedly large proportion of cases, and many of these organisms were resistant to some or all of the antibiotics used for primary and secondary empiric therapy. Third, we observed the highest rates of mortality in children infected with antibiotic-resistant bacteria. Taken together, these findings suggest that the emerging pandemic of antibiotic-resistant bacterial infection is already taking a toll on young children in Dhaka, Bangladesh. This is a significant finding, and we are not aware of previous studies that have addressed the microbial causes and outcomes of bacteremia childhood pneumonia in a similarly large cohort of children in South Asia, nor are we aware of other studies that demonstrate a clear increase in death associated with antibiotic resistance in childhood pneumonia.

As noted above, the distribution of infectious causes of bacteremia in this cohort is unexpected. *Enterobacteriaceae*, a family of intestinal Gram-negative bacteria, were among the most frequently isolated pathogens. With the exception of *K pneumoniae*, these pathogens are typically not associated with a primary respiratory infection, which suggests that young children with both clinical and radiographic evidence of pneumonia may have other or additional underlying source(s) of illness, particularly in a population where concomitant malnourishment and diarrheal illness are common. In addition to *Enterobacteriaceae,* we observed a high proportion of bacteremia due to *Pseudomonas*, *Acinetobacter*, and *Enterococcus*. These are all pathogens that frequently have antibiotic resistance and are not considered common community-acquired respiratory pathogens [5].

There are some notable limitations of this study. First, it is unlikely that the cause of infection in the 6% of young children in this cohort with bacteremia is reflective of the infectious causes of pneumonia in the larger number of children in whom no blood culture was obtained or whose blood cultures were negative. Although these nonbacteremic children are more likely to have a nonbacterial source of infection, the lack of accurate noninvasive diagnostic testing methods complicates this assessment. Nonetheless, it is possible that some of these antibiotic-resistant bacterial infections, even in the absence of detectable bacteremia, significantly contribute to the disease burden in this group of children. A second limitation of this study is the absence of posthospitalization follow-up that would aid in our understanding of the full spectrum of outcomes in this cohort [12]. A third limitation is that we did not have detailed immunization data on this cohort of young children. Pnuemococcal conjugate vaccination was introduced in Bangladesh in March 2015, and this may have influenced the distribution of blood culture results in this cohort. A fourth limitation is that we were unable to account for preadmission antibiotic usage in this cohort. This is significant, given that antibiotics are widely available and often used through the nonprescription retail drug sector in Bangladesh [13] and because self-reported data are not necessarily reliable indicators of outpatient antibiotic usage in this setting [14].

CONCLUSIONS

Our study identifies several pressing challenges. First, improved diagnostic testing and surveillance capacity for childhood pneumonia is needed. Second, there is an urgent need to identify children at risk for significant morbidity or death from antibiotic-resistant bacterial infections and to provide more effective empiric antibiotics for these children. Finally, to stop the pandemic of antibiotic resistance from killing young children, it will be necessary to develop better approaches to prevention. These approaches could focus on reducing predisposing factors (including diarrheal illness and malnourishment), improving antibiotic stewardship (particularly in the outpatient setting, where use of antibiotics through the retail drug sector is extremely common), and developing vaccines for pathogens that fuel the transmission of drug resistance (including *Enterobacteriaceae)*.

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