Critical Pertussis Illness in Children: A Multicenter Prospective Cohort Study*

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Objective: Pertussis persists in the United States despite high immunization rates. This report characterizes the presentation and acute course of critical pertussis by quantifying demographic data, laboratory findings, clinical complications, and critical care therapies among children requiring admission to the PICU.

Design: Prospective cohort study.

Setting: Eight PICUs comprising the *Eunice Kennedy Shriver* National Institute for Child Health and Human Development Collaborative Pediatric Critical Care Research Network and 17 additional PICUs across the United States.

Patients: Eligible patients had laboratory confirmation of pertussis infection, were younger than 18 years old, and died in the PICU or were admitted to the PICU for at least 24 hours between June 2008 and August 2011.

Interventions: None.

Measurements and Main Results: A total of 127 patients were identified. Median age was 49 days, and 105 (83%) patients were less than 3 months old. Fifty-five (43%) patients required mechanical ventilation and 12 patients (9.4%) died during initial hospitalization. Pulmonary hypertension was found in 16 patients (12.5%) and was present in 75% of patients who died, compared with 6% of survivors ($p < 0.001$). Median WBC was significantly higher in those requiring mechanical ventilation ($p < 0.001$), those with pulmonary hypertension ($p < 0.001$), and nonsurvivors ($p < 0.001$). Age, sex, and immunization status did not differ between survivors and nonsurvivors. Fourteen patients received leukoreduction therapy (exchange transfusion [12], leukopheresis [1], or both [1]). Survival benefit was not apparent.

Conclusions: Pulmonary hypertension may be associated with mortality in pertussis critical illness. Elevated WBC is associated with the need for mechanical ventilation, pulmonary hypertension,

and mortality risk. Research is indicated to elucidate how pulmonary hypertension, immune responsiveness, and elevated WBC contribute to morbidity and mortality and whether leukoreduction might be efficacious. (*Pediatr Crit Care Med* 2013; 14:356–365)
Key Words: intensive care; leukocyte reduction procedures; outcome; pertussis; pulmonary hypertension; respiratory failure

Pertussis outbreaks and fatalities persist even in areas of high immunization coverage. Critical pertussis is defined as pertussis disease that results in PICU admission or death. Critical pertussis occurs primarily in early infancy, and effective protection of this age group by direct immunization has been problematic. Alternate strategies, including adult immunization and "cocooning" where neonates are discharged into fully immunized households, have been used in several developed countries (1–3). In the United States and other developed countries, pertussis critical illness continues to occur (4).

Data presently available about the course of critical pertussis illness have come from retrospective studies of smaller cohorts (5–7). Although some markers of illness severity have been suggested (8–10), they have not been assessed in larger prospective series that might distinguish children with critical pertussis illness and those at elevated risk of fatal outcomes. Characterization of the acute course of critical pertussis in U.S. PICUs is the principal aim of the prospective cohort study underway in the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) Collaborative Pediatric Critical Care Research Network (CPCCRN). We describe interim findings and an analysis of data from 127 children with confirmed pertussis who either died or spent at least 24 hours in the PICU, especially focused on findings that appear to distinguish survivors from nonsurvivors.

METHODS

The NICHD Critical Pertussis Study is an ongoing prospective cohort study at the eight CPCCRN affiliated PICUs and 17 additional PICUs across the United States (11). The protocol is available at http://cpccrn.org/documents/PertussisProtocolVersion4.0003Aug10_000.pdf. Approximately 33,000 PICU admissions were screened annually for evidence of critical pertussis by passive and enhanced surveillance. All children from 0 to 18 years old with laboratory-confirmed (polymerase chain reaction and/or positive culture) pertussis were eligible for enrollment if they had a PICU stay of at least 24 hours or died (12, 13). Enrollment began in June 2008. All patients with complete data available on August 28, 2011 were included in the analysis.

Data were collected through daily chart abstraction and parental and staff interviews. Clinical, demographic, and laboratory data were collected at admission to the PICU, and daily until discharge from the PICU, 28 days or death. Parental telephone interviews and chart abstraction was used to collect data on patients identified with pertussis after death ($n = 2$). Data points recorded included presenting symptoms, immunization status, chronic illness, and critical care treatments. A WBC value obtained within 48 hours of admission was used for analysis. When multiple WBC counts were obtained in this time interval, the highest value was used. Sites reporting patients with pulmonary hypertension were queried regarding method of diagnosis. Echocardiograms were obtained at the discretion of the clinicians. In this analysis, patients were considered to have undergone leukoreduction if at least one exchange transfusion or leukopheresis session was reported.

Results of neurodevelopmental status at PICU discharge were recorded. In addition, health and quality of life measures using Infant and Toddler Quality of Life Questionnaire were obtained 6 and 12 months after hospital discharge. Developmental assessment for those patients who were less than 12 months old at enrollment was done 12 months after PICU discharge using the Mullen Scales of Early Learning. Analysis of neurodevelopmental and quality of life data is ongoing and not reported here. All data were transmitted to the NICHD-supported CPCCRN Data Coordinating Center at the University of Utah for data quality monitoring and analysis. The protocol was approved by the IRB at each participating institution, and written parental consent was obtained prior to enrollment. CPCCRN and outside site investigators are uniformly trained in study requirements.

Statistical Analysis

We used descriptive statistical techniques to describe patient characteristics and elements of the presenting illness and to characterize the course of the pertussis critical illness in the PICU. For this analysis, we sought evidence of associations of key characteristics with mortality and the need for invasive mechanical ventilation. Counts and percentages were reported for categorical variables and median and the interquartile range (IQR, 25–75th percentile) for continuous variables. Mortality risk ratios for clinical events occurring in the PICU and WBC value greater than 50×10^9 L^{-1} and 95% CI were described. Receiver operating curves were calculated to evaluate the predictive value of hematologic data. Statistical significance of observed associations was evaluated using a chi-square test or Fisher exact test for categorical variables and the Wilcoxon signed rank test for continuous variables. A significance level of 0.05 was used for all analyses. No adjustments were made for multiple comparisons as the nature of the statistical comparisons was descriptive and intended to generate hypotheses rather than provide inference about specific scientific questions.

RESULTS

During the initial study period, 143 eligible cases were identified. Three families could not be reached to obtain consent and eight parents/caregivers refused enrollment. Two families withdrew from the study before baseline data were obtained, and three patients were still hospitalized and their data were incomplete at the time of analysis. Complete datasets for interim analysis were therefore available for 127 patients.

Patients Characteristics

Demographics and illness history are summarized in **Table 1**. Half of the enrolled patients were female. Of the cohort, 92 (79%) patients were identified by parents/caregivers as white and 14 (12%) as African American. Hispanic ethnicity was identified in 71 of the cohort (56%). Median age at PICU admission was 49 days (IQR, 31; 74 days), and 105 of patients (83%) were less than 3 months old. Age distribution is displayed in **Figure 1**.

Thirty-three patients (26%) had received at least one pertussis immunization. Thirty-four (27%) were born prematurely (< 37 wk gestation), and 26 (21%) had been admitted to neonatal ICU (NICU) after birth. Of these, 11 (42%) were mechanically ventilated in the NICU. The incidence of preterm birth in the study cohort was significantly elevated ($p < 0.001$) compared with the national rate (12.3%) (15). Twenty-nine patients (23%) had a history of chronic disease, and 11 (9%) were technology dependent: six with gastrostomies and five

TABLE 1. Demographics and Illness History Prior to PICU Admission by Survival, *n* (%)

	Overall, *n* = 127	Survivors, *n* = 115	Deaths, *n* = 12	*p*
Demographics				
Women	64 (50)	60 (52)	4 (33)	0.21
Race				0.27
Black or African American	14 (12)	12 (11)	2 (17)	
White	92 (79)	84 (80)	8 (67)	
Other	11 (9)	9 (9)	2 (17)	
Hispanic or Latino ethnicity	71 (56)	65 (57)	6 (50)	0.64
Age				0.83
< 3 mo	105 (83)	95 (83)	10 (83)	
3–11 mo	15 (12)	13 (11)	2 (17)	
1 yr or older	7 (6)	7 (6)	0 (0)	
Past medical history				
Premature	34 (27)	29 (25)	5 (45)	0.17
Small for gestational age at birth[a]	6 (5)	6 (5)	0 (0)	1.0
Documented pertussis vaccinations	33 (26)	29 (25)	4 (36)	0.48
Chronic disease	29 (23)	26 (23)	3 (25)	1.0
Chronic device	11 (9)	9 (8)	2 (18)	0.25
History of current illness				
Cough during acute illness	125 (98)	114 (99)	11 (92)	0.18
Cough started relative to PICU admission				0.04
< 1 wk prior	40 (32)	33 (29)	7 (64)	
1–2 wk prior	57 (46)	53 (47)	4 (36)	
≥ 2 wk prior	27 (22)	27 (24)	0 (0)	
Respiratory distress/hard to catch breath	121 (95)	110 (96)	11 (92)	0.46
Cyanosis	92 (72)	85 (74)	7 (58)	0.31
Apnea	62 (49)	57 (50)	5 (42)	0.60
Whoop (parent report only)	53 (42)	52 (45)	1 (8)	0.02
Altered mental status	26 (20)	22 (19)	4 (33)	0.26
Seizures or convulsions	11 (9)	10 (9)	1 (8)	1.0
Bradycardia	31 (24)	28 (24)	3 (25)	1.0

[a]Small for gestational age based on < 10th percentile at birth (14).

with nasogastric feeding tubes, two with tracheostomies and one patient was on chronic mechanical ventilation.

The most frequent symptom in the history of the present illness was cough (98%). Median cough duration at PICU admission was 8 days (IQR, 5; 13). Other frequent symptoms and signs included respiratory distress (95%), cyanosis (72%), apnea (49%), and "whoop" (42%). Seizures were present in 9% of patients and altered mental status in 20%. Median weight percentile for age was 35, and median head circumference percentile for age was 25. Initial vital signs and hematologic values are presented in **Table 2**. Most patients in the cohort (92%) had an initial WBC value reported. Median initial WBC was 27.8×10^9 L^{-1} (IQR, 17.4; 43.5). Initial WBC counts greater than 100×10^9 L^{-1} were reported in two patients. Relative risk of death for patients with a maximum WBC value of greater than 50×10^9 L^{-1} was 9.8 (95% CI, 2.8–34.3), compared with those with lower values. The area under the curve was 0.84 (95% CI, 0.74–0.94) for WBC value, 0.88 (95% CI, 0.77–0.99) for absolute neutrophil count, and 0.75 (95% CI, 0.60–0.90) for absolute lymphocyte count.

Course, Treatment, and Outcomes

Table 3 summarizes clinical events reported during the PICU course. Signs of respiratory compromise were common: 67% of the patients had cyanosis and 54% had apnea. A new pneumonia developed in 19 patients (15%) with a median age of 60 days during their PICU course. Six patients with pneumonia were born prematurely. Sixteen patients with pneumonia required mechanical ventilation and nine also had pulmonary hypertension detected. The initial WBC count was significantly higher in patients with pneumonia (median 70.5×10^9 L^{-1} vs 25.1×10^9 L^{-1}, $p < 0.001$). Pneumonia was reported in 33% of patients who died compared with 13% of survivors ($p = 0.08$).

Bradycardia was present in 80 patients (63%). Fourteen patients (11%) had a cardiac arrest with arrests occurring in six patients prior to the end of study day 0. Pulmonary hypertension detected by echocardiogram was reported in 16 patients (13%). In patients with pulmonary hypertension, five were born prematurely although only one required mechanical ventilation in the neonatal period. None of the 16 patients had a history of pre-existing pulmonary hypertension recorded nor were any receiving sildenafil or bosentan. All 16 patients were mechanically ventilated and 14 received nitric oxide. Cardiac arrest occurred in seven patients with pulmonary hypertension. Pulmonary hypertension was reported in 75% of patients who died compared with 6% of survivors ($p < 0.001$). Initial WBC value was significantly higher in patients with pulmonary hypertension (median 68.4×10^9 L^{-1} vs 25.1×10^9 L^{-1}, $p < 0.001$).

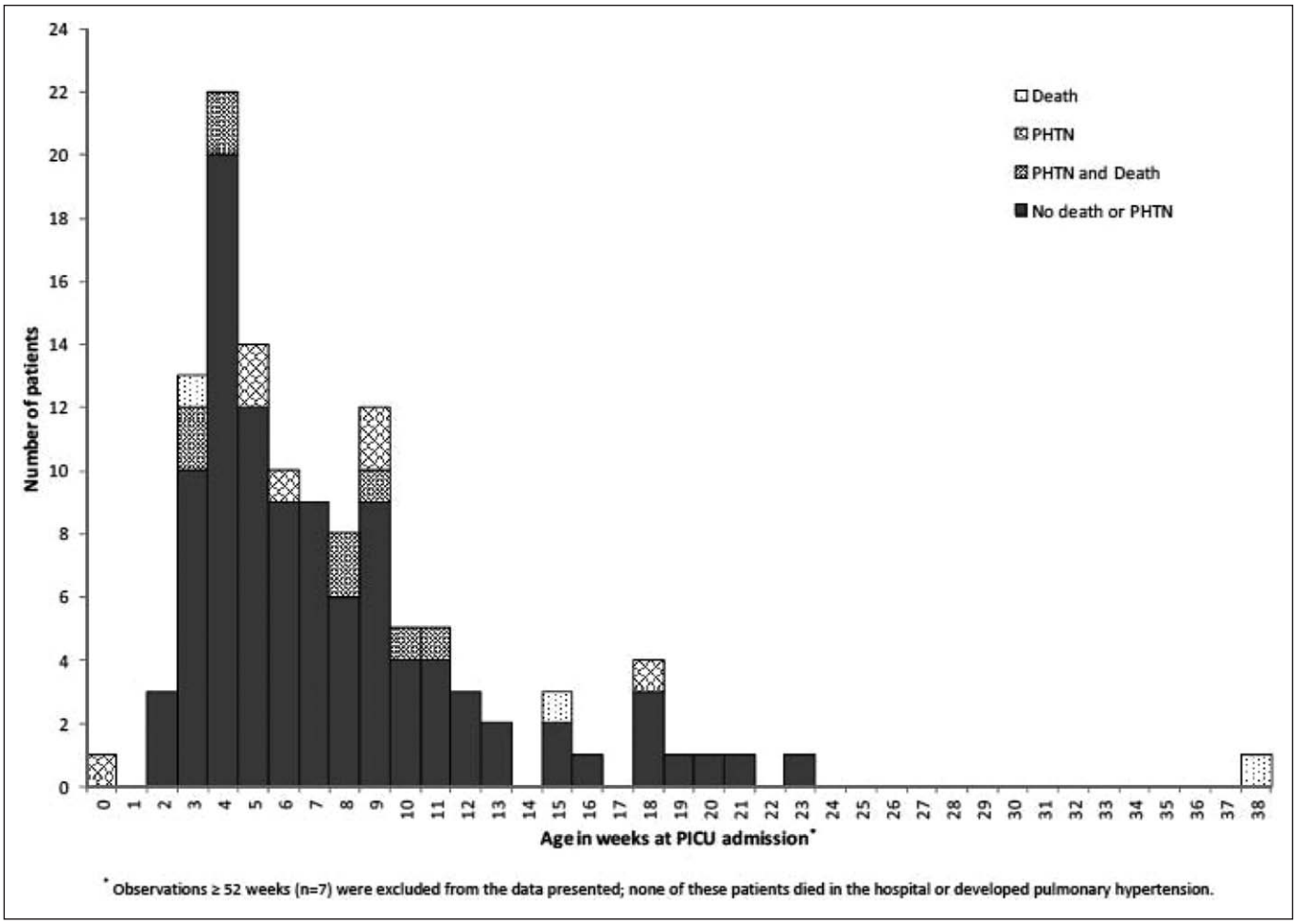

Figure 1. Patient age (wk) by death and pulmonary hypertension.

TABLE 2. Presenting Vital Signs and Hematology Values by Survival, Median (IQR)

	Overall, *n* = 127	Survivors, *n* = 115	Deaths, *n* = 12	*p*
Vital signs and measurements				
Weight (percentile for age)	35 (7, 58)	40 (7, 59)	17 (6, 25)	0.19
Head circumference (percentile for age)	25 (10, 50)	25 (10, 50)	18 (4, 50)	0.49
Temperature (°C)	36.8 (36.4, 37.3)	36.8 (36.4, 37.2)	37.0 (35.8, 37.4)	0.64
Respiratory rate	36 (28, 48)	36 (28, 48)	46 (27, 57)	0.48
Heart rate	162 (148, 179)	162 (148, 179)	165 (154, 186)	0.44
Oxygen saturation (%)	100 (97, 100)	100 (97, 100)	98 (94, 100)	0.33
Fio_2 at time of oxygen saturation (%)	35 (21, 60)	30 (21, 60)	50 (40, 90)	0.08
Pediatric Risk of Mortality score	1 (0, 4)	0 (0, 3)	6 (4, 13)	< 0.001
	***n* = 117**	***n* = 106**	***n* = 11**	
Initial CBC (based on max WBC within 48 hr of PICU admission)				
WBC count ($\times 10^9$ L^{-1})	27.8 (17.4, 43.5)	26.1 (17.0, 40.1)	66.3 (37.9, 74.7)	< 0.001
Platelets ($\times 10^9$ L^{-1})	479 (367, 580)	489 (372, 580)	408 (318, 599)	0.20
	***n* = 112**	***n* = 102**	***n* = 10**	
Initial CBC differential				
Absolute lymphocyte count ($\times 10^9$ L^{-1})	17.0 (10.0, 26.1)	16.2 (9.2, 23.9)	29.8 (19.4, 33.7)	0.01
Absolute neutrophil count ($\times 10^9$ L^{-1})	6.3 (4.2, 11.9)	6.1 (3.9, 10.5)	29.8 (24.4, 37.1)	< 0.001
	***n* = 117**	***n* = 106**	***n* = 11**	
Patients with initial WBC > 50 ($\times 10^9$ L^{-1}) (%)	25 (21)	17 (16)	8 (73)	< 0.001

CBC = complete blood count.

Blood cultures were obtained in 65 patients. Eight patients had at least one positive blood culture. In six of the eight patients, a coagulase-negative *Staphylococcus* species was the only organism isolated. Two patients who had positive blood cultures died: one with multiple blood cultures that grew *Staphylococcus epidermidis* and the other whose cultures from different study days grew *Serratia marcescens* and a coagulase-negative *Staphylococcus* species. Three patients had a positive urine culture with all surviving. Nine patients had other respiratory viruses detected by polymerase chain reaction from nasopharyngeal swabs (seven with rhino/enterovirus, one with influenza A, and one with respiratory syncytial virus). One patient with rhino/enterovirus detected died. Twenty patients had cerebral spinal fluid cultures obtained. All were negative.

Most patients in the study cohort (93%) required some form of respiratory support. A total of 27 patients (21%) were intubated and mechanically ventilated at the time of PICU admission, and an additional 16 patients were intubated prior to the end of study day 0. Overall, 55 patients required mechanical ventilation with a median duration of 8 days (IQR, 5; 18) (**Table 4**). Patients who received mechanical ventilation were smaller for age ($p = 0.01$) although not younger. Patients born prematurely tended to require mechanical ventilation more frequently; however, this difference did not reach statistical significance. Those mechanically ventilated had significantly higher initial WBC counts ($p < 0.001$) but not absolute lymphocyte counts. Survival for those requiring mechanical ventilation was 80% versus 99% in patients without respiratory failure ($p < 0.001$).

Table 5 summarizes treatments used during the PICU course. Seven patients received vasoactive agents prior to the end of study day 0 with a total of 24 receiving vasoactive agents during their PICU course. The need for vasoactive agents was significantly different between survivors and nonsurvivors ($p < 0.001$). The use of high-frequency oscillatory ventilation, inhaled nitric oxide, and other advanced cardiopulmonary support modalities was also significantly different between survivors and nonsurvivors.

Fourteen patients (11%) received leukoreduction therapy (exchange transfusion [12], leukopheresis [1], or both [1]). Four patients had leukoreduction initiated on study day 0. The median WBC value was 72.4×10^9 L^{-1} on the day that leukoreduction was initiated. There was a 52.2% reduction in the median WBC value when comparing the WBC value on the day of the first treatment to the next day. Eight of the patients undergoing leukoreduction had pulmonary hypertension reported. Of the 25 patients with initial WBC value greater than 50×10^9 L^{-1}, 13 received

TABLE 3. Clinical Events Reported During Days 0–28 of PICU Course by Survival, *n* (%)

	Overall, *n* = 127	Survivors, *n* = 115	Deaths, *n* = 12	Mortality Risk Ratio[a] (95% CI)	*p*
Respiratory					
Cyanosis	85 (67)	78 (68)	7 (58)	0.7 (0.2, 2.1)	0.53
Apnea	68 (54)	62 (54)	6 (50)	0.9 (0.3, 2.5)	0.80
Respiratory arrest	15 (12)	8 (7)	7 (58)	10.5 (3.8, 28.8)	< 0.001
Developed pneumonia	19 (15)	15 (13)	4 (33)	2.8 (0.9, 8.5)	0.08
Pneumothorax	8 (6)	3 (3)	5 (42)	10.6 (4.3, 26.1)	< 0.001
Cardiac					
Arrhythmia	22 (17)	16 (14)	6 (50)	4.8 (1.7,13.4)	0.006
Bradycardia	80 (63)	72 (63)	8 (67)	1.2 (0.4, 3.7)	1.0
Cardiac arrest	14 (11)	5 (4)	9 (75)	24.2 (7.4, 79.0)	< 0.001
Hypotension	45 (35)	33 (29)	12 (100)	Undefined[b]	< 0.001
Pulmonary hypertension	16 (13)	7 (6)	9 (75)	20.8 (6.3, 68.9)	< 0.001
Poor perfusion	34 (27)	23 (20)	11 (92)	30.1 (4.0, 224.4)	< 0.001
Other					
Abnormal bleeding	7 (6)	3 (3)	4 (33)	8.6 (3.4,21.7)	0.001
CNS bleed	6 (5)	2 (2)	4 (33)	10.1 (4.2, 24.2)	0.001
Seizure	14 (11)	10 (9)	4 (33)	4.0 (1.4, 11.7)	0.03

[a]Mortality risk ratio is the relative risk of death for patients with the clinical event.
[b]The mortality risk ratio for hypotension is undefined because the denominator (deaths without hypotension) is zero.

TABLE 4. Mechanical Ventilation Status by Key Patient Characteristics

	Received Mechanical Ventilation During PICU Course		
	Yes, *n* = 55	No, *n* = 72	*p*
Age (mo), median (IQR)	1 (1, 2)	1 (1, 2)	0.55
Women, *n* (%)	25 (45)	39 (54)	0.33
Premature, *n* (%)	19 (35)	15 (21)	0.07
Documented pertussis vaccinations, *n* (%)	14 (26)	19 (26)	0.95
Apnea history (current illness), *n* (%)	31 (56)	31 (43)	0.14
Weight (percentile for age), median (IQR)	22 (5, 50)	50 (13, 65)	0.01
Complete blood count (based on max WBC within 48 hr of PICU admission), median (IQR)			
WBC count ($\times 10^9$ L^{-1})	35.2 (21.3, 70.5)	22.2 (16.0, 33.5)	< 0.001
Absolute lymphocyte count ($\times 10^9$ L^{-1})	18.0 (10.1, 28.8)	15.0 (9.7, 22.9)	0.20
PICU length of stay (d), median (IQR)	11.8 (7.9, 24.1)	4.5 (2.8, 7.8)	< 0.001
Survival to hospital discharge, *n* (%)	44 (80)	71 (99)	< 0.001

TABLE 5. Therapies Received During Days 0–28 of PICU Course by Survival, *n* (%)

	Overall, *n* = 127	Survivors, *n* = 115	Deaths, *n* = 12	*p*
Nasal cannula	104 (82)	99 (86)	5 (42)	0.001
Nasal continuous positive airway pressure or other noninvasive ventilatory support	49 (39)	43 (37)	6 (50)	0.53
Mechanical ventilation	55 (43)	44 (38)	11 (92)	< 0.001
High-frequency ventilation	18 (14)	11 (10)	7 (58)	< 0.001
Extracorporeal membrane oxygenation or extracorporeal life support	12 (9)	5 (4)	7 (58)	< 0.001
Inhaled nitric oxide	17 (13)	10 (9)	7 (58)	< 0.001
Use of vasoactive drips	24 (19)	14 (12)	10 (83)	< 0.001
Renal replacement therapy	20 (16)	13 (11)	7 (58)	< 0.001
Exchange transfusion or leukopheresis	14 (11)	9 (8)	5 (42)	0.004
RBC transfusion	26 (20)	18 (16)	8 (67)	< 0.001

leukoreduction therapy. Of these 13, eight survived compared with nine survivors in the 12 patients with initial WBC greater than 50×10^9 L^{-1} who were not treated with leukoreduction. Median age of patients undergoing leukoreduction (47 days) did not differ from that of the study cohort as a whole.

Twelve patients (9%) died during the acute hospital course; 11 of these deaths occurred during the initial PICU admission. Time of death ranged from 0 to 70 days after admission; one patient was withdrawn from extracorporeal membrane oxygenation on day 70. Most patients who died expired after a shorter period of intensive care. Seven patients who died (58%) were less than 2 months old at admission, and all were less than 1 year old. Ethnicity, immunization status, history of prematurity, and history of chronic disease did not significantly differentiate patients who died from survivors.

DISCUSSION

In this interim analysis, we report data from 127 children with a median age of 49 days who had critical pertussis. We observed a higher mortality rate (9%) than the average across the CPCCRN PICUs (4%). We report an important association between mortality, echocardiographic evidence of pulmonary hypertension, and leukocytosis. Female patients neither had a higher rate of critical pertussis illness nor had a higher rate of pertussis-related death as been suggested in other reports (10). Although higher mortality rates have been reported for Hispanic children (10, 16), our data suggest that the higher number of deaths is due to higher number of Hispanic cases. Children with WBC greater than $50{,}000 \times 10^9$ L^{-1} had nearly a ten times higher risk of death. This is consistent with earlier reports in smaller cohorts (8, 9).

Pulmonary hypertension was associated with elevated WBC levels, the need for mechanical ventilation, and death. Seventy-five percent of patients who died had evidence of pulmonary hypertension by echocardiography. Pulmonary hypertension has been implicated in a report of fatal pertussis (16). This association is larger than that reported in other childhood diseases related to toxin-induced sepsis or forms of acute respiratory failure (17, 18). The pathophysiologic descriptions most commonly used to explain development of pulmonary hypertension are: 1) acute vasoconstriction from endothelial dysfunction and/or toxin-related mechanisms and 2) reduction of pulmonary vascular cross-sectional area from obstructive leukosequestration (19, 20). Clinical studies that might discriminate between these mechanisms are not available.

The efficacy of available therapies, including nitric oxide and extracorporeal membrane oxygenation to treat pulmonary hypertension in pertussis is uncertain. No single therapy offered a clear therapeutic advantage in this observational study. The association of high WBC with pulmonary hypertension in this and earlier reports (9) is consistent with autopsy reports showing WBC aggregates in lung microvasculature (19, 20). These findings support the hypothesis that leukosequestration may be important in the etiology of pulmonary hypertension and/or death. This suggests a possible therapeutic target. A single center reported that 80% (four of five) of patients with critical pertussis, pulmonary hypertension, and leukocytosis treated with leukoreduction therapy survived (21). In contrast, in our study cohort, a survival benefit for those undergoing leukoreduction was not apparent. The small number of children studied to date is not sufficient to recommend leukoreduction therapy as an intervention to reduce WBC count and pulmonary artery pressure. Descriptions of the nature of *Bordetella pertussis* strains circulating in the postvaccine era indicate that changes in regulon-directed virulence have occurred (22). Understanding of the significance and prevalence of these changes and how this change might relate to the resurgence in pertussis in developed countries is incomplete, and contemporary research efforts are ongoing. The importance of change in the organism itself and the onset of disease in developmentally

anergic infant hosts may emerge from these studies. *B. pertussis* has a large genome and induces complex effects on organ and cell function. The role of pertussis (PT) and Cya-A (adenylate cyclase) toxins is uncertain in the pathophysiology in human infants although the molecular characteristics of the substances have been described (23). Once thought to represent a fatal pneumonia, it seems likely that multiple organ systems and tissues are affected in children seriously ill with this disease.

Immune cell activation is a complex and tightly regulated event in sepsis syndromes. Resident alveolar macrophages are reported to be the primary innate immune cell effectors in the initial inflammatory response to *B. pertussis.* Macrophages express a series of pathogen recognition receptors, notably Toll-like receptors (TLR), capable of recognizing highly conserved sequences expressed by pathogens termed pathogen- or microbial-associated molecular patterns (24). *B. pertussis* has lipopolysaccharide as a constituent of its outer membrane. This lipid moiety binds to TLR4 receptors, triggering a cascade of events including activation of the NF-κB transcription and mutagen-activated protein kinesis pathways (25). Activation of these pathways drives transcriptional expression of proinflammatory cytokines (e.g., TNF-α, IL-1β, Interferon-γ, CXCL8/IL-8, and others) (26). This TLR-initiated immune signaling cascade results in activation of T_H1 (including TNF-α and interferon-γ) and T_H17 (IL-17) responses, both of which have been shown to be necessary for clearance of *B. pertussis* infection and development of immunity (27–31). The relevance of immune signaling function or specific perturbation in young infants with *B. pertussis* remains understudied.

Autopsy series of infants dying from critical pertussis illness in the United States and United Kingdom have reported that *B. pertussis* organisms persist (19) and that secondary infections are not uncommon (20). If humans respond to *B. pertussis* infection in a similar fashion as that reported in experimental models, failure to mount an adequate T_H1 and T_H17 response may contribute to course severity (32). In recent experimental reports, the adenylate cyclase toxin of *B. pertussis* increased IL-10 production, reducing T_H1 and T_H17 response, and diminishing pathogen clearance (33–38). Although not yet studied in human *B. pertussis* infection, increased levels of IL-10 have been associated with blunting of the T_H1 response, delayed pathogen clearance, and nosocomial infections in critically ill infants and children with other sepsis syndromes (39). Additionally, exploratory work suggests that pertussis vaccine may increase susceptibility to infection from nonpertussis organisms in children in Guinea Bissau (40). Further research is needed to clarify how altered function of T_H1 and T_H17 immune responsiveness in young infants with critical pertussis might contribute to course severity and/or persistence of the organism.

There are several important limitations of this study. First, patients were not systematically screened by echocardiogram for the presence of pulmonary hypertension nor was there rigorous definition of echocardiographic evidence or severity of pulmonary hypertension established a priori. Thus, the incidence of pulmonary hypertension may be underestimated and the association with mortality overestimated. Likewise, screening, diagnosis, and treatment for coinfections were based on clinician discretion. Also, the use of critical care therapies, including antibiotics with activity against *B. pertussis*, nitric oxide, leukoreduction, and mechanical ventilation, was not standardized across sites in this observational study and limited the ability to assess efficacy. Finally, details regarding the extent of organ dysfunction are not included in this dataset and should be included in future studies of the pathophysiologic basis underlying the most severe illness and causes of death in critical pertussis.

CONCLUSION

In this prospective cohort study of critical pertussis, elevated WBC and pulmonary hypertension were both associated with increased mortality risk. Most critical pertussis occurs in children too young to benefit from direct immunization. Studies to further characterize the course and immune biology of critical pertussis illness are needed to identify the risks and benefits of leukoreduction strategies, as well as other potential life-saving therapies. Furthermore, given that the vast majority of the world's children live in circumstances where advanced pediatric critical care services are unavailable, insight gained from contemporary pediatric critical care in the United States must provide readily assessed hematologic and hemodynamic data that can enhance our understanding of why *B. pertussis* still kills between 200,000 and 300,000 children annually, the vast majority developing world (41).

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