

The Collaborative Pediatric Critical Care Research Network (CPCCRN) Critical Pertussis Study: Collaborative research in pediatric critical care medicine

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Objective: To provide an updated overview of critical pertussis to the pediatric critical care community and describe a study of critical pertussis recently undertaken.

Setting: The six sites, seven hospitals of the Collaborative Pediatric Critical Care Research Network, and 17 outside sites at academic medical centers with pediatric intensive care units.

Results: Despite high coverage for childhood vaccination, pertussis causes substantial morbidity and mortality in US children, especially among infants. In pediatric intensive care units, *Bordetella pertussis* is a community-acquired pathogen associated with critical illness and death. The incidence of medical and

developmental sequelae in critical pertussis survivors remains unknown, and the appropriate strategies for treatment and support remain unclear. The Collaborative Pediatric Critical Care Research Network Critical Pertussis Study has begun to evaluate critical pertussis in a prospective cohort.

Conclusion: Research is urgently needed to provide an evidence base that might optimize management for critical pertussis, a serious, disabling, and too often fatal illness for US children and those in the developing world. (*Pediatr Crit Care Med* 2011; 12:000–000)

KEY WORDS: pertussis; respiratory failure; study design; outcomes; multiple organ system failure; advanced life support

Pertussis, also known as whooping cough, is a highly contagious acute respiratory illness caused by the Gram-negative bacterial pathogen, *Bordetella pertussis* (1). Children may present with a paroxysmal cough, posttussive vomiting, an inspiratory whoop, and duration of cough lasting 1–3 months (2). Clinical presentation of pertussis is thought to be influenced by a number of factors, including

age, immunocompetence, and acquired immunity. Coughing episodes caused by pertussis in infants and their management require skilled and meticulous nursing and medical care.

There is a distinction between classic pertussis and critical pertussis as described in the series reported by Halperin and others (3–5). Common reasons for hospitalization resulting from pertussis are apnea (with or without cough parox-

ysms), pneumonia, and seizures (6, 7). Pertussis illness requiring admission to the pediatric intensive care unit (PICU) is critical pertussis and defined as such in this report (7–9).

Although substantial morbidity is recognized in other age groups, most hospitalizations and nearly all deaths from critical pertussis are reported in infants aged <6 months (10). Death or disability after pertussis illness is probably more common than generally recognized (7). The young infants who constitute the majority of cohorts with critical pertussis illness present special diagnostic and therapeutic challenges in sepsis and organ failure (8). Furthermore, pathogenesis of organ failure in critically ill infants is complex and incompletely understood; specific host susceptibility and phenotypes interactions among *B. pertussis* strains are implicated (1, 11, 12).

The objectives of this review are to provide an overview of current knowledge about the problem and to describe a na-

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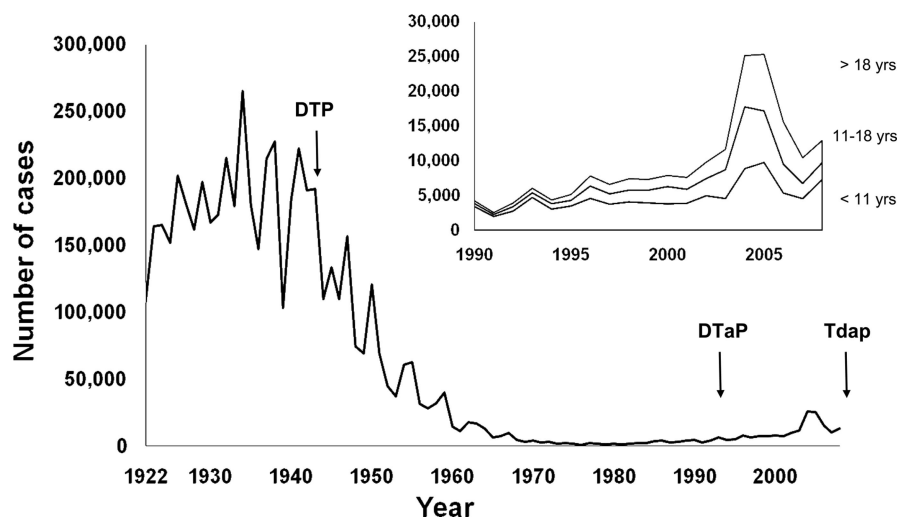


Figure 1. Number of reported pertussis cases, by year, United States, 1922–2006. Source: For 1950–2006, Centers for Disease Control and Prevention, National Notifiable Diseases Surveillance System; for 1922–1949, passive reports to the US Public Health Service (15).

tional study of critical pertussis presently underway.

Significance and Characteristics of Critical Pertussis

In recent years, reported pertussis cases in the United States have increased from a historic low of 1010 in 1976, after widespread immunizations in the 1950s, to a peak of 25,857 cases in 2004 despite high immunization coverage rates for childhood pertussis (10, 13, 14). During 2000–2008, a total of 127,672 cases of pertussis were reported to the Centers for Disease Control and Prevention's (CDC) National Notifiable Diseases Surveillance System (15). Resurgence of pertussis in the last 20 yrs is evident in Figure 1, from the CDC (15). Immunity after vaccination has limited duration, and studies show that natural immunity after pertussis infection is not much longer than that achieved by immunization (16).

Infants become infected before they are old enough either to respond to immunization or to mount an adequate response to the organism and may present already critically ill. Clinical symptoms may be atypical and diagnosis difficult. Those with critical pertussis illness may not uniformly have a paroxysmal cough nor exhibit an inspiratory "whoop." Rather, recurrent episodes of autonomic instability (apnea, cyanosis, and bradycardia) may dominate the clinical picture (17, 18). It has been suggested that apnea be added to the clinical definition of critical pertussis, which is further characterized by the development of pneumonia

that rapidly evolves to respiratory failure requiring mechanical support or extracorporeal membrane oxygenation (19).

Initially, the etiology of the critical illness may be unclear. Infants admitted to the PICU may be presumptively diagnosed with sepsis and later found to have pertussis. Most will have elevated white blood cell counts and marked lymphocytosis. Some are subsequently found to have coinfections with other viral (respiratory syncytial virus, influenza, adenovirus, others) and bacterial pathogens (20). One review of 72 children admitted with pertussis to a New Zealand PICU from 1991 to 2003 reported apnea as the leading reason for PICU admission (82%). Bradycardia (63%), pneumonia (28%), and hemoglobin desaturation (24%) as components of respiratory failure were also reported (7). It is likely that PICU admission criteria have evolved in recent years toward including only children with evidence of autonomic instability in pertussis illness; thus, cohort analysis over the 12-yr span in the New Zealand report may be difficult to interpret in present critical care practice.

In a retrospective 1999 Canadian study of 48 infants hospitalized for pertussis over an 11-yr period, Halperin et al (21) reported that 16 (33%) died. Although the study was retrospective and underpowered for statistical significance, various observations of interest were reported. Thirteen of the 16 fatalities occurred in females; greater female mortality is reported in other series (2). This observation at first glance seems counter-

intuitive to those accustomed to providing pediatric intensive care; the etiology of the differential mortality in females remains unclear (22). Eight of these children had postmortem examination; all showed evidence of alveolar hemorrhage and pneumonitis consistent with pulmonary hypertension resulting from veno-occlusive disease (19, 23, 24). Evidence of anoxic heart damage was present in half of those examined, and other findings of multiple organ system failure were found in several. Positive culture evidence of infection with other pathogens was reported in half of this postmortem series.

Differential diagnosis of pertussis is presented and taught in pediatric education and training, although distinguishing features are variable (25, 26). Respiratory failure with accompanying multiple organ system failure occurs in some children, and advanced life support is required (27). The exact relationship of length of symptoms to cardiopulmonary instability and the evolution of the course of pertussis critical illness is not described in detail in larger cohorts.

Disease Burden of Critical Pertussis

Critical pertussis causes substantial morbidity and mortality for children in the United States, although immunization coverage rates are high. During the 1990s, the mean annual incidence of pertussis among infants <4 months old increased to 88.7 per 100,000 population from 63.4 per 100,000 population in the 1980s (28). During 1990–1999, there were 84 pertussis-related known deaths among infants <4 months increasing to 111 in the same age group during 2000–2008. There were 289 pertussis-related deaths reported to the CDC from 1999–2008 (Table 1); infants aged <12 months accounted for 267 (92%) of fatal outcomes during that period (15). Longer-term outcomes for critical pertussis survivors have not been formally studied. Indeed, the incidence of temporary or permanent disability in survivors remains unknown.

Mortality

Mortality in most pediatric critical illness diagnostic groups has fallen dramatically in the United States, but it has not decreased to the same extent for critical pertussis (8). A recently published study summarized experience with infants ad-

Table 1. Reported pertussis-related deaths by age groups, United States, 1990–2008

Age Group	1990–1999	2000–2008	<i>p</i>
0–1 month	68	111	.30
2–3 months	16	56	<.05
4–5 months	5	6	.52
6–11 months	4	1	.06
1–10 yrs	8	4	<.05
11–17 yrs	0	2	.53
≥18 yrs	2	6	.71
Total (all ages)	103	186	

Source: Centers for Disease Control and Prevention.

mitted with pertussis to an Australian PICU over a 20-yr period (6). The investigators reported that infants dying of pertussis had severe pneumonia, circulatory failure, encephalopathy, and multiple organ system failure. Six of seven infants needing circulatory support died (including all four treated with extracorporeal membrane oxygenation), and all deaths (*n* = 7) occurred in infants who had pneumonia at presentation. Despite advances in life support and the treatment of organ failure in childhood critical illness, critical pertussis remains difficult to treat. Mortality in infants persists despite ventilation, nitric oxide, inotropic agents, and extracorporeal membrane oxygenation (7). Typically, the course of critical pertussis is characterized by decreasing oxygenation and ventilation, often with evidence of significant pulmonary hypertension (3, 20, 29). Treatment with extracorporeal membrane oxygenation has been instituted as a temporizing measure in critical pertussis when other methodologies of advanced life support are inadequate. Extracorporeal membrane oxygenation was used for the first time to treat critical pertussis in 1990. Since then, a total of 61 children (age range, 1 day to 2.7 yrs) with critical pertussis have been registered in the Extracorporeal Life Support Organization database (30). Overall mortality was >70% and significantly higher for infants who were <6 wks of age (84%) compared with those who were older.

Exchange transfusion and leukapheresis have been reported effective in small cohorts for correcting the pulmonary hypertension that characterizes critical pertussis and facilitating oxygenation. Removal of abnormal leukocytes in the pulmonary vasculature is reported to be of benefit, and pulmonary vasodilators such as inhaled nitric oxide and sildenafil

have also been used with some reported success (29, 31).

Morbidity

Overall mortality in US PICUs has decreased to approximately 1.5–8% (8). Understanding longer-term consequences (morbidity and disabilities) in survivors of pediatric critical illness and injury are research goals for pediatric critical care investigators. Children admitted to the PICU are at overall risk for adverse outcomes after hospital discharge. One study among 1032 persons (aged 0–29 yrs; median age, 19 months), admitted to an Australian PICU for any reason, reported that 7% of survivors died in the first 2 yrs after discharge, and 10% of survivors of PICU admission were likely to require dependent care (32). Developmental and cardiopulmonary sequelae may be common in critical pertussis survivors but remains undescribed. Sequelae might be triggered by one of the several toxins present in *B. pertussis* infection and/or untoward effects of therapeutic interventions. For example, extracorporeal membrane oxygenation, invasive vascular access and monitoring, right heart catheterization, and pressor agents for hemodynamic support are reported to increase morbidity risk in survivors (33, 34).

Hospitalization in technologically advanced PICUs might be expected to escalate costs substantially (35–38). Specific health and economic effects of critical pertussis on infants, their families, and society are understudied as well. Other costs such as pain and suffering, family stress, and the long-term productivity impact of caregivers of children with permanent sequelae are likely incalculable (39, 40).

Pertussis outbreaks result in substantial costs to hospitals and healthcare systems even when case numbers are low. Diagnosis is often delayed or missed increasing the likelihood of transmission and the numbers of exposures. Reported pertussis outbreak costs to hospitals range from \$68,130 to \$195,342 in direct containment costs (personnel time, laboratory, and medication) and from \$11,200 to \$68,015 in indirect costs (from hospital staff furlough or absenteeism) (41, 42).

Infection Control Challenges in the PICU

Beyond tending to the complex physiological needs of the child at risk for

evolving multisystem organ failure, there are central responsibilities in disease control in the PICU. Availability of appropriate isolation rooms may be minimal during seasons with a high incidence of infectious respiratory diseases such as respiratory syncytial virus. The diagnostic conundrum of critical pertussis means that children with critical illness of unclear or evolving etiology may have numerous tests as well as clinic, urgent care, and emergency department visits that expose large numbers of healthcare providers and visitors before critical pertussis is suspected and confirmed.

The American Academy of Pediatrics Red Book, CDC, and the Healthcare Infection Control Practices Advisory Committee each make specific recommendations for infection control in the inpatient setting (43–46). These are summarized here as follows: 1) a child with confirmed pertussis should be in a private room or may share a room with another child with confirmed pertussis until at least 5 days of a full antimicrobial therapy course have been completed (or 21 days after cough onset if unable to take the antimicrobial therapy); 2) children with suspected pertussis should be in a private room until pertussis is confirmed and other respiratory pathogens excluded and then may be cohorted with another pertussis patient; and 3) surgical masks, gowns, and gloves should be worn when entering the room of a child with confirmed or suspected pertussis and standard precaution guidelines for control of droplet mediated transmission followed. Additional means of infection control include limitation of patient movement or transport, precautions to prevent transmission when transport is essential, and exclusion of all visitors/family members with symptoms of respiratory infection (43, 44, 46, 47). Critical pertussis cases in any individual PICU occur with relatively low frequency, and the diagnosis may not be considered during acute stabilization. Staff and family may be extensively exposed before diagnosis (44, 46, 48, 49).

Chemoprophylaxis for Exposures

Control of nosocomial pertussis is costly and disruptive. Symptomatic healthcare workers (especially those with a cough illness) are treated with antimicrobials and on leave from work until completion of 5 days of therapy. For those who either cannot or refuse to receive antimicrobial therapy, exclusion

from work for 21 days from the time of cough onset is recommended (43, 44, 46). Healthcare personnel in hospitals or ambulatory settings who have direct patient contact should receive a single dose of tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis vaccine if they have not previously received acellular pertussis vaccine (50). The impact of pertussis on productivity can be significant, particularly in PICUs already dealing with manpower shortages on a chronic basis.

Theoretically, prophylactic antimicrobial treatment is not required for asymptomatic healthcare personnel who appropriately follow infection control guidelines. In practice, rapid control of potential and actual institutional outbreaks has followed simultaneous implementation of widespread chemoprophylaxis of all nosocomial exposures. For this reason, macrolide prophylaxis is recommended broadly to all potentially exposed individuals and healthcare personnel. First-line antimicrobial agents for pertussis treatment and postexposure prophylaxis include erythromycin, azithromycin, or clarithromycin for individuals ≥ 6 months of age. For children < 6 months of age, the risk vs. benefit ratio of each agent is considered. Erythromycin has been associated with the development of infantile hypertrophic pyloric stenosis, and although neither azithromycin nor clarithromycin has been approved by the US Food and Drug Administration for infants < 6 months of age, azithromycin may be the preferred macrolide for this age group because of the risk of infantile hypertrophic pyloric stenosis (43, 44, 46, 51). Trimethoprim-sulfamethoxazole is an alternative for individuals unable to tolerate macrolides although not appropriate for the very young (44).

The Collaborative Pediatric Critical Care Research Network Critical Pertussis Study

In June 2008, the Collaborative Pediatric Critical Care Research Network (CPCCRN) began enrolling subjects in a descriptive, prospective cohort study of critical pertussis. Specific aims are to characterize the acute course of pertussis critical illness admission, assess health and demographic characteristics of the children who develop critical pertussis, and to assess health status and family impact after PICU discharge through assessment of developmental sequelae and quality of life in survivors. Support is provided from the National Vaccine Pro-

gram Office in the Office of the Secretary, Department of Health and Human Services as well as the Eunice Kennedy Shriver National Institute of Child Health and Human Development at the National Institutes of Health.

The study is a trans-Federal project: a coinvestigator at the CDC provides collaboration with the laboratory, epidemiology, and public health expertise available at CDC, and a basic scientist (E.H.), supported by the National Institute of General Medical Sciences, is using the scientific opportunity afforded by the study to elucidate *B. pertussis* pathogenesis as a factor of microbial ecology and adaptive characteristics. CPCCRN investigators plan to enroll 200 children with critical pertussis at the seven CPCCRN sites across the United States. To date, 84 children have been enrolled over a period of 2 yrs. Currently, there are approximately 17,000 annual PICU admissions at seven CPCCRN sites where surveillance for critical pertussis is ongoing. In addition, investigators and staff at 17 outside sites at academic medical centers with PICUs have been recruited and trained to complete the study within 2 yrs. With the addition of the outside sites, nearly 33,000 annual PICU admissions are being screened for critical pertussis illness.

Developmental sequelae and quality of life will be assessed in infants who were < 12 months gestational age at PICU admission. That is, children who were premature with a gestational age < 40 wks at enrollment are included in developmental evaluation if they were enrolled at any time before being 12 months old after accounting for their gestational age at birth. Investigators are seeking evidence suggestive of association patterns linking characteristics of the critical illness (sup-

port required, evidence of organ failure) to longer-term outcomes in survivors.

Laboratory testing for *B. pertussis* at the CPCCRN sites will facilitate future hypothesis formation. *B. pertussis* isolates will be collected and shipped to a research laboratory that is conducting research in strain genetics. Researchers hope to identify the types of *B. pertussis* that causes lethal disease in US infants and children.

There are several lines of evidence suggesting that groups of organisms with different and characteristic dynamics may reflect independent epidemiology of pertussis infections in various child populations (52). For example, it is possible that the seasonal peak in the incidence of *B. pertussis* in infants (hospitalized and not hospitalized) precedes the seasonal peak in adolescents. This might indicate that seasonal epidemics in adolescents are probably not the main source infecting infants. Parents with pertussis, including new mothers, are the identified source of *B. pertussis* infection in approximately 25% of cases in early infancy, when rates for complications and fatalities are highest (53–55). The ability to distinguish the strains that cause severe disease in infants from other strains circulating in various populations will enable more exact understanding of the likely source of the infections.

The laboratory will use the Golden Gate platform to definitively characterize each isolate obtained from the study subjects by single nucleotide polymorphism type. The single nucleotide polymorphism types identified will be related to those present worldwide and to that present in other age groups in survey populations in Massachusetts. These studies will address pressing questions: Is

Table 2. CPCCRN patient population 2008

Hospital	Ethnicity or Race, %						Total Admissions
	NHW	H	AA	NA	A/PI	Other	
Arkansas Children's Hospital	66.9	5.0	24.8	0.1	0.7	2.4	2122
Children's Hospital of Los Angeles	16.9	57.6	6.7	0.1	7.5	11.2	1740
Children's Hospital of Michigan	39.5	2.7	42.3	0.1	0.6	12.8	1420
Children's National Medical Center	32.1	15.0	41.9	0.0	2.3	5.8	2216
Seattle Children's Hospital	51.9	15.0	5.7	1.7	6.4	8.4	1862
Mattel Children's Hospital UCLA	43.0	44.5	5.4	0.5	4.3	2.4	933
Children's Hospital of Pittsburgh	79.3	3.0	13.8	0.0	0.6	3.3	2085
Total admissions (2008)	48.5	18.1	21.1	0.3	3.0	6.5	12,378

CPCCRN, Collaborative Pediatric Critical Care Research Network; NHW, non-Hispanic white; H, Hispanic; AA, African American; NA, Native American; A/PI, Asian or Pacific Islander; UCLA, University of California–Los Angeles.

there a subset of strains that are most dangerous to young infants? Are these the same strains that cause the strong cyclic epidemics in adolescents or the strains that percolate at lower levels in vaccinated children or in adults or elderly? The finding that a subset of *B. pertussis* lineages is associated with severe disease in infants will inform epidemiologic and therapeutic interventions and generate hypothesis-driven research.

The National Institute of Child Health and Human Development CPCCRN sites are geographically diverse, and the populations available to study are representative of the sociodemographic characteristics of children in the United States (56) (Table 2). Translational hypotheses will be generated and understanding of how organ failure might be triggered in critical illness and injury will be enhanced. Detailed studies of critical pertussis illness among children in cohorts with specific demographic description, high acuity, and survivor follow-up assessment are largely absent from the literature (22).

CONCLUSION

Critical illness resulting from *B. pertussis* persists in the United States as well as other developed countries despite high immunization rates and modifications in immunization schedules. Limited data suggest that the burden of critical pertussis is substantial and that the economic, health, and developmental impacts for infants and their families may be underestimated (57). The CPCCRN Critical Pertussis Study, a trans-Federal project, has begun to evaluate critical pertussis in a prospective cohort. Detailed evidence of organ failure, level of support, disability, and the burden for families is being collected and represents a unique scientific opportunity. *B. pertussis* continues to evolve with new strains emerging and apparently displacing those previously described (58, 59). Isolation of these strains will allow future experimental work to determine both the virulence mechanisms and immune parameters involved in control and clearance. The National Institute of Child Health and Human Development CPCCRN Critical Pertussis Study is a scientific opportunity to look at a relatively homogeneous cohort of children during and after critical illness as well as to describe the pathogenesis of critical organ failure in the young. It is expected to be of benefit for US children as well as the 500,000 chil-

dren who still die annually of critical pertussis in the global community (25). Generation of hypotheses for further clinical and basic research will be a major benefit of this work.

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