

Clinical Profile of Critical Pertussis in Children at a Pediatric Intensive Care Unit in Northern India

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Objective: To delineate the clinical profile, complications, intensive care needs, and predictors of mortality in children with critical pertussis. **Methods:** Retrospective analysis of case records of children in the pediatric intensive care unit of a tertiary-care hospital, with a diagnosis of critical pertussis over 3 years. Diagnostic criteria included CDC case definition and confirmation by polymerase chain reaction (PCR), when available. Survivors and non-survivors were compared to identify predictors of mortality. **Results:** 36 records were analysed, most cases were infants (31, 86.1%). 10 (27.7%) were (below 6 weeks of age). In the rest, 16 (61.5%) were partially immunized or unimmunized against pertussis. Rapid breathing (88.9%), paroxysmal cough (86.1%) and apnea (41.7%) were common presenting complaints. Hypoxemia (97.2%), hyperleukocytosis (61.1%) and encephalopathy (52.8%) were common complications. Intensive care needs were mechanical ventilation in 11 (30.6%), vasoactive support in 7 (19.4%) and exchange transfusion in 3 (8.3%). Female gender, apnea, hyperleukocytosis, encephalopathy, need for vasoactive support, and mechanical ventilation predicted mortality. **Conclusion:** Pertussis demands attention due to its varied presentation, increased complications and higher mortality.

Key words: Apnea, DPT vaccine, Immunization, Outcome.

Pertussis has shown an alarming increase in global incidence recently [1]. Disease burden is high despite vaccination coverage of almost 85% among children [2]. Precise data from low- and middle-income countries (LMICs) are unavailable due to variable case definitions, limited awareness, inadequate infrastructure and weak surveillance systems. The exact cause of resurgence is unclear. Multiple factors like antigenic shifts in bacteria, waning vaccine immunity and reduced duration of protection by acellular pertussis vaccine have been implicated [1]. Studies suggest that source of infection may be identifiable only in about 27-43% of infant pertussis, and the most common source is usually mothers or siblings [3-5]. Critical pertussis is defined as pertussis requiring admission to an intensive care unit (ICU) or resulting in death [6]. It can lead to life-threatening complications like pulmonary arterial hypertension (PAH), respiratory failure and shock. Mortality rate ranges from 4.8-55% [7-13]. Data on critical pertussis is scarce, with very few reports from LMICs like India [13,14]. In this case series we describe the clinical profile, complications, intensive care needs and predictors of mortality in children with critical pertussis.

METHODS

This was a retrospective study in the Pediatric Intensive Care Unit of a tertiary-level teaching and referral hospital in Northern India. Cases were identified from the electronic database of the unit over a period of 3 years (2016-18), and those fulfilling the clinical and critical pertussis criteria as per WHO case definition were included. Clinical pertussis was defined as 'any patient with cough lasting ≥ 2 weeks with at least one of the following symptoms – paroxysmal cough, inspiratory whoop or post-tussive vomiting [2]. Critical pertussis was defined as pertussis requiring admission to an ICU or resulting in death. A total of 36 children with critical pertussis were retrieved for final analysis. No children were excluded. Demographic details (age, immunization status), presenting complaints, intensive care needs, complications, laboratory parameters and treatment modalities were recorded on a pre-designed performa. Hyperleukocytosis was defined as total leukocyte count (TLC) $>50,000/\mu\text{L}$ [15]. Real time polymerase chain reaction (PCR) targeting IS481 and Ptxs1 was done in 28 children. Serology using IgM ELISA antipertussis toxin was also done in 21 children. All children received

azithromycin 10 mg/kg/day for 5 days and other supportive measures, which included respiratory and vasoactive support, and exchange transfusion depending on clinical need.

Statistical analysis: Chi-square and Fisher's exact tests were used to compare proportions while Student t test and Mann Whitney test were used for means. Survivors and non-survivors were compared by univariate analysis to identify predictors of mortality. SPSS version 21 was used for statistical analysis.

RESULTS

Thirty-six cases (58.5% boys) of critical pertussis were enrolled. Median (IQR) age was 3.5 (1.5, 7) months. Most children were infants ($n=31$, 86.1%), with 10 (27.7%) being below six weeks and too young to be immunized against pertussis. The rest 16 (61.5%) were partially immunized or unimmunized against pertussis. Contact history with respiratory illness was evident in only two children. The major presenting symptoms were rapid breathing in 32 (88.9%), typical paroxysmal cough in 31 (86.1%) and apnea in 15 (41.7%) children. Most patients (35, 97.2%) had hypoxemia ($SPO_2 < 94\%$ in room air) at admission.

Hyperleukocytosis and thrombocytosis were noted in 22 (61.1%) and 26 (72.2%) patients, respectively. Median (IQR) total leukocyte count (TLC) (per μL) was 64,000 (23050, 100037). Out of 28 children tested for pertussis RT-PCR, 19 (52.8%) were positive. Of the 8 children in whom PCR was not done, 1 was positive, 4 showed intermediate positivity and 3 were negative by ELISA. When tested for co-infections with other viruses, two children were positive for RSV, and all were negative for H1N1.

Hypoxemia (35, 97.2%) was the commonest complication, followed by hyperleukocytosis, encephalo-pathy (19, 52.8%), seizures (17, 47.2%), and acute kidney injury (6, 16.6%). Out of 11 children who under-went neuroimaging, multiple CNS infarcts were seen in 3 children and 8 were normal. Pulmonary arterial hyper-tension (PAH) was seen in 5 of 15 children who under-went echocardiography (33.3%). Intensive care needs were mechanical ventilation in 11 (30.6%), vasoactive support in 7 (19.4%) and exchange transfusion (ET) in 3 (8.3%). The most common indication for intubation was apneic spells in 9 children, out of which 4 were emergent during spells, and remaining 5 were elective for recurrent spells and hypoxemic events. Two children were intubated for encephalopathy. In majority ($n=6$), the intubation was done within 24 hours. The problems faced during

ventilation were recurrent apnea ($n=9$), paroxysms of cough ($n=9$), air leaks ($n=2$), and ventilator associated pneumonia ($n=1$). Of the 7 ventilated children who underwent echocardiography, 4 had pulmonary arterial hypertension (PAH). Persistent hypoxemia and failure of conventional ventilation was seen in four children who required high frequency ventilation. Healthcare associated infections were seen in four children; ventilator-associated pneumonia in one child and blood stream infections in three children.

An increasing trend of hospital incidence (2 cases in 2016, 7 in 2017 and 27 in 2018), and mortality (no mortality in 2016, 1 in 2017 and 7 in 2018) of critical pertussis was observed over the 3 year study period. Eight patients (22.2%) with median (IQR) age of 3.5 (1.1, 5.5) months died; all were unimmunised including three who being <6 weeks old had yet to begin primary immunisation. All non survivors except one required mechanical ventilation. Major causes of death were hypoxemia and refractory shock (4), massive brain infarcts (2), secondary infection (1), and acute kidney injury and hyperkalemia ($n=1$ each). Female gender ($P=0.04$), apnea ($P=0.01$), hyperleukocytosis ($P=0.01$), encephalopathy (Glasgow coma score <14) ($P=0.04$), need for vasoactive support ($P<0.001$) and mechanical ventilation ($P<0.001$) were significantly associated with mortality on univariate analysis. PAH and need for ET did not determine mortality (**Table I**).

DISCUSSION

Our study has shown an increased hospital incidence of critical pertussis in young infants before completion of their primary vaccination. Major complications noted were hypoxemia, hyperleukocytosis, encephalopathy and seizures. PAH was present in few children. Intensive care needs were ventilation, vasoactive support and exchange transfusion. Female gender, apnea, hyperleukocytosis, encephalopathy, need for vasoactive support and mechanical ventilation were predictors of mortality.

The study: however, suffers from the inherent drawbacks of a retrospective analysis. Diagnostic tests like PCR could not be done in all. Details of maternal immunization status were unavailable and leukocyte count threshold for initiating exchange transfusion was not clearly defined.

Incidence of pertussis is increasing globally with periodic outbreaks being reported from different parts of the world including India [16-19]. Resurgence of a vaccine preventable disease like pertussis causing increasing hospitalization, costs and mortality is a

WHAT THIS STUDY ADDS?

- There was a high prevalence of seizures, encephalopathy, hyperleukocytosis and pulmonary artery hypertension in this cohort of critical pertussis compared to earlier studies.

Table I Predictors of Mortality in Children with Critical Pertussis (N=36)

Predictors of mortality	Survivors (n=28)	Non-survivors (n=8)	Odds ratio (CI)	P value
Male gender	19 (67.8)	2 (25)	0.15 (0.02-0.94)	0.043
Apnea	14 (50)	8 (100)	2 (1.38-2.89)	0.01
Hyperleukocytosis	14 (50)	8 (100)	2 (1.38-2.89)	0.01
*Peak leucocyte count, per μ L	44900 (17225-91357)	100025 (68200-144512)	-	0.002
Encephalopathy (GCS<14)	12 (42.8)	7 (87.5)	2.04 (1.23-3.37)	0.04
Vasoactive support needed	1 (3.5)	6 (75)	21 (2.94-149.95)	<0.001
Mechanical ventilation	4 (14.2)	7 (87.5)	6.12(2.38-15.74)	<0.001
Exchange transfusion	1(3.5)	2 (25)	7 (0.72-67.63)	0.12

All values in n (%) except *median (IQR); GCS: Glasgow coma scale.

worrisome trend, and has led to calls for relook of immunization schedules [16,20]. However, our patients were mostly young infants similar to previously published reports [8,13]. Over half of the patients were unimmunized against pertussis. Critical pertussis occurring before primary immunization highlights the importance of maternal immunization against pertussis. Pertussis masquerading as any other acute respiratory infection often runs the risk of under-diagnosis and under-reporting. None of our patients were suspected to have pertussis nor received macrolide antibiotics before referral. Delayed diagnosis can make 'benign' pertussis 'critical' due to evolving complications. The prevalence of seizures, encephalopathy, hyperleukocytosis in this cohort was significantly higher compared to earlier studies on critical pertussis which have reported seizures in 9-16%, encephalopathy in nearly 20% and hyperleukocytosis in 21-35% of children [8-13]. One-third of the screened patients had PAH. Increased pulmonary vascular resistance is postulated to be secondary to obstruction of pulmonary vasculature by lymphocytes accumulation resulting from hyperleukocytosis [21]. Leucocytosis, especially in young infants, was shown to be associated with PAH, encephalopathy, greater risk of PICU admission and mortality but a causal link is yet to be proven [10,15]. Therefore screening of all patients of critical pertussis for PAH is essential. Children with critical pertussis often require mechanical ventilation and inotropic support for hypoxemia, apnoea, shock, PAH and encephalopathy [13]. Exchange transfusion for hyperleukocytosis

especially if done before organ failure or immediately at the onset of shock was found to be associated with improved hemodynamics, hypoxemia and mortality in few case series and reports; the clear cut indications and mortality benefits are yet to be conclusively proven on a larger scale [14,22,23]. Mortality in critical pertussis varies between 4.8-55% [7-13]. Recognized predictors of mortality include younger age, comorbidities, need for ventilation, vasoactive use, PAH and a rapid course, similar to those identified in this study [7-13].

We have highlighted the important complications; intensive care needs and our limited experience with exchange transfusion in patients with hyperleukocytosis. To conclude, resurgence of pertussis demands attention due to its varied presentation, increased complications and higher mortality. The importance of clinical recognition and empirical treatment in such a setting cannot be overemphasised. Prospective studies on critical pertussis, its complications and the utility of various therapies are the need of the hour.

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