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Original Article

Pertussis-like syndrome or pertussis: a delay diagnosis

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Abstract

Background Recent reports of pertussis epidemiology from Asia, Africa and South America have been limited, but the World Health Organization estimates indicate that these regions have the highest disease burden. Difficulty in estimating the prevalence of pertussis is due to lack of access to diagnostic methods, misdiagnoses, under-reporting, and different countries' reporting criteria. A syndrome characterized by severe episodes of coughing resembling whooping cough (pertussis) has also been defined as pertussis-like syndrome.

Objective To report eleven cases of pertussis or pertussis-like syndrome in the pediatric ward of Hasan Sadikin Hospital.

Methods This retrospective study was conducted by reviewing medical records from 2008–2010. Characteristics of 11 pertussis-like syndrome patients were documented including age, gender, history of pertussis immunization, clinical manifestations, laboratory findings, initial diagnosis, treatment and clinical response. Isolation of *Bordetella pertussis* using Bordet-Gengou agar was also noted. Pertussis diagnoses were grouped based on two classifications: probable and confirmed.

Results Eleven patients were diagnosed with pertussis-like syndrome, including 5 boys and 6 girls. Most subjects were less than 6 months of age. Only one subject had received previous pertussis immunization. Dyspnea, paroxysmal cough, and fever were the most common symptoms. All were initially diagnosed to have had severe bacterial pneumonia, and later changed to probable pertussis. Three subjects exhibited post-tussive vomiting and cyanosis, while none had apneic symptoms. All *B. pertussis* isolations yielded negative results. Ampicillin or cephalosporin was initially administered. Patients receiving subsequent clarithromycin showed good clinical responses.

Conclusion All infants were likely considered to have pertussis, as most had no pertussis immunizations. However, *B. pertussis* isolation was unsuccessful in all cases. As such, diagnoses could not be confirmed. **[Paediatr Indones. 2012;52:28-31]**.

Keywords: *Pertussis, pertussis-like syndrome, Bordet-Gengou agar, clarithromycin*

Pertussis, also known as whooping cough, is a highly contagious respiratory tract infection, affecting an estimated 39 million people yearly and causing nearly 300,000 deaths in children yearly. Though recent reports of pertussis epidemiology from Asia, Africa and South America are limited, the World Health Organization (WHO) estimates that countries in these regions, including Indonesia, have the highest disease burden.[1] Estimating prevalence of pertussis is difficult due to the lack of access to diagnostic methods, misdiagnoses, under-reporting, and different reporting criteria between countries. However, the reemergence of pertussis has been reported even in countries with high vaccination coverage, and attributed to various factors, including increased awareness, improved diagnostics, decreased vaccination coverage, suboptimal vaccines, waning vaccine-induced immunity, and pathogen adaptation. The relative contribution of these factors may differ between countries and is the subject of ongoing debate.[2]

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Bordetella pertussis, a Gram-negative coccobacillus, was reported as a major etiologic agent of prolonged cough during childhood in unvaccinated populations.[1,3-5] Classic whooping cough is characterized by three distinct stages of illness, with initial symptoms being non-specific, sometimes resembling a cold or other viral illness, and lasting 1–2 weeks. Following this initial catarrhal stage, coughing becomes predominant, continuing to the paroxysmal stage, in which patients exhibit a "whoop" sound on inspiration, sometimes followed by vomiting. This stage lasts between 2–6 weeks. The final convalescent stage may persist for many weeks and involve coughing episodes of reduced severity. Whooping cough is most contagious during the 2-week catarrhal stage via respiratory droplets. Unfortunately, diagnosis is often not made until the paroxysmal stage, when the characteristic cough occurs.[1,4] To date, it is difficult to confirm pertussis, resulting in late diagnoses of pertussis or pertussis-like syndrome. In most cases, a working diagnosis has to be made on strong clinical suspicion. In order to assess the adequacy of clinical and investigational data in the diagnosis of pertussis or pertussis-like syndrome, we report the clinical profiles and treatment responses in 11 subjects with pertussis or pertussis-like syndrome.

Table 1. Characteristics of subjects

Subjects' characteristics	n=11
Gender, n	
Male	5
Female	6
Age distribution, n	
0-1 months	1
1-6 months	9
6-12 months	1
Symptoms present	
Cough, n	11
Average length of cough, days	10.5
Fever, n	9
Dyspnea, n	9
Average length of dyspnea, days	2
Cyanosis, n	3
Vomiting, n	3
Laboratory findings	
Leukocytosis, n	10
Lymphocytosis due to leukocytosis, n	5
Bordet Gengou cultures	
Positive, n	0
Negative, n	10
Case definitions	
Probable, n	11
Confirmed, n	0
Previous DTP immunization, n	1
Macrolide (clarithromycin) treatment	11

Methods

All pediatric inpatients in Hasan Sadikin Hospital diagnosed as having pertussis or pertussis-like syndrome from January 2008 - December 2009 were included in our study. Data was retrieved from hospital medical records and our own pertussis or pertussis-like syndrome registry.

According to 1997 Centers of Disease Control (CDC)[6] which was reformatted for clarification in 2010,[7] the diagnosis of pertussis was based on two case classifications: (1) probable, a case that meets the clinical case definition (a cough illness lasting ≥2 weeks with at least one of the following: paroxysms of coughing, inspiratory "whoop," or posttussive vomiting, without other apparent cause as reported by a health professional), is not laboratory confirmed, and is not epidemiologically linked to a laboratory-confirmed case; and (2) confirmed, a case of acute cough illness of any duration with isolation of *B. pertussis* from a clinical specimen, *or* a case that meets the clinical case definition and is confirmed by either culture or PCR.[6,7]

Records were reviewed in detail with regards to age, gender, history of pertussis immunization, clinical manifestations, laboratory findings, initial diagnosis, treatment and clinical response to therapy. *B. pertussis* isolation cultures using Bordet-Gengou agar were performed in the Bio Farma Laboratory (Bandung, Indonesia).

Results

Of all of pediatric inpatients admitted during the specified period, 11 were found to have been diagnosed as having pertussis or pertussis-like syndrome. Subjects' ages ranged from 1 to 12 months, with most subjects in the 1–6 month-old age group. Male to female ratio was similar. The leading symptoms at presentation were dyspnea and cough. Only 3 patients presented with cyanosis and vomiting. None reported apneic symptoms. Mean duration of symptoms before coming to the hospital

was 10.5 days, and the average time for diagnosis and initiation of macrolide antibiotic treatment in the ward after the initial hospital presentation was 4 days. Only 1 infant had received pertussis immunization. Leukocytosis with absolute lymphocytosis was observed in 5 patients. Bordet-Gengou agar cultures were performed for 10 patients, but all tests yielded negative results. Based on the two pertussis classifications (probable and confirmed), all 11 patients were thought to have probable pertussis. All patients were initially diagnosed as having suspected severe bacterial pneumonia, but were later diagnosed as having probable pertussis. Therefore, ampicillin or cephalosporin were initially given for treating severe bacterial pneumonia. Clarithromycin was given on the second week of initial symptoms, and after probable pertussis or pertussis-like syndrome was diagnosed.[8] Patients showed good clinical response.

Discussion

We only documented 11 patients with pertussis-like syndrome in the study period from Hasan Sadikin Hospital, a major referral centre for the West Java Province. Most subjects were infants which was the highest burden in the unimmunised age groups.[1] Although pertussis could not be confirmed, we assumed that all patients had probable pertussis. Dyspnea, paroxysmal cough, and fever were present in almost all infants. Generally, fever is low-grade throughout the course of illness.[4]

Only 3 infants had post-tussive vomiting and cyanosis while none reported apneic symptoms. Classic whooping cough is characterized by three distinct stages of illness where initial symptoms are non-specific, sometimes resembling a cold or other viral illness, and may last 1–2 weeks. Following the initial catarrhal stage, the cough becomes predominant. Continuing to the paroxysmal stage, patients exhibit a "whoop" sound on inspiration, sometimes followed by vomiting. This stage typically lasts 2–6 weeks. However, infants might have clear and hard whooping, partial whooping, or no whooping, which makes it difficult for clinicians to identify the disease. Whooping cough is most contagious during the 2-week catarrhal stage via respiratory droplets. Unfortunately, the diagnosis is often not made until the paroxysmal stage, when the characteristic cough occurs.[1,4] We have to consider pertussis if parents report infants with cough and apneic symptoms, the latter of which did not occur in our study. At the end of the catarrhal phase, leukocytosis with an absolute lymphocytosis frequently begins, reaching its peak at the height of the paroxysmal stage. At this time, the total blood leukocyte levels may resemble those of leukemia (100,000/mL), with 60–80% lymphocytes.[9] From our study we found only 5 infants with absolute lymphocytosis.

The final convalescent stage may persist for 1-3 weeks, and is characterized by a gradual decrease in cough before the patient returns to normal. However, paroxysms often recur with subsequent respiratory infections for many months after the onset of pertussis. This situation might confuse the parents.

Eventhough culturing *B. pertussis* is the gold standard, however its lack sensitivity, and maybe compromised by prior antiobiotics treatment, immunization status, duration of illness prior to culture, specimen transport time (greater than 3 days), poor specimen quality and lack of expertise.[9] However, the CDC Pertussis Laboratory recommend a Regan-Lowe medium because of its superiority over the non-selective Bordet-Gengou medium.[10] In our hospital the specimens must be sent to the Bio Farma Laboratory located near the hospital, as culturing cannot be done. Specimens are collected when the patient is coughing. Culture sensitivity decreases sharply if the specimen is taken more than 2 weeks after onset of cough. Three weeks after commencement of cough, culture sensitivity is only 1–3%, and rates decrease further in adults and adolescents who are more likely to present late in the course of illness.[4] This reason may explain the negative results in all infants in our study.

Delayed diagnosis typically occurs during hospitalization during the paroxysmal stage when patients present with dyspnea, not whooping cough. Furthermore, from patient histories, other classic symptoms of pertussis, especially those in the catharral phase, are not fully recognized and reported by parents or caregivers. Therefore, all cases were initially diagnosed as suspected severe bacterial pneumonia. Only later were the cases were diagnosed as probable pertussis based on positive clinical case

definition, though none were laboratory confirmed, nor epidemiologically linked to a laboratory-confirmed case.

It has been previously suggested that pertussis-like coughing may also be observed during infections such as adenovirus, parapertussis virus, parainfluenza viruses, respiratory syncytial virus, cytomegalovirus, *Mycoplasma pneumoniae* and *Chlamydia pneumoniae*.[11] Most of our patients had not received previous pertussis vaccination, thus supporting the presumption of pertussis diagnosis.

In these cases, antibiotics such ampicillin or cephalosporin were initially given for the severe bacterial pneumonia diagnosis. Clarithromycin, the drug of choice, was given on the second week following initial symptoms to most infants. Clarithromycin administration led to a good clinical response, mostly by the third day after its commencement.

Due to late stage hospitalizations, biased history-taking and negative culture results, delayed diagnosis of pertussis or pertussis-like syndrome occurred. At first, most patients were diagnosed to have severe pneumonia, due to their chief complaint of dyspnea and cough, since most came to the hospital after the catarrhal phase was complete. Furthermore, the late stage hospitalizations may have contributed to the negative cultures, as isolation of *B.pertussis* requires precise timing of the specimen collection, thus leading to difficulties in confirming the pertussis diagnosis. As such, all infants were considered to have had pertussis, in spite of the negative culture results, as most had not received pertussis immunizations.

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