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Case Study

Leukocytosis as a Predictor of Clinical Worsening and Complications in Children with Pertussis: A Systematic Review of Case Study

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ABSTRACT

Pertussis is a highly contagious disease with clinical features ranging from mild to severe and various complications. Hematological examination, especially the leukocyte count, can predict the possibility of clinical deterioration with several complications, such as pneumonia. This case study aimed to assess whether leukocytosis could indicate the clinical worsening of pertussis in children. This research method is a systematic review on a case study. The subject of this case study is a child with pertussis experiencing clinical deterioration. Prominent laboratory data in this case study includes leukocytosis. This systematic review aims to analyze the association between leukocytosis and the clinical deterioration of this case study. Literature search procedure using PubMed, Cochrane, and Google Scholar search instruments. The keywords used are "pertussis," "risk factor," and "and children." Using the limitations of randomized controlled clinical trials, systematic reviews, meta-analyses, cohorts, and cross-sectional or case series, the language of instruction is English, and publications within the last 20 years. Overall, 16,666 articles were obtained, consisting of 43 pieces from PubMed; only two papers were valid. Of the 3,123 articles on the Cochrane, only two are valid. Likewise, out of 13,500 articles on Google Scholar, only two are valid. Furthermore, it was traced based on the aspect of duplication, then three papers were found, which were cohort studies. It was concluded that leukocytosis predicts clinical deterioration and complications in children with pertussis.

Keywords: Pertussis, Clinical Deterioration, Pneumonia, Leukocytosis.

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INTRODUCTION

Pertussis is a highly contagious disease with clinical features ranging from mild to severe and various complications [1,2]. From various reports, pertussis is also a disease with a high mortality rate. World Health Organization (WHO) estimates that pertussis affects nearly 240 million children under five years of age each year and causes 160,000 deaths in this age group, with a mortality rate of 4%. In one study in infants, mortality was 70% and higher in infants under 6 weeks (84%) [3]. The infant mortality rate in the United States is 2.4 per 1 million, and 90% of all deaths from pertussis occur in infants under six months of age [4,5].

Pertussis is a highly contagious respiratory tract infection most commonly affecting young, unimmunized, or incompletely

immunized infants [6–8]. The typical clinical features of pertussis include recurrent paroxysmal coughing, inspiratory whoops, and vomiting after coughing. The classic disease characterized by three phases (catarrhal, paroxysmal and convalescent) has been seen less frequently since the start of immunization [6,9,10]. This clinical picture varies in each child, depending on the phase of the disease. In severe infections, pertussis causes several complications that begin with clinical worsening. One of these clinical worsening occurs when pertussis causes difficulties in the form of pneumonia (lung infection) [6,11,12].

Clinical worsening of pneumonia must be anticipated as an effort to prevent complications so that death does not occur. Because of this, clinical data must be sought which can be used as indicators for predicting clinical worsening of pertussis in children [1,12]. In several cases of pneumonia that occur as a complication of pertussis, an increase in leukocyte levels (leukocytosis) is always found. The clinical question here is whether the laboratory picture of leukocytosis can be used as an early indicator in predicting clinical worsening in children with pertussis. [1,10]. Therefore, this case study aimed to see whether clinical worsening or severe complications in pertussis were caused by leukocytosis. This pertussis case study was conducted using a systematic review approach.

METHOD

We conducted this case study with a focus on investigating the relationship between increased leukocytosis as a predictor of the likelihood of clinical deterioration in a child with pertussis. The research methodology employed in this study is a systematic review of a case study. The subject of this case study is a child with pertussis who experienced clinical deterioration. Prominent laboratory data includes leukocytosis. The association between leukocytosis and clinical deterioration in this case study is analyzed using systematic review procedures.

A systematic review of case study was carried out to answer whether leukocytosis indicates clinical deterioration in children with pertussis. Literature search procedure by searching literature online, using PubMed, Cochrane, and Google Scholar search instruments. The keywords used are "pertussis," "risk factor," and "and children." Using the limitations of randomized controlled clinical trials, systematic reviews, meta-analyses, cohorts, and cross-sectional or case series, the language of instruction is English, and publications within the last 20 years.

RESULTS

Pertussis is a highly contagious disease with clinical features ranging from mild to severe and various complications. The disese caused by infection with Bordetella pertussis can be divided into three phases: catarrhal, paroxysmal, and convalescent. A definite diagnosis is made based on laboratory tests, namely the finding of Bordetella pertussis, either by culture, Polymerase Chain Reaction (PCR), or serological examination. [6–8].

A 12-year-old girl was brought to the Emergency Room (IGD) at Zainoel Abidin General Hospital, Banda Aceh. This patient was a referral from the Teungku Chik Ditiro Hospital, Sigli, Pidie District, with a diagnosis of pneumonia, with a clinical picture of shortness of breath, who had previously been treated for four days. On examination at the Emergency room of Zainoel Abidin General Hospital, information was obtained that the child had before shortness of breath. Every cough experience feels continuous for a long time, followed by vomiting after every cough. The cough had been experienced for about two weeks before being treated at the Teungku Chik Ditiro Hospital. On physical examination at Zainoel Abidin General Hospital, it was found: blood pressure 110/70 mmHg, pulse 110 beats per minute, rapid respiration of 50 times per minute. The chest appeared retracted, and lung crackles were found on auscultation. The laboratory examination results showed Hb: 12.5gr/dL. Hematocrit: 37%, leukocytes: 20,400/mm3. Lung x-rays showed infiltrates in both lung fields.

Due to a history of severe, persistent cough and shortness of breath, this patient was diagnosed with pertussis and pneumonia. Other data that supporting pneumonia are of crackles on auscultation and an infiltrate is found on a chest X-ray. Concerning a loud cough, it must be proven whether it is caused by pertussis. Therefore, the Polymerase Chain Reaction (PCR) was examined against the Bordetella

Pertussis bacteria to determine the cause of pertussis. From the laboratory examination, the results were found: a positive PCR was found for Bordetella pertussis. With the discovery of these laboratory results, the definite diagnosis is pertussis. Pneumonia that occurs, in this case, is a clinical worsening and complications of pertussis. Because the diagnosis is pertussis and pneumonia, the therapy is antibiotics following causative germ, namely Bordetella pertussis.

The selected antibiotics are Azithromycin and Cefotaxime. These two antibiotics were chosen to anticipate the possibility of other bacteria causing pneumonia. Lang's selection of antibiotics is intended to prevent further deterioration, which can result in respiratory failure. Uncontrolled clinical worsening with the occurrence of respiratory failure can cause death. Other procedures for this patient during treatment include administering oxygen, traditional healers, and multivitamins. This patient was treated at Zainoel Abidin General Hospital for one week. Because it showed an excellent improvement, the infusion was stopped. Antibiotics was stop. Other medicines are only in the form of multivitamins. The patient was discharged from the hospital and was advised to seek outpatient treatment. Five days later, the patient returned to the children's polyclinic, Zainoel Abidin General Hospital. At the last examination, the patient was very healthy.

In this case, pneumonia was found in a child with pertussis as a form of clinical deterioration complication. Laboratory examination revealed the presence of leukocytosis. A systematic review was conducted to investigate whether leukocytosis can be used as a predictor of clinical deterioration.

Through the search method with the above criteria, a total of 16,666 articles were obtained in the early stages. Of the 43 articles searched with PubMed, two were valid. Of the 3,123 articles on the Cochrane, only two are valid. Likewise, out of 13,500 articles on Google Scholar, only two are valid. So only six papers are useful in the initial stage.

Furthermore, screening of titles and abstracts was carried out to determine articles that were relevant to the previous problem. However, when traced based on the duplication aspect, three papers were found: cohort studies (see Figure 1). The articles obtained are then summarized in Table 1.

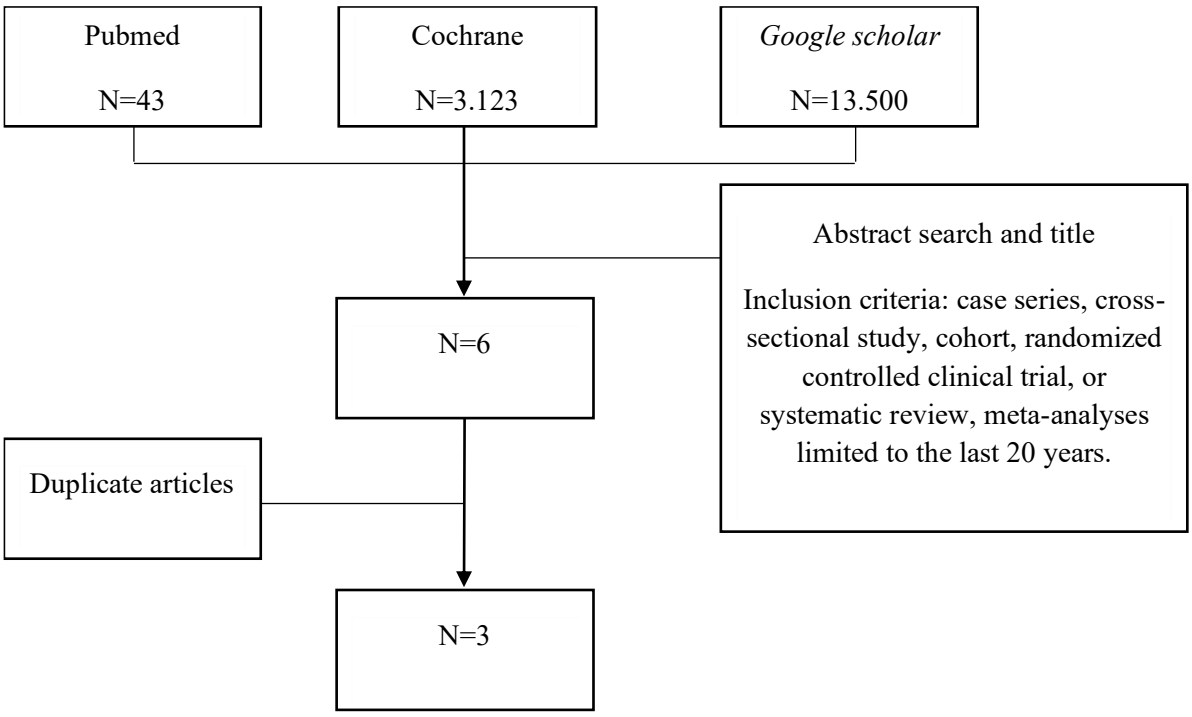

Figure 1. Literature selection flow

Table 1. Summary of Characteristic and Outcome of Included Studies.

Article	Kang, et al.,[2]	Shi, et al.,[3]	Palvo, et al.,[13]
Title	Clinical characteristics of 967 children with pertussis: a single-center analysis over an 8-year period in Beijing, China	Mortality risk factors among hospitalized children with severe pertussis	Severe pertussis infection A clinic pathological study
Design	Retrospective Cohort Study	Retrospective Cohort Study	Retrospective Cohort Study
Publication	2021	2021	2017
Location	Beijing, China	Guangzhou, China	Brazil
Aims	Knowing the clinical symptoms of severe pertussis, describing pertussis in infants under three months, assessing risk factors for severe pertussis.	Assessing risk factors for mortality in patients admitted with severe pertussis	Assessing the epidemiology and clinical symptoms of children with severe pertussis who were hospitalized in Brazil, investigating the risk factors for PICU admission and death, and evaluating the autopsy findings of children who died with pertussis.
Participant	967 children	144 children	55 children
Outcome	• Vomiting after coughing, paroxysmal cyanosis, decreased post-tussive heart rate, hypoxemia, severe pneumonia, and mechanical ventilation were significantly higher than in the ≥ three months group ($p < 0.05$). • Paroxysmal cough, post-tussive vomiting, paroxysmal cyanosis, flushing/cyanosis/fever during coughing, increased leukocytes (leukocytosis), and chest X-ray showing pneumonia/consolidation/ • atelectasis are essential indications of severe pertussis.	• The mortality for severe pertussis was 34.2%, with • patients younger than six • weeks making up most deaths. • WBC > 70.0 × 109/L and PH are independent prognostic variables associated with death.	• Leukocytosis on admission is associated with morbidity and mortality in children treated with pertussis. • Implementation of prevention strategies is crucial to reduce the incidence of disease, especially in young infants who are not immunized.

DISCUSSION

The first study was a retrospective cohort study conducted by Kang et al. [2] on 227 children with pertussis who were treated between March 2011 and December 2018. The researchers divided them into two groups, namely the severe and non-severe pertussis group. Patients with severe pertussis were defined as having any symptoms: recurrent apnea, hypoxemia (PaO_2 <80 mm Hg), pertussis encephalopathy, or cardiac compromise. Inclusion criteria in this study were age <18 years, symptoms with pertussis diagnostic criteria, and positive PCR results for pertussis. While the exclusion criteria were the emergence of cough due to congenital abnormalities of the airways, the appearance of cough due to airway compression due to various causes, personal or family history of allergic reactions and non-specific inflammatory reactions such as allergic cough or asthma, postnasal drip syndrome, eosinophilic bronchitis, and cough due to gastroesophageal reflux, cytomegalovirus pneumonia, and pulmonary tuberculosis.

The second study was a Randomized Controlled Trial study conducted by Shi et al. [3] On 144 pertussis patients treated at Guangzhou Women and Children's Medical Center China from January 2016 to December 2019. The recerchers divided them to into two outcame groups, namely group of patients who survived and who died during treatment. Criteria for severe pertussis include children aged 0-18 years with laboratory results confirming pertussis. They are included if there is treatment in the Pediatrics Intensive Care Unit (PICU) for at least 24 hours or death, hyperleukocytosis in the form of leukocyte values $\geq 50x10^3/mm^3$, pulmonary hypertension based on criteria from the European Society of Cardiology (ESC) and European Respiratory Society. The inclusion criteria in this study were that patients had to undergo all the following examinations: All patients must be positive for Bordetella pertussis based on the PCR test. All patients should undergo an immunofluorescence virus test for nasopharyngeal secretions in the acute phase. All patients should have a chest X-ray done. Patients with incomplete data were excluded from this study.

The third study was conducted by Palvo, et al. [13] , a randomized controlled trial on 55 patients treated at a tertiary-care university hospital in Brazil from 1 January 2008 to 31 December 2014. The researchers divided them into two groups, namely, the group of patients who died and recovered. The inclusion criteria were all children aged 0-18 years who were treated with laboratory confirmation of pertussis. Laboratory confirmation includes isolation of B. pertussis from nasopharyngeal aspiration with positive pertussis culture and/or PCR. Patients with clinical symptoms suspicious of pertussis but without laboratory confirmation were excluded from the study.

The World Health Organization (WHO) and the Centers for Disease Control and Prevention (CDC) provide case definitions of pertussis. A clinical case can be defined as a person with a cough for at least two weeks and any of the following symptoms: paroxysmal cough, inspiratory whoop, or post-cough vomiting. Confirmed cases are described as suspected by one of the following laboratory tests: (1) positive culture from the nasopharyngeal sample, (2) positive PCR test, and (3) positive serology result [14]. Diagnosis is often delayed or missed because pertussis mimics symptoms of respiratory tract infections. Upper infections caused by viruses and sometimes appear atypical 15–17 [15–17].

In this case study, the patient was referred from the district hospital with complaints of shortness of breath. The definite diagnosis of shortness of breath is pneumonia. The sound of crackles on lung examination reinforced this. An X-ray examination also found infiltrates in both lung fields. However, the diagnosis of pertussis in this patient was suspected due to the presence of persistent and persistent cough. A definite diagnosis of pertussis was obtained from the results of laboratory tests, namely a PCR examination with a positive outcome for Bordatella pertussis [1,12].

Clinical manifestations of pertussis are influenced by age, disease stage, previous immunization or infection history, passive immunity, and previous antibiotic treatment [18]. Studies show that the most common clinical symptoms of pertussis infection in children are paroxysmal cough, inspiratory whoop, and post-cough vomiting, with less common signs such as cyanosis and apnea. Cases of B. pertussis are often reported in spring and summer, according to those reported in several studies [1,14,19].

Infection caused by B. pertussis can be divided into three phases: catarrhal, paroxysmal, and convalescent [20]. The first phase is the catarrhal phase which begins 1-2 weeks after exposure and lasts 7-14 days. This condition is indistinguishable from an upper respiratory tract infection, and the symptoms include rhinorrhea, mild cough, malaise, and low-grade fever. The second phase is the paroxysmal phase. This phase lasts 1-4 weeks and is dominated by a heavy cough. This phase is characterized by paroxysmal coughing or a series of coughing during a single expiration, which causes a decrease in lung volume. Paroxysmal cough followed by forceful inspiration, which, in infants and children with the smaller trachea, is associated with the whooping sound characteristic of "whooping cough." Paroxysmal cough is often associated with vomiting and post-cough fatigue. The third phase is the recovery phase. This phase occurs after 2-3 months, and severity of the cough gradually decreases [10,15,21].

The incubation period for pertussis is usually 7-10 days, ranging from 4-21 days. However, in households, one-fifth of cases occur more than four weeks after the onset of

symptoms in the primary case. B. pertussis adheres to the mucosa of the nasopharynx, trachea, bronchi, and bronchioles, increasing the secretion of mucus, which is initially thin and thick. The classic disease is most often seen in non-immunized children, lasts 6-12 weeks, and is clinically divided into three stages: catarrhal, paroxysmal, and convalescent [10,16,20].

A meta-analysis study from Moore [22] states that "Posttussive vomiting" is a clinical symptom that can establish a clinical diagnosis in a sample of children with a sensitivity of 60% and a specificity of 66% with a CI of 95%, "Positive Likelihood Ratio" 1.76 and "Negative Likelihood Ratio" 0.6 . Other previous meta-analyses studies also showed similar results, namely the study of Cornia et al., providing results of clinical symptoms that can be used as a reference for establishing the diagnosis of pertussis. Paroxysmal cough with a sensitivity of 86% and a specificity of 24%, "Positive Likelihood Ratio" 1.1. “Posttussive vomiting” with 70% sensitivity and 61% specificity, “Positive Likelihood Ratio” [1,8]. While Inspiratory whoop with 50% sensitivity and 73% specificity, "Positive Likelihood Ratio" [4].

Pertussis is a disease caused by Bordetella pertussis. Therefore, the focus of laboratory tests to establish the diagnosis of this disease is to find evidence of infection with Bordetella pertussis. Another examination is to look at the hematological picture of the patient. The leukocyte count, for example, usually increases between 15,000 and 20,000/mm3 but can be normal or as high as 60,000/mm3. From the leukocyte count, usually, 60-80% are lymphocytes. Leukocytosis with a white blood cell count of more than 25,000/mm3 was seen in 40% of children [20].

Several complications may occur in pertussis with severe infection due to clinical deterioration. A series of rapid coughing characterize paroxysms without taking a breath, followed by a characteristic whoop, an attempt to inhale through a swollen glottis. During the paroxysmal phase, the patient may experience cyanosis and vomiting. Several paroxysmal steps may occur successively within minutes and can leave the patient exhausted. Paroxysms can be caused by stimuli such as eating, laughing, or crying, and are usually worse at night. During the paroxysmal phase, the patient may appear to average [23]. Pertussis is usually not associated with fever but with lymphocytosis, especially in infants and young children. A non-paroxysmal cough may persist for weeks 1,12,24 when the disease is cured. [1,12,24].

Clinical worsening of pertussis can be prevented by providing adequate therapy, especially by choosing the right antibiotics, which can be: erythromycin, azithromycin, or lincomycin. If leukocytosis is found (the number of leukocytes above average), it is anticipated immediately by looking at additional clinical possibilities or the possibility of early complications [16]. Antibiotics combine one of the standard antibiotics (erythromycin, azithromycin, or lincomycin) with other antibiotics, such as cefotaxime. This effort is more to minimize the risk of complications or clinical worsening [10,11,17,25].

CONCLUSION

Leukocytosis in children with pertussis can serve as a predictor for the likelihood of clinical deterioration and complications. Therefore, laboratory examinations (hematology) should be consistently performed in every child diagnosed with pertussis to facilitate adequate therapeutic planning, thereby preventing clinical deterioration and complications. Clinically, pertussis caused by *B. pertussis* infection is a highly contagious disease with clinical features ranging from mild to severe and various complications.

Due to the proven risk factor for the clinical worsening of pertussis, namely, increased levels of leukocytosis, managing pertussis patients requires hematological examination, especially the number of leukocytes. If leukocytosis is found, the selection of antibiotics must be adequate by combining standard drugs (Azithromycin, Erythromycin, or Lincomycin) with other antibiotics, such as a combination with cefotaxime.

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CONFLICTS OF INTEREST

The authors declare no conflict of interest.

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