Analysis of clinical characteristics of pertussis in 184 infants and children: a retrospective study

Caiying Wang (caicai_wcy@126.com)  
Capital Medical University Affiliated Beijing Ditan Hospital

Huilin Zhang  
Capital Medical University Affiliated Beijing Ditan Hospital

Yanlan Zhang  
Capital Medical University Affiliated Beijing Ditan Hospital

Lin Xu  
Capital Medical University Affiliated Beijing Ditan Hospital

Min Miao  
Capital Medical University Affiliated Beijing Ditan Hospital

Hongling Yang  
Capital Medical University Affiliated Beijing Ditan Hospital

Yuhuan Liu  
Capital Medical University Affiliated Beijing Ditan Hospital

Shuxin He  
Capital Medical University Affiliated Beijing Ditan Hospital

Lin Pang  
Capital Medical University Affiliated Beijing Ditan Hospital

Research article

Keywords: pertussis; clinical characteristics; severe pneumonia; hyperleukocytosis

DOI: https://doi.org/10.21203/rs.3.rs-31604/v1

License: This work is licensed under a Creative Commons Attribution 4.0 International License. Read Full License
Abstract

Background: The incidence of pertussis shows an increasing trend in recent years, but some clinicians often lack sufficient understanding of the clinical characteristics and risk factors for severe pertussis, and more effective measures should be taken to reduce the incidence and mortality of pertussis in young infants.

Methods: A retrospective study was conducted, and 184 infants and children with pertussis who had been hospitalized in the Department of Pediatrics of Beijing Ditan Hospital affiliated with Capital Medical University from January 2016 to December 2017 were included in the study. Clinical data of the patients were collected and the clinical characteristics were statistically analyzed.

Results: Among the 184 patients, 41.85% were infants < 3 months of age, and 65.22% were not vaccinated against pertussis. There were 22 critically ill children, among whom 4 died, and compared with moderate cases, they had a higher proportion of children younger than 3 months of age and infants not vaccinated against pertussis (63.64% vs. 38.89% and 100% vs. 60.49%, respectively); a higher proportion of children with pulmonary consolidation (77.27% vs. 1.85%); higher leukocyte count (× 10⁹/L, 35.80 ± 20.53 vs 19.41 ± 8.59); and a higher proportion of children with severe hyperleukocytosis (18.18% vs. 0%, respectively) (P<0.05).

Conclusions: 1. Infants aged < 3 months who were not vaccinated for pertussis tended to be infected with pertussis and had severe pertussis. Adjusting the immunization strategy to vaccinate pregnant women to produce protective effects for the infants should be considered. 2. Severe pneumonia and hyperleukocytosis are the main mechanisms underlying severe pertussis and the key points of prevention and diagnosis of severe pertussis.

Background

With the development of modern medicine, the incidence of many infectious diseases has significantly decreased, along with their threat to human health. However, the incidence of pertussis (whooping cough) shows an increasing trend. This phenomenon is known as “pertussis resurgence.” Severe pertussis can cause sudden infant death. This is almost completely unavoidable, even in developed countries such as the United States and France [1, 2]. Currently, the reported mortality rate of pertussis is 1.2–3.0% [3]. There are two unique circumstances contributing to this. First, this mortality occurs in part because the pathogenesis and lethality mechanisms of pertussis are not completely clear. Second, some clinicians often lack sufficient understanding of the clinical characteristics and risk factors for severe pertussis and thus do not focus their attention on these factors.

In the last few years, the number of pediatric patients with pertussis treated by our hospital has increased. This has included many severe cases and deaths. In this study, we employed a retrospective study design to analyze the clinical data of pediatric patients with pertussis treated by the department of pediatrics at Ditan Hospital in the 2 years of 2016 and 2017 in order to examine the clinical characteristics of pertussis and provide a clinical basis for the prevention and treatment of severe pertussis.

Materials And Methods
1. Study subjects

This was a retrospective study which had been approved by the ethics committee of Beijing Ditan Hospital, Capital Medical University (approval number2018-6-12B). 184 pediatric patients with pertussis, aged 0-6 years, who were treated at the Department of Pediatrics at Ditan Hospital from January 2016 to December 2017, were consecutively concluded as study subjects. All these infants met the diagnostic criteria for pertussis (see below).

2. Methods

2.1. The diagnostic criteria for pertussis were as follows [4]: 1) 0–3 months of age: no fever or low fever, cough with increasing frequency and severity, plus one of the following: cough with the characteristic whoop, apnea, vomiting after cough, cyanosis, convulsions, pneumonia, and close contact with patient with long-term fever-free cough (usually a family member); or only paroxysmal apnea, cyanosis, and convulsions without a cough. 2) 4 months to 9 years old: no fever or low fever, paroxysmal cough \( \geq 7 \) days, non-purulent rhinitis, and one of the following: cough with the characteristic whoop, vomiting after coughing, apnea, convulsions, pneumonia, exacerbated symptoms at night, and close contact with patient with a long-term fever-free cough. Laboratory diagnostic criteria: Bordetella pertussis was cultured in the laboratory, Bordetella pertussis was detected by polymerase chain reaction (PCR), or paired serological test was positive (immunoglobulin G (IgG) titer of single enzyme linked immunosorbent assay (ELISA) test was significantly increased > 80–100 U/ml). In this study, the pathogenic diagnosis was performed using a Bordetella pertussis nucleic acid detection kit, and deep sputum samples of the infants were collected for testing.

Infants with pertussis who also had hypoxemia, recurrent apnea, cardiovascular dysfunction, or pertussis encephalopathy were considered to have severe pertussis.

2.2. Treatment: Pertussis was treated with intravenous instillation of azithromycin at a dose of 10 mg/kg body weight, once a day for 3 days. After a 4-day interval, a second treatment course was performed if needed with the same dosage and treatment course. Azithromycin was administrated orally to neonates less than 28 days old, with the same dosage and course of treatment as above. According to the clinical manifestations, chest imaging findings, and sputum bacterial culture results of the infants, if the infants were found to have other bacterial infections, other antibiotics were added as needed. If the infants had respiratory failure, myocardial failure, pertussis encephalopathy, or other organ damage, appropriate symptomatic supportive treatments were administrated.

2.3. Clinical data collection and specimen collection: The patients’ age, sex, and vaccination status were collected, and blood and sputum samples were collected under sterile condition. The blood routine, alanine aminotransferase (ALT) and creatine kinase isozyme (CK-MB) were tested. When necessary, arterial blood gas analysis was performed. Bordetella pertussis was tested in sputum specimens using a Bordetella pertussis nucleic acid detection kit. Chest computed tomography (CT) and X-rays were used to evaluate the pulmonary infection status of the infants, and the complications (respiratory failure, heart failure, apnea, pertussis encephalopathy, pneumonia, liver damage, and myocardial damage) were evaluated using clinical manifestations and laboratory tests. Antibiotic use, length of hospital stay, and clinical data of blood routine, C-reactive protein, procalcitonin, and sputum bacterial culture results were collected.
3. Statistical Methods

SPSS 22.0 software was used for data analysis. Quantitative data such as age, leukocyte count, platelet count, and length of hospitalization were expressed as \( \pm s \). For comparison between moderate and severe cases, the t-test was used for normally distributed data, while the rank sum test was used for non-normally distributed data. Qualitative data such as pulmonary consolidation, fever, non-vaccination with pertussis vaccine, and C-reactive protein elevation were expressed as rates. The chi-square test was used for comparison between the two groups.

Results

1. General information

From January 2016 to December 2017, we enrolled 184 pertussis patients at our hospital, of which 102 were males and 82 were females. The youngest was 23 days old and the oldest was 4 years old. The mean age was 4.50 ± 3.95 months. 77 (41.85%) were < 3 months of age; 120 (65.22%) were not vaccinated against pertussis. 162 were moderate cases, and 22 (11.96%) were severe cases who were complicated with at least one of the following: respiratory failure, heart failure, recurrent apnea, or pertussis encephalopathy. Table 1.

| Total cases | n=184 |
|-------------|-------|
| Gender      |       |
| Male (n)    | 102 (55.43%) |
| Female (n)  | 82 (44.57%) |
| Age (months)| 4.50 ± 3.95 |
| <3months (n)| 77 (41.85%) |
| Not vaccinated with pertussis vaccine (n) | 120 (65.22%) |
| Severity    |       |
| Moderate cases (n) | 162 (88.04%) |
| Severe cases (n) | 22 (11.96%) |

2. Clinical characteristics of child pertussis

Of the 184 hospitalized infants with pertussis, in addition to the serious complications named above in 22 severe cases, 83.70% of the patients had pneumonia, 10.87% had pulmonary consolidation. Most patients had increased white blood cell count (23.01±14.01× 10^9/L), and the increase in white blood cells was mainly made up of lymphocytes. Over the course of the disease, 28.8% of the patients had fever, and 13.59% of them showed increased neutrophil percentage. C-reactive protein and procalcitonin increased in 16.85% and 5.98%
of the patients, respectively, suggesting the presence of other bacterial infections. In addition, 12.5% had positive sputum bacterial culture. Patients using 3 or more antibiotics and special-grade antibiotics (carbapenems and glycopeptides) accounted for 14.13% and 10.33% respectively, 14 cases (7.61%) required ventilator-assisted breathing. Except for 4 patients who died (2.17%), the remaining cured. The average hospital stay was 15.68 ± 8.11 days (Table 2).

Table 2. Clinical characteristics of child pertussis

| Clinical characteristic                        | Total cases (n=184) |
|-----------------------------------------------|---------------------|
| respiratory failure (n)                       | 18 (9.78%)          |
| heart failure (n)                             | 16 (8.70%)          |
| recurrent apnea (n)                           | 11 (5.98%)          |
| pertussis encephalopathy (n)                  | 3 (1.63%)           |
| pneumonia (n)                                 | 154 (83.70%)        |
| Pulmonary consolidation (n)                   | 20 (10.87%)         |
| Leukocyte count (× 10^9/L)                    | 23.01±14.01         |
| Fever (n)                                     | 53 (28.80%)         |
| Elevated neutrophilia percentage (n)*        | 25 (13.59%)         |
| Elevated C-reactive protein (n)*              | 31 (16.85%)         |
| Elevated procalcitonin (n)*                  | 11 (5.98%)          |
| Positive bacterial sputum culture (n)         | 23 (12.5%)          |
| Antibiotic usage                              |                     |
| Three or more antibiotics (n)                 | 26 (14.13%)         |
| Special-grade antibiotics (n)                 | 19 (10.33%)         |
| Ventilator-assisted breathing (n)             | 14 (7.61%)          |
| Length of hospitalization (days)              | 15.68 ± 8.11        |
| Cases of death (n)                            | 4 (2.17%)           |

* The normal range of neutrophilia percentage between the age of 6 days to 4 years is 30-35%, that of C-reactive protein is <5mg/L, and that of procalcitonin is <0.25ng/L. The columns labeled "n" in the brackets shows numbers of children with pertussis with various complications, with abnormal results of laboratory tests, special treatments, or treatment outcomes.

3. Clinical characteristics of severe pertussis
There were 22 severe cases, and 18 of them had respiratory failure, 16 had heart failure, 11 had recurrent apnea, and 3 had pertussis encephalopathy (table 2). Compared with the children with moderate cases, the 22 severe cases were younger, 63.64% were < 3 months of age, and the proportion of infants < 3 months of age was significantly higher than that of patients with moderate cases. None of the severe cases had been vaccinated against pertussis, showing a significantly higher rate of non-vaccination than in the children with moderate cases. The incidence of pulmonary consolidation and fever, and the percentage of children with elevated neutrophil percentage, elevated C-reactive protein and procalcitonin levels were higher, and the positive rate of sputum bacterial culture was significantly higher than the moderate cases. Moreover, the white blood cell count of severe cases was higher than those of moderate cases, and the proportions of patients with severe hyperleukocytosis (white blood cells > 50*10E9/L) were also significantly higher in the severe cases than in moderate cases. The length of hospitalization was significantly longer, and the proportions of using 3 or more antibiotics and special-grade antibiotics were also higher in the severe cases than in moderate cases (P<0.05, Table 3).

Table 3. Comparison of clinical characteristics of the severe and moderate cases
|                        | Severe cases | Moderate cases |
|------------------------|--------------|----------------|
|                        | (n = 22)     | (n = 162)      |
| **Gender**             | Male(n)      | 12             | 90             |
|                        | Female(n)    | 10             | 72             |
| **Age (months)**       | 2.80 ± 1.26  | 4.97 ± 4.30    |
| **3 months (n)**       | 14 (63.64%)  | 63 (38.89%)    |
| **Not vaccinated with pertussis vaccine (n)** | 22 (100%) | 98 (60.49%) |
| **Pulmonary consolidation (n)** | 17 (77.27%) | 3 (1.85%) |
| **Winn (n)**           | 19 (86.36%)  | 34 (20.99%)    |
| **Evaluated neutrophilia percentage (n)** | 15 (68.18%) | 10 (6.17%) |
| **Evaluated C-reactive protein (n)** | 11 (50.00%) | 20 (12.33%) |
| **Evaluated procalcitonin (n)** | 9 (40.91%) | 2 (1.23%) |
| **Positive bacterial sputum culture (n)** | 8 (36.36%) | 15 (9.26%) |
| **White cell count (× 10⁹/L)** | 35.80 ± 20.53 | 19.41 ± 8.59 |
| **White cell count > 50× 10⁹/L (n)** | 4 (18.18%) | 0 |
| **Antibiotic usage**   | Three or more antibiotics (n) | 18 (81.82%) | 8 (4.94%) |
|                        | Special-grade antibiotics (n) | 15 (68.18%) | 4 (2.47%) |
| **Length of hospitalization (days)** | 27.71 ± 11.19 | 14.56 ± 5.84 |
| **Cases of death (n)** | 4 (18.18%) | 0 |

*p<0.05, comparison between moderate and severe cases using statistical methods.

**4. Etiological analysis of pertussis-complicated pneumonia**

Of the 184 children with pertussis, 23 had positive sputum bacterial culture (12.50%), 15 in the moderate group and 8 in the severe group. The pathogens of the moderate group were common community infectious pathogens, such as *Staphylococcus aureus*, *Escherichia coli*, *Haemophilus influenzae*, and *Streptococcus pneumoniae*, while Gram-negative bacilli infections were more common in the severe group. These bacilli included *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, *Enterobacter cloacae*, and *Klebsiella pneumoniae* (Table 4). Among them, the sputum cultures of 4 severe cases were found to contain multi-drug resistant bacteria (2 cases of *Acinetobacter baumannii*, 1 case of *Pseudomonas aeruginosa*, and 1 case of *Stenotrophomonas maltophilia*), and 2 and more types of bacteria were cultured in the specimens of 3 severe cases.
Table 4. Etiological analysis of pertussis-complicated pneumonia

| Type of pathogen         | Severe cases | Moderate cases | Total  |
|--------------------------|--------------|----------------|--------|
|                          | (8 cases)    | (15 cases)     | (23 cases) |
| *Staphylococcus aureus*  | 1            | 3              | 4      |
| *Klebsiella pneumoniae*  | 1            | 2              | 3      |
| *Enterobacter cloacae*   | 1            | 2              | 3      |
| *Pseudomonas aeruginosa* | 2            | 1              | 3      |
| *Acinetobacter baumannii* | 3            | 0              | 3      |
| *Escherichia coli*       | 0            | 3              | 3      |
| *Haemophilus influenzae* | 0            | 2              | 2      |
| *Streptococcus pneumoniae* | 0            | 2              | 2      |
| *Klebsiella aerogenes*   | 1            | 0              | 1      |
| *Stenotrophomonas maltophilia* | 1        | 0              | 1      |
| *Burkholderia cepacia*   | 1            | 0              | 1      |

This table shows the results of sputum bacterial culture in severe and moderate cases respectively.

5. Clinical characteristics of 4 deaths

Of the 22 children with severe pertussis, 4 died, all of them were infants younger than 6 months of age and 2 younger than 3 months of age. None of them had been vaccinated with pertussis vaccine. The white blood cell count of 3 cases was \(> 50 \times 10^9/L\), with the highest count of \(106.68 \times 10^9/L\). All 4 cases were complicated with severe pneumonia (pulmonary consolidation), the percentage of neutrophils was high (44.00–81.54%), C-reactive protein was higher than normal in 3 cases (21.1–235.5 mg/L, with normal value of < 5 mg/L), and procalcitonin was high in 2 cases (1.05–8.22 ng/ml, with normal value of < 0.25 ng/ml). All had fever during the course of the disease. One case had positive sputum bacterial culture, which was *Enterobacter aerogenes*. The drug sensitivity test of the *Bordetella pertussis* isolated from a 56-day-old infant showed resistance to macrolides. The causes of death of 2 were respiratory and heart failure, 1 was septic shock, and 1 was acute respiratory distress syndrome (ARDS). (Table 5)

Table 5. Clinical characteristics of 4 deaths
|                | No.1     | No.2     | No.3#    | No.4     |
|----------------|----------|----------|----------|----------|
| Age (months)   | 2.90     | 5.20     | 1.87     | 4.00     |
| Gender         | female   | male     | female   | male     |
| Pertussis vaccination | no     | no       | no       | no       |
| Pulmonary consolidation | yes   | yes      | yes      | yes      |
| Fever          | yes      | yes      | yes      | yes      |
| Leukocyte count ($\times 10^9$/L) | 58.2   | 29.8     | 50.98    | 106.68   |
| Neutrophilia percentage | 44.66%  | 70.04%   | 81.54%   | 44.00%   |
| C-reactive protein (mg/L) | 0      | 23.90    | 235.50   | 21.10    |
| Procalcitonin (ng/ml) | 0.05   | 8.22     | 1.05     | 0.09     |
| Bacterial sputum culture | negative | negative | negative | *Enterobacter aerogenes* |
| Length of hospitalization (days) | 5       | 10       | 21       | 3        |
| Causes of death | septic shock | respiratory and heart failure | ARDS | respiratory and heart failure |

# The drug sensitivity test of the *Bordetella pertussis* isolated from this patient showed resistance to macrolides.

This table shows the general information and clinical data of 4 deaths in severe pertussis cases.

**Discussion**

Pertussis can occur in all age groups, with the highest incidence in infants and young children, and infants under 1 year of age have relatively severe conditions. The infants included in this study were hospitalized pertussis patients, with an average age of $4.50 \pm 3.95$ months. Most of them were young infants with relatively severe conditions. In this study, 65.22% of the infants were not vaccinated against pertussis, and 41.85% were infants younger than 3 months. None of the severe infants were vaccinated, of whom 63.64% were younger than 3 months of age. The study shows that nearly half of the patients experienced onset of pertussis before the standard age of pertussis vaccination in China (3 months of age), and the proportion of unvaccinated infants was significantly higher in the severe cases than in the moderate cases, which was
consistent with the results of previous studies [5]. In order to decrease the rate of pertussis overall and reduce the number of severe cases, the Chinese government may should consider to adjust the standard immunization schedule. Because IgG antibodies can cross the placenta, almost all IgG antibodies present in infants 6 months old and younger arise from the mother. A set of studies showed that when acellular pertussis vaccine was given to pregnant women in the second or third trimester, especially at 27–36 weeks of pregnancy, enough antibodies against Bacillus pertussis, such as the anti-pertussis toxin and anti-filament hemagglutinin antibodies, were detected in the blood of the neonates, and the antibodies persisted and gradually declined until completely attenuated at the age of 3 months[6, 7, 8]. Therefore, acellular pertussis vaccine for pregnant women could protect infants from pertussis infections before the standard age of pertussis vaccination (the age of 3 months). So far, acellular pertussis vaccination in pregnancy has been implemented in Brazil, Argentina, Britain, America, Belgium and New Zealand. An observational study showed that the strategy produced up to 90% protective effect for the infants due to its two effects, one was that the specific antibodies arising from the mother, and the other was protecting the mother from infections that could reduce maternal-neonatal transmission [9,10,11,12]. In Argentina the deaths of pertussis cases deceased 87% in 2013 compared with that in 2011, since the country implemented the strategy of acellular pertussis vaccination in pregnancy in 2012[13].

Pneumonia is the most common complication of pertussis. In this study, more than 80% of hospitalized infants with pertussis also had pneumonia. Some infants had fever, with increased neutrophils, C-reactive protein, and procalcitomin levels, indicating the presence of other bacterial infections. Moreover, 10% of the infants had pulmonary consolidation, suggesting severe infection. All severe cases also had pneumonia, and nearly 80% had pulmonary consolidation, more than 80% had respiratory failure, and more than 60% required ventilator-assisted breathing. All fatal cases were complicated by severe pneumonia. In this way, pneumonia is not only the most common complication of pertussis but also the leading cause of severe cases and death of pertussis [14,15,16].

Increased white blood cell count is a characteristic manifestation of pertussis. The white blood cell count of children in the severe group was significantly higher than that of the moderate group, and the white blood cell count was particularly high in fatal cases. Due the poor ability of white blood cells to change shape, they tend to obstruct stenosed alveolar capillary beds. White blood cells usually take 10-15 times longer than erythrocytes to pass through these vessels, resulting in embolism due to leukocyte clumps, causing hypoxemia and pulmonary hypertension [17, 18]. This affects cardiac function and causes heart failure in severe cases. Severe hyperleukocytosis (> 50 × 10^9 leukocytes/L) is an independent risk factor for malignant pertussis (life-threatening severe pertussis) [19, 20]. Many studies have indicated that when routine treatment was given even though the peripheral leukocyte count was > 100 × 10^9/L in pertussis patients, and no measures to lower leukocyte counts were carried out, death resulted in all cases [21, 22]. In this study, there were 4 infants the in the severe group whose white blood cell counts were > 50×10E9/L, of whom 3 died. This awaits confirmation in future work and exploration of related targeted treatment. Studies have shown that plasma exchange and leukapheresis can reduce leukocyte count and significantly improve fatal hypoxemia and pulmonary hypertension [23, 24]. Some researchers have used carbon monoxide and sildenafil to dilate pulmonary blood vessels and reduce pulmonary hypertension; some efficacy was observed [25].
Pertussis not only seriously endangers the life and health of infants, and also creates a heavy burden on families and society. Severe pneumonia and hyperleukocytosis are key issues in the prevention and treatment of severe pertussis. Adjusting the immunization strategy to vaccinate pregnant women has a clear effect on reducing the incidence and mortality of pertussis in young infants, which should be considered by the government.

**Conclusions**

1. Infants aged < 3 months who were not vaccinated for pertussis tended to be infected with pertussis and had severe pertussis. Adjusting the immunization strategy to vaccinate pregnant women to produce protective effects for the infants should be considered.

2. Severe pneumonia and hyperleukocytosis are the main mechanisms underlying severe pertussis and the key points of prevention and diagnosis of severe pertussis.

**List Of Abbreviations**

PCR: polymerase chain reaction

IgG: immunoglobulin G

ESISA: enzyme linked immunosorbent assay

ALT: alanine aminotransferase

CK-MB: creatine kinase isozyme

CT: computed tomography

ARDS: acute respiratory distress syndrome

**Declarations**

Ethics approval and consent to participate

This retrospective study has been approved by the ethics committee of Beijing Ditan Hospital, Capital Medical University (approval number2018-6-12B). Verbal informed consent was obtained from the legal guardians of the patients in this study because this is a retrospective study and the patients had been discharged when the study was carried out. This procedure was approved by the ethics committee of Beijing Ditan Hospital, Capital Medical University.

Consent for publication

Consent for publication have been obtained from the legal guardians of the patients included in the study.

Availability of data and materials
All data generated or analysed during this study are included in this published article.

Competing interests

The authors declare that they have no competing interests.

Funding

The study is funded by Beijing Ditan Hospital of Capital Medical University Key Laboratory Open Research Project (2209-25-111). The funding body contributed to the design of the study and analysis of data.

Acknowledgements

Not applicable.

Author’s contributions

LP and CW interpreted the patient clinical data, CW wrote the manuscript, CW and HZ performed statistical analysis, and YZ, LX, MM, HY, YL and SH collected the clinical data. All authors read and approved the final manuscript.

References

[1] Mbayei SA, Faulkner A, Miner C, et al. Severe Pertussis Infections in the United States, 2011-2015. Clin Infect Dis. 2019; 69(2): 218-226.

[2] Matthias J, Pritchard PS, Martin SW, et al. Sustained transmission of pertussis in vaccinated, 1-5-year-old children in a preschool, Florida, USA. Emerg Infect Dis. 2016; 22(2): 242-246.

[3] Straney L, Schibler A, Ganeshalingham A, et al. Burden and Outcomes of Severe Pertussis Infection in Critically Ill Infants. Pediatr Crit Care Med. 2016; 17(8):735-42.

[4] Infection Section of Pediatric Branch of Chinese Medical Association. Diagnosis and treatment of pertussis in children in China. Chinese Journal of Pediatrics. 2017; 55(8):568-572.

[5] Hu Y, Liu Q. Clinical analysis of 247 children with whooping cough and the risk factors of severe cases. Chinese Journal of Pediatrics. 2015; 53(9):684-689.

[6] Vilajeliu A, Ferrer L, Munros J, et al. Pertussis vaccination during pregnancy: antibody persistence in infants. Vaccine. 2016; 34 (33): 3719-3722.

[7] Maertens K, Caboré RN, Huygen K, et al. Pertussis vaccination during pregnancy in Belgium: Results of a prospective controlled cohort study. Vaccine. 2016; 34(1): 142-150.

[8] Cherry JD. Pertussis in young infants throughout the world. Clin Infect Dis. 2016; 63(S4):S119–S122.
[9] Fedele G, Carollo M, Palazzo R, et al. Parents as a source of pertussis transmission in hospitalized young infants. Infection. 2017; 45:171–178.

[10] Machado MB, Passos SD. Severe pertussis in childhood: update and controversy - systematic review. Rev Paul Pediatr. 2019;37(3):351-362.

[11] Dabrera G, Amirthalingam G, Andrews N, et al. A case-control study to estimate the effectiveness of maternal pertussis vaccination in protecting newborn infants in England and Wales, 2012-2013. Clin Infect Dis. 2015; 60(3): 333-337.

[12] Amirthalingam G, Andrews N, Campbell H, et al. Effectiveness of maternal pertussis vaccination in England: an observational study. Lancet. 2014; 384(9953): 1521-1528.

[13] Vizzotti C, Neym S, Katz N, et al. Maternal immunization in Argentina: a storyline from the prospective of a middle-income country. Vaccine. 2015; 33(47): 6413-6419.

[14] Sadiasa A, Saito-Obata M, Dapat C, et al. Bordetella pertussis infection in children with severe pneumonia, Philippines, 2012-2015. Vaccine. 2017; 35(7):993-996.

[15] Zhou K, Han Q. Mechanism and prevention of death caused by pertussis in infants. Chinese Journal of Applied Clinical Pediatrics. 2017;32(22):1699-1701.

[16] Kazantzi MS, Prezerakou A, Kalamitsou SN, et al. Characteristics of Bordetella pertussis infection among infants and children admitted to paediatric intensive care units in Greece: a multicentre, 11-year study. J Paediatr Child Health. 2017; 53(3): 257-262.

[17] Wei XM, Yang H, Lei M, et al. Blood exchange transfusion for treatment of severe pertussis in an infant. Chinese Journal of Contemporary Pediatrics. 2019; 21(3):214-217.

[18] James D. Cherry. The prevention of severe pertussis and pertussis deaths in young infants. Expert Rev Vaccines. 2019;18(3):205-208.

[19] Berger JT, Carcillo JA, Shanley TP, et al. Critical pertussis illness in children: a multicenter prospective cohort study. Pediatr Crit Care Med. 2013; 14(4): 356-365.

[20] Ganeshalingham A, McSharry B, Anderson B, et al. Identifying children at risk of malignant bordetella pertussis infection. Pediatr Crit Care Med. 2017; 18(1): e42-e47.

[21] Grzeszczak MJ, Churchwell KB, Edwards KM, et al. Leukopheresis therapy for severe infantile pertussis with myocardial and pulmonary failure. Pediatr Crit Care Med. 2006; 7(6): 580-582.

[22] Rowlands HE, Goldman AP, Harrington K, et al. Impact of rapid leukodepletion on the outcome of severe clinical pertussis in young infants. Pediatrics. 2010; 126(4): e816-e827.

[23] Tian SF, Wang HM, Deng JK. Fatal malignant pertussis with hyperleukocytosis in a Chinese infant. Medicine. 2018; 97(17): e0549.
[24] Xiang L, Cao Q, Xi Y, et al. Application of leukoreduction therapy in severe pertussis with leukocytosis and pulmonary hypertension: 3 infant cases reports and literatures review. Chin Pediatr Emerg Med. 2018; 25(11):801-806.

[25] Cherry JD, Wendorf KA, Bregman B, et al. An observational study of severe pertussis in 100 infants ≤120 days of age. Pediatr Infect Dis. 2018; 37(3):202–205.