The clinical characteristics and prognosis of pertussis among unvaccinated infants in the pediatric intensive care unit

Yoğun bakımda boğmaca tanısı ile izlenen aşısız süt çocuklarının klinik özellikleri ve seyri etkileyen etmenler

Güntülü Şık, Asuman Demirbuğa, Agageldi Annayev, Agop Çıtak

Department of Pediatric Intensive Care, Acıbadem Mehmet Ali Aydınlar University Faculty of Medicine, İstanbul, Turkey

The known about this topic

Pertussis is a vaccine-preventable disease. The causative agent is *Bordetella pertussis*. It frequently leads to pneumonia in infants. It may cause severe disease in unvaccinated infants.

Contribution of the study

Among patients admitted to intensive care unit, severe pertussis occurs more frequently in infants who are too young to be protected with active immunization. Maternal immunization and the cocoon strategy may provide success to protect this age group. Severe pulmonary hypertension on echocardiographic examination and presence of leukocytosis in laboratory tests are associated with poor prognosis.

Abstract

Aim: To evaluate the clinical characteristics, risk factors, and prognosis of *pertussis* in the pediatric intensive care unit.

Material and Methods: Patients who were hospitalized in pediatric intensive care unit between January 2017 and January 2019 and diagnosed as having *pertussis* were retrospectively evaluated. Samples were taken from tracheal aspirate material in intubated patients and nasopharyngeal swabs in the other patients. Samples for *Bordetella pertussis* were studied using multiplex real-time polymerase chain reaction.

Results: Eighteen patients were admitted to our pediatric intensive care unit with a diagnosis of *pertussis*. Ten patients were female (55.5%), and all patients were unvaccinated. The median age was 40 (range, 38–47.5) days and the median intensive care unit stay was 9 (range, 5–14) days. All patients had respiratory distress, 14 patients had cough (77.7%), four patients had fever (22.2%), and three patients had convulsions (16.6%). Seven patients were intubated. Three patients died of multiple organ failure and cardiogenic shock despite extracorporeal treatment. Respiratory syncytial virus was found in two patients and rhinovirus was found in one patient. The median leukocyte count was significantly higher in non-survivors than in survivors. Blood exchange was performed in

Öz

Amaç: Çocuk yoğun bakım biriminde boğmaca tanısıyla izlenen hastaların klinik özelliklerini, risk etmenlerini ve seyri etkileyen etmenleri değerlendirmeyi amaçladık.

Gereç ve Yöntemler: Çocuk yoğun bakım birimimizde Ocak 2017–Ocak 2019 tarihleri arasında yatan ve boğmaca tanısı alan hastalar geriye dönük olarak değerlendirildi. Örnekler entübe olarak izlenen hastalarda trakeal aspirat materyalinden, diğer hastalarda nazofaringeal sürüntüden alındı. *Bordetella pertussis* için örnekler multiplex real-time polimeraz zincir reaksiyonu yöntemi ile çalışıldı.

Bulgular: On sekiz hasta boğmaca tanısı ile çocuk yoğun bakım birimimize yatırıldı. Hastaların %55,5'i kızdı (n=10), tüm hastalar aşısızdı. Ortanca yaş 40 (38–47,5) gün, ortanca yoğun bakım yatış süresi 9 (5–14) gündü. Başvuru anında hastaların tümünde solunum sıkıntısı, 14 hastada (%77,7) öksürük, 4 hastada (%22.2) ateş, 3 hastada (%16,6) konvülziyon saptandı. Yedi hasta entübe edilerek izlendi. Üç hasta ekstrakorporeal tedavi yöntemleri uygulanmasına rağmen çoklu organ yetersizliği ve kardiyojenik şok nedeniyle kaybedildi. Ölen hastaların ikisinde respiratuar sinsityal virüs, birinde rhinovirüs ko-enfeksiyonu vardı. Toplam lökosit sayıları karşılaştırıldığında ölen hasta grubunda lökosit sayısı

Turk Pediatri Ars 2020; 55(1): 54–59

Şık et al. The clinical characteristic and prognosis of pertussis

three patients due to hyperleukocytosis. Pulmonary hypertension was the most common cardiac pathology detected in echocardiographic examinations.

Conclusion: We found that high leukocyte count, viral co-infection, and severe pulmonary hypertension were associated with mortality and morbidity in *pertussis*.

Keywords: *Bordetella pertussis*, cocooning strategy, extracorporeal membrane oxygentaion, pediatric intensive care, *Pertussis*, pulmonary hypertension, whooping cough

yaşayanlara göre belirgin oranda yüksekti. Hiperlökositoz nedeniyle 3 hastaya tam kan değişimi yapıldı. Ekokardiyografik inceleme ile en sık saptanan kardiyak patoloji pulmoner hipertansiyondu.

Çıkarımlar: Boğmaca tanısıyla yoğun bakımda izlenen hastalarda yüksek lökosit sayısı, eşlik eden viral enfeksiyon ve ciddi pulmoner hipertansiyonun mortalite ve morbidite ile ilişkili olduğunu saptadık.

Anahtar sözcükler: Boğmaca, *bordetella pertussis*, çocuk yoğun bakım, ekstrakorporeal membran oksijenasyonu, koza stratejisi, öksürük, pulmoner hipertansiyon

Introduction

Pertussis is an infectious disease caused by *Bordetella pertussis* (*B. pertussis*), which is frequently observed in infants, and it may lead to pneumonia, encephalopathy, apnea, pulmonary hypertension, and mortality. Worldwide, it ranks number five among the fatal but vaccine-preventable diseases in children aged below 5 years, and continues to be an important health problem. According to data of the World Health Organization (WHO), 139 535 patients with *pertussis* were reported worldwide in 2017 (1–3).

Pertussis causes severe disease especially in newborns and unvaccinated infants. The clinical picture may have a mild course or it may be manifested by respiratory failure, bronchopneumonia, and apnea attacks. Severe cases accompanied by pulmonary hypertension, cardiogenic shock, and hyperleukocytosis are defined as malignant *pertussis*. In these patients, the mortality rate is high despite supportive treatment (4).

In clinically suspicious patients, the definite diagnosis is made by examination of nasopharyngeal swab specimens or tracheal aspirate specimens through culture or with polymerase chain reaction (PCR). Culture is considerably specific, but its sensitivity varies depending on the presence of sufficent material, inappropriate transport, and previous antibiotic use. Examination with PCR is considered the gold standard because it provides definite and rapid diagnosis.

In this study, we aimed to retrospectively evaluate patients who were followed up in our pediatric intensive care unit (PICU) with a diagnosis of *pertussis*, to investigate the clinical charcteristics and risk factors, and to specify the factors influencing the prognosis.

Material and Methods

Eighteen patients who were followed up in the PICU between January 2017 and January 2019 and diagnosed as having *pertussis* were included in the study; the patients were evaluated retrospectively. Our study was conducted in accordance with the Declaration of Helsinki. Approval was obtained from Acıbadem Mehmet Aydınlar University Ethics Committee (2019-10/13).

Tracheal aspirate samples were obtained in the intubated patients who were followed up and nasopharyngeal swab specimens were obtained in the other patients. The samples were obtained by physicians or nurses who took preventive precautions (mask, sterile apron, protective glasses and gloves) and the transport boxes were kept open only during the time of sampling. In all patients, *B. pertussis* was found to be positive with PCR in nasopharyngeal swab specimens or tracheal aspirate material.

The patients' demographic properties, history of contact, vaccination status, duration of stay in the PICU, respiratory support and its duration, vital findings, use of inhaled nitric oxide, whole blood exchange, extracorporal supportive therapies, vasoactive inotropic score, Pediatric Risk of Mortality (PRISM) scores, and total leukocyte and lymphocyte counts were recorded.

A diagnosis of pneumonia was made with clinical evaluation and presence of pulmonary consolidation and parenchymal opacity. All patients were evaluated by a pediatric cardiologist with echocardiographic examinations.

Statistical Analysis

The SPSS software was used for the analysis of data. Median and minimum-maximum values were used for the descriptive data, and the Mann-Whitney U test was used for the comparison of continuous inter-group values. A p value of <0.05 was considered significant.

Results

In the two-year study period, a diagnosis of *pertussis* was made in 18 patients. The median age was 40 (range, 38–47.5) days, and 94.4% of the patients (n=17) were aged below 2 months; nine of these patients were aged below 6 weeks. Only one patient was aged 6 months. Ten (55.5%) patients (n=10) were female. All patients, their parents, and individuals living in the same house were unvaccinated.

All patients had respiratory distress at the time of presentation. Cough was found in 14 patients (77.7%). The median duration of cough before presentation to hospital was found as 4 (range, 2–9) days. Four patients had fever (22.2%), three

Şık et al. The clinical characteristic and prognosis of pertussis

Turk Pediatri Ars 2020; 55(1): 54–59

Table 1. Demographic and clinical properties

	Median (IQR) or n (%)
Age (days)	40 (38–47.5)
Sex (female/male)	10/8 (55.6/44.4)
Duration of cough (days)	4 (2–9)
Presence of viral co-infection	4 (22.2%)
Use of invasive mechanical ventilation	7 (38.8%)
Use of non-invasive mechanical ventilation	3 (16.6%)
Use of high-flow oxygen treatment	5 (27.7%)
Duration of hospitalization in intensive care unit (days)	9 (5–14)

IQR: Interquartile range

had convulsions (16.6%), and six patients had difficulty in feeding. There was no morbidity in the patients' personal medical histories. Macrolid group antibiotic treatment was initiated in all patients. *B. pertussis* was detected using PCR in nasopharyngeal secretion samples in 12 patients and in tracheal aspirate samples in six patients.

Fifteen patients needed respiratory support during hospitalizationn in the PICU (83.3%). Mechanical ventilation was performed in seven patients, non-invasive mechanical ventilation was administered in three patients, and high-flow nasal oxygen treatment was given in five patients (Table 1). The duration of mechanical ventilation was 8.8 days (range, 4–21 days). Five patients needed vasoactive-inotropic medications. Nitric oxide and sildenafil were administered to four patients and sildenafil alone was administered to three patients because of pulmonary hypertension. Hydrocortisone treatment was initiated in four patients with a diagnosis of catecholamine-resistant shock. Whole blood exchange was performed in three patients because of hyperleukocytosis.

Lung radiography revealed pneumonic infiltration and consolidation in 13 patients (72.2%) and pneumothorax in two patients. Chest tubes were placed in patients who were found to have pneumothorax.

Viral co-infection was found in four patients [respiratory syncytial virus (RSV) in two patients and rhinovirus (RV) in two patients]. In these patients, the need for mechanical ventilation and mortality rates were found to be higher compared with patients who were *B. pertussis*-positive only (n=14).

When the total leukocyte values at the time of admission to the PICU were evauated, the total leukocyte count in the patient group who died (median 37 100/mm^3, IQR 28 730–50 180/mm^3) was higher compared with the patients who survived (median 11 630/mm^3, IQR 8660–19 425/mm^3) (p=0.005). When the highest values obtained during hospitalization were evaluated, the total leukocyte count in the patient group who died (median 64 970/mm^3, IQR 50 180–76 280/mm^3) was again higher compared with the patients who survived (15 200/mm^3, IQR 11 785–21 750/mm^3) (p<0.001). The lymphocyte count was higher in patients who died (median 35 800/mm^3, IQR 26 200–44 200/mm^3) compared with patients who survived (median 9 940/mm^3, IQR 4515–16 000/mm^3) (p=0.005) (Table 2).

Three patients died of multi-organ failure, catecholamine-resistant cardiogenic shock, and severe pulmonary hypertension. Sildenafil, inhaled nitric oxide, and supportive treatment with veno-arterial extracorporal membrane oxygenation (VA ECMO) were administered to these patients. Comorbid viral infection was present in all three patients who died (2 RSV, 1 RV).

Discussion

Pertussis is a disease that can be prevented by immunization, and the most important way for protection is active

Table 2. Comparison of the patients who did and did not survive

	Total (n=18) Median (IQR)	Survivor (n=15) Median (IQR)	Lost (n=3) Median (IQR)	p
Age (days)	40 (38–47.5)	40 (37.25–51.25)	45 (38-45)	0.911[a]
Female/male	10/8	8/7	2/1	0.407[b]
Total leukocyte count (at the time of hospital admission)/mm^3	12365 (9505-28132)	11630 (8660–19425)	37100 (28730–50180)	**0.005**[a]
Total leukocyte count (maximum)/mm^3	18085 (11987–47720	15200 (11785–21750)	64970 (50180–76280)	**<0.001**[a]
Lymphocyte count (at the time of hospital admission)/mm^3	8015 (3412–20175)	4920 (2835–14750)	26200 (17500–28000)	**0.005**[a]
Lymphocyte count (maximum)/mm^3	10975 (4685–29800)	9940 (4515–16000)	35800 (26200–44200)	**0.005**[a]
Viral co-infection	4	1	3	0.952[b]

IQR: Interquartile range; a: Mann Whitney U test; b: Ki-kare test

Turk Pediatri Ars 2020; 55(1): 54–59

Şık et al. The clinical characteristic and prognosis of pertussis

immunization by way of vaccination. Vaccination at an early age is important because the mortality is high in infants (5). In our country, *pertussis* vaccine has been included in the Ministry of Health's vaccination schedule since 2009 as acellular vaccine and is given a total of four times at the 2nd, 4th, 6th, and $18–24^{th}$ months (rapel dose) as DaBT-IPA-Hib (diphteria, acellular *pertussis*, tetanus, inactive polio, Haemophilus influenzae type b vaccine/ pentavalent combination vaccine) (6).

Unvaccinated infants below the age of 6 weeks constitute 41.8% of patients who are hospitalized in PICUs because of *pertussis*, partially vaccinated infants aged between 6 weeks and 6 months constitute 46.7%, and fully vaccinated infants aged over 6 months constitute 11.5% (7, 8). In a study conducted in the United Kingdom, it was shown that vaccination of babies at the time of birth induced antibody response and contributed to protection against *pertussis* in patients aged under 6 months. In addition, maternal vaccination provides nearly 91% protection in children aged below 2 months (8–11). In 2011, the United Kingdom National Vaccination Program recommended that the first dose of *pertussis* vaccine should be given at the 6th week to provide early protection. At the end of 2011, the first dose of *pertussis* vaccine was applied in 50–70% of children aged between 6 and 8 weeks in some states of the United States of America, and it was shown that hospitalizations because of *pertussis* decreased by 10% (12). All these studies emphasize the importance of vaccination in preventing *pertussis* and protecting infants.

In our study, the median duration of cough was 4 (range, 2–9) days before presenting to hospital. This finding was similar to the findings of other studies (13–15). *Pertussis* may also be manifested by apnea and convulsions in infants (16). Although it has been reported that convulsions increase mortality and morbidity, convulsions were found in only two of our patients at the time of presentation and these convulsions could be easly controlled.

Severe inflammation is not observed during the natural course of *pertussis* unless bacterial or viral secondary infection is added to the picture. Therefore, fever may not be observed in patients, and this leads to a delay in presentation to hospital. In our study, 22.2% of patients (n=4) had fever and viral infection accompanied in three of these patients. The frequency of fever was similar to the literature (17, 18).

Studies conducted in our country have reported that the main source of *pertussis* for infants younger than one year was family members close to the infant (>55%) (5). It was found that *pertussis* was transmitted to children aged

below one year from their mothers with a rate of 42.8% (19). As a response to increasing *pertussis* reports across Turkey, the cocoon vaccination strategy was initiated. The cocoon strategy involves vaccination of all individuals who are in close contanct with the newborn who is vulnerable to infectious agents (20). In this way, the newborn is put under protection, because all individuals around have been vaccinated against the infectious agent (20, 21). In our study, all patients were unvaccinated because 17 patients were aged below 2 months and the family of one patient refused vaccination, and vaccination compatible with the cocoon strategy was not given to family members. In addition, all patients who were aged below 2 months had a history of being present in crowded environments approximately 5–7 days before the symptoms. This supports literature that emphasizes the protectiveness of the vaccine against *pertussis* and the importance of the cocoon strategy (1–3, 22–24).

In our study, three patients (16.6%) died of multi-organ failure and cardiogenic shock. Respiratory syncytial virus or RV was positive and severe pulmonary hypertension was found on echocardiographic examination in all these patients. The mortality rate was similar to other studies. In a study conducted in 2017, *B. pertussis* PCR was found to be positive in 11 of 301 infants who needed hospitalization in the PICU because of acute respiratory failure and 18% of these patients died. In contrast to our patients, coinfection was not found in these patients and the highest leukocyte count at the time of presentation was found to be 23 000/mm³ (25). In a study conducted in Brazil between 2008 and 2014, 55 patients were admitted to hospital with a diagnosis of laboratory-confirmed *B. pertussis*, 17 patients (30.9%) needed intensive care and six patients (10.9%) died (26). All patients who died were aged below 2 months and unvaccinated, and RSV was found to be positive in three patients. In addition, the total leukocyte count was found as 55 250/mm³ in patients who died and severe pulmonary hypertension unresponsive to nitric oxide tratment was found in five of these patients. In our study, comorbid viral infection was present in four patients (2 RSV, 2 RV). Two patients who were found to be respiratory syncytial virus positive and one patient who was RV positive died. In the patient group that died, comorbid RSV infection was found with a higher rate. With these results, we argue that comorbid viral or bacterial infection influences prognosis in children hospitalized with a diagnosis of *pertussis* (1).

High leukocyte and lymphocyte counts are associated with mortality and need for intensive care. Similar to our results, Guinto-Ocampo et al. (27) showed that a high lymphocyte count was predictive for poor prognosis in

patients with *pertussis* aged less than one year. In a study conducted by Murray et al. (28), it was found that a high leukocyte count was associated with an increased need for mechanical ventilation, severe pulmonary hypertension, and mortality in patients hospitalized with a diagnosis of *pertussis*. All these results show that increased leukocyte count (>30 000/mm³) in children with *B. pertussis* infection is associated with disease severity and mortality (28, 29).

In *pertussis*, the pathogenesis of pulmonary hypertension is complex and multi-factorial. Hyperleukocytosis leads to irreversible pulmonary hypertension because of leukocyte aggregates in the pulmonary artery, pulmonary vein, and lymphatic channels. Therefore, reducing the leukocyte count by blood exchange and leukopheresis decreases mortality (16, 28). In our study, we found pathologic findings on echocardiographic examinations in four patients. Three patients had severe pulmonary hypertension and one patient had mild pulmonary hypertension. Right heart failure findings accompanied in two of the patients who had severe pulmonary hypertension. Sildenafil and inhaled nitric oxide were administered to three patients and only sildenafil was administered to one patient. Supportive treatment with VA ECMO was administered in three patients because of multi-organ failure, catecholamine-resistant cardiogenic shock and severe pulmonary hypertension. However, all three patients died.

ECMO has been used in patients with *pertussis* with multi-organ failure and severe pulmonary hypertension for many years (30–32). However, mortality is considerably high in infants who undego ECMO because of *pertussis* (70%). This rate increases up to 84% in infants aged below 6 weeks (18, 33). In our study, three patients who received ECMO supportive treatment died of multi-organ failure and resistant cardiogenic shock.

The limitation of our study was that it was a single-center and retrospective study. A higher number of patients is needed to generalize the results. However, the strong aspect of our study was the fact that the diagnosis of *pertussis* was confirmed by the laboratory with *B. pertussis* PCR positivity in all patients.

Conclusion

Infants who are too young to be protected by active immunization are more frequently admitted to PICUs with severe *pertussis*. Maternal immunization and the cocoon strategy may provide success in protecting this age group. In addition, increased leukocyte and lymphocyte counts at the time of presentation and during hospitalization, and accompanying secondary infection and severe pulmonary hypertension, are associated with increased mortality and morbidity.

References

1. Marshall H, Clarke M, Rasiah K, et al. Predictors of disease severity in children hospitalized for *pertussis* during an epidemic. Pediatr Infect Dis J 2015; 34: 339–45. [CrossRef]
2. Elliott E, McIntyre P, Ridley G, et al. National study of infants hospitalized with *pertussis* in the acellular vaccine era. Pediatr Infect Dis J 2004; 23: 246–52. [CrossRef]
3. World Health Organization (WHO). *Pertussis* vaccines: WHO position paper-August 2015. Weekly epidemiological record. Vol 90. Switzerland: World Health Organization; 2015.p.433–60.
4. Beard FH. Pertussis immunisation in pregnancy: a summary of funded Australian state and territory programs.

Turk Pediatri Ars 2020; 55(1): 54–59

Şık et al. The clinical characteristic and prognosis of pertussis

Commun Dis Intell Q Rep 2015; 39: E329–36.

5. Otar G, Yıldız İ, Kılıç A, Varkal MA, Devecioğlu E. Principles of Protection from Whooping Cough. J Child 2014; 14: 52–9. [CrossRef]

6. T.C. Sağlık Bakanlığı Temel Sağlık Hizmetleri Genel Müdürlüğü. Genişletilmiş Bağışıklama Programı Genelgesi: 13.03.2009/ 7941. Available from: http://www.saglik.gov.tr/TR/dosya/1-44926/h/gbp- genelgesi-2009.doc.

7. Kaczmarek MC, Ware RS, McEniery JA, Coulthard MG, Lambert SB. Epidemiology of pertussis-related paediatric intensive care unit (ICU) admissions in Australia, 1997-2013: an observational study. BMJ Open 2016; 6: e010386.

8. Amirthalingam G, Andrews N, Campbell H, et al. Effectiveness of maternal pertussis vaccination in England: an observational study. Lancet 2014; 384: 1521–8. [CrossRef]

9. Swamy GK, Wheeler SM. Neonatal pertussis, cocooning and maternal immunization. Expert Rev Vaccines 2014; 13: 1107–14. [CrossRef]

10. Wood N, Marshall H, White OJ, Holt PG, McIntyre P. Antibody and cell-mediated immunity to pertussis 4 years after monovalent acellular pertussis vaccine at birth. Pediatr Infect Dis J 2014; 33: 511–7. [CrossRef]

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: 333–7. [CrossRef]

12. Klein NP. Licensed pertussis vaccines in the United States. History and current state. Hum Vaccin Immunother 2014; 10: 2684–90. [CrossRef]

13. Farizo KM, Cochi SL, Zell ER, Brink EW, Wassilak SG, Patriarca PA. Epidemiological features of pertussis in the United States, 1980-1989. Clin Infect Dis 1992; 14: 708–19.

14. Halperin SA, Wang EE, Law B, et al. Epidemiological features of pertussis in hospitalized patients in Canada, 1991-1997: report of the Immunization Monitoring Program--Active (IMPACT). Clin Infect Dis 1999; 28: 1238–43.

15. Bayhan Gİ, Tanır G, Nar-Otgun S, Aydın-Teke T, Metin-Timur Ö, Öz FN. The clinical characteristics and treatment of pertussis patients in a tertiary center over a four-year period. Turk J Pediatr 2012; 54: 596–604.

16. Winter K, Zipprich J, Harriman K, et al. Risk Factors Associated With Infant Deaths From Pertussis: A Case-Control Study. Clin Infect Dis 2015; 61: 1099–106. [CrossRef]

17. Cherry JD. Pertussis in Young Infants Throughout the World. Clin Infect Dis 2016; 63: S119–22. [CrossRef]

18. Cherry JD, Wendorf K, Bregman B, et al. An Observational Study of Severe Pertussis in 100 Infants ≤120 Days of Age. Pediatr Infect Dis J 2018; 37: 202–5. [CrossRef]

19. Tamburacı Uslu ZD, Ceyhan M, Dinleyici EC, et al. Detec-tion of the presence of bordetella pertussis by real-time polymerase chain reaction in children diagnosed with pertussis and among their household contacts. J Vaccines Vaccin 2013; 4: 199.

20. Terzi H, Kitiş Y. A Different Approach to Pertussis Immunization: Cocooning Strategy. Turkiye Klinikleri J Nurs Sci 2018; 10: 88–94. [CrossRef]

21. Aydın D, Şahin N, Akay B. Effects of immigration on children's health. İzmir Dr Behçet Uz Çocuk Hastalıkları Dergisi 2017; 7: 8–14. [CrossRef]

22. Wood N, Quinn HE, McIntyre P, Elliott E. Pertussis in infants: preventing deaths and hospitalisations in the very young. J Paediatr Child Health 2008; 44: 161–5. [CrossRef]

23. Pillsbury A, Quinn HE, McIntyre PB. Australian vaccine preventable disease epidemiological review series: pertussis, 2006-2012. Commun Dis Intell Q Rep 2014; 38: E179–94.

24. Akçaboy M, Oğuz MM, Altınel EA, Yüksel D, Şenel S, Zorlu P. A case of whooping cough with complications: the importance of "cocooning" immunization. Gazi Medical Journal 2016; 28: 48-50.

25. Phadke VK, McCracken JP, Kriss JL, et al. Clinical Characteristics of Hospitalized Infants With Laboratory-Confirmed Pertussis in Guatemala. J Pediatric Infect Dis Soc 2018; 7: 310–6. [CrossRef]

26. Palvo F, Fabro AT, Cervi MC, Aragon DC, Ramalho FS, Carlotti APCP. Severe pertussis infection: A clinicopathological study. Medicine (Baltimore) 2017; 96: e8823. [CrossRef]

27. Guinto-Ocampo H, Bennett JE, Attia MW. Predicting pertussis in infants. Pediatr Emerg Care 2008; 24: 16–20.

28. Murray EL, Nieves D, Bradley JS, et al. Characteristics of Severe Bordetella pertussis Infection Among Infants ≤90 Days of Age Admitted to Pediatric Intensive Care Units - Southern California, September 2009-June 2011. Pediatric Infect Dis Soc 2013; 2: 1–6. [CrossRef]

29. Cherry JD. Pertussis: challenges today and for the future. PLoS Pathog 2013; 9: e1003418. [CrossRef]

30. Berger JT, Carcillo JA, Shanley TP, et al. Critical pertussis illness in children: a multicenter prospective cohort study. Pediatr Crit Care Med 2013; 14: 356–65. [CrossRef]

31. Namachivayam P, Shimizu K, Butt W. Pertussis: severe clinical presentation in pediatric intensive care and its relation to outcome. Pediatr Crit Care Med 2007; 8: 207–11.

32. De Berry BB, Lynch JE, Chung DH, Zwischenberger JB. Pertussis with severe pulmonary hypertension and leukocytosis treated with extracorporeal membrane oxygenation. Pediatr Surg Int 2005; 21: 692–4. [CrossRef]

33. 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: e816–27.