JIDC | THE JOURNAL OF INFECTION IN DEVELOPING COUNTRIES

Original Article

Comparison of the clinical and laboratory characteristics of pertussis or viral lower respiratory tract infections

Suna Selbuz[1], Ergin Çiftçi[2], Halil Özdemir[2], Haluk Güriz[3], Erdal İnce[2]

[1] *Department of Pediatrics, Faculty of Medicine, Ankara University, Ankara, Turkey*
[2] *Department of Pediatric Infectious Diseases, Faculty of Medicine, Ankara University, Ankara, Turkey*
[3] *Microbiology Laboratory, Faculty of Medicine, Ankara University, Ankara, Turkey*

Abstract

Introduction: Whooping cough-like respiratory tract infections (WCLRTI) caused by factors other than the *Bordetella pertussis* are available. Clinical picture is difficult to differentiate between the *B. pertussis* and viral respiratory infections.

Methodology: Eighty-five patients with the diagnosis of WCLRTI were divided into 3 groups. Group 1 involved patients with pertussis shown by nasopharyngeal aspirate culture (NAC) and/or PCR. Group 2 consisted of patients who B. pertussis was not detected by NAC however, clinicians still evaluated them as potential patients of pertussis. Group 3 involved patients with the diagnosis of WCLRTI and those with VRTI detected by antigen detection/PCR.

Results: Patients with pertussis had longer duration of the symptoms prior to admission. Paroxysmal cough, whooping, vomiting after coughing, cyanosis, apnea, seizures and abdominal hernias were more common in patients with pertussis. Fever, wheezing, tachypnea, retraction, fine crackles and rhonchi were more common in Group 3. Chest radiographs of patients in Group 3 revealed more bronchopneumonic infiltration, increased aeration, and atelectasis. CRP (C-reactive protein) and ESR (erythrocyte sedimentation rate) were significantly higher in Group 3. Of the patients 43.6% had no pertussis vaccination due to being < 2 months in age and 29.4% had 1 dose.

Conclusions: Pertussis should be thought in differential diagnosis of children with complaints of episodes of paroxysmal cough, cough accompanied by gasping, vomiting after coughing; with leukocytosis, lymphocytosis and a normal chest X-ray. The majority of children with pertussis infection are those who have not had the opportunity for vaccination.

Key words: *Bordetella pertussis;* pediatric intensive care unit; pertussis vaccine; whooping cough.

J Infect Dev Ctries 2019; 13(9):823-830. doi:10.3855/jidc.10558

(Received 23 May 2018 – Accepted 30 April 2019)

Introduction

Pertussis (whooping cough) is an acute respiratory tract infection, caused by *Bordetella pertussis* [1]. Although it is vaccine preventable disease, it is endemic among children all over the world almost all the time and leads to outbreaks from time to time [2-3]. Other than *B. pertussis* there are respiratory tract infections which cause pertussis like coughing [4]. Clinical picture is difficult to differentiate between these entities. It is possible to differentiate pertussis and other respiratory infections only by showing pathogenic organisms [5]. However, it is difficult to reach diagnostic methods such as PCR in resource limited regions. In this case, the clinician has to make a diagnosis based on clinical findings. At this point, it may be useful to compare the clinical and laboratory findings of pertussis proven patients with cases confirmed viral infections but excluded pertussis. In present study, we describe the clinical and laboratory features of the patients, who were under 2 years old, who were with *B. pertussis* and viral respiratory infections and who were admitted with diagnosis of pertussis-like coughing.

Methodology

We retrospectively evaluated 85 patients admitted to Ankara University Pediatric Infections Disease Service with pre-diagnosis of pertussis like coughing between May 2002 and April 2013, Ankara, Turkey. Of all cases, 49.4% girls (n = 42), 50.6% boys (n = 43). Median age of all patients was 2 months (27 days to 17 months). Patients were divided into three groups based on the fact that the microorganism causing the disease was detected or not. Group 1 involved patients with *B. pertussis* shown by nasopharyngeal aspirate culture and/or PCR. Group 2 consisted of patients presenting with symptoms and signs compatible with pertussis without history of exposure to a confirmed case or in the absence of etiological confirmation; however,

Table 1. Pertussis severity scores for children hospitalized with pertussis infection (Modified by Marshall H. *et al*. [8]).

	Grade 1	Grade 2	Grade 3
Apnea frequency	Up to 1 per day	2-5 per day	> 5 per day
Duration of hospitalization	< 24 hours	2-7 days	> 1 week
Level of hospitalization	General ward	HDU	ICU
Hydration requirement	Nasogastric	IV hydration < 48 hrs	IV hydration > 48 hrs
Respiratory support	Suction/02	CPAP	Ventilation
Presence of complications	Hypoxia/ chest X-ray changes	Pneumonia	Encephalopathy Cardiomyopathy
Total	**6**	**12**	**18**

clinicians still evaluated them as potential patients of pertussis based on the WHO and Ir-CDC the criteria [6,7]. Group 3 involved patients with diagnosis of whooping cough like viral respiratory infections and those with viral respiratory infection confirmed by antigen detection/PCR in nasopharyngeal aspirates and nasopharyngeal aspirate culture and PCR was performed all patients and *B. pertussis* and other bacterial pathogens were excluded. Group 1 consisted of 25 and Group 2 and 3 consisted of 30 patients.

Demographic data, data of clinical signs and symptoms, laboratory findings and clinical follow up findings were taken from patients' hospital records. The ethics committee of our university approved the study protocol with the number 06-173-12.

The study groups were compared with the pertussis severity score (Table 1) [8].

Statistical analysis was performed using SPSS (Statistical Package for the Social Sciences) version 21.0 for personal computers (Chicago, IL, USA). The groups were compared in terms of demographic, clinical and laboratory characteristics. Group differences in categorical data were analyzed using the Chi-square test. In cases of normally distributed data student t test and of non-normally distributed data the Mann-Whitney U test were used to determine whether the difference between the groups was statistically significant. A value of $p < 0.05$ was considered as statistically significant.

Results

In present study we evaluated 85 patients admitted to Ankara University Pediatric Infections Disease Service with diagnosis of pertussis like coughing between May 2002 and April 2013. Of all cases, 49.4% girls (n = 42), 50.6% boys (n = 43). Median age of all patients was 2 months (27 days to 17 months); the median age was 2 months (27 days to 9 months) in Group 1, 2.5 months (29 days to 14 months) in Group 2 and 2.5 months (28 days to 17 months) in Group 3. No significant statistical difference was observed among groups regarding gender and age (p = 0.313, p = 0.406) respectively.

In Group 1, *B. pertussis* was detected in patients via culture (60%) and PCR (40%). Culture was taken from all patients in Group 2; however causative agent was not detected in anyone. In Group 2 PCR could only made in 2 patients but *B. pertussis* and other viral microorganisms were not detected. The most frequently identified microorganisms were influenza virus and RSV in Group 3 by PCR (Table 2).

The median interval between onset of disease's specific symptoms and admission to hospital where diagnosis was made, was 10 days (0-30 days) in Group

Table 2. Microorganisms detected by PCR in Group 3.

Organisms	Patients	
	n	(%)
Influenza A	10	33.3
Influenza A and RSV B	4	13.3
RSV B	4	13.3
RSV B and Rhinovirus A/B/C	4	13.3
Rhinovirus A/B/C	1	3.3
Influenza A, Bocavirus and Parainfluenza	1	3.3
Influenza A and Rhinovirus A/B/C	1	3.3
Influenza B	1	3.3
Parainfluenza A	1	3.3
RSV A	1	3.3
RSV A and Rhinovirus	1	3.3
Adenovirus A/B/C/D/E, Rhinovirus A/B/C, RSV B	1	3.3

Table 3. Clinical symptoms according to groups.

Findings	Group 1 n (%)	Group 2 n (%)	Group 3 n (%)	P value
Fever	4 (16)	5 (16.7)	20 (66.7)	< 0.001
Tachypnea	6 (24.0)	4 (13.3)	28 (93.3)	< 0.001
Retraction	6 (24.0)	2 (6.7)	23 (76.7)	< 0.001
Wheezing	3 (12.0)	1 (3.3)	16 (53.3)	< 0.001
Prolonged expiration	5 (20.0)	2 (6.7)	23 (76.7)	< 0.001
Rale	6 (24.0)	3 (10.0)	28 (93.3)	< 0.001
Rhonchi	4 (16.0)	3 (10.0)	21 (70.0)	< 0.001
Nasal discharge	6 (24.0)	5 (16.7)	19 (63.3)	< 0.001

*p < 0.05: significant.

1, 11.7 days (0-60 days) in Group 2, on the other hand it was 6.1 days (0-30 days) in Group 3. It was significantly longer in Group 1 and 2 than in Group 3 (p = 0.002). Of the patients in Group 1 60% (n = 15), in Group 2 60% (n = 18), in Group 3 46.7% (n = 14) had at least one coughing family member except index case. In patients with confirmed viral infection (Group 3) fever, nasal discharge, wheezing, tachypnea, fine crackles, rhonchi, retraction and prolonged expiration were more common than among patients in Group 1 and 2 (p < 0.001) (Table 3). When the three groups were compared regarding whooping accompanied coughing, whooping was more common in Group 1 and 2 (p < 0.001). Inspiratory whooping was observed in 23 (92%) of the patients in Group 1, 16 (53.3%) of the patients in Group 2; however, none of the patients in Group 3 was observed to have whooping.

Vomiting after coughing, cyanosis, apnea, seizure, hernia were observed significantly more common in Group 1 and 2 and pneumonia was observed significantly more common in Group 3 (Table 4). Hernia and facial swelling were observed only Group 1.

At admission, chest X-ray of patients with viral illnesses (Group 3) revealed more broncopneumonic infiltration, increased aeration and atelectasis (Table 5).

While mean white blood cell and thrombocyte count were higher in Group 1 than in Group 3, erythrocyte sedimentation rate and C-reactive protein were more commonly elevated in the patients of Group 3 (Table 6).

The treatments given to the patients after being hospitalized with pertussis like coughing were assessed. All patients received oxygen and intravenous fluid when necessary. Oral macrolide group of antibiotics initiated in all of the patients in Group 1 and 2. Of the patients in Group 3, 9 patients (30%) received oral oseltamivir. It was identified that while all patients in Group 1 and 2 were given oral salbutamol treatment, all patients in Group 3 were given inhaler salbutamol treatment.

There was no significant difference among groups regarding follow up in PICU and in mechanical ventilation. While 10 patients (40%) in Group 1 were followed up in PICU, only 1 (4%) was connected to ventilator support. Seven patients (23.3%) in Group 2 and 4 (13.8%) patients in Group 3 were followed up in PICU; none of the patients in these two groups (Group 2 and 3) required ventilation support. In the regarding leukocytosis and thrombocytosis, there was no difference between pertussis patients who were followed up in PICU and the patients who were not. It was identified that mean WBC (white blood cell) number was higher in patients followed up in PICU than those not followed up; there was no difference between groups regarding thrombocytosis. Median WBC number of the patients followed up in PICU was 15400/mm^3 (8600-65600/mm^3) while that of those not followed up was 11400/mm^3. The median platelet number of the patients followed up in PICU was 449058/mm^3 (19000-733000/mm^3) while that of those

Table 4. The some symptoms and complications according to groups.

Symptoms/complications	Group 1 n (%)	Group 2 n (%)	Group 3 n (%)	P value
Vomiting	14 (56.0)	15 (50.0)	6 (20.0)	0.012
Cyanosis after coughing	19 (76.0)	21 (70.0)	2 (6.9)	< 0.001
Pneumonia	4(16.0)	8(27.0)	16(53.3)	< 0.001
Apnea/seizure	8 (32.0)	3 (10.0)	2 (6.9)	0.038
Hernia	2 (8.0)	0 (0.0)	0 (0.0)	NS†
Conjunctival hyperemia	3 (12.0)	2 (6.7)	0 (0.0)	NS†
Facial swelling	1 (4.0)	0 (0.0)	0 (0.0)	NS†

*p < 0.05: significant; † NS: data not significant.

Table 5. Chest X-ray findings according to groups.

Finding	Group 1 n (%)	Group 2 n (%)	Group 3 n (%)	P value
Broncopneumonic infiltration	2 (6.7%)	2 (8%)	11 (37.9%)	< 0.0001
Increased aeration	4 (16%)	0	13 (44.8%)	< 0.0001
Atelectasis	0	3, 2 (6.7%)	4 (14.3%)	< 0.0001

not followed up was 427567/mm^3 (144000-733000/mm^3).

Average length of hospitalization was significantly longer in Group 1 than Group 2 and 3. Average length of hospitalization was 11.9, 5.5, 6.9 day in Group 1, 2 and 3, respectively.

Of the 85 patients, 37 (43.6%) had no pertussis vaccination due to being younger than 2 months; 25 (29.4%) had 1 dose, 8 (9.4%) had 2 doses and 15 (17.6%) had three doses pertussis vaccination. Of the 25 patients in Group 1, 11 (44%) had no vaccination, 10 (40%) had one dose, 2 (%8) had 2 doses, 2 (8%) had 3 doses pertussis vaccination; of 30 patients in Group 3, 13 (43.3%) had no dose, 8 (26.7%) had 1 dose, 1 (3.3%) 2 doses and 1(3.3%) had 3 doses vaccination. There was no significant statistical difference among groups regarding vaccination.

When we compared WBC number and lymphocyte ratio of the patients who had no vaccination with those of the patients who already had three doses of childhood pertussis vaccination, we did not observe significant difference (p = 0.377, p = 0.499). When we assessed relation between need for PICU and vaccination status in the patients with pertussis (Group 1 and 2), we did not identify significant difference. When we assessed relation between length of hospitalization and vaccination status; we observed that patients who had no pertussis vaccination had longer hospitalization than patients who had three doses of pertussis vaccination. Average length of hospitalization of the patients who had no vaccination was 10.74 days (2-37 days) while of the patients with 3 doses vaccination was 5.38 days (3-9 days).

Discussion

Pertussis has considerably decreased with vaccination against *B. pertussis* during childhood, and worldwide mortality and morbidity of pertussis has decreased significantly [9]. However, in recent years a significant increase in disease incidence and even epidemics has been reported even in the developed countries where pertussis vaccination ratio is high [10-12]. Studies indicate pertussis infection has increased among adolescents and adults [10-12]. However, infected adults and adolescents serve as a reservoir for infection of infants and children in whom disease progress severely and cause mortality [13].

Table 6. Laboratory findings according to groups.

	Group 1	Group 2	Group 3	P value
White blood cell (/mm^3)				0.04
Median	15,350	11,700	11,150	
Minimum	5,300	6,600	3,200	
Maximum	59,800	65,600	26,000	
Thrombocyte (/mm^3)				0.05
Median	471,333	404,733	366,464	
Minimum	144,000	190,000	100,000	
Maximum	733,000	733,000	752,000	
Lymphocyte ratio (%)				< 0.001
Median	68	63	45	
Minimum	20	20	10	
Maximum	80	90	80	
ESR (mm/h)				< 0.001
Median	10	10	28	
Minimum	2	2	2	
Maximum	68	80	76	
CRP (mg/dL)				< 0.001
Median	1.0	1.0	6.7	
Minimum	0	0	0	
Maximum	45.0	97.7	44.4	

*p < 0.05: significant.

The pertussis vaccine provides partial protection; full infant protection may not be achieved until after the completion of primary vaccination at 6 months [14]. Acceptable immunity against pertussis is accomplished one month after the third dose of the vaccine [15]. Thus, unvaccinated or incompletely vaccinated young infants are highly susceptible to pertussis. In our study, age of patients ranged from 27 days to 17 months, median of the patients in Group 1 was 2.48 months (27 days-9 months) and most of the patients were too young to benefit from immunization. Of the patients 43.6% had no pertussis vaccine because they were not yet 2 months old. In the study of Bayhan *et al*. it was recorded that 53.9% of the patients hospitalized with pertussis had no pertussis vaccination due to being under 2 months and 7.1% of those had no vaccination due to social causes [16].

Practically pertussis infection is diagnosed clinically but diagnosis of pertussis with only clinically based symptoms is difficult. Even in typical cases, clinicians resort microbiological methods for final diagnosis [17]. Culture is the gold standard method but sensitivity is considerably low. In recent years PCR has become more popular method and has contributed to increased laboratory diagnosis [18]. Several studies have reported that the possibility of determining *B. pertussis* with PCR method increased 2.6-13 fold when PCR compared with culture [19-20]. In our study *B. pertussis* was determined in 40% the patients via culture, and 60% of the patients via PCR method in Group 1.

Other than *B. pertussis* there are bacterial and viral microorganisms causing pertussis-like coughing. The differentiation of pertussis and respiratory infections with pertussis-like coughing is possible only by determining causative microorganisms. *B. parapertussis*, *Mycoplasma pneumoniae*, *Chlamydia pneumoniae*, RSV, influenza virus, parainfluenza virus, adenovirus, metapneumovirus, rhinovirus and bokavirus are other microorganisms which should be considered in the differential diagnosis of pertussis [4,20-23]. In our study, influenza virus, RSV, rhinovirus, parainfluenza virus, adenovirus, bocavirus and parainfluenza were causative agents in patients in Group 3. In a study by Luis A *et al*. they evaluated the newborn patients with pertussis-like coughing, of the 216 newborn patients with clinical pertussis, *B. pertussis* was determined in 16.2% and other causative agent in 16.2%. Of the patients with other than *B. pertussis* 66.6% had RSV, 18.2% rhinovirus, 9% parainfluenza virus and 6% had inluenza A virus [24].

In studies carried out in recent years even in developed countries with high vaccination rates, pertussis has seen in especially among adults and adolescents. Pertussis infection in them is asymptomatic or atypical. These adults and adolescents, source of infection, can transmit *B. pertussis* to small children and children without *B. pertussis* vaccination [25]. It is known that transmission of infection to children whose *B. pertussis* vaccination is incomplete between 0-1 years is frequently infected family members [13-14]. In our study, the 60% family members of Group 1 patients had pronged cough. In the other studies, the patients belong 6 months diagnosed with pertussis infection, 34-85.7% got infected via household contact, especially parent's contact similarly [26-27]. In 2016 reports of CDC it was emphasized that the disease has increased among adolescents (33.3% of the reported cases in 2016) and adults (22.1% of the reported cases in 2016) and these age group of patients are important risk factor to transmit infection to children whose pertussis vaccination is incomplete [1].

In our study, we identified that medium coughing times in Group 1 was 10 days, 11.7 days in Group 2 and in these two groups coughing time was significantly longer than coughing time of patients in Group 3. Similar to ours the study by Delma J *et al*. determined coughing time of the patients with *B. pertussis* before admission was 11 days and 3.4 days in control group [28]. In the study by Bayhan G *et al*. the interval between beginning of disease's symptoms and admission to third level hospital was identified as 11.6 days [16]. All those data make us think that time interval is needed remarkably long period of time between onset of the symptoms associated with pertussis and admission to hospital and final diagnosis.

Up to now there have been different severity scoring systems to assess severity of disease and risk factors of severe pertussis disease in children [8]. When we assessed whether there was any difference among groups as regards pertussis severity scores, the median score of the patients of Group 1 was 9 (4-18), of Group 2 was 5 (3-12) and of Group 3 was 4 (1-9) when compared pertussis severity scores of groups Group 1 had significantly higher pertussis severity score than Group 2 and 3 (Table 1). Accordingly pertussis severity scoring system, 6 points and less is mild disease and more than 6 points is severe disease [8]. In Group 1, 72% of the patients had more than 6 points and severe disease incidence in Group 1 was determined significantly higher ($p < 0.001$). In a study carried out during the pertussis outbreaks in Australia, 132 patients were evaluated and it was observed that 56.9% of the

patients were under 2 months and 23.5% of the patients had severe pertussis infection [8].

In pertussis infection in addition to typical coughing, vomiting, cyanosis, apnea, hernia, conjunctival bleeding and facial swelling were frequently observed. In our study it was determined that vomiting after coughing, cyanosis and apnea were significantly more common in the patients with pertussis (Group 1 and 2). In the study of Delma J *et al*. carried out in 2010 California epidemic, of the 32 patients with pertussis 63% had cyanosis after coughing, 25% had apnea or seizures and these were significantly higher in the patients with pertussis than in control subjects (6% and 11% respectively) [28]. Francis CM *et al*. reported that at first admission of the patients with pertussis 95.7% patients had paroxysmal coughing, 73.9% patients cyanosis, 58.7% patients whooping, 26.1% patients respiratory distress and 21.7% patients had vomiting after coughing [29]. Heininger U *et al*. observed that of the 259 patients with pertussis at first admission 90.2% had paroxysmal coughing, 53% had vomiting after coughing and 73.9% had whooping [30]. Pneumonia is a common complication of pertussis. According to CDC data, almost 1 in 4 (23.3%) of patients with pertussis get pneumonia [1]. We observed that of the patients in Group 1 16% and of those in Group 2 27% get pneumonia. In our study fever, nasal discharge, wheezing, tachypnea, retraction, prolonged expiration, fine crackles and ronchi accompanying coughing were significantly higher in patients in Group 3 ($p < 0.001$). Delma J *et al*. reported that fever and nasal discharge were more common in control subjects ($p < 0.001$) [28]. Heininger U *et al*. reported 38°C or higher fever only in 5.7% of 2592 patients with pertussis in at admission [30].

Leukocytosis with lymphocytosis in peripheral blood smear supports diagnosis of pertussis. But there is not a consensus about upper limits of leukocytosis and lymphocytosis in literature. In a study, it was reported that white blood cell number in patients hospitalized with pertussis was $18500 \pm 9300/mm^3$ that there was lymphocytosis in peripheral blood smear. Guinta Ocambo H *et al*. observed that sensitivity of lymphocytosis was 89% and specificity was 75% in pertussis diagnosis [31]. In our study while median WBC count of patients in Group 1 was $15.350/mm^3$, in Group 2 $11.700/mm^3$ and in Group 3 $11.250/mm^3$. When compared lymphocyte ratio of the groups in peripheral blood smear was significantly higher in Group 1 and 2 (68% (20-80%) in Group 1, 63% (20-90%) in Group 2 and 45% (10-80%) in Group 3).

Clinical pertussis is defined as *B. pertussis* infection which needs PICU following which may conclude with death. Clinical pertussis disease is more common in early childhood because in this period adequate immunization is problematic [32]. Therefore in developed countries this age group is protected from pertussis with alternative adulthood immunization and cocoon strategy. In our study we determined that 10 (40%) patients with demonstrated pertussis were followed in PICU and only 1 of the 10 patients were followed in PICU needed mechanical ventilation support. In the study of Villalobos Pinto E *et al*. 29.3% of the patients hospitalized with pertussis during 2008 and 2011 was recorded to be followed up in PICU [33]. Among our patients with pertussis followed up in PICU nobody died. We think that we stopped prognosis of disease with appropriate antibiotics and supportive therapy on early phase of the disease. Especially, the patients with pertussis and under 1 year need hospitalization.

All of the patients included in our study were hospitalized. Length of stay in hospital in the patients with pertussis was determined to significantly longer than the patients with viral infections. In our study the patients with pertussis had medium length of stay of 11.9 days. In the study of Villalobos *et al*. medium length of stay in hospital was 7.44 days (1-40 days) and Ferrer Marcelles A *et al*. was 11 days (1-70 days) which was similar to ours [34]. In the study of Costagnini *et al*. the patients with pertussis and pertussis like coughing were compared and while medium length of stay in hospital was 14.5 days in the patients with pertussis, it was recorded to be 5.5 days in the patients with pertussis like coughing [23].

The most important two limitations of our study are that all cases were not taken at the same time and Group 2 may be composed of both *B. pertussis* and viral infected cases. However, we cannot prove that since PCR was not available at that time.

Conclusion

We should firstly consider pertussis disease in differential diagnosis in patients with paroxysmal coughing episodes, whooping accompanying coughing, vomiting after coughing or cyanosis; leukocytosis or lymphocytosis by age and with normal chest X-ray.

We should consider viral infections which cause pertussis like coughing in differential diagnosis in patients' nasal discharge accompanying coughing, wheezing and fever, tachypnea, retractions, prolonged expiration, fine crackles and ronchi, elevated ESR and CRP in laboratory with infiltration in chest X-ray.

Patients with *B. pertussis* infection have higher pertussis severity scores and their length of stay in hospital should be longer. Although *B. pertussis* infection is still mortal disease mortality can be decreased with appropriate treatment and supportive care. Most of the patients with pertussis had no opportunity being vaccinated. That's why vaccination of adults and adolescents who can contaminate infection to infants should be attached importance. That's why importance should be given to vaccinating, adults and adolescents transmitting infection to infants.

Acknowledgements

We thank Zeynep Bıyıklı Gençtürk for statistical analysis.

References

1. The Centers for Disease Control and Prevention (CDC) (2017) Pertussis (Whooping cough) Available: https://www.cdc.gov/pertussis/about/index.html Accessed: 6 July 2017.
2. Mattoo S, Cherry JD (2005) Molecular pathogenesis, epidemiology, and clinical manifestations of respiratory infections due to *Bordetella pertussis* and other Bordetella subspecies. Clin Microbiol Rev 18: 326-382.
3. Nieves DJ, Heininger U (2016) *Bordetella pertussis*. Microbiol Spectr. 10: 311–339.
4. Saiki Macedo S, Valverde Ezeta J, Cornejo Tapia A, Castillo ME, Petrozzi Helasvuo V, Aguilar Luis MA, Del Valle LJ, Cieza Mora E, Bada C, Del Aguila O, Silva Caso W, Martins Luna J, Vasquez Achaya F, Del Valle Mendoza J (2019) Identfication of viral and bacterial etiologic agents of the pertussis-like syndrome in children under 5 years old hospitalized. BMC Infect Dis 21: 75.
5. Wirsing von König CH, Rott H, Bogaerts H, Schmitt HJ (1998) A serologic study of organisms possibly associated with pertussis-like coughing. Pediatr Infect Dis J 17: 645-649.
6. Barreto L, Blanc C, Hoffensbach A, Ortiz E, Hessel L, Bogaerts H, Kuykens L, Mast C, Matsunaga Y (2001). Pertussis surveillance. World Health Organization Pertussis surveillance: A global meeting (pp. 9-30) Geneva, Switzerland: Departments of Vaccines and Biologicals.
7. Shojaei J, Saffar M, Hashemi A, Ghorbani G, Rezai M, Shahmohammadi S (2014) Clinical and laboratory features of pertussis in hospitalized infants with confirmed versus probable pertussis cases. Ann Med Health Sci Res 4: 910-914.
8. Marshall H, Clarke M, Rasiah K, Richmond P, Buttery J, Reynolds G, Andrews R, Nissen M, Wood N, McIntyre P (2015) Predictors of disease severity in children hospitalized for pertussis during an epidemic. Pediatr Infect Dis J 344: 339-345.
9. Plotkin SA, Orenstein WA, Offit PA (1999) Pertussis Vaccine. In Edwards KM, Decker MD and Mortimer EA, editors. Vaccines, 3rd Edition. Philadelphia: WB Saunders Press. 35-45.
10. Guris D, Strebel PM, Bardenheier B, Brennan M, Tachdjian R, Finch E, Wharton M, Livengood JR. (1999) Changing epidemiology of pertussis in the United States: increasing reported incidence among adolescents and adults, 1990–1996. Clin Infect Dis J 28: 1230-1237.
11. Ntezayabo B, De Serres B, Duval B (2003) Pertussis resurgence in Canada largely caused by a cohort effect. Pediatr Infect Dis J 22: 22-27.
12. Baron S, Mjamkepo E, Gimprel E, Begue P, Desenclos JC, Drucker J, Guiso N (1998) Epidemiology of pertussis in French hospital in 1993–1994: thirty years after a routine use of vaccination. Pediatr Infect Dis J 17: 412-418.
13. Deen JL, Mink CA, Cherry JD, Pineda EF, Lewis K, Blumberg DA, Ross LA (1995) Household contact study of *Bordetella pertussis* infections. Clin Infect Dis J 21: 1211-1219.
14. Juretzko P, von Kries R, Hermann M, Wirsing von König CH, Weil J, Giani G (2002) Effectiveness of acellular pertussis vaccine assessed by hospital-based active surveillance in Germany. Clin Infect Dis 35: 162-167.
15. Mooi FR, de Greeff SC (2007) The case for maternal vaccination against pertussis. Lancet Infect Dis 7: 614–624.
16. Bayhan GI, Tanır G, Nar-Otgun S, Aydın-Teke T, Metin-Timur O, Oz FN (2012) The clinical characteristics and treatment of pertussis patients in a tertiary center over a four-year period. Turk J Pediatr 54: 596-604.
17. Cherry JD, Grimprel E, Guiso N, Heiniger U, Mertsola J (2005) Defining pertussis epidemiology: clinical, microbiologic and serologic perspectives. Pediatr Infect Dis J 24: 25-34.
18. Mattoo S, Cherry JD (2005) Molecular pathogenesis, epidemiology and clinical manifestations of respiratory infections due to *Bordetella pertussis* and other Bordetella subspecies. Clin Microbiol Rev 18: 326-382.
19. Schläpfer G, Cherry JD, Heininger U, Uberall M, Schmitt-Grohé S, Laussucq S, Just M, Stehr K (1995) Polymerase chain reaction identification of *Bordetella pertussis* infections in vaccinees and family members in a pertussis vaccine efficacy trial in Germany. Pediatr Infect Dis J 14: 209-214.
20. Dragsted DM, Dohn B, Madsen J, Jensen JS (2004) Comparison of culture and PCR for detection of *Bordetella pertussis* and *Bordetella parapertussis* under routine laboratory conditions. J Med Microbiol 53: 749-754.
21. Wirsing von König CH, Rott H, Bogaerts H, Schmitt HJ (1998) A serologic study of organisms possibly associated with pertussis-like coughing. Pediatr Infect Dis J 17: 645–649.
22. Cosnes-Lambe C, Raymond J, Chalumeau M, Pons-Catalano C, Moulin F, de Suremain N, Reglier-Poupet H, Lebon P, Poyart C, Gendrel D. (2008) Pertussis and respiratory syncytial virus infections. Eur J Pediatr 167: 1017–1019.
23. Versteegh FG, Mooi-Kokenberg EA, Schellekens JF, Roord JJ (2006) *Bordetella pertussis* and mixed infections. Minerva. Pediatr 58: 131-137.
24. Castagnini LA, Munoz FM (2010) Clinical characteristics and outcomes of neonatal pertussis: a comparative study. J Pediatr 156: 498-500.
25. Cherry JD (2019) The prevention of severe pertussis and pertussis deaths in young infants. Expert Rev Vaccines 18: 205-208
26. Kwon HJ, Yum SK, Choi UY, Lee SY, Kim JH, Kang JH (2012) Infant pertussis and household transmission in Korea. J. Korean Med Sci 27: 1547-1551.
27. Baron S, Njamkepo E, Grimprel E, Begue P, Desenclos JC, Drucker J, Guiso N (1998) Epidemiology of pertussis in French hospitals in 1993 and 1994: thirty years after a routine use of vaccination. Pediatr Infect Dis J 17:412-418.

28. Nieves DJ, Singh J, Ashouri N, McGuire T, Adler-Shohet FC, Arrieta AC (2011) Clinical and laboratory features of pertussis in infants at the onset of a California epidemic. Pediatr J 159: 1044-1046.
29. Francis Centeno M, Borque Andrés C, del Castillo Martín F, Díez Sebastián J, García Hortelano J (1998) Whooping cough: a retrospective study of the cases diagnosed over a period of 15 years. An Esp Pediatr 49: 280-283.
30. Heininger U, Klich K, Stehr K, Cherry JD (1997) Clinical findings in *Bordetella pertussis* infections: results of a prospective multicenter surveillance study. Pediatrics 100: 10-7.
31. Guinto-Ocampo H, Bennett JE, Attia MW (2008) Predicting pertussis in infants. Pediatr Emerg Care 24: 16-20.
32. Berger JT, Carcillo JA, Shanley TP, Wessel DL, Clark A, Holubkov R, Meert KL, Newth CJ, Berg RA, Heidemann S, Harrison R, Pollack M, Dalton H, Harvill E, Karanikas A, Liu T, Burr JS, Doctor A, Dean JM, Jenkins TL, Nicholson CE (2013) Critical pertussis illness in children, a multicenter prospective cohort study. Pediatr Crit Care Med 14: 356-365.
33. Villalobos Pinto E, Martínez-Villanueva J, Cano Fernández J, Flores Pérez P, Sánchez Bayle M. (2012) Risk factors for complications and length of hospital stay in pertussis patients. Rev Pediatr Aten Primaria 14: 207-215.
34. Ferrer Marcellés A, Moraga Llop FA, Olsina Tebar M, Campins Martí M, Planells Romeu I (2003) Culture-confirmed whooping cough in a tertiary center over a twelve-year period. An Pediatr 58: 309-315.

Corresponding author

Suna Selbuz, MD
Keçiören Eğitim ve Araştırma Hastanesi, Çocuk Gastroenteroloji Polikliniği
Address: Sanatoryum Cad. Pınarbaşı Mah. Ardahan Sok. No: 25, 06000, Pınarbaşı/Keçiören/ANKARA
Tel: 0905070073704
Fax: 090 312 356 90 02
E-mail: kaymaksuna@gmail.com

Conflict of interests: No conflict of interests is declared.