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Original Article

The incidence and clinical effects of *Bordetella pertussis* in children hospitalized with acute bronchiolitis

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ABSTRACT

Background. Pertussis is a disease leading to high morbidity and mortality in neonates and infants. Bronchiolitis is the most common cause of hospitalization especially in children <2 year-old. Although the clinical findings are different in these two diseases, it is sometimes difficult to make this distinction in partially or fully vaccinated children. This study aimed to identify the incidence, clinical and laboratory effects of *B. pertussis* as a causative agent in hospitalized children with acute bronchiolitis.

Methods. The study included patients diagnosed with acute bronchiolitis and admitted to the Division of Pediatric Infectious Diseases from January 2012 to December 2015, aged 24 months or younger, evaluated for viruses and bacteria with polymerase chain reaction in respiratory tract secretions.

Results. The study included 380 patients hospitalized with acute bronchiolitis. Of these patients, 85.8% were identified to be positive for at least one respiratory pathogen. The most commonly identified pathogens were respiratory syncytial virus (RSV) A/B, rhinovirus, parainfluenza virus, adenovirus, bocavirus and metapneumovirus A/B. *B. pertussis* was only detected in 5 patients (1.5%). In the patients with *B. pertussis* identified, coinfection with another virus was observed including rhinovirus (n= 2), influenza A virus (n= 1), coronavirus OC43 (n= 1) and RSV A/B (n= 1). The presence of *B. pertussis* did not appear to cause any significant clinical or laboratory differences in patients.

Conclusions. *B. pertussis* is a rare pathogen in patients admitted to hospital for acute bronchiolitis. However, in patients who do not respond to standard bronchiolitis treatment, *B. pertussis* should be considered as a causative agent. Early identification of this pathogen is important in terms of quarantining the patient, administering appropriate antimicrobial treatment, and prophylactic treatment to household and other close contacts.

Key words: acute bronchiolitis, *Bordetella pertussis*, hospitalized children, incidence.

Acute bronchiolitis is the most common lower respiratory tract disease which occurs due to inflammatory obstruction of the small airways in children. Generally, it is observed in the first 2 years of life.[1] Respiratory syncytial virus (RSV) is responsible for >80% of lower respiratory tract infections in children younger than 1 year.[2]

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Pertussis or whooping cough is an endemic disease with high morbidity and mortality in infants caused by *Bordetella pertussis*. Globally, nearly 16 million pertussis cases are observed each year and it causes 195,000 deaths. Pertussis typically causes a clinical picture characterized by three periods of catarrhal, paroxysmal and convalescent stages. Since the implementation of vaccinations, this classic clinical progression is observed less frequently.[3]

In patients presenting with bronchiolitis, coinfections caused by more than one

respiratory tract viruses may be seen. Similarly, *B. pertussis* can also be detected with respiratory tract viruses. However, there are different data in the literature about the frequency of pertussis in young children with bronchiolitis. Although the frequency is reported as high in some studies; it is detected too low in others.[4-9] This study aimed to identify the incidence of *B. pertussis* as pathogen in children with acute bronchiolitis, and to research the effect of its presence on clinical and laboratory features.

Material and Methods

The study included patients admitted to the Division of Pediatric Infectious Disease from January 2012 to December 2015 diagnosed with acute bronchiolitis, aged 24 months or younger, evaluated for both viruses and bacteria with polymerase chain reaction (PCR) in respiratory tract secretions. Within the first 48 hours of admission to hospital, patients had nasopharyngeal secretion samples taken with aspiration and were evaluated for the following viruses; RVS A/B, rhinovirus, adenovirus, bocavirus, metapneumovirus A/B, parainfluenza virus 1, 2, 3, 4, coronavirus 229E, NL63, OC43, HKU1, influenza virus A/B, H1N1, enterovirus and parechovirus) and bacteria; *B. pertussis, Mycoplasma pneumoniae, Legionella pneumophila, Chlamydophila pneumoniae, Streptococcus pneumoniae, Haemophilus influenzae* with the PCR method.

Statistical assessment was completed with the Statistical Package for Social Sciences (SPSS) Windows 20 (IBM SPSS Inc., Chicago, IL). Normal distribution of data was analyzed with the Kolmogorov-Smirnov test. As numerical variables did not display normal distribution, they are shown as median (interval; min-max). Differences between numerical variables in two category groups were examined with the Mann-Whitney U test. For all analyses, $p<0.05$ was accepted as statistically significant.

Informed consent was obtained from the patients included in the study. The study was approved by the local ethics committee with number of 12-560-16 (27/06/2016).

Results

Of 847 patients admitted to hospital with acute bronchiolitis diagnosis, a total of 380 patients aged 24 months or younger with PCR investigation of respiratory tract secretions for viruses and bacteria were included in the study. Of the patients 161 (42.4%) were girls and 219 (57.6%) were boys. The median age of diagnosis was 4 months (range; 1-23 months).

Of the 380 patients, 326 patients (85.8%) were identified to be positive for at least one respiratory pathogen. *B. pertussis* was detected in 5 (1.5%) of these patients. Significant differences were not observed between *B. pertussis* positive and negative patients in terms of gender, age of diagnosis, history of prematurity, previous attendance at health organizations, presence of individuals with cough in the family and vaccination history ($p >0.05$) (Table I).

The most common agents were *S. pneumoniae* (66.3%), *H. influenzae* (43.9%), RVS A/B (53.7%) and rhinovirus (25.3%) in children admitted to the hospital for acute bronchiolitis. Coinfections with more than one virus were identified in 93 (24.5%) patients. The most common of these were rhinovirus and RSV A/B (4.5%) and rhinovirus and adenovirus (2.4%). Simultaneously detected pathogens in patients with *B. pertussis* were as follows; influenza A (n= 1), coronavirus OC43 (n= 1), RSV A/B (n= 1), rhinovirus (n= 2), *M. pneumoniae* (n= 1), *S. pneumoniae* (n= 2) and *H. influenzae* (n= 3). The demographic, clinical and laboratory characteristics of patients with *B. pertussis* are given in Table II.

Significant differences were not identified in terms of clinical, radiologic and laboratory findings of patients according to the presence of *B. pertussis* ($p >0.05$) (Table III). The proportion of patients positive for *B. pertussis* with white cell count above 10,000 was 60%, while this rate was 54.5% for *B. pertussis* negative patients ($p= 0.807$). For white cell counts above 15,000, the

Table I. Demographic findings of patients according to *Bordetella pertussis* positivity.

Variables	*Bordetella pertussis*		p
	Negative (n= 321)	Positive (n= 5)	
Gender*			
Female	137 (42.7)	2 (40.0)	0.904
Male	184 (57.3)	3 (60.0)	
Age of diagnosis (months)**	4 (1-23)	4 (1-13)	0.765
Prematurity*	26 (8.1)	-	-
Previous admission to another health center*	150 (46.7)	4 (80.0)	0.193
Household member with cough*			
None	47 (14.6)	-	0.574
Unknown	109 (34.0)	1 (20.0)	
Yes	165 (51.4)	4 (80.0)	
Mother	20 (12.1)	1 (25.0)	0.934
Father	9 (5.5)	-	
Siblings	60 (36.4)	1 (25.0)	
Others	9 (5.5)	-	
Several people	31 (18.8)	1 (25.0)	
Unknown	36 (21.8)	1 (25.0)	
Number of pertussis vaccines*			
None	74 (23.1)	1 (20.0)	0.512
1	75 (23.4)	1 (20.0)	
2	40 (12.5)	2 (40.0)	
3	112 (34.9)	1 (20.0)	
4	19 (5.9)	-	
Uncertain	1 (0.3)	-	

* Categoric variables shown as number (%)
** Numerical variables without normal distribution shown as median (min-max)

rate was 20% for patients positive for *B. pertussis* and 19.6% for *B. pertussis* negative patients (p= 0.993).

In this study, the most frequent admissions occurred in January and February (19.7%), followed by December (11.8%). Median hospital stay was 5 days (interval; 1-43 days). *B. pertussis* positive patients were admitted in February, March, May, August and October. Median hospital stay for *B. pertussis* patients positive was 4 days (interval: 2-10 days), while it was 5 days for *B. pertussis* negative patients (interval: 1-43 days) (p= 0.778).

Of patients admitted for acute bronchiolitis, 12.1% (n= 46) were hospitalized in intensive care units and median duration of hospitalization was 3 days (interval: 1-37 days). Of patients, 10.5% (n= 40) required mechanical ventilation. The rate of patients readmitted within one month after discharge was 7.6% (n= 29). None of the patients positive for *B. pertussis* was admitted to the intensive care unit. All *B. pertussis* positive patients received oxygen, oral salbutamol and oral clarithromycin therapy during hospitalization. The rate of use of clarithromycin among patients positive for *B. pertussis* was 100%, while it was 24.6% for *B. pertussis* negative patients (p=0.016). There were no significant differences for other administered treatments in terms of the presence of *B. pertussis*.

Table II. Demographic, clinical and laboratory characteristics of patients positive for *Bordetella pertussis*.

Variables	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
Age (months)	13	1	5	4	3
Gender	Male	Female	Male	Female	Male
Year/month admitted to hospital	2015/August	2014/February	2013/March	2013/May	2014/October
Duration of complaint (days)	6	2	7	21	13
Dose of pertussis vaccination	3	0	2	2	1
Clinical findings	Fever, cough, rhinitis	Cough, rhinitis	Fever, cough, rhinitis, wheeze	Cough, wheeze	Cough, rhinitis, vomiting, facial flushing, wheeze
Physical examination findings	Tachypnea, retraction, prolonged expirium, rhonchi, rales	Prolonged expirium, rhonchi	Tachypnea, retraction, prolonged expirium, rhonchi, rales	Tachypnea, retraction, prolonged expirium, rhonchi, rales, wheezing	Tachypnea, prolonged expirium
Chest radiography findings	Infiltration	Hyperinflation	Infiltration + Hyperinflation	Infiltration + Hyperinflation	Hyperinflation
White cell/ lymphocyte count (/mm^3)	11100/3100	9300/6900	15300/6700	7300/2600	10600/6600
ESR/CRP values (mm/h, mg/L)	16/16.6	44/1	68/45.1	10/1	6/1
Coinfections	*Mycoplasma pneumoniae*	RSV, influenza A	Rhinovirus, *S.pneumoniae, H.influenzae*	Coronavirus OC43, *H. influenzae*	Rhinovirus, *S.pneumoniae, H.influenzae*
Bronchodilator / steroid treatment	+/+	+/-	+/+	+/+	+/+
Antibiotic treatment received	Clarithromycin	Clarithromycin	Clarithromycin, SAM	Clarithromycin	Clarithromycin

ESR: estimated sedimentation rate, CRP: C reactive protein

Discussion

Pertussis may result in severe progression in infants and children. Although the effective development of vaccination programs, globally each year it still causes millions of cases and thousands of deaths.[10] Acute bronchiolitis is the most common cause of hospitalization in children under 2 years of age.[11] Today, there is a great interest in the presence of pertussis in children hospitalized due to acute bronchiolitis and its effect on the clinical status. The detection of causative pathogens in respiratory tract infections by molecular methods and the life-threatening conditions of these two diseases in young children have aroused interest in the association of pertussis infection in hospitalized patients. In our study, *B. pertussis* was identified in only 5 patients; this suggests that it is a rare pathogen in patients with acute bronchiolitis. Many physicians prescribe macrolide treatment considering the possibility of pertussis in patients hospitalized. This in turn increases the use of macrolide antibiotics and contributes to

Table III. Clinical, physical examination, laboratory and imaging findings of patients according to *Bordetella pertussis*.

Variables	*Bordetella pertussis*		p
	Negative (n= 321)	Positive (n= 5)	
Clinical findings			
Cough*	321 (100)	5 (100)	-
Rhinitis*	240 (74.8)	4 (80.0)	0.789
Wheeze*	226 (70.4)	3 (60.0)	0.636
Fever*	153 (47.7)	2 (40.0)	0.733
Vomiting after cough*	27 (8.4)	1 (20.0)	0.364
Facial flushing during cough*	29 (9.0)	1 (20.0)	0.385
Conjunctival redness*	2 (0.6)	0 (0)	0.859
Facial swelling*	0 (0)	0 (0)	
Suspiration*	0 (0)	0 (0)	
Physical examination findings			
Prolonged expirium*	316 (98.4)	5 (100.0)	0.779
Rhonchi*	26 (83.5)	4 (80.0)	0.836
Rales*	247 (76.9)	3 (60.0)	0.331
Tachypnea*	235 (73.2)	3 (60.0)	0.614
Retraction	204 (63.6)	3 (60.0)	0.870
Wheezing*	46 (14.3)	1 (20.0)	0.543
Apnea*	6 (1.9)	0 (0)	0.758
Radiological findings			
Hyperinflation*	253 (79.1)	4 (80.0)	0.959
Infiltration*	158 (49.4)	3 (60.0)	0.683
Atelectasis*	35 (10.9)	0 (0)	0.434
Laboratory findings			
White cell (x103)**	10.6 (1.3-28.6)	10.6 (7.3-15.3)	0.819
Lymphocytes (x103)**	4.5 (0.9-16.5)	6.6 (2.6-6.9)	0.686
Platelets (x103)**	369 (39-896)	342 (269-764)	0.720
Eosinophil**	100 (0-1300)	300 (0-800)	0.194
Erythrocyte sedimentation rate**	20 (0-122)	16 (6-68)	0.493
C-reactive protein**	6.1 (0-117.2)	1 (1-45.1)	0.532

* Categorical variables shown as number (%)
** Numerical variables shown as median (min-mix)

the development of resistance. In our study, we have concluded that the frequency of pertussis is low in patients hospitalized due to acute bronchiolitis in the hospital and therefore macrolides should not be used unnecessarily.

Our findings are similar to Piedra et al.'s[4] study that identified only 4 cases (0.2%) among 2207 hospitalized children aged less than 2 year-old with acute bronchiolitis, whereas RSV was found in 72% of all children. In Korppi et al.'s[5] study respiratory viruses were responsible for 89% acute bronchiolitis in infants hospitalized aged under 6-months of age. RSV was found in 71% of cases, and *B. pertussis* was not detected in any patient. Similarly, Abu Raya et al.[6] analyzed 309 hospitalized children with bronchiolitis aged ≤2 years of age They found

that 7.7% of cases with *B. pertussis* and 67% of cases with RSV were hospitalized during the 2005-2006 peak acute bronchiolitis season. Just like the above studies Siberry et al.[7] identified only 1 of 166 patients admitted to the hospital with respiratory symptoms to have a positive *B. pertussis* PCR result during the RSV season. In contrast to these studies that found *B. pertussis* to be rarely detected in patients with acute bronchiolitis, in the literature, different data concerning the frequency is present. In Gökçe's et al.[8] study from Turkey, *B. pertussis* was identified 44 (25.6%) of 172 infants aged <6 months old and coinfection with other viruses was detected in 17 (38.6%) of 44 patients. Additionally, 51.1% of all infants had RSV which was a commonly isolated pathogen. The authors suggested that this high prevalence of *B. pertussis* was due to the fact that the patients had either not received any or only a single dose of the pertussis vaccine due to their small age. Another study in Finland reported that RSV was the most common causative pathogen and *B. pertussisis* was detected in 12 (8.5%) of 142 infants younger than 6 months hospitalized for acute bronchiolitis. In addition, coinfection with RSV was found in 8 of the patients with *B. pertussis*.[9]

Pertussis is commonly observed as coinfections with other respiratory tract pathogens. RSV with *B. pertussis* increases morbidity and mortality risk.[12] There are limited numbers of studies assessing the association of *B. pertussis* with RSV and coinfection varies from 0-78%.[4-6,13-16] The studies examining the relationship between RSV and *B. pertussis* coinfection in patients with acute bronchiolitis are summarized in Table IV.

Pertussis and acute bronchiolitis cause serious infections that require hospitalization especially in young children. In our study, the age interval for the whole population was 1.24 months, with 57.6% of patients being male. There were no significant differences identified between *B. pertussis* positive and negative patients related to gender and age.

In our research, cough was present in all patients. The rates of vomiting after coughing (8.4%) and facial flushing during coughing (8.9%) were low. Studies have identified the incidence of *B. pertussis* infection as 13-20% for patients admitted with long-term coughing complaints.[4] A study encompassing the 0-16-year age group in Turkey identified *B. pertussis* in 16.9% of patients with cough lasting more than two weeks.[5]

Leukocytosis along with lymphocyte dominance supports the diagnosis of pertussis. The increase in leukocyte count and degree of lymphocytosis is parallel to the severity of the disease. However, these findings are not unique to pertussis.[17,18] In our study, there were no significant differences observed in terms of laboratory findings between *B. pertussis* positive and negative patients.

Radiological investigation is not a necessity for pneumonia diagnosis in children; however, observation of infiltration on chest radiographs supports pneumonia diagnosis.[19] In our study, 49.4% of patients had infiltration and 79.1% had hyperinflation observed on chest radiographs, although there were no statistically significant radiological differences observed between *B. pertussis* positive and negative patients.

The information about the seasonality of pertussis is not clear. Epidemics are mainly observed in the winter and spring months.[4] Generally, the disease is endemic in the months of July to October.[20] Acute bronchiolitis peaks in the winter and spring months.[21] In our study, the majority of acute bronchiolitis patients were admitted to the hospital between December to May. Additionally, the majority of patients with *B. pertussis* identified were admitted from February to May. These findings lead to the consideration that admission for acute bronchiolitis accompanying *B. pertussis* increases during the winter and spring months. Though this hypothesis complies with the literature, there is a need for prospective studies with larger samples.

Table IV. *Bordetella pertussis* and RSV coinfection rates in patients with acute bronchiolitis.

Authors	Study years	Number of patients	Age	*B. pertussis* n (%)	BP-RSV Coinfection	*B. pertussis* Clinical findings
Frühwirth	1995-1998	183	< 18 years	71 (38.8%)	-	-
Greenberg	1998-2001	74	< 12 months	11 (15%)	6 (54%)	No
Crowcroft	1999-2000	142	< 5 months	33 (23%)	11 (33%)	No
Moore HC	2000-2005	1669	< 9 years	354 (21.2%)	-	-
Nuolivirta K	2001-2004	205	< 6 months	12 (8.5%)	8 (67%)	No
Guinto-Ocampo	2001-2005	141	< 12 months	18 (13%)	-	No
Cosnes-Lambe	2005-2006	126	< 4 months	19 (15%)	14 (73%)	No
Korppi M	2005-2006	117	< 6 months	9 (8%)	7 (78%)	No
Raya BA	2005-2006	309	< 24 months	24 (7.7%)	16 (67%)	43% prolonged coughing
Miron D	2005-2006	465	< 24 months	29 (6.2%)	-	-
Walsh PF	2005-2006	204	< 18 months	0	0	No
Pedro A	2007-2010	2207	< 24 months	4 (0.2%)	2 (50%)	2.4% prolonged coughing
Jolien T	2007-2010	3074	> 18 years	93 (3%)	-	37% prolonged coughing
Korppi M	2008-2010	408	< 24 months	0	0	No
Ivana PE	2009-2010	596	< 5 years	114 (19.2%)	15 (13.1%)	No
Gökçe Ş	2013-2016	172	< 6 months	44 (25.6%)	16 (36.4%)	9.1% prolonged coughing

Supportive care is the most important approach for pertussis treatment. Sufficient hydration and nutrition are important to reduce the frequency of coughing. Antibiotic treatment can only partly reduce symptoms and prevent infectiousness by eliminating microorganisms from the nasopharynx. Macrolide antibiotics are used for treatment.[22] In our study, all patients with *B. pertussis* used clarithromycin, and this was significantly high compared to the *B. pertussis* negative group.

There are some limitations of our research. Some patients did not have a viral or bacterial pathogen identified with the PCR method. These patients may have had non-infectious causes mimicking pulmonary infections like asthma or gastroesophageal reflux, or there may have been possible problems related to respiratory tract secretions not appropriately obtained, stored or studied, or infectious agents not yet identified or not included on the microbiology panel. Another limitation of the study was that we did not have data on whether patients received macrolide antibiotics before admission. PCR testing following antibiotic therapy also can result in false negative findings. Therefore, more extensive studies are needed.

In conclusion, *B. pertussis* is a rare pathogen in patients admitted to hospital for bronchiolitis. Clinical findings of pertussis may be atypical in partly-vaccinated infants and coinfection with a respiratory virus may create additional difficulties for pertussis diagnosis. For cases admitted to hospital who do not improve with conservative treatment, *B. pertussis* should be considered as a causative agent.

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