Mortality in Pertussis, a retrospective study in a pediatric hospital in Sonora, Mexico

Mortalidad en Tosferina, un estudio retrospectivo en un hospital pediátrico en Sonora, México

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ABSTRACT

Background. Pertussis is a reemerging disease worldwide and a public health problem. In Mexico, little is known about pertussis mortality. This study aims to identify factors associated with death due to pertussis among children in Sonora, Mexico, which may help guide therapeutic decisions in settings similar to the study site.

Methods. We compared fatal and nonfatal cases from a consecutive case series of 105 children under 5 years of age with diagnosis of pertussis treated in a pediatric hospital in Sonora, Mexico from 2009 to 2016. Clinical and epidemiologic data were retrieved and characterized from medical charts. The relationship between leukocyte count, pneumonia and death from pertussis was examined using multivariate logistic regression.

Results. The pertussis case fatality rate within our study sample was 17.1%. A larger proportion of fatal (88.9%) than non-fatal cases (56.1%) were less than 4 months of age (p-value=0.09). The odds of death were higher for children with leukocyte counts ≥50,000 cells per μL (odds ratio [OR]=34.2, 95% confidence interval [CI]: 5.1, 228.7) and children with pneumonia (OR=34.4, 95% CI: 3.3, 359.9).

Conclusions. Death due to pertussis remains a public health problem in Sonora, Mexico. Children diagnosed with pertussis who have leukocyte counts ≥50,000 cells per μL and have pneumonia may be at greatest risk of death.

Keywords: *Bordetella pertussis*, Leukocytosis, cough, Mexico

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INTRODUCTION

Pertussis is a reemerging disease worldwide,[1-3] and a public health problem characterized by a high fatality rate among children.[4-6] The true mortality and morbidity attributable to pertussis is unknown. Nonetheless, it is estimated that 40 to 50 million infections occur annually, of which 300,000 to 400,000 result in death.[7] In Mexico, only 20% of suspected cases of pertussis are confirmed by laboratory tests.[8] Of Mexico´s 579 confirmed cases of pertussis in 2009, 70% occurred among children less than 1 year of age and 62% occurred in northern states that border the United States.[8] In the state of Sonora, northwestern Mexico, during 2009-2010 the primary pediatric hospital reported a case fatality rate (CFR) of 15% among confirmed cases of pertussis.[9]

Pertussis remains a public health challenge worldwide, even in countries where vaccination rates are high, like the US.[10] In spite of that, some geographical regions such as the Sonora-US border (Arizona and California), have witnessed epidemic outbreaks with some remarkable data, for instance, the most affected group in a recent California outbreak was the Hispanic population, meanwhile the circulation of erythromycin-resistant strain of *B. pertussis* was observed in Arizona,[2,11] pointing this to a binational health problem, where a dynamic border approach is required to effectively control the disease.

Pertussis is associated with diverse medical complications related to the severity of its clinical expression, which may cause fatality in children. Factors associated with complications and fatal outcome include age less than 1-year, delayed diagnosis, leukocyte counts >100,000 cells per μL, pulmonary hypertension, coexisting pneumonia, and the use of assisted mechanical ventilation.[12,16] However, in Mexico little is known about potential predictors of death in children with pertussis, particularly the effect of elevated white blood cell (WBC) counts (≥50,000 cells per μL). In this study, we evaluated a large series of hospitalized children with pertussis (clinical cases and/or laboratory confirmed) to identify clinical characteristics associated with death to better guide future therapeutic decisions for patients in similar settings.

METHODS

Study design and case inclusion criteria

We conducted an observational, retrospective study of a consecutive case series of patients under 5 years of age, who were diagnosed with *Bordetella pertussis* infection (Code CIE-10, A37.0-A37.9) between January 1st of 2009 and March 31st of 2016, in the primary children´s hospital for the state of Sonora, Mexico.

We estimated a non-probabilistic sample of 225 patients with pertussis, however only 105 subjects were found among medical records, which were all included in the study. Patients were included in the study if *Bordetella pertussis* was detected in a clinical specimen by culture or polymerase chain reaction (PCR) or, in the absence of laboratory confirmation, the patient met a clinical definition characterized by cough for 2 weeks or more accompanied by paroxysms, vomiting, whoop, or cyanosis during cough, or episodes of apnea. Patients were excluded if they received a clinical diagnosis of bronchiolitis or pneumonia attributed to an infectious agent other than *B. pertussis*, bronchopulmonary dysplasia, cystic fibrosis, congenital lung or heart diseases.

Medical records review

Clinical data were retrieved from the subjects' medical charts including: signs, symptoms, medical complications, treatment, vaccination status and diagnostic testing. The first values at admission of WBC count, lymphocyte count, platelet count, erythrocyte sedimentation rate (ESR) and procalcitonin (PCT) values were retrieved from laboratory reports. We also retrieved a second WBC count (recorded in the medical record on the fifth to seventh day of hospitalization) to measure changes over time. A radiologist unfamiliar with the study objectives interpreted radiographic studies.

Statistical analysis

Chi square test (categorical variables), Fisher´s exact tests (categorical variables), Mann-Whitney´s tests (continuous variables with non-normal distribution) and Student´s t-tests (continuous variables with normal distribution) were performed to compare clinical and epidemiologic characteristics of cases by fatality (fatal vs. non-fatal) and type of diagnosis (laboratory test vs. clinical criteria). Normality was measured using Shapiro-Wilk´s test. Using bivariate logistic regression, we selected statistically significant clinical characteristics to include in the Multivariate logistic regression model to obtain an adjusted odds ratio (AOR) and corresponding 95% confidence interval (CI) for the relationship between having a WBC count ≥50,000 cells per μL (using the value recorded at hospital admission) and death adjusting for pulmonary hypertension and pneumonia. We established a WBC cutoff ≥50,000 cells per μL to see its relationship with death due to pertussis, this based in cutoffs similar to other studies.[4,15,17-18] An F test was used to examine the overall significance of the final model. All hypothesis tests were two-tailed and P values <0.05 were considered statistically significant. The statistical package used for all analyses was Number Crunching Statistical System (NCSS) version 8.0. This study was reviewed and approved by the hospital Institutional Review Board

RESULTS

The study sample consisted of 105 subjects, with a mean age of 94.9 ± 97.7 days-old and a median age of 60 days-old with an interquartile range (IQR) of 30-120 days-old. Approximately, half of the study sample was female (52.4 %). Parent's age was a mean of 23 ± 6 and 27 ± 7 years old for mother and father respectively. All patients had cough and the mean number of days between symptoms onset and clinical diagnosis was 9 ± 4 days. On average, the patients were hospitalized for 10 ± 13 days and received antibiotic treatment for 7 ± 4 days. The mean WBC count on patient's fifth to seventh day of hospitalization was 46,000 ± 33,600 cells per μL and was mainly constituted by lymphocytes (59.4%). Refer to Table 1.

There were 18 deaths within our study sample, resulting in a CFR of 17.1%. Most deaths occurred among infants less than four months of age (88.6%), and among those, 12 (66.6%) were less than two months of age (Table 2). We compared the 56 (53.3%) laboratory confirmed cases to the 49 (46.6%) cases that met clinical criteria for diagnosis (Table 1). Of the laboratory confirmed cases, 34 (60.7%) were confirmed by culture and 22 (39.2%) by PCR. The only significant difference was in the WBC count at time of hospital admission, which was higher for clinically diagnosed patients (45,300 cells per μL) than for laboratory confirmed patients (38,000 cells per μL) (p=0.0254). There were no other statistically significant differences between demographic or clinical variables among clinically and laboratory diagnosed patients.

When fatal and non-fatal cases were compared, there was no statistically significant difference in the mean age between groups with 65 ± 59 and 101 ± 103 days old for fatal and nonfatal patients respectively (p=0.1056). Likewise, no differences in sex distribution were observed between groups, with 10 (55.6%) and 40 (46 %) of patients in the fatal and non-fatal groups respectively (p=0.4589).

On average, fatal patients were diagnosed earlier (mean= 6 ± 3 days) than non-fatal patients (mean= 9 ± 5 days) (p=0.0064). Fatal cases had a higher mean WBC count (76,100 ± 23,600 cells per μL) at admission than non-fatal cases (34,100 ± 20,000 cells per μL) (p<0.001), while fatal cases had lower lymphocyte count (43 ± 11 %) than non-fatal cases (63 ± 15 %) (p<0.001) (Table 2). Remarkably, 88.8% of fatal cases had WBC counts ≥50,000 cells per μL compared to only 12.6% of non-fatal cases (p<0.001), also the WBC counts on fifth to seventh day were higher for fatal cases (91,350 ± 18,400 cells per μL) than for non-fatal cases (32,600 ± 24,000 cells per μL) (p<0.001).

Table 1. Comparison of clinical characteristics between probable (clinical diagnosis) and confirmed (laboratory test) cases of pertussis among hospitalized children in Sonora, Mexico (2009-2016)

	Mean ± Standard deviation			Median (IQR)			
	Confirmed	Probable	Total	Confirmed	Probable	Total	P[1/]
Variable	n= 56	n= 49	n=105	n=56	n=49	n=105	
Patient age (days)	92.1 ± 102.4	98.1 ± 93.1	94.9 ± 97.7	60.0 (30.0-120.0)	60.0 (32.0-120.0)	60.0 (30.0-120.0)	0.3258
Mother age (years)	24.0 ± 6.5	22.4 ± 6.0	23.2 ± 6.3	21.5 (19.0-29.7)	20.0 (18.0-24.7)	21.0 (18.25-28.0)	0.2458
Father age (years)	27.5 ± 7.0	26.5 ± 8.0	27.0 ± 7.3	26.0 (22.0-34.0)	25.0 (20.5-31.5)	26.0 21.0-33.0)	0.3936
Sex male (%)	28 (50.0)	22 (44.9)	50 (47.6)				
Symptoms							
-Cough (%)	56 (100.0)	49 (100.0)	105 (100.0)				1.00
-Paroxysmal (%)	45 (80.3)	32 (65.3)	77 (73.3)				0.0818[4]
-Cyanotic (%)	41 (73.2)	33 (67.3)	74 (70.5)				0.5108[4]
-Post-tussive vomiting (%)	27 (48.2)	24 (48.9)	51 (48.5)				0.9376[4]
-Whoop (%)	16 (28.5)	9 (18.3)	25 (23.8)				0.3296[3]
-Dyspnea (%)	27 (48.2)	32 (65.3)	59 (56.2)				0.2568[4]
Vaccination Scheme with DTaP							
-Complete for Age (%)	14 (25.0)	10 (20.4)	24 (22.9)				0.6352[4]
Clinical Complications							
-Pneumonia	15 (26.7)	20 (40.8)	35 (33.3)				0.1281[4]
-Sepsis	9 (16.0)	13 (26.5)	22 (19.0)				0.2309[3]
-Pulmonary hypertension	4 (7.1)	4 (8.1)	8 (7.6)				1.00[3]
-Pulmonary hemorrhage	0 (0.0)	3 (6.1)	3 (2.9)				0.1046[3]
-Nosocomial infection	3 (5.3)	0 (0.0)	3 (2.9)				0.2429[3]
-Mechanical ventilation	12 (21.4)	19 (38.7)	31 (29.5)				0.0518[4]
Chest radiography findings[5]							
-Diffuse interstitial infiltrate	28 (50.0)	31 (63.2)	59 (56.2)				0.1960[4]
-Micro - macronodulations	9 (16.0)	3 (6.1)	12 (11.4)				0.1268[3]
-Radio - opacity	7 (12.5)	10 (20.4)	17 (16.2)				0.4221[3]
-Overdistension of lung[6]	15 (26.7)	13 (26.5)	28 (26.7)				0.9055[4]
Days from onset of symptoms to diagnosis (days)	9.0 ± 4.7	8.6 ± 5.3	8.8 ± 4.9	8.0 (5.0-12.0)	8.0 (5.0-11.5)	8.0 (5.0-12.0)	0.6736
Days on Antibiotic treatment (days)	7.3 ± 4.4	7.0 ± 5.0	7.1 ± 4.6	7.0 (3.5-10.5)	7.0 (2-11.5)	7.0 (3.0-11.0)	0.6808
Hospital stay (days)	11.0 ± 14.2	10.7 ± 13.3	10.8 ± 13.7	8.0 (4.0-11.0)	7.0 (4.0-12.0)	7.5 (4.0-11.0)	0.8192
WBC count at admission (cells per $10^3/\mu L$)	38.0 ± 25.4	45.3 ± 26.4	41.3 ± 26.0	30.4 (19.6-46.5)	35.0 (26.6-63.2)	32.0 (24.2-54.2)	0.0254*
WBC count at 5th-7th day (cells per $10^3/\mu L$)	49.0 ± 36.9	42.8 ± 30.4	46.0 ± 33.6	41.7 (19.4-84.8)	32.5 (16.7-70.6)	35.1 (19.0-78.6)	0.6722
WBC count ≥50,000 (cells per $10^3/\mu L$) (%)	12 (21.4)	15 (30.6)	27 (25.7)				0.2827
Lymphocyte count (%)	63.0 ± 13.6	55.4 ± 19.2	59.4 ± 16.8	64.9 (54.5-74.1)	58.9 (45.0-70.9)	61.0 (51.4-72.9)	0.4800[4]

Table 1. Continuación...

	Mean ± Standard deviation			Median (IQR)			
	Confirmed n= 56	Probable n= 49	Total n= 105	Confirmed n= 56	Probable n = 49	Total	P[1/]
Platelets count (per $10^3/\mu L$)	560.2 ± 160.0	540.0 ± 179.0	550.8 ± 168.1	547.7 (430.5-673.5)	541 (393.5-653.5)	543.5 (412.0-672.7)	0.5524[2]
ESR (mm/hr)	12.3 ± 11.3	15.6 ± 15.8	13.8 ± 13.5	9.0 (4.5-19.5)	10.0 (4.0-21.0)	10.0 (4.2-20.0)	0.4938
PCT (ng/mL)	0.5 ± 1.3	5.5 ± 13.0	3.0 ± 9.5	0.1 (0.08-0.4)	0.2 (0.09-3.9)	0.19 (0.08-0.62)	0.1550

WBC: white blood cells; ESR: Erythrocyte Sedimentation Rate; PCT: Procalcitonin; IQR: Interquartile range

1/ Based on Mann-Whitney test. 2/Based on Student´s T test. 3/Based on Fisher´s exact test. 4/Based on Chi square test. 5/ X-ray in posterior-anterior position. 6/ Includes images of atelectasis and hyperinflation of intercostal spaces

Fatal cases had higher ESR (mean= 28.8 ± 21.4 mm/hr) than non-fatal cases (mean= 11.6 ± 10.4 mm/hr) (p=0.0122) (Table 2). Serum procalcitonin was also higher among fatal cases (mean= 12.7 ± 17.9 ng/mL) than non-fatal cases (0.4 ± 1.2 ng/mL) (p<0.001). The average length of stay in the hospital was also longer for fatal cases (mean= 7.5 ± 16 days) than for non-fatal cases (mean= 11.5 ± 13.2 days) (p<0.001). Platelet count and DTaP vaccination did not differ significantly between fatal and non-fatal cases.

Clinically, all cases had cough, with paroxysmal cough being the most common form among fatal (72.2%) and non-fatal (73.6%) cases. Dyspnea was present in all fatal cases, while only 47.1% of non-fatal cases presented with dyspnea (p<0.001). No other clinical manifestations differed between fatal and non-fatal cases.

Pneumonia was the most common clinical complication among fatal cases (94.4%) and occurred with lower frequency among non-fatal cases (20.7%) (p<0.001) (Table 3). Sepsis, hypertension and pulmonary hemorrhage were also more frequent among fatal cases. The frequencies of diffuse interstitial infiltrates and micro-macro nodularity also differed between fatal and non-fatal cases, but pulmonary over-distension did not differ statistically between groups.

In the bivariate analysis, death was associated with pneumonia [crude odds ratio (cOR)=65.1; CI 95% (8.1, 522.8)], pulmonary hypertension [cOR=54.7 CI 95% (6.1, 487.6)], and WBC count ≥50,000 cells per μL [cOR=55.26 CI 95% (11.1, 273.8)] (Table 4). In the final multivariate analysis, death remained associated with WBC counts ≥50,000 cells per μL [aOR=34.2 CI 95% (5.1, 228.7)] and pneumonia [aOR=34.4 CI 95% (3.3, 360.0) (Table 5).

DISCUSSION

This study of 105 clinical or laboratory confirmed cases of *pertussis* is, to our knowledge, the largest conducted among children in Mexico. Our findings were similar to those reported in other studies[12-16]; the majority of our fatal cases were too young to receive their first dose of DTaP vaccine and roughly 70% of our cases were younger than 4-month of age; also, WBC counts were higher in the fatal cases.

The CFR in our study (17.1%) is several times greater than the CFR of ≤1% reported in the United States and European countries, while in some Latin American countries reported CFRs vary from 2-13%.[3,15,19-20] The high CFR observed in our sample may be explained by low vaccination rates with DTaP among pregnant women, a protective factor for mortality due to pertussis.[1,21-23] Moreover, immunologic or nutritional deficiencies related with the social impoverishment of most of our patients might play a role in the observed CFR. Also, high *pertussis* case rates and mortality rates have been observed in the US among Hispanic/Latino infants, which indicates that genetic or cultural factors may contribute to the burden

of pertussis.[15] As such, in settings similar to our study, novel leukodepletion therapies such as leukofiltration or exchange blood transfusion, could reduce mortality rates when implemented in a timely manner.[4,24]

Table 2. Comparison of clinical characteristics between fatal and nonfatal cases of Pertussis among hospitalized children in Sonora, Mexico (2009-2016)

	Mean ± Standard deviation			Median (IQR)			P[1/]
	Fatal	Nonfatal	Total	Fatal	Nonfatal	Total	
Variable	n=18	n=87	n=105	n=18	n=87	n=105	
Patient age (days)	65.2 ± 59.8	101.0 ± 103.0	94.9 ± 97.7	38.0 (30.0-90.0)	60.0 (30.0-120.0)	60.0 (30.0-120.0)	0.1056
Patient aged <4 months (%)	16 (88.8)	59 (56.1)	75 (71.4)				0.0891[3]
Mother age (years)	24.6 ± 6.3	22.9 ± 6.3	23.2 ± 6.3	24.0 (18.7-31.0)	21.0 (18.0-27.0)	21.0 (18.2-28.0)	0.3197
Father age (years)	28.7 ± 6.1	26.7 ± 7.5	27.0 ± 7.3	30.0 (23.0-33.0)	24.5 (20.7-32.2)	26.0 (21.0-33.0)	0.2211
Sex male (%)	10 (55.6)	40 (46.0)	50 (47.6)				0.4589
Symptoms							
-Cough (%)	18 (100.0)	87 (100.0)	105 (100.0)				1.0[3]
-Paroxysmal (%)	13 (72.2)	64 (73.6)	77 (73.3)				1.0[3]
-Cyanotic (%)	10 (55.5)	64 (73.6)	74 (70.5)				0.1579[3]
-Post-tussive vomiting (%)	7 (38.9)	44 (50.6)	51 (48.6)				0.4420[3]
-Whoop (%)	6 (33.3)	19 (21.8)	25 (23.8)				0.5451[3]
-Dyspnea (%)	18 (100.0)	41 (47.1)	59 (56.2)				<0.001[3*]
Laboratory Confirmation by PCR/Culture (%)	7 (38.8)	49 (56.3)	56 (53.3)				0.2026[3]
Vaccination Scheme with DTaP							
-Complete for Age (%)	4 (22.2)	20 (23.0)	24 (22.9)				0.2784[3]
Days from onset of symptoms to diagnosis (days)	5.8 ± 3.6	9.4 ± 5.0	8.8 ± 4.9	7.0 (3.0-8.0)	9.0 (5.0-13.0)	8.0 (5.0-12.0)	0.0064[*]
Hospital stay (days)	7.5 ± 16.0	11.5 ± 13.2	10.8 ± 13.7	2.0 (1.0-6.5)	8.0 (5.0-12.2)	7.5 (4.0-11.0)	<0.001[*]
Days on Antibiotic treatment	3.5 ± 4.0	7.9 ± 4.3	7.1 ± 4.6	2 (1.0-4.7)	7.5 (5.0-12.0)	7 (3.0-11.0)	<0.001[*]
WBC count at admission (cells per $10^3/\mu L$)	76.1 ± 23.6	34.1 ± 20.0	41.3 ± 26.0	73.0 (62.9-83.7)	28.6 (20.9-39.5)	32.0 (24.2-54.2)	<0.001[*]
WBC count at 5th-7th day (cells per $10^3/\mu L$)	91.35 ± 18.4	32.6 ± 24.0	46.0 ± 33.6	92.9 (78.6-98.9)	24.0 (15.4-43.0)	35.1 (19.0-78.6)	<0.001[*]
WBC count ≥50,000 (cells per $10^3/\mu L$) (%)	16 (88.8)	11 (12.6)	27 (25.7)				<0.001[3*]
Lymphocyte count (%)	43.2 ± 11.0	62.8 ± 15.8	59.4 ± 16.8	46.0 (36.1-51.2)	65.9 (57.5-74.3)	61.0 (51.4-72.9)	<0.001[*]
Platelets count (per 10^3/uL)	569.3 ± 256.4	547.7 ± 150.6	550.8 ± 168.1	598.5 (341.7-702.2)	539.0 (416.5-674.2)	543.5 (412.0-672.7)	0.6581[2]
ESR (mm/hr)	28.8 ± 21.4	11.6 ± 10.4	13.8 ± 13.5	30.0 (3.0-44.0)	9.0 (4.5-15.0)	10.0 (4.2-20.0)	0.0122[*]
PCT (ng/mL)	12.7 ± 17.9	0.4 ± 1.2	3.0 ± 9.5	4.9 (0.4-22.8)	0.1 (0.07-0.3)	0.19 (0.08-0.6)	<0.001[*]

WBC: white blood cells; ESR: Erythrocyte Sedimentation Rate; PCR: Polymerase Chain Reaction; PCT: Procalcitonin; IQR: Interquartile range; DTaP: Diphtheria. Tetanus, acellular Pertussis vaccine

1/Based on Mann-Whitney test. 2/Based on Student´s T test. 3/Based on Fisher´s exact test.

Table 3. Clinical complications among hospitalized fatal and non-fatal cases of pertussis in Sonora, Mexico (2009-2016)

	N (%)			
	Fatal	Nonfatal	Total	P[1/]
Variable	[n=18]	[n=87]	[n=105]	
Pneumonia	17 (94.4)	18 (20.7)	35 (33.3)	< 0.001*
Sepsis	13 (72.2)	9 (10.3)	22 (19.0)	< 0.001*
Pulmonary hypertension	7 (38.9)	1 (1.2)	8 (7.6)	< 0.001*
Pulmonary hemorrhage	3 (16.7)	0 (0.0)	3 (2.9)	< 0.007*
Nosocomial infection	1 (5.6)	2 (2.3)	3 (2.9)	0.501
Mechanical ventilation	18 (100.0)	13 (14.9)	31 (29.5)	< 0.001*
Chest radiography findings[2]				
-Diffuse interstitial infiltrate	14 (77.8)	45 (51.7)	59 (56.2)	0.179
-Micro - macronodulations	5 (27.8)	7 (8.1)	12 (11.4)	0.047*
-Radio - opacity	7 (38.9)	10 (11.5)	17 (16.2)	0.017*
-Overdistension of lung[3]	8 (44.4)	20 (23.0)	28 (26.7)	0.153

1/Based on Fisher´s exact test. 2/ X-ray in posterior-anterior position. Chest Radiographs were available for 48 (85.7%) patients with laboratory confirmed disease and 47 (45.9%) with clinically confirmed disease, including 18 (100%) of the fatal cases and 77 (88.5%) of the non-fatal cases. 3/Includes images of atelectasis and hyperinflation of intercostal spaces

Table 4. Bivariate logistic regression of selected predictors of death due to pertussis in hospitalized children in Sonora, Mexico (2009-2016)

Variable	β	SE	cOR	CI 95%
Age (years)	0.01	0.01	1.01	(0.997, 1.015)
Sex (1=Male)	-0.38	0.52	0.68	(0.245, 1.890)
Diagnostic delay (1= Equal or greater than 14 days)	-0.40	0.68	0.67	(0.176, 2.550)
Pneumonia	4.18	1.06	65.17	(8.12, 522.89)*
Pulmonary hypertension	4.00	1.12	54.71	(6.14, 487.66)*
WBC count ≥50,000 cells per μL	4.01	0.82	55.26	(11.157, 273.818)*
Thrombocytosis ≥ 450,000 mm^3	-0.64	0.52	0.53	(0.189, 1.466)

SE=Standard error; cOR= Crude odds ratio. WBC= White blood cells

*Statistically significant at 95% confidence

Table 5. Factors associated with death among children hospitalized with pertussis in Sonora, Mexico (2009-2016)

Variable	β	SE	ORa	IC 95%
WBC count ≥ 50,000 cells per μL	3.53	0.97	34.2	(5.1, 228.7)*
Pneumonia	3.54	1.20	34.4	(3.3, 360.0)*
Pulmonary hypertension	1.69	1.44	5.4	(0.3, 91.5)

SE=Standard error; ORa= Adjusted-odds ratio for the contained variables in the final model

R^2 = 0.749 for the complete model

χ^2 for the complete model = 62.651, p<0.001.

Adjusted for pulmonary hypertension and pneumonia

*Statistically significant at 95% confidence

In that sense, consistent with several previous reports [12-16] we found that leukocytosis and pneumonia were important predictors of fatality. However, we observed high WBC counts in between five to seven days post hospitalization, which has not previously been documented. High WBC counts are also associated with the development of pulmonary hypertension and it has been hypothesized that such cases could benefit from leukodepletion therapies.[14,24-27]

Our findings indicate that leukocytosis (≥50,000 cells per μL) is associated with higher odds of death in children with pertussis, which is similar to the cutoff documented in other studies.[12,15,17] Compared with survivors, fatal patients were 34 times more likely to have a leukocyte count ≥50,000 cells per μL. This suggests that clinicians could consider leukocyte counts ≥50,000 cells per μL as a potential predictor of severe disease. However, we are not offering any conclusion about this effect because the potential for data bias and regional studies using a larger sample size may yield stronger results.

The fatality of pertussis has been associated with the degree of blood hyperviscosity, particularly with hyperleukocytosis (WBC > 100,000 cells per μL) that has been associated to a fatality rate close to 80%.[26] In our study, the majority of fatal cases had WBC counts above 50,000 cells per μL. Moreover, in 16 out of 18 (88.8%) fatal cases, leukocytes ranged between 58,000 and 97,000 cells per μL.

In addition to leukocytosis, thrombocytosis> 450,000 μL has also been suggested to increase risk of death in pertussis.[28] In our study we found no differences in platelet counts between fatal and nonfatal cases. However, 60% of all patients showed platelet counts > 450,000 cells per μL. Thrombocytosis, either reactive or secondary, which usually occurs in the second or third week from onset of symptoms, may support suspicion of whooping cough in the absence of other causes.[28]

The median age in our study was less than 60 days and the majority of fatal cases were less than two months of age, which is important because in Mexico, children are first vaccinated for pertussis at 8 weeks of age.[8] We did not observe differences in mortality between children with complete and incomplete vaccination schemes. Although this could be a result of the small sample size of our study, as it has been reported that patients with at least the first dose of immunization against *Bordetella* pertussis are less likely to die and have lower leukocyte counts,[10,29] similar to that observed in neonates whose mothers received Tdap during pregnancy.[1,22]

Finally, we also found that pneumonia was associated with death from pertussis, which is consistent with previous reports.[4,18] Pneumonia is a recurring clinical marker in severe forms of pertussis that require intensive care. In fact, children with pneumonia are more likely to have high leukocyte counts and lower arterial oxygen saturation.[18,28,30-31] Likewise, pneumonia is often accompanied by pulmonary hypertension, making it difficult to successfully treat severe pertussis, despite advances in life support.[27]

Our study has limitations including potential data bias caused by the retrospective collection of data, particularly due to the inability to appropriately document pulmonary hypertension in most of our patients. We assumed that this clinical condition existed if was documented in the patient's medical record; however, there was occasionally no recording of which method of measurement was done to establish the diagnosis. Pulmonary hypertension was documented in seven of the fatal cases and in one non-fatal case. This may have caused a bias in our multivariate model, making our 95% CI less accurate. Another limitation is selection bias because a proportion of our cases were severe cases, which would underestimate the actual burden of *pertussis* in general population. Also, nearly half of the cases included in our sample were not confirmed by laboratory tests because diagnostic methods (i.e., culture and PCR) were not available sometimes during the study period, which has also been reported in other parts of Mexico.[8]

Finally, despite having good vaccination coverage, *pertussis* remains a public health problem in Sonora, Mexico. The constraints in preventing cases and deaths may be due to the underestimation of carriers that keep transmission active and increases the risk of infection in the general population.[2,3,19] Furthermore, the low percentage of confirmed cases impedes estimating the real burden of the disease in Mexico. Nevertheless, the occurrence of pertussis in children should alert clinicians, as it has the potential to threaten their lives, particularly those under two months of age.[15] Leukocytosis ≥50,000 cells per μL and pneumonia are independent predictors of mortality. Educating physicians on early diagnosis and proper treatment of the most common complications of *pertussis* should be offered as part of a continuing medical education program.

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