Risk Factors Associated With Infant Deaths From Pertussis: A Case-Control Study

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Background. In the current era, most pertussis deaths occur in infants <3 months of age. Leukocytosis with lymphocytosis and pneumonia are commonly observed among cases of severe pertussis.

Methods. Risk factors associated with fatal pertussis were identified by comparing fatal pertussis cases among patients <120 days of age occurring from 1 January 1998 through 26 December 2014, matched by age (<120 days), county of residence, and closest symptom onset date with 1–4 nonfatal hospitalized cases. California Department of Public Health surveillance data were reviewed to identify cases; demographics, clinical presentation, and course were abstracted from corresponding birth and medical records. Logistic regression and classification tree analyses were used to examine the risk of fatal pertussis with respect to identified factors.

Results. Fifty-three fatal infant pertussis cases were identified and compared with 183 nonfatal hospitalized pertussis cases. Fatal cases had significantly lower birth weight, younger gestational age, younger age at time of cough onset, and higher peak white blood cell (WBC) and lymphocyte counts. Fatal cases were less likely to have received macrolide antibiotics and more likely to have received steroids or nitric oxide and to develop pulmonary hypertension, seizures, encephalitis, and pneumonia. Additionally, exchange transfusion, extracorporeal membrane oxygenation, and intubation occurred significantly more frequently among fatal cases. In multivariate analyses, peak WBC count, birth weight, intubation, and receipt of nitric oxide were predictors of death.

Conclusions. Early recognition of pertussis in young infants and treatment with appropriate antibiotic therapy are important in preventing death. Several risk factors are strongly associated with fatal pertussis in infants.

Keywords. infant pertussis; leukocytosis; lymphocytosis; pneumonia; pulmonary hypertension.

Pertussis is an endemic, underdiagnosed, bacterial respiratory infection caused by *Bordetella pertussis* [1–4]. After the introduction of pertussis vaccines in the United States in the 1940s, the number of reported pertussis cases fell precipitously from 157 cases per 100 000 population to <1 case per 100 000 and remained low until 1982–1984, when a gradual increase was first noted [1, 3].

Reported pertussis is cyclical with peaks in incidence every 3–5 years [4, 5]. In 2005, 2010, and 2014, major epidemics of pertussis occurred in California [6–8]. Most pertussis deaths occur in infants <3 months of age [4, 5]. During the 2010 California pertussis epidemic, infants <3 months of age had the highest disease rates, represented 55% of hospitalized pertussis cases, and had a case-fatality rate of 1.3% [6]. Ten infant pertussis deaths occurred; 9 infants were <8 weeks of age and had not yet received the diphtheria, tetanus, and acellular pertussis (DTaP) vaccine.

Previous small studies have described infant pertussis deaths [9–14]. Leukocytosis with lymphocytosis and pneumonia are commonly observed among severe pertussis cases, and are significantly associated with death [10–12]. In a larger study of pertussis deaths, female sex, birth weight <2500 g, and maternal education of <12 years were independently associated with death [12].

Received 25 February 2015; accepted 7 June 2015; electronically published 16 June 2015.

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Clinical Infectious Diseases® 2015;61(7):1099–106

DOI: 10.1093/cid/civ472

However, because live births were used as the reference group, rather than other infant pertussis cases, it is unclear which characteristics are associated with death rather than pertussis acquisition. To identify factors for death in young infants hospitalized for *B. pertussis* infections, a case-control study comparing 53 fatal cases and 183 matched nonfatal cases in California that occurred between 1 January 1998 and 26 December 2014 was performed.

METHODS

Cases and Controls

Pertussis cases reported to the California Department of Public Health (CDPH) from 1January 1998 through 26 December 2014 were used to identify infant pertussis deaths (cases); all fatal cases were <120 days of age at the time of symptom onset. An attempt was made to select 4 controls for each case from CDPH surveillance data. Controls were infants <120 days of age at the time of symptom onset who were hospitalized for *B. pertussis* infection and matched by county of residence and closest symptom onset date to the corresponding case. If appropriate controls could not be identified in the same county, an adjacent county was used. Siblings or household contacts were excluded as controls.

All cases and controls were either (1) laboratory confirmed by isolation of *B. pertussis* by culture, detection of *B. pertussis* DNA by polymerase chain reaction, or direct fluorescent antibody staining; or (2) met the Council of State and Territorial Epidemiologists clinical case definition for pertussis [15].

This project was reviewed by the California Committee for the Protection of Human Subjects and by the Los Angeles County Department of Public Health and was deemed nonresearch. The project was also reviewed and approved by the Institutional Review Board of the University of California, Los Angeles.

Medical Records Review

Hospital medical records were requested for all cases and controls; at least 3 attempts were made to procure each patient's record. A standardized medical record abstraction tool was used to collect data on symptoms, diagnostic testing, treatment, medical care prior to hospitalization, and medical history including underlying medical conditions, breastfeeding status, and vaccination status. The highest white blood cell (WBC) count, lymphocyte count, and changes in the WBC count over time were recorded, when available. Also recorded were the highest pulse rate and the lowest oxygen saturation level. Birth records were used to obtain data on birth weight, gestational age, type of payer, Hispanic ethnicity, race, maternal age, and parity for infants born in 1997–2012; for births occurring after 2012, these variables were abstracted from hospital birth records, where available. Vaccination status was collected using the California Immunization Registry, California pertussis surveillance data, or medical records data, prioritized in that order.

Statistical Analysis

The *P* values for univariate comparisons between deaths and nondeaths were computed using analysis of variance for normally distributed continuous data or the Wilcoxon–Mann–Whitney test to evaluate differences in nonnormally distributed continuous variables. Fisher exact test was used to evaluate associations for categorical variables, and the Cochrane-Armitage test was used to evaluate trends. Conditional logistic regression was used for the matched data to evaluate the association between the identified risk factors and death. Results from the matched and unmatched analyses were similar, so only the unmatched analysis is presented.

Two multivariable regression methods were used. First, forward stepwise logistic regression was used to construct 2 multivariate models to predict death. Variables were retained in each model if they were simultaneously significant at the $P \leq .15$ level. In model 1, 14 patient and illness characteristics were considered: birth weight, gestational age, paroxysmal cough, posttussive vomiting, age at onset of symptoms, highest pulse rate, lowest oxygen saturation, highest WBC count, pulmonary hypertension, seizures, encephalitis, pneumonia, and receipt of DTaP; highest lymphocyte count was not considered for inclusion as it was a subset of the WBC count. In model 2, 10 patient and treatment characteristics were considered: birth weight, gestational age, age at onset of symptoms, receipt of DTaP vaccine, steroid use, receipt of macrolide antibiotics, receipt of nitric oxide, receipt of sildenafil, extracorporeal membrane oxygenation (ECMO), and intubation.

Second, we constructed a classification tree by recursive partitioning (RPART) using candidate predictors to predict death due to pertussis by identifying patient, illness, and treatment characteristics that best split the data into deaths and nondeaths [16, 17]. The following 13 patient, treatment, and illness characteristics were considered as candidate predictors: birth weight, gestational age, age at onset of symptoms, highest pulse rate, lowest oxygen saturation, highest WBC count, highest lymphocyte count, seizure, encephalitis, receipt of nitric oxide, ECMO, steroid use, and pulmonary hypertension.

The concordance statistic (C) is reported for the logistic and tree models. For tree models, the sensitivity and specificity that maximized the unweighted accuracy is reported, which is defined as follows:

$$\text{Unweighted accuracy} = 0.5\,\text{sensitivity} + 0.5\,\text{specificity}.$$

For the tree, a resampling ("bootstrap") of 2000 random samples with replacement was carried out using the variables retained in the final tree to compute cross-validated sensitivity, specificity, and accuracy. For each sample, a tree was generated using two-

thirds of the data, and the sensitivity, specificity, and accuracy were computed on the remaining one-third. The average across all 2000 samples is reported as the cross-validated values.

All analyses were conducted using SAS software, version 9.3 (SAS Institute) and R software, version 3.1.1 (The R Foundation for Statistical Computing). All *P* values are 2-tailed.

RESULTS

From 1 January 1998 through 26 December 2014, 53 fatal pertussis cases were identified and matched with 210 hospitalized nonfatal pertussis cases; for 2 fatal infant cases, only 3 appropriate controls meeting criteria could be identified. After preliminary medical records review, 27 controls were excluded due to insufficient medical records (n = 24), having an emergency department visit only (n = 2), or being a household contact to a case (n = 1). A total of 183 controls were available for analysis: 31 sets matched 1 case to 4 controls; 16 sets matched 1 case to 3 controls; 5 sets matched 1 case to 2 controls; and 1 set matched 1 case to 1 control. Birth record information was missing for 17 (7%) infants (3 were born out of state, and 14 could not be located in California birth data).

Table 1. Maternal, Infant, and Clinical Characteristics of 53 Fatal and 183 Nonfatal Pertussis Cases

Characteristic	Deaths (n = 53)		Nondeaths (n = 183)		*P* Value	Unadjusted OR (95% CI)
	No. of Patients[a]	No. (%)	No. of Patients[a]	No. (%)		
Maternal characteristics						
Age, y, median (IQR)	46	26 (21–31)	171	28 (22–32)	.300	
Total children born, median (IQR)	50	2 (1–3)	173	2 (1–3)	.087	
Medicaid insurance	46	30 (65)	165	109 (66)	.915	1.0 (.5–1.9)
Infant characteristics						
Male sex	53	26 (49)	183	97 (53)	.612	0.9 (.5–1.6)
Hispanic, all races	51	41 (80)	181	131 (72)	.282	1.6 (.7–3.4)
White, non-Hispanic	51	6 (12)	179	26 (15)	.649	0.8 (.3–2.1)
Black, non-Hispanic	51	1 (2)	179	13 (7)	.313	0.3 (<.1–2.0)
Asian/Pacific Islander, non-Hispanic	51	2 (4)	179	9 (5)	1.000	0.8 (.2–3.8)
Birth weight, g, median (IQR)	49	3084 (2495–3390)	176	**3263 (2977–3627)**	**.003**	
Gestational age, d, median (IQR)	50	266 (252–280)	165	**273 (262–282)**	**.012**	
Underlying heart condition[b]	52	6 (12)	179	16 (9)	.574	1.3 (.5–3.6)
Other underlying medical condition[c]	52	3 (6)	179	9 (5)	.735	1.2 (.3–4.4)
Ever breastfed	43	21 (49)	159	81 (51)	.806	0.9 (.5–1.8)
Age, d, onset of symptoms, median (IQR)	53	29 (17–43)	183	**47 (29–75)**	**<.001**	
Symptoms						
Paroxysmal cough	47	30 (64)	177	**154 (87)**	**.002**	**0.3 (.1–0.6)**
Whoop	50	2 (4)	178	19 (11)	.178	0.4 (.1–1.6)
Apnea	49	23 (47)	175	71 (41)	.425	1.3 (.7–2.5)
Cyanosis	44	29 (66)	182	123 (68)	.832	0.9 (.5–1.9)
Posttussive vomiting	52	29 (56)	178	117 (66)	.189	0.7 (.4–1.2)
Laboratory confirmed	53	51 (96)	183	166 (91)	.194	2.6 (.6–11.7)
Prior medical visits						
Any prior visits	50	34 (68)	180	126 (70)	.786	0.9 (.5–1.8)
No. of prior visits, median (IQR)	53	1 (0–1)	183	1 (0–2)	.388	
Vaccination history						
Any DTaP	52	2 (4)	180	**28 (16)**	**.033**	**0.2 (.1–.9)**
DTaP ≥7 d prior to onset	52	2 (4)	180	23 (13)	.077	0.3 (.1–1.2)
DTaP ≥14 d prior to onset	52	2 (4)	180	19 (11)	.175	0.3 (.1–1.5)

Data are presented as No. (%) unless otherwise specified. Bold text indicates *P* values ≤.05.

Abbreviations: CI, confidence interval; DTaP, diphtheria, tetanus, and acellular pertussis vaccine; IQR, interquartile range; OR, odds ratio.

[a] The number of subjects for whom data were available.

[b] Includes heart murmur, tetralogy of Fallot, ventricular septal defect, and aortic septal defect.

[c] Includes trisomy 21, DiGeorge syndrome, failure to thrive, acetyl-coenzyme A dehydrogenase deficiency, Arnold-Chiari malformation, interuterine cocaine exposure.

The largest numbers of deaths per year occurred in 2005 (8 deaths) and 2010 (10 deaths). From 1998 to 2010, the case-fatality rate in infants aged <120 days was 1.2% (range, 0.4%–2.3%), with at least 1 death occurring each year. Notably, the case-fatality rate has remained ≤1% from 2011 to 2014.

Demographics, clinical symptoms, and medical history are presented in Table 1. Fatal cases had significantly lower birth weight and younger gestational age. Median age at symptom onset was significantly younger among fatal cases. Fatal cases were less likely to have received any doses of DTaP vaccine or to have received DTaP ≥7 days prior to illness onset. Fatal cases were less likely to have been reported to have had paroxysmal cough. No differences were observed between deaths and non-deaths with respect to demographics, other symptoms, underlying medical conditions, medical visits prior to hospitalization, and laboratory confirmation (Table 1).

Pertussis clinical course, complications, and treatment are presented in Table 2. Evidence of respiratory insufficiency

Table 2. Clinical Course of Illness and Treatment Characteristics of 53 Fatal and 183 Nonfatal Pertussis Cases

	Deaths (n = 53)		Nondeaths (n = 183)			
Characteristic	No. of Patients[a]	No. (%)	No. of Patients[a]	No. (%)	*P* Value	Unadjusted OR (95% CI)
Course of illness						
Days hospitalized, median (IQR)	53	5 (2–13)	183	7 (3–11)	.212	
Pulse rate, highest bpm, median (IQR)	53	**208 (200–223)**	172	170 (160–184)	**<.001**	
Pulse oxygen saturation, lowest %, median (IQR)	52	**67 (35–80)**	170	86 (72–95)	**<.001**	
WBC count, highest cells/μL, median (IQR)	53	**84 900 (71 500–99 700)**	170	19 400 (14 100–28 000)	**<.001**	
Highest cells/μL among unvaccinated only, median (IQR)[b]	50	**85 600 (71 500–100 300)**	153	19 700 (14 100–28 250)	**<.001**	
Lymphocyte count, highest cells/μL, median (IQR)	51	**30 700 (23 600–38 600)**	161	13 000 (8600–19 400)	**<.001**	
Days to highest WBC count, median (IQR)	49	9 (5–15)	41	9 (7–15)	.489	
WBC ≥30 000 cells/μL	52	**51 (98)**	167	**34 (20)**	**<.001**	**199.5 (26.6–1495.8)**
Days to WBC 30 000 cells/μL threshold, median (IQR)	51	6 (3–13)	34	9.5 (6–13)	.055	
Pulmonary hypertension	53	**34 (64)**	180	2 (1)	**<.001**	**159.3 (35.5–715.6)**
Seizures	52	**17 (33)**	180	5 (3)	**<.001**	**17.0 (5.9–49.1)**
Encephalitis	53	**8 (15)**	180	2 (1)	**<.001**	**15.8 (3.3–77.1)**
Pneumonia	53	**51 (96)**	160	58 (36)	**<.001**	**44.8 (10.5–191.0)**
Treatment						
Received macrolide antibiotics	53	45 (85)	180	**174 (97)**	**.002**	**0.2 (.1–.6)**
Days to macrolide initiation, median (IQR)	43	0 (0–1)	172	1 (0–1)	.308	
Received steroids	53	**27 (51)**	177	41 (23)	**<.001**	**3.4 (1.8–6.5)**
Received sildenafil	53	4 (8)	182	4 (2)	.079	3.6 (.9–15.1)
Received nitric oxide	53	**32 (60)**	182	3 (2)	**<.001**	**90.9 (25.6–322.7)**
Intubated	53	**52 (98)**	183	11 (6)	**<.001**	**813.1 (102.6–6446.7)**
Received exchange transfusion	53	**11 (21)**	183	0 (0)	**<.001**	**99.3 (5.7–1718.5)**
ECMO	52	**17 (33)**	181	1 (1)	**<.001**	**87.4 (11.3–678.5)**

Data are presented as No. (%) unless otherwise specified. Bold text indicates *P* values ≤.05.

Abbreviations: bpm, beats per minute; CI, confidence interval; ECMO, extracorporeal membrane oxygenation; IQR, interquartile range; OR, odds ratio; WBC, white blood cell.

[a] The numbers of subjects for whom data were available.

[b] Excludes all subjects vaccinated >14 days prior to illness onset.

Table 3. Model 1: Multivariate Logistic Regression Model of Illness Characteristics Associated With Death Due to Pertussis[a]

Characteristic	OR Estimate[b]	95% Wald CI	*P* Value
Birth weight, per 100 g	0.84	.73–.95	.006
Highest WBC count, per 1000 cells/μL	1.06	1.03–1.09	<.001
Pulmonary hypertension	30.32	4.08–225.02	.001
Seizure	4.20	.65–27.09	.131

Abbreviations: CI, confidence interval; OR, odds ratio; WBC, white blood cell.

[a] Variables for selection included birthweight, gestational age, age at symptom onset, receipt of diphtheria, tetanus, pertussis vaccine, highest WBC count, highest pulse, lowest pulse oxygen, paroxysmal cough, posttussive vomit, pulmonary hypertension, seizure, encephalitis, pneumonia.

[b] Concordance statistic = 98.2.

including higher peak pulse rates and lower oxygen saturation levels were significantly associated with death. Fatal cases had significantly higher peak WBC and lymphocyte counts and were also more likely to have a WBC count ≥30 000 cells/μL and to have reached this threshold more rapidly. Of the 167 controls with complete vaccination and WBC count data, 14 (8.4%) received DTaP >14 days prior to illness onset, and the mean and median WBC counts were 16 900 cells/μL and 16 000 cells/μL, respectively. In contrast, the mean and median WBC counts in the 153 control infants who were unimmunized or immunized ≤14 days prior to illness onset were 24 900/μL and 19 700/μL, respectively ($P = .103$).

Fatal cases were less likely to have received macrolide antibiotics and more likely to have received steroids or nitric oxide. Sixty-five percent of fatal cases had a diagnosis of pulmonary hypertension—significantly more than controls. Other pertussis complications (pneumonia, encephalopathy/encephalitis, and seizures) were also strongly associated with death (Table 2).

Exchange transfusion, ECMO, and intubation occurred significantly more frequently among fatal cases (Table 2). Only 1 survivor had received ECMO; this infant had severe brain damage and died several years later. Recipients of exchange transfusion had median WBC and lymphocyte counts of 82 800 cells/μL and 29 137 cells/μL, respectively, vs 22 900 cells/μL and 18 566 cells/μL, respectively, among infants who did not receive exchange transfusion (data not shown).

Table 4. Model 2: Multivariate Logistic Regression Model of Treatment Characteristics, Controlling for Patient Characteristics, Associated With Death to Pertussis[a]

Characteristic	OR Estimate[b]	95% Wald CI	*P* Value
Intubation	317.19	37.48 to >999.99	<.001
Nitric oxide	4.440	1.04–18.95	.044

Abbreviations: CI, confidence interval; OR, odds ratio.

[a] Variables for selection included birthweight, gestational age, age at symptom onset, receipt of diphtheria, tetanus, pertussis vaccine, steroid use, macrolide antibiotics, nitric oxide, extracorporeal membrane oxygenation, intubation.

[b] Concordance statistic = 94.1.

The results for the multivariate regression models are presented in Table 3 (model 1) and Table 4 (model 2). When examining patient and illness characteristics (model 1), only birth weight, highest WBC count, pulmonary hypertension, and seizure were retained in the model, with pulmonary hypertension demonstrating the largest increase in risk of death (Table 3). When examining patient and treatment characteristics (model 2), only intubation and receipt of nitric oxide were retained in the model and both strongly predicted death; because only 1 fatal case was not intubated, there is a large point estimate and wide confidence interval for intubation (Table 4).

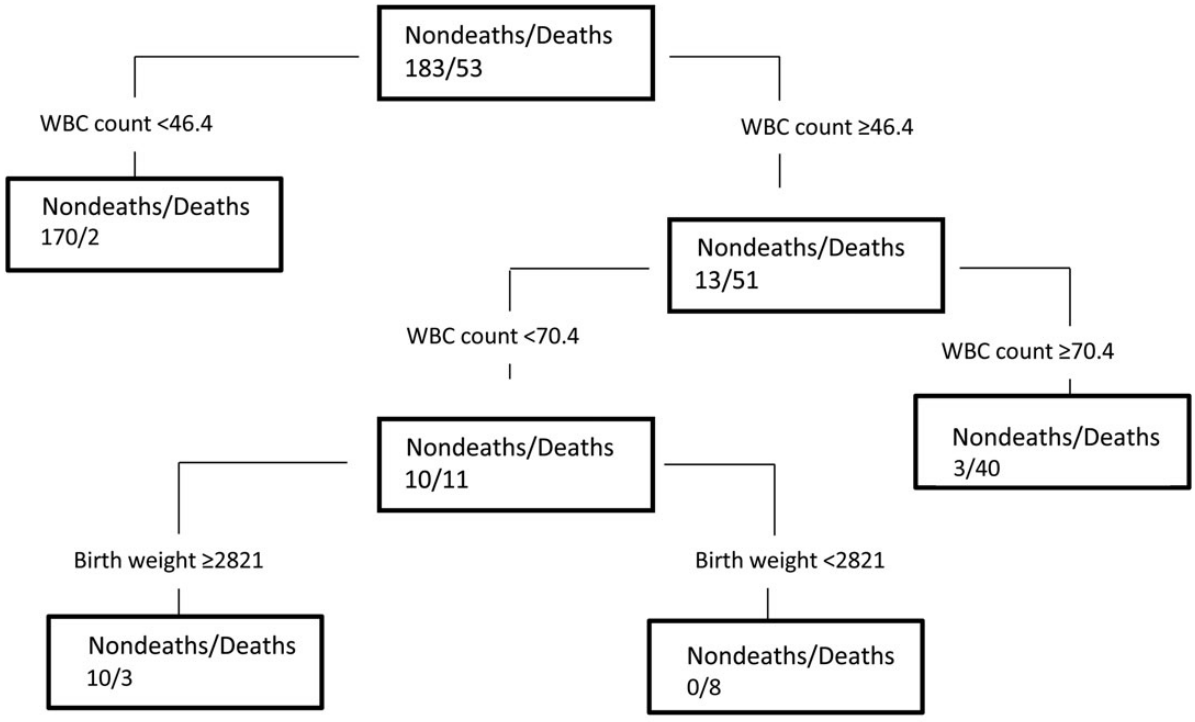
Similarly, in the multivariable classification tree analyses, only 2 of the evaluated characteristics were strongly independent, simultaneous predictors of death via recursive partitioning: a WBC count of ≥46 400 cells/μL, a WBC count of ≥70 400 cells/μL, and birth weight of <2821 g. These 2 factors partition the data into 4 groups, 2 predicting death and 2 predicting survival (Figure 1).

DISCUSSION

Our case-control analysis of 53 infant pertussis deaths and 183 hospitalized infants who survived from 1998 to 2014 is the largest comparison of fatal and nonfatal infant pertussis cases to date. Our findings were consistent with a recent investigation of 31 severe infant pertussis cases ≤90 days of age admitted to 5 different pediatric intensive care units in southern California [13].

Extreme leukocytosis with lymphocytosis is associated with death in young infants [4, 5, 9, 13, 18–23]. Only 2 fatal cases did not have marked leukocytosis (>45 000 WBC/μL); 1case had a WBC count (21 700 WBC/μL) performed early in the course of illness and no subsequent WBC counts before death at home 18 days later. The other infant was born at 28 weeks' gestation, and had bronchopulmonary dysplasia and a WBC count of 14 900 WBC/μL with 67% lymphocytes. This infant received DTaP 15 days before the onset of episodes of apnea and choking, was diagnosed with pneumonia, and developed a left pneumothorax; death was attributed to respiratory failure.

Pertussis toxin (PT) promotes leukocytosis with lymphocytosis, and luminal aggregates of leukocytes have been observed in pulmonary arterioles, veins, and lymphatics of postmortem lung tissue from infant pertussis deaths [4, 18, 21], suggesting that aggregates of leukocytes in small vessels in the lungs leads to irreversible pulmonary hypertension and death in infants [18–21].



	Predicted alive	Predicted dead	Total
True alive	**180**	3	183
True dead	5	**48**	53

Specificity = 0.984
Sensitivity = 0.906
Accuracy = 0.945
Concordance statistic = 97.1

Figure 1. Classification tree of illness characteristics predictive of death due to pertussis. Abbreviation: WBC, white blood cell.

However, PT is also a known inhibitor of many G proteins ($G_{i/o}$). The G_i family G proteins are cardioprotective; loss of G_i activity is associated with ischemia, myocyte apoptosis, and heart failure in mice [24, 25], and in dogs, PT altered the vagal control of the heart rate [26]. The rapid increase in pulse and respiratory rates observed in this study and described by Murray et al [13] lends support for a more widespread effect of PT than just extreme leukocytosis. It is possible that leukocytosis is a marker of PT activity but that inhibition of G proteins in the heart and lungs is the proximate cause of death by respiratory or heart failure in these young infants. More data are needed to assess this hypothesis, but our data suggest that virtually all deaths are associated with the effects of PT and not the result of apnea associated with cough illness.

Consistent with previous reports, most fatal cases were too young to receive their first dose of DTaP vaccine. The Advisory Committee on Immunization Practices (ACIP) and the American Academy of Pediatrics recommend DTaP immunization for infants at 2, 4, and 6 months, although the first dose may be given as early as 6 weeks of age [27]. One dose of DTaP vaccine produces serum neutralizing antibodies to PT and enzyme-linked immunosorbent assay antibodies to PT, filamentous hemagglutinin, and pertactin [28–30] and has been shown to reduce disease complications [31, 32]. In this investigation, immunized infants were less likely to die and also had lower WBC counts.

The ACIP now recommends that women receive tetanus, diptheria, and acellular pertussis (Tdap) vaccine during each pregnancy between 27 and 36 weeks' gestation to optimize

transplacental transfer of maternal antipertussis antibodies to the fetus [33]. This is preferred over postpartum Tdap vaccination, as it provides direct protection to the infant. Recent data indicate that infants born to vaccinated mothers have a lower risk of pertussis early in life [34–36]. As noted in Table 1, the occurrence of paroxysmal cough was significantly more common in nonfatal cases. The reason for this is unknown, but it is possible that the presence of paroxysmal cough increased clinical suspicion for pertussis, leading to earlier testing and empiric treatment with appropriate macrolide antibiotics, thus protecting against death. Additionally, older infants may be able to cough more effectively. A post hoc evaluation indicates that infants with paroxysmal cough were also significantly more likely to have received macrolide antibiotic treatment (odds ratio, 4.5 [95% confidence interval, 1.3–15.5]). Also, as noted in Table 2, 8 (15%) fatal cases did not receive macrolide therapy. The perceived lack of classic pertussis manifestations may have led to treatment with broad-spectrum antibiotic therapy targeted for other fulminant illnesses rather than *B. pertussis*.

Fatal cases were more likely to receive nitric oxide therapy, a vasodilator used to treat pulmonary hypertension (Tables 2 and 4). The *B. pertussis* antigen tracheal cytotoxin (TCT) was found to damage ciliated but not nonciliated respiratory epithelial cells in hamster tracheal organ culture, hamster tracheal epithelial cells, and human respiratory epithelial cells. TCT causes host cells to liberate nitric oxide, which is the mechanism for this cell damage [37, 38].

However, recent studies as well as studies done >100 years ago indicate that in fatal infections, the ciliated cells in the trachea and bronchi are normal unless there is a secondary viral or bacterial infection [18, 21, 39].

Steroid use was also associated with death; cortisone treatment in the murine model of pertussis has been found to increase the mortality rate [40]. In the multivariate model, steroid treatment was not identified as either a risk or beneficial factor.

In the multivariate analysis, the strongest risk factor for death was extreme leukocytosis (Table 3 and Figure 1). This supports the many reported clinical observations [9, 13, 18, 23]. Leukocyte reduction by leukofiltration or exchange transfusion is an accepted but unproven therapeutic approach; most experiences involve 1 or 2 cases. The largest number of treated infants at 1 center was 8. Four of these infants received exchange transfusion and 4 were treated by leukofiltration; 7 of the 8 infants survived [22].

In our study, all infants who had exchange transfusions (n = 11) died. The peak WBC count in this group ranged between 60 000 and 132 000 cells/μL. All of these infants had pneumonia and 9 had documented pulmonary hypertension. All of these infants had cardiogenic shock and respiratory failure, and 1 infant had multiorgan failure prior to the exchange transfusion procedure. Recent California data have shown that among 10 infants who received exchange transfusion, 5 died; all fatal cases, but none of the survivors, were hypotensive or had organ failure prior to the procedure [20]. These data indicate that if exchange transfusion is considered, it should be performed before hypotension or organ failure has occurred. Data from a study of 31 infants with severe pertussis suggest that exchange transfusion should be considered on the basis of the pulse rate, respiratory rate, the total WBC count and rapidity of rise, and the early occurrence of pneumonia [13]. Exchange transfusion may be preferred over leukodepletion methods because it removes PT as well as reduces the WBC count.

Our primary objective was to identify early markers of disease severity that would allow clinicians to recognize infants at risk for death from pertussis so that potentially lifesaving measures, such as exchange transfusion, could be implemented earlier. We were able to make several important observations. First, early recognition and treatment of pertussis with appropriate antibiotic therapy are important in preventing death. Second, several risk factors including birth weight, gestational age, age at cough onset, and WBC count >30 000 cells/μL are strongly associated with fatal pertussis in infants. Sequential monitoring of WBC counts in infants hospitalized with pertussis is important. Our data also suggest that nitric oxide should not be used in pertussis-related pulmonary hypertension.

Pertussis in young infants is associated with significant morbidity and mortality. Early diagnosis and treatment are important so that young infants receive macrolide treatment, hospital admission, and leukocyte monitoring. Additionally, strategies that confer earlier immunity to the infant, such as vaccinating pregnant women with Tdap or accelerating the first dose of DTaP vaccine to prevent pertussis in young infants, should be prioritized.

Notes

Acknowledgments. We thank Vi Peralta from the Los Angeles County Department of Public Health, and Darryl Kong, Rosie Glenn-Finer, and Carol Glaser of the California Department of Public Health for help obtaining records.

Financial support. This work was funded and conducted as a part of enhanced disease surveillance activities by the California Department of Public Health. J. D. C. was funded by the University of California, Los Angeles (Department of Pediatrics Academic Improvement Account).

Potential conflicts of interest. J. D. C. has given talks supported by Sanofi Pasteur and is also a member of the Global Pertussis Initiative, which is supported by Sanofi Pasteur. All other authors report no potential conflicts.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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