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MAJOR ARTICLE

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

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# Background

- Pertussis ist eine endemische unterdiagnostizierte bakterielle Erkrankung durch *Bordetella pertussis*
- Nach Einführung der Pertussis Impfung in den 1940ern sanken Fälle von 157/100000 auf  $< 1/100000$  in den USA und blieben auf einem niedrigen Niveau bis 1982 – 1984
- Pertussis tritt zyklisch auf mit Gipfeln in Inzidenz alle 3 – 5 Jahre
- Die meisten Todesfälle treten in Säuglingen  $< 3$  Monate auf
- Leukozytose und Pneumonie werden häufig in den schweren Fällen beobachtet und sind signifikant mit Tod assoziiert

## Ziel der Studie

Identifikation von Risikofaktoren, die in jungen hospitalisierten Säuglingen zum Tod aufgrund einer Infektion durch *Bordetella pertussis* führen

# Methodik

- Fall-Kontroll-Studie: 1:4
- Todesfälle Januar 1998 und Dezember 2014
- California Department of Public Health (CDPH)
- Todesfälle < 120 Tage alt ab dem Beginn der ersten Symptome
- Matching: Alter, Wohnort, Zeit
- Fallvalidierung:
  - Kultur oder PCR oder direkte Fluoreszenz-Antikörper-Färbung
  - Nach den Richtlinien „des Council of State and Territorial Epidemiologist case definition for pertussis“

# Ergebnisse

- 53 Todesfälle aufgrund Infektion durch *B. pertussis*
- Matching mit 183 hospitalisierten, nicht tödlichen Pertussisfällen (27 mussten ausgeschlossen werden)
- Geburtsdaten fehlten in 17 Säuglingen (7%)
- Case-fatality-rate: 1998 – 2010 1.2%, von 2011 – 2014  $\leq 1\%$

**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 <sup>a</sup>	No. (%)	No. of Patients <sup>a</sup>	No. (%)		
<b>Maternal characteristics</b>						
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)
<b>Infant characteristics</b>						
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	<b>3263 (2977–3627)</b>	<b>.003</b>	
Gestational age, d, median (IQR)	50	266 (252–280)	165	<b>273 (262–282)</b>	<b>.012</b>	
Underlying heart condition <sup>b</sup>	52	6 (12)	179	16 (9)	.574	1.3 (.5–3.6)
Other underlying medical condition <sup>c</sup>	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	<b>47 (29–75)</b>	<b>&lt;.001</b>	
<b>Symptoms</b>						
Paroxysmal cough	47	30 (64)	177	<b>154 (87)</b>	<b>.002</b>	<b>0.3 (1–0.6)</b>
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)
<b>Prior medical visits</b>						
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	
<b>Vaccination history</b>						
Any DTaP	52	2 (4)	180	<b>28 (16)</b>	<b>.033</b>	<b>0.2 (1–9)</b>
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.

<sup>a</sup> The number of subjects for whom data were available.

<sup>b</sup> Includes heart murmur, tetralogy of Fallot, ventricular septal defect, and aortic septal defect.

<sup>c</sup> Includes trisomy 21, DiGeorge syndrome, failure to thrive, acetyl-coenzyme A dehydrogenase deficiency, Arnold-Chiari malformation, interuterine cocaine exposure.

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

Data are presented as No. (%) unless otherwise specified. Bold text indicates  $P$  values  $\leq .05$ .

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

<sup>a</sup> The numbers of subjects for whom data were available.

<sup>b</sup> 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<sup>a</sup>**

Characteristic	OR Estimate <sup>b</sup>	95% Wald CI	P Value
Birth weight, per 100 g	0.84	.73–.95	.006
Highest WBC count, per 1000 cells/ $\mu$ L	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.

<sup>a</sup> 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.

<sup>b</sup> Concordance statistic = 98.2.

**Table 4. Model 2: Multivariate Logistic Regression Model of Treatment Characteristics, Controlling for Patient Characteristics, Associated With Death to Pertussis<sup>a</sup>**

Characteristic	OR Estimate <sup>b</sup>	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.

<sup>a</sup> 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.

<sup>b</sup> Concordance statistic = 94.1.



# Schlussfolgerung

- Grösster Vergleich fataler vs. non-fataler Pertussisfälle bis dato
- Pertussis in jungen Säuglingen ist assoziiert mit signifikanter Morbidität und Mortalität
- Assoziation mit fatalen Fällen: Geburtsgewicht, Gestationsalter, Alter bei Hustenbeginn, und Leukozyten > 30000/ul
- Frühzeitiges Erkennen und Behandlung von Pertussis mit Makroliden sind extrem wichtig
- Serielles Monitoring der Leukozytenzahlen
- Strategien um frühere Immunität zu gewähren sollten priorisiert werden

## Stärken

- Grosse Fallzahl
- grosse Anzahl von Variablen
- breite Statistik
- Fundierte Diskussion



## Schwächen

- Retrospektiv (Daten-  
erhebung/Risikofaktoren)
- Fallvalidierung



<http://www.nzz.ch/zuerich/nichts-zu-husten-auf-dem-saentis-1.18590976>

Vielen Dank für  
Ihre Aufmerk-  
samkeit!

