Risk Factors for Complications in Hospitalized Young Infants Presenting With Uncomplicated Pertussis

abstract

OBJECTIVE: We sought to identify risk factors for complications in hospitalized young infants with uncomplicated pertussis.

METHODS: Retrospective cohort study of hospitalized infants 0 to 6 months of age with confirmed pertussis from 2005 to 2009. Subjects presenting without complications or need for initial intensive care admission were deemed to have uncomplicated pertussis. Complications during hospitalization were defined as apnea, pneumonia, seizures, or encephalopathy. Univariate analysis was performed by estimating odds ratios (OR) and 95% confidence intervals (CI) for the association between each variable and the occurrence of complications. Multivariable analysis was performed using logistic regression. Clinical variables included demographics, historical, laboratory, and imaging data.

RESULTS: Of 126 study subjects, 46 (36.5%) developed complications in the hospital: 43 with apnea (two required endotracheal intubation), seven with pneumonia, and three with seizures; there were no cases of encephalopathy and no deaths. Age less than 60 days (OR, 2.71; 95% CI, 1.08-6.82), cough duration less than 7 days (OR, 5.38; 95% CI, 1.79-16.18), history of color change (OR, 5.24; 95% CI, 1.14-24.07), parental intervention (OR, 10.05; 95% CI, 1.67-60.39), and need for oxygen in the emergency department (OR, 3.94; 95% CI, 1.37-11.36) were associated with development of complications. The median duration of cough at the time of complication was 9 days (range 2-30 days). Initial complete blood cell count and radiographic findings were not associated with complications.

CONCLUSIONS: Infants with uncomplicated pertussis may be at low risk for developing respiratory failure or death. Historical information may assist practitioners in determining risk for serious complications.

Introduction

Pertussis continues to be a serious illness in young infants with increasing incidence and high rates of hospitalization. While young infants are more likely than older children to suffer from severe complications such as apnea, pneumonia, seizures, and encephalopathy, a spectrum of disease expression exists. Many young infants appear well between paroxysmal coughing episodes. The well-appearing infant with pertussis poses challenges to the emergency medicine physician as to which children would benefit from admission, and to the hospitalist physician as to the level of monitoring required for admitted patients.

Previous studies have sought to characterize entire cohorts of young infants with pertussis and those specifically requiring intensive care. It is known that infants...
with severe pertussis who require intensive care tend to be less than 6 weeks of age, born prematurely, have a short duration of cough, and cardiorespiratory comorbidities. However, little is known about the characteristics of infants who initially present without signs of complications.

In this study, we focus on infants with uncomplicated pertussis because this is the subset of infants most commonly treated by pediatric hospitalists outside the intensive care unit and the cases that pose the greatest management dilemma. Because these infants present with no evidence of complications, the practitioner must try to anticipate which infants will develop more severe disease and determine the appropriate level of monitoring and length of observation needed. In this study, we attempt to identify clinical and laboratory predictors for the development of severe complications during hospitalization. As a secondary outcome, we aim to delineate the time between onset of cough and development of complications during hospitalization.

**Methods**

**STUDY DESIGN**

This was a retrospective cohort study of infants admitted to Texas Children’s Hospital from January 1, 2005, through May 31, 2009. Subjects with and without complications were compared based on clinical variables as noted on chart review to determine their risk of developing complications during hospitalization.

**SUBJECTS**

Subjects were included if they were younger than 7 months old, had a positive polymerase chain reaction (PCR) for *Bordetella pertussis* or *parapertussis*, and were admitted to the hospital during the study period. PCR was the sole diagnostic test used at our institution. Subjects were identified by *International Classification of Diseases, 9th Revision* (ICD-9) discharge code for pertussis and by the microbiology database for positive results on PCR testing for pertussis. Medical records were reviewed by the principal investigator (SW) to determine study eligibility.

Subjects were deemed to have uncomplicated pertussis if they did not have evidence of complications or required intensive care on initial presentation. Exclusion criteria were created for infants who presented with evidence of serious complications to isolate a subgroup of infants with uncertain prognosis for progression of disease. Subjects were excluded if they met any of the following conditions: initial admission to pediatric intensive care unit, need for mechanical ventilation, history of recent seizure, encephalopathy, or apnea before admission. Apneic events were excluded only if witnessed by health care providers because it was uncertain whether parental description of events represented true apnea.

IRB approval was obtained before initiating the study.

**DATA COLLECTION**

Medical records were reviewed by the principal investigator (SW) and data were extracted using a standardized data collection form. Demographic information included age at the time of hospitalization, gender, and race/ethnicity. Clinical information included a history of premature birth (defined as <37 weeks’ gestation), low birthweight (<2,500 g), vaccination status (defined as complete or incomplete by parental report or vaccination record), number of diptheria-tetanus-acellular pertussis (DTaP) vaccines (defined as documentation of having received the 2-month, 4-month, or 6-month series), use of a macrolide antibiotic before admission (any duration of therapy), breastfeeding (exclusive or supplemented), environmental tobacco smoke exposure (indoor or outdoor smokers), contact with an ill person (anyone with respiratory symptoms), and history of any chronic cardiac or respiratory medical problem. Signs and symptoms included cough duration, parental description of apnea (defined as pause in breathing or absence of chest rise for any period), parental description of any color change, need for any parental intervention for apnea, or color change before arrival at the emergency department (ED; eg, cardiopulmonary resuscitation, tactile stimulation, or blowing on face), fever (temperature ≥100.4°F by history or ED vital signs), and need for supplemental oxygen in the ED before admission. Chest radiography findings were interpreted by the radiologists and were considered abnormal if they were reported to have any findings except “normal chest.” Abnormal findings were categorized as infiltrate, effusion, atelectasis, perihilar opacities, or pneumothorax. Viral coinfections were defined as isolation of a respiratory viral pathogen via any diagnostic test used to analyze upper or lower respiratory tract secretions. Bacterial coinfections were defined as isolation of a bacterial strain from blood, spinal fluid, or respiratory tract.

The hospital location to which the patient was admitted was determined and the clinical course in the hospital was evaluated for the occurrence of any complication. Complications
during hospitalization included the following: apnea, pneumonia, seizures, or encephalopathy. The hospital units included the ED observation unit, the floor, the level II nursery, and intermediate care unit. We included subjects admitted to intermediate care unit or level II nursery because most of our infants under 3 months of age are preferentially admitted to these units regardless of illness severity. Because of varying monitoring capabilities in our hospital units, apnea was defined as breathing cessation that required intervention. Pneumonia, seizures, and encephalopathy were defined as clinician diagnosis of those conditions as documented in daily progress note and/or discharge summary.

STATISTICAL ANALYSIS
In anticipation of the use of regression analyses, sample size was estimated to include at least 10 subjects per clinical variable studied for a total of 120 subjects.

We used the statistical software SPSS version 18 (SPSS Inc., Chicago Ill) to perform the analysis. Categorical and continuous variables related to subjects with and without complications were compared using chi-square and Mann Whitney U tests, respectively. Univariate analysis was performed by estimating odds ratios (OR) and 95% confidence intervals (CI) for the association between each variable and the occurrence of complications. Age and duration of cough were categorized to maximize the magnitude of their associations with the occurrence of complications. The optimal categorization was as follows: age younger than 60 days and 60 days or older, duration of cough 0 to 7 days and more than 7 days. Because of the small numbers of patients, all types of interventions and all types of color changes were grouped together for univariate and multivariate analyses.

Multivariate analysis was performed using logistic regression. Interactions between patient age and duration of cough were explored as well as those between patient age and hospital unit, and no interactions were found. Logistic regression then proceeded in a step-wise forward manner where variables were included in the model if they were statistically significant \( P<.20 \) and/or if they changed the regression coefficients by more than 10%.

Patient outcomes and bacterial coinfections were then described and statistically compared between the groups with and without complications. Receiver operating curve (ROC) techniques were used to analyze the usefulness of white blood cell (WBC) count and absolute lymphocyte count (ALC) in predicting complications.

Results
Two hundred and eight young infants were hospitalized with pertussis during the study period and 126 of these patients were eligible for the study (Figure 1). The median subject age was 63 days (range, 16 to 170 days). Four of the seven neonates (aged 0-28 days) experienced complications. Of 126 study subjects, 46 (36.5%) developed at least one complication in the hospital: 42 subjects developed apnea, seven pneumonia, three seizures, three apnea and seizures, three apnea and pneumonia, and no patients developed encephalopathy. Most patients (n=107) experienced color changes before ED evaluation: cyanosis (n=48), multiple colors (n=30), red (n=14),...
A purple (n=12), white/pallor (n=2), and missing (n=1). The frequencies of complications in the hospital were similar across these color change types (33%-53%) and were all higher than the frequency seen in infants without reported color changes (12%). No infant younger than 60 days of age had been vaccinated with DTaP. Of the 72 infants aged 60 days or older, 46 (64%) had received one dose of DTaP, none had received more than one DTaP dose, and one was missing information about previous vaccinations. The infants who received DTaP were as likely to experience a complication as the infants who did not receive DTaP (OR, 1.11; 95% CI, 0.33-3.71).

Twenty-eight patients required supplemental oxygen before admission and an additional 10 patients required supplemental oxygen during their hospitalization. The median duration of supplemental oxygen administration was 4 days (range, 1 to 15 days) for all patients requiring supplemental oxygen: 5 days for subjects with complications and 3 days for subjects without complications (P=.157 by Mann Whitney U test).

Data on environmental tobacco exposure were available for 40 patients, and was not associated with an increased risk of experiencing a complication in the hospital (OR, 0.49; 95% CI, 0.09-2.76).

Absolute lymphocyte count and WBC count were poor predictors of the occurrence of a complication in the hospital. Using ROC techniques, the area under the curve was 0.57 (95% CI, 0.46-0.68) for ALC and 0.60 (95% CI, 0.48-0.71) for WBC. For the univariate analysis, ALC was considered elevated if greater than 9,000, in accordance with standard definitions for absolute lymphocytosis.12

On univariate analysis, age less than 60 days, cough duration less than 7 days, parental description of patient color change, the need for an intervention at home, the need for supplemental oxygen before admission, and admission to a non-floor bed were all associated with the subsequent occurrence of a complication in the hospital (Table 2).

After adjusting for other variables, age less than 60 days, cough duration less than 7 days, use of a macrolide antibiotic before ED evaluation, the need for

### Table 1
Demographic Characteristics Associated with the Development of Complications in 126 Hospitalized Infants With Pertussis

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No Complication During Hospitalization, (%)</th>
<th>Complication During Hospitalization, (%)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median (range) age in days</td>
<td>67 (26-161)</td>
<td>49 (16-170)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td>0.438†</td>
</tr>
<tr>
<td>Male</td>
<td>44 (55)</td>
<td>22 (48)</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>36 (45)</td>
<td>24 (52)</td>
<td></td>
</tr>
<tr>
<td>Race/ethnicity</td>
<td></td>
<td></td>
<td>0.728†</td>
</tr>
<tr>
<td>Hispanic</td>
<td>54 (68)</td>
<td>29 (63)</td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>9 (11)</td>
<td>9 (20)</td>
<td></td>
</tr>
<tr>
<td>African-American</td>
<td>11 (14)</td>
<td>5 (11)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>5 (6)</td>
<td>2 (4)</td>
<td></td>
</tr>
<tr>
<td>Missing</td>
<td>1 (1)</td>
<td>1 (2)</td>
<td></td>
</tr>
</tbody>
</table>

* Mann Whitney U test.
† Chi-square test.

### Table 2
Univariate Analysis of Clinical, Laboratory, and Radiologic Features Associated with Complications in 126 Hospitalized Infants With Pertussis

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No Complication During Hospitalization (N=80)</th>
<th>Complication During Hospitalization (N=46)</th>
<th>OR (95% CI)*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patient characteristics</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age &lt;60 days†</td>
<td>24</td>
<td>30</td>
<td>4.38 (2.02-9.47)</td>
</tr>
<tr>
<td>Born prematurely</td>
<td>13</td>
<td>5</td>
<td>0.60 (0.20-1.82)</td>
</tr>
<tr>
<td><strong>Preventive measures</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Macrolide PTA</td>
<td>19</td>
<td>5</td>
<td>0.38 (0.13-1.10)</td>
</tr>
<tr>
<td>Breastfeeding</td>
<td>24</td>
<td>22</td>
<td>2.06 (0.97-4.38)</td>
</tr>
<tr>
<td><strong>Signs and symptoms</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cough duration &lt;7 days‡</td>
<td>8</td>
<td>17</td>
<td>5.28 (2.05-13.57)</td>
</tr>
<tr>
<td>Apnea PTA</td>
<td>26</td>
<td>18</td>
<td>1.34 (0.63-2.84)</td>
</tr>
<tr>
<td>Color change PTA</td>
<td>63</td>
<td>44</td>
<td>5.24 (1.14-24.07)</td>
</tr>
<tr>
<td>Intervention PTA</td>
<td>5</td>
<td>10</td>
<td>4.17 (1.33-13.09)</td>
</tr>
<tr>
<td>Fever PTA</td>
<td>16</td>
<td>5</td>
<td>0.49 (0.17-1.43)</td>
</tr>
<tr>
<td>Oxygen PTA</td>
<td>12</td>
<td>16</td>
<td>3.02 (1.28-7.16)</td>
</tr>
<tr>
<td><strong>Laboratory and radiographic features</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ALC ≥ 9000</td>
<td>50</td>
<td>30</td>
<td>1.09 (0.51-2.33)</td>
</tr>
<tr>
<td>CXR abnormal</td>
<td>44</td>
<td>23</td>
<td>0.61 (0.27-1.37)</td>
</tr>
<tr>
<td>Respiratory virus</td>
<td>8</td>
<td>9</td>
<td>2.19 (0.78-6.14)</td>
</tr>
<tr>
<td><strong>Hospitalization Unit</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NICU2, PCU, EDOU§</td>
<td>43</td>
<td>39</td>
<td>4.79 (1.92-11.99)</td>
</tr>
</tbody>
</table>

* Parameters reaching statistical significance are shown in bold.
† Compared with age of 60 days or more.
‡ Compared with cough duration of 7 days or longer.
§ Compared with floor bed.
an intervention and supplemental oxygen before admission, and admission to a non-floor bed were significantly associated with the occurrence of a complication in the hospital (Table 3). Of note, when chest radiography findings were added to the logistic regression model, all variables remained significant except admission to a non-floor bed. However, chest radiography findings themselves were not independently associated with the occurrence of complications in the hospital. When viral coinfections were added to the multivariate model, they were not significantly associated with the occurrence of complications and they had no effect on the association between the other variables and complications.

Subjects with complications had longer lengths of stay than subjects without complications. The median length of stay was 8 days versus 3 days, respectively ($P<.0001$ by Mann Whitney U test). No significant difference in bacterial coinfections was noted between the two groups, with one subject in the no complication group and two subjects in the group with complications having any coinfections ($P=.553$). Once discharged from the hospital, the frequency of readmission was similar between subjects with and without complications (4 versus 8, $P=1.000$ by Fisher exact test).

### TABLE 3 Multivariate Analysis to Determine Independent Clinical Features Associated With Complications in 126 Hospitalized Infants With Pertussis

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Adjusted* OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &lt;60 days</td>
<td>2.71 (1.08-6.82)</td>
</tr>
<tr>
<td>Duration of cough &lt;7 days</td>
<td>5.38 (1.79-16.18)</td>
</tr>
<tr>
<td>Macrolide before admission</td>
<td>0.19 (0.04-0.98)</td>
</tr>
<tr>
<td>Intervention required prior to admission</td>
<td>10.05 (1.67-60.39)</td>
</tr>
<tr>
<td>Supplemental oxygen required prior to admission</td>
<td>3.94 (1.37-11.36)</td>
</tr>
<tr>
<td>Admitted to NICU2, PCU, or EDU</td>
<td>3.30 (1.09-10.04)</td>
</tr>
</tbody>
</table>

*Adjusted for age, duration of cough, intervention, and supplemental oxygen before admission.

CI = Confidence interval; EDU: emergency department observation unit; NICU2 = level II neonatal intensive care unit; PCU: intermediate care unit; OR = odds ratio.

**Discussion**

This study differs from previous studies, which have focused on entire cohorts of infants with pertussis or infants solely requiring intensive care. We focused on infants presenting with uncomplicated pertussis because these children comprise the majority of cases and pose the most vexing questions about management. We found that this subgroup of infants had several distinguishing characteristics, including lower rates of respiratory failure and death than seen in previous US cohorts and lower percentages of patients with classic comorbidities, such as prematurity and chronic cardiopulmonary conditions. We found several clinical predictors for complicated hospital course, which include younger age, shorter cough duration, parental report of color changes, parental interventions, or supplemental oxygen administration before hospital arrival.

Our study reaffirms that younger age and shorter duration of cough are risk factors for development of severe, complicated illness. A study based on hospital surveillance data in France showed that age less than 2 months was associated with higher rates of admission to the intensive care unit, assisted ventilation, and death. Surridge et al showed that most infants requiring intensive care were younger than 3 months of age with almost half being younger than 6 weeks of age. Shorter duration of cough has also been described to be associated with more severe illness. Intensive care admissions had a median duration of cough of 7 days. Another study showed that symptom duration of more than 15 days had lower odds of developing severe pertussis. Given the high risk for complications in infants younger than 2 months of age with short duration of cough, we recommend closely observing these young infants with cardiorespiratory monitoring even if they appear well initially.

Our study reveals several parental concerns that may be markers for more severe illness. Parents describing color change during or after paroxysmal episodes is associated with higher odds of experiencing apnea in the hospital. Also, any type of parental intervention, whether minor or major, was significantly associated with higher odds of apnea during multivariate analysis. To our knowledge, these findings have not been reported previously. It will be important to closely monitor these infants when parents raise such concerns.

In addition, infants receiving oxygen before admission had higher odds of developing a complication during hospitalization. Because of the short duration of oxygen requirement and low rates of assisted ventilation, it is unlikely that this oxygen requirement was the result of pulmonary abnormality such as pneumonia or pulmonary hypertension. Oxygen placed by transport or ED providers is likely because more profound desaturations are seen in those settings, which may herald a higher risk for development of complications during hospitalization.

More than 80% of our subjects had complete blood count (CBC) with differential and chest radiograph obtained, but
few of our subjects with uncomplicated pertussis had test results known to be associated with adverse outcome. Only two subjects (1%) had an elevated WBC count higher than 55,000/µL (5.5×10⁹/L)⁷,¹⁸ and only eight subjects (6%) had radiographic pneumonia. In addition, elevated ALC was not associated with complications in our analysis. Our study suggests that CBC with differential and chest radiography may not be useful to determine the risk of adverse events in infants with uncomplicated pertussis. However, larger studies are needed to confirm these findings. A CBC with differential and chest radiographs may still be useful in a different instance, when the diagnosis of pertussis is uncertain. ALC has been shown to be a predictor of the diagnosis of pertussis.⁵ In infants with lower respiratory tract findings, chest radiography may be used to evaluate infants for other abnormalities, such as community-acquired pneumonia. Further studies are needed to fully elucidate the benefit of early macrolide treatment. Our study suggests that macrolides may be a protective factor against the development of complications during hospitalization, but it is difficult to assess the true effect on morbidity and mortality because our study excluded the most severely ill patients. Further studies also are needed to evaluate the association of viral coinfection with the development of complications during hospitalization because our study contained only a few subjects with isolated viral respiratory pathogens. Lastly, it would be prudent to examine the duration of cough before the onset of complications in a larger prospective study. Our data for this variable lacked precision because of the small sample size. Further analysis of this variable may allow us to delineate a safe time for discharge for those infants who remain asymptomatic during hospitalization.

Our study contains limitations inherent to retrospective studies. A selection bias exists, because many infants with pertussis are usually discharged from the ED, and the characteristics of these children in our study were unknown. There may have been a classification bias, in that some critically ill infants who were admitted to intermediate care units or transferred to a higher level of care were included in the study, but did not develop complications. The low frequency of medical comorbidities and low pertussis morbidity and mortality argue against this. However, by inadvertently including a few critically ill infants, we may still be able to draw the most conservative conclusions regarding the infant presenting with uncomplicated illness.

A potential confounder in our study is that infants were admitted to hospital units with different monitoring capabilities. It is possible that certain patients may have been admitted to a unit with a higher level of monitoring because of a more ill appearance. To account for this varying level of monitoring, we defined apnea as a cessation in breathing that required intervention. We postulated that apneic events requiring intervention would be documented in the chart in any unit, whereas self-resolving episodes may go unnoticed in units with a lower level of monitoring. Of note, floor patients did experience fewer complications than those in other units with higher levels of monitoring. This remained true even after adjusting for age and other possible confounders in multivariate analysis. Readmission rates were the same for subjects with and without complications, thus suggesting that floor patients did not progress to more severe disease than those in other units.

Conclusions

Young infants with uncomplicated pertussis may be at low risk for respiratory failure and death during hospitalization. Traditional screening via CBC and chest radiography may not be useful to predict the risk of in-hospital complication in this uncomplicated population; however, younger age, shorter cough duration, parental interventions or supplemental oxygen administration before hospital arrival may be associated with complicated hospital courses. Prospective studies are needed to confirm these findings and develop a risk-stratification tool and evidence-based management guideline for these young infants.

References


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