

ORIGINAL ARTICLE

Factors associated with disease severity in children with bronchiolitis

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*Department of Pediatric Critical Care, Connecticut Children's Medical Center, Hartford, CT, USA***Abstract**

Objective: Bronchiolitis is one of the top causes of hospitalization of infants in the United States. Several clinical factors have been associated with hospitalization; however, few studies have examined factors related to severe disease. Our goal was to describe the clinical characteristics and hospital course of children admitted with bronchiolitis and to identify factors related to intensive care unit (ICU) admission in this population. **Methods:** We conducted a retrospective review of all children less than 2 years of age admitted to a children's hospital with bronchiolitis between July 2008 and July 2011. Demographic and clinical data were collected including information regarding hospital course, treatments received and respiratory pathogens. **Results:** During the study period, 734 children were admitted to the hospital with bronchiolitis, 22% of whom were admitted to the ICU and 10% of whom were intubated and mechanically ventilated. Admission to the ICU was associated with younger age [110 (45–210) days versus 69 (35–149) days, $p < 0.001$] and history of premature birth (OR 1.7, 95% CI 1.1–2.4, $p = 0.01$), but not with race or ethnicity. The use of respiratory treatments was common in the children admitted to the ICU but was not associated with shortened durations of hospitalization. In addition, neither prematurity nor young age were associated with either increased duration of hospitalization or with increased likelihood of mechanical ventilation. **Conclusions:** During acute bronchiolitis infections, younger children and those with a history of prematurity were more likely to be admitted to the ICU with severe disease.

Keywords

Critical care, intubation, mechanical ventilation, pediatrics, RSV

History

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Introduction

Bronchiolitis is a common acute respiratory illness and the primary cause of hospitalization in infants [1–4]. It is characterized by respiratory distress, wheezing, cough, fever, and coryza and is most often associated with respiratory syncytial viral (RSV) infection [1–5]. More than one third of children will develop bronchiolitis during the first 2 years of their life. In the United States, approximately 3% of these infants will require hospitalization, a rate that has risen over the past few decades [1–2,6,7].

The American Academy of Pediatrics has identified several factors that place a child in a high risk category for developing severe RSV bronchiolitis. These risk factors include prematurity, congenital heart disease and chronic lung disease [8]. However, most children who are hospitalized with bronchiolitis are previously healthy and do not have these risk factors [9,10]. Several authors have explored clinical factors that are associated with hospitalization or mechanical ventilation in children with bronchiolitis [4,11–13]; however, few studies have examined factors related

to intensive care unit (ICU) admission in this population. Our goal was to describe the clinical characteristics and hospital course of children admitted with bronchiolitis and to identify factors related to ICU admission.

Methods

We conducted a retrospective review of all children less than 2 years of age admitted to Connecticut Children's Medical Center with bronchiolitis between July 2008 and July 2011. Connecticut Children's is a 150-bed, free-standing pediatric hospital with an 18-bed ICU. The study was approved by our Institutional Review Board and informed consent was waived. Demographic and clinical data were collected including information regarding hospital course, treatments received and respiratory pathogens.

The diagnosis of bronchiolitis was determined clinically by the primary admitting attending physician using criteria established by the American Academy of Pediatrics, who defines bronchiolitis according to clinical symptoms and signs that include a viral upper respiratory prodrome and increased respiratory effort and wheezing in children less than 2 years [14]. The diagnosis was based on history and physical examination and included children with and without identifiable viral infection. Prior wheeze was diagnosed clinically by the provider using information obtained from parental

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report and using the criteria of previous history of wheezing and previous bronchodilator use [15]. There were no study exclusion criteria.

Sputum cultures on intubated patients were obtained using suctioning of the endotracheal tube using a Lukens-Trap. Induced sputum cultures were used for those children who were not intubated. However, not all children had bacterial cultures obtained.

Criteria for ICU admission remained constant during the study period. Specific admission criteria included but were not limited to the following:

- (1) Saturation $<92\%$ in inspired oxygen $>50\%$.
- (2) New or worsening hypercarbia with acidemia.
- (3) Altered mental status secondary to respiratory dysfunction.
- (4) Respiratory rate outside 95% confidence interval for age, or a change from baseline respiratory rate of 30% or greater.
- (5) Significant work of breathing
- (6) Apnea >15 s.

In addition, a standardized bronchiolitis clinical pathway is utilized at our institution for all children aged 2–24 months who are admitted to the hospital with a primary diagnosis of bronchiolitis. According to this pathway, the ICU is to be consulted for patients with severe respiratory distress, apnea or bradycardia and if a higher level of care is needed then it can be provided on the Medical/Surgical units.

Data were analyzed using SPSS statistical software (version 17.0; Chicago, IL). Clinical characteristics of patients admitted to the general floors versus the ICU were compared using Students *t*-tests or Mann–Whitney U tests for continuous variables and chi-square tests for categorical variables. Calculations are presented as mean $\pm$ standard deviation or median and 25–75% interquartile range (IQR) for continuous variables and as frequencies (%) for categorical variables. Frequencies are rounded to the nearest whole number and *p* values of <0.05 are considered statistically significant.

Results

During the study period, 735 children were admitted to Connecticut Children's with bronchiolitis. One patient was excluded due to disposition issues not related to clinical status that resulted in a lack of follow-up data. Therefore, 734 patients were included in this study, 158 (22%) of whom were admitted to the ICU and 74 (10%) of whom were intubated and mechanically ventilated (Figure 1). The median age of patients was 95 (44–201) days and 56% ($n=412$) were male. More than half of the children admitted to the hospital with bronchiolitis were previously healthy (53%) and the majority (78%) had at least one identified viral or bacterial pathogen.

The demographic and clinical characteristics of bronchiolitic children admitted to the ICU and those admitted to the ward are shown in Table 1. Children admitted to the ICU were significantly younger than those admitted to the ward [69 (35–149) days versus 110 (45–210) days; $p<0.001$]; however, there were no significant differences in gender or race/ethnicity between the two groups. Children admitted to the ICU were significantly more likely to have been born prematurely (34% versus 24%; $p=0.01$) compared to those

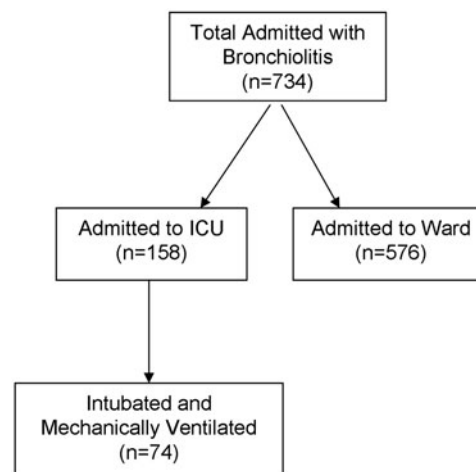


Figure 1. Study population.

admitted to the ward and of those who were premature, children admitted to the ICU had significantly younger gestational ages [33 (28–36) weeks versus 34 (32–36) weeks; $p=0.02$]. They were also more likely to have a history of apnea compared to children admitted to the ward (22% versus 5%; $p<0.001$). However, those admitted to the ICU were less likely to have prior wheeze than those admitted to the ward (5% versus 11%; $p=0.045$) and were less likely to be previously healthy (43% versus 55%; $p=0.01$).

Although prematurity and young age were associated with ICU admission in the entire patient population, in the subset of children admitted to the ICU ($n=158$), neither were associated with increased length of stay nor increased likelihood of mechanical ventilation. In this population, there was no significant difference in the ICU length of stay of premature versus non-premature babies [106 (42–252) days versus 106 (59–219) days; $p=0.94$] nor was there a significant difference in mechanical ventilation between babies with and without a history of prematurity (OR 1.1; 95% CI 0.6–2.1; $p=0.8$). There was no correlation between ICU length of stay and patient age ($r=-0.17$, $p=0.03$) and there was also a lack of a significant age difference between babies who did and did not receive mechanical ventilation [62 (32–98) days versus 74 (37–191) days; $p=0.054$]. Furthermore, in those children admitted to the ICU, no other demographic or clinical factors, including apnea, prior wheeze or other previous chronic disease, were associated with increased duration of hospitalization or with increased likelihood of mechanical ventilation.

Viral and/or bacterial infections were identified in 78% ($n=573$) of children admitted to the hospital with bronchiolitis. RSV was the most common pathogen, occurring in 89% of children admitted to the ICU and 75% of those admitted to the ward ($p<0.001$). Six percent ($n=45$) of our patient population were found to have a bacterial infection; *Haemophilus influenzae*, *Staphylococcus aureus* and *Streptococcus pneumoniae* being the most common. Compared to those without a bacterial infection, children infected with these pathogens were between 3 and 39 times more likely to be admitted to the ICU ($p<0.001$). In addition, children with RSV were more than four times more likely to

Table 1. Demographic and clinical characteristics of the study population.

	Admitted to ICU (n = 158)	Admitted to ward (n = 576)	p Value	OR (95% CI)
Age (days)	69 (35–149)	110 (45–210)	<0.001	^a
Male gender	57% (n = 90)	56% (n = 322)	0.88	1.0 (0.7–1.5)
Race/Ethnicity				
Caucasian	41% (n = 64)	43% (n = 246)	0.69	0.9 (0.6–1.3)
African-American	11% (n = 17)	9% (n = 54)	0.71	1.2 (0.7–2.1)
Hispanic	32% (n = 51)	35% (n = 202)	0.58	0.9 (0.6–1.3)
Other/Unknown	17% (n = 26)	13% (n = 74)	0.30	1.3 (0.8–2.2)
Medical Conditions				
Prematurity	34% (n = 54)	24% (n = 137)	0.01	1.7 (1.1–2.4)
Gestational age (weeks)	33 (28–36)	34 (32–36)	0.02	^a
Apnea	22% (n = 35)	5% (n = 30)	<0.001	5.2 (3.1–8.8)
Prior Wheeze	5% (n = 8)	11% (n = 62)	0.045	0.4 (0.2–0.9)
Reflux	12% (n = 19)	11% (n = 64)	0.86	1.1 (0.6–1.9)
Previously healthy	43% (n = 68)	55% (n = 317)	0.01	0.6 (0.4–0.9)
Viral and Bacterial Pathogens				
RSV	89% (n = 140)	75% (n = 429)	<0.001	2.7 (1.6–4.5)
Haemophilus influenzae	10% (n = 15)	0% (n = 0)	<0.001	^a
Staphylococcus aureus	6% (n = 10)	<1% (n = 1)	<0.001	38.9 (4.9–305.9)
Streptococcus pneumoniae	4% (n = 7)	<1% (n = 1)	<0.001	26.7 (3.3–218.3)
Other bacterial pathogens	13% (n = 21)	2% (n = 9)	<0.001	9.7 (4.3–21.6)

^aOR cannot be calculated.

Table 2. Respiratory treatments.

	Admitted to ICU (n = 158)	Admitted to Ward (n = 576)	p Value	OR (95% CI)
Albuterol	73% (n = 115)	41% (n = 236)	<0.001	3.9 (2.6–5.7)
Chest physiotherapy	72% (n = 114)	14% (n = 78)	<0.001	16.5 (10.8–25.2)
Hypertonic saline	42% (n = 66)	8% (n = 45)	<0.001	8.5 (5.5–13.1)
Intermittent percussive ventilation	15% (n = 23)	0% (n = 0)	<0.001	^a
Inhaled corticosteroids	8% (n = 12)	7% (n = 38)	0.79	1.2 (0.6–2.3)
Systemic corticosteroids	18% (n = 29)	11% (n = 64)	0.02	1.8 (1.1–2.9)
High-flow nasal cannula	8% (n = 13)	0% (n = 0)	<0.001	^a
Non-invasive positive pressure	61% (n = 97)	0% (n = 0)	<0.001	^a
Mechanical ventilation	47% (n = 74)	0% (n = 0)	<0.001	^a

^aOR cannot be calculated.

have a bacterial co-infection than those without RSV (OR 4.3; 95% CI 1.3–14.1; $p = 0.02$).

In children admitted to the ICU, infection with RSV was not associated with intubation and mechanical ventilation; however, children infected with *H. influenzae*, *S. aureus*, *S. pneumoniae*, and other bacterial pathogens were significantly more likely to be intubated compared to those without these bacterial infections (OR 13.6; 95% CI 4.5–41.2; $p < 0.001$). Additionally, although 41% ($n = 30$) of intubated children had a bacterial infection, these pathogens were not associated with a significant increase in the duration of mechanical ventilation in this population.

The use of respiratory treatments was widespread among patients hospitalized with bronchiolitis, particularly in those admitted to the ICU (Table 2). Within the entire patient population, the most commonly used treatments were albuterol (48%), chest physiotherapy (26%), hypertonic saline (15%), systemic corticosteroids (13%), and non-invasive positive pressure (13%). All of these treatments had significantly higher rates of use in children admitted to the ICU compared to those admitted to the ward ($p < 0.05$) and none of the respiratory therapies were associated with shortened durations of hospitalization. In fact, albuterol, chest physiotherapy, hypertonic saline, intermittent percussive

ventilation, systemic corticosteroids, high-flow nasal cannula, and non-invasive positive pressure were all associated with significantly longer durations of hospitalization in the entire study population ($p < 0.05$). Furthermore, in those patients admitted only to the ward, albuterol, chest physiotherapy and hypertonic saline were all associated with significantly longer lengths of stay ($p < 0.05$).

Discussion

In this large, multi-season study of children hospitalized with bronchiolitis, we found that more than half of all hospitalized children had no previous medical conditions, including 43% of all children admitted to the ICU. Younger children and those with a history of prematurity and apnea were more likely to be admitted to the ICU with severe disease, while previously healthy children and those with a history of prior wheeze were less likely to be admitted to the ICU. These findings replicate what others have found and what the AAP has established as risk factors for severe disease in bronchiolitis [14]. Race/ethnicity, gender, and other chronic medical conditions were not associated with ICU admission in this population. The use of adjunctive respiratory treatments was widespread, particularly in the children admitted to the ICU

where the majority of children received albuterol and/or chest physiotherapy. Bacterial co-infection was also common in children admitted to the ICU.

Several authors have explored clinical factors that are associated with hospitalization in children with bronchiolitis [4,11–13,16], but few have examined factors related to ICU admission [17,18]. Purcell and Fergie conducted a retrospective, single-center study examining hospital course of children hospitalized with RSV infection and risk factors related to ICU admission [17]. Similar to our results, the authors found that patients admitted to the ICU were more likely to have a history of prematurity, age less than 6 weeks and other chronic conditions, including congenital heart disease, neurologic disease, multiple congenital anomalies, and metabolic disease [17]. These findings were consistent with ours, although the study populations are not directly comparable, as Purcell and Fergie included significantly older children (up to 6.5 years of age) that had a higher incidence of chronic diseases than our population [17].

Damore et al. conducted a study examining predictors in the emergency department of factors associated with ICU admission in children less than 2 years of age with bronchiolitis [18]. They, too, found that younger age (less than 2 months) was associated with ICU admission; however, prematurity and previous medical conditions were not found to be significant predictors of ICU admission in this population [18]. However, the authors acknowledged that limited numbers of patients with prematurity may have limited the detection of differences between their two groups [18].

The association between prematurity and young age with ICU admission, but not with intubation or with duration of illness, is interesting. On one hand, the association with ICU admission implies that these factors are related to more severe disease in children with bronchiolitis. However, this severity is not associated with increased risk of mechanical ventilation or with increased length of stay. There are several potential explanations for this. Intubation and duration of hospitalization are tightly correlated. It may be that although these patients require additional monitoring in the ICU, their illness severity does not rise to the level of requiring intubation. Alternatively, since the decision to intubate is multifactorial and subjective, there may be undocumented patient or provider factors that are associated with the decision to intubate and therefore prolong length of stay. Unfortunately, it is difficult to discern these rationales in a retrospective study.

Unsurprisingly, viral infections were common among children admitted with bronchiolitis. The majority of children admitted to both the ICU and the ward were found to be infected with RSV, although children with RSV were almost three times more likely to be admitted to the ICU. This difference in admission location by RSV status was not found in Damore's study, as the authors found no significant difference in admission to the ICU versus ward among children with RSV infection [18]. However, in a 3-year prospective study of infants hospitalized with bronchiolitis, Calvo et al. reported that children with RSV required treatment in the ICU more frequently than those without RSV [19]. Unfortunately, assessment of other viral pathogens, such as human metapneumovirus, was not routinely

performed at the study institution and so we are unable to comment on additional viral infections.

The proportion of children with bronchiolitis and a bacterial co-infection is reported in the literature to range from <1% to 39% [20–23]. In our cohort, 6% ($n = 45$) of the total patient population and 22% ($n = 34$) of children admitted to the ICU were found to have a bacterial co-infection. The presence of a bacterial infection was significantly associated with ICU admission as well as intubation in children in our study. There are relatively few authors who explore this relationship between bacterial infection and severity of illness in children hospitalized with bronchiolitis. Thorburn et al. report in their study of children with RSV who were admitted to the PICU and mechanically ventilated that those with a bacterial co-infection had significantly longer durations of ventilation [24]. Moreover, Flamant et al. examined children with RSV bronchiolitis who required mechanical ventilation or extracorporeal membrane oxygenation (ECMO) support and found that those with a positive tracheal aspiration bacterial culture had significantly longer durations of mechanical ventilation [25]. While we failed to find an association between bacterial infection and duration of mechanical ventilation in our study, our results intimate that bacterial co-infection adds to the severity of illness in children with bronchiolitis.

This is the only study to our knowledge that provides a comprehensive summary of respiratory treatments received by children hospitalized with bronchiolitis. Current American Academy of Pediatrics Guidelines recommend against routine use of these therapies and as a result, frequency of routinely used treatments has declined in children with bronchiolitis [14,26]. However, in our population of critically ill children with bronchiolitis, frequency of these adjunctive treatments such as albuterol, chest physiotherapy and hypertonic saline remains high. This prevalence suggests that these therapies continue to be used routinely in the ICU setting, despite lack of evidence basis, perhaps due to perceived benefit. We found that children admitted to the ICU were significantly more likely than those admitted to the ward to receive respiratory therapies. The difference in treatment between the two groups was not surprising; however, it is interesting to note that none of these therapies were associated with shortened durations of hospitalization. In fact, all of the respiratory therapies examined were associated with significantly longer durations of hospitalization in the entire study population and in patients admitted only to the ward, albuterol, chest physiotherapy and hypertonic saline were all associated with significantly longer lengths of stay. This may provide further evidence of their lack of appropriateness for routine use in this population.

Several limitations exist in this study. The findings presented were the experience of a single center and therefore, may not be generalizable to all institutions. Second, due to the retrospective nature of our study, we were limited to data that was available in the medical record for clinical purposes only. While we are not aware of any significant changes in hospital practice or staffing over the study period, it is possible that such a change existed that may have impacted the results.

Another potential criticism of our study is that all infants with bronchiolitis were included, not just those with

diagnosed-RSV infection. We chose to include these infants in our study design since tests for RSV are not 100% sensitive and to make the study more generalizable. However, when we excluded from analysis those infants without identified RSV illness, young age and prematurity remained independent risk factors for ICU admission. Furthermore, we chose to include all children admitted to the hospital with bronchiolitis, even those with serious chronic conditions. Nonetheless, in an analysis excluding these patients, all of our results remained the same, except that prematurity was no longer significantly associated with ICU admission (20% of those admitted to the ICU were premature versus 18% of those admitted to the ward; $p = 0.67$).

An additional limitation of our study is that previous history of prior wheeze, apnea and other medical conditions were determined from parental report, which had the potential to introduce bias due to subjectivity. Finally, viral and bacterial tests were not performed on all children in this cohort, but only if felt to be clinically indicated by the attending physician. In those children with positive results, we did not have data on previous cultures. Therefore, some of these children may have been previously or chronically infected. We also did not have data on the total number of cultures performed (i.e. negative cultures), so estimating the overall frequency of positive cultures is not possible. This is a significant limitation to our study and may have impacted the results as well as the reported incidence of these infections in this population.

Conclusions

In summary, children with no identifiable risk factors for severe illness make up a relatively large percentage of those admitted for acute bronchiolitis. Among those with bronchiolitis, younger children and those with a history of prematurity and apnea were more likely to be admitted to the ICU with severe disease, while previously healthy children and those with a history of prior wheeze were less likely to be admitted to the ICU. These findings suggest that prematurity, apnea and young age may be associated with an increased risk of more severe disease, but not necessarily with a slower recovery. Additionally, the use of therapies such as albuterol and chest physiotherapy remained widespread, particularly in the ICU setting, despite lack of evidence of their efficacy. Further exploration is needed to validate these findings at different institutions.

Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the article.

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