

# Caffeine in bronchiolitis associated apnea: A retrospective cohort study

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**Abstract.** Young infants with bronchiolitis commonly present with apnea. Caffeine is effective in treating apnea of prematurity and has been used to treat apnea associated with bronchiolitis.

To evaluate whether caffeine administration to infants presenting with apnea in the setting of bronchiolitis was associated with a decreased rate of endotracheal intubation and mechanical ventilation, compared to infants who did not receive caffeine. Retrospective cohort study.

University affiliated tertiary care children's hospital. Twenty-eight infants less than 3 months of age, 13 of whom received caffeine. Fewer infants who received caffeine required endotracheal intubation and invasive mechanical ventilation (OR = 0.30 95% CI 0.07 to 1.4,  $p = 0.15$ ), but this was not statistically significant. Infants who received caffeine were more likely to be treated with non-invasive ventilation than infants in the control group (OR = 14; 95% CI 2.1 to 98  $p = 0.01$ ). Only one patient who was initially managed with non-invasive ventilation was subsequently intubated. There was no difference in the duration of total respiratory support, duration of invasive mechanical ventilation, hospital and pediatric critical care unit stay. All infants survived. This study does not provide adequate evidence to support or refute the routine use of caffeine in bronchiolitis associated apnea.

Keywords: Bronchiolitis, apnea, caffeine, respiratory syncytial virus, mechanical ventilation, critical care

## 1. Introduction

Acute viral bronchiolitis is one of the most common causes of respiratory disease in young children, and is responsible for 17 to 31 hospitalizations per 1000 person-years among children less than one year of age [1,2]. Ten to 15% of those who are hospitalized require admission to a pediatric intensive care unit for progressive respiratory failure, sepsis or apnea [3]. As many as 25% of these infants present with apnea [4]. Age less than one month is the primary independent

risk factor for bronchiolitis associated apnea [5]. The presence of apnea increases the relative risk for mechanical ventilation by more than six fold in children with bronchiolitis [4]. Suggested pathophysiologic mechanisms for bronchiolitis associated apnea include airway obstruction due to secretions, altered laryngeal chemoreceptor sensitivity, a direct effect of respiratory syncytial virus, and increased severity of illness and resultant hypoxemia [6–9].

Current management of apnea is primarily supportive and hence the role of respiratory stimulants such as caffeine and other methylxanthines in the setting of bronchiolitis has been explored. It has been suggested that caffeine may be a safe adjunctive treatment modality for these infants, particularly in centres that do not have pediatric intensive care unit support.

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Caffeine is effective in reducing the severity and need for mechanical ventilation in apnea of prematurity [10]. It has also been shown to reduce the episodes of desaturation in infants with postanesthetic apnea [11]. Current published data on the use of methylxanthines to treat bronchiolitis associated apnea is limited to four case reports totaling 13 infants (ten of whom received caffeine, two aminophylline and one theophylline) [12–15]. These reports suggest that caffeine may reduce the severity of apnea in this setting; all infants successfully avoided intubation. We found no comparative observational studies or clinical trials of caffeine use in this population. The objective of this retrospective cohort study was to evaluate whether caffeine administration to infants presenting with apnea in the setting of bronchiolitis was associated with a decreased rate of endotracheal intubation and mechanical ventilation, compared to infants who did not receive caffeine.

## 2. Methods

### 2.1. Study design and patient selection

Infants three months or less corrected age, who were admitted to McMaster Children's Hospital between January 2003 and April 2007, with a diagnosis of bronchiolitis and clinically significant episodes of apnea, were eligible for inclusion into this study. Patients were identified through the hospital's health records and Pediatric Critical Care Unit (PCCU) databases. Clinically significant apnea was defined as apnea requiring intervention such as physical stimulation, oxygen therapy, positive pressure ventilation or consultation with the Pediatric Critical Care service. We excluded infants if apnea was attributed to causes other than bronchiolitis, and patients who received caffeine within five days prior to admission. Two reviewers applied the eligibility criteria and extracted data for included infants using a standardized case report form. Within this cohort, infants who received caffeine were compared to controls that did not. This study was approved by the Hamilton Health Sciences/McMaster University Faculty of Health Sciences Research Ethics Board. The primary outcome was the rate of endotracheal intubation and mechanical ventilation. Secondary outcomes included the length of PCCU, length of hospital stay, duration of mechanical ventilation, and the total duration of respiratory support. We defined respiratory support as the need for either invasive, non-invasive ventilation (NIV), or oxygen therapy.

### 2.2. Statistical methods

We used SPSS, version 13.0 (SPSS, Chicago, IL) to perform the statistical analyses. For comparing outcomes, we used the Fisher's exact test for categorical variables and Mann-Whitney U tests for continuous variables. All tests were two-sided and we considered  $p$  values of  $\leq 0.05$  to be statistically significant.

## 3. Results

We included all twenty-eight infants who fulfilled all eligibility criteria, 13 of whom received caffeine. As shown in Table 1, the baseline characteristics of these two groups were similar. Eight of the 13 infants received a single dose of caffeine (median 10 mg/kg, range 6.7 to 11.4 mg/kg). The remaining five infants received a median maintenance dose of 2.5 mg/kg (range 1.9 to 3.4 mg/kg) once daily for a median of three days (range two to eight days). As shown in Table 2 fewer infants in the caffeine group required endotracheal intubation and invasive mechanical ventilation (OR = 0.30 95% CI 0.07 to 1.4,  $p = 0.15$ ), but this was not statistically significant. Infants who received caffeine were more likely to be treated with non-invasive ventilation than infants in the control group (OR = 14; 95% CI 2.1 to 98,  $p = 0.01$ ). Only one patient (in the caffeine group) who was initially managed with NIV was subsequently intubated. There was no statistical difference in the duration of total respiratory support, duration of invasive mechanical ventilation, hospital and PCCU stay. No adverse effects were reported and all infants survived. We were unable to assess any potential effect of dose or duration of treatment on any of these outcomes because of the small number of infants in each of these subgroups.

## 4. Discussion

In this retrospective cohort study of young infants with bronchiolitis associated apnea, there was a non-significant trend towards a reduction in intubation and mechanical ventilation in infants who were treated with caffeine. This trend however, was offset by a significantly greater proportion of NIV use in caffeine treated infants. There are several possible explanations for this result: caffeine may have reduced the severity of apneas, enabling these infants to be managed with NIV rather than invasive ventilation. Alternatively, physician bias

Table 1  
Baseline characteristics of the bronchiolitis study population

Characteristics	Infants who received caffeine (n = 13)	Control (n = 15)	P
Post-natal age (weeks) *	3.0 (2–8)	4.28 (2–11)	0.031
Gestational age at birth (weeks) *	38 (29–40)	37 (30–40)	0.981
Admission weight (kg) *	3 (2.5–4. 8)	3.78 (2.6–5.4)	0.062
Males n (%)	7 (54)	7 (47)	1.000
Preterm n (%)	6 (46)	9 (60)	0.705
Pediatric risk of mortality score III on admission **	3 (0–6)	3 (0–6)	1.000
Infants with comorbidities *** n (%)	4 (31)	2 (13)	0.639
Viral respiratory isolates n (%)			0.297
<i>Respiratory syncytial virus</i>	7 (54)	12 (80)	
<i>Parainfluenza</i>	1 (7)	0 (0)	
Bacterial respiratory isolates n (%)			0.206
<i>Hemophilus influenza</i>	1 (7)	0 (0)	
<i>Staphylococcus aureus</i>	1 (7)		

\*Data are expressed as median (minimum-maximum).

\*\*Pediatric risk of mortality score III (17).

\*\*\*Chronic lung disease (2), atrial septal defect (2), tetralogy of Fallot (1), ventricular septal defect (1).

Table 2  
Patient outcomes of the bronchiolitis study population

Outcome *	Infants who received caffeine (n = 13)	Control (n = 15)	P
Invasive mechanical ventilation n (%)	4 (31%)	9 (60%)	0.15
Non-invasive ventilation n (%)	9 (69%)	2 (13%)	0.01
Length of hospital stay (days)	8 (5–16)	8 (2–16)	0.61
Length of pediatric intensive care unit stay (days)	3 (1–10)	7 (1–15)	0.12
Duration of invasive mechanical ventilation (days)	0 (0–9)	2.5 (0–11)	0.12
Duration of non-invasive ventilation (days)	0.2 (0–5)	0 (0–5)	0.01
Duration of respiratory support (days) **	4 (1–9)	6 (1–12)	0.11

\*Data are expressed as median (minimum-maximum) unless otherwise indicated.

\*\*Respiratory support = total duration of oxygen therapy, invasive and/or non-invasive ventilation.

may have influenced the use of caffeine in conjunction with NIV in an attempt to avoid intubation and invasive mechanical ventilation. We also cannot exclude that changing practice patterns over the four year study period had an influence over the rate of NIV and invasive mechanical ventilation use. While it may be tempting to attribute the trend towards shorter duration of respiratory support and PCCU stay to caffeine in this group, it is unclear in this retrospective study whether this is due to the effect of caffeine or the co-intervention (NIV). Current literature suggests that NIV used for acute respiratory failure of other etiologies does not shorten length of stay when compared to invasive mechanical ventilation, but it is unclear if this can be generalized to infants presenting with apnea [16]. Such potential

for bias as well as the small sample size and the limitations of extracting data retrospectively from medical records underscores the major limitations of observational studies in this setting. Nevertheless, this is the largest reported cohort of infants with bronchiolitis associated apnea treated with caffeine to date and is the first published comparative study.

This study does not provide adequate evidence to support or refute the routine use of caffeine in bronchiolitis associated apnea. An adequately powered prospective trial to evaluate the efficacy of caffeine as an adjunct to the management of this condition is required. Such a study must be large enough to control for potential confounders such as the use of NIV and assessment of the safety of caffeine in this setting.

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