The Use of Diuretic in Mechanically Ventilated Children with Viral Bronchiolitis: A Cohort Study

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Abstract

Introduction: Viral bronchiolitis is a leading cause of admissions to pediatric intensive care unit (PICU). A literature review indicates that there is limited information on fluid overload and the use of diuretics in mechanically ventilated children with viral bronchiolitis. This study was conducted to understand diuretic use concerning fluid overload in this population. **Material and methods**: A retrospective cohort study performed at a quaternary children's hospital. The study population consisted of mechanically ventilated children with bronchiolitis, with a confirmed viral diagnosis on polymerase chain reaction (PCR) testing. Children with co-morbidities were excluded. Data collected included demographics, fluid status, diuretic use, morbidity and outcomes. The data were compared between groups that received or did not receive diuretics. **Result**: Of the 224 mechanically ventilated children with confirmed bronchiolitis, 179 (79%) received furosemide on Day 2 of invasive ventilation. Out of these, 72% of the patients received intermittent intravenous furosemide, whereas 28% received continuous infusion. It was used more commonly in patients who had a higher fluid overload. Initial fluid overload was associated with longer duration of mechanical ventilation (median days 6 vs 4, p<0.001) and length of stay (median days 10 vs 6, p<0.001) even with the use of furosemide. Superimposed bacterial pneumonia was seen in 60% of cases and was associated with a higher per cent fluid overload at 24 hours (9.1 vs 6.3, p = 0.003). **Conclusion**: Diuretics are frequently used in mechanically ventilated children with bronchiolitis and fluid overload, with intermittent dosing of furosemide being the commonest treatment. There is a potential benefit of improved oxygenation in these children, though further research is needed to quantify this benefit and any potential harm. Due to potential harm with fluid overload, restrictive fluid strategies may have a potential benefit.

Keywords: furosemide, mechanical ventilation, bronchiolitis

■ Introduction

Viral bronchiolitis is one of the leading causes of unplanned admission to a pediatric intensive care unit (PICU). At least 3% of children under 12 months are hospitalized every year with bronchiolitis, with a respiratory syncytial virus (RSV) being the most common cause [1]. With the growing body of evidence on the deleterious effects of fluid overload in critically ill children, intensivists continuously need to assess volume status and prevent, recognize, and treat fluid overload [2]. The percentage of fluid overload at 48 hours is a predictor of the oxygenation index and the number of required ventilator days in children [3]. Fluid overload is not just the consequence of fluid therapy but also indicative of capillary leakage in critically ill patients [4].

There is also evidence of hypervolemia from a syndrome of inappropriate antidiuretic hormone release in children with viral bronchiolitis [5,6]. Current management strategies may include fluid restriction, diuretic therapy, and renal replacement therapy, depending on the clinical setting. Furosemide is the most common loop diuretic used in clinical practice because of its potency and rapid onset of action [7]. It can be administered intermittently or by continuous intravenous infusion. There are only limited studies on the practice of diuretic administration and the effect of fluid overload in children with bronchiolitis [8,9].

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In the current study, intravenous furosemide in children with bronchiolitis, who required invasive mechanical ventilation, was evaluated. The clinical presentation and outcomes associated with furosemide use were also recorded.

MATERIAL AND METHODS

This single-center retrospective cohort study was conducted on patients admitted to the pediatric intensive care unit at Nemours/Alfred I. duPont Hospital for children, Delaware, USA; a quaternary care freestanding children's hospital; between 1st November 2012 to 31st March 2018. The hospital's Institutional Review Board approved the study protocol with the waiver of informed consent.

Inclusion criteria

All children aged < 2 years admitted to the PICU with a diagnosis of viral bronchiolitis confirmed by polymerase chain reaction (PCR) or rapid antigen testing obtained by nasal swab and requiring respiratory support by invasive mechanical ventilation, were included in the study.

Exclusion criteria

– All children with history or diagnosis congenital heart disease
– Tracheostomy dependency before the admission
– Chronic diuretic therapy before admission
– Those were supported with renal replacement therapy or extracorporeal life support during or before admission.

The electronic medical records were retrieved and reviewed using ICD 9 and 10 codes for patient selection.

Data included age, sex, admission and discharge weights, length of PICU stay. The virus type was identified by PCR or antigen testing from samples taken from all of the intubated children with bronchiolitis. Also, according to the unit protocol to identify any superimposed bacterial infection, mini-BAL (Bronchioalveolar lavage) cultures were harvested in the first 24 hours of admission to the PICU. These cultures were repeated subsequently at the discretion of the PICU's physician. The daily fluid intake and output, and cumulative fluid balance for 24 hours (CFB1) after invasive mechanical ventilation were recorded.

After 24 hours of mechanical ventilation (FO1), the percentage of fluid overload was calculated based on FO = (mL fluid in – mL fluid out from PICU admission)/ PICU admission weight in kg x 100% [10]. Enteral intake, intravenous fluid, medication infusions, and blood products were included in the calculation of CFB1.

Data regarding diuretic use included the type of diuretic, diuretic dosing, the number of days when diuretics were administered after the initiation of mechanical ventilation, the frequency of administration, and duration of use.

Mechanical ventilator parameters collected included initial fraction of inspired oxygen ratio (FiO2) and initial positive end-expiratory pressure (PEEP). Oxygen saturation and the fraction of inspired oxygen ratio (SpO2/FiO2, S/F) was calculated for each patient upon initiation of mechanical ventilation and before and 24 hours after furosemide initiation.

Laboratory data collected included blood urea nitrogen (BUN), serum creatinine, and bicarbonate (HCO3) before and 24 hours after initiation of intravenous furosemide. Additional data collected included demographic characteristics, admission diagnoses, and the Admission Pediatric Risk of Mortality score (PRISM IV) [11].

The study population was subdivide based on furosemide administration doses and regimes. Patients who received diuretics were identified as Group F, and those who did not receive diuretics were classified as Group N. Both groups were compared for demographic and clinical variables including age, sex, weight on admission and discharge from ICU, day of initiation of mechanical ventilation, days of mechanical ventilation, cumulative fluid balance in first 24 hours of initiation of mechanical ventilation, initial FiO2 and PEEP, and use of bronchodilator and steroids.

Categorical data expressed as proportions (%) were compared using Fisher's t-test. Continuous data with median and interquartile ranges [IQR] were compared using the Wilcoxon rank-sum test. Univariate and multivariate linear regression analysis on outcome variables was performed.

The significance level was set at α = 0.05.

The statistical analysis was performed using the R Stats Package statistical software version 3.6.1 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Two hundred twenty-four patients were identified for inclusion in this study. Of these patients, 179 (79%) re-

ceived furosemide and were assigned to group F, while 45 (20%) of the patients did not receive diuretic and were assigned to group N.

Demographic and clinical variable comparison between the groups is shown in Table 1.

Groups F and N had 59% and 60% of male patients, respectively (p=1). Patients' median age in Group F and N was similar, four months and five months, respectively (p = 0.42). They also had similar illness severity with comparable median PRISM IV scores of 1 with a range between 1 to 2 for both the groups, (p = 1).

Patients in both groups had undergone tracheal intubation early during PICU admission with an average day of intubation on day 1 of hospitalization with a range of day of intubation between 1 to 2 days. (p = 1).

Furosemide was started early, on median days 2 to 4 after the initiation of mechanical ventilation. Group F required a higher initial FiO2, 0.45 vs. 0.4, (p = 0.014) with no difference in PEEP, median 7 vs. 5 (p = 0.195). There was no difference in admission and discharge weights between the two groups (p = 0.48 and p = 0.58, respectively). The length of stay in the PICU was longer in group F, ten days vs six days (p < 0.001), with a longer duration of mechanical ventilation, six days vs four days (p < 0.001). Group F had higher CFB1 and FO1 at 24 hours (p = 0.03 and p = 0.003, respectively). Aerosolized bronchodilator, 68.7% vs. 51.1 (p = 0.04), and the systemic corticosteroids, methylprednisolone or prednisone, 46.8% vs. 26.4%, (p = 0.03) were also used more in Group F than in Group N.

Intermittent furosemide doses were administered in 72.5% of patients in group F, ranging from 0.5 mg/kg/dose to 1 mg/kg/dose with a maximum of 20 mg/dose. The frequency of intermittent dosing ranged from every 6 hours to every 24 hours. Continuous infusions with doses ranging from 0.05 mg/kg/hour to 0.3 mg/kg/hour were used in 27.5% of Group F.

Table 2 shows the comparison of clinical and laboratory variables before and 24 hours after furosemide initiation. There was no significant difference in CFB1 (Cumulative fluid balance at 24 hours); 849 ml pre vs 807 ml 24 hours post furosemide. (p = 0.47) Similarly, FO1 (Fluid overload percentage at 24 hours) was 14% pre vs 13.8 post use of furosemide (p = 0.59).

There was a statistically significant decrease in FiO2 supplementation, 0.40 vs 0.35 (p = 0.007) 24 hours after starting diuretic therapy, which was also reflected by improved S/F ratios 270 vs 280 (p = 0.03) at this interval. There was no significant PEEP change observed after 24 hours of diuretic therapy, with a median PEEP of 6 and range from 5 to 8, (p = 0.48). There was no significant rise in serum creatinine, median 0.2, (p = 1) or BUN, median 5 (p = 1) 24 hours after starting diuretics; however, there was significant increase in serum bicarbonate during this time (median - 26 vs. 32), (p = < 0.001).

Table 3 shows the microbiologic profile of the patients. The predominant virus causing bronchiolitis in the patient population was RSV (65%, n = 145). Sixty per cent of the patients (n = 135) had bacterial

Table 1. Demographic and epidemiologic characteristics of the two cohort groups

	Group N	Group F	p-value
Sample size (n) 224	45	179	
Males (%)	27 (60)	106 (59.2)	1.0
Age in months [median IQR]	5 [2-12]	4 [2-9]	0.42
PICU LOS in days [median IQR]	6 [4-8]	10 [7-13]	< 0.001
#HD MV [median IQR]	1 [1]	1 [1-2]	1
Duration of MV [median IQR]	4 [3-5]	6 [5-9]	< 0.001
Admission weight in kg [median IQR]	7.7 [4-10]	6.2 [4.2-9.15]	0.48
Discharge weight in kg [median IQR]	7.6 [4-10]	6.10 [4.4-9.2]	0.58
CFB1 in ml [median IQR]	376 [200-700]	573 [298.50-797.25]	0.03
FO1 [median IQR]	6.16 [3.12-8.24]	9.03 [5.29-12.87]	0.003
Initial FiO2 [median IQR]	0.40 [0.35-0.50]	0.45 [0.40-0.55]	0.014
Initial PEEP [median IQR]	5 [5-8]	7 [5-8]	0.195
PRISM IV [median IQR]	1 [1-2]	1 [1-2]	1.0
Bronchodilator (%)	23 (51.1)	123 (68.7)	0.04
Corticosteroids (%)	12 (26.7)	82 (45.8)	0.03

IQR = interquartile range; PICU = pediatric intensive care unit; LOS = length of stay; #HD MV = PICU day for initiation of mechanical ventilation MV = mechanical ventilation; CFB1 = cumulative fluid balance for 24 hours after invasive mechanical ventilation; FO1 = percent fluid overload after 24 hours of mechanical ventilation; FiO2 = fraction of inspired oxygen; PEEP = positive end-expiratory pressure; PRISM IV = Pediatric Risk of Mortality score

Table 2. Pre and post 24 hour clinical and laboratory variables among patients who received intravenous furosemide

N = 179	Pre diuretic	Post diuretic	p-value
CFB in ml [median IQR]	891 [588.50-1263]	807 [565-1368]	0.47
FO per cent [median IQR]	14 [9.30-19.02]	13.87 [10.55-19.06]	0.59
Weight in kg [median IQR]	6.10 [4.4-9.20]	6.55 [4.4-9.40]	0.73
FiO2 [median IQR]	0.45 [0.3-0.45]	0.35 [0.3-0.4]	0.007
PEEP [median IQR]	7 [5-8]	6 [5-8]	0.47
SpO2:FiO2 [median IQR]	270 [214-321]	280 [242-330]	0.034
Serum creatinine [median IQR]	0.2 [0.2-0.3]	0.2 [0.2-0.3]	1.0
Serum blood urea nitrogen [median IQR]	5 [2-7]	5 [3-9]	1.0
Serum bicarbonate [median IQR]	26 [23-29]	32 [28-36]	< 0.001

CFB = cumulative fluid balance; IQR = interquartile range; FO = fluid overload; FiO2 = fraction of inspired oxygen; PEEP = positive end-expiratory pressure; SpO2 = oxygen saturation

Table 3. Viral and bacterial isolate profile

Virus, n = 224 (%)	
RSV	65
Non-RSV	25
2 non-RSV	7
3 or more	3
Bacteria from mini-BAL, n = 135 (%)	
H. influenzae	40
M. catarrhalis	21.5
S. pneumoniae	15
A. streptococcus	4
P. aeruginosa	1.5
S. aureus (MSSA)	1.5
S. aureus (MRSA)	1.5
E. coli	1.5
Acinetobacter	1.5
2 or more organisms	12

RSV = respiratory syncytial virus; mini-BAL = mini bronchoalveolar lavage

Fig. 1. Correlation plot of percent fluid overload after 24 hours of mechanical ventilation (FO1) and duration of mechanical ventilation

Fig. 2. Box plot showing comparison of percent fluid overload after 24 hours of mechanical ventilation (FO1) and pneumonia status in patients

pneumonia isolated from mini bronchoalveolar lavage (mini-BAL) with the predominant organism being H. influenza, which was isolated from 40% of patients.

Figure 1 shows a positive correlation between FO1 and mechanical ventilation duration (Pearson's coefficient 0.17, p = 0.009). Univariate regression analysis showed a small but significant increase in mechanical ventilation duration with higher FO1 (95% CI: 0.024-0.163; p = 0.009).

Patients with pneumonia had a higher FO1 than those without (9.1% vs 6.3%, p = 0.003). Figure 2 shows a box plot of FO1 based on pneumonia status of patients. Univariate and multivariate linear regression analysis of children with bacterial pneumonia showed an increase of 2% fluid overload on average (95% CI: 0.52-3.66, p = 0.01, 0.23-3.36, p = 0.025) compared with those patients who did not have evidence of bacterial pneumonia when controlling for diuretic therapy.
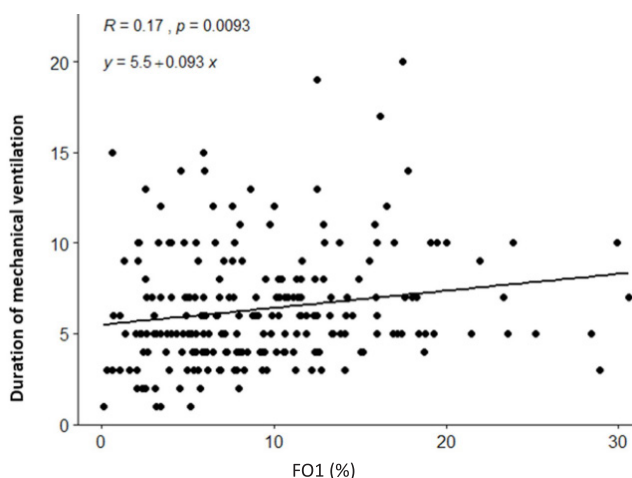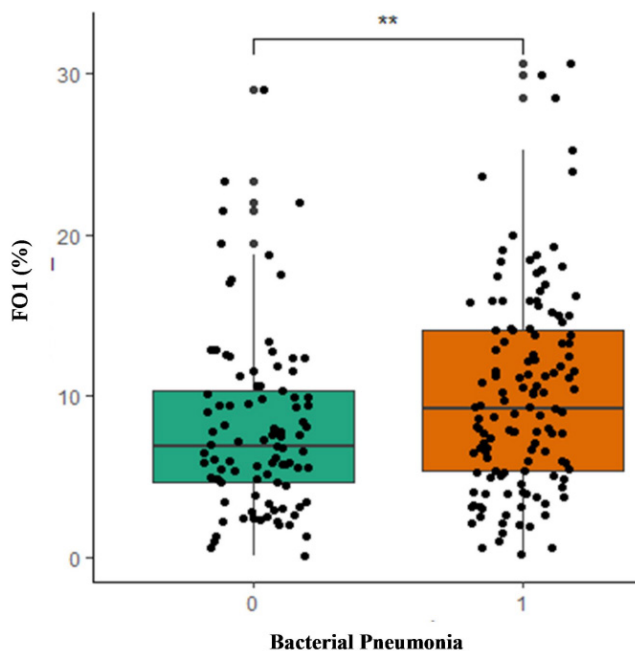
Both intermittent and continuous infusion of furosemide was well tolerated with 4% (n = 7) requiring fluid resuscitation of at least 10 ml/kg crystalloid, and 2% (n = 3) requiring initiation of vasoactive infusion, or those already on vasoactive infusion experienced doubling of their infusion rate for hypotension within six hours of furosemide administration.

◼ DISCUSSION

This study analysed the practice of using intravenous furosemide in children with severe bronchiolitis who required invasive mechanical ventilation. It was observed that most of the patients (79%) received furosemide, with intermittent dosing used in more than 2/3 of the cohort. This practice signifies perceived or actual fluid overload in these populations in the early phase of their illness and physician perception of diuretics' usefulness. Also evaluated was the occurrence and effect of fluid overload and its association with furosemide use and outcomes. It was observed that fluid overload is associated with longer duration of ventilation and PICU stay even with diuretics. A further observation was that secondary bacterial pneumonia in this population is associated with increased fluid overload.

Acute bronchiolitis is a prevalent respiratory infection in infants and young children. Though only 1% require PICU admission or experiencing death from its complications, it remains one of the most common reasons for admission to a PICU [12,13]. The most common virus isolated among patients in the current study was RSV, supported by the literature [14]. Endotracheal intubation rates in critically ill children with bronchiolitis vary widely with rates ranging from 5% to 43% [15]. Children with more than mild disease are often at risk of pediatric acute respiratory distress syndrome (P-ARDS) and more likely to have a longer length of stay in a PICU, increased use of mechanical ventilation, and longer duration of use of supplemental oxygen [16].

A previously published retrospective study looking at patients with respiratory failure from various etiologies showed that severe fluid overload ≥15%, was associated with longer duration of mechanical ventilation and hospitalization [17]. Similarly, a large multicenter trial and a study by Ingelse et al. (2017) evaluated viral bronchiolitis with early fluid overload. They found the fluid overload to be associated with longer mechanical ventilation duration [8,9] Also, worse outcomes have been described in severe sepsis and ARDS with fluid overload in critically ill children [18,19].

The present report adds to the existing literature by showing fluid overload in mechanically ventilated children with severe bronchiolitis is associated with longer mechanical ventilator days and length of stay. It also describes the association of secondary bacterial pneumonia with an increased fluid overload.

Furosemide is the most commonly used loop diuretic in critically ill patients [20]. Studies in pediatrics have shown comparable diuresis when used as regular intermittent bolus dosing and continuous infusion [21,22]. The initiation, dosing and frequency of furosemide in bronchiolitis are not well described in the literature. A randomized controlled trial showed that administering a single dose of furosemide (1 mg/kg) in the emergency department in moderate to severe bronchiolitis did not improve the severity of illness [23]. Studies have looked at furosemide's effect on oxygenation and fluid overload; however, there is limited information on the type, dose, mode, or frequency of diuretic used [8, 9, 24].

This study observed that 79% of children received furosemide between 2 to 4 days after tracheal intubation. This suggests a perception of fluid overload in these populations and a perception of improvement in clinical outcomes with the use of furosemide amongst PICU physicians.

Furosemide was administered mostly in an intermittent form (72.5%). Possible reasons for this include a limitation of intravenous access, a physician's plan for assessing response and limiting medication wastage with infusion formulations. The dose and frequency varied largely from 0.5 mg/kg to 1mg/kg every six hours to 24 hours. They may indicate the physician's discomfort with furosemide use in this population due to limited data and potential side effects. There was dosing variation with infusion formulation, with infusion rates ranging from 0.03 to 0.3 mg/kg/hour, likely due to similar reasons.

The immediate effects of furosemide initiation were studied and was shown to be well tolerated in the present patient cohort. A modest improvement in FiO2 requirement and S/F after just 24 hours of furosemide therapy was observed. The S/F ratio is a reliable non-invasive marker comparable with the P/F ratio, in pediatric acute respiratory distress syndrome [25]. It was also observed that furosemide usage in these settings did not lead to any hemodynamic instability or electrolyte imbalance in this population.

As fluid overload is the primary concern, perhaps adopting protocol-based conservative fluid management and diuretic initiation will help achieve a faster desired fluid balance.

Although variable, secondary bacterial pneumonia has been reported as between 17%-50% in children with mechanical ventilation [26, 27]: the present study rates were slightly higher at 60% and were likely due to universal screening of all intubated patient for bacterial pneumonia with mini-BAL in out PICU. Several studies have shown accurate isolation of bacterial organisms by non-bronchoscopic mini-BAL [28-31]. Patients with superimposed bacterial infections were noted to have higher per cent fluid overload after 24 hours of tracheal intubation. There is increasing evidence that fluid overload is associated with ventilator-associated events in adults and children [30-32]. The present study is the first, based on an extensive review. There was a reported association of increased fluid balance in the presence of superimposed bacterial pneumonia obtained by mini-BAL sample within 24 hours of mechanical ventilation.

∎ CONCLUSIONS

Early management of fluid overload with diuretics in children with viral bronchiolitis requiring mechanical ventilation may help prevent the prolonged need for mechanical ventilation and PICU stay. Early diuretics may help improve oxygenation. Those with bacterial pneumonia may be at higher risk for fluid overload. Conservative fluid strategies and protocol-driven diuretic therapy may help improve patient outcomes.

∎ ACKNOWLEDGEMENTS

∎ CONFLICT OF INTEREST

None to declare.

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