Association of Fluid Overload with Escalation of Respiratory Support and Endotracheal Intubation in Acute Bronchiolitis Patients

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Abstract

Fluid overload has been associated with increased oxygen requirement, prolonged duration of mechanical ventilation, and longer length of hospital stay in children hospitalized with pulmonary diseases. Critically ill infants with bronchiolitis admitted to the pediatric intensive care unit (PICU) also tend to develop fluid overload and there is limited information of its role on noninvasive respiratory support. Thus, our primary objective was to study the association of fluid overload in patients with bronchiolitis admitted to the PICU with respiratory support escalation (RSE) and need for endotracheal intubation (ETI). Infants $\leq$24 months of age with bronchiolitis and admitted to the PICU between 9/2009 and 6/2015 were retrospectively studied. Demographic variables, clinical characteristics including type of respiratory support and need for ETI were evaluated. Fluid overload as assessed by net fluid intake and output (net fluid balance), cumulative fluid balance (CFB) (mL/kg), and percentage fluid overload (FO%), was compared between patients requiring and not requiring RSE and among patients requiring ETI and not requiring ETI at 0 (PICU admission), 12, 24, 36, 48, 72, 96, and 120 hours. One-hundred sixty four of 283 patients with bronchiolitis admitted to the PICU qualified for our study. Thirty-four of 164 (21%) patients required escalation of respiratory support within 5 days of PICU admission and of these 34 patients, 11 patients required ETI. Univariate analysis by Kruskal-Wallis test of fluid overload as assessed by net fluid balance, CFB, and FO% between 34 patients requiring and 130 patients not requiring RSE and among 11 patients requiring ETI and 153 patients not requiring ETI, at 0, 12, 24, 36, 48, 72, 96 and 120 hours did not reveal any significant difference ($p > 0.05$) at any time interval. Multivariable logistic regression analysis revealed higher PRISM score (odds ratio [OR]: 4.95, 95% confidence interval [95% CI]: 1.79–13.66; $p = 0.002$), longer hours on high flow nasal cannula (OR: 4.86, 95% CI: 1.68–14.03; $p = 0.003$) and longer hours on noninvasive ventilation (OR: 11.16, 95% CI: 3.36–36.98; $p < 0.001$) were associated with RSE. Fluid overload as assessed by net fluid balance, CFB, and FO% was not associated with RSE or need for ETI in critically ill bronchiolitis patients admitted to the PICU. Further prospective studies involving larger number of patients with bronchiolitis are needed to corroborate our findings.

Keywords

- bronchiolitis
- fluid overload
- endotracheal intubation
- respiratory support
- pediatric intensive care unit

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Introduction

Fluid therapy is the cornerstone of resuscitation in critically ill children. Early fluid resuscitation has been effective in reducing morbidity and mortality in unstable sick children.[1] Patients continue to receive variable amounts of fluid intake after initial resuscitation that result in net positive fluid balance and fluid overload.[2] Fluid overload has been associated with increased oxygen requirement, prolonged duration of mechanical ventilation, and longer length of hospital stay in pediatric pulmonary diseases like asthma and children receiving mechanical ventilation for pediatric acute respiratory distress syndrome (PARDS).[3–7] There is however, limited information on the role of fluid balances on respiratory support in infants hospitalized with viral bronchiolitis.[8–11]

Viral bronchiolitis is the most common pulmonary disease in infants leading to hospital admission.[12] The mainstay of treatment for infants hospitalized for viral bronchiolitis continues to be supportive care with emphasis on maintaining oxygenation and fluid management.[13–15] Admission of infants with bronchiolitis to the pediatric intensive care unit (PICU) has been steadily rising in the past decade.[16–18] Management of oxygenation in critically ill infants with bronchiolitis in the PICU has however, undergone substantial changes in the same time period with greater usage of noninvasive ventilation.[16–18] Depending on the severity of illness, these patients undergo respiratory support escalation (RSE) from nasal cannula (NC) oxygen therapy to high-flow nasal cannula (HFNC), continuous positive airway pressure support (CPAP) or bi-level positive airway pressure support (BiPAP) before endotracheal intubation (ETI), and initiation of invasive mechanical ventilation.[19–23] Use of noninvasive respiratory support has resulted in a decrease of ETI and invasive mechanical ventilation of these patients in the PICU.[17,19–27] Maintenance of hydration is the second important component in the care of infants with bronchiolitis, with fluid-replacement required in approximately 30% of infants admitted to the hospital.[28] Most guidelines recommend either nasogastric or intravenous fluids to maintain hydration.[13–15] Despite the frequency of its use, the evidence to determine the best route of hydration therapy for infants admitted with bronchiolitis is sparse. After initial fluid resuscitation, critically ill infants hospitalized for bronchiolitis are at risk for the development of fluid overload.[29–32]

An association of fluid overload with increased oxygen requirement and prolonged duration of mechanical ventilation in mechanically ventilated bronchiolitis patients have revealed mixed results.[8–11] Limited studies of infants with bronchiolitis have evaluated the association of fluid overload with the need for ETI and no study has assessed the role of fluid overload with the need for RSE in these patients.[8] Given the current scenario of increased usage of noninvasive ventilation for management of critically ill patients with bronchiolitis in the PICU, we undertook this study to evaluate whether fluid overload had any role in RSE or in ETI in infants with bronchiolitis who were admitted to the PICU.

Material and Methods

The Cleveland Clinic Institutional Review Board approved the study and granted waiver of consent. Bronchiolitis was diagnosed in any infant less than 2 years of age based on history and clinical signs and symptoms including rhinorrhea, cough, tachypnea, and increased respiratory effort in the seasonal period.[13–15] All infants $\leq$24 months of age with bronchiolitis who were admitted to the PICU between September 2009 and June 2015 were retrospectively studied. Criteria for PICU admission included increased work of breathing, inability to maintain oxygen saturation $\geq$90% or requirement of respiratory support $\geq$2 L/min NC oxygen. Exclusion criteria included patients intubated prior to or $<$1 hour of PICU admission, tracheostomy in place, noninvasive or invasive positive pressure ventilation at home, oxygen dependence at baseline, bronchopulmonary dysplasia, congenital heart disease or congestive heart failure, chronic renal disease and any diuretic use at baseline. Data were collected from the hospital electronic medical records (EMR) and Virtual Pediatric Systems. Demographic variables studied were age, gender, race, body weight at PICU admission, origin of patient admission (emergency department, hospital floor or transfer from outside hospital), number of days of illness at the time of PICU admission, and severity of illness (Pediatric Index of Mortality-2 [PIM-2] score, and Pediatric Risk of Mortality [PRISM] score). Clinical characteristics studied were mode of respiratory support at PICU admission (room air [RA], NC, HFNC, noninvasive positive pressure ventilation [NIPPV] which included CPAP and BiPAP, or ETI and invasive mechanical ventilation), time duration (in hours) spent in the PICU on a particular respiratory support, type of viral infection based on nasopharyngeal swab polymerase chain reaction test results, medications administered (albuterol, racemic epinephrine, 3% hypertonic saline solution, systemic steroids and antibiotics), and daily fluid balances.

RSE was defined as escalation from one type to another form of noninvasive respiratory support culminating to ETI and invasive ventilation.[16,17,23] NC oxygen was delivered to a maximal level of 2 L/min, humidified HFNC was administered to a maximal level of 2 L/kg/min of gas flow, CPAP was administered with a pressure ranging between 5 and 8 cm of water, BiPAP was administered with variation in expiratory positive airway pressure and inspiratory positive airway pressure ranging between 5 and 8 cm of water and 10 to 14 cm of water, respectively. The patients underwent escalation of respiratory support from NC oxygen to HFNC followed by CPAP and BiPAP. ETI was generally undertaken for persistent desaturation $<$90% or significantly increased work of breathing or hypercarbia despite noninvasive respiratory support.

Intravenous fluids, enteral and parenteral nutrition, medications, and blood products administered were included for fluid intake assessment. Urine output, gastric output, output from other body cavities, and any blood loss were included for fluid output assessment. Insensible losses were not included in fluid output as they could not be adequately

quantified. Fluid intake and output in milliliters (mL) were assessed at the beginning of PICU admission and continued for up to 5 days. Patients were included for the time period of their PICU stay. Patients discharged from PICU prior to 5 days were studied to the time point they remained in the PICU. Fluid balance was recorded twice daily in the PICU corresponding to hospital-wide change of nursing shifts. Thus, patients requiring or not requiring RSE and ETI were compared in 12 hourly intervals initially at 0, 12, 24, 36, 48, and subsequently at 24 hours intervals at 72, 96, and 120 hours. Fluid balances for each patient were calculated based on previously reported parameters including net fluid balance (intake-output) in mL, percentage fluid overload percentage (FO%), and CFB.[4–6,33] Formulas used to calculate FO% and CFB were as follows[6,33]:

CFB for a given time point = [(Total fluid intake in mL since admission to the given time point) – (Total fluid output in mL since admission to the given time point)]/(PICU admission weight in kg).

FO% = [(Total fluid intake in mL – Total fluid output in mL)/PICU admission weight in kilograms (kg)] × 100.

Data were described using medians and interquartile ranges [IQR] for continuous variables and counts and percentages for categorical variables. Patients who did and did not require RSE and patients who were and were not ETI were compared for demographic and clinical characteristics using nonparametric Kruskal-Wallis tests for continuous and ordinal characteristics and Chi-square or Fisher's exact tests for categorical characteristics. Patients who did and did not require RSE and patients who were and were not ETI were compared for net fluid balances, FO%, and CFB for the first 5 days of PICU admission at 0, 12, 24, 36, 48, 72, 96, and 120 hours using Kruskal-Wallis test. A multivariable logistic regression model for RSE was constructed using a stepwise selection process of risk factors identified to be statistically significant in the univariable analysis model. All tests were two-tailed and performed at a significance level of 0.05. SAS 9.4 software (SAS Institute, Cary, North Carolina, United States) was used for all analyses.

Results

Two hundred and eighty-three infants with acute viral bronchiolitis were admitted to the PICU during the 5-year study period. Of these 283 patients, 119 patients met exclusion criteria (nine patients were ETI prior to PICU admission, two patients had ETI within 1 hour of PICU admission, 56 patients had comorbidities that fulfilled exclusion criteria and 52 patients had incomplete fluid balance data in EMR). One hundred and sixty-four patients were included in our final analysis. The demographic and clinical characteristics of these 164 patients are shown in ►**Table 1**. One hundred and three (59%) patients were Caucasian, 33 (20%) patients were Afro-American, one (1%) patient was Hispanic, and 27 (17%) patients were others. One hundred and eight (66%) patients were admitted from the emergency room, 25 (15%) patients from the hospital floor, and 31 (19%) patients were referrals from outside hospitals. Approximately, half of our patients presented in the first 3 days of their viral infection (day 1 of illness: 7%, day 2 of illness: 18%, day 3 of illness: 24%, >day 3 of illness: 51%). Respiratory syncytial viral (RSV) infection was the most common etiology for bronchiolitis (RSV: 54%, rhinovirus: 15%, human metapneumovirus: 3%, parainfluenza: 2%, adenovirus: 2%, and others: 24%). Thirty-four of 164 (21%) infants with bronchiolitis needed RSE. Seven of 24 (29%) patients in RA, 12 of 63 (19%) patients on NC, 15 of 71 (21%) patients on HFNC, and three of six (50%) patients on NIPPV support at PICU admission required RSE. Of these 34 patients who required RSE, 11 patients needed ETI. All patients had positive fluid balance at PICU admission. There was no significant difference in the epidemiologic and clinical characteristics between 164 patients included in the study and 52 patients that had incomplete fluid balance data in our study (►**Supplementary Table S1**, available in the online version only). Diuretic therapy was used in two of 130 (1.5%) patients who did not require RSE, whereas it was used in six of 34 patients (18%) who underwent RSE. It was however, used in all six of these patients after ETI and initiation of mechanical ventilation. No patient in our study required inotropic support and there was no mortality in our study population.

►**Table 2** reveals the comparison of demographic characteristics of infants with bronchiolitis admitted to the PICU between patients that did and did not require RSE and patients that did and did not require ETI. Female gender and elevated PRISM scores were significantly associated with RSE and the need for ETI. ►**Table 3** reveals the comparison of clinical characteristics of infants with bronchiolitis admitted to the PICU between patients that did and did not require RSE and patients that did and did not require ETI. Patients requiring RSE spent significantly longer hours on HFNC and NIPPV whereas patient requiring ETI spent significantly longer hours on NIPPV, received more racemic epinephrine and antibiotic therapy and were more likely to have RSV type B or rhinovirus infection.

Of the 34 patients requiring RSE, escalation occurred in six patients in the first 12 hours of PICU admission, seven patients in 12 to 24 hours, seven patients in 24 to 36 hours, five patients in 36 to 48 hours, five patients in 48 to 72 hours, three patients in 72 to 96 hours, and two patients in 96 to 120 hours. Comparison of fluid balances as analyzed by net fluid balance in mL, CFB and FO% at these time intervals between patients requiring and not requiring RSE did not reveal any significant differences from admission to 5 days of PICU stay as shown in ►**Table 4** and ►**Supplementary Fig. S1** (available in the online version only). Eleven of 164 (6.7%) patients in the study required ETI and invasive mechanical ventilation. Of these 11 patients, ETI occurred in two patients in first 12 hours of admission, two patients in 12 to 24 hours, two patients in 24 to 36 hours, one patient in 36 to 48 hours, two patients in 48 to 72 hours, one patient in 72 to 96 hours, and one

Table 1 Epidemiologic and clinical characteristics of patients with bronchiolitis included in the study

Variable	Values
Number of patients	164
Demographics:	
Age (months), median [IQR]	4.8 [2.1, 10.9]
Gender (male/female), *n* (%)	97/67 (59/41)
Weight (kg), median [IQR]	7.0 [4.7, 8.7]
Gestational age, median [IQR]	33.5 [32, 35.6]
Respiratory support upon PICU admission, *n* (%)	
RA	24 (15)
NC	63 (38)
HFNC	71 (43)
NIPPV	6 (4)
Escalation of respiratory support, *n* (%)	34 (21)
Need for endotracheal intubation, *n* (%)	11 (6.7)
Hours spent in room air, median [IQR]	0 [0, 8]
Hours spent on NC, median [IQR]	14 [5, 24]
Hours spent on HFNC, median [IQR]	8 [0, 36]
Hours spent on NIPPV median [IQR]	0 [0, 0]
Fluid balance:	
Net fluid balance at PICU admission (mL), median [IQR]	101 [10, 497]
CFB at PICU admission (mL/kg), median [IQR]	14.5 [1.3, 88]
FO% at PICU admission, median [IQR]	1.4 [0.13, 8.8]
Medications	
Albuterol	70 (43)
3% Hypertonic saline	8 (5)
Racemic epinephrine	45 (27)
Steroids	42 (25.6)
Antibiotics	61 (37)
• Rule out sepsis (48 h duration)	22 (13.4)
• Secondary pneumonia	22 (13.4)
• Bacteremia	1 (0)
• Acute otitis media	14 (8.5)
PICU length of stay in days, median [IQR]	1.8 [0.97, 3.0]
PRISM score, median [IQR]	0 [0,0]
PIM 2 score, median [IQR]	−6.3 [−6.4, −6.1]

Abbreviations: %, percentage; CFB, cumulative fluid balance; %FO, percentage fluid overload; HFNC, high flow nasal cannula; IQR, inter-quartile range; *n*, number of patients; NC, nasal cannula oxygen therapy; NIPPV, noninvasive positive pressure ventilation; PICU, pediatric intensive care unit; RA, room air.

patient in 96 to 120 hours. Comparison of fluid balances as analyzed by net fluid balance in mL, CFB and FO% at these time intervals between patients requiring and not requiring ETI did not reveal any significant differences from admission to 5 days of PICU stay as shown in ►**Table 5** and ►**Supplementary Fig. S2** (available in the online version only).

Univariable logistic regression analysis of demographic and clinical risk factors for RSE including gender, PRISM score, hours spent on HFNC, hours spent on NIPPV, antibiotics administration for secondary pneumonia, CFB and % FO at 120 hours revealed that female gender (odds ratio [OR]: 0.289, 95% confidence interval [95% CI]: 0.131–0.637; $p = 0.002$), higher PRISM score (OR: 1.446, 95% CI: 1.148–

Table 2 Comparison of demographic characteristics of patients with bronchiolitis admitted to the PICU requiring and not requiring respiratory support escalation (RSE) and patients requiring and not requiring endotracheal intubation (ETI)

Variables	Patients did not require RSE	Patients required RSE	*p*-Value	Patients did not require ETI	Patients required ETI	*p*-Value
Number of patients	130	34		153	11	
Demographics:						
Age (months)	5.1 [2.2, 10.7][b]	3.9 [2.0,11.0][b]	0.64[c]	5.1 [2.1,11.4][b]	2.5 [1.7, 4.8][b]	0.16[c]
Gender (male/female)	85/45 (65/35)[a]	12/22 (35/65)[a]	0.001[b]	94/59 (61/39)[a]	3/8 (27/73)[a]	0.026[b]
Weight (kg),	7.2 [4.7, 8.7][b]	6.4 [4.4, 8.5][b]	0.44[c]	7.2 [4.8, 8.7][b]	5.8 [3.9, 6.9][b]	0.089[c]
Origin of patients			0.079[d]			0.52[d]
Emergency Department	85 (65)[a]	23 (68)[a]		99 (65)[a]	9 (82)[a]	
Hospital floor	24 (18.5)[a]	1 (3)[a]		25 (16)[a]	0 (0)[a]	
Outside hospital floor	19 (14.6)[a]	9 (26.5)[a]		26 (17)[a]	2 (18)[a]	
Other	2 (1.5)[a]	1 (3)[a]		3 (2)[a]	0 (0)[a]	
Day of illness at admission			0.69[c]			0.72[c]
1 d	8 (6)[a]	4 (12)[a]		10 (6.5)[a]	2 (18)[a]	
2 d	21 (16)[a]	8 (23.5)[a]		27 (17.6)[a]	2 (18)[a]	
3 d	32 (25)[a]	7 (21)[a]		36 (23.5)[a]	3 (27)[a]	
4 d	20 (15)[a]	3 (9)[a]		23 (15)[a]	0 (0)[a]	
5 d	16 (12)[a]	6 (18)[a]		20 (13)[a]	2 (18)[a]	
6 d	9 (7)[a]	3 (9)[a]		11 (7)[a]	1 (9)[a]	
7 d	11 (8.5)[a]	2 (6)[a]		12 (8)[a]	1 (9)[a]	
> 7 d	10 (8)[a]	1 (3)[a]		11 (7)[a]	0 (0)[a]	
Not known	3 (2)[a]	0 (0)[a]		3 (2)[a]	0 (0)[a]	
Severity of illness:						
PRISM score	0 [0,0][b]	0 [0, 3][b]	0.003[c]	0 [0,0][b]	0 [0, 6][b]	0.018[c]
PIM 2 score	−6.3 [−6.4, −6.1][b]	−6.3 [−6.4, −6.1][b]	0.55[c]	−6.3 [−6.4, −6.1][b]	−6.3 [−6.4, −6.2][b]	0.39[c]
PICU length of stay in days	1.5 [0.9, 2.6][b]	3.7 [1.9, 10.2][b]	<0.001[c]	1.7 [0.96, 2.6][b]	11.9 [8.9, 14.6][b]	<0.001[c]

Abbreviations: ETI, endotracheal intubation; PICU, pediatric intensive care unit; RSE, respiratory support escalation.
[a]Number of patients (percentage).
[b]Median [Interquartile range].
[c]Kruskal-Wallis test.
[d]Pearson's Chi-square test.

1.821; $p = 0.002$), longer hours spent on HFNC (OR: 1.012, 95% CI: 1.002–1.023; $p = 0.024$), longer hours spent on NIPPV (OR: 1.024, 95% CI: 1.006–1.043; $p = 0.008$) were significantly associated with RSE. A multivariable logistic regression model for RSE using a stepwise selection process of risk factors identified by the above univariable logistic regression analysis was undertaken. PRISM score, longer hours spent on HFNC, and longer hours spent on NIPPV were classified as categorical values (0 or ≥1). In this model, PRISM score ≥1 (OR: 4.95, 95% CI: 1.79–13.66; $p = 0.002$), longer hours spent on high flow NC ≥1 (OR: 4.86, 95% CI: 1.68–14.03; $p = 0.003$), and longer hours spent on noninvasive positive pressure ventilation ≥1 (OR: 11.16, 95% CI: 3.36–36.98; $p < 0.001$) were significantly associated with RSE.

Discussion

Our study demonstrates a lack of association of fluid overload in the first 5 days of PICU illness as assessed by net fluid balance, CFB, FO% in critically ill infants with bronchiolitis with RSE to noninvasive and invasive mechanical ventilation or the need for ETI.

Severe bronchiolitis is characterized by small airway inflammation resulting in hypoxemia, hypercarbia, and increased work of breathing, all of which respond to the provision of positive pressure.[25] Traditionally, invasive ventilation used to be the cornerstone for delivery of positive pressure to critically ill infants with bronchiolitis in the PICU. However, over the past decade numerous options for

Table 3 Comparison of clinical characteristics of patients with bronchiolitis admitted to the PICU requiring and not requiring respiratory support escalation (RSE) and patients requiring and not requiring endotracheal intubation (ETI)

Variables	Patients did not require RSE	Patients required RSE	*p*-Value	Patients did not require ETI	Patients required ETI	*p*-Value
Number of patients	130	34		153	11	
Clinical characteristics						
Respiratory support at PICU admission			0.44[c]			0.39[c]
Room air	17 (13)[a]	7 (20.6)[a]		22 (14.4)[a]	2 (18.2)[a]	
NC	51 (39)[a]	12 (35)[a]		61 (40)[a]	2 (18)[a]	
HFNC	56 (43)[a]	15 (44)[a]		64 (42)[a]	7 (63.6)[a]	
NIPPV	6 (4.6)[a]	0 (0)[a]		6 (3.9)[a]	0 (0)[a]	
Hours spent in RA	0 [0, 7.5][b]	0 [0, 9][b]	0.81[d]	0 [0,0][b]	0 [0,0][b]	0.35[d]
Hours spent on NC	14 [5, 24][b]	12.5 [3, 18][b]	0.28[d]	14 [5, 24][b]	4 [0, 18][b]	0.063[d]
Hours spent on HFNC	0 [0, 36][b]	23 [7.5, 42][b]	0.008[d]	8 [0, 36][b]	10.5 [1, 34][b]	0.31[d]
Hours spent on NIPPV	0 [0,0][b]	0 [0, 32.5][b]	<0.001[d]	0 [0,0][b]	0 [0, 32][b]	0.011[d]
Viral infection:						
Respiratory syncytial virus type A	66 (50.8)[a]	14 (41.2)[a]	0.32[e]	75 (49)[a]	5 (45.5)[a]	0.82[e]
Respiratory syncytial virus type B	6 (4.6)[a]	4 (11.8)[a]	0.12[e]	7 (4.6)[a]	3 (27.3)[a]	0.002[e]
Influenza A and B	0 (0)[a]	0 (0)[a]		0 (0)[a]	0 (0)[a]	
Parainfluenza 1, 2 and 3	3 (2.3)[a]	0 (0)[a]	0.99[c]	3 (2)[a]	0 (0)[a]	0.99[c]
Human metapneumovirus	3 (2.3)[a]	1 (2.9)[a]	0.99[c]	4 (2.6)[a]	0 (0)[a]	0.99[c]
Rhinovirus	16 (12.3)[a]	8 (23.5)[a]	0.099[e]	20 (13.1)[a]	4 (36.4)[a]	0.035[e]
Adenovirus	1 (0.77)[a]	3 (8)[a]	0.19[c]	3 (2)[a]	1 (9.1)[a]	0.99[c]
Medications						
Albuterol	56 (43.1)[a]	14 (41.2)[a]	0.84[e]	63 (41.2)[a]	7 (63.6)[a]	0.15[e]
Hypertonic saline	6 (4.6)[a]	2 (5.9)[a]	0.76[e]	7 (4.6)[a]	1 (9.1)[a]	0.24[e]
Racemic epinephrine	33 (24.6)[a]	12 (35.3)[a]	0.25[e]	39 (25.5)[a]	6 (54.5)[a]	0.037[e]
Steroids	32 (24.6)[a]	10 (29.4)[a]	0.57[e]	37 (24.2)[a]	5 (45.5)[a]	0.12[e]
Antibiotics						
• Rule out sepsis	14 (10.8)[a]	8 (23.5)[a]	0.052[e]	16 (10.5)[a]	6 (54.5)[a]	<0.001[e]
• Secondary pneumonia	15 (11.5)[a]	7 (20.6)[a]	0.17[d]	18 (11.8)[a]	4 (36.4)[a]	0.021[d]
• Bacteremia	0 (0)[a]	1 (2.9)[a]	0.21[e]	1 (0.65)[a]	0 (0)[a]	0.99[e]
• Acute otitis media	14 (10.8)[a]	0 (0)[a]	0.045[d]	14 (9.2)[a]	0 (0)[a]	0.29[d]

Abbreviations: HFNC, high flow nasal cannula; NC, nasal cannula oxygen therapy; NIPPV, noninvasive positive pressure ventilation; PICU, pediatric intensive care unit; RA, room air.
[a]Number of patients (percentage.
[b]Median [Inter-quartile range].
[c]Fisher's Exact test.
[d]Kruskal-Wallis test.
[e]Pearson's Chi-square test.

respiratory support have become available. Although no strict evidence-based criteria exist, an increasing number of studies have reported early usage of HFNC and noninvasive continuous and bilevel positive airway pressure by various interfaces including nasal prongs or facial masks for the management of infants with bronchiolitis.[16,17,22,23,34] Within noninvasive ventilatory support for infants with bronchiolitis, there has been an increasing trend of HFNC usage over CPAP as the initial support.[17,22,23] This was also seen in our study where HFNC was the most common initial noninvasive respiratory support for infants with bronchiolitis admitted to the PICU. HFNC therapy seems to be beneficial in treating infants with bronchiolitis who do not respond to NC oxygen therapy as also seen in our study.[21,23,25] Potential advantages

Table 4 Comparison of fluid balances of patients with bronchiolitis admitted to the PICU requiring and not requiring respiratory support escalation (RSE)

Variable	Patients did not require RSE ($n = 130$)	Patients required RSE ($n = 34$)	p-Value[a]
	Median [IQR]	Median [IQR]	
At PICU admission			
CFB (mL/kg)	20.2 [1.6, 88.0]	2.1 [−8.8, 48.7]	0.28
Net I/O (mL)	116.5 [14.6, 757.0]	16.0 [−45.0, 462.0]	0.37
FO%	2.0 [0.16, 8.8]	0.21 [−0.88, 4.9]	0.28
At 12 h			
CFB (mL/kg)	24.5 [9.8, 44.3]	24.3 [3.5, 37.6]	0.49
Net I/O (mL)	177.2 [59.0, 355.0]	151.3 [18.0, 284.8]	0.56
FO%	2.4 [0.98, 4.4]	2.4 [0.35, 3.8]	0.49
At 24 h			
CFB (mL/kg)	44.5 [24.1, 68.6]	46.3 [26.1, 67.0]	0.96
Net I/O (mL)	269 [140.0, 455.2]	300 [112.0, 595.1]	0.80
FO%	4.4 [2.4, 6.9]	4.6 [2.6, 6.7]	0.96
At 36 h			
CFB (mL/kg)	64.3 [26.2, 97.8]	63.0 [43.1, 105.8]	0.64
Net I/O (mL)	344.0 [152.0, 668.0]	394.0 [212.0, 730.2]	0.62
FO%	6.4 [2.6, 9.8]	6.3 [4.3, 10.6]	0.64
At 48 h			
CFB (mL/kg)	83.9 [52.1, 128.0]	85.1 [62.9, 111.9]	0.93
Net I/O (mL)	467.0 [287.0, 764.0]	457.0 [314.5, 806.5]	0.94
FO%	8.4 [5.2, 12.8]	8.5 [6.3, 11.2]	0.93
At 72 h			
CFB (mL/kg)	122.3 [84.7, 152.4]	126.7 [101.5, 157.8]	0.86
Net I/O (mL)	590.0 [379.0, 978.0]	675.0 [405.0, 1080.0]	0.65
FO%	12.2 [8.5, 15.2]	12.7 [10.2, 15.8]	0.86
At 96 h			
CFB (mL/kg)	147.8 [119.3, 159.7]	172.4 [136.4, 234.1]	0.74
Net I/O (mL)	780.0 [532.0, 1229.0]	828 [382.0, 1477.0]	0.87
FO%	14.8 [11.9, 16.0]	17.2 [13.6, 23.4]	0.74
At 120 h			
CFB (mL/kg)	217.4 [187.0, 433.4]	199.8 [148.8, 251.0]	0.48
Net I/O (mL)	1,359.8 [760.0, 3,727.0]	1,059.0 [853.0, 1,883.0]	0.78
FO%	21.7 [18.7, 43.3]	20.0 [14.9, 25.1]	0.26

Abbreviations: %, percentage; CFB, cumulative fluid balance; FO%, percentage fluid overload; I, input; IQR, inter-quartile range; kg, kilograms; mL, milliliters; n, number of patients; O, output; PICU, pediatric intensive care unit.
[a]Kruskal-Wallis test.

of HFNC compared with NIPPV include a more comfortable interface, better patient tolerance, reduced risk of gastric insufflation, and low equipment cost.[27,35,36] Although failure rate for individual respiratory support varies in literature depending on the selection of patient population, timing of initiation of the respiratory support, and clinical criteria to define failure, our failure rates were similar to previously reported results.[17,18,21,24,25,37–39] Nineteen percent of infants supported by NC and 21% of patients supported by HFNC in our study required RSE that is similar to previous reports.[21,24,25,37,38] Likewise, infants with bronchiolitis in our study who failed HFNC support and required RSE, 80% patients were successfully managed with noninvasive ventilation and the remaining 20% patients required ETI similar to previous reports.[18,24,39] Increased usage of HFNC and noninvasive ventilation for the management of critically ill infant

Table 5 Comparison of fluid balances of patients with bronchiolitis admitted to the PICU requiring and not requiring endotracheal intubation (ETI)

Variable	Patients did not require ETI ($n = 153$)	Patients required ETI ($n = 11$)	p-Value[a]
	Median [IQR]	Median [IQR]	
At PICU admission			
CFB (mL/kg)	20.2 [1.6, 88.0]	−8.8 [−8.8, −8.8]	0.14
Net I/O (mL)	116.5 [14.6, 497.0]	−45 [−45.0, −45.0]	0.17
FO%	2.0 [0.16, 8.8]	−0.88 [−0.88, −0.88]	0.14
At 12 h			
CFB (mL/kg)	24.5 [10.8, 42.6]	20.5 [−15.4, 28.2]	0.18
Net I/O (mL)	176.0 [62.0, 337.0]	84.0 [−60.0, 267.8]	0.14
FO%	2.5 [1.08, 4.3]	2.0 [−1.5, 2.8]	0.18
At 24 h			
CFB (mL/kg)	46.0 [26.2, 68.1]	18.4 [10.0, 46.7]	0.17
Net I/O (mL)	284.5 [161.0, 511.5]	68.0 [32.0, 308.0]	0.12
FO%	4.6 [2.6, 6.8]	1.8 [1.0, 4.7]	0.17
At 36 h			
CFB (mL/kg)	64.2 [36.2, 100.0]	52.0 [20.4, 112.1]	0.65
Net I/O (mL)	349.0 [163.0, 716.0]	343.0 [61.0, 650.0]	0.51
FO%	6.4 [3.6, 10.0]	5.2 [2.0, 11.2]	0.65
At 48 h			
CFB (mL/kg)	84.8 [57.7, 119.0]	70.4 [45.0, 178.4]	0.54
Net I/O (mL)	468.0 [317.5, 783.0]	322.0 [146.0, 1035.0]	0.38
FO%	8.5 [5.8, 11.9]	7.0 [4.5, 17.8]	0.54
At 72 h			
CFB (mL/kg)	124.7 [97.6, 152.4]	119.0 [108.6, 186.2]	0.93
Net I/O (mL)	654.5 [405.0, 1000.0]	531.5 [304.0, 1080.0]	0.64
FO%	12.5 [9.8, 15.2]	11.9 [10.9, 18.6]	0.93
At 96 h			
CFB (mL/kg)	154.5 [116.3, 213.5]	193.5 [144.6, 244.4]	0.55
Net I/O (mL)	819.0 [532.0, 1,229.5]	929.5 [382.0, 1,698.5]	0.92
FO%	15.5 [11.6, 21.4]	19.3 [14.5, 24.4]	0.55
At 120 h			
CFB (mL/kg)	199.8 [176.7, 330.4]	254.4 [239.7, 251.0]	0.32
Net I/O (mL)	982.0 [760.0, 1,883.0]	1,710.9 [1,456.0, 1,965.7]	0.32
FO%	20.0 [17.7, 33.0]	24.5 [24.0, 25.1]	0.32

Abbreviations: %, percentage; CFB, cumulative fluid balance; FO%, percentage fluid overload; I, input; IQR, inter-quartile range; kg, kilograms; mL, milliliters; n, number of patients; O, output.
[a]Kruskal-Wallis test.

with bronchiolitis resulted in a low incidence (6.7%) of ETI in our patients as has been reported in numerous single center and multicentric studies.[17,19–26,34]

Critically ill infants with bronchiolitis tend to feed inadequately when their respiratory rate exceeds 60 to 70 breaths per minute and have copious nasal secretions.[13] These patients generally receive fluid resuscitation on presentation. This was also seen in our study as critically ill infants with bronchiolitis had positive CFB at the time of PICU admission. Subsequently, fluids are given either intravenously or via nasogastric tubes[13,40] Enteral nutrition delivery in sick infants with bronchiolitis on noninvasive respiratory support remains challenging. Critically ill infants with bronchiolitis are generally administered isotonic

intravenous fluids as nasogastric tubes for enteral feeding tend to increase mucus secretion, cause partial obstruction of the upper airway compromising respiratory function, and there is an increased risk of aspiration of food into the lungs.[40–43] A multicenter study of 759 infants younger than 12 months admitted to hospital with bronchiolitis showed no benefit of enteral feeding over intravenous fluids on rates of admission to intensive-care units, need for ventilatory support, and adverse events did not differ between groups.[44] In our study, infants with bronchiolitis admitted to the PICU who were not enterally fed received isotonic fluids at 80% of daily maintenance.[44] Despite restricting daily fluid delivery in our patients, fluid overload was seen to develop for the first 5 days of their PICU admission. Similar findings have been reported in a study of mechanically ventilated patients with bronchiolitis that revealed no difference in CFB on day 3 between patients randomized to a conservative (<70% of normal intake) or standard (>85% of normal intake) fluid strategy.[45]

Although our study was not designed to study the causality of fluid overload, it is possible that fluid overload in critically ill infants with bronchiolitis was related to elevated levels of antidiuretic hormone (ADH).[28–31] Infants with bronchiolitis have significantly elevated ADH levels in both non-intubated and intubated patients as compared with nonbronchiolitis patients of similar age.[28,30,31] In addition, bronchiolitis is a viral infection-induced inflammation of the airway epithelial cells.[46] Airway epithelial cell injury in bronchiolitis probably does not result in as profound leakage and accumulation of fluid as alveolar epithelial and vascular endothelial damage in PARDS.[47,48] Thus, in comparison to mechanical ventilated patients with PARDS, studies in mechanically ventilated patients with bronchiolitis evaluating association of fluid overload with increased oxygen requirement and prolonged duration of mechanical ventilation have revealed mixed results.[8–11] A retrospective study of bronchiolitis patients admitted to the PICU revealed that a positive fluid balance at 48 hours and 72 hours was not associated with longer duration of invasive mechanical ventilation and PICU stay.[8] Limited studies have evaluated the association of fluid overload with ETI in hospitalized bronchiolitis patients and there are no studies that have evaluated association of fluid overload in patients with bronchiolitis with RSE.[8] One previous study assessing fluid balances for 72 hours in bronchiolitis patients admitted to the PICU reported that patients requiring ETI had a significant positive fluid balance at 48 and 72 hours of PICU admission, but not at 24 hours.[8] These findings are in contrast to our results that reveal fluid overload up to 5 days of PICU stay was not significantly associated with an increased risk of ETI. It is possible that the severity of bronchiolitis illness in the two studies may vary as 24% of their patients underwent ETI as compared with 6.7% in our study.[8] Second, patients in their study achieved neutral balance by day 4 of PICU whereas patients in our study continued to have positive fluid balance on day 5 of PICU. Studies of hospitalized infants with bronchiolitis have reported positive fluid balance ranging from 3 to 7 days in ventilated and nonventilated bronchiolitis patients.[12,22,28] The number of infants with bronchiolitis in our study requiring RSE and ETI are similar to previously reported findings in bronchiolitis patients.[19–21,24,25,37,38] All infants with bronchiolitis in our study developed fluid overload during their PICU stay. There was no difference in fluid overload among infants with bronchiolitis requiring and not requiring RSE or ETI. It is possible that syndrome of inappropriate ADH and predominantly airway epithelial cell injury in viral bronchiolitis may have contributed to fluid overload in this patient population without risk of significant pulmonary edema leading to RSE and ETI. A retrospective study of mechanically ventilated bronchiolitis patients did not reveal any improvement in oxygenation following furosemide administration implying that pulmonary edema may not be a major contributor in patients with bronchiolitis.[49]

Our study had several limitations. It was retrospective and observational in nature that involved common interventions employed over time in the management of bronchiolitis patients in the PICU that makes it prone for bias and cannot always establish a causative relationship. As with any retrospective study of medical records, documentation may have been deficient as seen by incomplete data of 52 patients in our study. However, there was no difference in demographic and clinical features between these 52 excluded patients and 164 patients included in our study. We excluded high risk parameters including bronchopulmonary dysplasia, congenital heart disease, or congestive heart failure, and chronic renal disease from our study population that may have affected our analysis. However, over the past decade, there has been no significant increase in the number of infants with bronchiolitis admitted to the PICU with a comorbidity nor those born prematurely.[17,18] The fluid balance in our PICU patients was recorded as daily fluid intake and output and not on patient's daily weight that is prone to errors.[50,51] We were not able to accurately estimate insensible fluid losses in our study. Limited studies have included fixed insensible fluid losses in assessment of fluid balances for their bronchiolitis patients based on the patients' weight.[8] Bronchiolitis patients however, have varying degrees of work of breathing and respiratory support that may affect their insensible fluid losses. In addition, most of bronchiolitis patients in our study were on HFNC that provides warm and humidified flow of oxygen that may also affect insensible fluid losses. We did not differentiate fluid intake between infants receiving enteral feeds or those receiving intravenous fluids and some of these infants may have been breastfed that makes assessment of fluid intake further difficult. Patients did not have a foley catheter and urinary output may not have been accurately recorded. More objective assessment of fluid balances in children including use of ultrasound and electrical bioimpedance may be valuable in the future once these technologies are validated in children, more so in infants.[52,53] Lastly, the PICU did not have specific guidelines for RSE or need for ETI and these changes were done at the discretion of the clinical team that may have cognitive bias due to variability of individual provider preference and medical decisionmaking.[22]

In summary, fluid overload in critically ill infants with bronchiolitis in the PICU as assessed by net fluid balance, CFB, and FO% did not reveal an association with RSE and the need for ETI. Fluid overload seems to be a common feature of critically ill infants with bronchiolitis in the PICU and it may be related to excessive ADH secretion. Further prospective studies are needed to corroborate our findings and evaluate the mechanisms of fluid overload in these infants.

Conflict of Interest
None declared.

References

1 Davis AL, Carcillo JA, Aneja RK, et al. American College of Critical Care Medicine clinical practice parameters for hemodynamic support of pediatric and neonatal shock. Crit Care Med 2017;45 (06):1061–1093
2 Alobaidi R, Morgan C, Basu RK, et al. Association between fluid balance and outcomes in critically ill children: a systemic review and meta-analysis. JAMA Pediatr 2018;172(03):257–268
3 Kantor DB, Hirshberg EL, McDonald MC, et al. Fluid balance is associated with clinical outcomes and extravascular lung water in children with acute asthma exacerbation. Am J Respir Crit Care Med 2018;197(09):1128–1135
4 Valentine SL, Sapru A, Higgerson RA, et al; Pediatric Acute Lung Injury and Sepsis Investigator's (PALISI) Network Acute Respiratory Distress Syndrome Clinical Research Network (ARDSNet) Fluid balance in critically ill children with acute lung injury. Crit Care Med 2012;40(10):2883–2889
5 Flori HR, Church G, Liu KD, Gildengorin G, Matthay MA. Positive fluid balance is associated with higher mortality and prolonged mechanical ventilation in pediatric patients with acute lung injury. Crit Care Res Pract 2011;2011:854142
6 Arikan AA, Zappitelli M, Goldstein SL, Naipaul A, Jefferson LS, Loftis LL. Fluid overload is associated with impaired oxygenation and morbidity in critically ill children. Pediatr Crit Care Med 2012;13(03):253–258
7 Willson DF, Thomas NJ, Tamburro R, et al; Pediatric Acute Lung and Sepsis Investigators Network. The relationship of fluid administration to outcome in the pediatric calfactant in acute respiratory distress syndrome trial. Pediatr Crit Care Med 2013; 14(07):666–672
8 Flores-González JC, Valladares CM, Yun Castilla C, et al; Bronquiolitis en la Unidad de Cuidados Intensivos Pediátricos (BRUCIP) WorkGroup. Association of fluid overload with clinical outcomes in critically ill children with bronchiolitis. Bronquiolitis en la Unidad de Cuidados Intensivos Pediatricos (BRUCIP) study. Pediatr Crit Care Med 2019;20(03):e130–e136
9 Ferlini R, Pinheiro FO, Andreolio C, Carvalho PR, Piva JP. Characteristics and progression of children with acute viral bronchiolitis subjected to mechanical ventilation. Rev Bras Ter Intensiva 2016; 28(01):55–61
10 Mitting RB, Peshimam N, Lillie J, et al. Invasive mechanical ventilation for acute viral bronchiolitis: retrospective multicenter cohort study. Pediatr Crit Care Med 2021;22(03):231–240
11 Ingelse SA, Wiegers HM, Calis JC, van Woensel JB, Bem RA. Early fluid overload prolongs mechanical ventilation in children with viral-lower respiratory tract disease. Pediatr Crit Care Med 2017; 18(03):e106–e111
12 Jain S, Williams DJ, Arnold SR, et al; CDC EPIC Study Team. Community-acquired pneumonia requiring hospitalization among U.S. children. N Engl J Med 2015;372(09):835–845
13 Ralston SL, Lieberthal AS, Meissner HC, et al; American Academy of Pediatrics. Clinical practice guideline: the diagnosis, management, and prevention of bronchiolitis. Pediatrics 2014;134(05): e1474–e1502
14 Friedman JN, Rieder MJ, Walton JMCanadian Paediatric Society, Acute Care Committee, Drug Therapy and Hazardous Substances Committee. Bronchiolitis: Recommendations for diagnosis, monitoring and management of children one to 24 months of age. Paediatr Child Health 2014;19(09):485–498
15 Bronchiolitis in children: diagnosis and management. National Institute for Health and Care Excellence. NICE guideline; June 01, 2015. Accessed on August 7, 2021 at: https://www.nice.org.uk/Guidance/NG9
16 Pelletier JH, Au AK, Fuhrman D, Clark RSB, Horvat C. Trends in bronchiolitis ICU admissions and ventilation practices: 2010–2019. Pediatrics 2021;147(06):e202003915
17 Schlapbach LJ, Straney L, Gelbart B, et al; Australian & New Zealand Intensive Care Society (ANZICS) Centre for Outcomes & Resource Evaluation (CORE) and the Australian & New Zealand Intensive Care Society (ANZICS) Paediatric Study Group. Burden of disease and change in practice in critically ill infants with bronchiolitis. Eur Respir J 2017;49(06):1601648
18 Linssen RS, Bem RA, Kapitein B, et al; PICE Study Group. Burden of respiratory syncytial virus bronchiolitis on the Dutch pediatric intensive care units. Eur J Pediatr 2021 (e-pub ahead of print). Doi: 10.1007/s00431-021-04079-y
19 Ganu SS, Gautam A, Wilkins B, Egan J. Increase in use of noninvasive ventilation for infants with severe bronchiolitis is associated with decline in intubation rates over a decade. Intensive Care Med 2012;38(07):1177–1183
20 Fujiogi M, Goto T, Yasunaga H, et al. Trends in bronchiolitis hospitalizations in the United States: 2000–2016. Pediatrics 2019;144(06):e20192614
21 Clayton JA, McKee B, Slain KN, Rotta AT, Shein SL. Outcomes of children with bronchiolitis treated with high-flow nasal cannula or noninvasive positive pressure ventilation. Pediatr Crit Care Med 2019;20(02):128–135
22 Soshnick SH, Carroll CL, Cowl AS. Increased use of noninvasive ventilation associated with decreased use of invasive devices in children with bronchiolitis. Crit Care Explor 2019;1(08):e0026
23 Fainardi V, Abelli L, Muscarà M, Pisi G, Principi N, Esposito S. Update on the role of high-flow nasal cannula in infants with bronchiolitis. Children (Basel) 2021;8(02):66
24 Essouri S, Laurent M, Chevret L, et al. Improved clinical and economic outcomes in severe bronchiolitis with pre-emptive nCPAP ventilatory strategy. Intensive Care Med 2014;40(01):84–91
25 Schibler A, Pham TM, Dunster KR, et al. Reduced intubation rates for infants after introduction of high-flow nasal prong oxygen delivery. Intensive Care Med 2011;37(05):847–852
26 Franklin D, Babl FE, Schlapbach LJ, et al. A randomized trial of high-flow nasal oxygen therapy in infants with bronchiolitis. N Engl J Med 2018;378(12):1121–1131
27 Yurtseven A, Turan C, Erseven E, Saz EU. Comparison of heated humidified high-flow nasal cannula flow rates (1-L·kg·min^{-1} vs 2-L·kg·min^{-1}) in the management of acute bronchiolitis. Pediatr Pulmonol 2019;54(06):894–900
28 Johnson DW, Adair C, Brant R, Holmwood J, Mitchell I. Differences in admission rates of children with bronchiolitis by pediatric and general emergency departments. Pediatrics 2002;110(04):e49
29 Daneshmand KA, Zaritsky AL, Lamb MA, et al. Plasma concentration of N-terminal pro-brain natriuretic peptides and fluid balance in children with bronchiolitis. J Pediatr Intensive Care 2012; 1:143–151
30 Poddar U, Singhi S, Ganguli NK, Sialy R. Water electrolyte homeostasis in acute bronchiolitis. Indian Pediatr 1995;32(01):59–65
31 Gozal D, Colin AA, Jaffe M, Hochberg Z. Water, electrolyte, and endocrine homeostasis in infants with bronchiolitis. Pediatr Res 1990;27(02):204–209
32 van Steensel-Moll HA, Hazelzet JA, van der Voort E, Neijens HJ, Hackeng WH. Excessive secretion of antidiuretic hormone in

infections with respiratory syncytial virus. Arch Dis Child 1990; 65(11):1237–1239
33 Goldstein SL, Currier H, Graf Cd, Cosio CC, Brewer ED, Sachdeva R. Outcome in children receiving continuous venovenous hemofiltration. Pediatrics 2001;107(06):1309–1312
34 Pham H, Thompson J, Wurzel D, Duke T. Ten years of severe respiratory syncytial virus infections in a tertiary paediatric intensive care unit. J Paediatr Child Health 2020;56(01):61–67
35 Nishimura M. High-flow nasal cannula oxygen therapy in adults. J Intensive Care 2015;3(01):15
36 Sarkar M, Sinha R, Roychowdhoury S, et al. Comparative study between noninvasive continuous positive airway pressure and hot humidified high-flow nasal cannulae as a mode of respiratory support in infants with acute bronchiolitis in pediatric intensive care unit of a tertiary hospital. Indian J Crit Care Med 2018;22 (02):85–90
37 Kepreotes E, Whitehead B, Attia J, et al. High-flow warm humidified oxygen versus standard low-flow nasal cannula oxygen for moderate bronchiolitis (HFWHO RCT): an open, phase 4, randomised controlled trial. Lancet 2017;389(10072):930–939
38 Milési C, Essouri S, Pouyau R, et al; Groupe Francophone de Réanimation et d'Urgences Pédiatriques (GFRUP) High flow nasal cannula (HFNC) versus nasal continuous positive airway pressure (nCPAP) for the initial respiratory management of acute viral bronchiolitis in young infants: a multicenter randomized controlled trial (TRAMONTANE study). Intensive Care Med 2017;43 (02):209–216
39 Habra B, Janahi IA, Dauleh H, Chandra P, Veten A. A comparison between high-flow nasal cannula and noninvasive ventilation in the management of infants and young children with acute bronchiolitis in the PICU. Pediatr Pulmonol 2020;55(02):455–461
40 Florin TA, Plint AC, Zorc JJ. Viral bronchiolitis. Lancet 2017;389 (10065):211–224
41 Korppi M. Therapeutic strategies for pediatric bronchiolitis. Expert Rev Respir Med 2019;13(01):95–103
42 Stocks J. Effect of nasogastric tubes on nasal resistance during infancy. Arch Dis Child 1980;55(01):17–21
43 Khoshoo V, Edell D. Previously healthy infants may have increased risk of aspiration during respiratory syncytial viral bronchiolitis. Pediatrics 1999;104(06):1389–1390
44 Oakley E, Borland M, Neutze J, et al; Paediatric Research in Emergency Departments International Collaborative (PREDICT) Nasogastric hydration versus intravenous hydration for infants with bronchiolitis: a randomised trial. Lancet Respir Med 2013;1(02):113–120
45 Ingelse SA, Geukers VG, Dijsselhof ME, Lemson J, Bem RA, van Woensel JB. Less is more - a feasibility study of fluid strategy in critically ill children with acute respiratory tract infection. Front Pediatr 2019;7:496
46 Meissner HC. Viral bronchiolitis in children. N Engl J Med 2016; 374(01):62–72
47 Ware LB, Matthay MA. The acute respiratory distress syndrome. N Engl J Med 2000;342(18):1334–1349
48 Ware LB, Matthay MA. Alveolar fluid clearance is impaired in the majority of patients with acute lung injury and the acute respiratory distress syndrome. Am J Respir Crit Care Med 2001;163(06): 1376–1383
49 Kulkarni M, Slain KN, Rotta AT, Shein SL. The effects of furosemide on oxygenation in mechanically ventilated children with bronchiolitis. J Pediatr Intensive Care 2020;9(02):87–91
50 Bontant T, Matrot B, Abdoul H, et al. Assessing fluid balance in critically ill pediatric patients. Eur J Pediatr 2015;174(01):133–137
51 Wise LC, Mersch J, Racioppi J, Crosier J, Thompson C. Evaluating the reliability and utility of cumulative intake and output. J Nurs Care Qual 2000;14(03):37–42
52 Fu Q, Chen Z, Fan J, et al. Lung ultrasound methods for assessing fluid volume change and monitoring dry weight in pediatric hemodialysis patients. Pediatr Nephrol 2021;36(04):969–976
53 Saunders CE. The use of transthoracic electrical bioimpedance in assessing thoracic fluid status in emergency department patients. Am J Emerg Med 1988;6(04):337–340