Early Fluid Overload Prolongs Mechanical Ventilation in Children With Viral-Lower Respiratory Tract Disease*

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Objectives: Viral-lower respiratory tract disease is common in young children worldwide and is associated with high morbidity. Acute respiratory failure due to viral-lower respiratory tract disease necessitates PICU admission for mechanical ventilation. In critically ill patients in PICU settings, early fluid overload is common and associated with adverse outcomes such as prolonged mechanical ventilation and increased mortality. It is unclear, however, if this also applies to young children with viral-lower respiratory tract disease induced acute respiratory failure. In this study, we aimed to investigate the relation of early fluid overload with adverse outcomes in mechanically ventilated children with viral-lower respiratory tract disease in a retrospective dataset.

Design: Retrospective cohort study.

Setting: Single, tertiary referral PICU.

Patients: One hundred thirty-five children (< 2 yr old) with viral-lower respiratory tract disease requiring mechanical ventilation admitted to the PICU of the Academic Medical Center, Amsterdam between 2008 and 2014.

Interventions: None.

Measurements and Main Results: The cumulative fluid balance on day 3 of mechanical ventilation was compared against duration of mechanical ventilation (primary outcome) and daily mean oxygen saturation index (secondary outcome), using uni- and multivariable linear regression. In 132 children, the mean cumulative fluid balance on day 3 was + 97.9 (49.2) mL/kg. Higher cumulative fluid balance on day 3 was associated with a longer duration of mechanical ventilation in multivariable linear regression ($\beta = 0.166$; $p = 0.048$). No association was found between the fluid status and oxygen saturation index during the period of mechanical ventilation.

Conclusions: Early fluid overload is an independent predictor of prolonged mechanical ventilation in young children with viral-lower respiratory tract disease. This study suggests that avoiding early fluid overload is a potential target to reduce duration of mechanical ventilation in these children. Prospective testing in a clinical trial is warranted to support this hypothesis. (*Pediatr Crit Care Med* 2017; 18:e106–e111)

Key Words: bronchiolitis; children; critical illness; fluid overload; respiratory insufficiency

Acute-lower respiratory tract disease (LRTD) is common in young children. It is most often caused by viral infection, most notably respiratory syncytial virus (RSV). Annually, almost 3.5 million children under 5 years old need to be admitted to the hospital with RSV-induced LRTD worldwide (1). Severe LRTD frequently leads to acute respiratory failure (ARF) necessitating admission to the PICU for mechanical ventilation. As no fully effective preventive or curative (antiviral) therapy is available, current treatment of ARF due to viral-LRTD is limited to supportive measures.

An important component of the supportive care of critically ill patients, both children and adults, is fluid management. At presentation, rapid IV fluid administration is important for hemodynamic stabilization in these patients (2, 3). Thereafter, maintenance of adequate fluids and nutrition administration is necessary to aid clinical recovery. However, (early) fluid overload during (P)ICU admission is common (4), and more recently fluid overload was associated with adverse outcome, including prolonged mechanical ventilation and higher mortality (5–7). The mechanism underlying these adverse effects of fluid overload likely includes the accumulation of

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extravascular fluid with formation of interstitial (i.e., pulmonary) edema, which impedes oxygenation and perfusion of multiple tissues in the body (8).

Children with viral-LRTD requiring mechanical ventilation frequently have clinical symptoms of fluid overload (9). This is remarkable because, although these children have some degree of cardiovascular compromise (10), true hemodynamic instability at presentation necessitating vigorous fluid administration is in general less apparent when compared with patients with full-blown (septic) shock (11). In addition, after the initial acute phase, mechanically ventilated children with viral-LRTD run a relatively benign course of disease, resulting in low mortality in developed countries. Up to date, it remains yet unknown whether fluid overload in children with viral-LRTD leads to adverse outcome.

In the present study, we aimed to investigate the effects of early fluid overload in mechanically ventilated children with viral-LRTD. We deem it likely that fluid overload may lead to a higher degree of pulmonary edema and hence can be reflected by more severe oxygenation defects during admission and longer duration of mechanical ventilation. We hypothesized that early increasing cumulative fluid balance is associated with prolonged mechanical ventilation and increasing severity of oxygenation defect.

MATERIALS AND METHODS

Design, Setting, and Patients

This is a single-center retrospective study in patients admitted to the PICU of the Emma Children's Hospital/Academic Medical Center in Amsterdam, The Netherlands, between December 2008 and March 2014. Our PICU is a 14-bed, tertiary unit, serving the greater Amsterdam area in the Netherlands. All patients (< 2 yr old) who required invasive mechanical ventilation for viral-LRTD, with or without proven respiratory viral infection, were identified and included in the study. The study was presented to the Medical Ethical Committee of the Academic Medical Center Amsterdam and the need for ethical approval was waived.

Data Collection and Definitions

Data were retrospectively collected from a prospective patient clinical data management system. Fluid intake, fluid output, and fluid balance were collected daily for the first 7 days of mechanical ventilation. Fluid intake included blood products, parenteral and enteral nutrition, IV administered fluids, and medication. Daily fluid output included urine output, blood loss, gastric aspirate, stool, and losses from other body cavities. Insensible losses were not calculated. Fluid balance was calculated every 24 hours as intake minus output per kilogram (kg) body weight at admission. The cumulative fluid balance (CFB, mL/kg) was calculated as the sum of the daily fluid balances, excluding insensible losses. Both maximum CFB (CFBmax) and CFB on day 3 (CFB3) were assessed. As longer duration of mechanical ventilation may increase the likelihood of obtaining a positive CFB, we chose the CFB3, representing early fluid overload, as the main test variable for multivariable analysis, correcting for confounders. This is in accordance with other studies in children where the effect of fluid status is assessed (4–12). Of note, similar to previous studies (4, 13), body weight measurements of the children during mechanical ventilation were not included, as they were not protocolized, and as such not systematically performed. Importantly, fluid management in the patients in our study cohort was not subject to any study-based protocol, but in our PICU generally includes a maximum total fluid intake of 120–140 mL/kg/d for infants although many infants received less per decision of the attending physician. We could not discern between IV or enteral fluids and feeds, so it is important to realize that the fluid balance incorporates all fluids given, including possible fluid bolus(es). Prescription of diuretics also occurred at the decision of the attending physician.

In the patient management data system used in our PICU during the period under study, ventilation and oxygenation variables such as FIO_2, SpO_2, PaO_2, positive end-expiratory pressure (PEEP), peak inspiratory pressure (PIP), and mean airway pressure (Paw) were automatically reported and validated hourly each study day. The need for high dose oxygen has recently been identified as a strong predictor of disease severity in children with ARF due to viral-LRTD (14). To further, and more reliably, assess the severity of oxygenation defect in this study, the oxygen saturation index (OSI) was calculated as $OSI = ([Paw \times FIO_2]/SpO_2) \times 100$, only when SpO_2 was below the cutoff point of 97% (15). This metric is increasingly used to substitute the oxygenation index (OI). OI is defined by the formula $OI = ([Paw \times FIO_2]/PaO_2) \times 100$. As such, the OSI, derived from SpO_2 rather than PaO_2, does not require arterial blood sampling. The OSI is proven to correlate well with OI (16, 17) and has therefore recently been accepted as a valid parameter to assess oxygenation status in the Pediatric Acute Lung Injury Consensus Conference definition of pediatric acute respiratory distress syndrome (ARDS) (18). The Pediatric Index of Mortality (PIM) 2 score was obtained from each patient to assess for severity of illness. Other indicators of disease severity could potentially be inferred from medication exposure, including inotropes, antibiotics, and paralytic agents. At the decision of the attending physician, viral infection was tested by multiplex polymerase chain reaction and/or rapid antigen detection tests for multiple respiratory viruses in nasopharyngeal aspirate. Positive bacterial culture was noted if there was a positive culture of tracheal aspirate or bronchial lavage fluid.

Outcome

Primary outcome was duration of mechanical ventilation, which was measured as the total days of invasive ventilatory support until extubation. According to our standard of care, patients with viral-LRTD are eligible for extubation if transcutaneous saturation is greater than 94% with a PEEP less than or equal to 5 cm H_2O, FiO_2 less than or equal to 0.4, and tidal volume less than or equal to 8 mL/kg with a normal respiratory rate in a trial of spontaneous breathing for minimal 30 minutes with pressure support set at 10 cm H_2O

or less. If patients required reintubation, the days of ventilation following reintubation were only taken into account when reintubation was necessary for increasing oxygenation deficit. In the majority of patients, immediate reintubation was solely due to upper respiratory tract obstruction as a complication of the endotracheal tube (10/12 patients). In these patients, the period after reintubation was not included in the total duration of mechanical ventilation. The secondary outcome was OSI to determine the correlation between fluid status and severity of oxygenation defect. The OSI was assessed in two ways: as the mean OSI of day 3 and the mean OSI of days 4–7, the latter specifically addressing a potential delayed effect of fluid overload on the later course of disease. In addition to the OSI, PEEP and PIP values were evaluated in a similar manner to study ventilation and oxygenation more elaborately.

Statistical Analysis

Statistical analysis was performed using SPSS (v22; IBM SPSS Statistics, Chicago, IL). Continuous variables were presented as mean ± SD or median with interquartile range (IQR), depending on normality. Categorical variables were presented as proportions (%). Univariable and stepwise multivariable linear regression was used to analyze the association between CFB and duration of mechanical ventilation, adjusting for potential confounders. Variables were retained in the multivariable model if they were associated with duration of mechanical ventilation at an α of p value less than 0.1. To assess the correlation between CFB and OSI, PEEP and PIP Pearson correlation tests were performed. p values reported are two-sided and statistical significance was set as an α level of 0.05.

RESULTS

Patient Characteristics

A total of 135 mechanically ventilated children with viral-LRTD were identified and included in the retrospective cohort. **Table 1** shows their baseline and clinical characteristics. One patient died during PICU admission due to untreatable severe pulmonary hypertension, resulting in a mortality rate of 0.7%. Median age was 1.6 months (range, 0.2–18.0 mo). Twenty-two children (16%) had a history of chronic disease, including trisomy 21, bronchopulmonary dysplasia, and congenital heart disease. Mean (± SD) PIM2 score was 1.4% (± 1.0%). RSV was detected in the majority of children (n = 89, 65.9% of total 135 children; 76.7% of 116 children tested). Other viral infections, such as rhino-, corona-, or parainfluenzavirus, were found in 23 patients (17%). A substantial portion of the patients (n = 90; 66.7%) had a positive bacterial culture of tracheal aspirate or bronchial lavage fluid. The mean (± SD) duration of ventilation was 6.9 (± 3.0) days. Upon admission, the median (IQR) OSI was 6.0 (4.5–8.0). In the patients who had an arterial catheter for blood gas analysis at the day of admission (n = 92; 68%), there was a significant correlation between OI and OSI (r = 0.766; $p < 0.001$; data not shown).

Early Fluid Overload

In nearly all of 135 patients (n = 125; 92.6%), a positive CFB starting on day of admission was found. The mean daily CFB for the first 7 days after start of mechanical ventilation are shown in **Figure 1**. The maximum degree of fluid overload obtained during the study period (CFBmax [± SD]) was + 150 (± 79) mL/kg. The duration of mechanical ventilation was positively correlated with the mean CFB on multiple days during the study period (days 2–5; $p < 0.05$; Fig. 1). The CFBmax was strongly correlated with duration of mechanical ventilation in univariable analysis ($p < 0.001$; **Table 2**). CFB3 data were available for 132 children, excluding three that were extubated before 72 hours of mechanical ventilation. The mean (± SD) CFB3 was + 97.9 (± 49.2) mL/kg. Interestingly, there was only a modest correlation between the mean daily fluid intake during the first 3 days and the CFB3 (r = 0.495; $p < 0.05$; data not shown). In Table 2, variables from univariable analysis that were relevant for potential influence on duration of mechanical ventilation can be seen. Most notably, the cumulative fluid balance (CFB3 and CFBmax) and OSI at admission were strongly associated with duration of mechanical ventilation. Multivariable analysis shows that the CFB3 remained significantly associated with prolonged mechanical ventilation when corrected for the OSI at admission and other variables (p = 0.048; **Table 3**).

Oxygenation Defect

No association could be identified between oxygenation status (as defined by OSI) and fluid overload. Neither the mean OSI on day 3 nor the mean OSI of days 4–7 was correlated with CFB3 (p = 0.7 and p = 0.6, respectively; **Table 4**). Testing associations between fluid overload and ventilator pressures (both PIP and PEEP) revealed an association between mean PEEP levels at day 3 (p = 0.017; Table 4). PIP showed no association with fluid overload.

DISCUSSION

The goal of this study was to assess the relationship between early fluid overload and outcome in mechanically ventilated children with viral-LRTD. We found a positive association between cumulative fluid balance on day 3 and duration of mechanical ventilation, which remained significant after correction for confounding factors. However, cumulative fluid balance was not associated with oxygenation status, except for PEEP. These data suggest that fluid overload has an unfavorable effect on the course of disease in mechanically ventilated children with viral-LRTD.

In critically ill patients, (early) fluid overload is considered detrimental. A growing body of literature shows that increasing cumulative fluid balance during ICU admission and/or mechanical ventilation has important adverse effects, such as longer duration of mechanical ventilation and higher mortality (5, 6, 19, 20). Importantly, in adults with ARDS, a restrictive fluid management protocol in the ICU was shown to reduce fluid overload, improve the OI and shorten duration of mechanical ventilation (20, 21). Although fluid homeostasis and balance in children differs from adults (8), several studies in

TABLE 1. Demographic and Clinical Characteristics of Mechanically Ventilated Patients With Viral-Lower Respiratory Tract Disease

Variable		
Age (mo), median (IQR)	1.6	(1.0–2.9)
Male, *n* (%)	70	(51.9)
Weight (kg), median (IQR)	4.3	(3.5–5.4)
Gestational age, median (IQR)	39.6	(35.3–40.0)
Chronic condition on admission[a], *n* (%)	22	(16.3)
History of cardiac disease at admission, *n* (%)	15	(11.1)
Proven respiratory syncytial virus infection, *n* (%)	89	(65.9)
Second or other viral infection[b], *n* (%)	40	(29.6)
Second viral infection	17	(12.6)
Other viral infection[c]	23	(17)
Positive bacterial culture[d]	90	(66.7)
Pediatric Index of Mortality 2 score, % (mean ± SD)	1.4	± 1.0
Medication started on day of admission		
Bronchodilators, *n* (%)	2	(1.5)
Inotropics, *n* (%)	2	(1.5)
Antibiotics, *n* (%)	32	(23.7)
Diuretics, *n* (%)	9	(6.7)
Paralytic agents, *n* (%)	35	(25.9)
Corticosteroids, *n* (%)	1	(0.7)
Duration of mechanical ventilation (d), mean (± SD)	6.9	± 3.0
Ventilation variables on day of admission, median (IQR)		
Oxygen saturation index	6.0	(4.5–8.0)
Oxygenation index	7.0	(5.6–9.8)
Positive end-expiratory pressure (mm Hg)	6	(5.0–6.7)
Peak inspiratory pressure (mm Hg)	24	(22.0–27.2)

IQR = interquartile range.

[a]Chronic conditions include: trisomy 21, bronchopulmonary dysplasia, cardiac malformations or defects, Marfan syndrome.

[b]The presence of either a second virus next to respiratory syncytial virus, or one different virus found by polymerase chain reaction or rapid antigen detection tests.

[c]Other viral infections include rhinovirus, coronavirus, and (para)influenzavirus.

[d]Positive cultures of tracheal aspirate or bronchial lavage fluid included one or more of the following bacteria: *Escherichia coli*, *Haemophilus influenzae*, *Moraxella catarrhalis*, *Streptococcus pneumoniae*, *Staphylococcus aureus*.

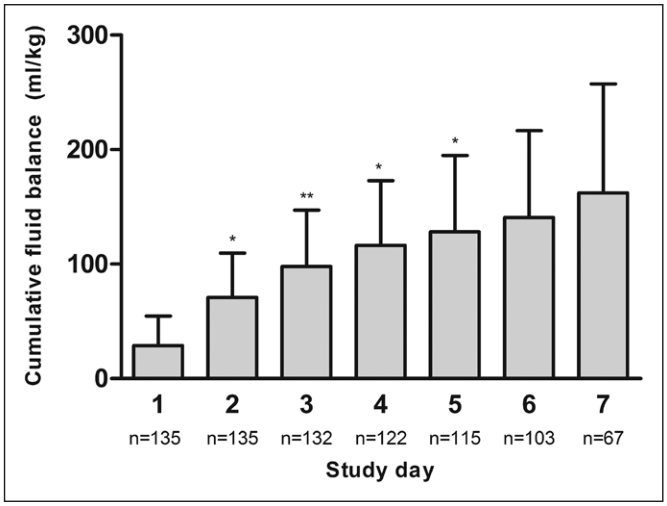

Figure 1. Cumulative fluid balance during the study period. Cumulative fluid balance (mL/kg) was positive on study days 1 (admission) to 7. On days 2–5, a statistical significant association was found between cumulative fluid balance and duration of mechanical ventilation; $^{*}p < 0.05$, $^{**}p < 0.01$. Bar graphs depict mean and SD.

critically ill children have found similar adverse effects of fluid overload (4, 12, 13, 22–24). In particular, early fluid overload, as defined by the CFB3, has been identified to correlate with mortality and fewer ventilator-free days in children with ARDS (12). The same relationship between fluid overload and ventilator-free days, but not mortality, was found studying a more general PICU population (13, 23). In addition, in children receiving continuous renal replacement therapy, higher fluid overload was associated with increased mortality rates (25, 26).

The current study extends on these insights as we investigated early fluid overload in a unique PICU patient population, namely, patients at a very young (infant) age with a relatively benign acute respiratory disease, being a single organ failure in general in less need for vigorous fluid resuscitation at presentation. Still, although a moderate restrictive fluid maintenance volume is given, these children accumulate large amounts of fluid, as reflected by the strong positive CFB3 in the vast majority of the patients. Remarkably, the CFB3 in our cohort (+ 97.9 [± 49.2] mL/kg) is even higher in comparison with a cohort of critically ill children with ARDS in whom the CFB3 was + 84 (± 93) mL/kg (4). Importantly, the severity of early fluid overload in our study was associated with the duration of mechanical ventilation and as such is in line with the current literature on the adverse effects of fluid overload in critically ill patients.

Fluid overload has a negative effect on outcome, presumably by an increase in extravascular lung water causing more severe oxygenation defects. Although some studies found a moderate positive correlation between CFB and oxygenation indices (13, 23, 24), from two large pediatric ARDS studies, this relationship does not become clear (4, 12). We did not find a relationship between the CFB and the OSI, a validated marker of oxygenation (16). This suggests the adverse effect of fluid overload in our patient cohort was independent of the severity of oxygenation defect. Nevertheless, we did find a positive association between CFB3 and PEEP on day 3, which might suggest an indirect association with

TABLE 2. Results of Univariable Analyses of Factors Associated With Duration of Mechanical Ventilation

Clinical Covariates	*p*	*R* square
Cumulative fluid balance day 3 (mL/kg)	0.006	0.057
Maximum cumulative fluid balance (mL/kg)	< 0.001	0.103
Age	0.675	0.001
Gender	0.596	0.002
Weight at admission	0.853	0.000
Chronic disease at admission	0.069	0.025
Cardiac disease at admission	0.020	0.040
Oxygen saturation index at admission	< 0.001	0.138
Pediatric Index of Mortality 2 score	0.903	0.000
Diuretics at admission	0.096	0.021
Antibiotics at admission	0.812	0.000
Inotropes at admission	0.946	0.000
Paralytics at admission	0.063	0.026
Proven respiratory syncytial virus infection	0.210	0.012
Second viral infection	0.032	0.034
Positive bacterial culture	0.566	0.002

Clinical covariates were retained in the model if univariable $p < 0.1$.

TABLE 3. Results of Multivariable Analysis of Factors Associated With Duration of Mechanical Ventilation and Cumulative Fluid Balance on Day 3

Clinical Covariates	*p*
Cumulative fluid balance day 3 (mL/kg)	0.048
Oxygen saturation index at admission	< 0.001
Second viral infection	0.125
Chronic disease at admission	0.188
Paralytics at admission	0.769
Diuretics at admission	0.227

R^2 total model = 0.228.

oxygenation defect. Evidently, a measurement of extravascular lung water as evidence of fluid accumulation in the lungs would be extremely helpful in investigating the potential adverse effects of fluid overload but is not routinely performed in our PICU.

Next to the assumption that fluid overload leads to lung edema and worsened oxygenation, fluid overload in itself may also have adverse effects on multiple organs in the body (e.g., the kidneys and liver), as well as lead to enhanced proinflammatory responses possibly aggravating the course of disease (8). One could also assume that more severely ill patients are more prone to develop fluid retention. Pediatric Risk of Mortality (PRISM) scores (i.e., PIM or PRISM III) are generally not reflecting disease severity in children with viral-LRTD, as mortality is low in this patient group and the course of disease benign (14, 27). Indeed, PIM2 scores were low in this patient cohort and were not associated with duration of mechanical ventilation. By including medication prescriptions (e.g., inotropic, antibiotic, and paralytic agents) and mean OSI at admission as extra indicators for disease severity, we were at least partly able to correct for disease severity in our cohort. Another consideration might be that the physician's view when observing high fluid balance or clinical fluid retention is to postpone extubation until fluid balance is restored using diuretics, regardless of oxygenation status. Yet, it seems unlikely that this is of major significance to mechanical ventilation duration, as our standard of care determines certain extubation criteria with consensus of all pediatric intensivists and because the CFB3 was not close to the time of extubation. Certainly, to determine the negative effects of fluid overload in children with ARF, such as viral-LRTD, further prospective testing and experimental studies are needed.

TABLE 4. Oxygenation and Ventilation Related to Cumulative Fluid Balance on Day 3

Oxygenation and Ventilation Variables	*p*	*R*
OSI mean day 3	0.702	0.034
OSI mean day 4–7	0.604	0.048
PIP mean day 3	0.874	0.015
PIP mean day 4–7	0.686	−0.040
PEEP mean day 3	0.017	0.208
PEEP mean day 4–7	0.106	0.148

OSI = oxygen saturation index, PEEP = positive end-expiratory pressure, PIP = peak inspiratory pressure.

A limitation of our study is the observational design, which makes it prone for bias and cannot always establish a causative relationship. Part of this design is that we were dependent on chart registrations for fluid balance values, which is known to be a rather inaccurate method to register fluid balance (28). Nevertheless, we found a striking positive relationship with mechanical ventilation on multiple time points making a potential inaccuracy less important. Second, we could not include fluid intake and output data prior to PICU admission, due to practical constraints. This could lead to an underestimation of the extent of fluid overload. However, from clinical observation, the accumulation of fluid in critically ill patients is most prominent starting at (P)ICU admission. Third, we need to emphasize that the amount of maintenance fluid intake in our cohort may differ from common practice in other PICUs. Importantly, many clinicians may already further restrict fluids in this patient population, as the notion that high

fluids may be detrimental to clinical recovery has certainly started to gain ground over the last few years. However, there is still a lack in guidelines on managing fluid intake and balance as no consensus on this topic yet exists. As our cohort studies children admitted from 2008 to 2014, there may well be an influence of this development over time. Nevertheless, the finding of only a modest correlation between the daily fluid intake and CFB3 suggests that the iatrogenic share in fluid overload, although probable, is limited. Likely, several factors, including capillary leak, development of Syndrome of Inappropriate Antidiuretic Hormone Secretion, use of sedation/paralysis, and positive pressure mechanical ventilation, play an important role in development of fluid overload, in part regardless of the level of fluid restriction. Lastly, we could not discern the fluid intake between infants receiving enteral feeds or those receiving IV fluids due to the retrospective nature of our study. This could have affected the degree of fluid overload as the free water content of feeds is substantially lower than that of IV given fluids.

In conclusion, relatively high early fluid overload is very common in mechanically ventilated children with viral-LRTD. Early fluid overload in these patients seems to have an adverse effect on the duration of mechanical ventilation, independent of severity of oxygenation defect. These data suggest that fluid overload should be avoided already at an early stage of PICU admission. This study underscores the importance of further clinical testing in prospective studies to elucidate the relation between fluid overload and disease outcome in the PICU.

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