CLINICAL RESEARCH ARTICLE

The impact of fluid balance on outcomes in critically ill near-term/term neonates: a report from the AWAKEN study group

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BACKGROUND: In sick neonates admitted to the NICU, improper fluid balance can lead to fluid overload. We report the impact of fluid balance in the first postnatal week on outcomes in critically ill near-term/term neonates.
METHODS: This analysis includes infants ≥36 weeks gestational age from the Assessment of Worldwide Acute Kidney injury Epidemiology in Neonates (AWAKEN) study ($N = 645$). Fluid balance: percent weight change from birthweight. Primary outcome: mechanical ventilation (MV) on postnatal day 7.
RESULTS: The median peak fluid balance was 1.0% (IQR: −0.5, 4.6) and occurred on postnatal day 3 (IQR: 1, 5). Nine percent required MV at postnatal day 7. Multivariable models showed the peak fluid balance (aOR 1.12, 95%CI 1.08–1.17), lowest fluid balance in 1st postnatal week (aOR 1.14, 95%CI 1.07–1.22), fluid balance on postnatal day 7 (aOR 1.12, 95%CI 1.07–1.17), and negative fluid balance at postnatal day 7 (aOR 0.3, 95%CI 0.16–0.67) were independently associated with MV on postnatal day 7.
CONCLUSIONS: We describe the impact of fluid balance in critically ill near-term/term neonates over the first postnatal week. Higher peak fluid balance during the first postnatal week and higher fluid balance on postnatal day 7 were independently associated with MV at postnatal day 7.

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INTRODUCTION

In sick neonates admitted to the neonatal intensive care unit (NICU), fluid balance depends on multiple factors including fluid provision, insensible losses, and renal function. Furthermore, these neonates have immature renal homeostatic mechanisms which in conjunction with critical illness can predispose to abnormalities in fluid balance including fluid overload (FO) or dehydration. Fluid balance can be adversely impacted by acute kidney injury (AKI), which has been shown to occur commonly in critically ill neonates. Single center studies report an AKI incidence of 15%–70% depending on the population under study, with associated adverse outcomes (increased mortality, length of stay).[1–6] The Assessment of Worldwide Acute Kidney Injury Epidemiology in Neonates (AWAKEN) study, a 3 month, 24-center retrospective study,[7] confirmed these findings and showed that AKI occurred in 30% of NICU admissions. Those with AKI had over 4 times higher adjusted odds of mortality compared to those without AKI.[8] Despite our acknowledgement of the impact of neonatal AKI on mortality, there remain no interventions to prevent or treat established AKI. As a result, current neonatal AKI management is focused on preventing further AKI, optimizing nutrition, monitoring electrolytes, and minimizing the development of FO.

Over the past decade pediatricians have been at the forefront of recognizing the deleterious impact of FO on outcomes in a variety of critically ill pediatric populations including septic patients and those who receive continuous renal replacement therapy, mechanical ventilation, and congenital heart surgery.[9–17] FO represents an attractive metric that can drive clinical practice as a target that is potentially amenable to both prevention or treatment by judicious fluid provision and early renal support therapy. While it is anticipated that well neonates will have a negative fluid balance of up to 5–10% over the first postnatal week, the optimal target for fluid balance in the first postnatal week in critically ill neonates is unknown. Preliminary research in premature infants suggests that abnormalities in fluid balance are associated with the development of chronic lung disease.[18] Improving our understanding of the

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distribution of, and outcomes related to fluid balance in the first postnatal week in critically ill neonates will help delineate the most appropriate fluid provision strategies. To date there has not been a large multicenter evaluation of the epidemiology and impact of fluid balance in any NICU population.

In 2014, the Neonatal Kidney Collaborative with 24 participating institutions from around the world conducted the AWAKEN study, the first multicenter study designed to capture data on AKI, fluid balance, and the impact of other renal-related risk factors on short term outcomes.[8] Using data collected in AWAKEN, we sought to[1] describe the pattern of changes in fluid balance in sick near-term/term neonates during the first postnatal week,[2] investigate the association of fluid balance with clinical outcomes (mechanical ventilation at postnatal day 7 and NICU mortality), and[3] evaluate the association of fluid balance with AKI. We hypothesized that fluid balance during the first postnatal week would be associated with the need for (1) mechanical ventilation at postnatal day 7, (2) hospital mortality, and (3) composite outcome of death or mechanical ventilation at postnatal day 28.

METHODS

Study population

The methodology and protocol for the AWAKEN study have previously been published.[7] Briefly, the records for all neonates admitted to 24 level 2–4 NICUs between 1 January 2014 and 31 March 2014, were reviewed. Inclusion criteria for enrollment was: (1) receipt of intravenous fluids (IV) for at least 48 h. Exclusion criteria included: (1) admission at ≥14 days after birth, (2) congenital heart disease requiring surgical repair at <postnatal day 7, (3) lethal chromosomal anomaly, (4) death within 48 h of NICU admission, and (5) severe congenital kidney and urinary tract abnormalities. We limited this analysis to those patients with gestational age ≥36 weeks, admission at ≤postnatal day 7, data sufficient to calculate AKI, and recorded weight by postnatal day 2. Weight outliers were reviewed by blinded principal investigators and those with weights that were thought to be invalid (impossible) were excluded. Each center involved in the study had received approval from their Institutional Review Board or Human Research Ethics Committee.

Data collection

A detailed description of data collection for AWAKEN has been previously published.[7] Briefly, data were organized in five components: baseline demographics, daily information for week 1, weekly "snapshots" for the remainder of the hospitalization, and discharge data (captured at discharge or 120 days of age, whichever came first). Day of birth was defined as postnatal day 1.

Fluid balance and FO definitions

The AWAKEN study protocol included abstraction of recorded daily weights, intake (intravenous and enteral fluids), and outputs (urine and total output, including all other documented fluid loss) for the first 7 postnatal days, when available. Documentation methods for intake and output were subject to local protocols.

Fluid intake included blood products, intravenous fluids and flushes, medications and all forms of nutritional support. Fluid output included urine output, drain output, blood loss, nasogastric tube output, stool volume, and wound drainage. Not all sites recorded all potential sources of intake and the amount of maternal breast milk ingested at breast could not be quantified. Similarly, quantification of urine output, usually based on diaper weights, as well as other sources of fluid loss were potentially incomplete. Therefore, the decision to use daily weight as a surrogate for fluid balance was made as the most feasible and reliable method in the AWAKEN cohort (analysis outlined below). Fluid balance was thus calculated based on a comparison of daily weight with birthweight: %change = (daily weight − birthweight)/birthweight × 100. We calculated the maximum and minimum weight change during the first postnatal week, %change from birthweight on postnatal days 3 and 7, and the highest and lowest change from birthweight during the first postnatal week.

The following 4 variables to capture fluid balance metrics were calculated: (a) the maximum %weight change that occurred on postnatal days 2–7 of age, (b) the minimum %weight change that occurred on postnatal days 2–7 of age (c) the % weight change at postnatal day 3, (d) the %weight change at postnatal day 7, and (e) negative fluid balance at postnatal day 7. The negative fluid balance at postnatal day 7 was defined as being below birthweight at postnatal day 7.

AKI definition

All serum creatinine (SCr) values obtained during the study period were recorded. A neonatal modification of the kidney disease: improving Global Outcomes workgroup AKI was used to define neonatal AKI.[8,19] Based on this criteria AKI was defined as urine output <1 cc/kg/hr in the first 7 days and/or SCr rise ≥0.3 mg/dl or 50% from previous trough. The urinary output threshold for AKI was set at 1 mL/kg per h or less averaged over 24 h normalized for the weight on the day urine output was measured.[8] AKI was evaluated as a risk factor for aberrant fluid balance throughout the manuscript

Outcomes

The primary outcome for this study was the need for mechanical ventilation (high frequency ventilation, or conventional ventilation) or ECMO at postnatal day 7. The secondary outcomes were NICU mortality and a composite outcome of death or mechanical ventilation at postnatal day 28.

Statistical analysis

Categorical variables were analyzed by proportional differences with the Chi-square test or Fisher exact test (where appropriate). Continuous variables were tested for normality using the Shapiro–Wilk Test. For normally distributed continuous variables, the mean ± standard deviation (SD) were reported and analyzed using the Student *t*-test. For non-normally distributed variables, the median and interquartile range (IQR) were reported and groups were compared using the Wilcoxon Rank Sum test. Logistic regression models were used to calculate crude odds ratios (OR) and associated 95% confidence intervals (CI) for the association between maximum fluid balance, minimum fluid balance, fluid balance on Day 3, and fluid balance on Day 7 with the likelihood of mechanical ventilation at day 7. Multivariable logistic regression models were run to account for potential confounding variables, and findings are reported as adjusted OR. Adjusted regression models were constructed using a backwards selection procedure with a significance level of <0.2. Separate regression models were created for each of the four main exposures of interest. In all analyses, a p-value < 0.05 was considered statistically significant. SAS 9.4 (Cary, North Carolina) was used for all analyses.

RESULTS

Patient characteristics

The AWAKEN study screened a total of 4273 neonates, of whom 2162 met the AWAKEN inclusion criteria, and 2022 had the required lab data to diagnose AKI. Of these, 833 infants were ≥36 weeks gestational age, with 148 of these neonates excluded because no weight was available during the first two days of ICU admission. A total of 645 neonates were included in the final analysis (Supplemental Figure S1). A comparison between the study population and those who were excluded showed similar rates of mechanical ventilation at postnatal day 7, but higher mortality in those that who excluded (Supplemental Table S1).

Table 1 summarizes the baseline characteristics of the study population as a whole and dichotomized by need for mechanical

Table 1. Demographics and variables related to the need for mechanical ventilation at postnatal day 7

	Whole cohort (*N* = 645)	Mechanical ventilation (*N* = 58)	No mechanical ventilation (*N* = 587)	*P*
Maternal and gestational variables				
Maternal age (years)		28.7 ± 6.4	28.2 ± 5.8	0.58
Infections				
Bacterial	63	1 (1.7%)	62 (10.6%)	0.03
Viral	15	1 (1.7%)	14 (2.4%)	1.00
Diabetes	82	8 (13.8%)	74 (12.6%)	0.79
Hypothyroidism	36	2 (3.4%)	34 (5.8%)	0.76
Chronic Hypertension	41	3 (5.2%)	38 (6.5%)	1.00
Kidney disease	4	1 (1.7%)	3 (0.5%)	0.31
Pre-eclampsia	52	3 (5.2%)	49 (8.4%)	0.61
Eclampsia	4	0 (0.0%)	4 (0.7%)	1.00
IUGR	51	7 (12.1%)	44 (7.5%)	0.21
Oligohydramnios	26	3 (5.2%)	23 (3.9%)	0.72
Polyhydramnios	34	9 (15.5%)	25 (4.3%)	0.002
Hemorrhage	9	0 (0.0%)	9 (1.5%)	1.00
Gestation	35	4 (6.9%)	31 (5.3%)	0.54
Assisted conception	19	2 (3.4%)	17 (2.9%)	0.25
Intrapartum complications				
Nuchal cord	60	7 (12.1%)	53 (9.0%)	0.45
Meconium	147	11 (19.0%)	136 (23.2%)	0.47
Severe vaginal bleeding	19	1 (1.7%)	18 (3.1%)	1.00
Shoulder dystocia	12	1 (1.7%)	11 (1.9%)	1.00
Resuscitation				
Intubation	125	29 (50.0%)	96 (16.4%)	<0.0001
Chest compression	31	7 (12.1%)	24 (4.1%)	0.01
Epinephrine	12	2 (3.4%)	10 (1.7%)	0.29
Normal saline	38	10 (17.2%)	28 (4.8%)	0.001
1-minute Apgar score	7	5 (2,8)	8 (4, 9)	0.0004
5-minute Apgar score	9	8 (6, 9)	9 (7, 9)	0.004
Infant Variables				
Gender (male)	367	33 (56.9%)	334 (56.9%)	1.00
Ethnicity				
Hispanic	77	5 (8.6%)	72 (12.2%)	0.25
Non-Hispanic	463	47 (81.0%)	416 (70.9%)	
Unknown	105	6 (10.3%)	99 (16.9%)	
Race				
White	375	43 (74.1%)	332 (56.6%)	0.03
Black	111	7 (12.1%)	104 (17.7%)	
Other	159	8 (13.8%)	151 (25.7%)	
Site of delivery (outborn)	335	33 (56.9%)	302 (51.5%)	0.43
Birthweight				
≤1000 gm	1	0 (0.0%)	1 (0.2%)	0.87
1001–1500 gm	6	0 (0.0%)	6 (1.0%)	
1501–2500 gm	108	10 (17.2%)	98 (16.7%)	
≥2501 gm	530	48 (82.8%)	482 (82.1%)	
SGA	144	15 (25.9%)	129 (22.0%)	0.50
LGA	56	2 (3.4%)	54 (9.2%)	0.22
Reason for admission				
Respiratory symptoms	180	12 (20.7%)	168 (28.6%)	0.20
Respiratory failure	199	31 (53.4%)	168 (28.6%)	<0.0001
Sepsis evaluation	289	23 (39.7%)	266 (45.3%)	0.41
HIE	79	11 (19.0%)	68 (11.6%)	0.10
Seizures	33	1 (1.7%)	32 (5.5%)	0.35
Hypoglycemia	85	3 (5.2%)	82 (14.0%)	0.07
Hyperbilirubinemia	17	0 (0.0%)	17 (2.9%)	0.39
Metabolic evaluation	9	1 (1.7%)	8 (1.4%)	0.57
Trisomy 21	9	2 (3.4%)	7 (1.2%)	0.19
Congenital heart disease	54	10 (17.2%)	44 (7.5%)	0.02
Necrotizing enterocolitis	3	0 (0.0%)	3 (0.5%)	1.00
Omphalocele/ Gastroschisis	28	4 (6.9%)	24 (4.1%)	0.30
Need for surgical evaluation	48	6 (10.3%)	42 (7.2%)	0.43
Meningomyelocele	12	2 (3.4%)	10 (1.7%)	0.29
Medication exposure				
Vasopressors	51	16 (27.6%)	35 (6.0%)	<0.0001[a]
Antimicrobials	403	39 (67.2%)	364 (62.0%)	0.43

IUGR intrauterine growth restriction, *Gm* grams, *SGA* small for gestational age, *LGA* large for gestational age, *HIE* hypoxic ischemic encephalopathy

ventilation on postnatal day 7. A total of 125 neonates were intubated during resuscitation. The median birthweight was 3140 grams (IQR: 2665, 3530 grams). A total of 530 (82.1%) infants had birthweight ≥2500 grams. The median 1-minute Apgar score was 7 (IQR: 4, 8) and the 5-minute Apgar score was 9 (IQR: 7, 9). The most common admission diagnoses for the infants in this study were respiratory diagnoses (27.9%), hypoxicischemic encephalopathy (12.2%), and/or intrauterine growth restriction (7.9%) and rule-out sepsis (44.8%). During the first postnatal week a total of 51 (7.9%) neonates received vasopressor support, and 403 (62.5%) neonates were treated with antimicrobials. Those who were ventilated at postnatal day 7 were more likely to have received chest compressions during resuscitation, had a lower 1-minute Apgar score, required admission for respiratory failure or congenital heart disease, and received vasopressors in the first postnatal week (Table 1).

Fluid balance

For the cohort there were 3870 potential days of data available for the first 7 postnatal days. On 74.3% of days there were complete intake and output data. A weight was available on 80.5% of the possible days. A description of the peak fluid balance in the first postnatal week stratified by MV at postnatal day 7 is presented in Table 2. The median peak fluid change from birth during the first postnatal week was 1.0% (IQR: −0.5, 4.6) and occurred on postnatal day 3 (IQR: 1, 5). The median lowest fluid balance during the first postnatal week was −3.1% (IQR: −5.6, −0.6) and occurred on postnatal day 3 (IQR: 2, 5). During the first postnatal week, 66.8% of the cohort had at least one day with a peak fluid balance above birthweight; 13.6% of patients developed a peak fluid balance ≥5% and 5.7% of patients developed a peak fluid balance ≥10% (Table 2). The characteristics of fluid balance presented by admission diagnosis during the first postnatal week are summarized in Supplemental Table S2.

Fluid balance by AKI status

AKI occurred in 25.7% (*N* = 166) of patients during the first postnatal week, of whom 13.9% (*N* = 90) had stage 1, 5.4% had stage 2 (*N* = 35), and 6.3% (*N* = 41) had stage 3 AKI. Eight (1.2%) patients in this cohort received renal replacement therapy. The characteristics of fluid balance in the first postnatal week by AKI status are presented in Table 3. Those with AKI had consistently higher fluid balance irrespective of the day on which fluid status was assessed during the first postnatal week.

Association of fluid balance with outcomes

A total of 9% of patients required mechanical ventilation on postnatal day 7. The association between maternal and patient

Table 2. Peak fluid balance severity distribution

Distribution	*N* (%)	Mechanical ventilation (*N* = 58)	No mechanical ventilation (*N* = 587)	*p*
<−5%	26 (4.0%)	3 (5.2%)	23 (3.9%)	0.64
−5 to <0%	162 (25.1%)	6 (10.3%)	156 (26.6%)	0.01
0 to <5%	306 (47.4%)	19 (32.8%)	287 (48.9%)	0.02
≥5 to 9.99%	88 (13.6%)	9 (15.5%)	79 (13.5%)	0.66
10 to 15%	37 (5.7%)	12 (20.7%)	25 (4.3%)	<0.0001

N number, % percent

Table 3. Trends of fluid balance by acute kidney injury in the first postnatal week

	Whole cohort	AKI in first postnatal week		
Outcome		Yes (*N* = 166)	No (*N* = 479)	*p*
Peak fluid balance 1st week	645	2.7 (0, 7.4)	0.5 (−0.8, 4.0)	<0.0001
Lowest fluid balance 1st week	645	−2.8 (−4.9, 0)	−3.1 (−5.8, -0.8)	0.09
Fluid balance at postnatal day 3	532	−0.8 (−2.3, 1.6)	−1.1 (−3.5, 0.6)	0.02
Fluid balance at postnatal day 7	471	1.1 (−3.5, 6.1)	−1.2 (−4.6, 2.5)	0.004
Negative fluid balance at postnatal day 7	471	55 (33.1%)	197 (41.1%)	0.02

AKI acute kidney injury

characteristics with need for mechanical ventilation on postnatal day 7 are summarized in Table 1. A description of the distribution of peak fluid balance by outcomes is outlined in Table 2. The associations between measures of fluid balance and the need for mechanical ventilation on postnatal day 7 are summarized in Table 4. Peak fluid balance, lowest fluid balance, fluid balance on postnatal day 3, and fluid balance on postnatal day 7 were all significantly higher among patients who required mechanical ventilation on postnatal day 7 compared to those who did not require mechanical ventilation. The median fluid balance by day in those who did and did not require mechanical ventilation on postnatal day 7 is shown in Fig. 1. The probability of mechanical ventilation on postnatal day 7 as determined by peak fluid balance during the first postnatal week and the fluid balance on postnatal day 7 are presented in Supplemental Figures S2 & S3.

In the unadjusted logistic regression analysis, fluid balance over the first postnatal week, including a negative balance at postnatal day 7, was independently associated with the need for mechanical ventilation on postnatal day 7. After adjusting for confounding variables, each fluid balance measure (peak fluid balance during the 1st postnatal week, lowest fluid balance during the 1st postnatal week, fluid balance on postnatal day 3, fluid balance postnatal day 7, and negative fluid balance at postnatal day 7) remained independently associated with the need for mechanical ventilation on postnatal day 7 (Table 5). The multivariable analyses showed that after adjusting for AKI, admission for respiratory failure or sepsis, for every 1% rise in maximum fluid balance there was a 12% increased odds of receiving mechanical ventilation at postnatal day 7 (adjusted OR 1.12, 95%CI: 1.08–1.17; $p < 0.0001$). Similarly, after controlling for the same variables, for every 1% increase in the fluid balance nadir in the first postnatal week there was a 14% increased odds of mechanical ventilation at postnatal day 7 (adjusted OR 1.14, 95%CI: 1.07–1.22; $p < 0.0001$). Furthermore, those with a negative fluid balance on postnatal day 7 had significantly lower odds of being mechanically ventilated on postnatal day 7 (adjusted OR 0.33, 95%CI: 0.16–0.67; $p < 0.0001$).

Survival to NICU discharge for the cohort was 98.3% (*N* = 634). The associations of different measures of fluid balance with NICU survival are shown in Supplemental Table S3. Briefly, only the lowest fluid balance in the first week was associated with improved survival on bivariate analysis. This was not significant on multivariable analysis.

In evaluating the composite outcome of interest, 96.6% of the cohort was alive and free of mechanical ventilation at postnatal day 28. The associations of different measures of fluid balance with the composite outcome are shown in Supplemental Table S4 and Supplemental Table S5. Briefly, there were no significant associations with fluid balance and the composite outcome, albeit that the number of patient with composite outcome of death/MV at day 28 was very small (*N* = 22).

DISCUSSION

In this analysis of the multicenter, multinational, retrospective cohort study of critically ill neonates AWAKEN study we report the epidemiology of fluid balance and its impact on outcomes in the first postnatal week in critically ill term/near-term neonates. In 66.8% of patients there was a positive peak fluid balance in the first postnatal week with 23.5% having a peak fluid balance of ≥5%. Our data confirm that of prior studies; AKI is associated with the development of abnormalities in fluid balance. Furthermore, the current study shows that fluid balance during the first postnatal week is independently associated with the need for mechanical ventilation on postnatal day 7 irrespective of the presence of AKI.

The concept of FO has been well studied in a multitude of pediatric and adult populations and consistently been shown to be associated with adverse outcomes including prolonged mechanical ventilation, increased length of stay, and increased mortality.[9–17,20–25] In critically ill neonates the concept of FO is confounded by the fact that healthy term neonates lose as much as 5–10% of their birthweight over the first postnatal week. Furthermore, altered fluid balance during the first postnatal week may have different etiologies and implications for critically ill neonates of different gestational ages. In a study of 58 critically ill near-term/term neonates, Askenazi et al demonstrated that abnormalities in fluid balance were common, with a median fluid balance excess of 8.2% on postnatal day 3 in those with AKI.

Table 4. Fluid balance stratified by the need for mechanical ventilation at postnatal day 7

Outcome		Whole cohort	Mechanically ventilated at postnatal 7		
			Yes ($N = 58$)	No ($N = 587$)	p
Peak fluid balance 1st week	645	1.0 (−0.5, 4.6)	5.2 (0, 11.9)	0.8 (−0.6, 4.1)	<0.0001
Lowest fluid balance 1st week	645	−3.1 (−5.6, −0.6)	0 (−3.2, 1.5)	−3.3 (−5.7, −1.0)	<0.0001
Fluid balance at postnatal day 3	532	−1.0 (−3.2, 1.0)	0 (−2.0, 2.7)	−1.1 (−3.3, 0.7)	0.03
Fluid balance at postnatal day 7	471	−0.7 (−4.5, 3.5)	3.6 (−0.3, 11.0)	−1.1 (−4.6, 2.7)	<0.0001
Negative fluid balance at postnatal day 7	471	252 (53.5%)	12 (20.7%)	240 (40.9%)	0.0001

Table 5. Crude and adjusted logistic regression modeling for mechanical ventilation in the first postnatal week

Exposure of interest	Crude (OR, 95%CI)	*p*-value	Adjusted (OR, 95%CI)	*p*-value
Peak fluid balance in 1st postnatal week	OR = 1.13 (1.08–1.17)	<0.0001	OR = 1.12 (1.08–1.17)	<0.0001
Lowest fluid balance in 1st postnatal week	OR = 1.15 (1.08–1.22)	<0.0001	OR = 1.14 (1.07–1.22)	<0.0001
Fluid balance postnatal day 3	OR = 1.06 (0.99–1.13)	0.07	OR = 1.05 (0.98–1.12)	0.19
Fluid balance postnatal day 7	OR = 1.12 (1.07–1.18)	<0.0001	OR = 1.12 (1.07–1.17)	<0.0001
Negative fluid balance at postnatal day 7	OR = 0.28 (0.14–0.56)	0.0003	OR = 0.33 (0.16–0.67)	0.002

*All logistic models for mechanical ventilation adjusted for AKI in the first postnatal week, admission for respiratory failure, and admission for sepsis evaluation

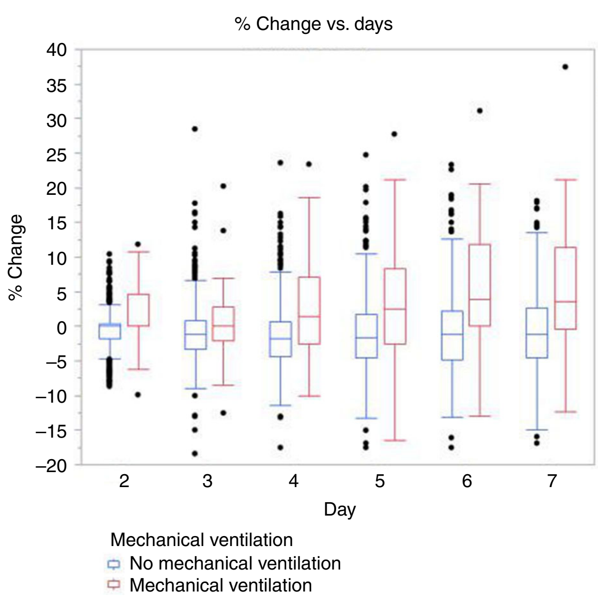

Fig. 1 The median fluid balance (*y*-axis) by postnatal day (*x*-axis) comparing the need for mechanical ventilation at postnatal day 7

However, abnormalities in fluid balance also existed in those without AKI, and suggests that FO may impact patient outcome, even in the absence of AKI.[1] This study did not evaluate the independent association of FO with outcomes. We extend these findings by showing that abnormalities in fluid balance are common in a cohort of 645 critically ill near-term/term neonates with over 60% having a positive fluid balance during the first postnatal week. We also show that the peak fluid balance during the first postnatal week is independently associated with the adverse outcome of need for mechanical ventilation on postnatal day 7. Perhaps more importantly we show that the ability to achieve a negative fluid balance at postnatal day 7 is associated with being ventilator free. We hypothesize that the etiology for this aberrant fluid balance is likely multifactorial in nature with contributions from AKI, extensive fluid provision and excess antidiuretic hormone secretion. Despite the likely multifactorial etiology, preventing FO during the first postnatal week may be a potential therapeutic target for improving outcomes, of which further study is warranted.

Over the past decade the epidemiology of AKI and its impact on outcomes in critically ill neonates has become clear. There have been numerous single center studies that have clearly shown that AKI occurs commonly and has consistently been shown to be associated with adverse outcomes. These research efforts have culminated in the publication of the AWAKEN study, which clearly demonstrated the association of AKI with adverse outcomes. An important finding in this study is that those with AKI were more likely to have higher fluid balance at each point evaluated over the first postnatal week. Impressively over 75% of those with AKI had a positive peak fluid balance during the first postnatal week, and 25% had a peak fluid balance of ≥7.4%. Our study also clearly shows that that abnormalities in fluid balance are independently associated with the adverse outcome of needing mechanical ventilation on postnatal day 7, even after adjusting for the presence of AKI. These data suggest that alternative fluid management strategies may be warranted in those who develop AKI and daily fluid balance should be discussed on each patient, particularly those with AKI. In addition, consideration for correction of serum creatinine for fluid balance, which has been proven to be useful in neonates after cardiac surgery by unmasking additional cases of AKI may also be beneficial in other critically ill neonates.[26]

The measurement of fluid balance in children has classically been performed by a cumulative fluid balance method, or based on changes in weight from a baseline, with both methods demonstrating an association of FO with adverse outcomes.[13,14,20,23,24] Utilization of these methods may prove challenging in neonates for several reasons including but not limited to; the need for daily measurement, the presence of insensible losses, difficulty of precisely measuring breast milk intake and urine output. As part of this study we systematically evaluated the recording of daily fluid balance over the first postnatal week and showed that each method had full data recorded on 74.3% of days. While on the surface this would seem equivalent, the absence of accurate in and out data for all days makes an accurate fluid balance impossible to calculate. Weight-based methodology in neonates allows for missed days and still provides the ability to accurately calculate fluid balance on subsequent days despite missed measurements. Our findings are consistent with a previous report in critically ill neonates that showed daily ins and outs were inaccurate.[27] The current study emphasizes the need for standardized measurement protocols to accurately assess fluid balance and identifies daily weights as an area for improvement.

The largest strength of this study is the number and variety of centers involved in this international multicenter study providing ample sample size to explore the impact of fluid balance accounting for confounders in the association with outcomes. Despite this strength, we acknowledge several limitations to this study. A limitation inherent to any chart review is the reliance on available data from the medical record including serum creatinine, urine output, and fluid composition. This may have resulted in missed cases of AKI. Furthermore, daily weights were not available for all days in the NICU, which may have impacted the results, although subsequent days' weights were utilized to account for this. It is also important to note that because of the inclusion and exclusion criteria, the healthiest neonates were not included in this which may limit generalizability to all neonates in the NICU. An important limitation of this study is that the daily data did not extend past postnatal day 7 limiting our detailed evaluation and conclusions. In future studies it will be important to extend the observation period and confirm our findings.

CONCLUSION

In this retrospective multicenter cohort study, we describe for the first time the distribution and impact of fluid balance in critically ill near-term/term neonates over the first postnatal week. In a cohort that may lose 5–10% of their body weight over the first postnatal week, we show that over 60% of the cohort had a positive peak fluid balance in the first postnatal week. The current study shows that the peak fluid balance and fluid balance on postnatal day 7 were independently associated with the need for mechanical ventilation on postnatal day 7. Furthermore, on adjusted analysis the fluid balance on postnatal day 7 and the inability to achieve a negative fluid balance at postnatal day 7 were the strongest predictors for the need for mechanical ventilation at postnatal day 7. Future prospective studies designed to evaluating different fluid strategies are warranted to determine their impact on outcomes.

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ADDITIONAL INFORMATION

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