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Title:

The effect of fluid bolus therapy on extravascular lung water measured using lung ultrasound in children with a presumptive clinical diagnosis of sepsis.

Category:

Original Research

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Running title:

Lung water changes following fluid resuscitation

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Abstract

Objective: Fluid bolus therapy for the treatment of sepsis may lead to the accumulation of extravascular lung water (EVLW) and result in respiratory dysfunction. We aimed to assess changes in EVLW using lung ultrasound in children with a presumptive clinical diagnosis of sepsis following fluid bolus therapy, and correlate these with respiratory signs.

Methods: A prospective observational study set in the Emergency Department of The Royal Children's Hospital, Melbourne, Australia. Children meeting international consensus criteria for sepsis receiving fluid bolus therapy were included. Respiratory signs were recorded and lung ultrasound performed immediately before, 5 minutes after, and 60 minutes after fluid bolus therapy. A Pediatric Emergency Physician blinded to the participant identity and timing of lung ultrasound calculated EVLW score.

Results: Fifty fluid boluses were recorded in 41 children. EVLW score (range 0-8) increased over the study period, median 1 (interquartile range 0-2) prior to fluid bolus therapy, 1

(interquartile range 0-3) 5 minutes after fluid bolus therapy, and 3 (interquartile range 1-4) 60 minutes after fluid bolus therapy. Respiratory effort, but not respiratory rate or the presence of rales, increased over the study period, and was correlated with EVLW score.

Conclusions: EVLW as measured using lung ultrasound increased following fluid bolus therapy in septic children, and was correlated with an increase in respiratory distress score. Respiratory rate and the presence of rales did not change over the study period. The role of lung ultrasound for titrating fluid bolus therapy in sepsis warrants further investigation.

Key words:

Septicemia, fluid therapy, ultrasonography, extravascular lung water, child

Introduction

Pulmonary edema results from the accumulation of extra-vascular lung water (EVLW), and has been classified as either permeability-induced (characterized by low pulmonary artery occlusion pressure) or cardiogenic (characterized by high pulmonary artery occlusion pressure) (1). Following fluid bolus therapy for sepsis, pulmonary edema may develop due both increased capillary permeability and cardiac dysfunction (2). Alveolar edema leads to impaired gas exchange and reduced lung compliance, and has been associated with acute respiratory distress syndrome, prolonged ventilation, prolonged intensive care unit and hospital length of stay, and mortality in septic patients when corrected for disease severity in experimental (3), adult (4-8) and pediatric studies (9-12). Current evidence suggests that fluid

overload plays a significant role in the development of acute respiratory distress syndrome (ARDS) in children (13), and that in adults with ARDS, an early restrictive approach to fluid management is effective in preventing fluid overload, and reducing the length of mechanical ventilation and intensive care unit (ICU) length of stay (14). Interstitial edema is a precursor to alveolar edema, though it does not impair gas exchange, and is therefore difficult to detect clinically (1, 15, 16). Its detection may, however, be a useful clinical marker for identifying patients at high risk for progression to alveolar edema (17-20).

The clinical gold standard for quantifying EVLW is by computed tomography (CT) (21). However, CT is relatively expensive, cumbersome, involves exposure to large amounts of ionizing radiation, and is not readily and serially available at the bedside to help with clinical fluid administration decisions (22). Thermodilution-based assessment of EVLW may be useful in some settings, but requires invasive monitoring which is usually not available early in resuscitation when the majority of fluid bolus therapy occurs, and its use has not been associated with patient centered benefit (23-25). Chest x-ray has limited utility in the detection of interstitial edema (26). Lung ultrasound is an imaging modality that may be helpful in the early identification of interstitial edema. It is readily available, inexpensive, technically feasible (easy, accurate, and reproducible), and can be performed serially to monitor the physiological effects of fluid bolus therapy over time (27, 28).

On lung ultrasound, normally aerated lung is anechoic, and interlobular septae are not visualized. When sub-pleural interlobular septae become fluid filled (edematous),

reverberation of echoes in surrounding air-filled alveoli generate a B-line artefact (29) (figure 1a). The development of B-lines is dynamic, with the number of B-lines decreasing in real-time during hemodialysis and in neonates during post-natal lung adaptation (30, 31). The presence and number of B-lines on lung ultrasound correlates in a close, linear fashion with EVLW measured post-mortem using gravimetry (16), CT (21, 32), and trans-pulmonary thermodilution (33, 34). Though multiple scanning and scoring systems exist, limited 4 region sonographic evaluation of the anterior chest correlates well with EVLW measured invasively (33-35), and the presence of three or more B-lines per intercostal space has been proposed as the sonographic appearance of interstitial edema (figure 1b) (15).

The primary aim of this study was to report the change in EVLW using the lung ultrasound in children with sepsis over the first hour after fluid bolus therapy. Secondary outcomes were to report changes in respiratory signs (respiratory rate, respiratory distress score, and the presence of rales) and their correlation with changes in lung ultrasound score.

Materials and Methods

The study was designed as a prospective observational cohort study. The study setting was the Emergency Department of The Royal Children's Hospital, Melbourne, Australia; a tertiary-level dedicated pediatric hospital with an annual census of >90 000 emergency presentations. The study was approved by the hospital institutional review board (The Royal Children's Hospital Human Research and Ethics Committee, approval #33169A) and registered with the Australian and New Zealand Clinical Trials Registry (ACTRN

12614000824662). Written informed consent from parents and / or study participants was obtained prior to enrolment.

Inclusion criteria were: clinically suspected sepsis according to international consensus criteria (fever or hypothermia AND tachycardia (mean HR >2 standard deviations above normal for age) OR bradycardia (for infants <1year old mean HR <10th percentile for age) OR tachypnea (respiratory rate >2 standard deviations above normal for age) (36), and treating clinician decision to administer fluid bolus therapy. The decision to administer fluid bolus therapy was not influenced by study procedures, and was informed by a state-wide sepsis guideline (37). Fluid bolus therapy was defined as a 10-20ml/kg bolus (at the discretion of the treating clinician) of intravenous crystalloid solution administered over 10 minutes. Repeat fluid boluses were defined as those administered within 60 minutes of the initial fluid bolus. Exclusion criteria included: underlying uncorrected structural cardiac disease, non-curative goals of therapy, and where the child's family were non-English speaking. Participant age was not an exclusion criterion, the Royal Children's Hospital ED treats patients aged 0-18 years.

Study procedures included recording vital signs, a 10 second video recording of the patient's upper body, and lung sonography immediately prior to, 5 minutes after, and 60 minutes after fluid bolus therapy. Video recordings were randomized and interpreted for Respiratory Distress Score by a Pediatric Emergency Physician blinded to patient's status pre / post fluid bolus therapy. The Respiratory Distress Score ranked clinical signs of increased work of

breathing on a scale of 0-2 (chest movement, intercostal retraction, xyphoid retraction, nasal flaring, and expiratory grunt), with a range of possible scores from 0 to 10 (0 indicating no respiratory distress and 10 indicating severe respiratory distress) (38). Lung ultrasound was performed using a Zonare Z.one (Zonare Medical Systems, Mountain View, CA, USA) with a 5-14MHz linear array transducer. Ultrasound settings were: depth of 6cm, tissue harmonics turned off, compound imaging turned off, and probe frequency set at 7MHz. Lung ultrasound windows were obtained according to the Fluid Administration Limited by Lung Sonography protocol (35). These included two anterior "Blue Points" located in the mid-clavicular line on each side of the chest (total of 4 windows per study) (39). With the participant in a supine position, a three second 2D cine-loop was recorded at each window, and lung ultrasound recordings were interpreted by a Pediatric Emergency Physician with a Diploma in Diagnostic Ultrasound (Australian Society for Ultrasound in Medicine) who was blinded to the patient identity and status pre / post fluid bolus. Lung ultrasound score was calculated as the cumulative total number of B-lines per patient (34), and interstitial edema defined as the presence of 3 or more B-lines in one intercostal space (15). The principal investigator performed all sonographic recordings, and has the qualification of Post-Graduate Certificate in Clinical Ultrasound (The University of Melbourne, Australia). Participant enrolment was limited to times when the principal investigator was available, and therefore represents a convenience sample.

Statistical methods: Non-parametric data were reported as median and interquartile range (IQR). Repeated measurements within the same patient were analyzed using Wilcoxon

signed-ranks test. Sensitivity analysis was performed excluding participants who received more than one fluid bolus (and therefore the same individual had more than one series of measurements taken). Analysis of covariance for potentially confounding baseline characteristics was performed (covariate=baseline lung ultrasound score, dependent variables=lung ultrasound score at 5 and 60 minutes, independent variables=participant age, primary respiratory illness, and volume of fluid bolus therapy (10 vs 20 ml/kg)). Spearman correlation coefficient was calculated for change in lung ultrasound score and change in respiratory rate / respiratory distress score at 5 and 60 minutes. Post hoc analysis of the changes in respiratory signs and lung ultrasound score restricted to those participants with a final (discharge) diagnosis of sepsis was performed. Statistical analysis was performed using Stata 14 (StataCorp. 2015. *Stata Statistical Software: Release 14*. College Station, TX: StataCorp LP).

Results

Between August 2013 and February 2017, 44 participants were assessed for eligibility and 41 included. Enrolment, allocation, follow-up, and analysis data are presented in figure 2.

Participant demographic and outcome data are presented in Appendix Table 1. The median patient age was 1.5 years (interquartile range 0.5-3.88 years, range 2 weeks to 18 years), and 26 (63%) were male. One participant had chronic lung disease, and 10 (24%) had a diagnosis of pneumonia / acute lower respiratory tract infection. Four participants were receiving heated, humidified, high flow nasal cannula oxygen therapy throughout the study period;

none experienced escalation of respiratory support during study investigations. Fluid bolus content was 0.9% saline for all participants, and fluid bolus volume was 10ml/kg in 6 cases, and 20ml/kg in 44 cases. All participants received empiric intravenous antibiotics to cover common bacterial pathogens prior to FBT. All participants were admitted to hospital with a presumptive clinical diagnosis of sepsis, none were discharged home from the Emergency Department. Five participants received inotropic support after being administered a total of 40 ml/kg of FBT according to our local sepsis guideline. Thirteen participants (32%) grew bacteria from a sterile site, 10 from blood, 2 from cerebro-spinal fluid, and 1 from urine.

Changes in lung ultrasound score and respiratory signs over the study period are presented in Table 1. The median respiratory rate did not change, while the median respiratory distress score and median lung ultrasound score increased (figure 3a, 3b, and 3c). Three participants developed 3 or more B-lines per intercostal space over the study period, meeting sonographic criteria for interstitial edema. It is possible that including posterior lung windows may have increased the sensitivity of lung ultrasound for detecting EVLW in this population. Their patient characteristics are presented in Table 2. Participant 1 was hypotensive prior to FBT, none had prolonged capillary refill time. No patient with interstitial edema required respiratory support or was admitted to the pediatric ICU. Nine participants received a repeat fluid bolus between 5 and 60 minutes. On sensitivity analysis, respiratory rate, respiratory distress score, the presence of rales, and lung ultrasound score were not significantly different after exclusion of these participants from analysis (Appendix Table 2). Changes in respiratory

signs and lung ultrasound score restricted to those with a final (discharge) diagnosis of sepsis were not significantly different to those observed overall (Appendix Table 3).

There was a significant positive correlation between the change in lung ultrasound score and change in respiratory distress score over the study period (rho=0.33, p=0.02), but no significant correlation between change in lung ultrasound score and change in respiratory rate (rho=0.13, p=0.46).

On linear regression analysis, participant age, presence of a primary respiratory illness, and the volume of fluid bolus administered were not significantly associated with lung ultrasound score at 5 or 60 minutes after fluid bolus therapy.

Discussion

In children with sepsis, we observed an increase in the lung ultrasound score over the first hour following fluid bolus therapy, suggestive of an increase in EVLW. This may have resulted from increased permeability of pulmonary vessels, or from cardiac dysfunction, both of which are well described in sepsis (2). Without measuring pulmonary artery occlusion pressure, however, we cannot be certain which of these was the primary contributor. Mindful of these limitations, the increase in lung ultrasound score within the first hour after fluid bolus therapy suggests rapid redistribution of administered fluid out of the intravascular space and into the pulmonary interstitium in septic children.

All participants were enrolled in this study with a presumptive clinical diagnosis of sepsis, yet only 9 (22%) had a discharge diagnosis of sepsis. There is a well-recognized discrepancy between the initial presumptive diagnosis of sepsis and the diagnosis applied at patient discharge (40-42), yet this is inevitable given the limitations of current prospectively applied sepsis definitions in children (43-45).

Respiratory rate and the presence of rales did not change over the study period, while respiratory effort increased. Only respiratory effort was correlated with lung ultrasound score. Interstitial edema is associated with a reduction in lung compliance (16), perhaps explaining the observation in our study that respiratory effort increased following fluid bolus therapy and was correlated with an increase in lung ultrasound score. Interstitial edema does not, however, impair gas exchange, which may explain the observation that respiratory rate did not significantly change over the study period. Current sepsis guidelines suggest using the presence of rales as a stop-point for administering fluid bolus therapy (46), though no participants developing rales over the study period despite evidence of increasing EVLW on lung ultrasound. It remains unclear at what point rales develop following fluid bolus therapy, it is possible that their development was not captured during the study period, or that the fluid volume administered was insufficient to result in the development of rales.

The development of interstitial edema on lung ultrasound has been advocated as stop-point for fluid bolus administration in the treatment of ongoing circulatory failure in sepsis (35). The results of this study indicate that lung ultrasound score increases following fluid bolus

therapy for sepsis, though the development of interstitial edema over the first hour following fluid bolus therapy was rare. Furthermore, no participants with interstitial edema on lung ultrasound required respiratory support or ICU admission, making the clinical implications unclear. The role of lung ultrasound as a hemodynamic monitoring tool and its utility in titrating fluid bolus therapy in sepsis requires further study.

Limitations

Study observations only occurred in the first hour after fluid bolus administration. Though EVLW seen on lung ultrasound is thought to develop in real-time (30), it is possible that further changes in lung ultrasound may have occurred at later time points. Furthermore, we cannot rule out the possibility that the increase in lung ultrasound score over the study period was due to the natural progression of disease, as we did not include a control group with sepsis who did not receive fluid bolus therapy. The study population was a convenience sample, and may have systematically excluded some patient groups. We found, however, a similar range of ages, initial and final diagnoses, and rate of positive bacteriological diagnoses to previous sepsis audits performed in our unit using the same inclusion criteria (47). All participants had an initial presumptive diagnosis of sepsis, yet some had an alternate final (discharge) diagnosis. The response to fluid bolus therapy in these patients may have been different to that in patients with sepsis. Further study is needed in the patient group with a final (discharge) diagnosis of sepsis. Nine participants had more than one series of measurements taken due to repeat fluid bolus administration over the study period, though this did not seem to affect the overall study results on sensitivity analysis. As an exploratory

study, the increase in lung ultrasound score and respiratory distress score observed over the study period have unknown clinical significance. Further study is warranted to evaluate the clinical implications of these findings.

Conclusions

EVLW as detected on lung ultrasound increased over the first hour following fluid bolus therapy in septic children, and was correlated with an increase in respiratory effort. These changes suggest the rapid development of interstitial edema with decreased lung compliance. Lung ultrasound may have a role as a hemodynamic monitoring tool for titrating fluid bolus therapy in sepsis.

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Tables:

Table 1. Changes in respiratory signs and lung ultrasound score in the first hour after treatment with fluid bolus therapy.

	Immediately prior to fluid bolus therapy (n=50)	**5 minutes after fluid bolus therapy (n=50)**	**60 minutes after fluid bolus therapy (n=41)**
Respiratory rate (breaths per minute); median (IQR)	36 (28-54)	36 (26-51)	39 (28-45)
Respiratory distress score; median (IQR)	2 (0-4)	2 (1-3)	3 (1-4)

Presence of rales; n (%)	3 (7)	3 (7)	4 (10)
Lung ultrasound score; median (IQR)	1 (0-2)	1 (0-3)	3 (1-4)

IQR=interquartile range

Table 2. Characteristics of participants meeting sonographic criteria for interstitial edema*.

Participant number	**Age**	**Volume of fluid administered (ml/kg)**	**Total prior volume of fluid administered (ml/kg)**	**Hospital length of stay (hours)**	**Discharge diagnosis**
Participant 1	2 weeks	20	0	168	meningitis
Participant 2	2 months	20	0	336	Congenital neutropenia
Participant 3	3.5 years	10	10	144	sepsis

*interstitial edema was defined as >3 B-lines per intercostal space.

Figures:

Figure 1. a) Sonographic appearance of B-lines (arise from the pleural line, extend to the edge of the screen, and erase A lines). A lines represent reverberation artefact of the pleural line. b) three or more B-lines per intercostal space thought to represent interstitial edema.

Figure 2. Enrolment flow-chart for study participants.

Figure 3. Lung ultrasound score, respiratory rate, and respiratory distress score at each study time point (median, interquartile range, range).