Less is more

*Fluids in critically ill children with acute respiratory failure*

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General Discussion and Future Perspectives
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Fluid overload is a common phenomenon in critically ill patients that has an important impact on comorbidity and recovery. Its importance has been recognized in recent years.

PATHOPHYSIOLOGY OF FLUID OVERLOAD

During critical illness, fluid overload may arise due to increased pro-inflammatory damage leading to increased permeability and vascular leak. Fluid extravasation into the interstitium leads to edema in specific organs prone to fluid accumulation, such as the lungs (1). In chapter 2, we have elaborately discussed the adverse effects of fluid overload and possible age-dependent pathophysiological differences.

Inflammation during critical illness or syndromes such as acute respiratory distress syndrome (ARDS), causes extensive endothelial and epithelial tissue damage and increases permeability enhancing the vascular leak and accumulation of fluid (2). The endothelium itself also seems to have a pro-inflammatory role in situations of increasing intravascular pressure with corresponding mechanical stress, which activates further cytokine release, adding to further damage and leakage of fluids into the interstitium (3-5). A rather recently discovered player in the field of endothelial research, is the glycocalyx, a layer of luminal membrane-bound glycosaminoglycans and associated glycoproteins involved in the maintenance of the integrity of the endothelial barrier, regulation of leukocyte and platelet adhesion and transmission of shear stress to the endothelium (6). In critically ill adult patients with septic shock, ARDS, post-cardiac surgery, but also in hypervolemic states, the glycocalyx has been found to disintegrate (7-11). Components of the glycocalyx hereby shed into the bloodstream and can be measured to lead to activation of pro-inflammatory and coagulatory pathways as well as increased endothelial permeability (6, 10). One study comparing fluid loading to normovolemic hemodilution prior to elective surgery in adult patients has shown an increased degree of glycocalyx shedding in patients receiving hypervolemic fluid loading (8). Moreover, a recent study in adult patients with septic shock has shown that higher volumes of intravenous fluid loading are associated with increased glycocalyx degradation (12). As the glycocalyx itself ranges from a thickness of 2-4.5 μm depending on the size of the artery, it takes up quite a
large part of the intravascular volume. Disintegration of the glycocalyx might therefore lead to relative hypovolemia as there is more intravascular volume left (13). Hypothetically this effect might contribute to the need to resuscitate critically ill patients. Although fluid resuscitation clearly has its place in critically ill patients, care should be taken as overzealous volume loading might lead to glycocalyx degradation with ensuing activation of inflammatory pathways (14).

As mentioned above, fluid overload in itself might enhance different pro-inflammatory pathways (1-3). In chapter 3, we aimed to study the impact of fluid overload on the inflammatory response in a model for ARDS in rats. Animals were inoculated with LPS to induce ARDS and subsequently ventilated for 6 hours. During the 6 hours ventilation period, rats were randomized to receive either a conservative fluid strategy or a more liberal fluid strategy. We assessed for inflammation in all groups by neutrophil influx in the lungs and pulmonary inflammatory cytokines IL-6, MIP-2, IL-10, TNF-α and IL-1β. While no difference between fluid strategy was found in neutrophil influx, we did find higher concentrations of IL-1β and TNF-α in the animals receiving conservative fluids. This is a striking contrast with previously mentioned studies, although comparison is hindered by substantial differences in study population and set-up. For example, in patients with acute lung injury, a decrease in plasma angiopoietin-2 level in patients receiving conservative fluid therapy as compared with a more liberal fluid strategy was found over the course of time (3). Kuebler et al. specifically studied the effect of increased vascular pressure on isolated lung venular capillaries, thereby observing that increased pressure elevates endothelial calcium, endothelial exocytosis and luminal expression of P-selectin, indicating activation of early vascular inflammatory response (4). Another study observed C-reactive protein to be independently associated with a higher extracellular fluid/total body water ratio in adult patients on peritoneal dialysis (5).

In chapter 4, we similarly assessed for inflammation in an ovine model of ARDS as induced by oleic acid (OA) comparing conservative versus liberal fluid strategy. We again assessed for neutrophil influx in the lungs and IL-8, which showed no differences between fluid groups for both parameters. Yet, this may also have been related to the OA model, since the inflammatory response in this model may differ from other non-chemical induced ARDS models (15). While these studies together with the existing literature do not provide us with any conclusive evidence concerning the role of fluid overload, it is evident that fluid strategies may have an effect on inflammation even in animal models with brief duration of mechanical ventilation and clinical illness. Currently, the choice of fluid maintenance strategy in animal models varies widely (16, 17) and we believe this is an important point of attention to ensure optimal translation of experimental animal research.

Another aspect of the pathophysiology of fluid overload is the occurrence of increased permeability. While disputably going hand-in-hand with increased inflammatory damage, in both our experimental animal models as described in chapter 3 & 4, we did not find an effect on pulmonary permeability as measured by immunoglobulin-M (IgM) in bronchoalveolar
lavage fluid. Yet, in chapter 3 we did observe a higher degree of lung wet-to-dry ratio in adult rats suggesting increased pulmonary edema. As permeability itself did not show any change in this group, this increase in pulmonary fluid may merely be the result of increased extravascular water distribution in similarly injured lungs between groups.

While in chapter 4, we did not find a significant effect of fluid strategy on wet-to-dry ratios of either lung or kidney, we did see a substantial decrease in microvascular flow of at the end of our experiment in the restrictive fluid strategy group as compared to both the control animals as well as the animals in the liberal fluid group. This suggests that being too restrictive in fluids has an important downside as microcirculation may be compromised and, while other clinical parameters not yet show any significant changes, this might be the first indication of possible risks associated with restricting fluids and subsequent clinical implications should be considered.

**AGE-DEPENDENCY IN FLUID OVERLOAD**

Earlier in this thesis, we described a difference in fluid homeostasis and fluid distribution between adults and infants. In chapter 3 we therefore investigated the effect of different fluid strategies in two different age categories of animals; adults and infants. In all organs studied, lung, kidney, liver and heart, we found higher wet-to-dry ratios in infant rats as compared to adults. We believe this may be partially attributable to baseline differences in fluid distribution at this age. Overall body water content of infants is higher than that of adults, who thus have a lower extracellular water/total body water (ECW/TBW) ratio (18). This is corroborated by a study in children admitted to PICU investigating extravascular lung water (EVLW) content after resolution of their illness. This study showed a relatively high EVLW content when corrected for body weight in children as compared to known adult benchmarks (19). On the other hand, this could also be explained by the fact that children have lesser aeration of the lung as compared to adults and therefore relatively more interstitial tissue. As tissue always contains fluid, it makes sense that younger children have higher extravascular lung water content per kg body weight. Moreover, there may be substantial differences in alveolar fluid clearance, i.e. the expression of different epithelial ion channels in the lung. In chapter 3, we assessed Na+/K+/ATPase activity, which is an important ion pump and marker of alveolar fluid clearance in the lung. Interestingly, we found a lower activity of Na+/K+/ATPase in infants when compared to adult rats, which too might in part explain the higher lung water content in infants as compared to adult rats. This is in line with developmental changes in Na+/K+/ATPase expression (20). Another type of ion channels for fluid clearance in the lung are the epithelial sodium channels (ENaC), of which their expression is also suggested to be age-dependent (21-23). In contrast to the Na+/K+/ATPase pump, higher expression of ENaC is found in children, which might help making children less prone to develop clinically relevant pulmonary edema.
It is important to note that there are already differences in severity of ARDS between ages, with adults being more severely affected than infants (16, 24, 25). In chapter 3, we have therefore also investigated the differences in inflammatory and permeability responses to equivalent doses of LPS and indeed found these to be less severe in infant rats as compared to adult rats. Similar age-dependent effects have been described in several experimental animal studies of different acute lung injury models (21-23). It seems adult animals are more susceptible to development of inflammatory damage with corresponding increased permeability. This might also explain why we did see a beneficial effect of the conservative fluid regimen on lung wet-to-dry ratios in adult rats, yet not in infant rats. Adult rats thus have a higher susceptibility to develop fluid overload and therefore benefit more from a conservative fluid management strategy.

**ADVERSE EFFECTS OF FLUID OVERLOAD**

Investigating the pathophysiological mechanisms of fluid overload would not be necessary were it not that fluid overload has been associated with adverse outcome in a staggering amount of published research in many different populations of adult and pediatric critically ill patients. In adults, fluid overload is associated with mortality, less ventilator-free days and ICU stay in patients with ARDS (26-28), septic shock (29, 30), post-surgery (31) and in a general ICU population (32, 33). Similarly, many different pediatric ICU populations have been studied. In pediatric ARDS (PARDS), fluid overload is also associated with higher mortality, longer duration of mechanical ventilation and worse oxygenation status (34-37). Children with shock or sepsis (38-40), post-cardiac surgery (41-45), but also in the general PICU population there are similar associations of fluid overload with adverse outcome (46, 47). Most of these, however, are extremely critically ill and complex patients. We were curious to investigate the effect of fluid overload in pediatric patients admitted to the PICU with relatively mild, single organ failure. Therefore we studied children with respiratory insufficiency due to bronchiolitis. This is a prevalent patient group, although respiratory insufficient, usually running a more benign course of illness with little cardiovascular compromise. The results of this study are presented in chapter 5 in which we studied the effect of fluid overload in a population of 135 pediatric patients mechanically ventilated for respiratory insufficiency due to severe bronchiolitis. We found a significant association between early fluid overload, measured by the cumulative fluid balance on day 3 of mechanical ventilation, and duration of mechanical ventilation. This is similar to all other previously mentioned cohorts of critically ill children. We did not research the possible association between fluid overload and mortality in this cohort, as mortality is negligible in this illness. Moreover, we did not find an effect of fluid overload on oxygenation, though oxygenation due to an increase in EVLW is often not the main concern in patients with bronchiolitis, as the cause of respiratory insufficiency is mainly due to mucus plugging.
and recurrent apneas. In existing literature of other PICU populations some studies do find a correlation with oxygenation (37, 46, 47), while in others it is not clear (34, 35). An important systematic review has recently been published covering the whole range of pediatric critically ill patients and the association of fluid overload with adverse outcome (48). This review also included our study on bronchiolitis patients. Importantly, our results have recently been mirrored by Flores-Gonzalez et al. in a prospective multicenter study further underlining the worsened outcome in severe bronchiolitis patients in the PICU associated with a positive fluid balance after 24 hours. These patients were found to have longer duration of both invasive and non-invasive ventilation, as well as longer hospital and PICU stay (49).

TIMING OF FLUID OVERLOAD

In the context of timing many studies focus on fluid overload developing in the first 72 hours of critical illness or mechanical ventilation. Several studies show that the increase in fluid overload is substantial in the first 24-72 hours of mechanical ventilation, reaching a percentage of fluid overload ranging from 7-11% (34, 46, 47). More so, association with adverse outcomes, such as prolonged duration of mechanical ventilation, has been found for fluid overload developing within 24 hours (40, 41, 50), 48 hours (46, 51, 52) and 72 hours (39, 53). In our study presented in chapter 5 we also investigated this correlation at 72 hours, but in addition analysed the same correlation for days 1 through 7 of invasive mechanical ventilation. We found a significant association between cumulative fluid balance and ventilation duration on days 2-5, yet the strongest association was on day 3. These studies suggest that the first 72 hours in fluid management are essential in preventing fluid overload.

On the other hand, there are also studies investigating the occurrence of fluid overload during the entire PICU admission. These studies mainly focus on whether or not fluid overload, using different definitions and cut-off points, occurred during PICU admission or they used the maximum fluid overload during PICU admission. Likewise both occurrence of fluid overload and higher peak fluid overload in these studies were associated with poorer outcome such as oxygenation failure, ventilation days, pediatric organ dysfunction scores and risk of mortality (38, 47, 54).

Scrutinizing this association we were curious to see if we could already see an effect of restrictive fluid strategy very early in disease as we believe that this is the best window for prevention of fluid overload. In chapter 3 & 4, we evaluated this effect in two experimental ARDS models, yet found no significant effect on gas exchange and similar hemodynamic stability in both fluid groups. Of course, experimental animal studies provide us only with a relatively short intervention of approximately 6 hours, which may not be sufficient enough time to develop detectable clinical differences. Yet, in chapter 3 we did already see a reduction in pulmonary edema in adult rats, alas not in the infant rats or in the lambs studied in chapter
4. As mentioned above, this may be another indication that there is an age-specific difference within the effect of fluid management strategies as adult animals seem more susceptible to develop fluid overload and thus have greater reduction of pulmonary edema when receiving conservative fluids.

**PREVENTION OF FLUID OVERLOAD**

Fluid therapy may be administered for different reasons in different phases in a patient’s illness. Vincent et al. (55) describes these phases by the SOSD principle: Salvage, Optimization, Stabilization and De-escalation. During the resuscitation, or salvage phase, fluid boluses have generally been proven as beneficial, yet their positive effect on mortality has also been subject of debate (56-58). It is important to note that fluid resuscitation is only beneficial, i.e. leading to an increase in cardiac output, if a patient is a responder (59). Responders can be recognized in different ways, most commonly by performing a fluid challenge. During a fluid challenge a small amount of fluid is administered and the immediate effects on cardiac output and central venous pressure (CVP) are observed (55). Being a responder, cardiac output increases with only minimal change of CVP. This is a physiological response so this does not inherently mean fluid boluses should be given continuously. One should always have a good reason to increase cardiac output. The elasticity of the arterial system determines whether an increase in cardiac output, or stroke volume, will also lead to an increase in blood pressure. Advanced hemodynamic monitoring is needed to assess and guide this process. In chapter 4, it seems that resuscitation is equally successful when employing a conservative fluid protocol using more vasopressor medication and less fluids, in contrast to a liberal fluid protocol (more fluids, less vasopressors). Of course, this was an experimental protocol and the clinical setting calls for a less extreme version of this set-up. Nevertheless, this study shows that there does not seem to be much, if any, benefit of administering liberal fluids over restrictive fluids.

After the resuscitation phase, the maintenance phase, or optimization phase, ensues. In this phase, fluids are still administered, leaving a lot more time for fluid overload to develop. The accumulation of fluid already early in disease with associated adverse outcome calls for an intervention. In a recent trial in critically ill adult patients investigators took stock of all fluid sources in the ICU to assess the burden of ongoing fluid administration (60). They classified fluid input into sub-categories; resuscitation fluids, blood products, maintenance and replacement fluids, nutrition and fluid creep. The latter is defined as all the fluid going in as vehicle for intermittent and continuous medication, volumes used to keep venous catheters open and volume due to concentrated electrolytes. This fluid creep was responsible for a total of 32.6% of mean total daily volume, next to 24.7% of maintenance and replacement fluids, whereas only a small percentage of 6.5% was defined as resuscitation fluids (60). We agree
with the authors that this stresses the underestimation of volume that patients receive during ICU admission and believe that this happens on a similar scale in our pediatric ICU patients.

In children, causative evidence up until recently was lacking entirely. Recently an implementation study was performed in critically ill children with ARDS and sepsis, in whom a stricter fluid strategy was implemented to prevent early fluid overload (61). Patients were treated with maintenance fluids at 50% of requirements, reduction of vehicle volumes for medication, early start of enteral feeding and diuretics and active dynamic monitoring of preload markers. Hereby, they succeeded in lowering peak fluid overload percentage to 6.3% compared to a historical cohort in whom this was 12%. The restrictive group had a shorter duration of mechanical ventilation and PICU length of stay as compared to the historical cohort treated with standard fluid protocols.

With this increasing amount of evidence, we believe it is time for a large multicenter RCT in critically ill children to really determine the causative relation between fluid management and outcome. Therefore, we have performed a feasibility study as described in chapter 6. Patients were randomized to a conservative or standard fluid maintenance regimen based on current clinical practice at that moment in our PICU. We aimed to investigate the feasibility of conducting a large-scale trial comparing two different types of fluid strategy in an easy and pragmatic protocol in mechanically ventilated patients with bronchiolitis. As this was a feasibility study, our main outcomes were feasibility markers such as adherence and safety parameters. We reached a moderate adherence of 75% in the conservative fluid group. When fluid intake exceeded our target intake, this was principally due to high parenteral load, i.e. high medication needs or parenteral feeding. This corresponds to the earlier mentioned fluid creep and suggests that this is the main portion of fluid volume management that leaves room for improvement and further fluid restriction.

Fluid restriction is the first and simplest strategy to start reducing fluid overload. Yet, in children many impeding factors arise from this. Accomplishing sufficient nutrition especially in children is of utmost importance to prevent nutritional depletion, muscle wasting and decreased immune function and is also associated with better outcome (62-64). In the study presented in chapter 6, we have carefully chosen our nutritional requirements and succeeded in accomplishing these needs in caloric and protein intake in both fluid management arms, although we did not yet succeed in reducing fluid balances by restricting fluids in comparison to patients receiving standard fluids. The patients in the standard fluid arm had significantly higher diuresis without receiving higher dosages of diuretics, indicating that these patients were still capable of maintaining adequate fluid balance without the aid of medication. A potential explanation for this could be that there was little to no renal failure in this patient cohort. It also shows that fluid administration exceeded actual needs, making this type of fluid management strategy a potential harmful form of overtreating our patients. These outcomes suggest that there might be room for further fluid restriction in the future to lower fluid balances. Earlier important research in this field describes a large randomized controlled trial
in adult patients with acute lung injury comparing a conservative versus a liberal fluid management protocol (65). This study was published in 2006 and follows an extensive algorithm based on various intravascular pressures and urine output. A conservative fluid strategy led to a significantly lower cumulative fluid balance with corresponding better outcomes such as more ventilator-free days and improved lung function. They did not detect a benefit on their primary outcome of 60-day mortality.

An effective way to achieve increased diuresis is the early use of diuretics (66). As the study by Diaz et al. (61) suggested, the use of diuretics was helpful in preventing the accumulation of fluid overload. Furthermore, other studies in adult patients with acute lung injury show that furosemide in combination with albumin also improved oxygenation, hemodynamic markers and fluid balance (67, 68). Furosemide has also been shown to improve lung injury scores and oxygenation in experimental animal models (69). We therefore believe that early use of diuretics could play an important role in improving fluid balance and should be incorporated in any future randomized controlled trial protocol.

Another more invasive way of reducing fluid overload is the use of continuous renal replacement therapy (CRRT). Studies in patients receiving CRRT show that greater fluid overload at the start of CRRT has been associated with mortality, also after adjusting for confounding disease severity parameters (70-74). Earlier start of CRRT might therefore even be more beneficial, as survivors after CRRT have significantly less days in the PICU prior to start of CRRT than non-survivors do (71, 74).

**DETECTING FLUID OVERLOAD**

Fluid overload is associated with increased amounts of pulmonary edema, as can be measured by extravascular lung water (EVLW). EVLW increases due to greater lung permeability, increased hydrostatic pressure or both (75). Increased EVLW is associated with mortality in both critically ill adults (76) and children (77).

EVLW may be measured by bedside chest radiography (CXR), computed tomography (CT) or transpulmonary thermodilution (TPTD). All of these methods have their own drawbacks constraining their usefulness. EVLW signs on CXR lag behind clinical changes. Moreover, the diagnostic accuracy of CXR is relatively low, ranging from 58-72% (78, 79). CT is considered more accurate, yet transporting a critically ill patient to the radiology department comes with considerable risks. In addition, exposure to radiation is, specifically in children, a main limitation. Transpulmonary thermodilution is accurate and can be performed bedside, yet is costly and requires multiple invasive catheters (80). A relative new-comer in the field is lung ultrasonography (LUS). Fluid-filled interstitial interlobular septae form multiple vertical artefacts on lung ultrasound, called B-lines, useful in the assessment of interstitial pulmonary edema (81) (EVLW), fluid management and in the definition of ARDS (39). LUS is a bedside,
non-invasive, easy, repeatable and radiation-free diagnostic tool, with potential for obtaining
essential information on pulmonary hydration status. The correlation between B-lines and
e extravascular lung water has been demonstrated in a variety of clinical settings showing good
sensitivity and specificity (82-84). For example, in critically ill adults with ARDS, the correlation
between EVLW and B-lines was found to be significant (85). In order to study this we inves-
tigated the correlation between fluid overload and LUS scores in mechanically ventilated
critically ill children with severe bronchiolitis (chapter 7). Performing serial lung ultrasounds
on days 1, 2, 3 and 6 of mechanical ventilation, we however found no correlation between
ultrasound scores and cumulative fluid balance. Findings on this subject in the literature are
not always consistent, as in a study in children on dialysis, changes in B-line scores did corre-
late with fluid overload as judged by weight in- and decrease (86). However, in another study
in pediatric patients after congenital heart defect surgery, LUS scores were not associated
with reported fluid balances (87).

Different theories might follow from these results. Firstly, this was a LUS study in patients
with severe bronchiolitis, in which besides B-lines due to increased lung water content,
other anomalies based on the underlying respiratory disease might also be present. This is
suggested by multiple studies in children with less severe bronchiolitis in emergency depart-
ment or general pediatric ward settings (88, 89). Bronchiolitis in itself also shows images
of B-lines, consolidations and pleural line abnormalities, possibly hindering the scoring of
B-lines solely due to fluid overload. Another explanation might be that fluid overload might
not always accumulate in the lungs as much, but spreads to other, yet unknown, tissues. This
is also suggested by the fact that in our ovine ARDS model described in chapter 4, we found a
significantly higher cumulative fluid balance at the end of the experiment of the lambs in the
liberal fluid group, yet no difference in EVLW.

After performing the study described in chapter 7, it seems that LUS is not sensitive enough
to distinguish limited amounts of pulmonary congestion in this particular population of severe
bronchiolitis patients. Of course, the lung disease itself might obscure the occurrence of pulmo-
nary fluid overload in these images. Moreover, these patients have not received large amounts
of fluid during resuscitation. LUS might have more potential during resuscitation, wherein fluid
boluses are given fast and in repetition, to detect the occurrence of (pulmonary) edema ear-
lier than when it becomes clinically apparent (i.e. liver enlargement, increased lung crackling
sounds). We believe LUS may also provide major diagnostic possibilities in other pediatric
populations, such as post-cardiac surgery or in the less severely affected bronchiolitis patient.

**FUTURE PERSPECTIVES ON FLUID OVERLOAD**

While research on the adverse effects of fluid overload is mounting up and the current notion
arises to be more restrictive in our fluid management, there is currently still no consensus
on the exact fluid strategy protocol. Future research should therefore focus on reaching this consensus and investigating the optimal fluid strategy protocol.

In order to reach this objective, a national, or even international, survey among pediatric intensivists should be held in order to record fluid therapy goals, targets of cumulative fluid balance and current use of fluids and diuretics in a wide range of PICUs. The outcomes of this survey can be incorporated in the composition of a large multicenter randomized controlled trial in collaboration with a delegation of experts in the field of pediatric intensive care. As we have already discussed briefly in the paragraph on management of fluid overload, the restrictive fluid strategy will need to be adapted to include further fluid restriction, early use of diuretics and maybe even other methods of fluid removal such as the use of CRRT. Given the controversial effects of different fluid strategies on the final most relevant outcome, i.e. the CFB, not the fluid strategy itself but the cumulative fluid balance should be considered as an endpoint in these studies.

In any future trial, it is important to realize the difficulty of synchronizing extubation protocols, which implies the need for strict and unambiguous extubation readiness tests. Moreover, it is not possible to blind for the amount of fluids used, which may potentially influence physician’s decision making. Our experimental animal study in lambs in chapter 4, proposed a possible effect of fluid restriction on microcirculation in the early resuscitation phase of ARDS. Although this was an extremely restrictive fluid strategy in an experimental animal model, this should be taken into account when designing a future trial. Next to this, kidney function should be warranted to prevent acute kidney injury from occurring.

Sample size is a major issue in pediatric critical care research, which is why for a future study a larger collaboration in the PICU field should be organized to obtain optimal inclusion of patients and external validity of the results. In chapter 6 we proposed a sample size calculation based on a minimal clinically important difference (MCID) in ventilation duration between fluid treatment groups of one day. This MCID should be considered in any future collaboration between PICUs, as well as that the inclusion of a wide range of pathologies in any future study potentially increases the needed sample size further.

**CONCLUSION**

By performing a series of studies in a translational project, including experimental animal studies and both retrospective as prospective clinical studies, we have investigated the occurrence and effect of fluid overload in a PICU setting. This thesis underlines the importance of early recognition of fluid overload and to start focusing on treating our patients with optimally chosen, tailor-made fluid strategies. Blindly restricting fluids however, may potentially be harmful and therefore care should be taken in carefully monitoring and managing all aspects
accompanying fluid overload as discussed in this thesis. In other words, less is more, only when more is too much.
REFERENCES


Chapter 8


