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Indications and management of mechanical fluid removal in critical illness

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Editor's key points

- The authors provide guidelines on the mechanical management of fluid overload based on a Delphi analysis.
- Further work is needed on the role and practice of mechanical fluid removal in critically ill patients not meeting fluid balance goals.

Background. The Acute Dialysis Quality Initiative (ADQI) dedicated its Twelfth Consensus Conference (2013) to all aspects of fluid therapy, including the management of fluid overload (FO). The aim of the working subgroup 'Mechanical fluid removal' was to review the indications, prescription, and management of mechanical fluid removal within the broad context of fluid management of critically ill patients.

Methods. The working group developed a list of preliminary questions and objectives and performed a modified Delphi analysis of the existing literature. Relevant studies were identified through a literature search using the MEDLINE database and bibliographies of relevant research and review articles.

Results. After review of the existing literature, the group agreed the following consensus statements: (i) in critically ill patients with FO and with failure of or inadequate response to pharmacological therapy, mechanical fluid removal should be considered as a therapy to optimize fluid balance. (ii) When using mechanical fluid removal or management, targets for rate of fluid removal and net fluid removal should be based upon the overall fluid balance of the patient and also physiological variables, individualized, and reassessed frequently. (iii) More research on the role and practice of mechanical fluid removal in critically ill patients not meeting fluid balance goals (including in children) is necessary.

Conclusion. Mechanical fluid removal should be considered as a therapy for FO, but more research is necessary to determine its exact role and clinical application.

Keywords: fluid balance; fluid therapy; kidney failure

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Volume overload or fluid overload (FO) (here defined as a positive value of the total input − total output/the initial body weight) is a common occurrence in critically ill adult and paediatric patients and is associated with deleterious consequences that worsen with increasing severity of FO.[1–6] For instance, a paediatric study found a 3% increase in mortality for every 1% increase in FO and children with more than 20% FO had an odds ratio for mortality of 8.5 compared with <20% FO.[4] In particular, there appears to be a significant interaction between FO and acute kidney injury (AKI) in determining the risk of adverse outcomes. Positive fluid balance has been associated with increased AKI incidence,[7] and non-recovery of renal function in AKI survivors.[5 8] A large number of observational studies have associated FO in patients with AKI and death in both adults[9 10] and children,[3 11] and FO remains independently associated with adverse outcomes in AKI after accounting for illness severity and haemodynamic instability in multivariate analyses.[2 3 9 10–13] However, without prospective data, it is difficult formally to separate the effect of FO as a marker of illness severity and its treatment, from a direct causative role in outcomes that might be modifiable by mechanical or pharmacological fluid removal.

† These authors contributed equally to the manuscript and fulfill criteria for first authorship.

Broadly, FO occurs either secondary to increased fluid intake (such as i.v. fluid or blood product administration), decreased urinary output, or a combination of both (Table 1). In many cases, FO is iatrogenic, secondary to continuous i.v. fluid therapy over a period of days without adequate attention to daily fluid balance. In other cases, FO results from obligate daily fluid needs (such as for total parenteral nutrition and i.v. antibiotics) in the setting of poor urine output. The magnitude of FO can be staggering; in an analysis of the Vasopressin and Septic Shock trial, fluid accumulation over the first 12 h of care ranged from 8 to as high as 30 litres in patients presenting with sepsis.[14] In those patients who develop progressive FO, pharmacological, mechanical modes of therapy, or both may be utilized to restore an optimal volume status and improve outcomes (Fig. 1). This paper describes the indications and use of mechanical fluid removal techniques in the critically ill patient and represents the work of the Twelfth Acute Dialysis Quality Initiative (ADQI) workgroup on mechanical fluid therapy held in London, UK, in September 2013.

Table 1 Causes of FO

Excessive fluid intake
Early
Need for blood products
Aggressive fluid administration
Late
Continued fluid administration despite positive fluid balance
Obligate daily fluid therapy in excess of losses
Oliguria or anuria (inadequate fluid losses)
AKI (+/− chronic kidney disease)
'Third spacing' (sepsis, pancreatitis, burns)
Severe heart failure—poor cardiac output from any causes
Pre-existing severe chronic kidney disease

Methods

The 12th ADQI meeting on Fluid Therapy assembled experts in the area, including nephrologists, intensivists, paediatricians, emergency physicians, and physiologists and performed a modified Delphi analysis of the existing literature. The Delphi method is a structured and standardized process for collecting, summarizing, and disseminating knowledge from a group of experts focused on a specific problem or task. Further information is available at: www.adqi.net.

Before the meeting, the working subgroup 'Mechanical fluid removal' developed a list of preliminary questions and objectives with particular focus on indications, prescription, and monitoring of fluid removal using mechanical devices. It was recognized that the work was a continuation from the work of other groups, in particular the work of the subgroup 'pharmacological management of fluid overload'.[15]

The group performed a literature search using the MEDLINE database (via the PubMED interface) and the following search terms: 'fluid balance', 'fluid overload', 'fluid accumulation', 'extracorporeal', 'ultrafiltration', and 'mechanical'. The bibliographies of relevant review articles or editorials and personal records of participating members were searched for any additional potentially relevant studies. After review of the literature, the group summarized the existing evidence. In the case of lack of evidence on specific key areas, the working subgroup formulated consensus statements and questions for future research.

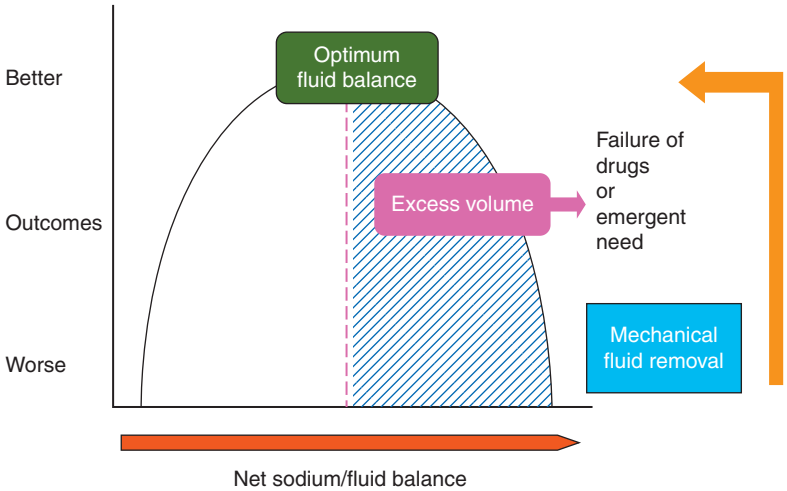

Fig 1 Pathways in fluid management. Each patient has an optimal fluid balance that can be disturbed in critical illness. In some cases, patients may become fluid overloaded as a consequence of aggressive fluid resuscitation. In other situations, patients may present with FO, such as in acute decompensated heart failure. In any event, therapies to reverse the FO are required to restore optimum fluid balance. Mechanical fluid removal should be considered when emergent and rapid fluid removal is needed or when pharmacological therapies have failed. Figure reproduced with permission from ADQI 12 (Acute Dialysis Quality Initiative. http://www.adqi.org/).

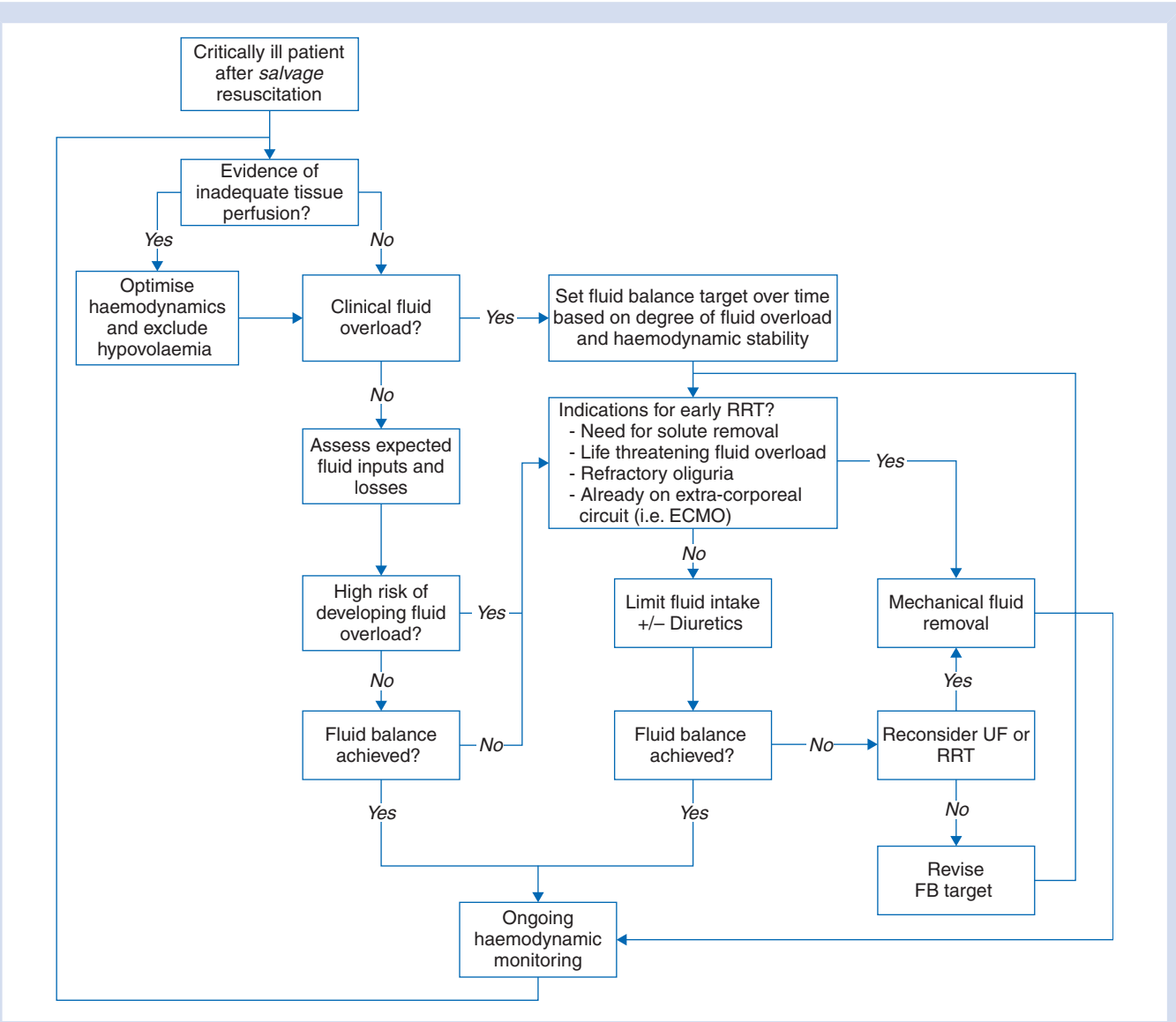

Fig 2 Fluid management strategies in critical illness: the place of mechanical fluid removal. Once hypovolaemia has been corrected, FO needs to be avoided. If clinically significant FO occurs or is anticipated, it needs to be quantified. Early mechanical fluid removal should be considered if specific indications exist. During therapy, haemodynamic and intravascular volume status should be monitored and fluid removal rate and fluid balance targets reassessed regularly aiming for clinical stability and tolerance of fluid removal. Within this pathway, RRT should be considered at any point if additional solute clearance is necessary. ECMO, extracorporeal membrane oxygenation; FB, fluid balance; RRT, renal replacement therapy; UF, ultrafiltration. Figure reproduced with permission from ADQI 12 (Acute Dialysis Quality Initiative. http://www.adqi.org/).

Results

We considered the place of mechanical fluid removal within overall fluid management strategies of the critically ill (Fig. 2). From this process, we highlighted decision-making around the assessment of FO, including indications for mechanical methods to resolve or limit FO, and also targets and management of mechanical fluid removal techniques.

Assessment of FO

In order to determine the timing for mechanical fluid removal in the critically ill patient and also safely prescribe the goals and rates of fluid removal, it is critically important to continuously assess the volume status of the patient. A combination of clinical, laboratory, and haemodynamic (both static and dynamic) variables and their trends should be utilized to best assess the patient's effective volume status and inform clinical decision-making (Table 2).[16–20] The particular methods chosen to monitor fluid status are at the discretion of the clinician as no study has determined the superiority of a particular method and it is advised to utilize a combination of these variables to make treatment decisions and guide therapy. Furthermore, accurate records of all fluid intakes and outputs must be kept and reviewed regularly. In fact, charted fluid input and output may be more accurate in quantifying fluid balance than measuring body weight changes with a scale which has typically

Table 2 Methods to assess volume status (based on ref. 8)

Clinical variables
Serial weight
Cumulative fluid balance ('ins and outs')
Vital signs (arterial pressure, pulse, orthostatic changes)
Urine output
Physical examination (capillary refill, skin turgor, skin perfusion, urine output)
Chest radiograph
Historical information (recent fluid losses, oral intake, medications)
Laboratory variables
Blood lactate and lactate clearance
Central or mixed venous oxygen saturation
Urinary biochemistry (fractional excretion of sodium, urea)
Bioelectrical impedance and vector analysis
Static haemodynamic variables
Central venous and pulmonary artery pressure measurements
Echocardiographic variables (ventricular sizes and diastolic volumes)
Dynamic haemodynamic variables
Stroke volume or pulse pressure variation, dynamic changes in central venous or pulmonary artery occlusion pressure
Oesophageal Doppler-corrected aortic flow time
Changes in vena cava diameter in response to positive pressure ventilation
Passive leg raising induced changes in haemodynamic variables
End-expiratory occlusion induced changes in haemodynamic variables
Echocardiographic variables (ejection fraction, fractional shortening)

been difficult and highly variable.[21] Charting of fluid balance has been simplified with the availability of electronic medical records and can be represented graphically, thus aiding clinicians in identifying patients with net positive fluid accumulation.

Pharmacological failure

Fluid balance can be attempted with pharmacological means such as with diuretics, aquaretics ('vaptans'), and inotropes. However, in some cases, these therapies are not effective. This may be because of inadequate urine output in the face of continuing fluid needs, development of electrolyte complications (such as metabolic alkalosis, hypokalaemia, hypomagnesaemia, and hyponatraemia), development or concern about side-effects (such as ototoxicity from high-dose loop diuretics), and worsening kidney function.[22 23] In these circumstances, mechanical fluid removal should be considered (consensus statement #1).

Indications for mechanical fluid removal

Established FO

(i) After failed diuretic therapy: in situations where FO has not responded to diuretics, cannot be corrected safely without serious adverse effects, or both, mechanical fluid removal should be considered.

(ii) When diuretics are unlikely to be effective: in patients with life-threatening FO and significantly reduced renal function (i.e. glomerular filtration rate <15 ml min^{-1} 1.73 m^{-2}) or poor renal perfusion (i.e. cardiogenic shock), diuretics are unlikely to be effective. In this case, treatment with diuretics is likely to result in prolongation of the negative effects of FO and mechanical fluid removal should be considered early.

High risk of developing FO

Mechanical fluid removal should be considered early in situations associated with a high risk of fluid accumulation (i.e. need for massive blood products, parenteral nutrition, or high-volume drug therapy), in order to prevent significant FO and negative patient outcomes. This is particularly important if patients also suffer from poor kidney function and are unlikely to respond adequately to diuretics. In other situations, the underlying clinical condition may warrant aggressive interventions to avoid FO. For instance, patients with established acute lung injury are very sensitive to FO and tolerate fluid accumulation less well than those with normal lung function.[24] In these patients, it is particularly important that FO is avoided, corrected, or both early.

FO and refractory electrolyte disorders

The use of diuretics may be associated with the development of severe metabolic complications such as hyponatraemia, hypokalaemia, metabolic alkalosis, hypomagnesaemia, and worsening kidney function. The effects may occur *de novo* or may be present initially and worsen further with diuretic therapy. In this case, mechanical fluid removal should be considered early.

FO and uraemic symptoms

Patients with FO in the context of severe acute or chronic kidney disease will require fluid removal and also clearance of uraemic metabolites. Since this can only be achieved with haemodialysis or haemofiltration but not diuretics, mechanical (renal replacement) therapy is the treatment of choice.

Goals of mechanical fluid removal

Prescription of mechanical fluid removal requires consideration of the extent of FO, the total amount of fluid that would need to be removed to achieve euvolaemia and the appropriate rate at which this goal should be achieved. The total extent of FO may be best assessed by serial weights, cumulative fluid balance, and clinical examination possibly aided by specific investigations such as bioelectrical impedance analysis. In contrast, the rate at which fluid should be removed requires consideration of expected fluid inputs and losses, the expected speed of vascular refilling after fluid removal, and the patient's physiological tolerance to transient reduction in intravascular volume during this process.

It is also important to establish whether fluid has accumulated globally in the intra- and extravascular space or just in a single compartment, for instance, in the pleural or peritoneal space. In the case of localized fluid accumulation, symptoms may be relieved by relatively simple techniques, that is, chest drain insertion or paracentesis. These therapies should be considered, especially if there are no other indications for mechanical fluid removal or renal replacement therapy (RRT).

Knowledge of a patient's acute and chronic illness and monitoring of adequacy of cardiac output and tissue perfusion and also dynamic indices suggestive of haemodynamic fluid responsiveness can help clinicians set safe rates for fluid removal. These are likely to require regular reassessment, particularly when fluid removal is first attempted and in patients who are more severely ill. Occasionally, these concerns may be overridden by life-threatening consequences of FO, which may dictate faster rates of fluid removal initially. Examples of rates of fluid removal appropriate to differing clinical contexts are shown in Figure 3.

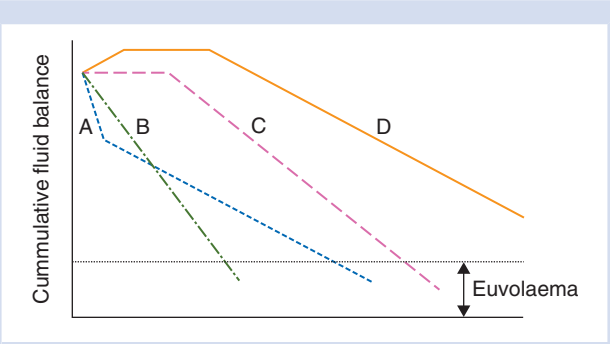

Fig 3 Rate of mechanical fluid removal. Examples of patients with FO as a result of disease or fluid resuscitation requiring mechanical fluid management to illustrate how different rates of fluid removal are appropriate to different clinical settings. Rapid early fluid removal may be indicated in cardio-renal syndrome (A), but a slower removal may be required for haemodynamic tolerability after resolution of pulmonary oedema. Patients with single organ renal failure (B) may tolerate more rapid fluid removal than those with AKI complicating severe sepsis (C) or septic shock (D). In septic shock, mechanical fluid removal may at first be targeted to limit the accumulation of further fluid until clinical stabilization allows slow resolution of accumulated fluid excess. Figure reproduced with permission from ADQI 12 (Acute Dialysis Quality Initiative. http://www.adqi.org/).

Choosing a mechanical fluid removal modality

There are several forms of mechanical fluid removal that can be effectively utilized in the therapy of the FO patient (Table 3). Ultrafiltration is the primary modality for fluid removal in these techniques. This process consists of the production of plasma water from whole blood across a semi-permeable membrane in response to a transmembrane pressure gradient. Because the semi-permeable membrane effectively sieves larger molecules such as plasma proteins, the ultrafiltrate is effectively an iso-osmotic crystalloid solution of plasma water and electrolytes. Continuous veno-venous haemofiltration

Table 3 Mechanical fluid removal techniques. SCUF, slow continuous ultrafiltration; CVVH, continuous veno-venous haemofiltration

Modality	Blood flow rates (ml min^{-1})	Fluid removal rates (ml h^{-1})	Anti-coagulation	Advantages	Disadvantages
Intermittent ultrafiltration	250–400	0–2000	Desirable	Widely available	Less effective in reaching fluid balance goals Can lead to haemodynamic instability Requires venous access
Continuous ultrafiltration	50–100	0–300	Desirable	Can be performed as either SCUF or CVVH Haemodynamically better tolerated CVVH allows for a replacement solution and dissociation of sodium and water clearance	Requires venous access Not as widely available
Peritoneal dialysis	Not applicable	0–500	Not required	Modality of choice for paediatrics No venous access Haemodynamically more stable	Cannot be used in patients with abdominal surgery or trauma Not available at all sites Requires technical expertise to place catheters
Haemodialysis (intermittent)	250–400	0–2000	Desirable	Widely available Adds clearance of solutes	Less effective in reaching daily fluid balance goals Can lead to haemodynamic instability Requires venous access
Haemodialysis (continuous)	50–100	0–300	Desirable	Adds clearance of solutes Haemodynamically more stable	Requires venous access Not as widely available

Table 4 Prescription strategies to minimize hypotension during ultrafiltration

Intermittent therapies	Continuous therapies
Cooling of the dialysate to ≤36°C or use of isothermic dialysis	Regular reassessment of clinical response to ultrafiltration rate and readjust accordingly
Keeping the dialysate sodium 10 mEq litre^{-1} greater than the plasma sodium concentration	Regular checks for signs of reduced effective circulating volume, by monitoring cardiac output and markers of volume responsiveness
Prescription of an initial blood flow ≤250 ml min^{-1}	
Extension to longer sessions	
Increased frequency of treatment sessions	
Use of dialysis machines equipped with biofeedback	
Regular review of patient response to ultrafiltration rate and re-adjustment of prescription accordingly	
Avoidance of vasodilatory medications	

(CVVH) is unique in that it allows for both ultrafiltration and the use of an i.v. replacement solution and thus is able to dissociate the correction of sodium and water balance. During CVVH, the ultrafiltrate is similar to plasma water and the net sodium balance can be affected by the sodium concentration in the replacement solution. This may be particularly useful in states where there is significant sodium retention or where hypertonic fluids were utilized and have led to large net positive sodium balances.

A major difference between intermittent and continuous fluid removal techniques is that continuous therapy, by virtue of slow, sustained fluid removal enabling vascular refilling, is much more likely to achieve net negative balance with greater haemodynamic stability.[5] Retrospective analyses have suggested that first use of intermittent rather than continuous modalities for the treatment of AKI in the intensive care unit (ICU) may be associated with long-term non-recovery of renal function,[25] an association that might be related to greater haemodynamic instability during intermittent fluid removal. However, despite clinical data and experience suggesting that continuous modalities are most appropriate to safely achieve fluid balance goals in critically ill patients, formal evidence for the superiority of continuous RRT (CRRT) for treatment of AKI in the ICU is not available.[26 27]

In some cases, diuretics may be considered as an adjunct mode of fluid removal to be utilized in combination with mechanical techniques.[15] This may be appropriate when using intermittent ultrafiltration to ensure some continued urine output and control of fluid balance while the mechanical therapy is not operative.

Prescribing ultrafiltration

Safe prescription of ultrafiltration for mechanical fluid removal requires an appreciation of the patient's underlying condition, understanding of the process of ultrafiltration, and close monitoring of the patient's cardiovascular response to fluid removal. The rate of fluid removal will depend upon the individual patient's effective circulating volume at the time of assessment before starting RRT and also their capability to refill the vasculature to enable continued net fluid removal. Ultrafiltration should only be commenced once the patient has been stabilized on RRT. Thereafter, the net ultrafiltration rate should be adjusted according to changes in physiological parameters. Table 4 shows prescription strategies to minimize hypotension during ultrafiltration by intermittent and continuous therapies.

The process of ultrafiltration can occur in different modes: isolated, sequential, or concomitant to diffusive processes. The extracorporeal system is not the sole component in overall fluid balance, as many anuric patients may also have other sources of fluid loss including insensible losses, losses from burns, wounds, gastrointestinal tract, and drainage of ascites and pleural fluid. It is also possible that patients become hypervolaemic during the fluid removal process because of administration of additional parenteral fluids, such as antibiotics, inotropic infusions, and repeated colloid infusions. These sources of fluid loss and simultaneous fluid intake must be regularly assessed and the prescription of CRRT needs to be adjusted accordingly.

In summary, targets for rate of fluid removal and net fluid removal should be based upon the overall fluid balance of the patient and also physiological variables, individualized, and reassessed frequently (Consensus statement #2).

Monitoring ultrafiltration

Hypotension is the major complication when the rate of removal of plasma water exceeds the refilling capacity of compensatory fluid movement from the extravascular compartments. Available monitoring techniques include bioimpedance spectroscopy,[20 28 29] online-haematocrit and relative blood volume monitoring,[30] dynamic measures of preload responsiveness such as pulse pressure and stroke volume variation, and biomarkers such as brain natriuretic peptide in patients with heart failure.[31] While some of these techniques (e.g. bioimpedance spectroscopy) are occasionally used to examine FO in non-critically ill patients receiving intermittent haemodialysis,[28 29 32] none of these techniques has been sufficiently evaluated to reliably predict intra-dialytic hypotension and adequacy of fluid removal in haemodynamically unstable

patients.[30 33 34] Furthermore, it is not clear whether fluid removal monitoring impacts short- and long-term outcomes and more study in this area is needed.

Endpoints of therapy and individualizing therapy

The aim of pharmacological and mechanical fluid removal is to correct FO and to improve patient outcomes. However, there is no valid marker, which indicates when euvolaemia has been achieved. Individual treatment targets may differ between individual patients, and furthermore, patients vary in their ability to tolerate fluid removal. Although the aim is to remove excess fluid without haemodynamic compromise, in some patients with life-threatening FO, it may be necessary to accept an increase in vasopressor or inotropic support to facilitate fluid removal in an effort to improve critical physiological parameters such as oxygenation. Typical examples are patients with acute lung injury and severe vasoplegic sepsis or patients with pulmonary oedema and cardiogenic shock.

Criteria for stopping mechanical fluid removal

Most patients who survive critical illness complicated by AKI recover sufficient kidney function to be independent of long-term renal support.[35–37] However, criteria to determine the optimal time-point to discontinue RRT have not been extensively studied. Similarly, there may be conflicting imperatives between the correction of FO and metabolic status and the desire to avoid invasive extracorporeal therapy if it is not required. Again sufficient urine output to maintain water and electrolyte homeostasis may be the best indicator that a patient will remain independent of RRT. In the BEST study, a retrospective review of 1006 patients treated with CRRT, urine output was the strongest predictor of a patient not requiring further RRT with an area under the receiver-operator characteristic curve (ROC-AUC) of 0.85.[38] Optimal urine output cut-off for diagnosis of RRT independence was 436 ml day^{-1} in patients not prescribed diuretics. In a similar study in critically ill patients, low urine output after cessation of CRRT was strongly associated with need for further RRT on that admission (median of 66 *vs* 10 ml h^{-1}).[39] Diuretics are often prescribed in an attempt to assist cessation of RRT. However, these have been shown to confound the use of urine output to predict RRT independence with the ROC-AUC for urine volume decreasing to 0.67 in the BEST kidney data with an optimal cut-off of 2330 ml 24 h^{-1}.[38] Furthermore, the use of loop diuretics to aid discontinuation of RRT has not been shown to be beneficial; in a small double-blind randomized controlled trial of 72 patients, furosemide by continuous infusion in the recovery phase of haemofiltration-dependent AKI increased urinary output and sodium excretion but did not lead to a shorter duration of renal failure or more frequent renal recovery.[40] While the evidence base is limited, we would suggest that the decision to electively discontinue mechanical fluid removal should be guided by urine output and that loop diuretics should not be routinely prescribed to patients weaning from RRT in the absence of other indications.

Research agenda

While there is a wealth of observational evidence that FO is associated with adverse patient and renal outcomes in adult and paediatric patients, there are little prospective data to confirm that mechanical fluid removal to treat FO improves outcomes. Research strategies are required to investigate active management of fluid balances during critical illness after the initial resuscitation phase aiming to best maintain tissue perfusion while minimizing FO. Within these strategies, the indications for and timing of mechanical fluid removal will need to be considered. Better methods are required to quantify the degree of FO (to set overall target) and to predict the tolerance of fluid removal (to set rate of removal). Finally, the ability of different mechanical modalities to achieve fluid removal effectively and safely and also their effect on longer-term outcomes requires further assessment.

Consensus statements

(1) In critically ill patients with FO and with failure of or inadequate response to pharmacological therapy (inadequate fluid balance, complications), mechanical fluid removal should be considered as a therapy to optimize fluid balance.
(2) When using mechanical fluid removal or management, targets for rate of fluid removal and net fluid removal should be based upon the overall fluid balance of the patient and also physiological variables (haemodynamics, oxygenation), individualized, and reassessed frequently.
(3) More research on the role and practice of mechanical fluid removal in critically ill patients not meeting fluid balance goals (including in children) is necessary.

Authors' contributions

M.H.R., M.O., R.M., J.R.P., and C.R.: literature search and data analysis, writing up of first draft, and revision of draft. J.A.K., M.G.M., and A.D.S.: study design, interpretation of data, and review of drafts. All authors read and approved the final manuscript.

Supplementary material

Supplementary material is available at *British Journal of Anaesthesia* online.

Declaration of interest

None declared.

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