Introduction

Contemporary management of critically ill patients increasingly recognizes the importance of accurate assessment of volume status and use of fluid therapy to optimize patient outcomes. Several studies suggest that excess fluid is related to adverse outcomes in critically ill patients. However it is not clear if this is a marker of underlying severity of illness or a cause of morbidity and mortality. Although specific protocols and guidelines exist for fluid management in critically ill patients they are not always applicable for patients with acute renal dysfunction. Additionally, fluid management during renal replacement therapy, particularly continuous renal replacement therapy (CRRT), is most often based on local practice and the role of fluid in dialysis prescription and delivery is largely unrecognized. These issues were discussed by the ADQI workgroup with a view to identify the most pertinent questions that need to be addressed. The questions that were found to be relevant can be classified under 4 main headings: 1. monitoring; 2. choice of fluids; 3. effect of volume status on outcomes from ARF; and 4. fluid balance in ARF and during renal replacement therapy.

Monitoring

Which monitoring tool(s) should be used to detect volume deficit or excess?

The kidney is very sensitive to decreases of intravascular volume, reacting promptly with increased sodium and water resorption. Oliguria, low fractional excretion of sodium (FeNa) and an increased urea/creatinine ratio are signs of intravascular volume depletion. Other clinical signs (hypotension, tachycardia, oliguria, poor capillary refill, core peripheral temperature gradient, altered mental state) are poor and late indicators that only detect overt hypovolemia [1-5]. The presence of these signs therefore indicates the need for urgent

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intervention. Lesser degrees of hypovolemia, if uncorrected, also compromise tissue perfusion and may result in organ dysfunction. The recognition of this occult hypovolemia requires a high index of suspicion combined with more subtle and often more invasive monitoring. Monitoring of blood or plasma volume provides little information since what constitutes and “adequate” circulating volume may differ according to size of the intravascular space and cardiac function.

Since the aim of fluid therapy is to assure adequate tissue perfusion, fluid resuscitation should be targeted to a specific preload, stroke volume and/or cardiac output rather than to a specific mean arterial pressure (MAP). Filling pressure (central venous pressure (CVP) and pulmonary capillary wedge pressure (PCWP) are the most popular surrogate markers of preload, although the use of the pulmonary artery catheter (PAC) has been the subject of extensive criticism [6,7]. Low filling pressures are indeed sensitive indicators of hypovolemia, but high values do not necessarily mean that the patient is well filled [4,8-15]. The relation between filling pressures and ventricular end-diastolic volume is often obscured by changes in ventricular compliance or changes in the pericardium or the thorax. They are therefore least helpful in the sickest patients and relying solely on filling pressures may result in incorrect therapeutic decisions. Dynamic tests such as fluid challenges or lifting the legs with observation of trends in filling pressure and stroke volume responses give much more information [2,3,16,17]. The volume administered during fluid challenges should take into account the presence or suspicion of myocardial dysfunction.

Volume-related preload indices show a better correlation with stroke volume [9,10,13-15,18-23]. End-diastolic ventricular volume can be measured with transesophageal echocardiography. This method requires training and experience and may be subject to interobserver variability [24-26]. Right ventricular end-diastolic volume can be measured with a pulmonary artery catheter equipped with a fast-response theremistor [19-22]. Intrathoracic blood volume measured with the COLD or PiCCO system (transpulmonary thermo-dye dilution or transpulmonary thermodilution) has also been shown to be a good preload indicator. In addition, these systems allow determination of extravascular lung water (EVLW) [9,14,15].

A positive response to fluid administration or preload responsiveness can be predicted by the presence of (mechanical ventilation-induced) respiratory variations of systolic pressure [27-31], pulse pressure [32-36], stroke volume [37], or aortic flow velocity [38], that are currently considered the most reliable parameters to diagnose volume deficit [36,39]. The ultimate goal of fluid therapy is to maintain or to restore tissue perfusion and organ function. Parameters of global tissue perfusion include lactate, pH, BE or SvO2. However, these global perfusion indices as well as measures of regional perfusion and/or organ function are non-specific markers of volume status since organ dysfunction and derangement in cellular metabolism may occur in the absence of tissue flow abnormalities, particularly in sepsis. The gut mucosa is one of the earliest tissues to be compromised and is especially vulnerable to hypoperfusion because of the countercurrent flow in the microcirculation. Gastric tonometry has been shown to be more sensitive than global hemodynamic parameters in detecting occult hypovolemia [40,41]. The gastric mucosal-arterial
pCO2 gap (Pg-aCO2) is the variable of choice because, it is independent of systemic acid-base disturbances [42,43]. Other parameters of regional perfusion and/or organ function are sublingual tonometry [44] and hepatic veinO2 saturation [45].

Fluid management during critical illness must be aimed at improving perfusion, but may have the disadvantage that, in severe inflammation, major fluid shifts occur in the extravascular space resulting in tissue edema despite ongoing intravascular volume depletion. There are currently no methods that allow determining the presence of capillary leak, apart from the absence of an effect of fluid administration on intravascular volume. Intravascular volume excess can be assessed with the same parameters as volume deficit. Monitoring of pulmonary capillary pressure is important if hydrostatic forces causing pulmonary edema are to be minimized. During acute lung injury pulmonary artery occlusion pressure is a poor estimate of pulmonary capillary pressure [46,47].

Excess of interstitial fluid can be assessed clinically (body weight, peripheral edema, parameters of gas exchange), with radiologic techniques (X-ray) or with bioimpedance. Body weight changes do not correlate with changes in fluid balance [48]. Bioimpedance measurements have been used with variable success to identify changes in total body water and compartmental distribution[49-51]. Some investigators have found a good correlation with clinical assessment of hydration [52], while others have [50,51,53] found that changes in total body water can be tracked but absolute volumes differ from those measured by isotope dilution. X-ray changes of fluid overload may be of help but require accurate assessment of radiological and clinical parameters [54-56].

**What should be the end-point of fluid resuscitation?**

As already stated, fluid resuscitation should be targeted to a specific preload, stroke volume and/or cardiac output rather than to a specific MAP. Careful assessment of the hemodynamic response to fluid challenge not only allows the diagnosis of hypovolemia but also allows to titrate the optimal dose of fluid. Parameters of preload responsiveness are probable the best variables to define the adequacy of fluid resuscitation[36,39]. Whether gastric tonometry-guided treatment improves outcome remains a matter of controversy. It is unclear whether increasing hemodynamic variables to supranormal values has a beneficial effect on outcome. Trauma and perioperative patients seem to benefit whereas septic patients do not [57]. It is also not clear whether the endpoints of fluid resuscitation should be different in patients with ARF because of the limited capacity to eliminate fluid excess. Whether the use of more invasive monitoring improves outcome remains to proven. Data on the use of the PAC even suggest the opposite [5,6] . A small randomized trial showed that fluid resuscitation based on the measurement of EVLW results in a less positive fluid balance and a shorter duration of mechanical ventilation and ICU stay [58]. In patients on renal replacement therapy, blood volume [59-61] and cardiac output [62,63] can be monitored with specific techniques applied to the extracorporeal circuit.
Choice of Fluids

Which fluid should be used for fluid resuscitation and management in the critically ill patient is an area of considerable controversy and has been the subject of several meta-analysis [64-66]. There have been no specific studies of fluid resuscitation regimens in patients with ARF[67], however the following issues should be considered.

**Does the choice of the fluid matter?**

In a hypovolemic patient any volume is better than none and an appropriate volume amount is probably more important than the choice of the fluid. There is no clear evidence that any given fluid type results in improved survival [68-72].

**Are there specific recommendations to make for patients with or at risk of ARF?**

There is little evidence to suggest that the choice of fluids for resuscitation in patients at risk of or with ARF should be different from other critically ill patients. The requirement for larger volumes with the use of crystalloids versus colloids could represent a problem in patients with limited capacity to eliminate fluid excess [67]. Colloids result in a more rapid restoration of circulating volume, which might be important in patients at risk of renal failure. The use of large amounts of saline may induce metabolic acidosis [73-75] and, in animal trials, have been shown to decrease survival compared with Ringer’s lactate [75-76]. Isotonic saline has been shown to be superior to half-isotonic saline in prevention of radiocontrast nephropathy, defined as 0.5mg/dL increase of serum creatinine [77]. In patients with cerebral edema large volumes of isotonic crystalloids should probably be avoided. In patients with liver cirrhosis, albumin has only been proven to be successful in the prevention of deteriorating renal function after large volume paracentesis, in spontaneous bacterial peritonitis and in hepatorenal syndrome if combined with vasopression [78].

The effect of colloids on renal function remains a matter of controversy. Possible mechanisms of colloid-induced renal dysfunction are hyperoncotic renal failure (related to dose), tubular reabsorption of macromolecules resulting in oncotic nephrosis-like lesions and tubular obstruction by hyperviscosity [79,80]. Starches have been suggested to adversely affect renal function [81-84]. However the randomized trial showing a higher incidence of ARF in septic patients treated with hydroxyethyl starch (eloHAES) compared with gelatin used an inappropriate definition of ARF [82]. The effect of resuscitating brain death organ donors with starches on the function of the transplanted kidney also remains a matter of controversy [81,85-87]. In addition, the potential deleterious effect of starches on renal function has only been showed with starches with high MW and/or a high degree of substitution. Experimental work suggests a beneficial effect of medium MW starches on the capillary leak, endothelial activation and immune function [69,88,89]. The clinical relevance of these findings has not been shown.

Acute hypervolemia is better tolerated than hypovolemia. The transfusion trigger in critically ill patients still remains a matter of controversy [90-93]. A large prospective randomized trial showed that maintaining
the Hb level at 7-9mg/dL is safe and might even be better than aiming for 10-12mg/dL [94]. However the low consent rate in this study could raise questions about its generalizability. With regard to artificial O2 carriers, a recent phase III trial in trauma patients showed a higher mortality compared with transfusion of RBC [95], however a study in cardiac surgery patients showed reduced transfusion needs [96].

**Effect of Volume Status on Outcomes from ARF**

It is well recognized that alterations in renal function influence volume status; however the relationship of volume status and renal functional impairment is often not easily discerned. This is particularly true in critically ill patients who are often on pressor support and subject to varying demands for hemodynamic and renal support. Pertinent issues that emerge include the following:

**What are the consequences of volume deficit and excess and what is the relationship to renal functional impairment?**

Volume depletion in critically ill patients is associated with decreased cardiovascular performance, impaired organ perfusion and renal impairment. Non-oliguric ARF can contribute to volume depletion particularly in the recovery phase if volume replacement does not keep pace with urine output. Increases in intravascular volume can similarly contribute to pulmonary edema, cardiac failure and tissue edema, however the effects of increase in total body water on organ function are not well defined [79,97-101]. Several studies have demonstrated the influence of increased extravascular lung water (EVLW) on increased mortality in patients with pulmonary edema and ARDS [102-107]. The influence of ARF on volume related complications are not well documented. Several studies have demonstrated a 3-8 fold increased risk of mortality in patients with ARF in the ICU [108-113]. The increased risk of mortality has been associated with an increased incidence of infection, respiratory failure and bleeding [108,110,114-117].

**Is the effect of volume deficit or excess time dependent?**

Volume deficits are recognized to result in impaired organ function and both the extent and duration of deficit are contributory [79,111,118]. It is likely that the development of ARF is affected by the duration of deficit. Two epidemiologic studies of ARF have demonstrated that the time of development of ARF influences outcomes from ARF[109]. Brivet et al [119] showed an odds ratio of 2.97 for mortality for severe ARF (defined as a serum creatinine > 3.5 mg% and urine output of < 500ml/min) developing during the ICU. Mehta et al [120] have demonstrated increased mortality and reduced renal recovery in a cohort of patients with ARF on ICU admission who had delayed (> 48 hrs) consultation for ARF. Mortality increased with increasing duration of ARF and delayed patients had a larger amount of fluid accumulation. Dialyzed patients in the delayed groups had dialysis initiated at lower serum creatinines than the early groups suggesting possible volume excess. Although indirect this evidence suggests a time dependent effect of ARF on outcome with volume a possible factor.
Does the composition of plasma volume affect outcome?

It is well recognized that patients with metabolic acidosis have an increased risk of adverse outcomes. There is emerging evidence from critically ill patients of increased mortality with hypernatremia[121,122] and hyponatremia [123-125]. Thus volume deficit and free water excess can contribute to worse outcome at the extremes of the continuum. Saline induced acidosis is well recognized, however its effect on outcome is not well established [74].

Fluid Balance in ARF and during Renal Replacement Therapy

As discussed earlier, volume depleted patients require appropriate correction of volume deficit and an ongoing assessment of volume status is required to maintain euvoilema. Once ARF is established, volume overload becomes the main problem in fluid management, necessitating intervention with dialysis. However trigger points for dialytic intervention and management of fluid balance with different techniques is subject to wide variation. Key issues that should be considered are:

At which levels do the results of monitoring dictate correction by fluid administration or fluid removal?

There are no established guidelines for intervention with diuretics or dialysis for fluid removal other than the broad recommendations of “fluid excess” contributing to organ dysfunction particularly the lung and heart. There is some evidence that patients with acute lung injury or ARDS benefit from reduction in the EVLW, however there is limited data on the role of dialysis as a specific intervention [126-128].

What is the role of diuretics versus extracorporeal treatment?

Diuretics are commonly used to enhance urine output, convert oliguric to non-oliguric ARF or to maintain a urine volume in the face of large infusions of fluid. Despite the frequent use of diuretics there is no evidence that this intervention shortens the duration of ARF, reduces the subsequent need for dialysis or improves outcomes in patients with ARF [129-133]. Loop diuretics might even be deleterious for the kidney [131] because they disturb the protective corticomedullary redistribution of blood flow [134]. On the other hand, a combination of furosemide, mannitol and dopamine, initiated before the start of cardiac surgery, has been shown to have a beneficial effect on renal function [135]. The choice of diuretic, frequency and route of administration and timing of intervention are subject to wide variation. Continuous infusions of diuretics did not appear to have any additional benefit to intermittent doses [136], however other studies have shown that continuous infusion of loop diuretics results in a better diuretic response with fewer side effects [137,138]. Intermittent and continuous dialysis techniques can remove large volumes of fluid, however the timing of intervention and goals for therapy are subject to prevailing practice patterns and are strongly influenced by the dialysis provider. Other than broad indications for dialytic intervention for gross fluid overload or compromised organ function there are no specific criteria for extracorporeal support. While continuous therapies offer the advantage of more gradual and prolonged volume control
there is no definitive evidence that this improves outcome[139,140]. Isolated ultrafiltration appears to have a beneficial effect in patients with congestive heart failure that are resistant to diuretics (Agostini). Guiding this treatment with blood volume monitoring improves the tolerance [141,142].

**How does volume status influence dose of dialysis**

One of the foundations of urea-based quantification techniques is assumption of essential equivalence between urea distribution volume (V) and total body water (TBW) in end-stage renal disease patients [143-148]). This fundamental relationship allows the use of relatively simple anthropometric formulae to estimate urea space in the prescription and delivery of chronic dialysis. However, the marked differences between stable chronic dialysis patients in metabolic steady state and critically ill, dialysis dependent patients with ARF call into question the validity of the relationship between V and TBW in the latter population. Himmelfarb et al [149]have demonstrated recently that estimates of V derived from urea kinetic modeling are significantly greater than TBW estimated by both anthropometric formulae and bioelectrical impedance (BIA). This same group of investigators has also published data suggesting that this phenomenon contributes to inadequate prescription and delivery of hemodialysis in this patient population [150,151].

Numerous factors, some of which may play a role in the altered relationship between V and TBW, contribute to the disturbances in volume homeostasis in critically ill ARF patients. The volume overload that exists commonly increases both V and TBW and is typically associated with deranged compartmental fluid distribution. This fluid maldistribution is particularly marked in the setting of increased capillary permeability (“capillary leak syndrome”). In this setting, the pronounced interstitial accumulation of fluid as a potential explanation for the discrepancy between V and TBW has not been assessed. In addition, previous data suggest CRRT and intermittent HD differ in their ability to correct volume excess [152]. Another potentially contributing factor is the significant loss of lean body mass [147] that critically ill ARF patients typically display during their pre-ARF and ARF course. Again, no systematic examination of the effect of lean body mass loss on urea kinetics in ARF has been performed. However, it is clear that this phenomenon alters the relationship between TBW and body weight. Finally, it should be considered that, based on pharmacokinetic principles, the kinetically-derived estimate of V is an “apparent” value that may or may not have an anatomic correlate. Consequently, the increased estimates of V in ARF may simply be a reflection of impaired removal of urea. Based on the regional blood flow model [153], this impairment in urea removal could be explained by alterations in regional perfusion. An alternative explanation is anatomic sequestration of solute (i.e., slow transfer from the intracellular to extracellular space) [154].

The interaction between fluid and dose in ARF patients also depends on the specific dialytic therapy being used. In diffusion-based therapies (i.e., IHD and SLED), the net ultrafiltration rate is usually equivalent to the absolute ultrafiltration rate, such that convection contributes minimally to overall solute removal. Therefore, dose delivery and net fluid removal are dissociated and can be regarded independently. On the other hand, the absolute ultrafiltration rate in continuous therapies having a convective component (i.e.,
CVVH and CVVHDF) is a direct determinant of solute removal. Thus, due to the interaction between absolute ultrafiltration rate, substitution flow rate, and net ultrafiltration rate, treatment dose and fluid balance are closely related in these therapies. In addition, specifically in CVVHDF, the manner in which solute removal related to ultrafiltration supplements that occurring by diffusion (i.e., the “interaction” between convection and diffusion [155] has not been considered carefully in the high dose range [156].

**How should fluid balance be achieved in patients on RRT?**

Different strategies are in use for achieving fluid balance in patients who are dialyzed for ARF. During intermittent hemodialysis, the amount of fluid to be removed is largely determined by computing the negative fluid balance desired and adding the amount of estimated intake to be accommodated. The short duration of intermittent hemodialysis limits the capacity for fluid balance and the most common approach is to remove a set amount of fluid per hour. This is often associated with increased morbidity particularly hemodynamic instability [157]. Several protocols have been described to reduce the risk of dialysis induced hypotension in these patients [158-162] and have had varying success. Use of a variable sodium profile and protocol based ultrafiltration have been shown to be superior in a cross-over study but did not entirely eliminate intradialytic events [158]. Use of mannitol and albumin solutions to maintain intravascular volume and prevent dialysis disequilibrium during dialysis is frequently employed but have not been evaluated in randomized trials [163]. Recently blood volume monitoring during dialysis has been advocated as a possible method of targeting fluid removal rates however there is limited experience in ARF [61,164-168].

Fluid balance in continuous techniques can be achieved in a variety of ways [140]. Accurate fluid balance requires three steps: a method to accurately measure fluid changes (intakes and outputs) over a period of time, a technique to record these changes and perform calculations for establishing interval fluid balance and a mechanism for making changes in the fluid removal or replacement rates to correct any discrepancy in the desired fluid balance. Newer CRRT systems incorporate scales that measure changes in the effluent bag, dialysate and replacement solutions that are hung on the scale. Microprocessors can control the pump speeds to achieve a particular negative or zero balance but none of the currently available machines permit a positive fluid balance to be achieved through the CRRT system. Most current techniques of CRRT require an hourly or more frequent assessment of fluid balance. Several methods are used by individuals and currently no standard approach is followed. Some users record the information as part of the routine ICU flow sheet while others use a separate CRRT flowsheet. No studies have specifically looked at the optimum method for fluid balance in CRRT. Preliminary data suggest techniques to utilize CRRT for fluid regulation may be of benefit [140,169].

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