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Diuretics and Ultrafiltration in Heart Failure

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Abstract
Fluid overload is a risk factor for increased morbidity and mortality, especially in patients with heart disease. The treatment options are limited to diuretics and mechanical fluid removal using ultrafiltration or renal replacement therapy. This paper provides an overview of the challenges of managing fluid overload, outlines the risks and benefits of different pharmacological options and extracorporeal techniques, and provides guidance for clinical practice.

Introduction

Decompensated heart failure, a condition characterized by signs and symptoms of congestion due to fluid overload, is one of the main causes of hospitalization among adults. It is associated with an increased risk of pulmonary oedema, acute kidney injury, need for renal replacement therapy (RRT), prolonged and recurrent hospitalization, and mortality [1–7]. Nowadays, the term "congestive heart failure" is used less; instead, it is preferred to differentiate between acute and chronic heart failures depending on duration. Furthermore, different types of heart failure are recognized based on left ventricular systolic function (normal, mildly reduced, reduced) or right ventricular dysfunction [8]. Renal congestion is a common complication in heart failure [7, 9, 10]. Kidney interstitial oedema might disrupt the anatomic intimacy between renal tubules, peritubular capillaries, and vasa recta [11]. Eventually, increased hydrostatic interstitial pressure may partially collapse renal tubules and peritubular capillaries resulting in reduced kidney function.

Diuretic Therapy

In all types of decompensated heart failure, prevention and management of fluid overload are key therapeutic goals [12]. Diuretics are the cornerstone treatment acting through increased renal sodium and water excretion. They are recommended on a class I-level evidence in international guidelines for all clinical presentations of decompensated heart failure [8, 13]. However, robust data from clinical trials are lacking. Instead, most

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Table 1. Diuretics

Diuretics	Site of action	Mechanism of action
Carbonic anhydrase inhibitor Acetazolamide	Proximal nephron	Inhibition of sodium bicarbonate reabsorption in proximal convoluted tubule
Loop diuretics Furosemide Torasemide Bumetanide	Ascending limb of the loop of Henle	Inhibition of the sodium-potassium-2 chloride (Na+-K+-2 Cl–) co-transporter
Thiazide and thiazide-like diuretics Hydrochlorothiazide Chlortalidone Metolazone	Early distal convoluted tubule cells	Inhibition of sodium chloride transport
Potassium-sparing diuretics Spironolactone Eplerenone Potassium canrenoate Amiloride	Late distal tubule	Inhibition of mineralocorticoid receptor or its effectors Inhibition of distal epithelial sodium channels (ENaCs)
SGLT2 inhibitors Empagliflozin Dapagliflozin	Proximal tubule	Inhibition of the sodium-glucose co-transporter subtype-2
Vaptans Tolvaptan	Distal nephron	Reduction of distal nephron-free water re-uptake by counteracting arginine vasopressin

SGLT2, sodium-glucose co-transporter 2.

recommendations are based on experience gained over many years of clinical practice [14]. Further, diuretics should always be administered with other recommended therapies to improve cardiovascular morbidity.

Diuretics are classified according to their chemical structure, mechanisms, and the site of action within the nephron [14, 15] (Table 1). Loop diuretics reversibly inhibit the Na+/2Cl–/K+ co-transporter of the thick ascending loop of Henle, leading to decreased sodium and chloride reabsorption and increased diuresis. Furosemide has a relatively rapid action and is the most commonly used diuretic to maintain an adequate fluid balance in chronic heart failure [16] and to achieve a negative water balance in acute decompensated heart failure [17]. There is no clear evidence on the optimal dosage of furosemide or mode of administration (continuous infusion vs. intermittent bolus therapy) [18–22]. In general, there is a tendency to start with a low dose as a bolus or infusion and to titrate the dose according to urinary output, fluid balance, and biochemical biomarkers. Excessive neurohormonal activation, electrolyte imbalance, and worsening of kidney function are potential concerns [8, 13–17, 23]. Current guidelines recommend close monitoring of the response to diuretics, including measurement of hourly urine output and spot urine sodium content after 2 or 6 h [8]. An adequate diuretic response is defined as urine output >100–150 mL/h during the first 6 h and/or an urinary sodium content >50–70 mEq/L at 2 h [17].

Recent evidence suggests that more intensive diuretic therapy with the aim to restore compensation more rapidly may be beneficial despite a temporary increase in serum creatinine. Moreover, an aggressive approach with rapid resolution of fluid overload and congestion may even have a nephroprotective effect in the long term [12, 24, 25].

Diuretic Combination Strategies

Combining diuretics with different sites of action is recommended for patients with persistent congestion despite high-dose furosemide administration (class IIa level of evidence B) [8]. Thiazide diuretics (hydrochlorothiazide and chlorthalidone) promote natriuresis and diuresis through the inhibition of reabsorption of 3–5% of luminal sodium in the distal convoluted tubule of the nephron. They are rarely used as first-line treatment of acute heart failure because of limited potency especially when used as monotherapy. Instead, they are more frequently administered in combination with loop diuretics in what is termed "sequential nephron blockade," in

particular, in case of loop diuretic resistance [26]. Their efficacy is reduced in patients with impaired renal function. Metolazone is a potent thiazide-like diuretic that produces a diuretic response even if glomerular filtration rate (GFR) is low. The greater efficacy of metolazone compared to common thiazide drugs in patients with reduced GFR appears to be due to its additional inhibitory effect on sodium and chloride reabsorption in the proximal convoluted tubules. The main side effect of thiazide diuretics is electrolyte imbalance, particularly hypokalaemia and hyponatraemia as a consequence of aldosterone-mediated actions of the Na^+/K^+ pump in the convoluted tubule. Although the concept of "sequential renal blockade" dates back to more than 40 years ago, there are no large randomized clinical trials (RCTs) to support combination therapy with thiazide diuretics and loop diuretics in patients with acute heart failure.

Acetazolamide is a carbonic anhydrase inhibitor that blocks the proximal convoluted tubular absorption of sodium, leading to increased natriuresis. It also mitigates neurohormonal activation through reduced renin production, promoting greater chloride concentration in the macula densa, and corrects metabolic alkalosis. Although the net diuretic effect of acetazolamide is considered to be modest, combination therapy with furosemide seems to increase the effectiveness, as demonstrated in observational and interventional studies [27, 28]. A multi-centre double-blind RCT in patients with acute decompensated heart failure and fluid overload showed that the addition of acetazolamide (500 mg once daily) to intravenous loop diuretics resulted in higher cumulative urine output and natriuresis and greater incidence of successful decongestion [28].

Mineralocorticoid receptor antagonists (MRAs) are potassium-sparing diuretics which have been shown to improve mortality in chronic heart failure patients with reduced left ventricular systolic function. Their use is supported by the fact that aldosterone levels are often elevated in heart failure. The diuretic effect of MRAs is modest and based on modulation of the expression/activity of sodium and potassium channels in the distal nephron where only 3% of filtered sodium is reabsorbed. In the ATHENA-HF trial, high doses of spironolactone (100 mg) in combination with furosemide showed no difference in terms of efficacy and safety compared to low-dose spironolactone (25 mg) combined with furosemide [29]. However, this trial did not specifically study patients with diuretic resistance. A consensus of experts recommends that the use of MRAs in the acute settings should be individualized with close monitoring of electrolyte balance, in particular serum potassium [17].

Amiloride exerts diuretic effects through the inhibition of distal epithelial sodium channels, but the evidence on its potential role in decompensated heart failure is scarce. Sodium-glucose co-transporter 2 (SGLT2) inhibitors are weak diuretics. Recent evidence supports their use to improve heart failure outcomes and quality of life in patients with chronic heart failure, acute decompensated heart failure, and recently worsened heart failure [30–36]. The benefit appears to be consistent in both heart failures with reduced or preserved ejection fraction. The Empagliflozin Outcome trial (EMPEROR-Reduced trial in patients with chronic heart failure with reduced ejection fraction) and the Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure trial (DAPA + HF) investigated patients with chronic heart failure and reduced ejection fraction [30, 37]. The Empagliflozin Outcome trial in patients with chronic heart failure with preserved ejection fraction (EMPEROR-Preserved) and the Dapagliflozin in Heart Failure with Mildly Reduced or Preserved Ejection Fraction trial (DELIVER) studied chronic heart failure patients with preserved ejection fraction. In all 4 trials, SGLT2 inhibitors showed a 20–25% relative reduction in hospitalization for heart failure or cardiovascular death compared to placebo [34, 36]. Quality of life improved, too. The EMPULSE trial (a study to test the effect of empagliflozin in patients who are in hospital for acute heart failure) showed that empagliflozin improved the primary outcome which was a composite of 90-day mortality, total heart failure events, time to first heart failure event, or severe symptoms [35]. In addition, there was an improvement in quality of life. Finally, the Empagliflozin in Acute Decompensated Heart Failure (EMPAG-HF) trial investigated empagliflozin in patients with acute decompensated heart failure and confirmed that the addition of a higher dose of empagliflozin (25 mg once daily) to standard medical treatment resulted in a 25% increase in cumulative urine output over 5 days without affecting renal function [32]. These different trials suggest that SGLT2 inhibitors are an all-encompassing therapy for heart failure and can be initiated in all patients with heart failure who do not have contraindications [38].

Vasopressin receptor antagonists (VRAs) have also been studied in acute decompensated heart failure. Despite some evidence indicating that VRAs may improve signs and symptoms of congestion, the EVEREST trial showed no improvement in long-term morbidity, mortality, or hospitalization rates when VRAs were added to standard care [39].

Monitoring during Diuretic Therapy

Providing optimal pharmacological care to patients with decompensated heart failure is challenging,

Table 2. Monitoring during fluid removal

Parameter of interest	Monitoring strategies	Examples
Volume status	Clinical signs	Skin turgor, JVP, capillary refill time
	Imaging techniques	Chest X-ray, echocardiography
	Haemodynamic monitoring	Depending on technique Stroke volume, stroke volume variation, pulmonary artery wedge pressure, oesophageal Doppler-corrected aortic flow time
Effectiveness	Clinical parameters	Urine output, cumulative fluid balance, serial weights
	Clinical signs	Oedema, JVP
	Symptoms	Breathlessness
	Haemodynamic monitoring	Depending on technique Stroke volume, stroke volume variation, pulmonary artery wedge pressure, oesophageal Doppler-corrected aortic flow time
Adverse effects	Biochemistry	Serum electrolytes, renal function, serum pH, uric acid
	Clinical signs	Heart rate and rhythm, BP, JVP, arrhythmias, response to passive leg raising test
	Symptoms	Dizziness, hearing problems, gout attack
	Imaging techniques	Echocardiography

BP, blood pressure; JVP, jugular venous pressure.

especially due to limited therapies, delays in clinical effectiveness, potential risks of adverse effects, and important gaps in knowledge. A major challenge relates to fluid management and the assessment of fluid status which even experienced clinicians can find difficult [40–42]. In practice, clinical signs, laboratory results, and information from imaging techniques (radiology, echocardiography) are used to determine volume status and guide diuretic prescribing (Table 2). However, clinical signs like central venous pressure, skin turgor, or peripheral oedema lack sensitivity and specificity. It has been clearly shown that patients with decompensated heart failure without any symptoms and no clinically recognized oedema were in fact hypervolaemic. Similarly, imaging techniques can only provide intermittent information.

Diuretic Failure/Resistance

Diuretic failure is defined by the inability of diuretics to achieve a target negative fluid balance [17]. It is not defined by the correlation between the dose diuretic and urine output alone. Loop diuretics have little diuretic or natriuretic effect below a given plasma concentration (identified as threshold), above which the response increases sharply [43]. Diuretic resistance refers to situations where diuretic therapy has failed or diuretics can no longer be safely administered due to serious adverse effects [44].

A RCT of 308 patients with acute decompensated heart failure published in 2011 provides some of the best evidence on ideal loop diuretic handling [22]. The authors concluded that the administration of furosemide in continuous infusion or bolus produced equivalent results. However, it should be acknowledged that the continuous infusion was not preceded by a bolus dose. Ideally, a bolus dose would be necessary to surpass the plasma threshold concentration. Thus, it is possible that a proportion of patients in the continuous infusion arm who were deemed as diuretic resistant may have had an appropriate diuretic response if a bolus dose had been administered first. This situation illustrates that the criteria for diuretic failure and diuretic resistance are not completely objective.

Mechanistically, the concept of diuretic resistance involves the adaptions and remodelling of tubular kidney cells. In chronic kidney disease (CKD), the GFR is reduced and the re-uptake of the sodium in the ultrafiltrate by tubular cells is downregulated. As a consequence, there is less room for further increment in natriuresis by loop diuretics leading to diuretic failure and potentially resistance [43]. Patients with heart failure often have high concentrations of natriuretic peptides [45]. In fact, brain natriuretic peptide and NT-pro-brain natriuretic peptide are the clinical biomarkers of choice for the diagnosis and prognostication of decompensated heart failure. These peptides play a major role in counterbalancing the enhanced potential for sodium and water retention caused by an upregulated renin-angiotensin-aldosterone system.

Although the administration of synthetic natriuretic peptides has not improved outcomes in acute heart failure, the modulation of the natriuretic system through inhibition of the enzyme that degrades natriuretic peptides, neprilysin, has proven to be successful [46]. In fact, one of the pillars in the treatment of patients with heart failure and reduced ejection fraction is the use of sacubitril [8]. Sacubitrilat, the active metabolite, inhibits neprilysin [47]. Natriuretic peptides are also elevated in patients with CKD irrespective of heart failure [48]. This scenario blunts the response to loop diuretics, too.

In patients with heart failure, remodelling of the distal nephron, presumably secondary to hyperplasia and hypertrophy of tubular cells, is responsible for diuretic resistance. Rao and co-workers investigated the tubular location of diuretic resistance by measuring the fractional excretion of lithium after loop diuretic administration [49]. In brief, endogenous lithium reabsorption occurs in parallel with sodium in the proximal tubule and loop of Henle, whereas the distal tubule is relatively impermeable to lithium and therefore uncoupled to sodium transport in this segment. Thus, the fractional excretion of lithium is expected to be higher than the fractional excretion of sodium after loop diuretic administration because the distal portions of the nephron can reabsorb sodium but not lithium. The researchers enrolled patients with heart failure after hospital discharge and elegantly demonstrated that after high-dose intravenous bumetanide or an additional oral dose of torsemide (equivalent to the total daily oral dose), there was an increment in the fractional excretion of lithium but not in the fractional excretion of sodium, pointing towards a distal tubular compensatory sodium reabsorption [49].

The intravenous route is preferable for the administration of diuretics. In patients with fluid overload, enteral absorption of drugs is often impaired, reducing the bioavailability of diuretics without intravenous formulations such as MRA, thiazides (except for chlorothiazide), amiloride, vasopressin receptor 2 antagonist, and gliflozins [50]. This reduction in dose-response and the necessity of a higher enteral dose to achieve the expected effect might be misinterpreted as a state of diuretic resistance. Hypoalbuminemia has also been considered a culprit of diuretic resistance. However, to date, only associative but not causative relations between hypoalbuminaemia and the reduced effects of loop diuretics have been demonstrated [51]. Indeed, the co-administration of intravenous loop diuretics and albumin failed to demonstrate a sustained enhancement in diuretic effect [52, 53].

Furosemide Stress Test

The standardized furosemide stress test (FST) has been proposed as a practical bedside tool to interrogate tubular cell function in patients with AKI, including the likelihood of AKI progression and need for extracorporeal fluid removal [54–57]. The methodology is based on the fact that furosemide gains access to the tubular lumen by active secretion via the human organic anion transporters 1 and 3 in the proximal convoluted tubule. From within the tubular lumen, furosemide acts by inhibiting luminal active chloride transport in the thick ascending limb of Henle. The FST consists of a single dose of intravenous furosemide (1.0 mg/kg for loop diuretic naïve patients and 1.5 mg/kg for those who had prior loop diuretic exposure) and replacement of urine output ml for ml each hour with an isotonic solution for 6 h to minimize the risk of hypovolaemia [58]. Fluid replacement is not mandatory in patients who are considered to be fluid overloaded. A urine output of >200 mL in 2 h after furosemide administration is considered an indicator of preserved renal tubular function [57]. Patients should not be hypovolemic before undertaking any type of furosemide challenge. A multi-centre pilot study confirmed that the FST had a role in screening AKI patients at high risk for extracorporeal support [55]. Only 14% of patients with a positive FST ultimately received RRT, while 78% of non-responders randomized to a standard RRT initiation strategy received RRT or died ($p < 0.001$).

Extracorporeal Fluid Removal

The role of extracorporeal fluid removal has been investigated in several landmark trials comparing ultrafiltration (UF) versus diuretic-based regimens in patients with acute heart failure or cardiorenal syndrome or at risk of developing cardiorenal syndrome type 1 [59–64] (Fig. 1). In this review, we will discuss in detail the two more recent trials, the continuous UF for congestive heart failure (CUORE) trial [63] and the Aquapheresis Versus Intravenous Diuretics for Heart Failure (AVOID-HF) trial [64]. The CUORE trial enrolled 56 participants hospitalized with acute heart failure presenting with congestion and weight gain above 4 kg. Patients were randomized to receive extracorporeal UF plus diuretics versus standard pharmacologic treatment. For patients in the UF arm, treating physicians were encouraged to apply mechanical and pharmacologic decongestive therapies, because in a real-world scenario, these therapies are not mutually exclusive but rather complementary. The UF

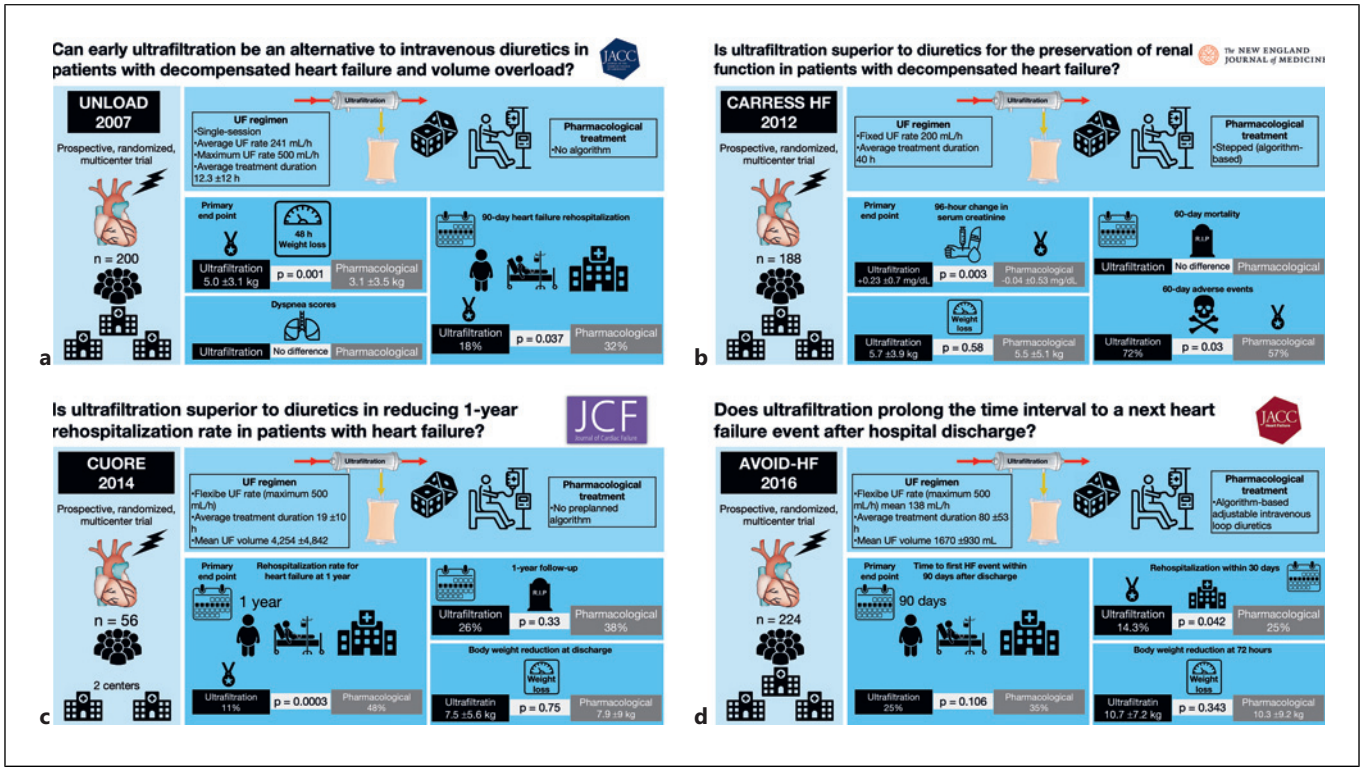

Fig. 1. a–d Selected landmark trials comparing extracorporeal ultrafiltration versus diuretic-based regimens in patients with heart failure. UF, ultrafiltration. Please refer to the online supplementary material to view the full-scale version of this figure (click here).

group had a lower 1-year incidence of re-hospitalization, patients needed fewer prescription adjustments, and there were fewer variations in body weight and kidney function. In this trial, the UF rates could be adjusted based on the physicians' judgement resulting in rates ranging from 168 to 485 mL/h. Only patients with heart failure and reduced ejection fraction were included in the trial which raises doubts whether the findings also apply to patients with heart failure and preserved ejection fraction. The AVOID-HF trial included 224 patients hospitalized with decompensated heart failure [64]. Algorithms dictating adjustments in the treatment for both arms were used, leaving less room for subjective conduct. Variables considered in the decision-making process included vital signs, kidney function, and urine output. Sessions were carried out for a median of 70 h, and the mean UF rate was 138 mL/h. There was no difference in the primary outcome (first heart failure event within 90 days). Nevertheless, during the first month after treatment, less patients in the UF arm required re-admission to hospital and spend fewer days in hospital because of heart failure. The ideal range of net UF rates in mechanical decongestive therapies for acute heart failure patients remains to be established.

The effects of mechanical fluid removal on renal function are variable. Some studies showed improved renal function that could be explained by better cardiac performance and relief of renal congestion. In contrast, a sub-study of the "Ultrafiltration versus Intravenous Diuretics for Patients Hospitalized for Acute Decompensated Heart Failure (UNLOAD)" trial showed a reduction in GFR which was similar in both groups (3.4 and 3.6 mL/min, respectively) [65]. The subsequent Cardiorenal Rescue Study in Decompensated Heart Failure (CARRESS-HF) trial was terminated early due to a higher incidence of renal dysfunction in the UF group [62]. These discrepancies in reported renal effects may be attributable to differences in the rate of fluid removal and potential imbalances between the UF rate and vascular refill capability, together with variations in the medical management of heart failure. In subsequent trials, attempts were made to correct for this variability. In the UF arm of the CUORE trial [63], haematocrit was continuously monitored and fluid removal was adjusted accordingly.

The role of peritoneal dialysis (PD) has been explored as add-on therapy in patients with heart failure with reduced ejection fraction and non-dialysis CKD, aiming to reduce

Table 3. Techniques of mechanical fluid removal*

Modality	Blood flow rate, mL/min	Fluid removal rate, mL/h	Advantages	Disadvantages
SCUF	50–100	0–300	Slower and more sustained fluid removal	Immobilization
Intermittent UF	250–400	0–2,000	Shorter procedure than continuous UF	Higher risk of hemodynamic instability
CRRT	50–100	0–300	UF and solute clearance Slower and more Sustained fluid removal	Immobilization
IRRT	250–400	0–2,000	UF and solute clearance	Higher risk of hemodynamic instability with fluid removal Fluctuating fluid balance
Peritoneal dialysis	Not applicable	0–500	UF and solute clearance No need for venous access Hemodynamically more stable No need for anticoagulation	Need for peritoneal catheter Contraindicated in patients immediately after abdominal surgery Special expertise required

UF, ultrafiltration; IRRT, intermittent renal replacement therapy; CRRT, continuous renal replacement therapy; SCUF, slow continuous ultrafiltration. *Adapted from Rosner et al. [44].

episodes of decompensated heart failure [66, 67]. However, no RCTs have directly compared PD versus diuretic therapy or extracorporeal UF as a decongestive strategy for hospitalized patients with heart failure. An observational study including 64 patients with acute heart failure (mainly secondary to ischemic heart disease) demonstrated that the mean peritoneal UF rate with the use of dextrose-based solutions was 104 mL/h [68]. This represents 75% of the mean UF rate in the AVOID-HF trial [64], underpinning the potential of PD to be investigated in future trials. Moreover, the use of icodextrin-based solutions appears attractive because this colloid does not activate peritoneal aquaporins; therefore, all aquaresis occurs via intercellular pores, allowing more effective sodium removal compared to dextrose solutions [69–71].

Prescription of Mechanical Fluid Removal

As suggested by the Acute Disease Quality Initiative (ADQI) expert group [44], the main indications for mechanical fluid removal in heart failure are as follows:

- Fluid overload after diuretic failure;
- Presence of serious adverse effects of diuretics, i.e., where treatment with diuretics cannot be continued;
- High chance of diuretic failure, i.e., in case of significantly reduced renal function where diuretics are unlikely to be effective and the risk of prolonged/progressive fluid overload is high;
- Combined fluid overload and advanced renal failure, i.e., situations where both fluid removal and solute clearance are necessary [72].

The choice and prescription of mechanical fluid removal require consideration of the urgency of fluid removal, the individual patient's clinical needs (fluid +/− solute removal), and their haemodynamic tolerance to fluid removal [12] (Table 3). The prescription should include the method (isolated UF or RRT, intermittent versus continuous, with or without diuretics), the target fluid balance, dose of RRT [if RRT is required], and endpoints detailing when to stop fluid removal [44, 73]. The target fluid removal rate needs to be set and adjusted according to the patient's effective circulating volume, their capability to refill the vasculature from the extravascular compartments, and the associated risk of haemodynamic instability. In some cases, diuretics may be added to extracorporeal fluid removal, especially when using intermittent techniques and sufficient renal function is maintained. This approach may provide ongoing diuresis and control of fluid balance, while the extracorporeal therapy is not operative.

Conclusions

Mechanical fluid removal has a role in patients with heart failure and congestion in whom pharmacological treatment has failed, and is unsafe or unlikely to be effective [12] (Fig. 2). Clinical practice remains variable, but current European practice guidelines state that UF should be considered in patients with heart failure who fail to respond to diuretic-based strategies [8, 74, 75]. The decision between UF alone versus RRT depends on the clinical needs of the individual

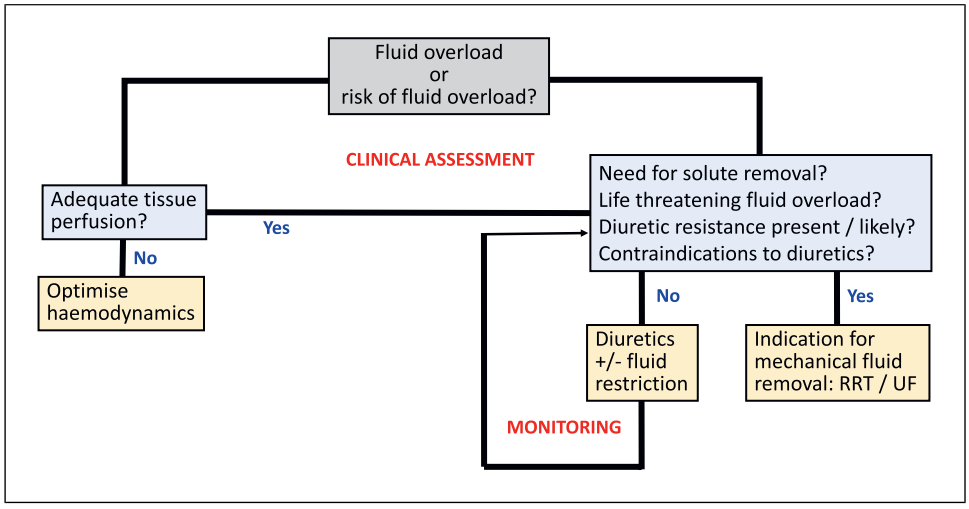

Fig. 2. Algorithm to guide fluid removal management. RRT, renal replacement therapy; UF, ultrafiltration.

patient [76]. When using extracorporeal fluid removal, implementation of a customized and individualized UF rate is essential to avoid harm from intravascular hypovolaemia and haemodynamic instability.

Conflict of Interest Statement

The authors have no conflict of interest to declare.

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Author Contributions

Thiago Reis contributed to the development of the concept of the manuscript, reviewed the existing literature, wrote the first draft related to ultrafiltration and other chapters, and created Figure 1. Federico Ronco wrote the first draft of the paragraph related to heart failure and the role of diuretics and developed Table 1. Marlies Ostermann contributed to the concept of the manuscript, wrote the first draft related to diuretic resistance, created Figure 2, and developed the first complete draft of the manuscript. Thiago Reis, Federico Ronco, and Marlies Ostermann reviewed the drafts several times, suggested edits, and approved the final manuscript. Marlies Ostermann agreed to be corresponding author and to be accountable for all aspects of the work.

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