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Review Article

CRITICAL CARE

Diuretics in critically ill patients: a narrative review of their mechanisms and applications

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Summary

Diuretics remain the cornerstone therapy of critically ill patients with volume overload as a result of cardiac failure, acute kidney injury or aggressive fluid resuscitation. This review summarises the principles of applied renal physiology, describing the mechanisms of action, the clinical applications, and the adverse effects of commonly used diuretics during critical illness. Loop diuretics, and in particular furosemide, remain the most popular, despite evidence of any effect on mortality or, indeed, on the need for renal replacement therapy. The efficacy of loop diuretics after administration depends on three factors. Firstly, the tubular concentration of the diuretic: continuous infusion of furosemide seems to provide a higher and more stable tubular concentration of furosemide with respect to bolus injection. Secondly, the interaction with albumin both in the plasma and in the renal tubule: despite a strong physiological rationale supporting this approach, albumin supplementation in hypoalbuminaemic patients does not seem to result in a higher diuretic efficacy. Thirdly, diuretic resistance, which can be addressed by optimising loop diuretic dose and by using combination therapy with other agents, including thiazides or thiazide-like diuretics or carbonic anhydrase inhibitors. These drugs constitute a useful adjunct to overcome loop diuretic resistance. Other agents such as distal potassium-sparing diuretics and osmotic diuretics can also be considered. The latter have been used successfully in hypokalaemia, rhabdomyolysis-associated acute kidney injury or to prevent ischaemia–reperfusion injury in kidney transplantation. Finally, this review provides the basic concepts of the interplay between acid–base equilibrium and diuretic therapy.

Keywords: congestive heart failure; diuretic; diuretic resistance; fluid overload; ICU; renal physiology

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Editor's key points

- Diuretics are important in the management of fluid overload. They should be selected depending on clinical conditions, including electrolyte and acid–base disturbances.
- Their effectiveness in managing fluid overload secondary to aggressive fluid resuscitation after capillary leak syndrome and acute kidney injury is not clear.
- This narrative review provides an overview of diuretic mechanisms of action, clinical indications during critical illness, and side-effects.
- Future work should focus on producing robust evidence for diuretic selection and use during critical illness.

In the early phase of critical illness, intravascular volume depletion secondary to capillary leak is common and requires aggressive fluid resuscitation with the aim of improving cardiac output and tissue perfusion.[1–3] After volume resuscitation, patients may develop fluid overload, either directly or secondary to acute kidney injury (AKI), leading to further volume retention, oedema, and positive fluid balance.[4–8] Consequently, diuretics are generally used to combat fluid overload through improving diuresis and promoting a negative fluid balance. In up of 70% of critically ill patients, diuretics have been administered at least once during intensive care stay.[6,9] Furosemide remains the most commonly prescribed diuretic, being administered in 94% of cases.[10,11] In addition, critically ill patients can present reduction of renal perfusion, acid–base alterations, and hypoalbuminaemia, which may all reduce diuretic efficacy.

This clinical narrative review will revise the main renal physiological mechanisms, the current available relevant data on the mechanisms of action, and the possible indications of diuretics in critically ill patients, according to the different clinical scenarios.

Renal physiology

Most diuretics act on the renal tubule; nevertheless, they may indirectly affect glomerular filtration rate (GFR) through activation of the renin–angiotensin–aldosterone system (RAAS) consequently leading to the reduction in blood volume, which leads to efferent arteriole constriction. Diuretic-induced changes in electrolyte balance, however, might also affect GFR.[12,13]

Sodium and water are mainly reabsorbed (65–70%) in the proximal convoluted tubule, resulting in a tubular fluid osmolarity similar to plasma, obtained by specific transporters within the proximal convoluted tubule brush border (e.g. the Na^+-H^+ exchanger). The reabsorption of Na^+ occurs in exchange for H^+ to maintain electroneutrality across the membrane. The H^+ ions then combine with filtered HCO_3^- ions to form carbonic acid (H_2CO_3) in the lumen, which, through the actions of carbonic anhydrase (CA), generate water and CO_2:

$$H^+ + HCO_3^- \leftrightarrows H_2CO_3 \leftrightarrows H_2O + CO_2$$

CO_2 freely diffuses back into the cell and water is reabsorbed via aquaporin-1 channels. The hypertonic osmotic gradient observed in the renal medulla is established by the loop of Henle, facilitated by passive reabsorption of water in the thin descending limb and reabsorption of Na^+, K^+, and Cl^- in the water-impermeable thick ascending limb (TAL) of the tubule. The active transport of solutes across the TAL is primarily carried out by the electroneutral sodium–potassium–chloride co-transporter 2 (NKCC) on the luminal surface of its cells, which reabsorbs 25–30% of the luminal Na^+, together with K^+ and Cl^-.[14,15]

The distal end of the loop of Henle contains the *macula densa*, a group of modified tubular epithelial cells forming part of the juxtaglomerular apparatus. The *macula densa* plays a role in autoregulation of renal blood flow and GFR by sensing the composition of the tubular fluid and performing the two major renal regulatory functions on circulating volume: the *tubuloglomerular feedback* (i.e. afferent arteriole vasoconstriction induced by high distal delivery of NaCl, which induces a decrease in GFR and tubular flow rate) and the release of renin, induced by a low distal [Na^+] and [Cl^-], which increase sodium and water retention.[16] The distal convoluted tubule starts at the *macula densa* and ends at the collecting duct, which reabsorbs ~0–2% of Na^+ and water.[17] Some 5–10% of the filtered sodium load is reabsorbed at the distal convoluted tubule by the Na–Cl co-transporter (NCC), with ~10–15% of calcium (Ca^{2+}) reabsorbed.

Below we provide an overview of the most commonly used diuretics in terms of mechanisms of action, clinical uses, and adverse effects. In addition, an algorithm is proposed for daily diuretic clinical use in critically ill patients.

Loop diuretics

Mechanism of action

Loop diuretics inhibit the largest amount of Na^+ reabsorption (25% of filtered Na^+) and have the most potency in terms of diuretic effect. Absorption kinetics vary among the different molecules, but loop diuretics are all largely protein-bound (>90%), with a limited volume of distribution. Loop diuretics undergo active secretion via the human organic anion transporter system to the proximal tubule; they subsequently reach the TAL of the Henle's loop, where they act on NKCC receptors,[18] inhibiting reabsorption of Na^+, K^+, and Cl^-, thereby reducing interstitial tonicity water reabsorption. The final effect is to produce natriuresis, accompanied by a greater loss of water than sodium. Of note, the *macula densa* cells also contain NKCC receptors: binding with loop diuretics leads to an inhibition of the *tubuloglomerular feedback* mechanism.[19] In patients with preserved renal function, a steep dose-response curve is observed, reaching a plateau at commonly used doses, with no further increase in effect with increasing doses.[20] The half-life of furosemide is 1.5–2 h. Comparing i.v. to oral administration, the first has twice the potency of the latter and an onset of action of 5 min compared with 30–60 min after oral administration.

Clinical use

Furosemide is the diuretic of choice in >90% of the cases of AKI with fluid overload,[21] although a meta-analysis of 20 randomised controlled studies comparing prevention or treatment of AKI with furosemide with a placebo, demonstrated that furosemide has neither an impact on mortality nor the requirement for renal replacement therapy (RRT).[22] Studies that found a worsening of AKI and increased mortality may

have included hypovolaemic AKI.[23] There is a lack of evidence to suggest that loop diuretics can improve mortality, although it seems they can improve AKI when used in the presence of fluid overload, when they may result in a reduction in kidney congestion.[24]

Adverse effects

Loop diuretics can more commonly provide side-effects compared with the other diuretics, particularly in terms of hypotension, renal impairment, and electrolyte disturbances. The increased distal Na^+ delivery at the *macula densa* and the volume depletion indirectly activate the RAAS pathway; consequently, aldosterone causes sodium reabsorption with a concomitant higher excretion of K^+, Cl^-, and H^+ in the lumen, leading to hypokalaemia. Of note, the increased fractional excretion of Cl^- with respect to that of Na^+ may induce hypochloraemic metabolic alkalosis.[25] Despite the ability of loop diuretics to inhibit electrolyte transport in the TAL and to limit both the concentrating and the diluting capacity of the kidney, some cases of severe hyponatraemia have been described.[26,27] In these cases, it can occur that, on the one hand, diuretic-induced volume depletion prevents water excretion and, on the other hand, a reduced electrolyte intake, together with an unchanged water intake, can lead to a reduction in body electrolyte stores with respect to total body water, leading to a resultant decrease in serum sodium.[28]

Intermittent and continuous administration

The continuous infusion of loop diuretics should ideally maintain luminal drug concentration and increase urine output for as long as possible,[29] whereas intermittent administration has a less predictable urine response, because of a higher variability in luminal drug concentration. In critically ill patients, the continuous infusion of furosemide has been associated with a higher urine output with a more controlled diuresis response with a lower dosage.[30–33] Similarly, a retrospective case–control study in surgical patients showed that a continuous infusion rate of 2 mg h^{-1} of furosemide, compared with a bolus of 10 or 20 mg daily, significantly improved diuresis with a more negative fluid balance, without a significant difference in intensive care or hospital stay.[34] A small study in post-cardiac surgery patients comparing the diuretic effect of the same dose of furosemide given as a bolus or continuous infusion (45.5 *vs* 45.8 mg) reported that the mean total urine volume and sodium excretion over 12 h were similar[35]; however, the continuous infusion of furosemide resulted in less variation in diuresis throughout the treatment. In a subsequent study, a higher dose of furosemide given as a continuous infusion compared with a bolus (188 *vs* 170 mg) produced a greater amount of urine and improved renal function.[36] Thus, in critically ill patients, with or without AKI, the continuous infusion of a diuretic is safe and should be provided to ensure a more constant diuretic response compared with intermittent administration.[37–39]

In the authors' opinion, in critically ill patients with fluid overload without AKI, bolus dosing is the first-line treatment, starting from 1 mg kg^{-1} day^{-1} to a maximal dose 4 mg kg^{-1} day^{-1}. In case an adequate diuretic response (urine output >150 ml h^{-1} in the first 2 h) is not achieved, we suggest switching to continuous infusion. The continuous infusion dose should be titrated towards 40 mg h^{-1} to obtain an adequate urine output. Higher doses have been tested only in specific clinical conditions, such as acute pulmonary oedema or severe congestive heart failure.

Furosemide and albumin

As loop diuretics are largely and reversibly albumin-bound, hypoalbuminaemia can lead to loop diuretic resistance through several mechanisms[40]: hypoalbuminaemia can both reduce the amount of albumin-bound diuretic in plasma and increase the diuretic distribution volume, thus impairing the efficient transport of the drug to the site of action and its availability; in addition, hypoalbuminaemia is often associated with conditions such as nephrotic syndrome or congestive heart failure, characterised by fluid retention, which can further reduce plasmatic drug concentration and reduce its effectiveness.

Several authors have addressed this issue with conflicting results. Mahmoodpoor and colleagues[41] randomised 49 ICU patients with normal renal function and moderate hypoalbuminaemia to receive furosemide or furosemide–albumin complex and found that furosemide excretion was initially greater in those treated with albumin and diuretic, with no difference in terms of urinary excreted sodium and urinary furosemide excretion at 4 and 8 h.

Martin and colleagues[42] conducted a randomised study enrolling patients with acute lung injury, mechanically ventilated for >24 h, with a serum protein concentration <6 g dl^{-1}, randomised to receive albumin followed by a loading dose of i.v. furosemide (20 mg) and a continuous infusion of furosemide between 4 and 10 g h^{-1} for 3 days or an identical i.v. bolus and continuous infusion of furosemide, with an equivalent volume of sodium chloride 0.9% solution. During the first 3 days, similar increases in serum albumin, daily urine output and similar changes in weight loss, cardiac index, and respiratory mechanics occurred; however, albumin-treated patients had a higher net fluid loss and higher oxygenation at 24 h.[42]

Finally, Lee and colleagues,[43] in a meta-analysis enrolling a more heterogenous population that included not only critically ill patients but also patients affected with nephrotic syndrome or liver cirrhosis, found that furosemide with albumin co-administration increased urine output by 31.4 ml h^{-1} in patients with baseline serum albumin concentrations <2.5 g dl^{-1} and creatinine >1.2 mg dl^{-1}.

In conclusion, despite the rationale, the addition of albumin to furosemide in critically ill patients has not demonstrated an improvement of the diuretic effect.

Thiazides

Mechanism of action

Thiazide and thiazide-like diuretics work by competitively binding to the chloride binding site of the NCC symporter, preventing Na^+ and Cl^- reabsorption; however, as the distal convolute tubule physiologically reabsorbs only about 5–10% of filtered Na^+, their natriuretic effect is relatively weak.[44,45] The high amount of NaCl in the collecting duct enhances sodium reabsorption independently from chloride, stimulating the excretion of H^+ and K^+. With the exception of indapamide, these albumin-bound thiazides are not metabolised and are excreted unchanged in urine and faeces with variability in metabolism, bioavailability, and plasma half-life among agents within the class. Most thiazides have an estimated time

of effect of ~12–18 h with a half-life of ~2–5 h for hydrochlorothiazide and 14 h for indapamide.[46,47]

Clinical uses

This diuretic family is the most commonly used when loop diuretic resistance occurs in patients with fluid overload. Côté and colleagues,[30] in a retrospective study of 6358 patients treated with furosemide >1 mg kg^{-1} day^{-1}, found that the co-administration of a second diuretic such as a thiazide was associated with a moderate increase in 24 h urine output. This combination to increase urine output and negative fluid balance is also recommended by European heart failure guidelines in acute heart failure patients, when diuresis remains inadequate despite adequate dose of loop diuretics.[48]

Adverse effects

Increasing Na^+ excretion but enhancing water reabsorption by both antidiuretic hormone (ADH)-dependent and independent mechanisms in the collecting ducts, thiazides provide a higher net sodium loss in comparison with water, with consequent hyponatraemia.[49] Severe necrotising pancreatitis can also be a rare complication of thiazides, and acute allergic interstitial nephritis, which can develop abruptly or some months after therapy.[50–52]

Carbonic anhydrase inhibitors

Mechanisms of action

Carbonic anhydrase is a zinc metalloenzyme found on the proximal convoluted tubule existing as membrane-bound (CA IV) or free (CA II), where it induces the reabsorption of almost 80% of bicarbonate, along with sodium and chloride.[44] The only CA inhibitor used as a diuretic is acetazolamide, which is rapidly absorbed orally. It is highly albumin-bound in plasma and ~90% is excreted unchanged into the urine through tubular secretion. The main effect of acetazolamide is the increase in sodium bicarbonate excretion in the proximal and distal tubules; consequently, it also impairs excess water reabsorption, leading to alkaline diuresis and ultimately metabolic acidosis. Its diuretic effect is weak, given the fast onset of a compensatory increase in distal tubular Na–Cl co-transport activity, which limits its efficacy[53]; however, precisely because of the increase in distal tubular sodium delivery, acetazolamide can increase the efficacy of loop diuretics.[54] The duration effect of acetazolamide is 8–10 h, with a half-life of ~6–10 h.

Clinical uses

Acetazolamide can be used in combination with loop diuretics in acute heart failure patients with fluid overload to improve natriuresis. In a prospective randomised controlled trial (RCT), patients with acute heart failure randomised to receive acetazolamide 250–500 mg day^{-1} plus bumetanide increased natriuresis with respect to patients receiving a high dose of bumetanide alone.[55] Similarly, in 6358 critically ill patients, the combination of acetazolamide plus furosemide provided an increase in the negative fluid balance after 24 h compared with furosemide alone[30]; however, the same authors did not find any differences in a subsequent meta-analysis.[56] Additionally, the ADVOR trial[57] demonstrated a greater incidence of successful decongestion when acetazolamide was added to furosemide, in terms of reduction of signs of volume overload, with a slightly increased effect in patients with reduced GFR.[58]

Moreover, acetazolamide seems to have a role in the treatment of metabolic alkalosis attributable to diuretics, steroids and in patients with chronic obstructive pulmonary disease (COPD) receiving mechanical ventilation.[59] The first RCT that compared acetazolamide with placebo did not find any beneficial effects in reducing invasive mechanical ventilation length in COPD patients.[60]

In conclusion, acetazolamide can be used in critically ill patients to overcome diuretic resistance in patients with acute heart failure by increasing negative fluid balance and natriuresis in combination with loop diuretics; and to treat metabolic alkalosis in COPD patients receiving mechanical ventilation.

Adverse effects

The use of acetazolamide can induce hyperchloraemic metabolic acidosis because of the loss of bicarbonate in the urine, with a compensatory increase of plasma [Cl^-], released from the intracellular compartment maintaining the same anion gap.[61] Additionally, acetazolamide use increases the distal delivery of sodium, which leads to hyperstimulation of Na–K co-transporter in the distal tubule, with consequent potassium excretion and, possibly, hypokalaemia.[62]

Osmotic diuretics

Mechanisms of action

Mannitol, a non-metabolised sugar which is freely filtered across the glomerulus, is the most clinically used among osmotic diuretics; it primarily acts by increasing the osmolarity of the tubular fluid in the proximal convoluted tubule and TAL; therefore, it does not actively affect electrolyte flow across the tubule. After being filtered in the tubular lumen, mannitol is poorly reabsorbed and remains in the lumen, increasing the osmolarity of the luminal fluid and blocking the urine-concentrating function of the countercurrent mechanism, thereby promoting water transport into the collecting ducts. Because of its poor oral absorption, mannitol is only administered i.v. with a bioavailability of 100% and a half-life of 70–150 min.[17] More than 90% of absorbed mannitol is excreted unmetabolised in the urine.

Clinical uses

Mannitol has been recommended for the treatment or prevention of rhabdomyolysis-associated AKI, when a urinary output of at least 300 ml h^{-1} is not achieved although adequate fluid resuscitation.[63] More recently, however, it has not been demonstrated superior to hydration alone.[64]

Beyond its diuretic effect, mannitol might have a beneficial effect in preventing ischaemia–reperfusion injury in kidney transplantation. A recent meta-analysis showed that administration of mannitol during kidney transplantation resulted in decreased AKI without any increase in urinary output.[65]

Adverse effects

Because of its molecular weight, mannitol leads to a direct increase in plasma osmolality, which induces water shift from

the intracellular to intravascular compartment, causing dilutional hyponatraemia and hypokalaemia. By decreasing water reabsorption, mannitol impairs tubular sodium reuptake, which contributes to hyponatraemia and hypokalaemia, because of higher distal Na–K co-transport activity. In cases of frequent administration in patients with altered vascular permeability, it can worsen pulmonary oedema and cerebral oedema by crossing the vessel wall and depositing into the extracellular matrix. Finally, mannitol accumulation, characterised by a plasma osmolar gap >60–75 mOsm L^{-1}, can induce reversible AKI as a result of renal vasoconstriction and significant osmotic injury to tubules, resulting in acute tubular necrosis. This effect is limited to patients receiving >200–300 g day^{-1}.[66]

Distal potassium-sparing diuretics

Mechanism of action

Potassium-sparing diuretics can be divided into two subgroups: mineralocorticoid receptor antagonists (e.g. spironolactone) and epithelial Na^+ channel (ENaC) inhibitors, such as amiloride and triamterene. ENaC inhibitors are pteridine analogues and are secreted in the proximal tubule to bind to ENaC receptors located in the principal cells of the aldosterone-sensitive distal nephron, while mineralocorticoid receptor antagonists are synthetic steroid analogues which act indirectly by suppressing the activation of ENaC receptors. Both act on the distal part of the nephron (distal convoluted and collecting tubules), promoting sodium and water excretion and potassium retention. By acting at the distal level, where Na^+ reabsorption is lower than 3%, these diuretics do not have a potent diuretic effect. Both spironolactone and eplerenone are metabolised by the liver and they do not need to be secreted into the luminal portion of the tubules to exert their effect, whereas amiloride is excreted unmetabolised in the urine via tubular secretion and in the faeces.[17] The estimated time of effect ranges from 6 h for amiloride and 24–48 h for spironolactone with a half-life from 21 h to 15 h for active metabolites, respectively.

Clinical use

The most commonly used mineralocorticoid receptor antagonist is spironolactone. It causes increased amounts of sodium and water to be excreted while potassium is retained. Its limited clinical use as a diuretic in the ICU is mainly aimed to correct hypokalaemia induced by other diuretics and to correct hypomagnesaemia. Because of its scarce diuretic effect, it should not be used to treat congestion, but persistent hypokalaemia attributable to other diuretics.[17,67]

Adverse effects

The main adverse effect is hyperkalaemia, which is dose-dependent and manifests in particular in patients also taking potassium supplements, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, or beta-blockers.[68] The increase in intracellular K^+ could directly cause impairment in ammonia excretion by the collecting tubule, thus causing HCO_3^- wasting and hyperchloraemic metabolic acidosis as a result of Cl^- shift from cells to plasma.[69]

Sodium–glucose co-transporter-2 (SGLT-2) inhibitors

Mechanism of action

In normal physiological conditions, glucose filtered from the glomerulus enters the tubules and is reabsorbed mainly by SGLT-2 on the proximal convoluted tubules. Glucose reabsorption in the kidney is dependent on the electrochemical gradient of sodium, which is sustained by basolateral Na^+-K^+ ATPase; glucose enters tubular cells passively in a 1:1 ratio with sodium through SGLT-2. Consequently, SGLT-2 inhibition leads to a reduction of sodium and glucose reabsorption in the proximal tubule, theoretically increasing urinary sodium concentration and urine output. This inhibits the *tubuloglomerular feedback*, decreasing glomerular hyperfiltration and preserving renal function.

Augmentation of natriuresis and glycosuria in the absence of activation of distal compensatory mechanisms of sodium (e.g. by the Na^+-H^+ exchanger) and glucose reabsorption are thought to be the main mechanisms of increased diuresis by SGLT-2 inhibitors.[70] Over time, sodium reabsorption in the distal part of the nephron increases by increase in NKCC co-transport activity and the activation of the RAAS; therefore, natriuresis gradually reduces, limiting the effects of SGLT-2 inhibitors on urine output, while glucosuria persists.

Clinical use

SLGT-2 inhibitors are currently recommended in outpatients with type 2 diabetes mellitus (T2DM) to treat hyperglycaemia with or without renal disfunction and in patients with heart failure with reduced ejection fraction to reduce the risk of cardiovascular death and progression of heart failure[48]; they are also proved to be beneficial in case of chronic kidney disease to limit progression.[48] Concerning SLGT-2 inhibitors use during critical illness, Mårtensson and colleagues[71] conducted a pilot case–control study in which empagliflozin was used to reduce insulin use in critically ill patients with T2DM; they found that empagliflozin use was associated with increased free water loss, greater diuretic response to furosemide, and less worsening of kidney function. Patients treated with empagliflozin were more likely to have positive urine culture, with no difference in terms of hypoglycaemia or ketoacidosis. Recently, the DEFENDER randomised clinical trial investigated the tolerance and the effect of the treatment with dapagliflozin 10 mg daily in critically ill patients with at least one among circulatory, respiratory, or renal failure in terms of a composite outcome including hospital mortality, need for kidney replacement therapy, and ICU length of stay.[72] Although the benefit in terms of the primary outcome could not be proved, patients in the treatment group had a non-significantly lower risk of initiating kidney replacement therapy; moreover, the trial demonstrated the tolerability of dapagliflozin in critically ill patients for future research.

Adverse effects

The most frequently reported side-effect of SGLT-2 inhibitors is urinary tract infection (UTI), probably mediated by enhanced glucose excretion. The incidence of UTI has been recently found to be identical between critically ill patients treated with or without dapagliflozin for up to 14 days.[72]

Additionally, euglycaemic ketoacidosis has been reported to be a rare side-effect of the use of SGLT-2 inhibitors in patients with other risk factors, such as surgery, fasting or pregnancy; once again, in the DEFENDER trial, no cases of ketoacidosis were reported both in the control and in the treatment group.[72]

Diuretic resistance

Diuretic resistance is commonly defined as a failure to increase diuresis when a maximal dose of diuretic (typically furosemide) is used.[73] Adequate diuretic response can be defined as a urine output >150 ml h^{-1} at 2 h or a spot urinary sodium >50–70 at 2 h.

Diuretic resistance can be attributable to three different mechanisms (Fig 1), including: (1) a decreased amount of the drug transferred to the site of action because of reduced tubular secretion secondary to reduction in renal perfusion, hypoalbuminaemia, or accumulation of organic acids, which compete with furosemide in terms of tubular secretion[74]; (2) increased sodium retention because of prolonged loop diuretic therapy, which promotes higher sodium reabsorption, mainly at the distal part of the nephron by hypertrophy and hyperplasia of the distal collecting tubule and RAAS activation and ADH release after volume depletion (the so called *breaking phenomenon*); and (3) reduced NaCl sensing from tubular sodium transporter.[75] As the main mechanism of diuretic resistance seems to be represented by the breaking phenomenon, it should mainly affect patients already treated with loop diuretics.[76,77] Three RCTs in critically ill patients with fluid overload, excluding cirrhotic patients, showed that the addition of acetazolamide[53] or thiazide-like diuretics[78] or spironolactone[79] to furosemide provided variable results in terms of urinary volume and urinary sodium loss.[53,78,79] A subsequent meta-analysis enrolling patients with acute respiratory failure and fluid overload found that the addition of a thiazide to a loop diuretic may promote diuresis and negative fluid balance,[56] while Côté and colleagues[30] demonstrated a similar effect with the addition of acetazolamide.

Moreover, it should be remembered that the presence of AKI constitutes by itself another cause of resistance to diuretics. It has been demonstrated that the application of the furosemide stress test (i.e. the administration of a one-time dose of 1.0–1.5 mg kg^{-1}, depending on prior furosemide exposure) in critically ill patients with early AKI accurately predicted the progression of kidney injury to Acute Kidney Injury Network stage III when urine volume in response to diuretic administration was <200 ml in the first 2 h,[80] identifying patients who can benefit from RRT.

In conclusion, to overcome diuretic resistance in critically ill patients with fluid overload without AKI, it has been suggested first to increase diuretic doses to a maximal dose (until

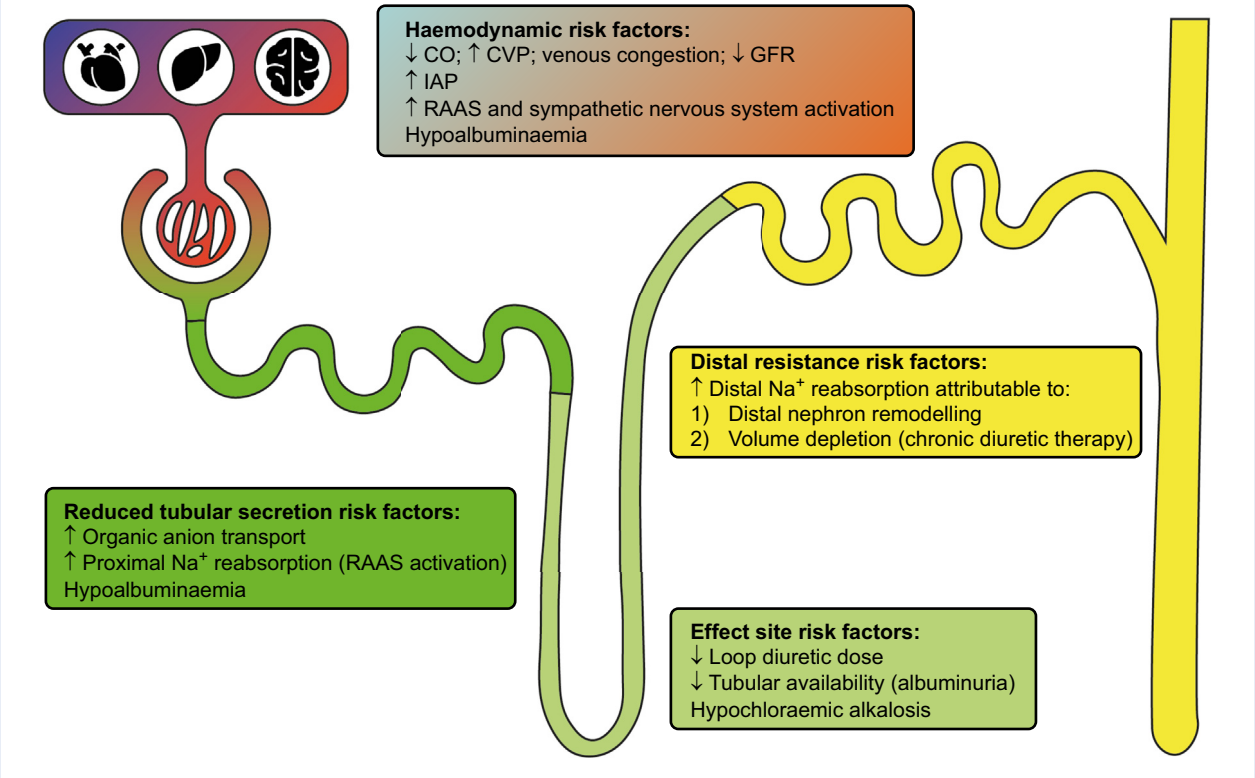

Fig 1. Pre-renal and intra-renal mechanisms of loop diuretic resistance according to their physiopathology and nephron segment involvement (red: glomerulus; dark green: proximal convoluted tubule; light green: loop of Henle; yellow: distal convoluted tubule and collecting duct). Heart, liver, and brain are represented as icons. CO, cardiac output; CVP, central venous pressure; GFR, glomerular filtration rate; IAP, intra-abdominal pressure; RAAS, renin–angiotensin–aldosterone system.

4 mg kg^{-1} day^{-1}) in patients requiring more than 1 mg kg^{-1} day^{-1} of furosemide, in order to increase the luminal dose of the drug; then, to add a second diuretic, such as a thiazide or acetazolamide, in order to increase the negative fluid balance within the 24 h (Fig 2).[30,74]

Acid–base alterations

Volume depletion after prolonged diuretic therapy is associated with decreased renal perfusion and GFR. At the tubular level, it causes an increase in Na^+, HCO_3^-, and urea reabsorption, allowing more H^+ to be secreted. Furthermore, intravascular volume depletion can promote an increase in renin and aldosterone release, which increases H^+ loss through the action of the distal H^+-ATPase pump, with concomitant Na^+ reabsorption in the collecting duct and the development of metabolic alkalosis.[75,81] In addition, loop diuretics can increase H^+ secretion at the TAL by Na^+ reabsorption in exchange of H^+.

Huang and colleagues[29] studied the short-term effect (i.e. after 6 h) of a bolus of furosemide (40 mg) on plasma and urine electrolytes and acid–base equilibrium in non-intubated critically ill patients. Furosemide significantly increased urinary sodium and chloride excretion and decreased plasma chloride, while plasma sodium was not affected. The plasma strong ion difference (SID) increased, promoting metabolic alkalosis with a concomitant increase in bicarbonate and base excess. In mechanically ventilated patients, a bolus of furosemide (an average of 12 plus or minus 5 mg) caused an increase in urinary sodium and chloride losses after 10 min, with an associated metabolic alkalosis that persisted for up to 3 h.[82] Furthermore, during continuous infusion of furosemide, a progressive increase in plasma SID and pH was observed from day 1 up to day 3, as a result of a concomitant decrease in chloride concentration.[82]

Similarly to furosemide, an i.v. infusion of mannitol significantly increased arterial pH and HCO_3^- after 60 min and up to 24 h.[83] The resulting metabolic alkalosis was attributable several concomitant factors, such as a possible increase in

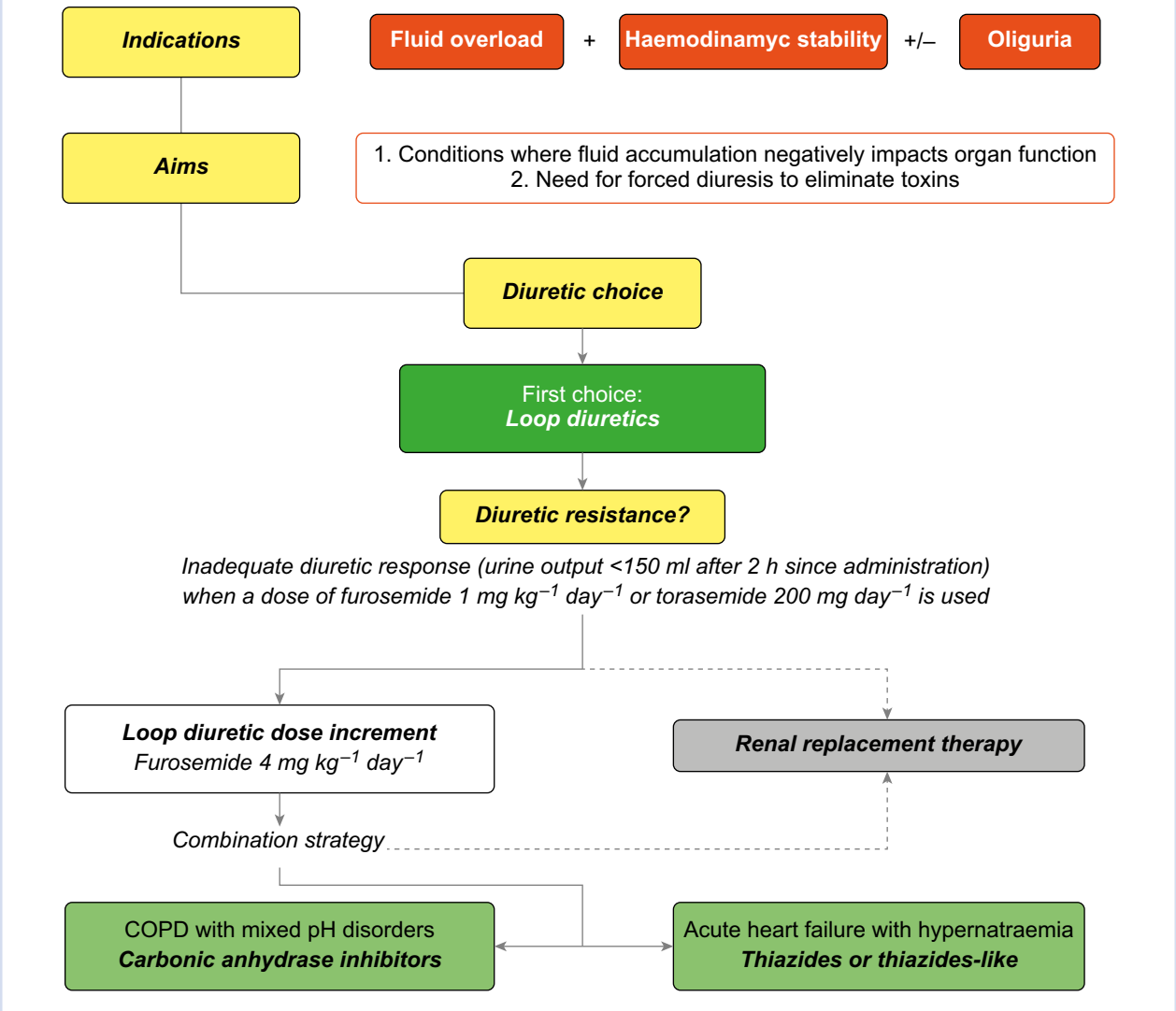

Fig 2. Flow chart of diuretic indication, rationale, and selection in ICU patients. COPD, chronic obstructive pulmonary disease.

renal HCO_3^- production, increased tubular HCO_3^- reabsorption and distal tubular H^+ secretion.[83]

CA has an important role in the regulation of acid–base equilibrium, hydroelectric state, and control of ventilation.[59,60] Among the possible inhibitor agents, acetazolamide is a non-selective inhibitor of CA. Typically, acetazolamide has been suggested in COPD patients in the presence of metabolic alkalosis as respiratory stimulant decreasing the serum bicarbonate and pH.[59]

Conclusions

Diuretics are among the most commonly prescribed drugs in the critically ill. Despite this, there is a relative lack of information regarding outcome data and most appropriate dosing regimens. Moreover, the use of different diuretic classes and indeed combination therapy is an area where further data are needed. We have outlined a practical approach to diuretic administration with consideration given to diuretic resistance. The effects of diuretic on acid–base balance are considerable and the reader should now be versed in the effects of diuretics to this end. Although pragmatically diuretic administration is almost universal in the ICU, there is a dearth of evidence to support not only our treatment approach, but also much of our daily practice. Starting from physiological knowledge, in the clinical practice we should aim for nephroprotection, choosing the most appropriate diuretic in the most effective dose for every clinical scenario.

Authors' contributions

Designed the structure of the manuscript: SC, DC, LF, LG.
Drafted the first version of the manuscript: SC, LF, DC.
Revised the manuscript: AA, TP, LG.
Approved the final version of the manuscript: all authors.

Declaration of interest

The authors declare that they have no conflicts of interest.

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