Diuretic resistance and its management

Fluid overload and oedema are common presentations in hospitalized patients and diuretics are the mainstay of their treatment. Not infrequently some of these patients become resistant to diuretics, making their management difficult and prolonging their hospital stay. Suboptimal diuretic therapy and lack of proper understanding of underlying causes can often compound the problem. This article examines the pathophysiology of diuretic resistance and provides practical guidance and clinical strategies which can be used to overcome this problem.

Diuretic mechanism of action and classification: an overview

Sodium (Na^+) is the main ion in extracellular fluid and it plays a major role in regulating the extracellular fluid volume. A large amount of Na^+ and water is filtered into the renal tubules every day, but most of the solutes and water is reabsorbed and only a small fraction appears in the urine. Na^+ is primarily reabsorbed through special transporters and channels on the apical (luminal) surface of the renal tubular cells. Water reabsorption is mainly passive through the process of osmosis and is coupled to the solute (mainly Na^+) reabsorption (*Figure 1*).

Under normal conditions the salt and water balance is tightly regulated and extracellular fluid volume stays constant. Under disease conditions, e.g. heart failure and hepatic cirrhosis, this regulation is impaired and leads to excessive Na^+ and water retention resulting in fluid overload and oedema. Diuretics act by inhibiting Na^+ reabsorption. Each diuretic acts on a specific segment of the nephron and this forms the basis for the diuretic classification. There are four main classes of diuretics – *Table 1* summarizes the agents and mechanism of action of each class (Rose, 1991; Knauf and Mutschler, 1994).

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Diuretic resistance

To date, diuretic resistance has not been formally defined, but it can be described as a clinical state in which the patient fails to achieve the therapeutic target of decongestion and fluid removal despite large doses of diuretics. In clinical practice, failure to lose 0.5–1 kg of weight per day on adequate diuretic therapy may indicate diuretic resistance. It should be distinguished from suboptimal diuretic therapy and this is explained in detail in the following sections.

Diuretic resistance is a relatively common problem and can affect up to 20–30% of patients admitted with symptoms of fluid overload and oedema (Neuberg et al, 2002; Fonarow, 2003).

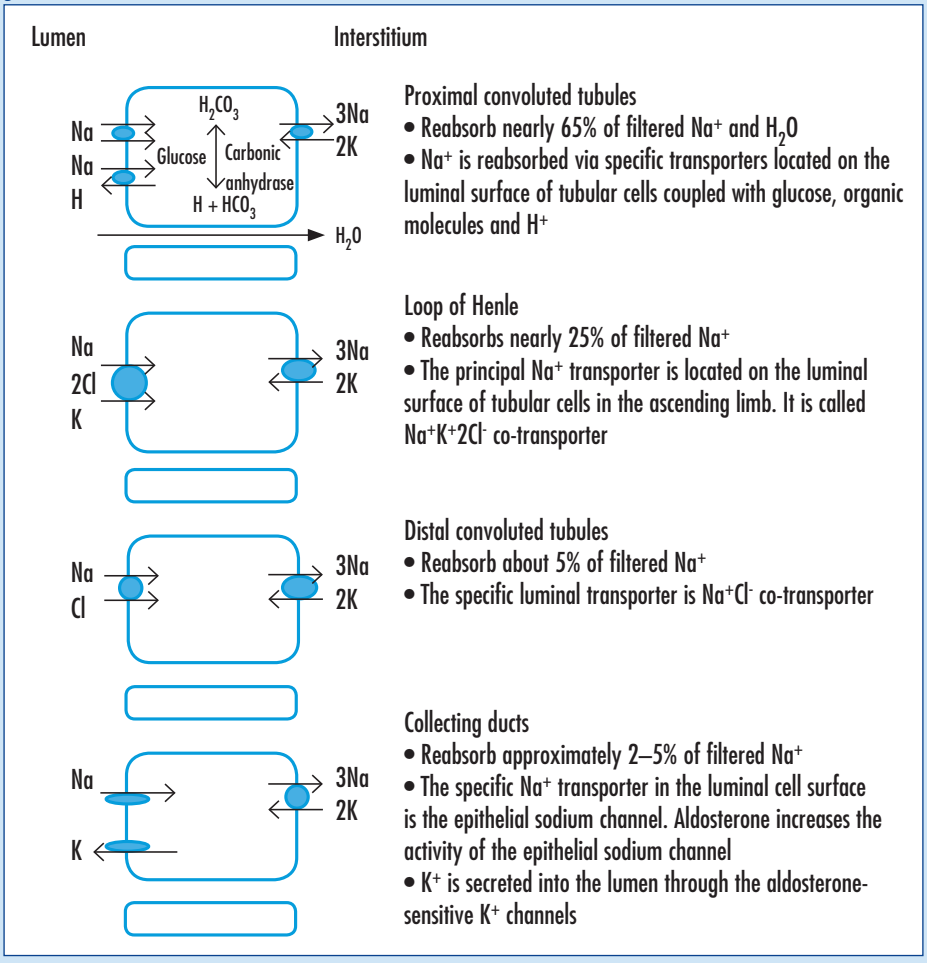
Pathophysiology of diuretic resistance

The pathogenesis of diuretic resistance is complex and multifactorial. Reduced delivery of diuretics to their luminal site of action, drug interactions, neurohormonal activation and tubular adaptation all play an important role (*Table 2*).

Reduced delivery of diuretics in tubular lumen

Diuretics act by blocking Na^+ transport in the apical (luminal) membranes of the renal tubular epithelial cells and diuretic

Figure 1. Schematic illustration of sodium reabsorption in different nephron segments: each tubular cell has a sodium-potassium pump in the basolateral surface which drives sodium out and potassium into the cells. This is an active process driven by enzyme sodium-potassium ATPase. The sodium concentration gradient thus created moves the sodium from tubular lumen to the cells.



levels need to reach a therapeutic threshold in the tubular fluid before they can exert their effect (Rose, 1991; Ellison, 1999). Reduced bioavailability of diuretics as a result of poor absorption from the oedematous gastrointestinal tract, diminished drug delivery to the tubular lumen secondary to sluggish renal blood flow seen in congestive cardiac failure, and reduced tubular secretion of diuretics in severe renal impairment can result in sub-optimal drug level in the tubular lumen resulting in diuretic failure (Brater, 1985).

Both loop and thiazide diuretics are highly protein bound, mainly to albumin, and as a consequence cannot reach the tubular lumen through glomerular filtration. They are delivered to their luminal site of action by organic anion transporters in the straight segment of the proximal convoluted tubule and are subsequently transported to their site of action. This renal secretion of diuretics is strongly dependent on serum albumin concentration and diuretic delivery to the tubular lumen is significantly impaired in hypoalbuminaemic patients. In patients with nephrotic syndrome diuretics tend to bind to albumin in the tubular fluid, reducing the amount of free active unbound drug available to act on the tubular receptors (Brater, 1985).

Drug interactions

Prostaglandins stimulate renal Na^+ and water excretion. Aspirin and other non-steroidal anti-inflammatory drugs interfere with prostaglandin synthesis by inhibiting cyclooxygenase and thereby antagonize the natriuretic response to the diuretics. Kirchner et al (1986) showed that administration of prostacyclin E_2 restored furosemide response in indomethacin-treated rats. The finding was consistent with the hypothesis that non-steroidal anti-inflammatory drugs reduce diuretic responsiveness by prostaglandin synthesis inhibition.

Table 1. Diuretic classification and mechanism of action

Site of action	Diuretic agents	Mechanism of action
Proximal convoluted tubules	Acetazolamide	Inhibits carbonic anhydrase which reduces hydrogen ion formation in tubular cells leading to a decreased ability to exchange sodium for hydrogen ions and reabsorption of bicarbonate
Loop of Henle (loop diuretics)	Furosemide Bumetanide Torsemide Ethacrynic acid	Block sodium uptake at sodium/potassium/chloride co-transporter in thick ascending limb of loop of Henle
Distal convoluted tubules (thiazide and related diuretics)	Bendroflumethiazide Chlorthalidone Indapamide Metolazone	Blocks sodium uptake at sodium/chloride co-transporter
Collecting ducts (potassium-sparing diuretics)	Amiloride Triamterene Spironolactone Eplerenone	Blocks sodium uptake at apical sodium channel. Spironolactone and eplerenone are aldosterone antagonists. Amiloride and triamterene directly reduce the activity of the sodium channels, independent of aldosterone

Table 2. Causes of diuretic failure and resistance

Use of sub-therapeutic dose	
Poor absorption from oedematous gut	
Poor diuretic delivery to its site of action: the nephron lumen	Congestive cardiac failure
	Hypoalbuminaemia and nephrotic syndrome
	Renal failure
	Hepatic cirrhosis
High dietary salt intake	
Concomitant use of non-steroidal anti-inflammatory drugs	
Increased sodium delivery and absorption in distal tubular segments	
Compensatory retention of sodium after the effective period of the diuretic	
Activation of renin–angiotensin–aldosterone system and renal sympathetic nerves	
Hypertrophy and hyperplasia of distal tubular cells: braking phenomenon	

Increased sodium absorption in distal tubular segments

Blockage of Na^+ reabsorption in one nephron segment results in increased Na^+ delivery to the distal tubular segments. Renal Na^+ transport is directly related to the luminal Na^+ concentration and in animal models, a twofold increase of Na^+ concentration in the distal tubular lumen of rats resulted in a threefold increase in transepithelial Na^+ transport (Ellison et al, 1989). The net effect of the acute diuresis is the sum of the inhibition of Na^+ reabsorption in the diuretic-sensitive segment and increased Na^+ reabsorption in the distal segments (Preisig et al, 1987; Rose, 1991; Ellison, 1999).

Structural and functional changes in the distal tubular cells: the braking phenomenon

With long-term use of diuretics, continual increased Na^+ delivery to the distal tubules causes structural and functional changes in these segments. The epithelial cells undergo both hypertrophy and hyperplasia and as a consequence their Na^+ transport capacity becomes significantly higher (Ellison et al, 1989; Ellison, 1999). In experimental models, continuous infusion of furosemide for 7 days increased the volume of the distal convoluted tubules by 100% (Ellison et al, 1989). Chronic administration of loop diuretics also increases the Na^+K^+ ATPase activity in distal convoluted tubule and collecting ducts and increases the number of thiazide-sensitive Na-Cl co-transporters (Scherzer et al, 1987; Obermuller et al, 1995).

All these changes lead to significantly increased Na^+ transport across the distal tubules and Na^+ reabsorption in distal convoluted tubules and collecting ducts reaches levels as high as those seen in the proximal convoluted tubule (Ellison et al, 1989). This leads to a progressive reduction in diuretic efficacy and the dose–response curve shifts downward and to the right

(*Figure 2*). The magnitude of diuresis following each diuretic dose declines. This chronic renal adaptation to diuretics is termed 'the braking phenomenon' (Brater, 1985; Ellison, 1999).

Post-diuretic sodium retention

Most diuretics, especially loop diuretics, have a relatively short half-life and when given as a single daily dose, their serum concentration declines with time and reduces below their therapeutic threshold. At that point not enough diuretic is present in the tubular fluid to block Na^+ reabsorption and this results in a period of increased Na^+ reabsorption, a process termed 'post-diuretic Na^+ retention'. This continues until the next diuretic dose is given and the net diuretic effect during 24 hours is a sum of the natriuresis and the post-diuretic Na^+ retention (Ellison, 1999).

If dietary Na^+ intake is high, post-diuretic Na^+ retention can entirely eliminate the effect of the diuretic and a negative Na^+ balance is not achieved. If Na^+ intake is low, compensatory Na^+ retention is incomplete and there is a net loss of Na^+ (Bosch et al, 1977; Ellison, 1999).

Activation of renin–angiotensin–aldosterone system

Diuretics activate the renin–angiotensin–aldosterone system. This leads to Na^+ and water retention and contributes to the development of both post-diuretic Na^+ retention and the braking phenomenon. Diuretic-induced extracellular fluid volume contraction activates cells in the juxtaglomerular apparatus leading to secretion of renin and also leads to stimulation of renal sympathetic activity which in turn stimulates renin release via β-adrenergic receptors on the juxtaglomerular cells. Loop diuretics can also directly stimulate renin secretion from the macula densa by blocking Na^+ uptake in these cells. These factors can be especially significant in patients with congested cardiac failure where the same neurohormonal activation is central to the pathogenesis of heart failure (Ellison, 1999).

Management of diuretic resistance

The following strategies can be used in fluid overloaded patients if diuretic therapy fails to achieve the desired targets (*Figure 3*).

Dietary salt restriction

Poorly regulated Na^+ intake can limit the net negative Na^+ balance which might otherwise occur with an appropriate dose of diuretic. Restricting the Na^+ intake to less than 100 mmol/day attenuates the effect of post-diuretic Na^+ retention and helps achieve a negative Na^+ balance. A 24-hour urinary Na^+ excretion of more than 100 mmol/day indicates non-compliance with Na^+ restriction and excludes true diuretic resistance.

Obtaining a 24-hour urine sample can often be cumbersome and inaccurate. Fractional excretion of sodium gives the percentage of filtered Na^+ excreted in the

Figure 2. Diuretic dose–response curve.

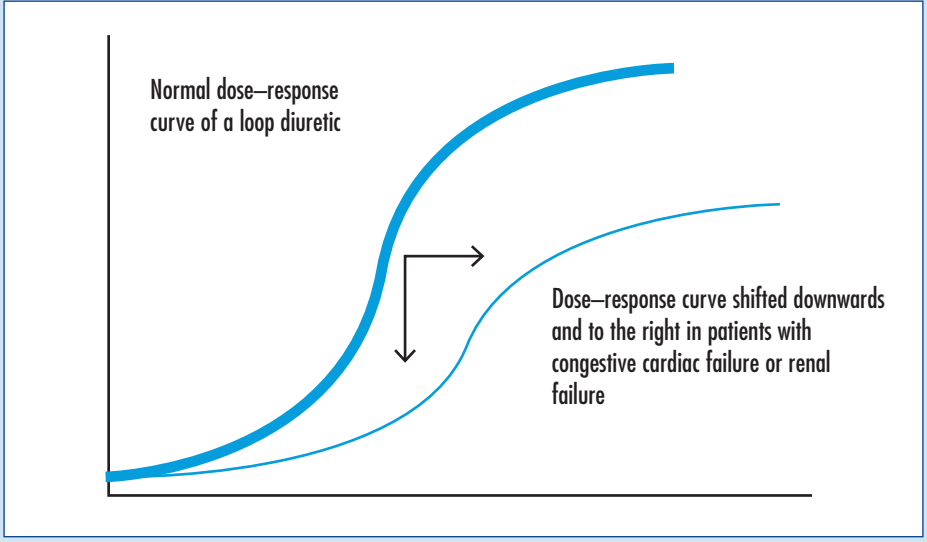
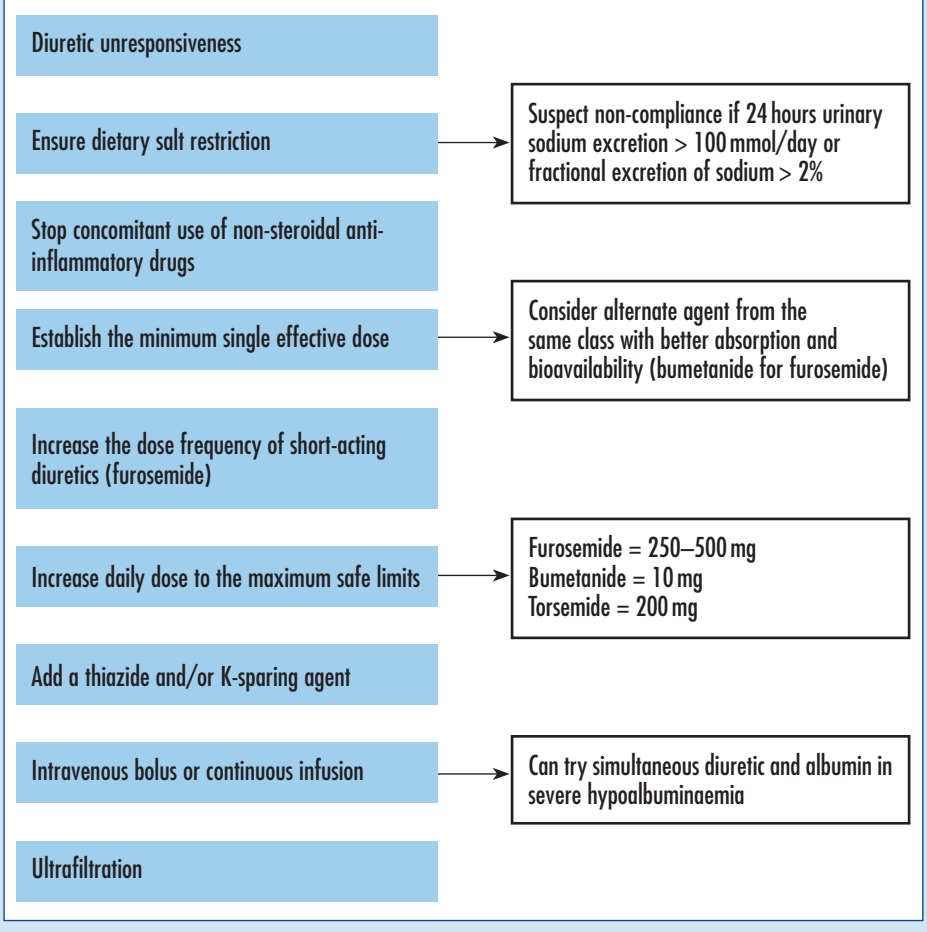


Figure 3. Algorithm for the management of loop diuretic resistance.



urine and can be calculated using a spot urine sample (*Figure 4*). A value above 2% indicates non-compliance with salt restriction (Epstein et al, 1977; Somber and Molnar, 2009).

Stop concomitant use of non-steroidal anti-inflammatory drugs

Concomitant use of non-steroidal anti-inflammatory drugs is a major cause of diuretic failure and withdrawing them can significantly improve the effectiveness of the diuretics. Hall (2001) noted an impressive reduction in diuretic requirements when daily administration of as small a dose as aspirin 100 mg was stopped.

Establish the effective single dose

Diuretics have a dose–response curve and the effect only begins once the diuretic level reaches a therapeutic threshold within the renal tubular lumen. The effective diuretic dose required to achieve the threshold concentration can vary between different individuals. In conditions affecting the renal blood flow and in patients with renal impairment the dose–response curve shifts downwards and towards the right and these patients need higher doses of loop diuretics to achieve the therapeutic drug level at their site of action. Increasing the frequency of a sub-therapeutic dose would remain ineffective (*Figure 2*).

Patients with advanced heart failure, cardio-renal syndrome, nephrotic syndrome and severe renal failure may need very high doses of loop diuretics, e.g. furosemide 250–500 mg a day, to achieve therapeutic effects (Gerlag and van Meijel, 1988). However, care must be exercised in patients with pre-renal acute kidney injury where high dose diuretic therapy can exacerbate renal hypoperfusion and worsen renal dysfunction.

Increase dose frequency of loop diuretics

Most loop diuretics are short acting. When given in a single daily dose their effect wears off with time and post-diuretic Na^+ retention can obviate their diuretic effect. Increasing the dose frequency to two to three times a day can help overcome this problem and restore the diuretic response.

Figure 4. Calculation of fractional excretion of sodium (FENa).

$$FENa = \frac{\text{Urinary sodium x plasma creatinine}}{\text{Plasma sodium x urinary creatinine}} \times 100$$

Diuretic substitution

Gastrointestinal absorption and bioavailability of different diuretics from the same class may vary considerably and this might be a factor for the poor response. On average only 50% of oral furosemide is absorbed. In contrast absorption of bumetanide and torsemide is nearly complete, ranging from 80% to 100%. At times switching furosemide to comparable doses of bumetanide or torsemide can do the trick (Sagar et al, 1984; Vargo et al, 1995).

Combination diuretic therapy

Sequential blockage of Na^+ uptake in different nephron segments by using a combination of two or more diuretics of different classes may produce an additive or synergistic diuretic response and can be an effective approach in resistant cases. This strategy can overcome the problem of increased sodium absorption in the distal nephron segments and can be helpful in negating the effect of the braking phenomenon.

Although all variations of diuretic combinations have been tried, the use of a loop diuretic and a thiazide or thiazide-like diuretic with or without a potassium-sparing agent is most common in practice (Fliser et al, 1994; Dormans and Gerlag, 1996). Although metolazone is the commonly used thiazide agent, studies have not shown superiority of any single thiazide diuretic over the others. In one study, bendrofluazide 10 mg and metolazone 10 mg were equally effective in establishing a diuresis when combined with loop diuretics. Bendrofluazide was associated with fewer electrolyte disturbances (Channer et al, 1994). A potassium-sparing diuretic is usually added if hypokalaemia becomes a problem. Spironolactone can be more suitable in conditions associated with high circulating aldosterone concentrations such as advanced heart failure or liver cirrhosis. The combination of a proximal convoluted tubule diuretic (acetazolamide) and a loop diuretic can be very effective by blocking >90% of Na^+ reabsorption in nephrons, but long-term use of acetazolamide can cause metabolic acidosis and this combination is rarely used in clinical practice (Knauf and Mutschler, 1994).

Combination diuretic therapy can be associated with an increased incidence of side effects such as electrolyte imbalance, dehydration and renal impairment. Careful monitoring of fluid and electrolyte balance and renal function, and prompt readjustment of treatment is of paramount importance.

Intravenous bolus and continuous infusion therapy

Loop diuretics (furosemide) can often be used as intravenous boluses or continuous infusion when oral treatment is not possible or has failed, or when treatment is urgent. Continuous intravenous infusion avoids the troughs in diuretic concentration and might prevent post-diuretic Na^+ retention completely. Smaller studies using both furosemide and bumetanide have shown that administration of loop diuretics by continuous infusion provides greater diuresis and natriuresis than bolus administration and has fewer undesirable side effects (Rudy et al, 1991; Lahav et al, 1992). However, a larger prospective, double-blind, randomized trial involving 308 patients with acute decompensated heart failure did not show any significant difference in patients' global assessment of symptoms when furosemide was administered by bolus as compared with continuous infusion (Felker et al, 2011).

High dose intravenous bolus therapy can be associated with higher risk of ototoxicity which can be minimized by limiting the rate of administration to less than 15 mg/minute. Continuous intravenous infusion avoids the very high peaks of diuretic concentration seen after a high dose bolus and has a lower risk of ototoxicity (Ellison, 1999).

Infusion with albumin

Hypoalbuminaemia reduces the delivery of diuretic to its site of action and thus can lead to diuretic unresponsiveness. Simultaneous infusion of diuretic and albumin might improve diuretic resistance (Inoue et al, 1987), but the effect of such intervention is only modest and this approach should only be considered in severely hypoalbuminaemic patients when more traditional approaches discussed above have failed (Fliser et al, 1999; Chalasani et al, 2001).

Ultrafiltration

Isolated ultrafiltration can be useful in patients with diuretic-resistant oedema, particularly in patients with acute decompensated heart failure. Ultrafiltration allows more effective fluid removal than diuretics resulting in more rapid symptomatic improvement, reduced length of hospital stay and readmission rates (Costanzo and Ronco, 2012).

Idiopathic oedema and lymphoedema

Patients with idiopathic oedema and lymphoedema can be difficult to manage and diuretics can sometimes make things worse. In such patients non-pharmacological approaches such as avoiding prolonged periods of standing, weight loss, low salt diet and compression bandaging might be more appropriate than using higher doses of diuretics. Leg oedema is also a common side effect of some commonly used vasodilators, such as calcium-channel blockers (e.g. amlodipine) and alpha-blockers (e.g. doxazocin). This form of oedema is not related to volume overload and overuse of diuretics can cause intravascular dehydration leading to symptoms of postural hypotension and renal insufficiency.

Conclusions

Diuretic resistance is common and can affect up to one third of patients with fluid overload. The pathogenesis is multifactorial. A methodical and multipronged approach is needed to overcome this situation. **BJHM**

Conflict of interest: none.

Bosch JP, Goldstein MH, Levitt MF, Kahn T (1977) Effect of chronic furosemide administration on hydrogen and sodium excretion in the dog. *Am J Physiol* **232**: F397–404

Brater DC (1985) Resistance to loop diuretics. Why it happens and what to do about it. *Drugs* **30**: 427–43

Chalasani N, Gorski JC, Horlander JC Sr, Craven R, Hoen H, Maya J, Brater DC (2001) Effects of albumin/furosemide mixtures on responses to furosemide in hypoalbuminemic patients. *J Am Soc Nephrol* **12**(5): 1010–16

Channer KS, McLean KA, Lawson-Matthew P et al (1994) Combination diuretic treatment in severe heart failure: a randomised controlled trial. *Br Heart J* **71**: 146–50

Costanzo MR, Ronco C (2012) Isolated Ultrafiltration in Heart Failure Patients. *Curr Cardiol Rep* **14**(3): 254–64

Dormans TPJ, Gerlag PGG (1996) Combination of high-dose furosemide and hydrochlorothiazide in the treatment of refractory congestive heart failure. *Eur Heart J* **17**: 1867–74

Ellison DH (1999) Diuretic Resistance: Physiology and Therapeutics. *Semin Nephrol* **19**(6): 581–97

Ellison DH, Velázquez H, Wright FS (1989) Adaptation of the distal convoluted tubule of the rat. Structural and functional effects of dietary salt intake and chronic diuretic infusion. *J Clin Invest* **83**(1): 113–26

Epstein M, Lepp BA, Hoffman DS et al (1977) Potentiation of furosemide by metolazone in refractory edema. *Curr Ther Res* **21**: 656–67

Felker GM, Lee KL, Bull DA et al (2011) Diuretic strategies in patients with acute decompensated heart failure. *N Engl J Med* **364**(9): 797–805

Fliser D, Schröter M, Neubeck M et al (1994) Coadministration of thiazides increases the efficacy of loop diuretics even in patients with advanced renal failure. *Kidney Int* **46**: 482–8

Fliser D, Zurbrüggen I, Mutschler E, Bischoff I, Nussberger J, Franek E, Ritz E (1999) Coadministration of albumin and furosemide in patients with the nephrotic syndrome. *Kidney Int* **55**(2): 629–34

Fonarow GC (2003) The Acute Decompensated Heart Failure National Registry (ADHERE): opportunities to improve care of patients hospitalized with acute decompensated heart failure. *Rev Cardiovasc Med* **4**(suppl 7): S21–S30

Gerlag PGG, van Meijel JJM (1988) High-dose furosemide in the treatment of refractory congestive heart failure. *Arch Intern Med* **148**: 286–91

Hall D (2001) Controversies in heart failure. Are beneficial effects of angiotensin-converting enzyme inhibitors attenuated by aspirin in patients with heart failure? *Cardiol Clin* **19**: 597–603

Inoue M, Okajima K, Itoh K et al (1987) Mechanism of furosemide resistance in analbuminemic rats and hypoalbuminemic patients. *Kidney Int* **32**(2): 198–203

Kirchner KA, Martin CJ, Bower JD (1986) Prostaglandin E2 but not I2 restores furosemide response in indomethacin-treated rats. *Am J Physiol* **250**: F980–5

Knauf H, Mutschler E (1994) Functional state of the nephron and diuretic dose-response-rationale for low-dose combination therapy. *Cardiology* **84**(suppl 2): 18–26

Lahav M, Regev A, Ra'anani P et al (1992) Intermittent administration of furosemide vs. continuous infusion preceded by a loading dose for congestive heart failure. *Chest* **102**: 725–31

Neuberg GW, Miller AB, O'Connor CM et al (2002) Diuretic resistance predicts mortality in patients with advanced heart failure. *Am Heart J* **144**: 31–8

Obermuller N, Bernstein P, Velazquez H et al (1995) Expression of the thiazide-sensitive Na-Cl cotransporter in rat and human kidney. *Am J Physiol* **269**(6): F900–10

Preisig PA, Toto RD, Alpern RJ (1987) Carbonic anhydrase inhibitors. *Ren Physiol* **10**(3-4): 136–59

Rose BD (1991) Diuretics. *Kidney Int* **39**(2): 336–52

Rudy DW, Voelker JR, Greene PK, Esparza FA, Brater DC (1991) Loop diuretics for chronic renal insufficiency: a continuous infusion is more efficacious than bolus therapy. *Ann Intern Med* **115**(5): 360–6

Sagar S, Sharma BK, Sharma PL et al (1984) A comparative randomized double-blind clinical trial of bumetanide and furosemide in congestive cardiac failure and other edema states. *Int J Clin Pharmacol Ther Toxicol* **22**: 473–8

Scherzer P, Wald H, Popovtzer MM (1987) Enhanced glomerular filtration and Na+-K+-ATPase with furosemide administration. *Am J Physiol* **252**(5): F910–15

Shah SU, Anjum S, Littler WA (2004) Use of diuretics in cardiovascular diseases: (1) heart failure. *Postgrad Med J* **80**: 201–5

Somber JC, Molnar J (2009) The management of acute heart failure and diuretic therapy. *Am J Therapeut* **16**: 93–7

Vargo DL, Kramer WG, Black PK, Smith WB, Serpas T, Brater DC (1995) Bioavailability, pharmacokinetics, and pharmacodynamics of torsemide and furosemide in patients with congestive heart failure. *Clin Pharmacol Ther* **57**(6): 601–9

KEY POINTS

- Diuretic resistance is a common problem in hospitalized patients, resulting in prolonged hospital stays.
- The pathogenesis is complex and multifactorial.
- A proper understanding of underlying pathophysiology is vital for devising management strategies.

TOP TIPS

- Consider diuretic unresponsiveness if a patient fails to lose 0.5–1.0 kg of weight per day.
- Review the drug charts and stop non-steroidal anti-inflammatory agents.
- Restrict daily sodium intake to less than 100 mmol.
- Measure 24-hour urine sodium excretion or calculate fractional excretion of sodium to check compliance with sodium restriction in non-responsive patients.
- Ensure the patients is taking the minimum effective single dose of loop diuretics before increasing the dose frequency.
- Be aware that patients with renal impairment or hypoalbuminaemia may need higher doses of loop diuretics to be effective.
- Continuous infusion of loop diuretics may be more effective and safer than high dose bolus therapy.