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REVIEW

Diuretic resistance and the role of albumin in congestive heart failure

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Abstract

Diuresis with loop diuretics is the mainstay treatment for volume optimization in patients with congestive heart failure, in which perfusion and volume expansion play a crucial role. There are robust guidelines with extensive evidence for the management of heart failure; however, clear guidance is needed for patients who do not respond to standard diuretic treatment. Diuretic resistance (DR) can be defined as an insufficient quantity of natriuresis with proper diuretic therapy. A combination of diuretic regimens is used to overcome DR and, more recently, SGLT2 inhibitors have been shown to improve diuresis. Despite DR being relatively common, it is challenging to treat and there remains a notable lack of substantial data guiding its management. Moreover, DR has been linked with poor prognosis. This review aims to expose the multiple approaches for treatment of patients with DR and the importance of intravascular volume expansion in the response to therapy.

Keywords: acetazolamide, diuretic resistance, furosemide, heart failure, loop diuretics, pedal oedema, sequential blocking, SGLT-2 inhibitor, thiazide, torsemide.

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Introduction

Diuretics are an integral component in the comprehensive management of congestive heart failure (HF).[1] Whilst their direct impact on mortality is null, diuretics effectively mitigate symptoms, avoid potential complications (including pulmonary oedema), improve quality of life and reduce hospital readmissions.[2] The cause of fluid retention may be multifactorial (fluid intake, diet, medications, bowel oedema, kidney disease, etc.) and, despite diuretic therapy responsiveness being present in most cases, the effectiveness of these medications in certain patients is a subject of discussion.[3]

Currently, multiple diuretics are available that facilitate options for the patient and help the clinician to explore a better response. However, a subset of individuals experiences a lack of therapeutic response when utilizing conventional diuretics, leading to the development of diuretic resistance (DR). Multiple mechanisms have been proposed to elucidate this phenomenon, with poor medication adherence, low perfusion, reduction of concentration in the renal tubules, drug interactions or side-effects (e.g. steroids, non-steroidal anti-inflammatory agents), hypoalbuminaemia, and alterations in pharmacokinetics being amongst the most common causes of DR.[3] This article aims to explore the aetiologies of DR and provide guidance on its management.

Methods

We reviewed 48 prominent original papers regarding diuretic therapy resistance. These publications were selected from multiple journals and libraries, including but not limited to *Journal of the American Heart Association*, *NEJM*, *Journal of the American College of Cardiology*,

JAMA, *Journal of Heart Failure*, Levy Library (Icahn School of Medicine), *BMJ*, Medscape and PubMed. The search was based on the following keywords: "furosemide", "metolazone", "torsemide", "albumin infusion", "thiazide", "hydrochlorothiazide", "diuresis therapy", "diuretics", "diuretic combination" and "diuretic resistance". The authors conducted the search and comparison of relevant articles following the PRISMA statement (Supplementary file 1; available at: https://www.drugsincontext.com/wp-content/uploads/2023/12/dic.2023-6-5-Suppl.pdf).

Review

Oedema is the most common sign in patients with underlying disease processes involving a volume expansion state and is most seen in patients with HF, nephrotic syndrome and chronic kidney disease (CKD), where volume expansion can manifest as hypertension.[4] Patients generally respond positively to diuretics, sodium restriction and fluid restriction from the diet. However, some patients fail to respond to the highest recommended diuretic dose; this is when the term DR comes into play amongst this population. DR or poor diuretic response has been linked with decreased survival.[5] The prevalence of DR in patients with HF is estimated between 21% and 30%.[6,7] Furthermore, DR is a potential cause of residual congestion after hospitalization, increasing the risk of recurrent admissions and death.[8]

Compared with patients with congestive HF alone, DR appears to be more prevalent in individuals with primary kidney disease. Several studies have reported a high incidence of DR, ranging from 50% to 70%, in patients with renal syndromes. Paradoxically, in patients with kidney disease, diuretics themselves exert a significant influence on renal neuromodulation and drug pharmacodynamics, which significantly affects the development of DR.[9] This resistance in patients with HF has been widely studied, but there are limited data in patients with CKD and nephrotic syndrome. Moreover, in patients with cirrhosis, the studies are controversial.

Accurately identifying the underlying causes of DR is crucial to effectively manage fluid overload and oedema. However, the lack of a practical and measurable definition for DR challenges its recognition. In clinical practice, the combined use of quantifiable parameters and monitoring of symptomatic progression plays a vital role in identifying appropriate strategies for managing fluid overload and recognizing the presence of DR.[6]

Volume optimization is imperative in treating patients with oedematous status, including patients with HF, regardless of their ejection fraction. Loop diuretics are extensively employed to alleviate fluid overload states. Furosemide is the initial loop diuretic approved in the United States and remains widely utilized in clinical practice.[10] Its effects span approximately 6–8 hours, whilst the appropriate dosing varies significantly based on renal function.[11] As glomerular filtration rate decreases, there is a proportional escalation in the required dosage. For treatment initiation in naive patients, intravenous doses typically range from a single dose of 20–40 mg to as high as 250 mg in patients with end-stage renal disease.[12]

Different approaches are currently followed to manage DR, such as titrating the loop diuretic dose, using intravenous loop diuretic as a bolus or continuous infusion form, or combining diuretics with different mechanisms of action (Table 1). There is a robust body of literature discussing the treatment of HF such as guideline-directed medical therapy in DR.[13]

Loop diuretics function by targeting the thick ascending limb of the loop of Henle by inhibiting the sodium–potassium–chloride cotransporter, thus decreasing the reabsorption of sodium chloride.[1] The secretion of this therapy is mainly in the proximal tubule, primarily due to it being highly protein bound.[14,15] Amongst this class of drugs, the most used are furosemide, bumetanide and torsemide. Ethacrynic acid, which is not a sulfonamide derivative, is rarely used but can be an alternative in patients with a hypersensitivity reaction to another loop diuretic. The initial dose conversion for intravenous furosemide for patients admitted to the hospital would be doubling the home dose.[16] Based on clinical evidence, the ideal strategy for administering loop diuretics is still uncertain. In a prospective randomized trial including 308 patients, the comparison of bolus with continuous loop diuretic infusion did not show more efficacy.[16] However, a later meta-analysis, including eight randomized controlled trials, revealed possible benefits with continuous loop diuretic infusion described as weight loss, increased urine output and decreased brain natriuretic peptide. Nevertheless, it did not show any difference in hospital length of stay.[17] Moreover, a large retrospective cohort study also failed to demonstrate the difference between continuous *versus* bolus administration.[18]

The exact reasons for the potential differences in resistance between torsemide and furosemide are not fully understood. It is noteworthy that torsemide has a longer half-life compared with the other loop diuretics. Furosemide has a bioavailability of approximately 50%; in contrast, torsemide and bumetanide have a bioavailability of 80–100%.[19] Therefore, patients resistant to furosemide might respond to torsemide or bumetanide with improved diuresis. However, very recently, in a randomized trial of 2859 participants, torsemide was not superior to furosemide and had similar all-cause mortality.[20] In patients with HF, the maximum dose of torsemide is 200 mg divided into two doses to decrease the chances of ototoxicity.[13]

Table 1. Therapeutic approaches in diuretic resistance.

Medication	Mechanism	Adverse reactions	Comment
Furosemide Torsemide	Targeting the thick ascending limb of the loop of Henle by inhibiting the sodium–potassium–chloride cotransporter	Diuresis related: electrolyte abnormalities, hypovolaemia; hypersensitivity reactions; ototoxicity at higher doses, especially with intravenous therapy	Patients resistant to furosemide might respond to torsemide with improved diuresis; however, a recent trial showed that torsemide was not superior to furosemide and had similar all-cause mortality[20]
Subcutaneous furosemide	Targeting the thick ascending limb of the loop of Henle	Similar to regular furosemide and skin affections on the puncture site	Recently approved by the FDA; most of the literature reports are from animals
Hydrochlorothiazide Chlorothiazide Metolazone	Block the Na-Cl symporter in the distal convoluted tubule	Hyperuricaemia, electrolyte abnormalities, and hyperglycaemia; possible systemic lupus erythematosus exacerbation with hydrochlorothiazide	Hydrochlorothiazide or placebo in addition to the intravenous showed no improvement in all-cause mortality or rehospitalization;[25] chlorothiazide was not superior to metolazone[23]
Acetazolamide	Carbonic anhydrase inhibitor	Fatigue, nausea, vomiting, abdominal pain and diarrhoea; paraesthesia, taste alteration	Combination of acetazolamide with loop diuretic was associated with greater incidence of successful decongestion[26]
Albumin	Albumin infusion enhances natriuresis[34]	Adverse effects are rare, anaphylactoid reactions	Mixed results[42–47]
Dopamine Milrinone Dobutamine	Can increase renal perfusion[31]	Angina, tachycardia, dyspnoea, headache, piloerection, cardiac arrhythmia, hypertension, azotaemia, gangrene; milrinone has been related to hypotension	Dopamine did not demonstrate a positive effect on renal function and diuresis[32]
SGLT2 inhibitors	Decrease renal glucose reabsorption with an increase in urinary glucose excretion; also associated with natriuresis	Xerostomia, fatigue, polydipsia, parathyroid hormone disbalance, recurrent genital infection and urinary incontinence	Early initiation of empagliflozin 25 mg daily to the standard diuretic therapy led to increased urine output[47]

Limited options and scarce data are available for patients who fail to achieve accurate diuresis with first-line diuretics. However, combining diuretics with different mechanisms of action is another option when titration of loop diuretics does not meet the expectation, using an intravenous loop diuretic in a bolus or continuous infusion form (Table 2). Another approach is sequential blocking, which refers to combined diuretic therapy using different mechanisms of action to enhance diuretic response.[21] This method is initiated with a loop diuretic, followed by the addition of a thiazide diuretic; if the patient is coursing with hypokalaemia, a potassium-sparing diuretic may be added. The rationale is based on targeting different sites in the kidney to increase urine production and sodium excretion. Amongst these options are thiazide and thiazide-like diuretics, which block the Na-Cl symporter in the distal convoluted tubule.[22] It has been recommended that patients with intestinal oedema or any other reason to avoid oral medications might benefit from the intravenous form, which is chlorothiazide. Otherwise, metolazone as an oral formulation has been shown to have comparable effects.[23] In a prospective, single-centre randomized trial, patients were randomly assigned to either oral metolazone, IV chlorothiazide or tolvaptan in addition to IV loop diuretics in patients admitted with HF exacerbation; the trial showed a similar increase in urine output.[24]

Recent trials attempted to determine if add-on diuretic therapy would cause greater decongestion in patients with HF exacerbation. In a recent multicentre trial including 300 patients hospitalized with HF exacerbation, patients were randomized to receive hydrochlorothiazide or placebo in addition to intravenous furosemide; the

Table 2. Clinical guidance for diuretic resistance.

Increasing diuretic dose	In the DOSE trial, increasing the dose of loop diuretic medication to 2.5 times the patient's usual outpatient dose was safe and effective for individuals who require long-term treatment with these drugs
Intermittent *versus* continuous intravenous administration loop diuretics	The continuous infusion of diuretics in patients with heart failure results in greater diuretic efficacy compared with the bolus diuretic regimen, not affecting the hospital length of stay or mortality
Combined diuretic therapy: thiazide-like drugs with loop diuretics	Whilst this approach results in strong diuretic effects, there is a significant potential for electrolyte imbalances; the exact point at which combination nephron blockade should commence with loop diuretic agents remains unclear
Combined diuretic therapy: acetazolamide with loop diuretics	Combining acetazolamide and loop diuretics might achieve early clinical decongestion along with the added advantage of reducing the length of hospital stay and similar adverse events
Coadministration of diuretics with albumin	Patients with hypoalbuminaemia might benefit from albumin infusion at the time of the diuretic dose

study concluded with no improvement in all-cause mortality or rehospitalization at 30 days between groups.[25] Nevertheless, a positive trial amongst patients admitted with acute HF, who were randomly assigned to either acetazolamide 500 mg IV or placebo in conjunction with standardized IV loop diuretic treatment, showed a higher incidence of successful decongestion and decreased hospital stay when compared with the placebo arm.[26]

A well-recognized benefit of mineralocorticoid antagonists (spironolactone and eplerenone) in HF with reduced ejection fraction is reduced mortality.[27,28] The dose is usually low, primarily to avoid hyperkalaemia with spironolactone, with a target dose of 25–50 mg daily and 50 mg daily of eplerenone.[29] A small prospective blinded study that included 100 patients with acute decompensated HF compared high doses of spironolactone 50–100 mg daily with standard acute HF therapy. Higher doses of mineralocorticoid antagonists were found to be safe and with possible earlier improvement of symptoms and decongestion.[30]

Organ perfusion compromise is usually present in patients with low cardiac output, another component affecting diuresis. Dopamine and milrinone are inotropes that can increase renal perfusion.[31] Dopamine in patients with acute decompensated HF was studied in a randomized clinical trial with the unfavourable outcome of increased risk of arrhythmias without an increase in diuresis or improved decongestion compared with placebo.[32] Dopamine is used when additional blood pressure support is required. However, dobutamine is preferred in HF because it has less incidence of arrhythmias and causes peripheral vasodilation, reduces the afterload and improves cardiac output. The use of milrinone also failed to demonstrate increased diuresis in patients with acute decompensated HF and otherwise haemodynamically stable.[33]

Another approach commonly discussed is the coadministration of diuretics with albumin infusion. It has been proposed that albumin infusion enhances natriuresis.[34] Proper perfusion is required for the secretion of loop diuretics at the tubular lumen. In hypovolaemia or hypoproteinaemia, albumin infusion would impact the oncotic pressure, improving fluid accumulation in the interstitial spaces and expanding the blood volume, indirectly stimulating diuresis. A randomized controlled study in CKD showed that furosemide with albumin had a superior short-term efficacy over furosemide alone in hypoalbuminaemia.[35] However, studies have reported mixed results. For instance, in patients with nephrotic syndrome, albumin infusion and diuretics have been hypothesized to improve oedema.[34] Some studies have indicated that coadministration of albumin and furosemide might exert a transient positive effect.[36–38] Consistent with these studies, a meta-analysis determined temporary impact albeit with only modest clinical significance.[39] However, multiple other studies have reported negative results, including in patients with cirrhosis and hypoalbuminaemia.[40,41]

Contradictory data have also been obtained for patients with acute decompensated HF, as shown in a recent retrospective observational study where coadministration of albumin and loop diuretic did not demonstrate better or worse outcomes.[42] On the contrary, in a study with a sicker population, namely patients with hypoalbuminaemia and HF, albumin infusion was associated with a high risk of in-hospital mortality and increased length of stay in the intensive care unit.[43] Limited data are available in patients with severe hypoalbuminaemia, which is defined

as plasma albumin of <2 g/dL. However, combining loop diuretics and albumin might benefit this population with refractory oedema.[44,45]

A large multicentre randomized controlled trial compared ultrafiltration with diuretic therapy in patients admitted for acute decompensated HF and cardiorenal syndrome. In the ultrafiltration arm, results were inconsistent with superiority in decongestion and associated with catheter-related adverse events and bleeding complications.[46] However, criticism occurred due to the rapid removal of fluid (200 mL/h), with the concern that it could potentially be the reason for worsening creatinine in the ultrafiltration arm. Nevertheless, evidence is still lacking regarding possible better outcomes with a slower rate.

Schulze et al. addressed a randomized prospective, double-blind, placebo-controlled study in patients with decompensated HF, measuring the urine output for 5 days, and reported that the early addition of empagliflozin 25 mg daily to the standard diuretic therapy increased urine output without affecting renal function.[47]

When deciding on decongestion in acute decompensated HF, it is essential to consider the impact of loop diuretic administration on neurohormonal activity and the activation of the sympathetic nervous system. A novel strategy using subcutaneous administration of buffered furosemide is introduced for outpatient use, including self-administration at home. This may help to reduce the patient and economic burden of HF and potentially impact HF readmissions.[48]

Conclusion

Accurate identification of the underlying causes of DR is crucial to effectively manage fluid overload and oedema. Volume optimization is vital in treating oedematous conditions in patients with HF, loop diuretics, such as furosemide, being the commonly used as the initial therapy. Different approaches to managing DR, such as titrating the loop diuretic dose, can be considered. Clinically, torsemide can be an alternative to furosemide due to its longer half-life. Thiazide and thiazide-like diuretics, such as chlorothiazide and metolazone, can also be used as options in patients with decreased response to loop diuretics. Combining diuretics with different mechanisms of action can be attempted in cases where loop diuretic titration does not yield the desired effect. In decompensated HF, the first line of therapy is intravenous loop diuretics; however, studies have shown mixed results between bolus and continuous infusion administration. New drugs, like empagliflozin, would positively impact the urine output in acute HF when added within 12 hours of admission. Further research is needed to better understand the optimal strategies for managing DR and improving outcomes in patients with fluid overload oedema and to establish clear guidelines for these patients.

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