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Loop diuretic resistance complicating acute heart failure

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Abstract
Acute heart failure hospitalizations complicated by diuretic resistance are associated with worse outcomes. Yet, quantification of the frequency and accompanying risk from loop diuretic resistance is limited by the absence of a comprehensive definition with universal clinical application. Herein, we outline limitations of the current metrics used to identify and define diuretic resistance. We discuss the best available methods to identify and prognosticate outcomes in diuretic resistance. We propose a mechanism-based classification system of diuretic resistance by anatomical location as follows: pre-nephron resistance, pre-loop of Henle resistance, loop of Henle resistance, and post-loop of Henle resistance. Within this paradigm, we compare and contrast historical beliefs of resistance mechanisms with current literature specific to patients with heart failure. We recommend a treatment pathway to restore diuretic efficacy with a literature review of the various combination diuretic strategies and ongoing clinical trials that may impact current best practices.

Keywords Diuretic resistance · Acute heart failure · Heart failure · Loop diuretic · Diuretic · Combination nephron blockade · Combination diuretic therapy

Defining loop diuretic resistance in acute heart failure

Intravenous (IV) loop diuretic therapy is required in 80–90% of acute heart failure (AHF) hospitalizations to treat symptoms of hypervolemia[1, 2]. Quantifying the incidence of loop diuretic resistance is limited by the absence of a universal definition for this complication. Qualitatively, diuretic resistance is an unsatisfactory rate of diuresis/natriuresis despite an adequate diuretic regimen. This qualitative description consists of three subjective evaluations: (1) presence and magnitude of hypervolemia; (2) adequacy of the diuretic regimen; and (3) rate of net negative urine and sodium balance. Each component is interdependent, subjective to the evaluator, and problematic to measure (Table 1).

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Diuretic response will decrease as euvolemia is approached, even if all other parameters remain constant. Ensuring the patient remains hypervolemic by the best available methods is the first step in defining diuretic resistance. Second, the adequacy of the diuretic dose and frequency must be addressed. Diuretic resistance is only considered when the loop diuretic regimen should yield diuresis, yet the rate of decongestion is inadequate. The determination of a diuretic regimen's adequacy is subjective and may be evaluated relative to the oral outpatient dose, historical response, frequency, utilization of other concomitant diuretics, and kidney function. Although lacking a defined value for diuretic resistance, diuretic efficiency has significant prognostic implications [24]. Finally, the rate of decongestion must be assessed. Commonly used metrics such as weight changes and net input-output measurements are imprecise in clinical practice due to inaccurate measurements and other influential factors. Agreement between these two metrics is poor even in the setting of rigorous clinical trials ($r = -0.381$ in the ASCEND-HF and $r = 0.55$ in DOSE-AHF clinical trials) [29, 30]. Furthermore, many AHF hospital admissions are not associated with weight gain, limiting the application of weight changes [31, 32].

Given these ambiguities, a quantitative definition of diuretic resistance with universal application remains elusive. Spot urinary sodium measurements are an emerging method to

Table 1 Fallacies of metrics required to define diuretic resistance

Metric	Fallacy
Presence and magnitude of hypervolemia	
Physical exam	○ Learned skill with inter-rater variability ○ Requires synthesis of multiple exam findings with low sensitivity and specificity for volume assessment [3–5] ○ Sensitivity of 58% for hypervolemia when compared to a hemodynamically measured standard [6, 7]
Serum creatinine and BUN	○ Increases can be secondary to multiple etiologies and are unreliable marker of volume status [8–13]
Natriuretic peptides	○ Obesity, age, kidney function, severity of disease, comorbidities, and medications can alter concentrations despite hypervolemia [14] ○ No absolute value or percentage decrease indicates euvolemia [15–17]
Serum bicarbonate	○ Increases are result of diuretic action and do no correlate with euvolemia or decongestion in DOSE-AHF, ROSE-AHF, or the CARRESS-HF populations [18]
Patient-reported dyspnea	○ Poor correlation with decongestion or euvolemia DOSE-AHF and CARRESS-HF populations [17, 19]
Hemodynamics	○ Gold-standard but invasive nature limits widespread utility ○ Assumes elevated pressure indicates elevated volume [20]
Adequate diuretic regimen	
Loop diuretic dose	○ Absolute and weight-based dose thresholds [21–23] alone ignore the urine volume and sodium output, which may be adequate
Diuretic efficiency	○ Expresses the diuretic response relative to the loop diuretic dose, as urine output, weight change, or sodium output per milligram of furosemide equivalents [24] ○ Primary limitation is the absence of a threshold to define resistance with differing median values between populations [24]
Urine sodium output	○ Urinary sodium output < 50–100 mmol in 6-h natriuretic period predicts a positive sodium balance with twice daily IV loop diuretic and is associated with worse heart failure outcomes [25–27] ○ Fluctuates significantly during consecutive days of diuresis despite consistent urine output, requiring serial measurements [28] ○ Primary limitation is lack of evidence including diuretic dose during interpretation
Adequate rate of net negative urine and sodium balance	
Weight loss	○ Influenced by non-diuretic factors such as measurement methods and bowel movements ○ Poor predictor of euvolemia and decongestive rate in AHF clinical trials [17, 29] ○ Weak correlation with net urine output in AHF clinical trials, highlighting the inaccurate measurement even in the best of circumstances [17, 29, 30]
Urine output	○ Quantification of urine volume alone neglects the urinary sodium concentration, which has wide interpatient variability [28] ○ 40% of patients excrete < 50 mmol sodium within 6 h after an IV loop diuretic dose [25]
Net input and output	○ Osmoregulation is preserved in the majority of HF patients with fluid intake strongly impacting urine output ○ Fluid intake is poorly regulated and recorded, falsely inflating net input and output ○ Weak correlation with weight loss in AHF clinical trials, highlighting the inaccurate measurement even in the best of circumstances [17, 29, 30] ○ Needs interpretation in context diuretic dose and frequency to define diuretic resistance

DOSE-AHF Diuretic Optimization Strategies Evaluation trial in Acute Heart Failure, *ROSE-AHF* Renal Optimization Strategies Evaluation in Acute Heart Failure, *CARRESS-HF* Cardiorenal Rescue Study in Acute Decompensated Heart Failure, *IV* intravenous, *AHF* acute heart failure

measure diuretic resistance. The spot urine sodium from a urine sample collected 1–2 h (h) after the administration of an IV loop diuretic dose can predict the total sodium excretion over the 6-h natriuretic duration of the loop diuretic with strong correlation with the measured 6-h sodium output ($r = 0.91$, $p < 0.0001$) by the following equation [25]:

$$\text{Na output (mmol)} = \text{eGFR} \times (\text{BSA}/1.73) \times (\text{Cr}_{\text{serum}}/\text{Cr}_{\text{urine}}) \times 60\ \text{min} \times 2.5\ \text{h} \times (\text{Na}_{\text{urine}}/1000\ \text{mL})$$

Na = sodium; eGFR = estimated glomerular filtration rate, BSA = body surface area, Cr_{Serum} = serum creatinine; Cr_{Urine} = urine creatinine; Na_{Urine} = urinary sodium concentration

Patients with a calculated cumulative sodium output < 100 mmol will not achieve a significantly negative sodium balance with twice daily diuretic dosing assuming a normal sodium restricted diet [25]. By identifying patients with natriuretic resistance within 1–2 h, clinicians can make rapid diuretic titrations to overcome diuretic resistance compared to traditional monitoring practices (Fig. 1). During consecutive days of diuresis, urinary sodium concentrations undergo

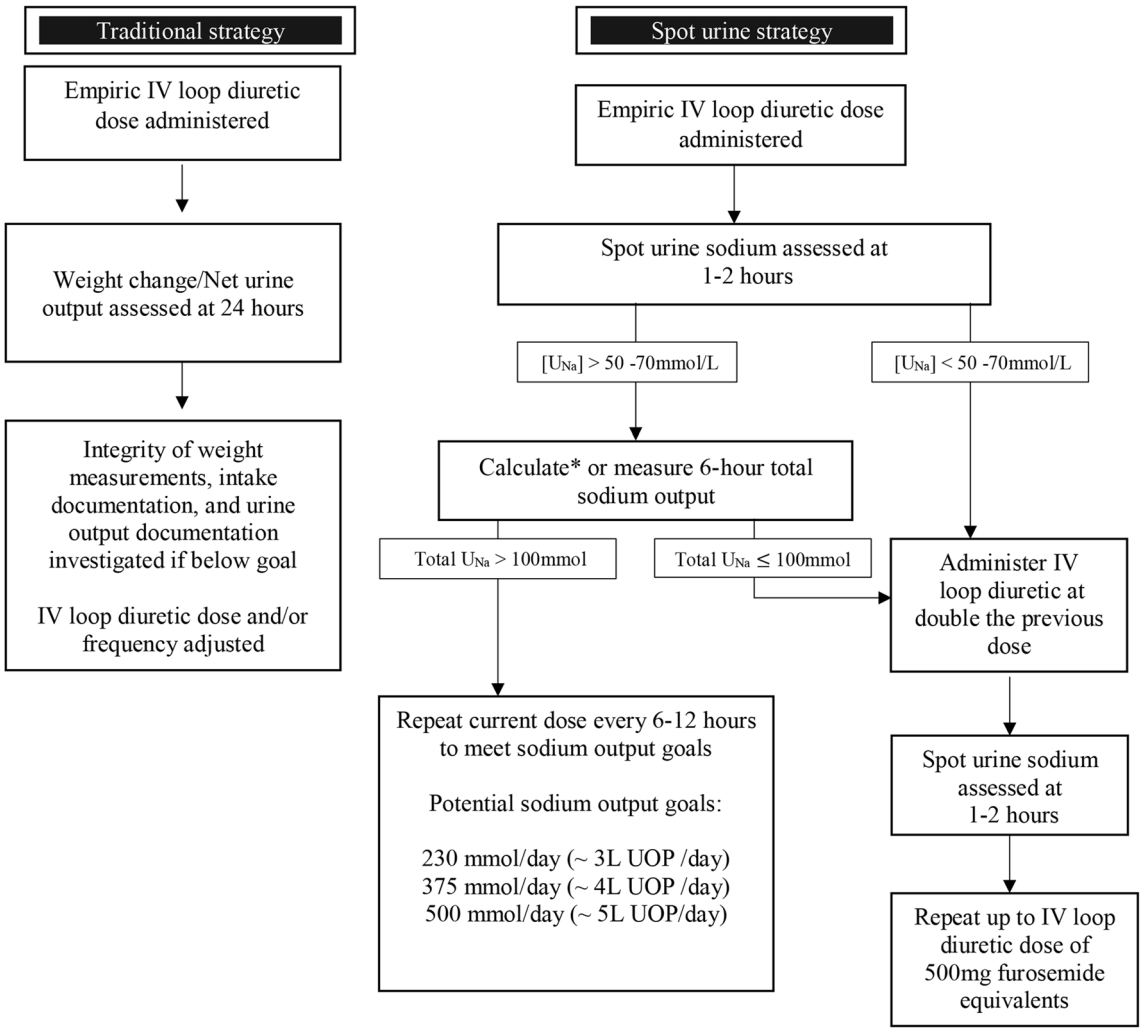

Fig. 1 Comparison of potential diuretic adjustment strategies. *Calculated 6-h total sodium output can be done using the equation in the text above, which is available as a free, online calculator at www.cardiorenalresearch.net. UOP, urine output; IV, intravenous; [U_{Na}], spot urinary sodium concentration in millimole/liter; Total U_{Na}, 6-h cumulative sodium output in millimole

significant fluctuation, can diminish despite preserved volumes of urine output, and may require serial measurement [3, 28].

Prognostic impact of diuretic resistance in acute heart failure

Diuretic resistance confers a worse prognosis, with the prognostic impact depending on the definition employed [33–35]. In the absence of randomized trials comparing therapies for diuretic resistance, it is difficult to discern the relative potential harm between the intertwined elements: diuretic resistance itself, the resultant increased loop diuretic doses, and the increased risk of not achieving decongestion. While the contribution of diuretic resistance is unknown, AHF hospitalizations ending without adequate decongestion are associated with worse outcomes and higher readmissions [36].

Loop diuretics increase neurohumoral activation regardless of the dose, diuretic response, or volume state [37, 38]. DOSE-AHF provides insight into the net balance between the decongestive benefits from higher diuretic doses and the potentially harmful neurohumoral activation, as it randomized patients to a high- or low-dose loop diuretic strategy [39]. The DOSE-AHF trial found no effect on 60-day death or rehospitalization between the high- or low-dose strategy, although the prevalence of diuretic resistance was unknown [40]. Patients randomized to a high-dose strategy had better 60-day outcomes, after adjusting for cumulative dose. However, the benefit was eliminated after adjusting for the resulting net urine output [39]. Changes in neurohormonal biomarkers during diuresis did not differ between the high- and low-dose groups and were not associated with 60-day outcomes in the DOSE-AHF trial [38]. While the potential for dose-related harm from loop diuretics cannot be excluded, the decongestive benefits of high-dose loop diuretics appear to offset potential harm.

Regarding the prognostic implications of diuretic resistance itself, a spot urine sodium less than 50–70 mmol/L after the first dose of IV loop diuretic is associated with higher risk of worsening kidney function, worsening heart failure (HF), and long-term adverse events [26, 41–43]. Yet, this metric does not consider the diuretic dose. Change in serial measures of spot urine sodium after diuretic adjustment may provide further prognostic value toward decongestive and long-term outcomes [44]. Diuretic efficiency is the best available metric to separate the prognostic effect of decongestive therapy intensity from resistance itself. Patients with diuretic efficiency below a population median had increased mortality (HR 3.57; 95% CI 1.46–8.73; $p = 0.005$), with those exhibiting low diuretic efficiency on high loop diuretic doses having the worst prognosis [24]. Consequently, diuretic resistance is known to confer a worse prognosis when high-dose loop diuretics are required with sustained low diuretic efficiency or resistance prohibits achievement of euvolemia with medical therapy.

Lastly, one must acknowledge that a mild resistance to diuretics can be beneficial. The term *diuretic braking* illustrates a beneficial adaptation to diuretics. *Diuretic braking* describes a diminished response to the same diuretic regimen [45]. If the initial diuretic response of excreting 20% of filtered sodium persisted, a continuous loop diuretic infusion would excrete 280 g of salt and 50 L of urine daily in a patient with an glomerular filtration rate (GFR) of 120 mL/min filtering 1400 g of sodium/day. In response to the immediate natriuresis, renal autoregulation and *diuretic braking* preserve the GFR. *Diuretic braking* is beneficial by ensuring loop diuretics do not have an unacceptably small therapeutic window. The term *diuretic braking* in clinical practice fails to characterize a specific mechanism of resistance or distinguish between beneficial renal adaptation and maladaptive diuretic resistance. Thus, a clinically actionable classification system should be employed instead.

Classification of loop diuretic resistance mechanisms

Diuretic resistance limiting decongestive goals, which may be similar or different mechanistically as beneficial *diuretic braking*, can be broadly categorized as pre-nephron diuretic resistance and intra-nephron diuretic resistance (Fig. 2). Intra-nephron diuretic resistance can further be divided into pre-loop of Henle diuretic resistance, loop of Henle diuretic resistance, and post-loop of Henle diuretic resistance. When evaluating diuretic resistance mechanism literature, one must consider the population studied. Many of the historical studies of diuretic resistance were performed in healthy controls or patients with hypertension or chronic kidney disease. The presumption that these findings can be intuitively applied to the AHF patient on modern medical therapies is flawed and has been challenged by recent literature specific to patients with HF.

Pre-nephron diuretic resistance

Historical diuretic studies focused on pre-nephron and pre-loop of Henle resistance mechanisms in healthy subjects and patients with hypertension or chronic kidney disease [47–53]. Low cardiac output to the kidney, once thought to be a predominant driver of cardiorenal syndrome and diuretic resistance, has been proven by multiple recent analyses to be of minimal importance at the AHF population level [8, 9, 54].

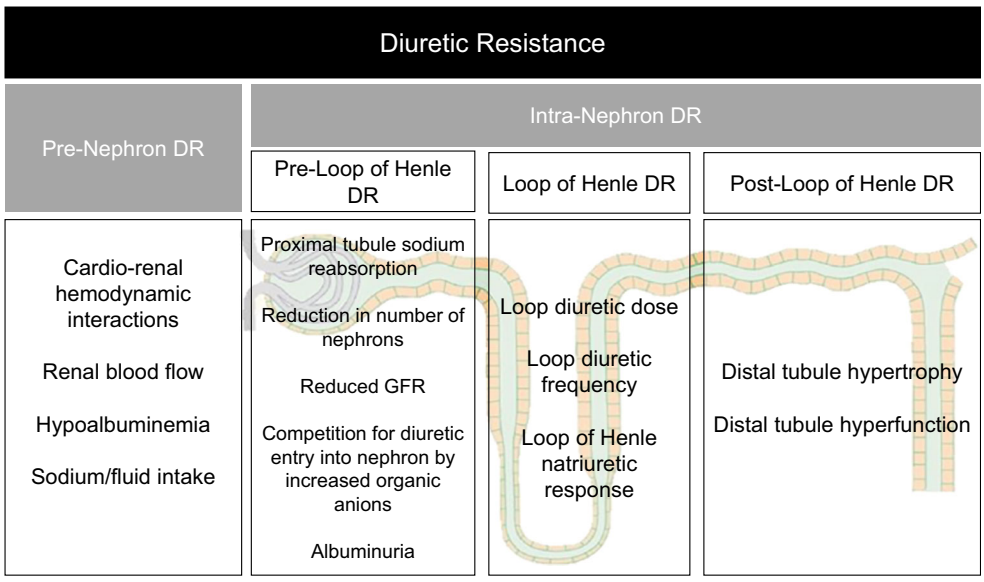

Fig. 2 Classification of potential IV loop diuretic resistance mechanisms. *Adapted with permission from *Cardiorenal Syndrome in Heart Failure* [46]

Venous congestion, hypothesized to initiate diuretic resistance through a reduction in the arterial to venous pressure gradient at the glomerulus, was also unrelated to diuretic efficiency [24]. Vasodilators, dopamine, and milrinone failed to augment diuresis or weight loss in patients with AHF [55–60]. While dopamine trended toward increasing urine volume in those with a baseline systolic blood pressure (BP) less than 114 mmHg [57], antagonism of the renin-angiotensin-aldosterone system (RAAS) may improve natriuresis even in the setting of BP reduction [61, 62]. Activation of the RAAS varies significantly during decongestion and lacks association with diuretic dose or diuretic response, although the timing of RAAS biomarkers during decongestive therapy limits definitive conclusions [38, 63]. It remains unclear which patients with lower BP and diuretic resistance should have a temporary cessation in medications that lower BP versus those in whom RAAS antagonists should be continued or increased. Lastly, non-steroidal anti-inflammatory drugs should be discontinued, as they impair renal blood flow and natriuresis by inhibiting prostaglandin synthesis [64, 65].

Hypoalbuminemia has been investigated as a pre-nephron diuretic resistance mechanism because all loop diuretics are > 90% bound to albumin [66–68]. Hypothesized mechanisms include a reduced intravascular volume available for diuresis and decreased delivery of loop diuretics to the nephron [69]. The majority of literature evaluating the benefit of IV albumin replacement with IV furosemide was performed in nephrotic syndrome or cirrhosis utilizing IV furosemide doses of only 40 mg [50, 70, 71]. In a cohort of patients with HF and a medium serum albumin of 3.70 g/dL (IQR 3.50 to 4.10), serum albumin had no correlation with urinary diuretic delivery nor diuretic resistance measured as diuretic efficiency after adjustment for inflammatory markers [72]. Recent AHF trials have validated these results, finding no association between baseline serum albumin concentrations and weight loss ($p = 0.43$), diuretic efficiency ($p = 0.53$), or freedom from congestion ($p = 0.30$) [73].

The relationship between sodium and heart failure outcomes is complex, with insufficient evidence to recommend any specific dietary sodium intake for patients with AHF undergoing diuresis [74, 75]. Traditional paradigms consider high sodium intake to be a cause of pre-nephron diuretic resistance [47, 76]. In contrast, higher sodium intake might be beneficial in AHF populations if a greater net sodium removal is achieved [74]. Co-therapy with hypertonic saline and high-dose loop diuretics produced greater natriuresis and urine volume than high-dose loop diuretics alone among AHF patients with diuretic resistance [77–79]. However, the quality of data supporting this approach is limited. Hypertonic saline therapy cannot be recommended presently until the safety and efficacy is demonstrated in a larger, diverse population achieving a net negative sodium balance [80].

Pre-loop of Henle diuretic resistance

Kidney function and albuminuria, which are hypothesized to impair diuretic delivery to the site of action, are less influential mechanisms of diuretic resistance compared to tubular handling of sodium in HF. Animal models of nephrotic syndrome [81–83] indicated albuminuria caused diuretic resistance by binding loop diuretics in the urine as in the serum [84]. A recent study in humans with nephrotic syndrome has disproven albuminuria as a primary mechanism of diuretic resistance [85]. Patients with AHF and normal albuminuria (43%), microalbuminura (39%), or macroalbuminuria (18%) exhibited no correlation between diuretic efficiency and urinary albumin concentrations ($r = -0.145$, $p = 0.08$) [72].

In the novel "The House of God," we see renally based diuretic adjustments taught as "age + BUN = Lasix dose" [86], which contemporary medical pocket resources continue [84]. Unlike chronic kidney disease populations, renal dysfunction is less relevant in HF as a cause of diuretic resistance and is responsive to increased diuretic dose. Estimated glomerular filtration rate (eGFR) poorly correlates with net fluid output ($r^2 = 0.0$; $p = 0.35$) and diuretic efficiency ($r^2 = 0.02$; $p < 0.001$) in patients with AHF [24]. Elevated BUN but not reduced eGFR predicted urine output in the ASCEND-HF trial, which could reflect neurohumoral activation and/or reduced diuretic delivery to the site of action [55]. A cohort of patients with HF were studied to evaluate the relative importance of diuretic delivery and renal tubular response in diuretic resistance [87]. Urea clearance ($r = 0.75$; $p = 0.001$) and low eGFR ($r = 0.58$; $p = 0.001$) strongly correlated with decreased diuretic delivery to the kidney, but interestingly, patients with lower eGFR compensated for decreased diuretic concentrations by producing approximately 2-fold greater fractional excretion of sodium at 6 h. Kidney function in HF has no impact on the individual nephron's net filtrate, but does influence total natriuresis through a reduction in the total number of nephrons. In summary, kidney dysfunction is much less of an important mediator of diuretic resistance in AHF than loop of Henle and post-loop of Henle diuretic resistance.

The proximal tubule is responsible for reabsorbing approximately 60% of filtered sodium [3]. Decreases in renal blood flow and increases in renal lymphatic flow secondary to HF may increase the percentage of filtered sodium reabsorbed up to 75% [88]. Further research is needed to quantify the contribution of the proximal convoluted tubule to diuretic resistance relative to resistance in the loop of Henle and distal tubules, although current literature indicates post-loop of Henle resistance is of greater significance.

Loop of Henle diuretic resistance

Loop diuretic's dose-response curve exhibits a sigmoidal pattern along a logarithmic scale, with both a threshold and ceiling effect. The diuretic concentration in the lumen of the loop of Henle relative to the diuretic threshold determines the peak rate and duration of diuresis (Fig. 3). A dose exceeding the ceiling can still cause a greater diuretic response by maintaining a concentration above the threshold for a longer time. An IV loop diuretic dose that fails to cross the diuretic threshold will result in diuretic resistance. Likewise, a diuretic dose that elicits an adequate response can fail to meet the decongestive goals for the day if it is given with an inadequate frequency. Following a dose, urinary concentrations of loop diuretics fall below the diuretic threshold quickly (half-life 1–2 h) with a duration of action that rarely exceeds 6 h [67, 68]. Typical twice daily dosing may provide diuretic concentration below the diuretic threshold for the majority of the day, allowing compensatory sodium reabsorption [45, 89].

Post-loop of Henle diuretic resistance

Continuous loop diuretic exposure in animals has shown rapid distal tubular hypertrophy and hyperfunction [90–92]. The few contemporary studies in AHF patients indicate that the majority of diuretic resistance is primarily mediated by post-loop of Henle diuretic resistance. In patients with AHF, a median dose of IV furosemide 160 mg (40–270 mg) increased the amount of sodium estimated to exit the loop of Henle by 12.6 ± 10.8% ($p < 0.001$) compared to a pre-diuretic baseline [93]. The net fractional excretion of sodium only increased 4.8 ± 3.3%, indicating 66% (25–85%) of the sodium leaving the loop of Henle underwent distal tubular reabsorption. The authors controlled for loop of Henle diuretic resistance by using urine diuretic concentration and reported the increase in sodium leaving the loop of Henle only accounted for 6.4% of the increase in net fractional excretion of sodium. A separate study of AHF patients receiving IV loop diuretic corroborated these findings, quantifying the majority (71%) of diuretic response was related to intra-renal diuretic resistance via renal tubular changes [87].

Diuretic strategies to overcome diuretic resistance

The following discussion assumes the patient exhibiting diuretic resistance is hemodynamically stable and hypervolemic. Additionally, it assumes the clinician has excluded causes of pseudo-resistance, such as drug interactions (NSAIDs, probenecid), urinary tract obstruction, or total body euvolemia with edema secondary to lymphedema or hypoalbuminemia. Medical therapy should always be individualized to the diuretic resistance mechanism when known to restore diuretic efficacy and achieve clinical euvolemia. A stepwise approach to diuretic titration based upon diuretic response with prioritization of loop diuretic optimization was employed

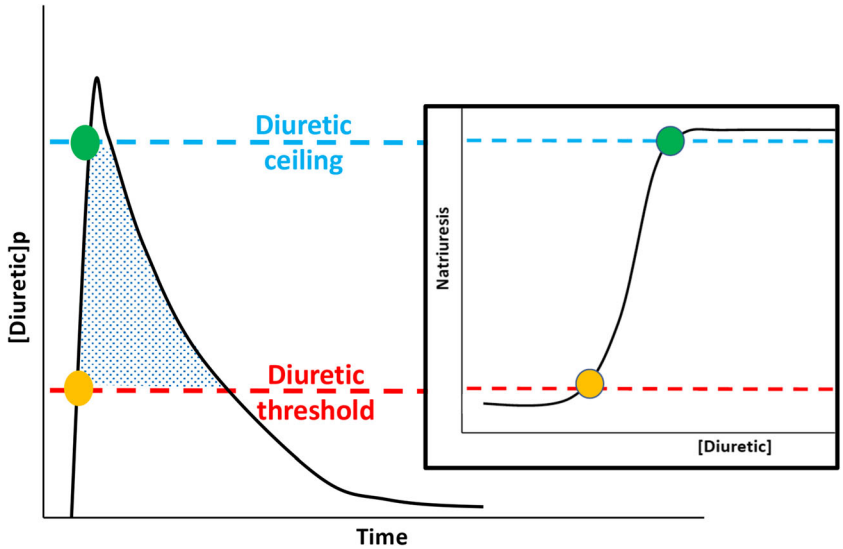

Fig. 3 Loop diuretic pharmacokinetics and dose-response curve. The loop diuretic plasma concentration (y-axis) is plotted over time (x-axis) when given as an intravenous bolus. The Diuretic Threshold (red dotted line) is the diuretic concentration that must be exceeded to cause diuresis. The Diuretic Ceiling (blue dotted line) is the diuretic concentration above which no further increases in diuretic response are gained. The shaded area illustrates the area of the curve between the Diuretic Threshold and Ceiling. The boxed graph within the graph on the right shows the simultaneous sigmoidal dose-response relationship between the diuretic concentration (x-axis) and the natriuretic response (y-axis). The orange circle represents the moment the diuretic concentration crosses the Diuretic Threshold simultaneously in both graphs. The green circle represents the when the diuretic concentration reaches the Diuretic Ceiling simultaneously in both graphs

in CARRESS-HF and represents the current best practice of overcoming diuretic resistance [3, 94]. We propose the following approach to the patient with AHF and diuretic resistance based upon the relative incidence of diuretic resistance mechanisms and the current literature supporting efficacy and safety of the diuretic therapies.

1. Address loop of Henle resistance mechanisms

Diuretic dose and frequency are interdependent in loop of Henle diuretic resistance and both must be considered. When evaluating for loop of Henle diuretic resistance, the natriuretic response to the dose should first be considered. A spot urine sodium less than 50 to 70 mmol/L or a urine output rate less than 600 mL over 6 h necessitates an increase in the loop diuretic dose [3] (Fig. 1). If the spot urine sodium is > 70 mmol/L, calculation of the 6-h cumulative urine sodium output provides additional guidance. Using the 6-h cumulative sodium output, clinicians can modify the loop diuretic regimen's dose and/or frequency to produce a net negative sodium balance relative to the daily dietary sodium intake (2 g sodium diet = 87 mmol). If an adequate natriuretic response is achieved, the frequency should be addressed next (Fig. 4). Continuous infusions of loop diuretics should be advantageous by consistently exceeding the diuretic threshold [95]. Yet, the DOSE-AHF trial found no difference in symptom improvement, urine output, or weight loss when administering the same total loop diuretic daily dose divided twice daily versus a continuous infusion in patients with an unknown prevalence of diuretic resistance [40]. In patients exhibiting diuretic resistance but with adequate natriuretic response to an IV bolus dose, consideration can be given to the use of IV loop diuretics at greater frequencies to overcome frequency-mediated diuretic resistance, although data proving this theoretical approach is lacking. This strategy differs from the DOSE-AHF trials' null findings in that more frequent dosing also represents an increase of the total daily diuretic dose in addition to increased frequency.

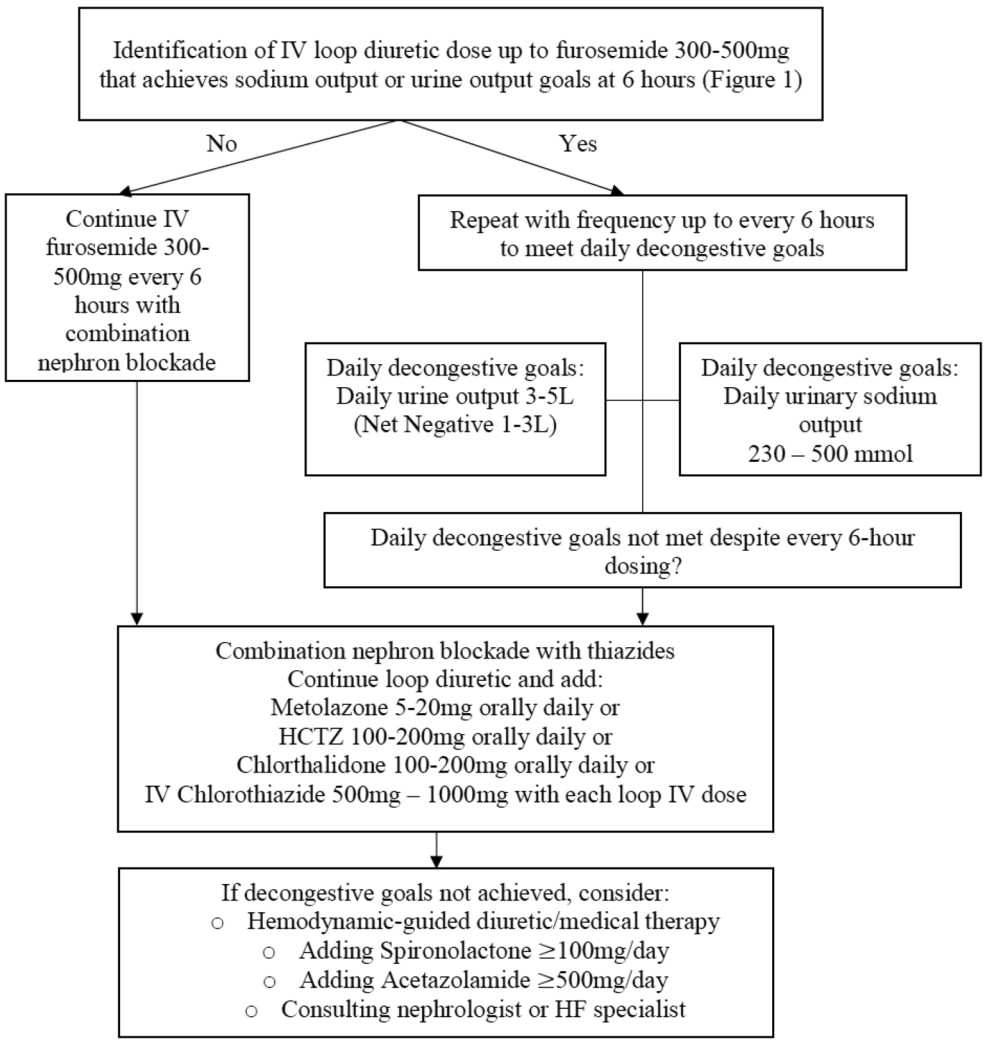

Fig. 4 Diuretic strategies to overcome diuretic resistance

2. Address post-loop of Henle diuretic resistance

Although post-loop of Henle is the resistance mechanism in the majority of patients AHF, clinicians should first ensure an adequate loop diuretic dose and frequency are prescribed before employing combination nephron blockade targeting post-loop of Henle diuretic resistance (Fig. 4). Combination nephron blockade with metolazone was investigated in an observational cohort of 13,898 AHF hospital admissions, of which 1048 utilized adjuvant metolazone [96]. After propensity and covariate adjusted analyses, adding metolazone was associated with increased risk of hypokalemia (OR 2.80; 95% CI 2.25–3.50), hyponatremia (OR 2.13; 95% CI 1.73–2.62), worsening renal function (OR 3.02; 95% CI 2.55–3.58), and mortality (OR 1.20; 95% CI 1.04–1.39) [96]. In contrast, the use of high-dose loop diuretics did not have any association with harm. Interestingly, the harm associated with metolazone was only in patients who did not have metolazone added to high-dose loop diuretics. Together with the DOSE-AHF trial's absence of harm between high and low dose diuretics, the limited current literature indicates escalation of loop diuretic doses may be the preferred method until randomized, comparative trials (NCT01647932) can better inform practice [3, 40, 97].

Thiazide (and thiazide-like) medications are the most commonly utilized medications to overcome post-loop of Henle diuretic resistance [98–100]. Since thiazides inhibit sodium reabsorption in the distal convoluted tubules where the majority of remaining sodium reabsorption occurs after the loop of Henle, these agents should be the initial agent chosen for combination nephron blockade. Despite experience spanning 50 years, common misconceptions regarding thiazides in combination nephron blockade persist [99]. Thiazides appear to have equal efficacy at equipotent doses [101]; therefore, decisions between agents should be based upon pharmacokinetic differences, particularly among agents with additional carbonic anhydrase antagonistic ability. Although metolazone is often considered superior to other thiazides, no solid evidence supports this perception, even in patients with low eGFR [99, 102–104]. Administration of thiazides 30 min prior to loop diuretics is not based upon evidence, as most studies administered both agents simultaneously [99]. The erratic and delayed absorption of metolazone makes this practice clinically irrelevant and unnecessarily increases complexity [105, 106].

While oral chlorothiazide is not utilized secondary to poor absorption, IV chlorothiazide offers the pharmacokinetic advantages of a quicker onset of action compared to metolazone's slow absorption and has a shorter duration of action that may better facilitate titration to diuretic response [101]. To date, no randomized trials have compared IV chlorothiazide to oral thiazides, limiting definitive conclusions on efficacy differences [107]. Two ongoing randomized clinical trials (NCT02606253 and NCT03574857) comparing metolazone and IV chlorothiazide will provide further insight into this issue.

Careful monitoring for electrolyte abnormalities, kidney function, and volume status is warranted with all thiazides to avoid adverse events [99]. The risk of hypochloremia increases in combination nephron blockade and is emerging as a research target [96, 108]. Hypochloremia has been associated with increased mortality risk and diuretic resistance [109–112]. No data currently exists to guide chloride supplementation or modification of combination diuretic therapy on the basis of serum chloride.

Mineralocorticoid receptor antagonists and epithelial sodium channel inhibitors impact the late distal tubule and collecting duct. Given the reduced capacity for sodium reabsorption in this anatomical area compared to the site of action of thiazides, these agents are thought unlikely to provide superior diuretic effects in combination with loop diuretics [3, 113]. Diuretic doses of mineralocorticoid receptor antagonists are combined with loop diuretics in cirrhotic ascites as the primary combination nephron blockade strategy [114, 115]. In chronic HF, non-diuretic doses (< 50 mg/day) of mineralocorticoid receptor antagonists reduce morbidity and mortality [116]. Literature examining higher doses of mineralocorticoid receptor antagonists with the intent of augmenting diuresis is scarce [117, 118]. The ATHENA-HF trial compared spironolactone 100 mg/day to placebo or continued non-diuretic dose spironolactone (25 mg) in patients with hypervolemic AHF treated with IV loop diuretics [119]. No difference in the primary endpoint of natriuretic peptide change or secondary diuretic outcomes such as net urine output, weight change, or IV loop diuretic doses required were found [119]. Several factors should be considered when interpreting these results. The population studied did not exhibit diuretic resistance, receiving a median IV furosemide daily dose of 160 mg (IQR 100, 320). Spironolactone has a short half-life (1.5 h), and the active metabolite canrenone (half-life ~ 17 h) is responsible for the majority of the medication's effects [120]. As steady-state canrenone concentrations are not achieved until day 3 of therapy, the 96-h time period might be insufficient to measure the effects [119]. Serum potassium levels were no different between spironolactone and placebo, supporting this possibility [119]. Future studies should investigate higher doses of spironolactone (200–400 mg/day) or other mineralocorticoid receptor antagonists in a diuretic resistance population. Currently in AHF with diuretic resistance, this class can be utilized for hypokalemia management and continued as a part of chronic neurohormonal therapies, but diuretic doses should be reserved until failure of combination nephron blockade with loops and thiazides.

Vasopressin-2 receptor antagonists have been extensively investigated in AHF. Earlier trials evaluated the impact on mortality and hyponatremia [121, 122]. Recent investigations have re-focused the primary efficacy endpoints to study their decongestive effects. Vasopressin-2 receptor antagonists exert diuretic effects by blocking vasopressin-mediated aquaporin

channels in the collecting duct, causing an increase in urinary water (aquaresis) when used alone [123]. The natriuretic potential when combined with high-dose loop diuretics in patients with diuretic resistance is not described to date. Ongoing clinical trials are investigating the natriuretic effects with this application (NCT02606253), which will be critical if a urine sodium-based diuretic strategy is employed (Fig. 4). Three trials comparing tolvaptan to placebo in patients with hypervolemic AHF without diuretic resistance treated with only modest IV loop diuretics (mean daily IV furosemide equivalent 80–160 mg) found increases in weight loss and urine output [124–126]. Tolvaptan cannot be recommended over thiazides in combination nephron blockage at this time given the limited study in loop diuretic resistance.

The proximal convoluted tubule reabsorbs the largest percentage of filtered sodium, making it an attractive target for diuretic therapies [113]. Medications acting in the proximal convoluted tubules with potential for combination nephron blockade include acetazolamide and sodium-glucose co-transporter 2 (SGLT2) inhibitors. Acetazolamide has a number of potentially positive extra-diuretic effects, including increased salt delivery to the macula densa reducing neurohormonal activation [127]. When combined with low doses of oral and IV furosemide in small cohorts of patients with HF but without diuretic resistance, acetazolamide increased the natriuretic response [128, 129]. Acetazolamide is currently being investigated in combination with IV loop diuretics in the ADVOR trial (NCT03505788) [127]. SGLT2 inhibitors have several ongoing clinical trials to establish the acute natriuretic effects in patients with HF, but their use as adjunctive diuretic agents cannot be recommended currently. Acetazolamide may be a promising diuretic to add when diuretic resistance persists despite combination nephron blockade with loop diuretics and thiazides, but there is no conclusive evidence to recommend its use over thiazides currently.

In conclusion, a universally applicable, quantitative definition of diuretic resistance in AHF remains elusive. The mechanisms behind diuretic resistance are diverse. A mechanism-based classification can guide medical strategies to restore diuretic efficacy. Optimization of loop diuretic regimens based upon diuretic response should be the primary strategy followed by combination nephron blockage with thiazides. Novel diuretic combination strategies are emerging but require further research before they can be recommended.

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