Diuretic Resistance in Acute Heart Failure: Bridging Bench Discoveries to Bedside Solutions

Résistance aux diurétiques dans l'insuffisance cardiaque aiguë : de la recherche au chevet du patient

Emna Derbel [1,2], Naziha Turki [1,2], Rania Hammami [1,2]

1. *Military University Hospital of Sfax , Cardiology Department, Sfax, Tunisia*
2. *University of Sfax, Faculty of Medicine of Sfax , Sfax, Tunisia*

Summary

Diuretic resistance affects approximately 30% of hospitalized patients with acute heart failure and is associated with poor prognosis. This overview examined the pathophysiological mechanisms underlying fluid retention in heart failure, the pharmacology and clinical application of established and novel diuretic agents, and practical approaches to overcome diuretic resistance. We proposed integrated treatment algorithms, emphasizing early, protocolized therapy to optimize decongestion and improve clinical outcomes.

Keywords

acute heart failure, loop diuretics, sequential nephron blockade, SGLT2 inhibitors, acetazolamide, natriuresis-guided therapy

Résumé

La résistance aux diurétiques touche environ 30 % des patients hospitalisés pour insuffisance cardiaque aiguë et est associée à un mauvais pronostic. Cette revue examine les mécanismes physiopathologiques à l'origine de la rétention hydrique dans l'insuffisance cardiaque, la pharmacologie et l'utilisation clinique des diurétiques classiques et innovants, ainsi que les approches pratiques pour surmonter la résistance aux diurétiques. Nous proposons des algorithmes thérapeutiques intégrés, en insistant sur une prise en charge précoce et protocolisée afin d'optimiser la décharge liquidienne et d'améliorer les résultats cliniques.

Mots-clés

insuffisance cardiaque aiguë, diurétiques de l'anse, blocage néphronique séquentiel, inhibiteurs de SGLT2, acétazolamide, traitement guidé par la natriurèse

Correspondance

Dr Emna DERBEL
Military university hospital of Sfax, Cardiology department, Thyna, Sfax, Tunisia
Email: derbelemna4@gmail.com

INTRODUCTION

Acute heart failure (AHF) is a major global medical emergency, affecting over 26 million people worldwide and causing more than one million hospitalizations annually in Europe and North America (1). Despite advances in chronic heart failure management with guideline-directed therapies, treatment of acute decompensation remains largely empirical and varies substantially in practice (2). Congestion in AHF is multifactorial, involving neurohormonal activation, renal sodium and water retention, and ventricular-vascular alterations. Incomplete relief of congestion before discharge strongly predicts adverse outcomes, with 30-day readmission rates exceeding 25% and nearly doubled mortality (3). Loop diuretics remain the mainstay therapy for congestion, with ESC, AHA, and ACC guidelines recommending intravenous loop diuretics as first-line treatment in AHF with fluid overload (Class I, Level B) (4,5). However, high-quality randomized controlled trial evidence for specific dosing, administration routes, or combination strategies is limited (6). Recent developments include the concept of "door-to-diuretic time," emphasizing early IV loop diuretic administration within 90 minutes of ED arrival, which reduces inpatient mortality (7). Natriuresis-guided, protocolized diuretic strategies have improved decongestion efficiency (8). Novel agents, including SGLT2 inhibitors and acetazolamide, have expanded options for managing diuretic-resistant patients (9). This update reviews the pathophysiology of fluid retention, pharmacology of diuretics, strategies for acute decompensation—including combination therapies—management of diuretic resistance, and emerging precision medicine approaches. Practical, evidence-based algorithms are provided to guide clinical decision-making in both hospital and outpatient settings.

PATHOPHYSIOLOGY OF FLUID RETENTION AND CONGESTION

Neurohormonal Activation and Sodium Retention

Congestion in heart failure arises from maladaptive neurohormonal responses to reduced cardiac output and altered hemodynamics. Three key systems drive sodium and water retention: the renin-angiotensin-aldosterone system (RAAS), the sympathetic nervous system (SNS), and the arginine vasopressin (AVP) system.

Reduced renal perfusion and decreased sodium delivery to the macula densa activate RAAS, leading to angiotensin II–mediated sodium reabsorption in the proximal tubule and aldosterone release, which further promotes distal sodium retention via ENaC activation. This cascade increases intravascular volume and contributes to myocardial fibrosis and vascular remodeling (10).

SNS activation, triggered by baroreceptor unloading and enhanced chemoreceptor sensitivity, elevates norepinephrine levels, causing renal vasoconstriction, stimulating renin release via β1 receptors, and enhancing tubular sodium reabsorption (11).

Non-osmotic AVP release, induced by arterial underfilling, increases water retention through V2 receptor–mediated aquaporin-2 upregulation in collecting duct cells, leading to dilutional hyponatremia and representing the therapeutic target for vasopressin antagonists (vaptans).

Renal Tubular Adaptation and Diuretic Resistance

Chronic exposure to loop diuretics induces structural and functional adaptations in the distal nephron that contribute to progressive diuretic resistance. The most significant adaptation is distal convoluted tubule hypertrophy with upregulation and increased apical membrane expression of the thiazide-sensitive Na-Cl cotransporter (NCC). This compensatory mechanism allows the distal tubule to reclaim sodium escaping inhibition in the thick ascending limb, thereby blunting the natriuretic response to loop diuretics. This phenomenon underlying the efficacy of sequential nephron blockade with combination diuretic therapy (12).

Furthermore, loop diuretic-mediated inhibition of chloride uptake at the macula densa paradoxically stimulates renin release and RAAS activation, triggering enhanced proximal tubular sodium-bicarbonate reabsorption. This compensatory response termed "braking phenomenon", reduces sodium delivery to the loop of Henle, further diminishing diuretic efficacy (13). The fractional excretion of sodium (FENa) decreases from 20-25% in diuretic-naïve individuals to 10-15% in patients on chronic loop diuretic therapy, reflecting the magnitude of tubular adaptation.

CLASSIFICATION AND MECHANISM OF ACTION OF DIURETICS

Loop Diuretics: Furosemide, Bumetanide, Torsemide

Loop diuretics functions by inhibiting the Na-K-2Cl cotransporter-2 (NKCC2) situated on the luminal membrane of the thick ascending limb of Henle's loop. This inhibition prevents reabsorption of 25-30% of filtered sodium chloride, decreases the medullary osmotic gradient necessary for water reabsorption in distal segments, and promotes excretion of hypotonic urine.

Beyond natriuresis, loop diuretics produce acute venous vasodilation through NKCC1 inhibition in vascular smooth muscle cells, reducing preload independently of diuretic effects, a mechanism critical for rapid symptomatic relief in pulmonary edema (14).

Loop diuretics follow a sigmoid dose-response curve with three distinct phases: a threshold below which natriuresis is minimal, a steep response phase, and a ceiling beyond which peak effects plateau. Notably, doses exceeding the ceiling continue to enhance cumulative natriuresis by maintaining plasma concentrations above the natriuretic threshold (15).

In acute decompensated heart failure, this curve shifts rightward (elevated threshold) and downward (reduced ceiling) due to decreased renal perfusion, reduced drug delivery to tubular sites, and enhanced compensatory distal sodium reabsorption. Consequently, higher loop diuretic doses are required, and dose doubling is justified when response is inadequate, as the logarithmic dose-response relationship demands proportional dose increases to achieve clinically meaningful effects.

Thiazide and Thiazide-like Diuretics

Thiazide diuretics (e.g., hydrochlorothiazide) and thiazide-like agents (metolazone, chlorthalidone, indapamide) act by inhibiting the Na –Cl cotransporter (NCC) located on the apical membrane of epithelial cells within the distal convoluted tubule. Although this nephron segment normally reabsorbs only 5–10% of filtered sodium, thiazides provide substantial therapeutic benefit in heart failure through their synergistic action with loop diuretics. Chronic exposure to loop diuretics leads to distal tubular hypertrophy and upregulation of NCC, enhancing compensatory sodium reabsorption and thereby diminishing loop diuretic efficacy. By inhibiting this adaptive mechanism, thiazide or thiazide-like agents restore natriuretic response and achieve potent synergistic effects, overcoming diuretic resistance in approximately 70–80% of refractory case (16).

Carbonic Anhydrase Inhibitors: Acetazolamide

Acetazolamide represents a rediscovered therapeutic approach for overcoming diuretic resistance in acute heart failure. This carbonic anhydrase inhibitor acts on the proximal convoluted tubule, responsible for reabsorbing approximately 65% of filtered sodium and water under normal physiological conditions. Carbonic anhydrase catalyzes the intracellular hydration of CO_2 to H_2CO_3, which dissociates to H and HCO_3 . The H is secreted luminally via the Na-H exchanger (NHE3) in exchange for sodium reabsorption, while HCO_3 exits basolaterally. By inhibiting carbonic anhydrase, acetazolamide reduces H availability for NHE3-mediated sodium reabsorption, resulting in natriuresis and bicarbonaturia (9).

Carbonic Anhydrase Inhibitors: Acetazolamide

Acetazolamide represents a rediscovered therapeutic approach for overcoming diuretic resistance in acute heart failure. This carbonic anhydrase inhibitor acts on the proximal convoluted tubule, responsible for reabsorbing approximately 65% of filtered sodium and water under normal physiological conditions. Carbonic anhydrase catalyzes the intracellular hydration of CO_2 to H_2CO_3, which dissociates to H and HCO_3 . The H is secreted luminally via the Na-H exchanger (NHE3) in exchange for sodium reabsorption, while HCO_3 exits basolaterally. By inhibiting carbonic anhydrase, acetazolamide reduces H availability for NHE3-mediated sodium reabsorption, resulting in natriuresis and bicarbonaturia (9).

Mineralocorticoid Receptor Antagonists

Mineralocorticoid receptor antagonists (spironolactone, eplerenone) block aldosterone-responsive epithelial sodium channels (ENaC) in the distal nephron and collecting tubules. While these agents produce only weak natriuresis (fractional sodium excretion ~2%), they have established mortality and morbidity benefits in chronic heart failure with reduced ejection fraction through neurohormonal modulation and prevention of myocardial fibrosis (17). MRAs serve an important role in preventing and treating hypokalemia during aggressive

combination diuretic therapy. Potassium-sparing diuretics reduce potassium and magnesium losses, potentially decreasing requirements for intravenous electrolyte replacement.

Sodium-Glucose Cotransporter-2 Inhibitors

Mechanisms and advantages

Sodium-glucose cotransporter-2 inhibitors (empagliflozin, dapagliflozin) have transformed heart failure management through pleiotropic cardiovascular and renal benefits beyond diabetes treatment. These agents block SGLT2 on proximal tubular epithelial cells, which normally reabsorb 90% of filtered glucose coupled to sodium.

Key advantages over traditional diuretics include: no neurohormonal activation (unlike loop diuretics), preserved/improved renal function (through reduced intraglomerular pressure), cardiovascular protection independent of ejection fraction, anti-inflammatory effects, and metabolic benefits.

Evidence in Acute Heart Failure

Several recent trials have evaluated SGLT2i initiation during acute decompensated heart failure hospitalization: The EMPAG-HF trial (n=60) demonstrated that early initiation of empagliflozin (25 mg within 12 h of admission) increased 5-day urine output by 25%, enhanced NT-proBNP reduction, improved NYHA class, and better preserved renal function versus placebo (18). In the larger EMPULSE trial (n=530), empagliflozin (10 mg within 5 days) significantly improved the hierarchical composite of death, HF events, and KCCQ-TSS at 90 days (win ratio 1.36; p=0.0054), with greater weight loss and decongestion (19). Similarly, DICTATE-AHF (n=240) evaluated early dapagliflozin initiation, showing a favorable trend toward improved diuretic efficiency, supporting the early in-hospital use of SGLT2 inhibitors in acute heart failure (20).

Vasopressin Receptor Antagonists

Tolvaptan, a selective V2 receptor antagonist, produces aquaresis (free water excretion without natriuresis) by blocking AVP-mediated aquaporin-2 insertion in collecting duct principal cells. The EVEREST trial (n=4133) evaluated tolvaptan added to standard therapy in hospitalized AHF patients, demonstrating improved dyspnea and weight loss but no mortality or rehospitalization benefit. Severe hepatotoxicity concerns have limited tolvaptan use to selected cases of severe, refractory hyponatremia (serum sodium <125 mmol/L). Other vaptans (conivaptan, lixivaptan) remain investigational in heart failure (21).

Figure 1 summarizes the sites and mechanisms of action of diuretics along the nephron.

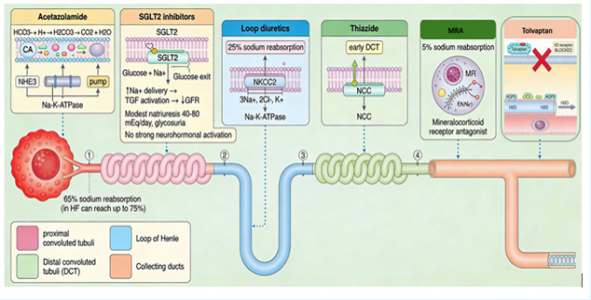

Figure 1. Sites of action and molecular targets of diuretic classes

THERAPEUTIC STRATEGIES IN ACUTE DECOMPENSATED HEART FAILURE

LOOP DIURETICS AS FIRST-LINE THERAPY

Loop diuretics constitute the cornerstone of initial management for acute decompensated heart failure presenting with signs or symptoms of congestion, with Class I recommendation in current guidelines.

Oral or Intravenous Administration?

Intravenous administration demonstrates clear superiority over oral delivery through multiple pharmacokinetic advantages. The intravenous route achieves rapid onset within 5 minutes compared to 30-60 minutes for oral administration, while bypassing intestinal edema that compromises drug absorption (22). Additionally, intravenous delivery produces higher peak plasma concentrations necessary to exceed the natriuretic threshold and enables frequent dose titration based on therapeutic response.

What Initial Dosing?

Current guidelines recommend stratified initial intravenous dosing based on prior diuretic exposure (4). For diuretic-naïve patients, furosemide 20-40 mg IV or equivalent doses (bumetanide 0.5-1 mg, torsemide 10-20 mg) are appropriate. For patients receiving chronic oral loop diuretics, the initial intravenous furosemide dose should equal 1-2.5 times the total daily oral maintenance

dose, with higher multipliers (2-2.5×) recommended when aggressive decongestion is required.

The DOSE trial (Diuretic Optimization Strategies Evaluation, n=308) employed a 2×2 factorial design comparing low-dose (intravenous equivalent of oral home dose) versus high-dose (2.5× oral home dose) furosemide, alongside intermittent bolus every 12 hours versus continuous infusion strategies. Although the primary composite endpoint (global symptom relief by visual analog scale and serum creatinine change at 72 hours) revealed no differences between groups, secondary analyses demonstrated that high-dose furosemide produced significantly greater dyspnea relief (p=0.04), weight loss (−4.0 vs −2.8 kg, p=0.01), and net fluid loss (−4899 vs −3575 mL, p=0.001) without increased worsening renal function, while showing trends toward more frequent decongestion and fewer treatment failures (23). These findings established the safety and efficacy of early aggressive diuretic dosing, informing current guideline recommendations favoring higher initial doses (2-2.5× home dose) for hospitalized acute heart failure patients.

Dosing: Bolus versus Continuous Infusion?

The optimal method of intravenous loop diuretic administration remains subject to debate. Continuous infusion theoretically offers several advantages, including maintenance of plasma concentrations consistently above the natriuretic threshold, prevention of post-diuretic sodium retention, and more stable diuresis avoiding peaks and troughs. However, the DOSE trial demonstrated no significant differences in symptom relief, renal function changes, or clinical outcomes between bolus (every 12 hours) and continuous infusion strategies. Multiple subsequent meta-analyses have consistently shown modest differences, with no differences in mortality, length of stay, renal function, or electrolytes (24, 25).

Based on current evidence, practical recommendations suggest initiating therapy with intermittent boluses (every 12 hours or more frequently if needed) as the default strategy, given simplicity, nursing convenience, and equivalent outcomes. Continuous infusion (starting 5 mg/hour furosemide, titrated to 40 mg/hour) should be considered in specific scenarios: hemodynamic instability or significant hypotension where boluses may cause blood pressure fluctuations, severe diuretic resistance requiring very high cumulative doses, or outpatient infusion center settings where prolonged infusions are logistically feasible.

The Best Timing to Start?

The concept of "door-to-diuretic time" has emerged as a critical quality metric for acute heart failure care. In a prospective multicenter observational cohort of 1,291 emergency department patients, Matsue et al. demonstrated that administration of intravenous furosemide within 90 minutes of arrival was associated with significantly lower inpatient all-cause mortality compared to delayed administration (2.3% vs 6.0%, p=0.002), an effect that persisted after multivariable adjustment for confounders (7).

Response Assessment?

• Weight Loss and Fluid Balance

Daily weight monitoring represents the most practical bedside marker of decongestion progress, with target weight loss during hospitalization ranging from 0.5 to 1.5 kg per 24 hours during active diuresis. Net negative fluid balance, calculated as total urine output minus oral/intravenous intake, should exceed 3-5 liters per 24 hours in adequately responding patients (26). However, weight and fluid balance alone provide incomplete assessment, as they do not distinguish fluid compartments; patients may lose intravascular volume with persistent interstitial edema, or vice versa. Therefore, clinical examination for peripheral edema, jugular venous pressure, pulmonary rales, and orthopnea must accompany weight-based assessments.

• Urine Output Monitoring

Hourly urine output measurement during the first 6-24 hours after initial diuretic administration provides early assessment of diuretic responsiveness. Targets include 100-150 mL/hour during the first 6 hours. Urine output below these thresholds despite adequate initial diuretic dosing indicates diuretic resistance and necessitates dose escalation or addition of a second agent.

• Natriuresis-Guided Therapy

Spot urine sodium concentration has emerged as a powerful early predictor of diuretic response and clinical outcomes. An adequate natriuretic response is indicated by a urine sodium concentration >50–70 mmol/L within 2–4 hours after diuretic administration. Multiple observational studies demonstrated that spot urine sodium <50 mmol/L may indicate diuretic resistance or insufficient dosing. In such cases, increasing the loop diuretic dose or adding

a diuretic from another class, may help to overcome resistance and enhance natriuresis (27).

The ENACT-HF trial (Natriuresis-Guided Therapy in Acute Heart Failure, n=401) represented the first multicenter randomized evaluation of protocolized, natriuresis-guided decongestion versus standard care. In the intervention arm, spot urine sodium was measured 2 hours after each diuretic dose, with protocol-mandated dose doubling if UNa <70 mmol/L. The natriuresis-guided strategy achieved higher 24-hour natriuresis (median 408 vs 318 mmol, p<0.01), greater urine output (4.4 vs 3.8 liters, p<0.01), and shorter hospital length of stay (median 6 vs 7 days, p=0.03), with no difference in all-cause mortality at 30 days (28). Based on this evidence, natriuresis measurement is recommended for early identification of diuretic resistance and to guide dose escalation decisions. Practical implementation involves collecting first voided urine 2-6 hours after initial intravenous loop diuretic dose and measuring spot urine sodium.

HOW TO MANAGE RESISTANCE TO LOOP DIURETICS IN AHF?

Diuretic resistance represents one of the most challenging clinical scenarios in acute heart failure management, affecting 20-30% of hospitalized patients. It is clinically defined as persistent signs and symptoms of congestion despite administration of loop diuretic doses equivalent to ≥80-160 mg intravenous furosemide per day, or failure to achieve net negative fluid balance >3 liters per 24 hours, alternative definitions include spot urine sodium <50 mmol/L at 2 hours (29).

Optimize Loop Diuretic Therapy

Before adding second agents, loop diuretic therapy should first be fully optimized by maximizing the total daily dose up to 400–600 mg furosemide equivalent (or higher in cases of severe resistance), shortening the dosing interval to every 6–8 hours instead of every 12 hours to maintain plasma concentrations above the natriuretic threshold, considering a continuous infusion of furosemide at 5–40 mg/hour to achieve steady-state levels, and ensuring the intravenous route in hospitalized patients to avoid impaired gastrointestinal absorption (6).

Sequential Nephron Blockade

When maximized loop diuretic therapy fails to achieve decongestion targets, adding a second diuretic acting at a different nephron segment produces synergistic natriuresis constitute the cornerstone of managing diuretic resistance (Table 1).

Table 1. Review of diuretic types and mechanism of action

Class	Example Drugs	Main Site of Action	Primary Mechanism	Role in Diuretic Resistance	Effect on Natriuresis	Effect on Diuresis
Loop diuretics	Furosemide, Bumetanide, Torsemide	Thick ascending limb (NKCC2)	Block $Na^+/K^+/2Cl^-$ cotransporter	First-line decongestive therapy; resistance develops due to distal tubular hypertrophy and RAAS activation	Very strong	Very strong
Thiazide / thiazide-like	Metolazone, Chlorthalidone, Indapamide	Distal convoluted tubule (NCC)	Block Na^+–Cl^- cotransporter	Overcome distal nephron compensation, the main cause of chronic loop resistance	Moderate (synergistic)	Moderate
Mineralocorticoid receptor antagonists	Spironolactone, Eplerenone	Collecting duct (ENaC regulation)	Block aldosterone-mediated Na^+ reabsorption	Counteract RAAS-driven sodium retention and diuretic braking	Mild	Mild
Carbonic anhydrase inhibitors	Acetazolamide	Proximal tubule	Reduce $NaHCO^+$ reabsorption	Reverse proximal sodium reabsorption caused by RAAS activation and macula densa chloride sensing	Moderate	Moderate
SGLT2 inhibitors	Dapagliflozin, Empagliflozin	Proximal tubule (S1)	Block Na^+–glucose cotransport	Improve proximal natriuresis and restore loop diuretic sensitivity	Mild–moderate	Mild–moderate
Vasopressin antagonists (vaptans)	Tolvaptan	Collecting duct (V2 receptor)	Block aquaporin-2 insertion	Treat water retention when sodium excretion is limited	None	Strong aquaresis

- First-line combination: Loop diuretic+ Thiazide

The combination of a loop diuretic and a thiazide represents the first-line sequential nephron blockade strategy to overcome diuretic resistance by inhibiting compensatory distal tubular sodium reabsorption mediated by sodium–chloride cotransporter (NCC) upregulation. Commonly used agents include metolazone (2.5–10 mg orally once daily; preferred for its long half-life and preserved efficacy at low glomerular filtration rates), hydrochlorothiazide (25–100 mg orally once daily; less effective when eGFR <30 mL/min/1.73 m^2), and chlorothiazide (500 mg intravenously twice daily when the oral route is not feasible). Indapamide may also be considered, although data in acute settings are limited (30).

Administration generally involves giving the thiazide 30–60 minutes before the loop diuretic to maximize sequential blockade, though this timing has not been formally validated. The CLOROTIC trial demonstrated greater weight loss with the combination of hydrochlorothiazide and loop diuretics compared with loop diuretics alone, but at the expense of hypokalemia, occurring in 30–50% of patients and hypomagnesemia, which may aggravate potassium loss and necessitates correction (31). A transient increase in serum creatinine (>0.5 mg/dL) may occur but is considered acceptable when effective decongestion is achieved.

- Alternative combination: Loop diuretic+ Acetazolamide

The rationale for acetazolamide use in heart failure lies in its ability to inhibit the compensatory proximal sodium–bicarbonate reabsorption induced by loop diuretics. It also corrects metabolic alkalosis, a common consequence of intensive loop diuretic therapy, which otherwise blunts respiratory drive, reduces cardiac contractility, worsens hypokalemia, and decreases diuretic efficacy.

The ADVOR trial (n=519) evaluated intravenous acetazolamide 500 mg daily for 3 days versus placebo added to standardized loop diuretics in acute decompensated heart failure. Successful decongestion at 72 hours (absence of volume overload without diuretic escalation) was achieved in 42.2% versus 30.5% (RR 1.46, 95% CI 1.17-1.82, p=0.001). Acetazolamide additionally produced higher discharge decongestion scores (78% vs 62.5%), enhanced natriuresis, and reduced hospital length of stay, with no differences in mortality or rehospitalization at three months (9).

Loop diuretic plus acetazolamide represents an alternative combination particularly effective in patients with chronic obstructive bronchitis, when metabolic alkalosis is present (serum bicarbonate ≥27 mmol/L), thiazides are contraindicated or ineffective, or severe hypokalemia, or hyponatremia limits thiazide use.

- Novel combination: Loop Loop Diuretic + SGLT2 inhibitor

Loop diuretic plus sodium-glucose cotransporter-2 inhibitor (SGLT2i) represents a novel combination that blocks proximal sodium-glucose reabsorption without triggering neurohormonal activation while providing prognostic cardiovascular and renal benefits beyond decongestion. Standard dosing includes empagliflozin 10 mg orally daily or dapagliflozin 10 mg daily. The DAPA-RESIST trial showed similar weight loss with dapagliflozin versus metolazone in diuretic-resistant patients, but dapagliflozin was associated with fewer episodes of hypokalemia, hypotension, and worsening renal function. Many experts now favor SGLT2i as first-line combination therapy over thiazides when available and affordable (32).

- Triple Diuretic Therapy

In severe refractory cases, triple diuretic therapy combining a maximized-dose loop diuretic plus thiazide plus acetazolamide and/or SGLT2i may be necessary to achieve simultaneous blockade at the proximal tubule, thick ascending limb, and distal convoluted tubule. This approach requires extremely close monitoring of electrolytes (potentially every 12 hours), renal function, and blood pressure due to high risk of severe hypokalemia, hypotension, and prerenal azotemia (22).

- Loop Diuretics and Albumin Co-Administration

The combination of furosemide and albumin remains debated. Since furosemide must bind to albumin for effective tubular secretion, low albumin levels may impair its delivery to the nephron. An observational study showed that higher albumin-binding capacity increased urinary free furosemide and urine output (33). A meta-analysis in hypo albuminemic, diuretic-resistant patients (10 studies) found only short-term improvement in diuresis at 8 hours, which disappeared by 24 hours. A more recent meta-analysis (13 trials, 422 patients) reported that coadministration enhanced diuretic response compared with furosemide alone, particularly in patients with marked hypoalbuminemia, suggesting potential benefit in this subgroup only (34).

- Inotropes administration

In patients with diuretic resistance secondary to low-output cardiogenic shock; characterized by a cardiac index <2.2 L/min/m^2, elevated filling pressures, and end-organ hypoperfusion, loop diuretics alone are often ineffective and may aggravate hemodynamic compromise by further decreasing cardiac output. In such cases, inotropic support with agents such as dobutamine (2.5–10 µg/kg/min) or milrinone (0.375–0.75 µg/kg/min) can enhance renal perfusion and restore diuretic responsiveness by increasing cardiac output and renal blood flow (35).

However, the OPTIME-CHF trial demonstrated that milrinone did not shorten hospital stay and was associated with higher rates of hypotension and arrhythmias in patients without clear inotropic indications (36). Consequently, inotropes should be reserved strictly for patients with true low-output states rather than used routinely for diuretic resistance.

Figure 2 presents an integrated treatment algorithm for protocolized therapy to optimize decongestion and overcome diuretic resistance in AHF.

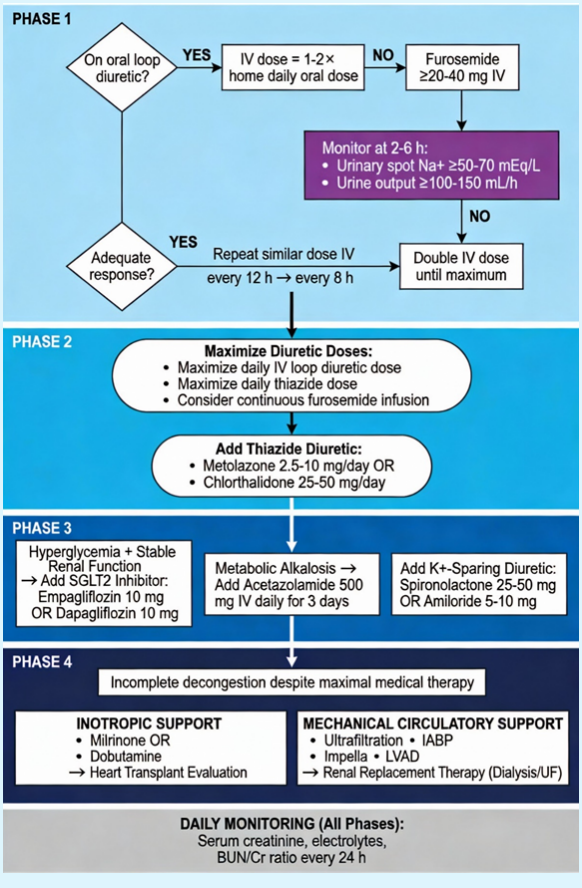

Figure 2. Stepwise diuretic escalation protocol for patients with acute heart failure

CONCLUSION

Diuretics remain the cornerstone of acute heart failure management, but diuretic resistance is a major driver of poor outcomes. Early, adequately dosed intravenous loop diuretics guided by objective measures such as urine output and natriuresis are essential. When resistance develops, sequential nephron blockade using thiazides, acetazolamide, mineralocorticoid receptor antagonists, and SGLT2 inhibitors can effectively restore decongestion. Achieving complete decongestion before discharge is critical, as residual congestion strongly predicts rehospitalization and mortality. Future advances will rely on protocolized, biomarker-guided, and personalized diuretic strategies to improve both short- and long-term outcomes.

REFERENCES

1. Savarese G, Becher PM, Lund LH, Seferovic P, Rosano GMC, Coats AJS. Global burden of heart failure: a comprehensive and updated review of epidemiology. Cardiovasc Res. 2023;118(17):3272-87.
2. Wu L, Rodriguez M, El Hachem K, Krittanawong C. Diuretic Treatment in Heart Failure: A Practical Guide for Clinicians. J Clin Med. 2024;13(15):4470.
3. Rubio-Gracia J, Demissei BG, Ter Maaten JM, Cleland JG, O'Connor CM, Metra M, et al. Prevalence, predictors and clinical outcome of residual congestion in acute decompensated heart failure. Int J Cardiol. 2018;258:185-91.
4. McDonagh TA, Metra M, Adamo M, Gardner RS, Baumbach A, Böhm M, et al. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. Eur Heart J. 2021;42(36):3599-726.
5. Heidenreich PA, Bozkurt B, Aguilar D, Allen LA, Byun JJ, Colvin MM, et al. 2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. Circulation. 2022;145(18):e895-1032.
6. Felker GM, Ellison DH, Mullens W, Cox ZL, Testani JM. Diuretic Therapy for Patients With Heart Failure: JACC State-of-the-Art Review. J Am Coll Cardiol. 2020;75(10):1178-95.
7. Matsue Y, Damman K, Voors AA, Kagiyama N, Yamaguchi T, Kuroda S, et al. Time-to-Furosemide Treatment and Mortality in Patients Hospitalized With Acute Heart Failure. J Am Coll Cardiol. 2017;69(25):3042-51.

8. Dauw J, Charaya K, Lelonek M, Zegri-Reiriz I, Nasr S, Paredes-Paucar CP, et al. Protocolized Natriuresis-Guided Decongestion Improves Diuretic Response: The Multicenter ENACT-HF Study. Circ Heart Fail. 2024;17(2):e011105.
9. Mullens W, Dauw J, Martens P, Verbrugge FH, Nijst P, Meekers E, et al. Acetazolamide in Acute Decompensated Heart Failure with Volume Overload. N Engl J Med. 2022;387(13):1185-95.
10. Boorsma EM, Beusekamp JC, Ter Maaten JM, Figarska SM, van Veldhuisen DJ, van der Meer P, et al. Congestion in heart failure: a contemporary look at physiology, diagnosis and treatment. Nat Rev Cardiol. 2020;17(10):641-55.
11. Floras JS. Sympathetic nervous system activation in human heart failure: clinical implications of an updated model. J Am Coll Cardiol. 2009;54(5):375-85.
12. Rao VS, Planavsky N, Hanberg JS, Ahmad T, Brisco-Bacik MA, Wilson FP, et al. Compensatory Distal Reabsorption Drives Diuretic Resistance in Human Heart Failure. J Am Soc Nephrol. 2017;28(12):3414-24.
13. Ellison DH, Felker GM. Diuretic Treatment in Heart Failure. N Engl J Med. 2017;377(20):1964-75.
14. Felker GM, Ellison DH, Mullens W, Cox ZL, Testani JM. Diuretic Therapy for Patients With Heart Failure: JACC State-of-the-Art Review. J Am Coll Cardiol. 2020;75(10):1178-95.
15. Ellison DH. Clinical Pharmacology in Diuretic Use. Clin J Am Soc Nephrol. 2019;14(8):1248-57.
16. Ernst ME, Fravel MA. Thiazide and the thiazide-like diuretics: review of hydrochlorothiazide, chlorthalidone, and indapamide. Am J Hypertens. 2022;35(7):573-86.
17. Pitt B, Zannad F, Remme WJ, Cody R, Castaigne A, Perez A, et al. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. Randomized Aldactone Evaluation Study Investigators. N Engl J Med. 1999;341(10):709-17.
18. Schulze PC, Bogoviku J, Westphal J, Aftanski P, Haertel F, Grund S, et al. Effects of Early Empagliflozin Initiation on Diuresis and Kidney Function in Patients With Acute Decompensated Heart Failure (EMPAG-HF). Circulation. 2022;146(4):289-98.
19. Voors AA, Angermann CE, Teerlink JR, Collins SP, Kosiborod M, Biegus J, et al. The SGLT2 inhibitor empagliflozin in patients hospitalized for acute heart failure: a multinational randomized trial. Nat Med. 2022;28(3):568-74.
20. Cox ZL, Collins SP, Hernandez GA, McRae AT III, Davidson BT, Adams K, et al. Efficacy and Safety of Dapagliflozin in Patients With Acute Heart Failure. J Am Coll Cardiol. 2024;83(13):1295-306.
21. 21. Gheorghiade M, Konstam MA, Burnett JC Jr, Grinfeld L, Maggioni AP, Swedberg K, et al. Short-term clinical effects of tolvaptan, an oral vasopressin antagonist, in patients hospitalized for heart failure: the EVEREST Clinical Status Trials. JAMA. 2007;297(12):1332-43.
22. Mullens W, Damman K, Harjola VP, Mebazaa A, Brunner-La Rocca HP, Martens P, et al. The use of diuretics in heart failure with congestion—a position statement from the Heart Failure Association of the European Society of Cardiology. Eur J Heart Fail. 2019;21(2):137-55.
23. Felker GM, Lee KL, Bull DA, Redfield MM, Stevenson LW, Goldsmith SR, et al. Diuretic strategies in patients with acute decompensated heart failure. N Engl J Med. 2011;364(9):797-805.
24. Ng KT, Yap JLL. Continuous infusion vs. intermittent bolus injection of furosemide in acute decompensated heart failure: systematic review and meta-analysis of randomised controlled trials. Anaesthesia. 2018;73(2):238-47.
25. Chan JSK, Kot TKM, Ng M, Harky A. Continuous infusion versus intermittent boluses of furosemide in acute heart failure: a systematic review and meta-analysis. J Card Fail. 2020;26(9):786-93.
26. Ambrosy AP, Pang PS, Khan S, Konstam MA, Fonarow GC, Traver B, et al. Clinical course and predictive value of congestion during hospitalization in patients admitted for worsening signs and symptoms of heart failure with reduced ejection fraction: findings from the EVEREST trial. Eur Heart J. 2013;34(11):835-43.
27. Singh D, Shrestha K, Testani JM, Verbrugge FH, Dupont M, Mullens W, et al. Insufficient natriuretic response to continuous intravenous furosemide is associated with poor long-term outcomes in acute decompensated heart failure. J Card Fail. 2014;20(6):392-9.
28. Dauw J, Charaya K, Lelonek M, Zegri-Reiriz I, Nasr S, Paredes-Paucar CP, et al. Protocolized Natriuresis-Guided Decongestion Improves Diuretic Response: The Multicenter ENACT-HF Study. Circ Heart Fail. 2024;17(2):e011105.
29. Wilcox CS, Testani JM, Pitt B. Pathophysiology of Diuretic Resistance and Its Implications for the Management of Chronic Heart Failure. Hypertension. 2020;76(4):1045-54.
30. Jentzer JC, DeWald TA, Hernandez AF. Combination of loop diuretics with thiazide-type diuretics in heart failure. J Am Coll Cardiol. 2010;56(19):1527-34.
31. Trullas JC, Morales-Rull JL, Casado J, Carrera-Izquierdo M, Sánchez-Marteles M, Conde-Martel A, et al. Combining loop with thiazide diuretics for decompensated heart failure: the CLOROTIC trial. Eur Heart J. 2023;44(5):411-21.
32. Yeoh SE, Osmanska J, Petrie MC, Brooksbank KJM, Clark AL, Docherty KF, et al. Dapagliflozin vs. metolazone in heart failure resistant to loop diuretics. Eur Heart J. 2023;44(29):2966-77.

33. Kitsios GD, Mascari P, Ettunsi R, Gray AW. Co-administration of furosemide with albumin for overcoming diuretic resistance in patients with hypoalbuminemia: a meta-analysis. J Crit Care. 2014;29(2):253-9.

34. Lee TH, Kuo G, Chang CH, Huang YT, Yen CL, Lee CC, et al. Diuretic effect of co-administration of furosemide and albumin in comparison to furosemide therapy alone: an updated systematic review and meta-analysis. PLoS One. 2021;16(12):e0260312.

35. Jentzer JC, Lawler PR, Van Diepen S, Khanna AK, Jones P, Hernandez AF, et al. A Review of Inotropes and Inopressors for Effective Utilization in Patients With Acute Decompensated Heart Failure. J Card Fail. 2021;27(9):1034-49.

36. Cuffe MS, Califf RM, Adams KF Jr, Benza R, Bourge R, Colucci WS, et al; OPTIME-CHF Investigators. Short-term intravenous milrinone for acute exacerbation of chronic heart failure: a randomized controlled trial. JAMA. 2002;287(12):1541-7