Diuretic Resistance

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Introduction
**Definitions/Metrics of Diuretic Resistance**

- **Persistent congestion despite adequate and escalating doses of diuretics [>80 mg furosemide or > 2 mg bumetanide per day] (1)**

- **Amount of sodium excreted as a percentage of filtered load <0.2% (2)**

- **Failure to excrete ≥ 90 mmol of sodium within 72 hours under treatment with furosemide 160 mg iv bid (3)**

- **Reduced weight loss per unit of 40 mg furosemide [or equivalent] (4, 5)**

- **Reduced net fluid loss per milligram of loop diuretic [40 mg of furosemide or equivalent] during hospitalization (6)**

- **Poor natriuretic response to furosemide (< 2 mmol/mg) expressed as the ratio of urinary sodium to urinary furosemide (7)**

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ADHERE Registry (Oct/2001 to Feb/2005)

ADHERE Registry: Risk and Propensity Adjustments

Diuretic Resistance Predicts Mortality in Advanced HF

The prognostic importance of diuretic resistance (as evidenced by a high-dose requirement) was retrospectively evaluated in 1153 pts with advanced CHF who were enrolled in PRAISE. The relation of loop diuretic and ACEi doses (defined by their median values) and other baseline characteristics to total and cause-specific mortality was determined by proportion hazards regression.

Unadjusted mortality and mode of death in treatment groups

<table>
<thead>
<tr>
<th>Group</th>
<th>Diuretic dose</th>
<th>ACE inhibitor dose</th>
<th>n</th>
<th>Total mortality</th>
<th>%</th>
<th>HR</th>
<th>Sudden death</th>
<th>%</th>
<th>HR</th>
<th>Pump failure death</th>
<th>%</th>
<th>HR</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>High</td>
<td>Low</td>
<td>240</td>
<td></td>
<td>44.8</td>
<td>1.45*</td>
<td>20.4</td>
<td>1.53*</td>
<td>17.9</td>
<td>1.58</td>
<td></td>
<td></td>
</tr>
<tr>
<td>B</td>
<td>High</td>
<td>High</td>
<td>160</td>
<td></td>
<td>31.0</td>
<td>1.33</td>
<td>13.3</td>
<td>1.13</td>
<td>11.3</td>
<td>1.13</td>
<td></td>
<td></td>
</tr>
<tr>
<td>C</td>
<td>Low</td>
<td>Low</td>
<td>526</td>
<td></td>
<td>30.2</td>
<td>0.78*</td>
<td>14.8</td>
<td>0.91</td>
<td>7.0</td>
<td>0.42*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>D</td>
<td>Low</td>
<td>High</td>
<td>224</td>
<td></td>
<td>38.5</td>
<td>1.63</td>
<td>16.7</td>
<td>1.67</td>
<td>16.7</td>
<td>1.67</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Chi-square = 33.83
P = 0.0001

Loop Diuretics
Mechanism of Loop Diuretic Action

Diuretic Strategies in ADHF (DOSE Trial)

In a prospective, double-blind, RCT, 308 pts with ADHF assigned to furosemide IV every 12 hours or continuous infusion and at either a low dose (=previous oral dose) or a high dose (2.5 times previous oral dose). Protocol allowed specified dose adjustments after 48 hours. The coprimary end points were pts’ global assessment of symptoms, quantified as AUC of the score on a visual-analogue scale over the course of 72 hours, and the change in the serum creatinine level from baseline to 72 hours.

DOSE Trial: Change is Serum Creatinine

Caveats of the **DOSE Trial**

- Continuous infusions not routinely preceded by loading doses, which speed the achievement of a steady state level.

- The initial rates of furosemide infusion averaged *5 mg per hour* (the low-dose regimen) and *10 mg per hour* (the high-dose regimen), which are lower than often recommended.

- The population studied was not selected for resistance to diuretics and had a mean serum creatinine level of 1.5 mg per deciliter (132.6 μmol per liter); thus, these patients did not have marked kidney dysfunction.

Patients with diuretic resistance, moderate/severe renal dysfunction, and severe right ventricular dysfunction may have a better response to continuous infusion therapy than to boluses.


*Ellison DH, Felker GM. N Engl J Med 2017; 377:1964-75*
## Pharmacologic Properties of Loop Diuretics

<table>
<thead>
<tr>
<th>Property</th>
<th>Furosemide</th>
<th>Tor(a)semide</th>
<th>Bumetanide</th>
</tr>
</thead>
<tbody>
<tr>
<td>Relative potency</td>
<td>1x</td>
<td>2x</td>
<td>40x</td>
</tr>
<tr>
<td>Bioavailability (%)</td>
<td>10-100</td>
<td>80-100</td>
<td>80-100</td>
</tr>
<tr>
<td>Typical oral dose</td>
<td>40-160 mg 1-2 times/day Maximum: 600 mg/day</td>
<td>20-80 mg /day Maximum: 200 mg/day</td>
<td>0.5-4.0 mg 1-2 times/day Maximum: 10 mg/day</td>
</tr>
<tr>
<td>Oral : IV dosing</td>
<td>2:1</td>
<td>1:1</td>
<td>1:1</td>
</tr>
<tr>
<td>Time to onset (min)</td>
<td>60</td>
<td>60</td>
<td>30-60</td>
</tr>
<tr>
<td>Time to peak serum concentration (hours)</td>
<td>1</td>
<td>1</td>
<td>1-2</td>
</tr>
<tr>
<td>Absorption affected by food</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Average half-life (hours)</td>
<td>2</td>
<td>3.5</td>
<td>1-1.5</td>
</tr>
<tr>
<td>Duration of effect (hours)</td>
<td>6-8</td>
<td>6-16</td>
<td>4-6</td>
</tr>
<tr>
<td>Decreased kaliuresis</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
</tr>
</tbody>
</table>


Mechanisms of Diuretic Resistance
Loop Diuretic Resistance

Pathophysiology

- Failing heart
- Reduced absorption of loop diuretic
- Unable to bind to albumin
- Intestines
- Reduced filtration
- Bowman’s capsule
- Proximal Na reabsorption
- RBF and GFR
- RAAS and SNS
- Organic acids like blood urea nitrogen competitively bind to OAT, reducing diuretic availability in the tubule
- Albuminuria
- Filtered albumin binds to furosemide, reducing availability at cotransporter
- OAT

Mechanisms

- Na-K-Cl cotransporter
- Distal Na reabsorption
- Braking phenomenon
- RAAS and SNS
- Plasma albumin
- CVP
- CO

Reference:

Pharmacokinetics/Pharmacodynamics of Loop Diuretics in Heart Failure

Nephron Remodeling as a Mechanism of Diuretic Resistance

Effect of Furosemide on Macula Densa

Management of Diuretic Resistance
Practical Approach to Diuretic Resistance

- Assessment of compliance with salt restriction and medicine intake (if necessary measure salt and diuretic in the urine).
- Discontinue NSAIDs.
- Adjust the dose of the diuretic in patients with renal impairment.
- Switch from furosemide to tor(a)semide or bumetanide
- Switch to IV administration to overcome problems associated with oral absorption.
- Combine loop diuretics with other diuretics, preferably a thiazide diuretic.
- Consider tolvaptan, dopamine (HFrEF) or hypertonic saline when other options have failed (?)

188 patients with ADHF, WRF, and persistent congestion randomly assigned to a strategy of stepped pharmacologic therapy (94 patients) or ultrafiltration (94 patients). The primary end point was the bivariate change from baseline in the serum creatinine level and body weight, as assessed 96 hours after random assignment. Patients were followed for 60 days.

Loop Diuretics + Thiazides

**Stepped Diuretic Approach in CARRESS-HF Trial**

<table>
<thead>
<tr>
<th>Time period</th>
<th>Urine output</th>
<th>Recommended treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td></td>
<td>Reduce current diuretic regimen if desired&lt;br&gt;Continue current diuretic regimen&lt;br&gt;See Table</td>
</tr>
<tr>
<td>Persisting congestion</td>
<td>&gt; 5 L/day</td>
<td>Reduce current diuretic regimen if desired&lt;br&gt;Continue current diuretic regimen</td>
</tr>
<tr>
<td>Persisting congestion</td>
<td>3-5 L/day</td>
<td>Reduce current diuretic regimen if desired&lt;br&gt;Continue current diuretic regimen</td>
</tr>
<tr>
<td>Persisting congestion</td>
<td>&lt; 3 L/day</td>
<td>Reduce current diuretic regimen if desired&lt;br&gt;Continue current diuretic regimen</td>
</tr>
</tbody>
</table>

24 hours

| > 5 L/day | Reduce current diuretic regimen if desired<br>Continue current diuretic regimen |
| 3-5 L/day | Reduce current diuretic regimen if desired<br>Continue current diuretic regimen |
| < 3 L/day | Reduce current diuretic regimen if desired<br>Continue current diuretic regimen |

Persisting congestion

48 hours

| > 5 L/day | Reduce current diuretic regimen if desired<br>Continue current diuretic regimen |
| 3-5 L/day | Reduce current diuretic regimen if desired<br>Continue current diuretic regimen |
| < 3 L/day | Reduce current diuretic regimen if desired<br>Continue current diuretic regimen |

Persisting congestion

72 and 96 hours

| > 5 L/day | Reduce current diuretic regimen if desired<br>Continue current diuretic regimen |
| 3-5 L/day | Reduce current diuretic regimen if desired<br>Continue current diuretic regimen |
| < 3 L/day | Reduce current diuretic regimen if desired<br>Continue current diuretic regimen |

Persisting congestion

**Diuretic Dosing Table**

<table>
<thead>
<tr>
<th>Current Dose</th>
<th>Suggested Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Step</td>
<td>Loop (l/day)</td>
</tr>
<tr>
<td>A</td>
<td>≤ 80</td>
</tr>
<tr>
<td>B</td>
<td>81 - 160</td>
</tr>
<tr>
<td>C</td>
<td>161 - 240</td>
</tr>
<tr>
<td>D</td>
<td>&gt; 240</td>
</tr>
</tbody>
</table>

**Consider inotrope or vasoactive therapies**

**Consider advanced cardiorenal therapies**

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Stepwise Algorithm vs. Standard Therapy in ADHF with WRF

Decongestion and Renal Function during Decongestive Therapy in ADHF with WRF

A

\[ \Delta \text{Weight [lbs]} \]

\[ \begin{array}{c}
\text{Standard Therapy} \\
\text{SPCA}
\end{array} \]

\[ P = 0.0001 \]

B

\[ \Delta \text{Net Fluid [L]} \]

\[ \begin{array}{c}
\text{Standard Therapy} \\
\text{SPCA}
\end{array} \]

\[ P < 0.0001 \]

C

\[ \Delta \text{Creatinine [mg/dL]} \]

\[ \begin{array}{c}
\text{Standard Therapy} \\
\text{SPCA}
\end{array} \]

\[ P = 0.03 \]

D

\[ \Delta \text{BUN [mg/dL]} \]

\[ \begin{array}{c}
\text{Standard Therapy} \\
\text{SPCA}
\end{array} \]

\[ P = 0.1 \]
Future Therapeutic Strategies
IV Furosemide vs. SC Furosemide in Outpatients with Worsening HF

Outpatients presenting with decompensated HF were randomized to receive a single SC (n=21; fixed dose of 80 mg over 5 h) or IV (n=19; mean dose: 123±47 mg) dose of furosemide. Primary outcome was 6-h urine output, and secondary outcomes were weight change, natriuresis, and adverse events.

Gilotra NA, et al. JACC Heart Fail 2018;6:65-70
A per-protocol analysis of the Cardiorenal Rescue Study in Acute Decompensated Heart Failure (CARRESS-HF) trial (n = 188) was performed. Participants were included if randomized to UF and had UF output collected, or if randomized to the pharmacological arm and had urine but not UF output collected. Using these definitions, there were 163 participants at 24 h, 156 at 48 h, 129 at 72 h, and 106 at 96 h.
CARRESS-HF: Fluid Balance Through 96 h by Treatment Arm

CARRESS-HF: Serial Laboratory Testing by Treatment Arm

Ultrafiltration for Fluid Overload in Heart Failure

Decreased cardiac output due to chronic heart failure

Renal dysfunction:
Abnormal hemodynamics, neurohormonal activation, excessive tubular sodium reabsorption, inflammation, oxidative stress and nephrotoxic medications

Decreased water clearance and increased sodium reabsorption

LOOP DIURETICS to eliminate hypotonic urine
- Unpredictable elimination of sodium and water
- Development of diuretic resistance
- Risk of hypokalemia (low potassium levels) and hypomagnesemia (low magnesium levels)
- Insufficient symptom relief: Persistent congestion, failure to lower sodium levels
- Worsening heart failure, increased mortality after discharge, increase in re-hospitalization rates

ULTRAFILTRATION to remove isotonic plasma water
- Predictable removal of sodium and fluids
- Restoration of diuretic responsiveness
- No change in electrolytes, particularly potassium and magnesium
- More effective decongestion and fewer heart failure events compared to loop diuretics
- Improved glomerular filtration rate
- Efficacy, and improved outcomes

Conclusions
Impaired response to diuretics (diuretic resistance) is common in patients with ADHF and advanced HF and is associated with adverse outcomes.

Diuretic resistance is thought to result from a complex interplay between cardiac and renal dysfunction, and specific renal adaptation and escape mechanisms, such as neurohormonal activation and the braking phenomenon.

Several strategies have been proposed to overcome diuretic resistance, the most popular being the combination of loop diuretics with thiazides but prospective studies in patients who are truly unresponsive to diuretics are lacking.

Decongestion with SC furosemide may allow treatment at home and prevent development of diuretic resistance and warrants further investigation.

At present, ultrafiltration in patients with diuretic resistance appears to be indicated primarily when dialytic treatment is indicated in patients with combined heart failure and kidney failure. Results of ongoing trials anticipated.
Diuretic response (DR, urine output per 40 mg furosemide-equivalent diuretics dose) was measured from 0 to 6 hours (DR6), 6 to 48 hours (DR6-48), and 0 to 48 hours (DR48) of the patient’s arrival to the emergency department (ED) in 1551 patients with AHF (mean age 78 years old; 56% were male; and 48% were de-novo patients with heart failure).

Mortality for 60-day according to the tertiles of DR6, DR6-48, and DR48

Kuroda S, et al.
J Card Fail. 2018 Sep 13
REALITY-AHF: Early Mortality According to Diuretic Response

Kuroda S, et al.
J Card Fail. 2018 Sep 13
The ESCAPE Trial (n=395)
Maximal Daily Diuretic Dose and 180 Day Mortality

Cell Types and Transporters in Cortical Collecting Duct

Wall SM, Lazo-Fernandez Y. Annu. Rev. Physiol. 2015 77:363–78
Transporters within B Intercalated Cells

Pendrin Mediates HCO3- Excretion which Stimulates ENaC Abundance and Function

Wall SM, Lazo-Fernandez Y. Annu. Rev. Physiol 2015; 77:363–78
Pendrin Changes ENaC Abundance and Function by Modulating Luminal ATP

Wall SM, Lazo-Fernandez Y. Annu. Rev. Physiol. 2015 77:363–78
Sites of Na+ Reabsorption along the Nephron

Proximal Convoluted Tubule (≈65%)

Glomerulus

Thick Ascending Limb of Henle’s Loop (≈25%)

Distal Convoluted Tubule (≈5%)

Cortex

Medulla

Collecting Duct (≈4-5%)
DOSE Trial: Death, Rehospitalization, Emergency Department

Mechanisms Leading to Impaired Diuretic Responsiveness

Reduced GFR
This may occur secondary to:
- Abnormal glomerular haemodynamics (e.g. NSAIDs)
- Reduced renal perfusion from low cardiac output states or venous congestion
- Worsening renal function and chronic kidney disease
These states can reduce delivery of diuretics, reduce active secretion of loop diuretic into tubule

Excessive sodium uptake in the proximal tubule
This may occur secondary to:
- Excessive neuro-hormonal activation;
- Breaking phenomenon (No diuretic in the tubule, leading to rebound excessive sodium resorption);
- Reduce active secretion of loop diuretic into tubule therefore less diuresis
- Excessive sodium intake

Excessive sodium resorption in the Loop of Henle because of:
- Breaking phenomenon (No diuretic in the tubule, leading to rebound excessive sodium resorption)

Renal Adaptation:
- Chronic diuretic use can lead to excessive amounts of sodium arriving in the distal tubule leading to distal tubule hypertrophy leading to rebound sodium retention

Excessive Sodium and water retention in the distal Nephron and collecting ducts may occur secondary to:
- Excessive Aldosterone and vasopressin

Non-nephron related cause of diuretic resistance:
- Reduced drug bioavailability (especially with oral furosemide) due to reduced absorption from the oedematous bowel

Vazir A, Cowie MR. Indian Heart J 2016; 68 Suppl 1:S61-8
Neurohumoral Activation Induces Na+ and H₂O Retention in Heart Failure

- **Renin**
  - ↑
  - → Aldo, AngII

- **Catecholamines**
  - ↑
  - →Na+ reabsorption proximal tubule (direct effect)
  - →Passive Na+ and H₂O reabsorption proximal tubule via efferent constriction (indirect effect)

- **Vasopressin**
  - ↑
  - →Free H₂O excretion collecting duct

- **Natriuretic Peptides (NP)**
  - ↑
  - →NP resistance
  - →Na+ reabsorption collecting duct
  - →Inhibition of Renin and Aldo secretion

- **Thirst**
  - ↑
  - →Na+ reabsorption proximal tubule (indirect effect)

- **Na+ reabsorption collecting duct**
  - ↑

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