HEART FAILURE UPDATE 2021 VIRTUAL

Canadian Heart Failure Society
Société canadienne d'insuffisance cardiaque
Treatment of the Diuretic Resistant Patient with Acute Heart Failure

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- **Other**: 
Objectives

• 1. Understand the contributors to diuretic resistance in patients with volume overload.
• 2. Describe a stepped approach to diuretic management in the resistant patient.
• 3. Describe potential alternatives to traditional diuretic treatment for volume overload.
OBJECTIVE 1:

CONTRIBUTORS TO DIURETIC RESISTANCE IN PATIENTS WITH ACUTE HEART FAILURE
Case: Ms. Anne Uric

- 33 year old woman
- Past medical history:
  - Bioprosthetic tricuspid and mitral valve replacements (2018) for infective endocarditis, complicated by embolic events including anterior MI requiring PCI to LAD
  - Now has severe biventricular dysfunction (LVEF 27%) with failing bioprosthetic valves as a result of recurrent endocarditis due to ongoing iv drug use (IVDU)
  - Not a candidate for advanced therapies due to medication non-adherence and IVDU
- To ER with increasing dyspnea, worsening lower limb edema and 1 episode of vomiting
- Had been taking ibuprofen for generalized “muscle aches” and furosemide 80 mg BID at home
- On examination: 109/80 mmHg, 86 beats/min, 98% on 3L nasal prongs, JVP 5 cm above the sternal angle, moderate pitting edema to mid-shins
- Labs: hemoglobin 101 (stable), wbc 5.1, platelets 270, sodium 137, potassium 2.5, creatinine 166 (baseline), lactate 1.5
- Admitted to GIM ward with decompensated heart failure (HF)
- Given furosemide 80 mg iv in ER and ibuprofen stopped
- Next day, creatinine increased to 214
- Furosemide held, since patient appeared euvolemic and hemodynamically still stable
- Two days later: creatinine up to 355, potassium 6.8, lactate 4.1
- Transferred to ICU, Cardiology and Nephrology consulted
Ms. Anne Uric: ICU

- Potassium shifted by ICU team
- Patient given furosemide 80 mg iv and started on furosemide infusion at 20 mg/h
- On examination: 108/71 mmHg, 85 beats/min, 95% 2L NP
- Urine output only 20-30 cc/h and fluid balance positive 750 cc for past 24 hours
- Labs: sodium 135, potassium 5.7, creatinine 344, lactate 2.1
- What should we do next?
Overview of Key Cardio-Renal Interactions

Haemodynamic mechanisms
- Fluid overload and retention of salt and water
- Renal and cardiac congestion (renal venous hypertension)
- Limited organ perfusion (forward failure)
- Vasoconstriction in end organs

(Neuro)hormonal mechanisms
- Activation of the RAAS
- Activation of the sympathetic nervous system

Cardiovascular disease-associated mechanisms
- Chronic inflammation and activation of cellular immunity
- Malnutrition, cachexia and wasting
- Bone–mineral disorder
- Acid–base metabolism disorder
- Anaemia and cardio-renal anaemia

Definitions of Cardio-renal Syndromes (CRS)

Type 1: acute cardio-renal syndrome
Acute HF leading to AKI
- Altered cardiac and/or renal haemodynamics might be of particular importance

Type 2: chronic cardio-renal syndrome
Chronic HF leading to progressive and permanent CKD
- Accelerated renal cell apoptosis and replacement fibrosis might be of particular importance

Type 3: acute reno-cardiac syndrome
AKI causing acute HF
- Salt and water imbalance, uraemia-induced effects and neuro-hormonal dysregulation might be key in this setting

Type 4: chronic reno-cardiac syndrome
CKD leading to chronic HF and CKD progression
- CKD-induced myopathy might be of particular importance in this setting

Type 5: secondary cardio-renal syndrome
- Systemic insult (e.g. in severe sepsis and/or septic shock)
- Microcirculatory dysfunction, altered innate and adaptive immune responses and cytokine release, and other effects result in simultaneous organ injury

Schefold, J. C. et al. (2016) Heart failure and kidney dysfunction: epidemiology, mechanisms and management
Nat. Rev. Nephrol. doi:10.1038/nrneph.2016.113
Reasons for Worsening Kidney Function in CRS

- Patients with heart failure (HF) may be unable to generate forward blood flow, resulting in kidney hypoperfusion and activation of the renin-angiotensin-aldosterone system (RAAS)
- Activation of the RAAS leads to further salt and water retention, increased preload, and worsening pump failure.
- Conversely, medications used in the treatment of HF, such as diuretics and RAAS inhibitors, can also worsen kidney function
- Diuretic resistance is defined as a failure to achieve the therapeutically desired reduction in edema despite a full dose of diuretic
Common Causes of Diuretic Resistance

- Nonadherence to recommended sodium and/or fluid restriction
- Drug not reaching the kidney
  - Nonadherence
  - Dose too low or too infrequent
  - Poor absorption
- Reduced diuretic secretion
  - Tubular uptake of diuretic impaired by uremic toxins
  - Decreased kidney blood flow
  - Decreased functional kidney mass
- Insufficient kidney response to drug
  - Low glomerular filtration rate
  - Decreased effective intravascular volume despite elevated total extracellular fluid volume
  - Activation of the renin-angiotensin system
  - Nephron adaptation
  - Use of nonsteroidal anti-inflammatory drugs
OBJECTIVE 2:
MEDICAL MANAGEMENT OF AKI AND CRS
Basic Principles of Medical Management for AKI and CRS

• 1. Optimize hemodynamics and fluid balance
• 2. Avoid or discontinue potential nephrotoxins (ex. aminoglycosides, NSAIDs, iodinated radiocontrast).
• 3. Consider holding RAAS inhibitors during severe AKI, since they can reduce GFR
  • However, RAAS inhibitors have beneficial effects in patients with cardiovascular disease, so continuing these medications initially may be reasonable during mild AKI and CRS
• 4. Avoid excessive fluid administration to prevent harmful volume overload.
CARRESS-HF: Ultrafiltration in Decompensated Heart Failure with Cardiorenal Syndrome

- 188 patients with acute decompensated heart failure, worsened renal function, and persistent congestion.
- Stepped pharmacologic therapy (94 patients) or ultrafiltration (94 patients).
- Primary endpoint: 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.

Volume Management in Patients with Acute HF and CRS

Initiate intravenous loop diuretic based on prior dose
- Bolus dosing (most patients)
- Continuous infusion (if hemodynamic instability)

Increase loop diuretic as needed

INEFFECTIVE:
- Increase loop diuretic dose
- Consider diuretic infusion using stepped protocol

EFFECTIVE:
- Continue current loop diuretic dose

### Stepped Diuretic Algorithm Used in CARRESS-HF

<table>
<thead>
<tr>
<th>Step</th>
<th>Current Diuretic Regimen</th>
<th>Suggested Diuretic Regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Furosemide Dose (PO)</td>
<td>Furosemide Dose (IV)</td>
</tr>
<tr>
<td>1</td>
<td>≤ 80 mg/day</td>
<td>40 mg + 5 mg/h</td>
</tr>
<tr>
<td>2</td>
<td>81-160 mg/day</td>
<td>80 mg + 10 mg/h</td>
</tr>
<tr>
<td>3</td>
<td>161-240 mg /day</td>
<td>80 mg + 20 mg/h</td>
</tr>
<tr>
<td>4</td>
<td>&gt;240 mg/day</td>
<td>80 mg + 30 mg/h</td>
</tr>
</tbody>
</table>

- The starting diuretic dose is determined by the outpatient or current inpatient diuretic dose
- Patient is moved to a higher diuretic dose if urine output is < 3L/day on current dose
- All loop diuretic doses are given in furosemide equivalents, although alternative could be used
- Vasodilator or inotrope can be added for patients who have urine output < 3L/day on Step 4

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Consider diuretic infusion using stepped protocol

EFFECTIVE:
Continue current loop diuretic dose

Increase second diuretic as needed

INEFFECTIVE:
Add second diuretic
- Thiazide diuretic first-line
- Spironolactone or tolvaptan second-line

EFFECTIVE:
Continue current loop diuretic dose

General Principles of Managing Diuretic Resistance

A key strategy to overcome diuretic resistance frequently relies on combining 2 types of diuretic (diuretic synergism).

There are several classes of diuretics, dictated by their site of action in the nephron.

Because loop diuretics are the first drug of choice in edematous disorders, this implies adding a diuretic that targets another tubular segment.

Especially for patients with liver cirrhosis and ascites, the specific combination of furosemide and spironolactone is supported by data.

For the other edematous disorders, the evidence for specific combinations of diuretics is less obvious, and usually a thiazide diuretic is recommended as a second diuretic.

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Schematic of a nephron shows sites of action of diuretics along the various segments. Abbreviations: CNT, connecting tubule; DCT, distal convoluted tubule; G, glomerulus.
OBJECTIVE 3:

ALTERNATIVES TO DIURETIC TREATMENT FOR VOLUME OVERLOAD
Volume Management in Patients with Acute HF and CRS

Initiate intravenous loop diuretic based on prior dose
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  - EFFECTIVE: Continue current loop diuretic dose

- Increase second diuretic as needed
  - INEFFECTIVE: Add second diuretic
    - Thiazide diuretic first-line
    - Spironolactone or tolvaptan second-line
  - EFFECTIVE: Continue current loop diuretic dose

- Titrate vasoactive therapy as needed
  - INEFFECTIVE: Hemodynamic assessment
    - Vasoactive therapy if inadequate cardiac output
  - EFFECTIVE: Continue current combination diuretic regimen

Use of Inotropes and Vasodilators in Treatment of AKI or CRS

• Inotropic therapy is most likely to be effective in patients with CRS who are also hypotensive and/or have objective evidence of reduced cardiac output
• Empirical use of inotropes should be avoided due to their potential toxicity
• No specific vasoactive drug has been shown to prevent or treat AKI or CRS, including inotropes or vasodilators\(^1\), \(^2\)

• Recommend the following intravenous vasodilators, titrated to a systolic blood pressure (sBP) over 100 mm Hg, for relief of dyspnea in hemodynamically stable patients (sBP over 100 mm Hg):
  • Nitroglycerine (Strong Recommendation, Moderate-Quality Evidence);
  • Nesiritide (Weak Recommendation, High-Quality Evidence);
  • Nitroprusside (Weak Recommendation, Low-Quality Evidence).

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\(^1\) Jentzer JC, Chawla LS. Crit Care Clin 2015;31:685-703
At 3 hours, the mean (SD) decrease in PCWP from baseline was -5.8 mmHg for nesiritide, -3.8 mmHg for NTG, and -2 mmHg for placebo.

VMAC trial compared nesiritide (n=204), nitroglycerine (n=143), or placebo (n=142) to standard therapy for 3 h, followed by nesiritide (n=278) or NTG (n=216) added to standard treatment for 24 h in acute HF patients with dyspnea at rest.
Dopamine has cardiac inotropic effects and can enhance kidney function as well as diuresis in some patients.

However, dopamine has not consistently improved kidney function, diuresis, or clinical outcomes in patients with CRS\(^1\).

There is a possible beneficial effect of low-dose dopamine (2 mcg/kg/min) in patients who have CRS and HFrEF\(^2\).

• ROSE AHF enrolled AHF patients (n=360; any EF) with renal dysfunction.
• The effect of dopamine (interaction \(P=0.001\)) and nesiritide (interaction \(P=0.039\)) on urine volume varied by EF group.
• In HFrEF, urine volume was higher with active treatment versus placebo.

\(^1\)Jentzer JC et al. J Am Coll Cardiol 2020;76:1084-101
Volume Management in Patients with Acute HF and CRS

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Bolus dosing (most patients)
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INEFFECTIVE: Add second diuretic
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Titrte vasoactive therapy as needed

INEFFECTIVE: Hemodynamic assessment
Vasoactive therapy if inadequate cardiac output

EFFECIVE: Continue current combination of diuretic regimen

INEFFECTIVE: Consider hypertonic saline
Initiate RRT if poor response
• SCUF if no/mild AKI
• CRRT if severe AKI

EFFECIVE: Continue current medication regimen

Direct Modulation of Sodium Avidity with Hypertonic Saline to Promote Excretion

- Use of hypertonic saline solution (HSS) in combination with high-dose furosemide has long been considered a controversial treatment strategy for acute CRS in advanced HF
- HSS increases intracellular NaCl concentration, resulting in instantaneous mobilization of extravascular fluid into the intravascular space through osmotic action¹
- Through the baroreceptor reflex, plasma volume expansion leads to a reduction in systemic vascular resistance²
- This small increase in preload and significant decrease in afterload translates into increased cardiac output, renal blood flow and enhanced organ perfusion
- Meta-analysis showed small-volume HSS may improve diuretic responsiveness and renal function in patients with CRS³

¹ Paterna S et al. Adv Ther 1999;16:219-228
² Liszkowski M and Nohria A. Curr Heart Fail Rep 2010;7:134-139
³ Gandhi S et al. Int J Cardiol 2014;173:139-45
Real World Use of Hypertonic Saline in Refractory Acute Decompensated Heart Failure

A U.S. Center’s Experience

Matthew Griffin, MD, Aaron Soufer, MD, Eden Goljo, MD, Matthew Colna, MD, Veena S. Rao, PhD, Sanghoon Jeon, PhD, Parinita Raghavendra, BS, Julie D’Ambrosi, PA-C, Ralph Riello, PA-C, Steven G. Coca, DO, MS, Devin Mahoney, BS, Daniel Jacoby, MD, Tariq Ahmad, MD, MPH, Michael Chen, MD, W.H. Wilson Tang, MD, Jeffrey Turner, MD, Wilfried Mullens, MD, PhD, Francis P. Wilson, MD, MSCE, Jeffrey M. Testani, MD, MTR

• Retrospective analysis of 58 hypertonic saline episodes were identified across 40 patients with diuretic-therapy refractory ADHF at Yale University
• Received 150 ml of 3% NaCl to be given over 30 min (300 ml/h), administered simultaneously with high doses of loop diuretic agents:
  - Both total urine output and weight loss significantly improved with hypertonic saline
  - No significant changes in respiratory status or overcorrection of serum sodium with the intervention
  - Additional study of hypertonic saline as a diuretic adjuvant is warranted.

<table>
<thead>
<tr>
<th>Day</th>
<th>Admissions (n)</th>
<th>Diuretic Dose (Average ± SD, furosemide equivalents)</th>
<th>Diuretic Efficiency (change in UOP per doubling of loop diuretic dose)</th>
</tr>
</thead>
<tbody>
<tr>
<td>-3</td>
<td>45</td>
<td>568 ± 489mg</td>
<td>656±362 mL</td>
</tr>
<tr>
<td>-2</td>
<td>54</td>
<td>586 ± 525mg</td>
<td>657±364mL</td>
</tr>
<tr>
<td>-1</td>
<td>58</td>
<td>606 ± 594mg</td>
<td>627±427mL</td>
</tr>
<tr>
<td>1</td>
<td>58</td>
<td>749 ± 655mg</td>
<td>841±496mL</td>
</tr>
<tr>
<td>2</td>
<td>58</td>
<td>667 ± 634mg</td>
<td>909±470mL</td>
</tr>
<tr>
<td>3</td>
<td>58</td>
<td>517 ± 487mg</td>
<td>878±542mL</td>
</tr>
</tbody>
</table>

Online Table 1. Dose of loop diuretic and diuretic efficiency by day.
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EFFECTIVE:
Continue current combination diuretic regimen

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- CRRT if severe AKI

EFFECTIVE:
Continue current medication regimen

## Potential General and CICU-Specific CRRT Indications

<table>
<thead>
<tr>
<th>General Acute RRT Indications</th>
<th>Proposed CICU-Specific CRRT Indications</th>
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<tbody>
<tr>
<td>A: Severe metabolic acidosis (i.e. Severe lactic acidosis with refractory shock and multiorgan failure)</td>
<td>Patients with severe cardiac and/or valvular dysfunction and borderline blood pressure with AKI and volume overload</td>
</tr>
<tr>
<td>E: Severe electrolyte disturbances, most commonly hyperkalemia</td>
<td>Cardiogenic shock or HF with pulmonary edema on mechanical ventilation and high FiO₂ (&gt;80-90%) despite diuretic therapy</td>
</tr>
<tr>
<td>I: Intoxication with dialyzable drugs or toxins</td>
<td>Refractory cardiorenal syndrome with progressive AKI (e.g. Stage 2-3 AKI plus volume overload with inadequate diuretic response)</td>
</tr>
<tr>
<td>O: Medically refractory volume overload</td>
<td>Pre-cardiac surgical volume removal to improve likelihood of chest closure and prevent post-operative right ventricular failure</td>
</tr>
<tr>
<td>U: Severe azotemia or symptoms of uremia</td>
<td></td>
</tr>
</tbody>
</table>
This study was designed to compare the safety and efficacy of veno-venous ultrafiltration and standard intravenous diuretic therapy for hypervolemic HF patients.

Two hundred patients (63±15 years, 69% men, 71% LVEF ≤ 40%) were randomized to ultrafiltration or intravenous diuretics.

Conclusion: in decompensated HF, ultrafiltration safely produces greater weight and fluid loss than intravenous diuretics, reduces 90-day resource utilization for HF, and is an effective alternative therapy.
• Nephrology on standby for possible initiation of CRRT since urine output 30 cc/h
• Patient transferred to Cardiology, under CICU team
• Diuretics escalated stepwise to furosemide 120 mg iv BID with metolazone 5 mg BID and furosemide 30 mg/h
• Following this, urine output increased to 200 cc/h
• Potassium 3.0, so lasix decreased and patient started on spironolactone.
• Creatinine decreased from 355 back down to 188, lactate normalized
• Patient now transitioned to and stable on bumetanide 4 mg BID with spironolactone 50 mg OD and intermittent use of metolazone
Cardiorenal syndrome (CRS) involves the interplay between hemodynamic, inflammatory, and neurohumoral abnormalities to produce worsening heart and kidney function.

Management of patients with CRS involves multidisciplinary care, starting with medical management and avoidance of further acute kidney injury (AKI).

Initial therapy of CRS and diuretic resistance involves a stepped diuretic regimen, vasoactive therapies if appropriate, and possible consideration of hypertonic saline solution.

For medically refractory CRS and severe AKI, renal replacement therapy may be necessary.