A case of heart failure with kidney dysfunction
What do the Guidelines say?

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Disclosures

Advisory boards / Lecture fees (minor):

• Galenica
• Pfizer
• BIANEX
• Novartis
• Boehringer Ingelheim
• Astra-Zeneca
• Bayer HealthCare
• Servier
• MSD
• Actelion
• AMGEN
Case # Heart Failure with kidney dysfunction

A 78 year old woman, with chronic kidney disease stage 3 and ischemic / valvular cardiomyopathy with ejection fraction of 20% is admitted to hospital with 1 week of progressive dyspnea and weight gain (+6 Kg). Several days prior, furosemide intake was increased from 40mg to 120 mg daily.

At admission,

- Blood pressure was 120/70 mmHg and heart rate 120 beats/min.
- Jugular venous pressure was 18 cm H₂O.
- A 3/6 diastolic murmur at the right sternal border, a 4/6 systolic murmur at the left mid-axillary line, bibasilar rales, and bilateral pitting edema (3+) to the thighs.
Case # Heart Failure with kidney dysfunction
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Patient Medical History

- Known Heart Failure from 2010 (Ischemic / Valvular Cardiomyopathy)
- Coronary Artery Disease (PCI RCA x2 stents 2012)
- Moderate to severe MR / moderate to severe AR
- Arterial Hypertension
- Chronic Atrial Fibrillation
- Known Chronic Kidney Disease from 2014 (stage 3A – 3B)

Treatment

- Tbl Furosemide 40 mg x3
- Tbl Acenocoumarol
- Tbl Irbesartan 300mg x1
- Tbl Bisoprolol 5mg x1
- Tbl Simvastatin / Ezetimibe 20/10mg x1
- Tbl Amlodipine 10mg x1
- Tbl Eplerenone 25mg x1
Case # Heart Failure with kidney dysfunction
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**Case # Heart Failure with kidney dysfunction**

**Laboratory results upon admission**

<table>
<thead>
<tr>
<th>Lab result</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>NT-pro BNP</td>
<td>28,300 pg/mL</td>
</tr>
<tr>
<td>Urea</td>
<td>140 mg/dL</td>
</tr>
<tr>
<td>Creatinine</td>
<td>1.8 mg/dL</td>
</tr>
<tr>
<td>Na</td>
<td>128 mmol/L</td>
</tr>
<tr>
<td>K</td>
<td>5.3 mmol/L</td>
</tr>
<tr>
<td>GFR</td>
<td>30 mL/min/1.73m²</td>
</tr>
<tr>
<td>Uric acid</td>
<td>13.8 mg/dL</td>
</tr>
<tr>
<td>Bilirubin</td>
<td>1.6 mg/dL</td>
</tr>
<tr>
<td>SGOT</td>
<td>29 IU/L</td>
</tr>
<tr>
<td>SGPT</td>
<td>14 IU/L</td>
</tr>
<tr>
<td>LDH</td>
<td>208 IU/L</td>
</tr>
<tr>
<td>CPK</td>
<td>109 IU/L</td>
</tr>
<tr>
<td>CRP</td>
<td>1.10 mg/dL</td>
</tr>
<tr>
<td>Ht</td>
<td>39%</td>
</tr>
<tr>
<td>Hb</td>
<td>12.8 g/dL</td>
</tr>
<tr>
<td>WBC</td>
<td>5530 K/μL</td>
</tr>
<tr>
<td>INR</td>
<td>2.3</td>
</tr>
</tbody>
</table>

Higher than her baseline of 1.4-1.5 mg/dL
Case # Heart Failure with kidney dysfunction
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The patient received i.v furosemide bolus at 160 mg, followed by a continuous infusion of 200 mg / daily; patient was hemodynamically stable
Question #1
Is this worsening of renal function significant? If yes, what to do next?

1. No, this an anticipated worsening of renal function; do nothing
2. Yes, withhold ARB, BBL and MRA
3. Yes, withhold ARB, BBL, MRA and add thiazide diuretic
4. Yes, withhold ARB, BBL, MRA and increase furosemide dose
A further deterioration in renal function, termed worsening renal function (WRF), is used to indicate an increase in serum creatinine, usually by ≥26.5 μmol/L (0.3 mg/dL) and/or a 25% increase or a 20% drop in GFR. The importance of these apparently small changes is that they are frequent, they promote the development and progression of CKD and, as a consequence, can worsen the prognosis of HF. Increases in creatinine during an AHF hospitalization are not always clinically relevant, especially when they are accompanied by appropriate decongestion, diuresis and haemoconcentration.

Large increases in serum creatinine, termed acute kidney injury (AKI), are relatively rare in HF and are probably associated with the combination of diuretic therapy with other potentially nephrotoxic drugs such as some antibiotics (gentamicin and trimethoprim), contrast media, ACEIs, ARBs, NSAIDs, etc. Of relevance, some of these drugs may accumulate if they are renally excreted. In HF, WRF is relatively common, especially during initiation and up-titration of RAAS inhibitor therapy. Despite the fact that RAAS blockers can frequently cause a decrease in GFR in patients with HF, this reduction is usually small and should not lead to treatment discontinuation unless there is a marked decrease, as the treatment benefit in these patients is probably largely maintained. When large increases in serum creatinine occur, care should be taken to evaluate the patient thoroughly and should include assessment of a possible renal artery stenosis, excessive hyper- or hypovolaemia, concomitant medication and hyperkalaemia, which frequently coincides with WRF.
ESC 2016 Guidelines Reference

Acute heart failure patient with renal impairment

- Stable Renal Dysfunction
  - Yes
  - Aggressively dose loop diuretics
  - Check renal function and electrolytes daily
  - No (Worsening Renal Function)
    - Favourable Diuretic Response
      - Yes
      - Possible Pseudo WRF
      - Re-evaluate congestion and hemodynamic status. If continued volume overload, accept change and check renal function and electrolytes at least daily
      - No (Diuretic Resistance)
        - Signs of Hypoperfusion and/or Hypotension
          - Yes
          - Increase diuretic intensity
          - No
          - Improvement
            - True WRF – Congested kidney
              - Reduce loop diuretic dose when renal function has stabilized and/or patient is euolemic. Recheck regularly
            - No Improvement
              - True WRF – Refractory Hypoperfused and/or Congested kidney
                - Consider invasive monitoring, ICU, Mechanical Support and possible Ultrafiltration or RRT
          - Attempt hemodynamic optimization
            - No Improvement
              - True WRF – Hypoperfused and/or Congested Kidney
                - Consider invasive monitoring if further clinical or renal deterioration, regularly recheck renal function and electrolytes

DOSE trial: low vs. high dose of furosemide

<table>
<thead>
<tr>
<th>End Point</th>
<th>Bolus Every 12 Hr (N=156)</th>
<th>Continuous Infusion (N=152)</th>
<th>P Value</th>
<th>Low Dose (N=151)</th>
<th>High Dose (N=157)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC for dyspnea at 72 hr</td>
<td>4456±1468</td>
<td>4699±1573</td>
<td>0.36</td>
<td>4478±1550</td>
<td>4668±1496</td>
<td>0.04</td>
</tr>
<tr>
<td>Freedom from congestion at 72 hr</td>
<td>22/153 (14)</td>
<td>22/144 (15)</td>
<td>0.78</td>
<td>16/143 (11)</td>
<td>28/154 (18)</td>
<td>0.09</td>
</tr>
<tr>
<td>— no./total no. (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Change in weight at 72 hr — lb</td>
<td>−6.8±7.8</td>
<td>−8.1±10.3</td>
<td>0.20</td>
<td>−6.1±9.5</td>
<td>−8.7±8.5</td>
<td>0.01</td>
</tr>
<tr>
<td>Net fluid loss at 72 hr — ml</td>
<td>4237±3208</td>
<td>4249±3104</td>
<td>0.89</td>
<td>3575±2635</td>
<td>4899±3479</td>
<td>0.001</td>
</tr>
</tbody>
</table>

**Case # Heart Failure with kidney dysfunction**

I.V furosemide was increased to 600 mg / day, ARB, MRA and BBL were stopped; patient was hemodynamically stable.
Question #2
Patient deteriorated despite measures; what to do next?

1. This an anticipated worsening of renal function; do nothing
2. Add metolazone (sequential nephron blockade)
3. Add IV dopamine
4. Add metolazone and admit to CCU for monitoring
Insufficient diuretic response/diuretic resistance:
- Check adherence and fluid intake.
- Increase dose of diuretic.
- Consider switching from furosemide to bumetanide or torasemide.
- Add MRA/increase dose of MRA.
- Combine loop diuretic and thiazide/metolazone.\(^b\)
- Administer loop diuretic twice (or more times) daily or on empty stomach.
- Consider short-term i.v. Infusion of loop diuretic.
- Consider ultrafiltration.
Sequential nephron blockade

documented in a single patient resistant to chlorothiazide plus furosemide (24). Numerous TD have been evaluated in combination with various LD with similar results overall, and no clear evidence that any single TD is superior, suggesting a class effect. The most commonly used TD were metolazone, bendroflumethiazide, quinethazone, and hydrochlorothiazide. In addition to metolazone (45), LD augmentation was demonstrated using chlorothiazide (13,42), hydrochlorothiazide (43,47), quinethazone (20,21), indapamide (48), bendroflumethiazide (21,25), and butizide (49). Metolazone has been suggested to be superior to other TD in patients with advanced kidney disease (24,50), but other TD augment the response to LD, even in patients with advanced renal failure (26,47,49,51). Finally, the assertion that a TD should be given at least 30 min before the LD was not studied in any article we reviewed (52). Most studies reporting benefits of CDT administered the 2 drugs at the same time. Metolazone has slow and variable absorption in edematous patients, such that the peak effect occurs only after several hours (15,45). The benefit of TD (with their long duration of action) added to LD appears to be primarily in maintaining diuresis after the shorter-acting LD has worn off (49,53).
Sequential nephron blockade

Table 3. Comparative Effect on Urine Output and Net Fluid Balance While on Diuretic-Enhancing Regimen.

<table>
<thead>
<tr>
<th></th>
<th>Continuous Infusion Furosemide</th>
<th>Furosemide Plus Metolazone</th>
<th>Continuous Infusion Bumetanide</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean hourly UO at baseline, mL</td>
<td>114 ± 85</td>
<td>96 ± 52</td>
<td>89 ± 58</td>
<td>.383</td>
</tr>
<tr>
<td>Mean hourly UO on treatment, mL</td>
<td>168 ± 105</td>
<td>208 ± 187</td>
<td>177 ± 125</td>
<td>.302</td>
</tr>
<tr>
<td>Mean difference between baseline and on treatment hourly UO, mL</td>
<td>48 ± 103</td>
<td>109 ± 171</td>
<td>89 ± 90</td>
<td>.0087*</td>
</tr>
<tr>
<td>Total UO at 24 hours on treatment, mL</td>
<td>3378 ± 1616</td>
<td>3793 ± 2005</td>
<td>4046 ± 3040</td>
<td>.505</td>
</tr>
<tr>
<td>Total UO at 48 hours on treatment, mL</td>
<td>6376 ± 1584</td>
<td>6022 ± 3054</td>
<td>7637 ± 5778</td>
<td>.832</td>
</tr>
<tr>
<td>Net hourly fluid balance baseline, mL</td>
<td>−63 ± 152</td>
<td>−28 ± 71</td>
<td>−3 ± 66</td>
<td>.048*</td>
</tr>
<tr>
<td>Net hourly fluid balance on treatment, mL</td>
<td>−106 ± 119</td>
<td>−142 ± 203</td>
<td>−99 ± 112</td>
<td>.298</td>
</tr>
<tr>
<td>Mean difference in net hourly fluid balance between baseline and on treatment, mL,</td>
<td>−36 ± 150</td>
<td>−114 ± 199</td>
<td>−98 ± 116</td>
<td>.045*</td>
</tr>
</tbody>
</table>
### ROSE trial; Dopamine vs placebo

<table>
<thead>
<tr>
<th>Table 2. Coprimary End Points: Effect of Low-Dose Dopamine vs Placebo or Low-Dose Nesiritide vs Placebo on Cumulative Urine Volume During 72 Hours and Change in Cystatin C Level From Baseline to 72 Hours</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mean (95% CI)</strong></td>
</tr>
<tr>
<td><strong>Placebo</strong></td>
</tr>
<tr>
<td><strong>Dopamine strategy</strong></td>
</tr>
<tr>
<td><strong>Cumulative urine volume from randomization to 72 h, mL</strong></td>
</tr>
</tbody>
</table>

### DAD-HF II trial; Dopamine vs placebo

**Table 3**

<table>
<thead>
<tr>
<th>Time after initiation of treatment</th>
<th>High-dose furosemide</th>
<th>Low-dose furosemide plus dopamine</th>
<th>Low-dose furosemide</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 h</td>
<td>735 (338–1108)</td>
<td>900 (428–1370)</td>
<td>750 (400–1420)</td>
<td>0.362</td>
</tr>
<tr>
<td>4 h</td>
<td>1190 (585–1720)</td>
<td>1330 (763–1873)</td>
<td>1175 (743–1925)</td>
<td>0.525</td>
</tr>
<tr>
<td>6 h</td>
<td>1390 (858–2263)</td>
<td>1620 (1048–2483)</td>
<td>1680 (1186–2465)</td>
<td>0.522</td>
</tr>
<tr>
<td>8 h</td>
<td>1845 (1088–2640)</td>
<td>1950 (1440–2950)</td>
<td>1990 (1438–3000)</td>
<td>0.700</td>
</tr>
<tr>
<td>24 h</td>
<td>2900 (2100–4640)</td>
<td>3515 (2500–4460)</td>
<td>3500 (2510–4485)</td>
<td>0.686</td>
</tr>
</tbody>
</table>
Acute heart failure patient with renal impairment

1. Stable Renal Dysfunction
   - Yes: Aggressively dose loop diuretics. Check renal function and electrolytes daily.
   - No (Worsening Renal Function):
     - Favourable Diuretic Response
       - Yes: Possible Pseudo WRF
         - Re-evaluate congestion and hemodynamic status. If continued volume overload, accept change and check renal function and electrolytes at least daily.
       - No (Diuretic Resistance):
         - Signs of Hypoperfusion and/or Hypotension
           - No: Increase diuretic intensity
           - Yes: Attempt hemodynamic optimization
             - No Improvement:
               - No Improvement:
                 - True WRF – Congested kidney
                   - Consider invasive monitoring, ICU, Mechanical Support and possible Ultrafiltration or RRT
               - Improvement:
                 - True WRF – Hypoperfused and/or Congested Kidney
                   - Consider invasive monitoring if further clinical or renal deterioration, regularly recheck renal function and electrolytes

Case # Heart Failure with kidney dysfunction

Metolazone 2.5mg x1 was added (sequential nephron blockade); was admitted to CCU; CVP 32 cm H₂O with prominent V waves; patient was hemodynamically stable.
Case # Heart Failure with kidney dysfunction

- Patient still unresponsive to therapy

- Anuria / Oliguria < 20mL/h for 6 hours

- Compensating renal function decline and borderline hypoxemic on Arterial Blood
  Gases: pH 7.48, pCO₂ 45 mmHg, pO₂ 57 mmHg, Na 125 mmol/L, K 3.6 mmol/L, HCO₃
  31.7 mmol/L, SO₂ 91%

- Patient hemodynamic stable
Question #3

Patient deteriorated despite measures; what to do next?

1. Wait and observe
2. Add an inotrope
3. Mechanical support of the circulation
4. Renal replacement therapy
Renal replacement therapy

Ultrafiltration involves the removal of plasma water across a semipermeable membrane in response to a transmembrane pressure gradient. There is no evidence favouring ultrafiltration over loop diuretics as first-line therapy in patients with AHF. At the present time, routine use of ultrafiltration is not recommended and should be confined to patients who fail to respond to diuretic-based strategies.

The following criteria may indicate the need for initiation of renal replacement therapy in patients with refractory volume overload: oliguria unresponsive to fluid resuscitation measures, severe hyperkalaemia (K^+ > 6.5 mmol/L), severe acidaemia (pH < 7.2), serum urea level > 25 mmol/L (150 mg/dL) and serum creatinine > 300 μmol/L (> 3.4 mg/dL).
## Recommendations regarding renal replacement therapy in patients with acute heart failure

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>Class</th>
<th>Level</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ultrafiltration may be considered for patients with refractory congestion, who failed to respond to diuretic-based strategies.</td>
<td>IIb</td>
<td>B</td>
<td>578–580</td>
</tr>
<tr>
<td>Renal replacement therapy should be considered in patients with refractory volume overload and acute kidney injury.</td>
<td>IIA</td>
<td>C</td>
<td></td>
</tr>
</tbody>
</table>
Renal replacement therapy

**UNLOAD** trial; 2007

200 patients;

baseline creatinine 1.5 ± 0.5 mg/dL

*J Am Coll Cardiol* 2007;49:675–83
Renal replacement therapy

**CARESS trial** ; 2012

188 patients;

baseline creatinine

IQR 1.6 – 2.7 mg/dL

*P* = 0.003

Renal replacement therapy was implemented for Days #10, #11, #12; then patient was re-started IV furosemide 600 mg / day; patient was hemodynamically stable.

Increase of furosemide dose

Add metolazone

Creatinine (mg/dL)

Urine output (mL)

Weight (Kg)
Knowledge Gaps

1. Definition of clinical significant and insignificant WRF
2. When to withhold ACE-inhibitor / ARB / MRA therapy
3. When and how (metolazone vs thiazides vs MRA) to implement sequential nephron blockade
4. Is there a role for IV Dopamine
5. When and how to implement renal replacement therapy
PREVENTION COMES FIRST