Acute Kidney Injury, Elevated Creatinine

**Definition:** A disorder characterized by the acute loss of renal function and is traditionally classified as pre-renal, renal, and post-renal.

**Grading Toxicity**

<table>
<thead>
<tr>
<th>Grade 1 (Mild)</th>
<th>Grade 2 (Moderate)</th>
<th>Grade 3 (Severe)</th>
<th>Grade 4 (Potentially Life-Threatening)</th>
<th>Grade 5 (Death)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Creatinine increased &gt;ULN - 1.5 X ULN</td>
<td>Creatinine 1.5–3.0 X baseline; &gt;1.5–3.0 X ULN</td>
<td>Creatinine &gt;3.0 X baseline; &gt;3.0–6.0 X ULN</td>
<td>Creatinine &gt;6.0 X ULN; life-threatening consequences; dialysis indicated</td>
<td></td>
</tr>
</tbody>
</table>

**Mild elevation in creatinine (Grade 1)**
- Anticipate immunotherapy to continue
- Perform detailed review of concomitant medications (prescribed and OTC), herbal supplements, vitamins, anticipating possible discontinuation of nephrotoxic agents
- Avoid/minimize addition of nephrotoxic agents, such as contrast media for radiology tests
- Anticipate close monitoring of creatinine and urine protein (i.e., weekly)
- Educate patient/family on importance of adequate daily hydration and set individualized hydration goals
- Review symptoms to watch for with patient and family and remember to assess at subsequent visits

**Moderate elevation in creatinine (Grade 2)**
- Ipilimumab to be withheld for any Grade 2 event (until Grade 0/1) and discontinued for events persisting >6 weeks or inability to reduce steroid dosage to 7.5 mg prednisone/day
- Pembrolizumab or nivolumab to be withheld for Grade 2 events
- Anticipate increase in frequency of creatinine monitoring (i.e., every 2–3 days until improvement)
- Immunosuppressive medications to be initiated to treat immune-mediated nephritis
  - Systemic corticosteroids (e.g., prednisone) 0.5–1 mg/kg/day until symptoms improve to baseline followed by slow taper over at least 1 month
  - Steroids cause indigestion; provide antacid therapy daily as gastric ulcer prevention while on steroids (e.g., proton pump inhibitor or H2 blocker if prednisone dosage is >20 mg/day)
- Be alert to recurring symptoms as steroids taper down & report them (taper may need to be adjusted)
- Anticipate that renal biopsy may be considered
- Assess patient & family understanding of recommendations and rationale
- Identify barriers to adherence

**Severe (Grade 3) or Potentially Life-Threatening (Grade 4)**
- Pembrolizumab to be permanently discontinued for G3 (severe) or G4 (life-threatening) nephritis
- Nivolumab to be withheld for G3 (severe) and permanently discontinued for G4 (life-threatening) serum creatinine elevation
- Consider hospital admission
- Ipilimumab to be discontinued for any Grade 3/4 event
- Immunosuppressive medications to be initiated to treat immune-mediated nephritis
  - Mycophenolate mofetil
  - Azathioprine, cyclophosphamide, cyclosporine, infliximab, mycophenolate mofetil
  - Anticipate nephrology consultation will be initiated by provider
- Anticipate that renal biopsy will be considered
- Consider hemodialysis may be considered

**Management**

**Overall Strategy**
- Assess for other etiologies such as dehydration (common), infection, and recent IV contrast exposure
- Eliminate potential nephrotoxic agents
- Evaluate for progressive kidney/adrenal/pelvic metastases that may be contributing to kidney dysfunction
- Early intervention to maintain or improve physical function and impact on QOL

**Care Step Pathway**

**Grading T**

**Look:**
- Does the patient appear uncomfortable?
- Does the patient look ill?
- Any generalized or lower extremity edema?

**Listen:**
- Has there been change in urination?   
  - Urine colour?
  - Frequency?
  - How much fluid is the patient taking in?
  - Any flank pain?
- Are associated symptoms present?   
  - Nausea?
  - Headache?
  - Malaise?
  - Shortness of breath?
- Are there symptoms concerning for:   
  - Urinary tract infection?
  - Pyelonephritis?
  - Worsening CHF?
- Are symptoms limiting ADLs?
- Current or recent use of nephrotoxic medications (prescribed and OTC), other agents?
  - NSAIDs
  - Antibiotics
  - Contrast media or other nephrotoxic agents?

**Recognize:**
- Laboratory abnormalities (elevated creatinine, electrolyte abnormalities)
- Urinalysis abnormalities (casts, proteinuria)
- Abdominal or pelvic disease that could be causing symptoms
- Prior history of renal compromise
- Other immune-related adverse effects
- Presence of current or prior immune-mediated toxicities, including rhabdomyolysis
- Is patient volume depleted?

**Implementation:**
- Identify individuals with pre-existing renal dysfunction prior to initiating immunotherapy. Ensure baseline creatinine has been obtained
- Check kidney function prior to each dose of immunotherapy
- Continue assessing for nephrotoxic medications over the treatment course
- Monitor creatinine and urine protein more frequently if levels appear to be rising, and for Grade 1 toxicity
- Educate patients that new urinary symptoms should be reported immediately
- Anticipate the steroid requirements to manage immune-mediated nephritis are high (up to 1–2 mg/kg/d) and patients will be on corticosteroid therapy for at least 1 month
- Educate patients and family about the rationale for discontinuation of immunotherapy in patients who develop severe nephritis

**Systemic corticosteroids**
- Steroid taper instructions/calendar as a guide but not an absolute
- Taper should consider patient’s current symptom profile
- Close follow-up in person or by phone, based on individual need & symptomatology
- Steroids cause indigestion; provide antacid therapy daily as gastric ulcer prevention while on steroids (e.g., proton pump inhibitor or H2 blocker if prednisone dosage is >20 mg/day)
- Review steroid medication side effects: mood changes (angry, reactive, hyperactive, euphoric, manic), increased appetite, interrupted sleep, oral thrush, fluid retention
- Be alert to recurring symptoms as steroids taper down & report them (taper may need to be adjusted)

**Long-term high-dose steroids**
- Consider antimicrobial prophylaxis (sulfamethoxazole/trimethoprim double dose MWF; single dose if used daily) or alternative if sulf-a-allergic (e.g., atovaquone [Mepron®] 1500 mg po daily)
- Consider additional antiviral and antifungal coverage
- Avoid alcohol/cocaine/other hepatotoxic medicines
- If extended steroid use, risk for osteoporosis; initiate calcium and vitamin D supplements

**RED FLAGS:**
- Risk of acute onset
- Risk of mortality if unrecognized or treatment is delayed
- Consider discontinuation of nephrotoxic agent once patients receiving combination immunotherapy regimens and PD-1 inhibitors
- In addition to acute interstitial nephritis seen from PD-1 inhibitors, there are case reports of lupus-like nephritis and granulomatous acute interstitial nephritis

**ADLS = activities of daily living; CHF = congestive heart failure; NSAIDs = nonsteroidal anti-inflammatory drugs; OTC = over the counter; po = by mouth; PPI = proton pump inhibitor**

**QOL = quality of life; ULN = upper limit of normal.**

*Copyright © 2018 IO Essentials.*