### Gradating Toxicity

**Acute Kidney Injury, Elevated Creatinine**

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

<table>
<thead>
<tr>
<th>Grade</th>
<th>Creatinine increase</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (Mild)</td>
<td>&gt;1 × to 1.5 × baseline</td>
<td>- Anticipate immunotherapy to continue</td>
</tr>
<tr>
<td>2 (Moderate)</td>
<td>&gt;1.5–3.0 × baseline; &gt;3.0–6.0 × ULN</td>
<td>- Perform detailed review of concomitant medications (prescribed and OTC), herbal products, vitamins, and other potentially nephrotoxic agents</td>
</tr>
<tr>
<td>3 (Severe)</td>
<td>&gt;&gt;6.0 × ULN</td>
<td>- Identify individuals with pre-existing renal dysfunction prior to initiating immunotherapy. Ensure baseline creatinine has been obtained</td>
</tr>
<tr>
<td>4 (Potentially Life-Threatening)</td>
<td>&gt;6.0 × ULN; life-threatening (Grade 4)</td>
<td>- Consider hospital admission</td>
</tr>
<tr>
<td>5 (Death)</td>
<td>&gt;6.0 × ULN; life-threatening (Grade 4)</td>
<td>- Consider nephrology consultation</td>
</tr>
</tbody>
</table>

**Moderate elevation in creatinine (Grade 2)**

- Pembrolizumab to be withheld for Grade 2 events
- Ipilimumab to be withheld for any Grade 3 event (until Grade 0/1)
- Strong consideration for renal biopsy
- Hemodialysis may be considered

**Severe (Grade 3) or Potentially Life-Threatening (Grade 4)**

- Pembrolizumab to be permanently discontinued for G3 (severe) or G4 (life-threatening) nephritis
- Ipilimumab to be discontinued for any G3 event
- 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, hyperaware, euphoric, manic), increased appetite, interrupted sleep, oral thrush, fluid retention
- If symptoms do not improve within 48–72 hours, consider noncorpectic immunosuppressive medications
- Anticipate nephrology consultation will be initiated by provider
- Strong consideration for renal biopsy
- Hemodialysis may be considered

**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
- 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
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- 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

### *Administering Corticosteroids:*

- Steroid taper instructions/calculator 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 induction; 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, hyperaware, 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
- Consider additional antiviral and antifungal coverage
- Avoid alcohol, acetaminophen, or other hepatotoxic agents
- 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
- Risk of immune-mediated nephritis is greater in 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:

- 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
- ULN = upper limit of normal

### Care Step Pathway – Nephritis (inflammation of the kidneys)

<table>
<thead>
<tr>
<th>Look</th>
<th>Assessment</th>
<th>Recognise</th>
<th>Implementation</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Does the patient appear uncomfortable?</td>
<td>- Creatinine increased &gt;1 × to 1.5 × baseline</td>
<td>- Pathology abnormalities (elevated creatinine, electrolyte abnormalities)</td>
<td>- Identify individuals with pre-existing renal dysfunction prior to initiating immunotherapy. Ensure baseline creatinine has been obtained</td>
</tr>
<tr>
<td>- Does the patient look ill?</td>
<td>- Grade 1 (Mild)</td>
<td>- Urinalysis abnormalities (casts)</td>
<td>- Check kidney function prior to each dose of immunotherapy</td>
</tr>
<tr>
<td></td>
<td>- Grade 2 (Moderate)</td>
<td>- Abdominal or pelvic disease that could be causing symptoms</td>
<td>- Continue assessing for nephrotoxic medications over the treatment course</td>
</tr>
<tr>
<td></td>
<td>- Grade 3 (Severe)</td>
<td>- Prior history of renal compromise?</td>
<td>- Educate patients that new urinary symptoms should be reported immediately</td>
</tr>
<tr>
<td></td>
<td>- Grade 4 (Potentially Life-Threatening)</td>
<td>- Other immune-related adverse effects?</td>
<td>- 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</td>
</tr>
<tr>
<td></td>
<td>- Grade 5 (Death)</td>
<td>- Presence of current or prior immune-mediated toxicities, including rhabdomyolysis</td>
<td>- Educate patients and family about the rationale for discontinuation of immunotherapy in patients who develop severe nephritis</td>
</tr>
</tbody>
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**Definition:** A disorder characterised by the acute loss of renal function and is traditionally classified as pre-renal, renal, and post-renal.

- Does the patient appear uncomfortable?
- Does the patient look ill?
- Current or recent use of nephrotoxic medications
- Early intervention to maintain or improve physical function and impact on QOL

- Urinary tract infection?
- Pyelonephritis?
- Nausea?
- Urinary frequency?
- Urinary urgency?
- Frequency?
- How much fluid is the patient taking in?
- Are associated symptoms present?
- Odynophagia?
- Melena?
- Shortness of breath?
- Are there symptoms concerning for:
  - Urinary tract infection?
  - Pyelonephritis?
  - Worsening CHF?

- Consider antimicrobial prophylaxis
- Consider additional antiviral and antifungal coverage
- Close follow-up in person or by phone, based on individual need & symptomatology

- 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
- Anticipate increase in corticosteroid dosing (i.e., treat as if Grade 3 nephritis) if creatinine does not improve within 48–72 hours
- Anticipate use of additional supportive care medications
- Upon symptom resolution to patient’s baseline, or Grade 1, begin to taper corticosteroid dose slowly over 1 month

| Pathology abnormalities (elevated creatinine, electrolyte abnormalities) |
| - Antibiotics |
| - Contrast media or other nephrotoxic agents (contrast dye, aminoglycosides, PPI)? |

- Steroid taper instructions/calculator as a guide but not an absolute
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- Consider antimicrobial prophylaxis
- Consider additional antiviral and antifungal coverage
- Avoid alcohol, acetaminophen, or other hepatotoxic agents
- If extended steroid use, risk for osteoporosis; initiate calcium and vitamin D supplements

Otherwise:

- Consider hospice if end-of-life care is appropriate for the patient and family

- Does the patient look ill?
- Does the patient appear uncomfortable?

- Current or recent use of nephrotoxic medications

- Early intervention to maintain or improve physical function and impact on QOL

- Urinary tract infection?
- Pyelonephritis?
- Nausea?
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