Care Step Pathway – Renal Toxicity (nephritis [inflammation of the kidneys] or acute kidney injury [AKI])

Assessment

Look:
- Does the patient appear uncomfortable?
  - Abdominal or pelvic pain?
- Nausea and/or vomiting?
- Does the patient look ill?
- Fluid retention: face, abdomen, extremities
- Sudden weight gain
- Changes in blood pressure, mental status changes (drowsiness)

Listen:
- Has there been change in urination?
  - Is urine dark or cloudy?
  - Increased frequency?
- How much fluid is the patient taking in?
- 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, (aminoglycosides, PPIs)?

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

Grading Toxicity

AKI, Elevated Creatinine

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

Grade 1 (Mild)	Grade 2 (Moderate)	Grade 3 (Severe)	Grade 4 (Potentially Life-Threatening)	Grade 5 (Death)
Creatinine increased >ULN - 1.5 X ULN	Creatinine >1.5–3.0 X baseline; >1.5–3.0 X ULN	Creatinine >3.0 X baseline; >3.0–6.0 X ULN	Creatinine >6.0 X ULN; life-threatening consequences; dialysis indicated	

Management

Overall Strategy
- Identify risk factors for ICI related injury: low baseline GFR and medications, use of PPIs (can induce an allergic immune response)
- Assess for common causes of AKI: volume depletion, infection, recent IV contrast
- Eliminate potentially nephrotoxic medications
- 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

Mild Elevation in Creatinine (Grade 1)
- Consider holding ICI therapy; essential to assess for other potential causes
- Perform detailed review of concomitant medications (prescribed and OTC), herbals, vitamins, anticipating possible discontinuation of nephrotoxic agents (PPIs, NSAIDs)
- Avoid/minimize addition of nephrotoxic agents, consider pre/post hydration for contrasted imaging studies
- Anticipate close monitoring of creatinine and urine protein (i.e., weekly)
- Consider nephrology consult for persistent G1
- 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)
- Hold ICI therapy; evaluate for other possible causes, immunosuppressive medications to be initiated to treat immune- mediated nephritis or AKI
  - Systemic corticosteroids* (e.g., prednisone or equivalent) 0.5–1 mg/kg/day until symptoms improve G1 or baseline followed by slow taper over at least 1 month
  - Anticipate increase in corticosteroid dosing if worsening or persistent G2 (i.e., treat as if Grade 3 nephritis) if creatinine does not improve within 1 week
  - Anticipate use of additional supportive care medications
- Consider resuming ICI therapy once steroids have been tapered to <10 mg/d or discontinued
- Anticipatory guidance on proper administration
- Anticipate the use of IV fluid to ensure adequate hydration
- Anticipate that nephrology consultation may be initiated by provider
- Assess patient and family understanding of recommendations and rationale
- Identify barriers to adherence

Severe (Grade 3) or Potentially Life-Threatening (Grade 4)
- Permanently discontinue ICI therapy
- Consider hospital admission
- Immunosuppressive medications to be initiated to treat immune-mediated nephritis/AKI
  - Systemic corticosteroids (e.g., prednisone or equivalent 1–2 mg/kg/day) until symptoms improve to G1 or baseline and then slow taper over at least 1 month
  - If creatinine > G2 after 1 week, additional immunosuppressive medications will be considered (e.g., azathioprine, cyclophosphamide, infliximab, mycophenolate mofetil)
- Anticipate nephrology consultation will be initiated by provider
- Anticipate that renal biopsy will be considered
- Hemodialysis may be considered

Implementation:
- Identify individuals with pre-existing renal dysfunction prior to initiating immunotherapy. Ensure baseline creatinine has been obtained, consider baseline UA and quantification of proteinuria or microalbuminuria. If present, 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

***Administering Corticosteroids:**

Corticosteroid 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 and symptomatology
- Corticosteroids may cause indigestion; provide antacid therapy daily as gastric ulcer prevention while on corticosteroids (e.g., proton pump inhibitor or H2 blocker if prednisone dosage is >20 mg/day)
- Review corticosteroid 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 and report them (taper may need to be adjusted)

Long-term high-dose corticosteroids:
- Consider antimicrobial prophylaxis (sulfamethoxazole/trimethoprim double dose M/W/F; single dose if used daily) or alternative if sulfa-allergic (e.g., atovaquone [Mepron®] 1500 mg po daily)
- Consider additional antiviral and antifungal coverage
- If extended corticosteroid use, risk for osteoporosis; initiate calcium and vitamin D supplements
- Patients with asthma or who smoke may have decreased sensitivity to corticosteroids

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 = activities of daily living; CHF = congestive heart failure; GFR = glomerular filtration rate; ICI = immune checkpoint inhibitor; NSAIDs = nonsteroidal anti-inflammatory drugs; OTC = over the counter; po = by mouth; PPI = proton pump inhibitor; QOL = quality of life; UA = urinalysis; ULN = upper limit of normal.