Care Step Pathway – Nephritis (inflammation of the kidneys)

Assessment

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

Listen:
- Has there been change in urination?
  - Urine colour?
  - 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 (contrast dye, aminoglycosides, PPI)?

Recognise:
- Pathology abnormalities (elevated creatinine, electrolyte abnormalities)
- Urinalysis abnormalities (casts)
- 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?

Grading 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.

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

Management

Overall Strategy
- Evaluate to exclude other causes of renal injury, including infection, disease progression, dehydration (common), and recent IV contrast
- Eliminate potentially nephrotoxic medications
- Early intervention to maintain or improve physical function and impact on QOL

Mild elevation in creatinine (Grade 1)
- Anticipate immunotherapy to continue
- Perform detailed review of concomitant medications (prescribed and OTC), herbals, 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
- Order urinalysis for casts and protein
- 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
  - 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
- Anticipatory guidance on proper administration
- Anticipate the use of IV fluid to ensure adequate hydration
- Anticipate that nephrology consultation may be initiated by provider
- Consider renal biopsy
- 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
- Ipilimumab to be discontinued for any Grade 3/4 event
- Consider hospital admission
- Immunosuppressive medications to be initiated to treat immune-mediated nephritis
  - Urgent administration of corticosteroid therapy (IV methylprednisolone 1-2 mg/kg/day (up to 1g) for 3 days followed by high-dose oral prednisolone 1-2 mg/kg/day or equivalent)
  - If symptoms do not improve within 48–72 hours, consider noncorticosteroid 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
- 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:**

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, 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 hepatoxins
- 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 = 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.