

Care Step Pathway – Nephritis (inflammation of the kidneys)

Assessment

Look:

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

Listen:

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

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?

Grading Toxicity

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.

Grade 1 (Mild)

Creatinine increased >ULN - 1.5 X ULN

Grade 2 (Moderate)

Creatinine >1.5–3.0 X baseline;
>1.5–3.0 X ULN

Grade 3 (Severe)

Creatinine >3.0 X baseline;
>3.0–6.0 X ULN

Grade 4 (Potentially Life-Threatening)

Creatinine >6.0 X ULN; life-threatening consequences; dialysis indicated

Grade 5 (Death)

Management

Overall Strategy

- Assess for other etiologies such as dehydration (common), infection, and recent IV contrast
- Eliminate potentially nephrotoxic
- 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)

- 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
- 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
 - o 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
 - o Anticipate increase in corticosteroid dosing (i.e., treat as if Grade 3 nephritis) if creatinine does not improve within 48–72 hours
 - o 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
- 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
 - o Corticosteroids (e.g., prednisone 1–2 mg/kg/day, in divided doses) until symptoms improve to baseline and then slow taper over at least 1 month
 - o If symptoms do not improve within 48–72 hours, additional immunosuppressive medications will be considered (e.g., azathioprine, cyclophosphamide, cyclosporine, 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
- 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 (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
- 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.