DISCLAIMER:
This algorithm has been developed for MD Anderson using a multidisciplinary approach considering circumstances particular to MD Anderson’s specific patient population, services and structure, and clinical information. This is not intended to replace the independent medical or professional judgment of physicians or other health care providers in the context of individual clinical circumstances to determine a patient’s care. This algorithm should not be used to treat pregnant women.

EVALUATION AND MANAGEMENT OF SUSPECTED IMMUNE-MEDIATED NEPHRITIS

Department of Clinical Effectiveness V2
Approved by the Executive Committee of the Medical Staff on 05/16/2023

Patient presents with increased serum creatinine (SCr) after immune checkpoint inhibitor (ICI) initiation and up to 12 months after last dose of immunotherapy.

**PRESENTATION**

**ASSESSMENT**

- Laboratory evaluation: CBC with differential, basic metabolic panel (BMP), cytokine 3 assay, urinalysis (UA), urine electrolytes, spot protein to creatinine ratio, urine eosinophils
- Consider non-ICI related AKI
  - Pre-renal/obstruction: check for presence of Foley and obtain renal ultrasound
  - Infection/sepsis
  - Presence of nephrotoxins: previous history of antibiotics, IV contrast, NSAID and/or PPI use, current nephrotoxic chemotherapies

Is the AKI based on non-ICI related AKI?

**TREATMENT**

- Initiate appropriate treatments based on determined non-ICI related etiology
- Hold immunotherapy and order the following:
  - Nephrology consult/referral
  - Laboratory evaluation:
    - Inpatient: Daily BUN, SCr, and electrolytes
    - Outpatient: Weekly BUN, SCr, electrolytes, UA, and spot urine protein/creatinine ratio
  - If hematuria and/or proteinuria present, consider ICI-induced etiologies such as vasculitis and glomerulonephritis by checking the following serologies, in addition to obtaining a kidney biopsy:
    - ANA, double stranded DNA, RF, C3, C4, ANCA, anti-GBM, hepatitis B and C, HIV, RPR, SPEP, UPEP, IFE

AKI = acute kidney injury
ANA = antinuclear antibody
ANCA = antineutrophil cytoplasmic antibodies
Anti-GBM = anti-glomerular basement membrane
C3 = complement component 3
C4 = complement component 4
NSAID = nonsteroidal anti-inflammatory drugs
PPI = proton pump inhibitor
RF = rheumatoid factor
RPR = rapid plasma reagin
SPEP = serum protein electrophoresis
UPEP = urine protein electrophoresis
IFE = immunofixation electrophoresis

---

1 Refer to AKI grading chart, see Appendix A
2 PD-1 inhibitors (pembrolizumab, nivolumab, cemiplimab), PD-L1 inhibitors (atezolizumab, avelumab, durvalumab), CTLA-4 inhibitor (ipilimumab, tremelimumab)
Evaluation and Management of Suspected Immune-Mediated Nephritis

Disclaimer: This algorithm has been developed for MD Anderson using a multidisciplinary approach considering circumstances particular to MD Anderson's specific patient population, services and structure, and clinical information. This is not intended to replace the independent medical or professional judgment of physicians or other health care providers in the context of individual clinical circumstances to determine a patient's care. This algorithm should not be used to treat pregnant women.

**IMMUNE-MEDIATED AKI GRADE**

<table>
<thead>
<tr>
<th>Grade 1</th>
<th>(SCr 1.5 times above the baseline)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Improvement seen in SCr?</td>
<td>Repeat BMP in 3-7 days</td>
</tr>
</tbody>
</table>

| Grade 2 | (SCr > 1.5-3 times above baseline) and Grade 3 | (SCr > 3 times the baseline) |
|---------|-----------------------------------------------|
| Grade 4 | (SCr > 6 times the baseline) |

**TREATMENT**

- **SCr returns to baseline:**
  - Continue to monitor labs with each cycle of immunotherapy
  - Resume immunotherapy
    - Order with each cycle: UA, urine/protein ratio, cytokine 3 panel, urine eosinophil, BMP

- **SCr continues to increase:**
  - Order kidney biopsy even if no WBC or RBC found in the urine (i.e., bland urine)

**Note:** Evaluate the risks and benefits of a kidney biopsy with the patient and the oncology team, especially with patients with a solitary kidney. In addition, coordinate with the oncology team if the patient is on anti-VEGF treatments and/or anticoagulation to be held prior to the biopsy to decrease the risk of bleeding.

anti-VEGF = anti-vascular endothelial growth factor

1 Refer to AKI grading chart, see Appendix A

Department of Clinical Effectiveness V2
Approved by the Executive Committee of the Medical Staff on 05/16/2023
Evaluation and Management of Suspected Immune-Mediated Nephritis

Disclaimer: This algorithm has been developed for MD Anderson using a multidisciplinary approach considering circumstances particular to MD Anderson’s specific patient population, services and structure, and clinical information. This is not intended to replace the independent medical or professional judgment of physicians or other health care providers in the context of individual clinical circumstances to determine a patient's care. This algorithm should not be used to treat pregnant women.

BIOPSY RESULT

Acute interstitial nephritis (AIN) with or without acute tubular necrosis (ATN) → If not started, start steroid treatment
- Start prednisone 0.5-1 mg/kg/day, if not already started. Once SCr starts to improve, start taper over 2-4 weeks.
- Weekly labs (outpatient) while on steroid treatment

Glomerulonephritis (GN) (SLE, MC, FSGS, MN, IgA without crescentic changes) → Start prednisone 1 mg/kg (maximum dose 80 mg/day)
- Rituximab* 375 mg/m² IV weekly for 4 doses or 1,000 mg IV flat dose 2 weeks apart for 2 doses
- After initial rituximab dose, start prednisone taper over 1-2 months to 5 mg, based on response

Pauci-immune GN (ANCA positive**/ANCA negative), crescentic GN, and anti-GBM → Start prednisone 1 mg/kg (maximum dose 80 mg/day)
- Rituximab* 375 mg/m² IV weekly for 4 doses or 1,000 mg IV flat dose 2 weeks apart for 2 doses
- After initial rituximab dose, start prednisone taper over 1-2 months to 5 mg, based on response

TREATMENT

Increase in SCr? Yes
- Consider infliximab† 5 mg/kg IV for one dose
- Increase prednisone back to initial dose (0.5-1 mg/kg/day) and start taper over two weeks after dose of infliximab
- If contraindication to infliximab or no response, consider mycophenolate 500 mg PO every 12 hours and titrate over 2 weeks to 1 gm PO every 12 hours and continue for a maximum of 3 months, based on response
- Resume immunotherapy after completion of prednisone taper and SCr stabilizes
- Weekly labs † (outpatient) once a month to ensure stability
  - Continue labs while on immunotherapy and up to 6 months after last dose of immunotherapy

No
- Resume immunotherapy after completion of prednisone taper and SCr stabilizes
- Weekly labs † (outpatient) once a month to ensure stability
  - Continue labs while on immunotherapy and up to 6 months after last dose of immunotherapy

- Consider other immunosuppressive options per Kidney Disease; Improving Global Outcomes (KDIGO) guidelines if relapse or any contraindications to rituximab
- Refer to Nephrology for resumption of immunotherapy

1. Labs: electrolytes, BUN, SCr
2. Follow TNF-alpha every 2 weeks if coincides with increase in SCr after initial dose; can re-dose in 2-4 weeks
3. Screening tests to be performed prior to starting infliximab: quantiFERON-TB gold (QFT-GIT) or T-SPOT TB test to screen for latent TB infection and hepatitis B panel. Consider screening for fungal infections, if indicated.
4. See Appendix B for Contraindications to Infliximab or Rituximab
5. Review hepatitis B panel; consult/refer to Infectious Diseases if positive core Ab
6. Start PCP prophylaxis for patients on high dose steroids and starting rituximab; avoid sulfamethoxazole/trimethoprim as an option.
7. Follow Anti-PLA2R if positive for response and ANCA serologies if positive
8. If already on prednisone, switch to methylprednisolone after biopsy confirmation
9. Hold plasmapheresis after rituximab dose to avoid removal of drug

* ANCA = antineutrophil cytoplasmic antibodies
† FSGS = focal segmental glomerulosclerosis
‡ ANCA = antineutrophil cytoplasmic antibodies
§ MC = minimal change disease
∥ MN = membranous nephropathy
© SLE = systemic lupus erythematosus

Copyright 2023 The University of Texas MD Anderson Cancer Center

Department of Clinical Effectiveness V2
Approved by the Executive Committee of the Medical Staff on 05/16/2023
APPENDIX A: Grades of Immune-Mediated AKI

<table>
<thead>
<tr>
<th>Determine Grade (G) of AKI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 1 (G1): creatinine 1.5 times above the baseline</td>
</tr>
<tr>
<td>Grade 2 (G2): creatinine &gt; 1.5-3 times above the baseline</td>
</tr>
<tr>
<td>Grade 3 (G3): creatinine &gt; 3 times the baseline</td>
</tr>
<tr>
<td>Grade 4 (G4): creatinine &gt; 6 times the baseline</td>
</tr>
</tbody>
</table>

APPENDIX B: Contraindications to Infliximab and Rituximab

**Contraindications to infliximab**
- Tuberculosis exposure
- Hepatic impairment
- Heart failure

**Contraindication to rituximab**
- Hepatitis B exposure
SUGGESTED READINGS


Disclaimer: This algorithm has been developed for MD Anderson using a multidisciplinary approach considering circumstances particular to MD Anderson’s specific patient population, services and structure, and clinical information. This is not intended to replace the independent medical or professional judgment of physicians or other health care providers in the context of individual clinical circumstances to determine a patient's care. This algorithm should not be used to treat pregnant women.

DEVELOPMENT CREDITS

This practice consensus statement is based on majority opinion of the Nephritis experts at the University of Texas MD Anderson Cancer Center for the patient population. These experts included:

Core Development Team Leads
Ala Abudayyeh, MD (Nephrology)
Jamie Lin, MD (Nephrology)
Omar Mamlouk, MBBS (Nephrology)

Workgroup Members
Adi Diab, MD (Melanoma Medical Oncology)
Khalid Elsayes, MD (Abdominal Imaging)
Wendy Garcia, BS*
Amy Pai, PharmD*
Amishi Shah, MD (Genitourinary Medical Oncology)
Bilal Siddiqui, MD (Genitourinary Medical Oncology)
Sumit Subudhi, MD, PhD (Genitourinary Medical Oncology)
Cassian Yee, MD (Melanoma Medical Oncology)

*Clinical Effectiveness Development Team