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.

**PRESENTATION**

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

**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 reversible etiologies of 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

**TREATMENT**

- Initiate appropriate treatments based on determined reversible etiology

  - No
  - Hold immunotherapy and order the following:
    - Nephrology consult/referral
    - Logistics evaluation:
      - Inpatient: Daily BUN, SCR, and electrolytes
      - Outpatient: Weekly BUN, SCR, and electrolytes
    - 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

- Yes

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)

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**IMMUNE-MEDIATED AKI GRADE**

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
<th>TREATMENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(Scr 1.5 times the baseline)</td>
<td>Repeat BMP in 3-7 days</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Improvement seen in Scr?</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td></td>
<td>No</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Scr returns to normal:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Continue to monitor labs after each cycle of immunotherapy</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Resume immunotherapy</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Order prior to each cycle: UA, urine/protein ratio, cytokine 3 panel, urine eosinophil, BMP</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Scr continues to increase:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Order kidney biopsy even if no WBC or RBC found in the urine (i.e., bland urine)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>See Page 3 for treatment based on biopsy results</td>
</tr>
<tr>
<td>2</td>
<td>(Scr &gt; 1.5-3 times above baseline)</td>
<td>Continue to hold immunotherapy</td>
</tr>
<tr>
<td></td>
<td></td>
<td>See Page 3 for treatment based on biopsy results</td>
</tr>
<tr>
<td>3</td>
<td>(Scr &gt; 3 times the baseline) and Grade 4</td>
<td>Continue to hold immunotherapy</td>
</tr>
<tr>
<td></td>
<td></td>
<td>See Page 3 for treatment based on biopsy results</td>
</tr>
</tbody>
</table>

**NOTES**

- Prednisone 0.5-1 mg/kg/day
- Kidney biopsy to be performed within 3 days of steroid initiation (even in the setting of bland urine)
- If kidney biopsy unable to be performed, defer to Nephrology for further management
  - Order weekly labs to follow response to steroids: UA, urine protein/creatinine ratio, cytokine 3 panel, urine eosinophil, BMP
- Prednisone 0.5-1 mg/kg/day
- Kidney biopsy to be performed within 3 days of steroid initiation (even in the setting of bland urine)
- If kidney biopsy unable to be performed, defer to Nephrology for further management
  - Order weekly labs to follow response to steroids: UA, urine protein/creatinine ratio, cytokine 3 panel, urine eosinophil, BMP

**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
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**BIOPSY RESULT**

- Acute interstitial nephritis (AIN) with lymphocytic infiltration with or without eosinophils with or without granulomas **and**
- Acute tubular necrosis (ATN)
- Glomerulonephritis (GN)
  - (SLE, MC, FSGS, MN, IgA)
  - without crescentic changes
- Pauci-immune GN
  - (ANCA positive^6^/ANCA negative), crescentic
  - GN, and anti-GBM

**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^1^ (outpatient) while on steroid treatment

For Contraindications to Infliximab or Rituximab

- Consider infliximab^2^3^3^ 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^3^ 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^1^ (outpatient) once a month to ensure stability
  - Continue labs while on immunotherapy and up to 6 months after last dose of immunotherapy

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Consider other immunosuppressive options per Kidney Disease; Improving Global Outcomes (KDIGO) guidelines if relapse or any contraindications to rituximab^4^.

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

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ANCA = antineutrophil cytoplasmic antibodies
FSGS = focal segmental glomerulosclerosis
MC = minimal change disease
MN = membranous nephropathy
SLE = systemic lupus erythematosus

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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 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

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**SUGGESTED READINGS**


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