THE UNIVERSITY OF TEXAS MD Anderson Cancer Center
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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)[1] after immune checkpoint inhibitor (ICI) initiation and up to 12 months after last dose of immunotherapy[2]

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

Yes → Initiate appropriate treatments based on determined non-ICI related etiology

No → 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

Treatment based on immune-mediated AKI grading[1], see Page 2

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)

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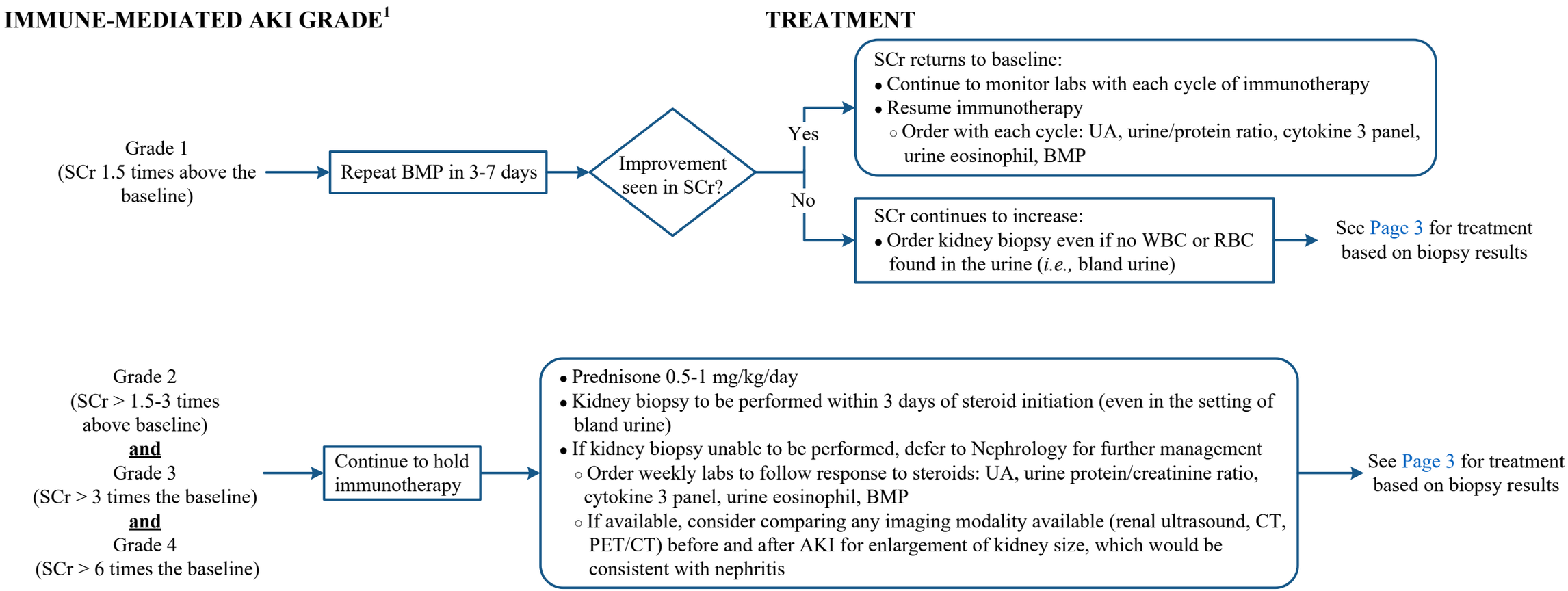

anti-VEGF = anti-vascular endothelial growth factor

[1] Refer to AKI grading chart, see Appendix A

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.

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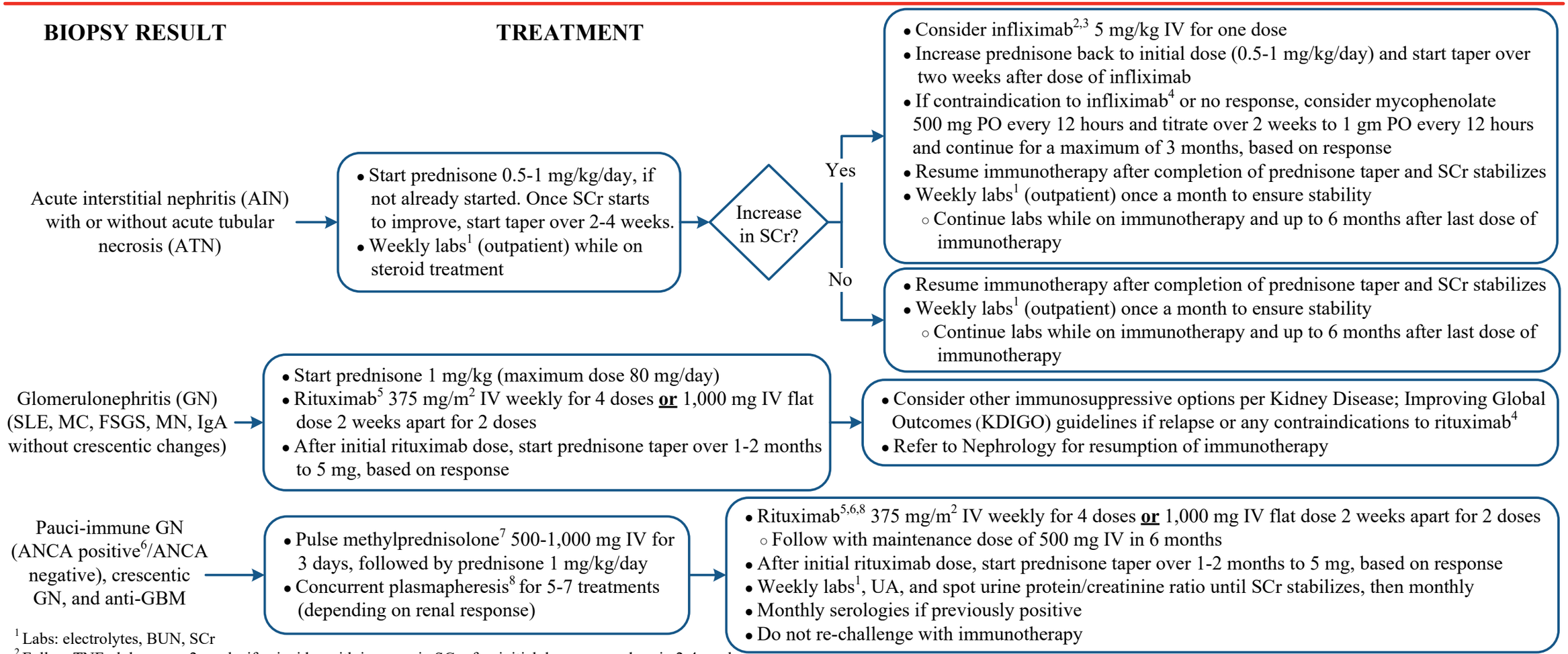

[1] Labs: electrolytes, BUN, SCr
[2] Follow TNF-alpha every 2 weeks if coincides with increase in SCr after initial dose; can re-dose in 2-4 weeks
[3] Screening tests to be performed prior to starting infliximab: quantiFERON-TB gold (QFT-GIT) or T-SPOT TB test to screen for latent TB infection and hepatitis 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
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

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

Determine Grade (G) of AKI

- Grade 1 (G1): creatinine 1.5 times above the baseline
- Grade 2 (G2): creatinine > 1.5-3 times above the baseline
- Grade 3 (G3): creatinine > 3 times the baseline
- Grade 4 (G4): creatinine > 6 times the baseline

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

Abudayyeh, A., Abdelrahim, M., & Albiges, L. (2019). Renal toxicities associated with immune checkpoint inhibitors. In M. S. Ernstoff, I. Puzanov, C. Robert, A. Diab, & P. Hersey (Eds.), *SITC's Guide to Managing Immunotherapy Toxicity* (pp. 171-183). DemosMedical, Springer Publishing. https://doi.org/10.1891/9780826172150.0012

Awiwi, M. O., Abudayyeh, A., Abdel-Wahab, N., Diab, A., Gjoni, M., Xu, G., . . . Elsayes, K. (2023). Imaging features of immune checkpoint inhibitor-related nephritis with clinical correlation: A retrospective series of biopsy-proven cases. *European Radiology, 33*(3), 2227-2238. https://doi.org/10.1007/s00330-022-09158-8

Brahmer, J. R., Lacchetti, C., Schneider, B. J., Atkins, M. B., Brassil, K. J., Caterino, J. M., . . . Thompson, J. A. (2018). Management of immune-related adverse events in patients treated with immune checkpoint inhibitor therapy: American Society of Clinical Oncology Clinical Practice Guideline. *Journal of Clinical Oncology, 36*(17), 1714-1768. https://doi.org/10.1200/JCO.2017.77.6385

Cortazar, F. B., Kibbelaar, Z. A., Glezerman, I. G., Abudayyeh, A., Mamlouk, O., Motwani, S. S., . . . Leaf, D. E. (2020). Clinical features and outcomes of immune checkpoint inhibitor-associated AKI: A multicenter study. *Journal of the American Society of Nephrology, 31*(2), 435-446. https://doi.org/10.1681/ASN.2019070676

Haanen, J. B. A. G., Carbonnel, F., Robert, C., Kerr, K. M., Peters, S., Larkin, J., & Jordan, K. (2017). Management of toxicities from immunotherapy: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Annals of Oncology, 28*(Suppl 4), iv119–iv142. https://doi.org/10.1093/annonc/mdx225

KDIGO Clinical Practice Guideline. (2020). *Glomerular Diseases* (KDIGO Guideline June 2020). Retrieved from https://kdigo.org/wp-content/uploads/2017/02/KDIGO-GN-GL-Public-Review-Draft_1-June-2020.pdf

Lee, M. D., Seethapathy, H., Strohbehn, I. A., Zhao, S. H., Boland, G. M., Fadden, R., . . . Sise, M. E. (2021). Rapid corticosteroid taper versus standard of care for immune checkpoint inhibitor induced nephritis: A single-center retrospective cohort study. *Journal for Immunotherapy of Cancer, 9*(4), e002292. https://doi.org/10.1136/jitc-2020-002292

Lin, J. S., Mamlouk, O., Selamet, U., Tchakarov, A., Glass, W. F., Sheth, R. A., . . . Abudayyeh, A. (2021). Infliximab for the treatment of patients with checkpoint inhibitor–associated acute tubular interstitial nephritis. *OncoImmunology*, *10*(1), 1877415. https://doi.org/10.1080/2162402X.2021.1877415

Lin, J. S., Wang, D. Y., Mamlouk, O., Glass, W. F., Abdelrahim, M., Yee, C., & Abudayyeh, A. (2020). Immune checkpoint inhibitor associated reactivation of primary membranous nephropathy responsive to rituximab. *Journal of ImmunoTherapy of Cancer, 8*(2), e001287. https://doi.org/10.1136/jitc-2020-001287

Mamlouk, O., Lin, J., Abdelrahim, M., Tchakarov, A., Glass, W., Selamet, U., . . . Abudayyeh, A. (2020). Checkpoint inhibitor-related renal vasculitis and use of rituximab. *Journal for Immunotherapy of Cancer, 8*(2), e000750. https://doi.org/10.1136/jitc-2020-000750

Mamlouk, O., Selamet, U., Machado, S., Abdelrahim, M., Glass, W. F., Tchakarov, A., . . . Abudayyeh, A. (2019). Nephrotoxicity of immune checkpoint inhibitors beyond tubulointerstitial nephritis: Single-center experience. *Journal for ImmunoTherapy of Cancer, 7*(1), 2. https://doi.org/10.1186/s40425-018-0478-8

National Comprehensive Cancer Network. (2023). *Management of Immunotherapy-Related Toxicities* (NCCN Guideline Version 1.2023). Retrieved from https://www.nccn.org/professionals/physician_gls/pdf/immunotherapy.pdf

Ratanasrimetha, P., Reddy, V. D., Kala, J., Tchakarov, A., Glass, W. F., Msaouel, P., & Lin, J. S. (2022). Case Report: Successful treatment of late-onset immune checkpoint inhibitor-associated membranous nephropathy in a patient with advanced renal cell carcinoma. *Frontiers in Immunology*, *13*, 898811. https://doi.org/10.3389/fimmu.2022.898811

Seethapathy, H., Zhao, S., Chute, D. F., Zubiri, L., Oppong, Y., Strohbehn, I., . . . Sise, M. E. (2019). The incidence, causes, and risk factors of acute kidney injury in patients receiving immune checkpoint inhibitors. *Clinical Journal of the American Society of Nephrology, 14*(12), 1692-1700. https://doi.org/10.2215/CJN.00990119

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