Immune Checkpoint Inhibitor Nephrotoxicity: Update 2020

Shruti Gupta,1 Frank B. Cortazar,2,3 Leonardo V. Riella,1 and David E. Leaf1

Abstract
Immune checkpoint inhibitors (ICPIs) have transformed the landscape of oncology, but are associated with a variety of autoimmune adverse events, including AKI. ICPI-associated AKI (ICPI-AKI) is emerging as an increasingly frequent cause of AKI in patients with cancer, and poses unique diagnostic and management challenges to clinicians who care for these patients. In this review, we describe the incidence and risk factors for ICPI-AKI, including proton pump inhibitor use, CKD, and combination immunotherapy. We discuss the limitations of the various definitions used for ICPI-AKI in prior studies, and propose a novel classification system (definite, probable, and possible ICPI-AKI) that recognizes the diagnostic uncertainty inherent in many cases. We discuss the key clinicopathologic features and treatment strategies for ICPI-AKI, including the role of kidney biopsy versus empirical treatment with steroids. We also explore the under-studied area of ICPI use in the setting of solid organ transplantation, where nephrologists and oncologists must balance the risk of rejection versus treating the underlying malignancy. Finally, we summarize existing data on the role of ICPI rechallenge after an episode of ICPI-AKI.

How Is ICPI-AKI Defined?
Initial case reports and small case series of ICPI-AKI were based exclusively on biopsy-proven findings (15–17). However, because patients are increasingly diagnosed and treated for ICPI-AKI according to clinical features alone, there is a need for standardization of definitions across studies. The National Cancer Institute’s Common Terminology Criteria for Adverse Events defines AKI, in part, by comparing changes in serum creatinine (SCr) to the “upper limit of normal” (18). However, patients with cancer often have decreased muscle mass and these definitions may therefore be insensitive to relatively large increases in SCr that fall within the “normal range.” In contrast, the Kidney Disease: Improving Global Outcomes Work Group (KDIGO) consensus criteria define AKI according to relative changes in SCr (Table 2) (19). Even among studies that use the KDIGO criteria to define ICPI-AKI, some define ICPI-AKI as any stage (20), whereas others include only stage 2 or higher (21). Thus, there is a need for harmonization of definitions of ICPI-AKI across studies (discussed further below). Additionally, for all definitions of ICPI-AKI, it is

1Division of Renal Medicine, Brigham and Women’s Hospital, Boston, Massachusetts; 2New York Nephrology Vasculitis and Glomerular Center, Albany, New York; and 3Division of Nephrology, Massachusetts General Hospital, Boston, Massachusetts

Correspondence: Dr. Shruti Gupta, Brigham and Women’s Hospital and Harvard Medical School, 75 Francis Street, MRB-4, Boston, MA 02115. Email: Sgupta21@bwh.harvard.edu

Review Article

KIDNEY360 1: 130–140, 2020. doi: https://doi.org/10.34067/KID.0000852019
critical that the renal injury be directly attributable to the ICPI and not to an alternative etiology.

### What Is the Incidence of ICPI-AKI?

Reliable data on the incidence of ICPI-AKI are scarce. We estimated the incidence of ICPI-AKI using pooled data from all phase 2 and 3 clinical trials published between 2014 and 2015 that included at least 100 patients treated with ICPIs (15). In this combined analysis of 3695 patients, the overall incidence of ICPI-AKI was 3%; the incidence among patients receiving combination ICPI therapy was 5%; and the incidence of severe AKI, defined as an increase in SCR more than threefold above baseline, an increase in SCR to >4.0 mg/dl, or the need for RRT, was 0.6% (15). A more recent meta-analysis of 48 clinical trials that included 11,482 patients reported similar findings, with an estimated incidence of ICPI-AKI of 2% (22). Although clinical trial data may not reflect the true incidence of ICPI-AKI, Seethapathy et al. (20) examined the incidence of ICPI-AKI in a real-world setting of 1843 patients treated at a single large academic center, and determined the incidence to be 3%, consistent with earlier estimates.

### What Are Possible Mechanisms of ICPI-AKI?

The precise mechanisms of ICPI-AKI are poorly understood, with hypotheses about its pathogenesis largely derived from data on extrarenal irAEs or from mouse models. Mutated mice that lack coinhibitory molecules such as PD-1 or CTLA-4 may develop autoimmunity against specific organs, which is driven by the emergence of antigen-specific T cells against self-antigens (23–25). Interestingly, the transfer of infiltrating T cells specific for a certain organ from one mouse to another leads to trafficking of those T cells to the same organ of origin, supporting the notion of antigen specificity of the response (25). Because self-reactive T cells are present in significant numbers in otherwise healthy humans (26,27), blockade of PD-1 or CTLA-4 with ICPIs may break self-tolerance and trigger an autoimmune response against a specific self-antigen on an organ like the kidney. The exact antigen is currently unknown, but is most likely expressed by tubular cells based on the dominant finding of acute tubulointerstitial nephritis (ATIN) on biopsy. An alternative hypothesis is that ICPI-associated ATIN occurs through loss of tolerance to effector T cells primed during prior drug exposure (e.g., proton pump inhibitors [PPIs]). A drug exposure may, in some cases, act as an exogenous antigen and trigger an immune response either by itself or after binding to tubular antigens and acting as haptens (28). Further mechanistic studies in kidney biopsies from patients treated with ICPIs may allow the determination of the specificity of the T-cell response and elucidation of the potential antigen target of the immune response in the kidneys.

### What Are the Key Clinical Features of ICPI-AKI?

Unfortunately, no clinical features reliably distinguish ICPI-AKI from alternative etiologies of AKI, although certain features are suggestive. Patients with ICPI-AKI often
Table 3. Summary of clinical characteristics of patients with immune checkpoint inhibitor–associated AKI

<table>
<thead>
<tr>
<th>Reference</th>
<th>n</th>
<th>Centers, n</th>
<th>Drugs Received</th>
<th>AKI Criteria</th>
<th>Time to AKI (wk)</th>
<th>Concomitant ATIN Medications, n (%)</th>
<th>Combined Therapy*, n (%)</th>
<th>Concomitant or Prior Extrarenal irAEs, n (%)</th>
<th>Pyuria or WBC Casts, n (%)</th>
<th>Biopsy, n (%)</th>
<th>ATIN, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shirali et al. (16)</td>
<td>6</td>
<td>1</td>
<td>Nivo, n=3; Pembro, n=2; Ipi and Nivo, n=1</td>
<td>Biopsy-proven ATIN</td>
<td>40</td>
<td>PPIs, n=33 (83); NSAIDs, n=2 (33)</td>
<td>1 (17)</td>
<td>3 (50)</td>
<td>5 (83)</td>
<td>6 (100)</td>
<td>6 (100)</td>
</tr>
<tr>
<td>Cortazar et al. (15)</td>
<td>13</td>
<td>7</td>
<td>Ipi, n=6; Nivo, n=1; Pembro, n=2; Ipi and Nivo, n=4</td>
<td>Biopsy-proven AKI</td>
<td>13</td>
<td>PPIs, n=6 (46); NSAIDs, n=1 (8)</td>
<td>4 (31)</td>
<td>8 (62)</td>
<td>8 (62)</td>
<td>13 (100)</td>
<td>12 (92)</td>
</tr>
<tr>
<td>Izzedine et al. (17)</td>
<td>12</td>
<td>1</td>
<td>Pembro, n=12</td>
<td>Biopsy-proven AKI</td>
<td>36</td>
<td>0</td>
<td>0*</td>
<td>NR</td>
<td>4 (33)</td>
<td>12 (100)</td>
<td>4 (33)</td>
</tr>
<tr>
<td>Mamlouk et al. (28)</td>
<td>16</td>
<td>1</td>
<td>Nivo, n=6; Pembro, n=6; Atezo, n=1; Treme, n=1; Ipi and Nivo, n=2</td>
<td>Biopsy-proven AKI</td>
<td>14</td>
<td>PPIs, n=9 (56); NSAIDs, n=3 (19)</td>
<td>13 (81)</td>
<td>9 (56)</td>
<td>7 (44)</td>
<td>16 (100)</td>
<td>14 (88)</td>
</tr>
<tr>
<td>Seethapathy et al. (20)</td>
<td>30</td>
<td>1</td>
<td>Ipi, n=12; Nivo, n=9; Pembro, n=7; Durva, n=1; Ipi and Nivo, n=1</td>
<td>SCr ≥1.5× baseline for ≥3 d; expert adjudicated</td>
<td>15</td>
<td>PPIs, n=23 (77); NSAIDs, n=13 (43)</td>
<td>3 (10)</td>
<td>26 (87)</td>
<td>13 (43)</td>
<td>1 (3)</td>
<td>1 (100)</td>
</tr>
<tr>
<td>Cortazar et al. (21)</td>
<td>138</td>
<td>18</td>
<td>Nivo, n=40; Pembro, n=47; Durva and pembro, n=1; Ipi, n=4; Atezo, n=5; Ipi and nivo, n=32; Ipi and pembro, n=6; Other combination tx, n=3</td>
<td>SCr ≥2× baseline or need for RRT</td>
<td>14</td>
<td>PPIs, n=75 (54); NSAIDs, n=30 (22)</td>
<td>28 (20)</td>
<td>59 (43)</td>
<td>76 (55)</td>
<td>60 (43)</td>
<td>56 (93)</td>
</tr>
<tr>
<td>Total*</td>
<td>215</td>
<td>21</td>
<td>Nivo, n=59; Pembro, n=76; Atezo, n=6; Durva, n=1; Ipi, n=22; Treme, n=1; Any combination tx, n=50</td>
<td>—</td>
<td>16</td>
<td>PPIs, n=146 (68); NSAIDs, n=49 (23)</td>
<td>49 (23)</td>
<td>105 (49)</td>
<td>113 (53)</td>
<td>108 (61)</td>
<td>93 (91)</td>
</tr>
</tbody>
</table>

ATIN, acute tubulointerstitial nephritis; irAEs, immune-related adverse events; WBC, white blood cell; nivo, nivolumab; pembro, pembrolizumab; ipi, ipilimumab; PPI, proton pump inhibitor; NSAID, nonsteroidal anti-inflammatory drug; NR, not recorded; atezo, atezolizumab; treme, tremelimumab; AKIN, Acute Kidney Injury Network (70); durva, durvalumab; SCr, serum creatinine; tx, treatment.

*From immune checkpoint inhibitor initiation, mean or median.

*This refers to combination therapy with a cytotoxic T lymphocyte–associated protein 4 inhibitor and a programmed cell death protein 1 (PD-1)/PD-ligand 1 inhibitor.

*Two patients with hypophysitis; one patient with concomitant rash.

*Seven patients had an irAE preceding AKI onset; one had one concomitantly.

*All patients were treated with pembrolizumab, although one patient had received ipilimumab in the past.

*Five irAEs before diagnosis; three at the time of diagnosis; one after the diagnosis.

*Concurrent irAEs; thyroiditis most common, occurring in 13 patients.

*Concurrent or prior irAE; rash most common.

*Weighted average, based on number of patients in each study.
What Are the Risk Factors for Development of ICPI-AKI?

In our multicenter study of 138 patients with ICPI-AKI, which included 276 unmatched control patients who received ICPIs contemporaneously but did not develop AKI, we identified three independent risk factors for development of ICPI-AKI: concomitant use of PPIs, combination treatment with anti–CTLA-4 and anti–PD-1/PD-L1 agents, and lower baseline eGFR (Figure 1) (21). Smaller studies have also implicated PPI use as a risk factor for ICPI-AKI (15,16,20), and PPI use is associated with an increased risk of ATIN in the general population (33). One possible explanation for the finding that PPI use increases the risk of ICPI-AKI is that T cells may be primed by prior exposure to drugs such as PPIs, and ICPIs reactivate these drug-specific latent T cells, leading to loss of tolerance. PPIs, along with other drugs known to cause ATIN such as nonsteroidal anti-inflammatory drugs, should thus be used with caution in patients receiving ICPIs, and should be discontinued in those who develop ICPI-AKI. Our finding that combination therapy is a risk factor for ICPI-AKI is not surprising because combination therapy is known to result in greater immune activation and a higher risk of irAEs in general (3,34–37). Given the heightened risk of ICPI-AKI associated with each of the above risk factors, patients receiving PPIs, those receiving combination ICPI therapy, and those with a lower baseline eGFR may warrant closer renal surveillance to detect ICPI-AKI earlier.

What Are the Histopathologic Features of ICPI-AKI?

ATIN is far by the most common histopathologic finding of ICPI-AKI on kidney biopsy (15,16,20,28). In our multicenter study, extrarenal irAEs occurred before or concomitantly with AKI in 43% of patients (16) to 62% (15). Thus, the presence of concomitant or prior extrarenal irAEs is an important clinical clue that should heighten suspicion for ICPI-AKI.

Figure 1. | PPI use lower baseline eGFR and combination treatment with anti–CTLA-4 and anti–PD-1/PD-L1 agents are independently associated with ICPI-AKI. Combined therapy refers to combination therapy with a cytotoxic T lymphocyte–associated protein 4 inhibitor and a programmed cell death protein 1 (PD-1)/PD-ligand 1 inhibitor. Ipilimumab/nivolumab was the combination therapy regimen in 75% of cases and 66% of controls. CKD was defined as a baseline (pre-treatment) eGFR <60 ml/min per 1.73 m². P values were calculated with the chi-squared test. Data from Cortazar et al. (21). PPI, proton pump inhibitor.
study, we defined ICPI-AKI as doubling of SCr or need for RRT (21). Additionally, the AKI had to have been attributed to the ICPI by the treating provider. Kidney biopsy was performed in 60 (43%) patients, 56 (93%) of whom had ATIN as the dominant lesion. Other pathologic entities have also been observed, including various glomerulonephritides (28,40). In one study of 16 patients with biopsy-proven ICPI-AKI, ATIN was present in 14 of the 16 cases, but co-occurred with glomerular disease in nine cases, including IgA nephropathy, pauci-immune GN, and other pathologies (28). Other small series have reported nephrotic syndrome with minimal change disease (41). These observations underscore the heterogeneity of histopathologic patterns of injury from ICPIs, as well as the immune activation seen in patients with ICPI-AKI, including both B cell–driven, autoantibody-mediated disease and T cell–driven lesions. These studies also highlight the importance of performing a kidney biopsy even in patients with a clinical history highly suggestive of ICPI-AKI.

**How Should Patients with Suspected or Confirmed ICPI-AKI be Treated?**

Glucocorticoids are the mainstay of treatment for ICPI-AKI (Table 4). Although no randomized placebo-controlled trial has ever established the efficacy of steroids for treatment of ICPI-AKI, observational data supporting the efficacy of steroids in this setting are quite strong: in our multicenter study, 103 of 119 patients (87%) treated with steroids had complete or partial renal recovery (21). Interestingly, although the route of administration, dose, and
duration of steroid treatment is highly variable across studies (15,16,28), we did not identify any differences in the steroid regimen between patients who achieved complete renal recovery versus those who did not (21). However, defining the optimal glucocorticoid regimen from retrospective data is challenging, because dosing is often confounded by severity of injury and response to treatment.

Other immunosuppressive agents have also been investigated in the setting of ICPI-AKI. Mycophenolate mofetil was used in seven patients with ICPI-AKI in our multicenter study; complete renal recovery was achieved in one patient, with partial recovery in the remaining six (21). Other agents that have been studied include rituximab and cyclophosphamide. Mamlouk and colleagues (28) observed a case of ATIN that was refractory to high-dose steroids but responded partially to infliximab. Two patients did not receive IS and had no renal recovery. Two cases had no renal recovery after prednisone, one of whom was also treated with infliximab. Two cases had no renal response; 3/16 died because of disease progression.

### Table 4. Renal outcomes among patients with immune checkpoint inhibitor–associated AKI

<table>
<thead>
<tr>
<th>Reference</th>
<th>Patients, n</th>
<th>Treatment with Steroids, n (%)</th>
<th>Renal Outcome Data</th>
<th>Rechallenge</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shirali et al. (16)⁴</td>
<td>6</td>
<td>5 (83)</td>
<td>4/5 patients treated with steroids had return of SCr back to baseline; one had an improvement from a peak SCr of 2.5 mg/dl to 1.3 mg/dl, but not back to baseline.</td>
<td>One patient rechallenged and had recurrence of AKI; one patient with ATIN continued on pembrolizumab</td>
</tr>
<tr>
<td>Cortazar et al. (15)⁵</td>
<td>13</td>
<td>11 (92)</td>
<td>9/10 patients with ATIN treated with steroids had complete or partial renal recovery. Two patients did not receive IS and had no renal recovery.</td>
<td>Two patients rechallenged without AKI</td>
</tr>
<tr>
<td>Izzedine et al. (17)⁶</td>
<td>12</td>
<td>7 (58)</td>
<td>10/12 patients had ICPIs stopped, of whom seven received steroids; one died because of disease progression, the other six had some renal recovery. 2/12 were continued on ICPIs, with some improvement in renal function.</td>
<td>One patient rechallenged with recurrence of ATIN</td>
</tr>
<tr>
<td>Mamlouk et al. (28)⁷</td>
<td>16</td>
<td>14 (88)</td>
<td>3/5 ATIN cases all had partial renal recovery after prednisone, one of whom was also treated with infliximab. Two cases had no renal response; 3/16 died because of disease progression.</td>
<td>NR; 13 survivors continued treatment</td>
</tr>
<tr>
<td>Seethapathy et al. (20)⁸</td>
<td>30</td>
<td>21 (70)</td>
<td>Of the 82 patients with sustained AKI, 54 (67%) died in the follow-up period, death occurred a median of 22 d (IQR 6–84) after the sustained AKI episode.</td>
<td>17 patients (57%) rechallenged, with nine developing recurrent AKI</td>
</tr>
<tr>
<td>Cortazar et al. (21)⁹</td>
<td>138</td>
<td>119 (86)</td>
<td>Complete, partial, and no renal recovery after ICPI-AKI occurred in 40%, 45%, and 15% of patients, respectively. Treatment with steroids associated with a 1.7 greater odds of renal recovery in multivariable models among biopsied patients. Patients with no renal recovery had higher mortality than those with complete or partial recovery.</td>
<td>22% of patients were rechallenged, with recurrent AKI in 23%</td>
</tr>
</tbody>
</table>

SCr, serum creatinine; PPI, proton pump inhibitor; ATIN, acute tubulointerstitial nephritis; IS, immunosuppression; ICPI, immune checkpoint inhibitor; NR, not recorded; IQR, interquartile range.

⁴Renal recovery not explicitly defined.
⁵Complete recovery defined as return of SCr to <0.35 mg/dl above the baseline value. Partial renal recovery defined as a return of SCr to >0.35 mg/dl but less than twice the baseline value, or liberation from RRT.
⁶Renal recovery not explicitly defined; six patients had a “favorable” renal recovery defined as 50% improvement in eGFR.
⁷Complete recovery defined as return of SCr to <0.35 mg/dl above the baseline value. Partial renal recovery defined as a return of SCr to >0.35 mg/dl but less than twice the baseline value.
⁸Renal recovery not explicitly defined.
⁹Complete recovery was defined as a return of SCr to <0.35 mg/dl of the baseline value, and partial recovery was defined as a return of SCr to >0.35 mg/dl but less than twice the baseline value, or liberation from RRT.
Our practice is to use prednisone 1 mg/kg daily as a starting dose, with a slow taper over 2–3 months. Rapid tapers may lead to AKI recurrence; however, in some patients with side effects from steroids, shorter tapers can be considered. In patients with severe ICPI-AKI requiring inpatient hospitalization, intravenous steroids (e.g., methylprednisolone 250–500 mg daily for 3 days) may be used as initial therapy.

Regardless of the treatment strategy, we recommend prompt initiation of immunosuppressive therapy in patients with ICPI-AKI. Although we did not detect an association between treatment delay and complete renal recovery in our multicenter study (21), an association between longer treatment delay and worse renal outcomes has been reported in patients with ATIN from other causes (44). Finally, although treatment with immunosuppressive medications could theoretically interfere with the antitumor immune response elicited by ICPIs, most studies have found that such treatment does not appear to negatively affect tumor response or survival (31,45,46).

**Which Patients Can Be Safely Rechallenged?**

When treating patients with severe ICPI-AKI, it is reasonable to temporarily hold the ICPI. However, permanently discontinuing an ICPI in patients who have exhausted other options for chemotherapy can have dramatic implications on overall survival. Deciding which patients should be rechallenged with ICPIs after experiencing a serious irAE such as AKI is extremely challenging and carries enormous weight. According to the American Society of Clinical Oncology guidelines, ICPI therapy should be permanently discontinued in all patients who develop grade 3 or higher AKI (i.e., an increase in SCR more than three times baseline or need for RRT) (39); however, in our view this approach may deprive patients of a potentially life-saving therapy. In our multicenter study, 31 patients were rechallenged with an ICPI after the initial episode of ICPI-AKI, and only seven (23%) experienced recurrent AKI, six of whom had complete or partial renal recovery. Thus, only one of 31 patients (3%) who were rechallenged developed AKI that did not recover. Clearly additional data on the safety of rechallenge after ICPI-AKI are needed, but based on currently available data and the life-saving nature of these medications, rechallenge should not be routinely withheld due to concern for recurrence of AKI. Rather, we recommend reinitiating ICPIs once renal injury has resolved or stabilized.

**What Are Special Considerations in Transplant Patients?**

Cancer is the third leading cause of death in solid organ transplant recipients, and the risk of cancer is fourfold higher in transplant recipients compared with matched patients in the general population (47). Immunosuppression may predispose to cancer by inhibiting immune surveillance, suppressing DNA repair, and predisposing to oncogenic viral infections (48–50). Although transplant recipients have been excluded from all clinical trials of ICPIs to date, based on the concern of triggering rejection upon blockade of immune inhibitory signals, case reports and small case series of transplanted recipients receiving ICPIs have begun to emerge with conflicting results (51–62). We reviewed all published case reports and case series and found that the rejection rate with ipilimumab monotherapy was 33% compared to 52% in patients receiving anti–PD-1 monotherapy (Figure 3) (63). Sequential use of ipilimumab followed by anti–PD-1 was associated with rejection in 55% of cases (Figure 3) (63). Only two cases of combined anti–CTLA-4 and anti–PD-1 therapy have been reported, one of whom developed rejection (64). Based on the importance of PD-1 to PD-L1 signaling in peripheral organ transplant homeostasis (65), the higher rate of rejection with PD-1 as compared to CTLA-4 blockade is not surprising. However, it is difficult to draw any definitive conclusion because patients had undergone different reductions or changes of immunosuppression upon metastatic cancer diagnosis, which could strongly influence the rejection rates.

The high rates of rejection with ICPI use in transplant recipients has led to the development of potential preventative strategies, including the use of pre-emptive steroids and sirolimus at the time of ICPI initiation in one case report (61). The aggressiveness of immunosuppression reduction in the setting of cancer is also under debate. Although immunosuppression reduction is a crucial management strategy in some cancers, such as post-transplant lymphoproliferative disorders and skin cancer, its importance in other solid cancers such as prostate or breast cancer is less clear (66). Based on the high rate of rejection with anti–PD-1 therapy, continuation of calcineurin inhibitors (CNIs) during treatment with anti–PD-1 medications may be warranted. An alternative approach is to convert patients from CNIs to mammalian target of rapamycin (mTOR) inhibitors due to their potential antiangiogenic properties in skin cancer and their reduced immunosuppressive effects as compared to CNIs (49,67). However, mTOR inhibitors are associated with a higher risk of rejection than CNIs, even in

![Figure 3](image-url)
the absence of cancer (68). Depending on the individual immunologic risk between donor organ and recipient pair, a decision about reduction or interruption of immunosuppression must be balanced with the higher risk of rejection. Clinical decision about reduction or interruption of immunosuppression should include analyses of overall survival after irAEs, rather than solely focusing on renal survival. Finally, studies are needed to better characterize the underlying mechanisms of ICPI-AKI.

**Author Contributions**
S. Gupta, F. Cortazar, L. Riella, and D. Leaf conceptualized the study, were responsible for data curation, wrote the original manuscript, and reviewed and edited the manuscript; S. Gupta and L. Riella were responsible for the visualization; S. Gupta was responsible for the investigation; and F. Cortazar and D. Leaf were responsible for supervision and validation.

**Disclosures**
F. Cortazar served as a consultant for ChemoCentrxy and Momenta Pharmaceuticals. S. Gupta is a scientific coordinator for the ASCEND trial and reports grants from the National Institutes of Health during the conduct of the study and other from Glasko-SmithKline, outside the submitted work. D. Leaf received grant support from BioPorto Diagnostics. L. Riella had received grant support from Bristol-Meyers-Squibb and honorarium from Mallinckrodt.

**Funding**
S. Gupta is supported by the National Institute on Deafness and Other Communication Disorders, grant F32DC017342. D. Leaf is supported by the National Institute of Diabetes and Digestive and Kidney Diseases, grant K23DK106448; and by the National Heart, Lung, and Blood Institute, grant R01HL144566. L. Riella is supported by the Division of Intramural Research, National Institute of Allergy and Infectious Diseases, grant R01AI143887.

**References**

**Table 5. Proposed definition and classification of immune checkpoint inhibitor–associated AKI**

<table>
<thead>
<tr>
<th>Classification</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Definite ICPI-AKI</td>
<td>Kidney biopsy confirmed diagnosis compatible with ICPI-AKI, and after clinical review of risk factors, sustained increase in SCr ≥50% on at least two consecutive values or need for RRT, after clinical review of risk factors, absence of an alternative plausible etiology AND at least one of the following: Sterile pyuria (≥5 WBCs/hpf), Concomitant or recent extrarenal irAEs eosinophilia (≥500 cells per µl)</td>
</tr>
<tr>
<td>Probable ICPI-AKI</td>
<td>BOTH of the following: Sustained increase in SCr ≥50% on at least two consecutive values or need for RRT, after clinical review of risk factors, absence of an alternative plausible etiology</td>
</tr>
<tr>
<td>Possible ICPI-AKI</td>
<td>Increase in SCr ≥50% or need for RRTAKI is not readily attributable to alternative causes</td>
</tr>
</tbody>
</table>

ICPI-AKI, immune checkpoint inhibitor–associated AKI; SCr, serum creatinine; WBC, white blood cell; hpf, high-power field; irAE, immune-related adverse event.

*“Risk factors include prior or concomitant proton pump inhibitor use, prior or concomitant extrarenal irAEs.”*

68. 3C Study Collaborative Group: Campath, calcineurin inhibitor reduction, and chronic allograft nephropathy (the 3C Study) - results of a randomized controlled clinical trial. *Am J Transplant* 18: 1424–1434, 2018
