Introduction

Acute interstitial nephritis (AIN) is a well-known cause of acute kidney disease (AKD) and CKD and is associated with progression to ESKD (1–6). Accordingly, it represents an important problem for clinicians caring for these patients. AIN is primarily an immune-mediated kidney injury triggered by use of certain medications, in particular antibiotics, PPIs, NSAIDs, and immune checkpoint inhibitors (ICPIs), or by autoimmune diseases, such as Sjogren syndrome, sarcoidosis, IgG4-related tubulo-interstitial disease, and TINU. In developed countries, medications are the most common cause of AIN (>70%), whereas the number approximates 50% in developing countries. Infectious agents are a less common cause of AIN, except in developing countries. Where systemic symptoms or signs, such as rash, fever, or flank pain (7–10). Most often, they manifest nonspecific constitutional symptoms, symptoms of kidney failure (when advanced), or no symptoms at all. Currently available diagnostic tests, including serum and urine eosinophils, and urine sediment examination for leukocytes and leukocyte casts have poor sensitivity and specificity for AIN diagnosis. Imaging tests, such as ultrasonography, CT scan, gallium scan, and PET/CT scan, are also suboptimal. In a retrospective analysis of 76 patients, of which 23 were considered to have AIN, renal 67Ga uptake showed an AUC of 0.75. However, only 20 of 76 patients were biopsied to confirm or exclude AIN, and those who determined diagnostic outcome were likely not blinded to 67Ga results (11). Thus, the diagnosis of AIN currently relies entirely on maintaining a high index of clinical suspicion for this disease and often requires confirmation by a kidney biopsy. Biopsy may not be feasible or delayed during optimization in some patients due to underlying bleeding risk (12,13). The lack of a diagnostic biomarker for AIN and the need for a kidney biopsy to establish AIN diagnosis often delay diagnosis, which is associated with permanent kidney damage. Unfortunately, delay in diagnosis and management of AIN is associated with lower recovery of kidney function (4,14–16).

A potential solution to this diagnostic challenge has recently been identified. On the basis of the fact that CD4+ T cells play an important role in the pathogenesis of AIN (17–19), 12 cytokines in the Th1 (IFN-γ, IL-2, and IL-12), Th2 (IL-4, IL-5, and IL-13), and Th9 (IL-9) pathways as well as other inflammatory cytokines (TNF-α, IL-1β, IL-6, IL-8, and IL-10) were measured in the urine and plasma in patients with biopsy-proven AIN and various other diagnoses. In this prospective study, urine TNF-α and IL-9 levels were consistently higher in participants with biopsy-proven, adjudicated AIN compared with other causes of AKD (20). These cytokine biomarkers were higher in AIN than ATI, glomerular diseases, and diabetic kidney disease, as well as in participants without kidney disease. Urine TNF-α and IL-9 improved discrimination for AIN diagnosis as compared with the clinical nephrologist’s prebiopsy AIN diagnosis and a model consisting of currently available blood and urine tests.

Clinical Diagnostic Challenges of AIN

Because the clinical diagnosis of AIN is difficult, delayed or missed diagnosis frequently occurs. Most patients with AIN do not have any characteristic
Overall, these results suggest that concomitantly elevated levels of urine TNF-α and IL-9 are specific to AIN and may be a useful biomarker to distinguish AIN from other clinical causes of AKD. Furthermore, a higher ratio of urinary M1 (proinflammatory) to M2 (anti-inflammatory) macrophages was shown to differentiate between AIN and other kidney pathologies (21). Importantly, new insights into the pathogenesis of AIN as well its diagnosis and therapy may be garnered from this study. A recent study measured urinary retinol-binding protein/Cr in patients with ICPI-associated AKI (14 of 37 had biopsy-proven AIN) and 13 patients with non–ICPI-associated AKI (two of four with biopsy-proven ATI) (22). In a subgroup of patients, urinary retinol-binding protein/Cr was statistically increased in the ICPI AKI group versus the ICPI non-AIN group. All of these data offer hope for a noninvasive diagnostic test for AIN.

Pathologic Diagnostic Challenges of AIN
Kidney biopsy with histology is considered the “gold standard” for diagnosis of AIN. However, in the absence of consensus guidelines regarding histologic diagnosis of AIN, there is significant heterogeneity in reporting by pathologists. Currently, histologic diagnosis of AIN is on the basis of two major components. These include (1) an interstitial infiltrate consisting of lymphocytes, monocytes, macrophages, plasma cells, and sometimes, eosinophils and (2) the presence of tubulitis, which represents the extension/invasion of the inflammatory cells into tubules. ATI, interstitial edema, and interstitial fibrosis often may accompany AIN. Unfortunately, the presence and severity of these findings are often interpreted subjectively without a standard approach. It is increasingly recognized that the reliability of kidney biopsy reports by a single pathologist has limitations. In a prospective observational study, we noted that a majority
of adjudicating pathologists reclassified clinically reported AIN cases into non-AIN controls in a third of cases. This reclassification was lower when AIN was listed as the first diagnosis (18%) than when it was listed as second or later diagnosis (41%) (20). In addition, there was low inter-rater agreement among pathologists. We noted a low κ for agreement for AIN diagnosis (0.35), as well as features of interstitial infiltrate (0.22), tubulitis (0.20), and eosinophils (0.39). Furthermore, an acute interstitial infiltrate is commonly associated with other diagnoses on the biopsy, including ATI, diabetic kidney disease, lupus nephritis, and ANCA-associated vasculitis. It is unclear when AIN is thought to be secondary to these associated diagnoses, which would not warrant management changes directed at AIN or a separate diagnosis that would require therapeutic intervention. This poses a significant challenge for treating clinicians in making management decisions, particularly if a kidney pathologist is not available on site for discussion, which is increasingly common at many centers. Clinicians in our study seemed to understand the uncertainty in histologic diagnosis. Nineteen percent of AIN diagnoses were in our study seemed to understand the uncertainty in histologic diagnosis as well as guide treatment. For example, although it is accepted that withdrawal of the offending drug is the best first step after diagnosis of drug-induced AIN, prescription of corticosteroid therapy is more controversial. Observational studies of corticosteroid use in AIN show conflicting results in terms of benefit for kidney function recovery, potentially indicating heterogenous treatment effects (16). It is possible that there are certain subgroups of patients with AIN who derive the most benefit from corticosteroids (e.g., those with highly active immune responses), whereas others gain little benefit and only experience treatment side effects. However, there are currently no guidelines around which patients are best suited to this therapy.

Recent data suggest that urine biomarkers may help select appropriate patients for therapy (25). In a prospective cohort of participants with biopsy-proven, adjudicated AIN, higher urine IL-9 levels were associated with lower kidney function only in patients who did not receive corticosteroid therapy (25). Corticosteroid therapy was noted to be most beneficial in the patient subgroup with higher urine IL-9 levels and higher baseline eGFR before the onset of AIN. These findings provide a potential framework for IL-9-guided clinical trials to test the efficacy of immunosuppressive therapy in patients with AIN. In addition, higher interstitial fibrosis is associated with lower kidney function recovery, whereas higher interstitial inflammation is associated with greater kidney function recovery (25). These findings could assist clinicians in providing a more accurate estimate of prognosis to patients with AIN. However, it remains unclear what the appropriate dose, route of delivery (oral versus intravenous), and duration of therapy should be for patients. Thus, clinicians rely on expert opinion, and local practices vary by center. In addition to corticosteroids, other agents with potential utility for AIN, such as mycophenolic acid, infliximab, and other agents, should undergo study in biopsy-proven AIN.

**Prognosis and Management Challenges of AIN**

There are no evidence-based guidelines available to aid clinicians in the management of patients with AIN. This results in a substantial variation in practice. For example, although it is accepted that withdrawal of the offending drug is the best first step after diagnosis of drug-induced AIN, prescription of corticosteroid therapy is more controversial. Observational studies of corticosteroid use in AIN show conflicting results in terms of benefit for kidney function recovery, potentially indicating heterogenous treatment effects (16). It is possible that there are certain subgroups of patients with AIN who derive the most benefit from corticosteroids (e.g., those with highly active immune responses), whereas others gain little benefit and only experience treatment side effects. However, there are currently no guidelines around which patients are best suited to this therapy.

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**Approach to Challenges Associated with AIN**

We propose that the key diagnostic and management issues relevant to patients with AIN be the focus of basic research and clinical investigation. This area of acute tubulointerstitial disease needs evidence-based guidelines and/or expert consensus opinion to assist clinicians in their care of these patients. Focus on key aspects of clinical and histologic diagnosis and management of patients suspected of having AIN is an important first step. The field sorely needs useful clinical and laboratory criteria to confirm a clinical diagnosis of AIN. In the same vein, consensus histologic criteria are needed to determine a pathologic diagnosis of AIN. Additionally, a consensus approach for prognosis and treatment of AIN that addresses issues of patient selection for immunosuppressive therapy, dose, and duration of therapy as well as predictors of prognosis...
is required. Finally, knowledge gaps and areas of needed research in each of the three AIN domains must be identified. Table 1 lists areas and challenges that must be addressed.

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### Author Contributions

D.G. Moledina and M.A. Perazella conceptualized the manuscript; D.G. Moledina and M.A. Perazella wrote the original draft; and D.G. Moledina and M.A. Perazella reviewed and edited the manuscript.

### References


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