


# The Challenges of Acute Interstitial Nephritis: Time to Standardize

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## 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 tubulointerstitial 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.

The overall incidence of AIN in kidney biopsy registries is 2%–5%, whereas AIN is observed in approximately 15%–20% of patients with AKI or AKD who undergo kidney biopsy (1–3). The actual number is likely higher as many patients with AKI/AKD do not undergo biopsy and are presumed to have acute tubular injury (ATI). Importantly, diagnosing AIN clinically is often quite challenging, making kidney biopsy a frequent requirement to definitively confirm the diagnosis and guide therapy (Figure 1). Furthermore, delayed or missed AIN diagnosis leads to ongoing inflammation with resulting interstitial fibrosis, tubular atrophy, and permanent kidney damage, which may be the explanation for CKD occurring in 40%–60% of patients after an episode of AIN (4,5). Approximately 2% of CKD is considered to be due to AIN, which is equivalent to 10 million prevalent worldwide cases. Furthermore, AIN is the primary cause of ESKD in 3%–4% of incident patients (6). It is one of the few potentially treatable causes of AKI if identified and treated early. In view of these data, three key challenges that limit the diagnosis and management of patients suspected of having AIN are discussed.

## 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

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 <sup>67</sup>Ga 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 <sup>67</sup>Ga 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).

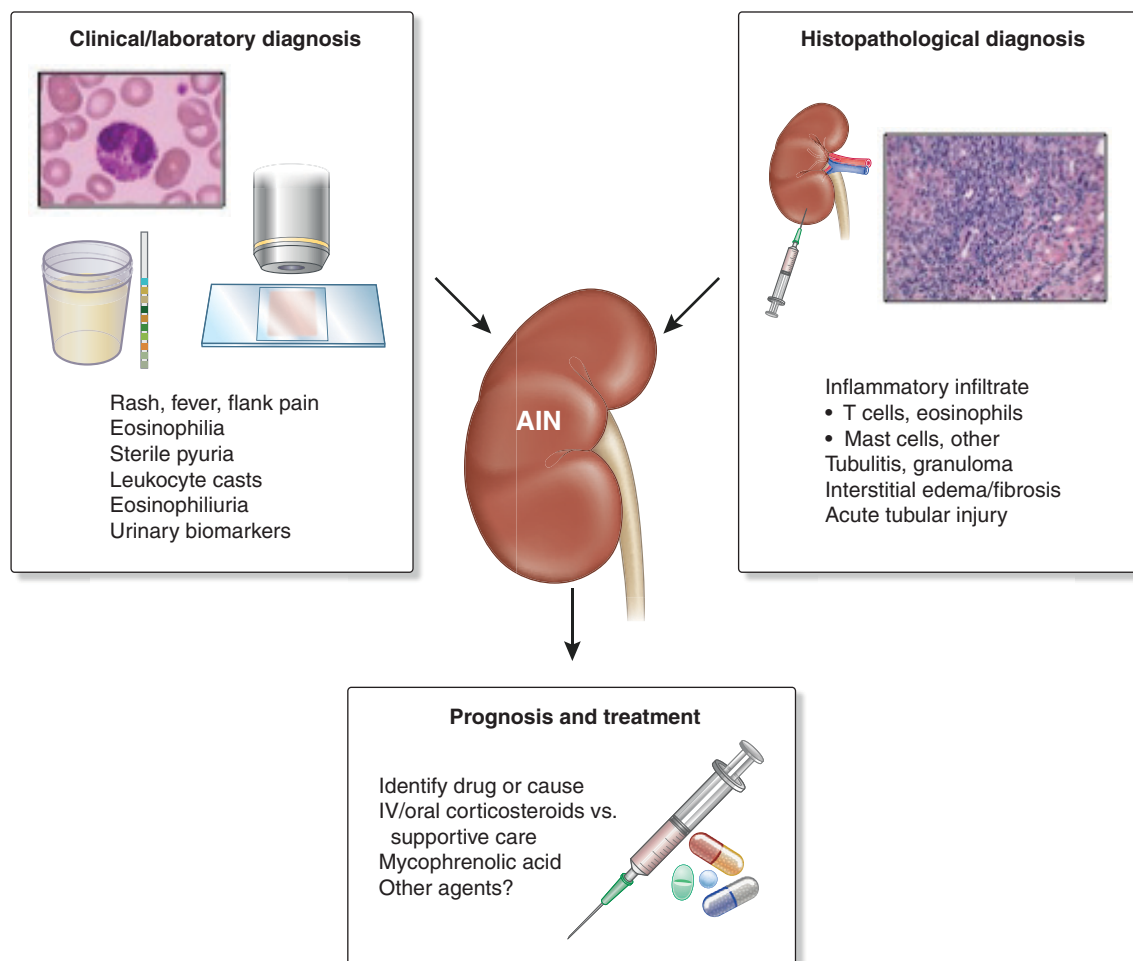
A potential solution to this diagnostic challenge has recently been identified. On the basis of the fact that CD4+ T cells play an important role in the pathogenesis of AIN (17–19), 12 cytokines in the Th1 (IFN- $\gamma$ , IL-2, and IL-12), Th2 (IL-4, IL-5, and IL-13), and Th9 (IL-9) pathways as well as other inflammatory cytokines (TNF- $\alpha$ , IL-1 $\beta$ , 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- $\alpha$  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- $\alpha$  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.

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**Figure 1. | Clinical and histopathologic diagnosis and therapy of acute interstitial nephritis (AIN).** Clinical symptoms and signs and laboratory and imaging tests are sometimes useful to make a diagnosis of AIN. However, histopathology obtained through kidney biopsy is frequently required to make a diagnosis of AIN and ultimately, guide management. IV, intravenous.

Overall, these results suggest that concomitantly elevated levels of urine TNF- $\alpha$  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  $\kappa$  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 subsequently reclassified as not AIN; this reclassification was lower when AIN was listed as first diagnosis (8%) than when it was listed as second or later diagnosis (29%).

Pathologists are often asked to determine if AIN is due to a drug or other etiology, such as a systemic disease (Sjogren syndrome, sarcoidosis, IgG4 disease, TINU, *etc.*), infection, or idiopathic. An eosinophil-predominant infiltrate often raises the possibility of drug-induced AIN; however, several drugs do not have an eosinophilic infiltrate, and nondrug causes may have eosinophils. In some cases, the histology can identify nondrug causes, such as IgG4 disease (IgG4 staining plasma cells and storiform fibrosis) and sarcoidosis with lymphocyte-dominant infiltrate and noncaseating granuloma. Most important to determining etiology is an ongoing discussion of the patient's clinical data and histologic data by the nephrologist and pathologist. Unfortunately, this approach may not be common practice for many clinicians and pathologists.

There are a few solutions to the challenges with histopathologic diagnosis of AIN, which at this time appears to be a suboptimal "gold standard." First, pathologists in the NEPTUNE study improved concordance on glomerular diagnoses through an iterative adjudication process using a description-based scoring system (23). Thus, it might be possible to improve the agreement among pathologists by establishing consensus criteria for AIN. Certainly, such criteria exist for the histopathology in many other kidney diseases. Second, reporting of interstitial features should be undertaken in a standardized manner (*e.g.*, percentages or percentage ranges). Terms, such as mild, moderate, minimal, and severe, should be avoided, as they are subjective and not helpful to the clinician. This approach would improve patient care and research by allowing comparison across centers, studies, and pathologists; help develop models to diagnose AIN using interstitial features; and allow application of machine learning techniques to biopsy slides. Finally, identification of etiology-specific subsets of immune cells involved in AIN may lead to improved histologic diagnosis as well as guide treatment. For example, recent studies have shown involvement of mast cells and

Th17 cells in AIN, which are not routinely tested in clinical histopathology (18,24).

### 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.

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.

### 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

**Table 1. Specific challenges to be addressed in acute interstitial nephritis****Clinical diagnostic challenges of AIN**

Utility of clinical features of immune and drug-induced causes of AIN  
 Accuracy of currently available clinical features for AIN  
 Accuracy of currently available blood tests for AIN  
 Accuracy of currently available urinary tests for AIN  
 The role of imaging tests  
 The role of novel biomarkers  
 Features that establish the diagnosis of AIN

**Pathologic diagnostic challenges of AIN**

Relevance of histologic features, such as inflammatory interstitial infiltrate (lymphocytes, eosinophils, plasma cells, *etc.*), tubulitis, and granuloma  
 Relevance of associated diagnoses, including acute tubular injury, glomerular diseases, and other pathology  
 Utility of novel studies of the kidney tissue, including T cell subsets, mast cells, and macrophages

**Prognosis and management challenges of AIN**

Accuracy of data in determining the prognosis of AIN  
 Approach to identifying and discontinuing the offending agent in drug-induced AIN  
 Appropriate use of corticosteroids in the treatment of AIN  
 Intravenous versus oral corticosteroids to initially treat AIN  
 Oral steroids alone to treat AIN  
 Combination of intravenous and oral corticosteroids to treat AIN  
 Appropriate duration of corticosteroid therapy for AIN  
 Appropriate discontinuation and tapering of corticosteroids prior to reaching the intended duration  
 Utility of other drugs appropriate for the treatment of AIN (*e.g.*, mycophenolic acid, azathioprine, *etc.*)  
 Utility of potential novel, targeted therapies to treat AIN (anti-TNF- $\alpha$  drugs, antihistamines, *etc.*)

AIN, acute interstitial nephritis.

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.

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