



# Clinicopathological Spectrum and Outcomes in Patients with Acute Interstitial Nephritis

## Abstract

**Background:** Acute interstitial nephritis (AIN) is an important cause of AKI, with significant variation in the etiology between low- and middle-income countries (LMICs) and high-income countries (HICs). The study aimed to analyze the etio-pathological factors and long-term outcomes of AIN over the past 10 years. **Materials and Methods:** This retrospective study included 55 patients with biopsy-proven AIN admitted from February 2014 to February 2024. Patients with solid organ/bone marrow transplants, primary glomerular lesions, or <3 months of follow-up were excluded. Clinical data, histopathology, and renal function outcomes were collected. Recovery was categorized into complete recovery (CR), partial recovery (PR), or non-recovery (NR) based on serum creatinine and eGFR. **Results:** AIN constituted 1.6% of kidney biopsies. Drugs (44%) and envenomation (29%) were the most common causes. At presentation, 34.5% required dialysis, and systemic features were infrequent. At three months, CR was observed in 29%, PR in 18%, and NR in 53%. Envenomation and immunological causes had better outcomes compared with drug-induced AIN. Underlying chronicity significantly correlated with poor recovery. **Conclusion:** AIN's etiological spectrum differs in LMICs, with envenomation contributing substantially. Despite corticosteroid therapy, >50% of the patients exhibited incomplete recovery, emphasizing the need for early diagnosis and timely intervention to improve outcomes.

**Keywords:** Acute kidney injury, Interstitial, Nephritis


## Introduction

Acute interstitial nephritis (AIN) is one of the frequent causes of AKI. It is a cell-mediated immunologic response against an exogenous or endogenous nephritogenic antigen processed by the tubular epithelial cells. In 1898, Councilman described AIN in children associated with scarlet fever and Diphtheria.<sup>1</sup> Since then, the clinicopathological spectrum and etiological factors have expanded. Currently, drugs are the most common cause of AIN. With the advent of newer drugs, including cancer chemotherapeutic agents, the list of agents capable of inducing AIN keeps growing. There are notable differences in AIN etiology between low- and middle-income countries (LMIC) and high-income countries (HIC). In HIC, AIN is predominantly drug-induced, while in LMIC, infections and envenomation often contribute to a significant proportion of cases.<sup>2,3</sup> Corticosteroids remain the mainstay of treatment with severe kidney

failure despite in AIN the unavailability of randomized trials.<sup>4</sup> In the present study, we aim to assess the etio-pathological spectrum and long-term outcomes of AIN.

## Materials and Methods

All patients who underwent kidney biopsies from February 2014 to February 2024, admitted under the Department of Nephrology, Jawaharlal Institute of Postgraduate Medical Education and Research, Puduchery, India, diagnosed with AIN, were included in this study. Patients with solid organ/bone marrow transplants and those with <3 months of follow-up data were excluded. Those with a primary glomerular lesion with secondary interstitial inflammation were excluded. The data on clinical presentation, histopathology, and follow-up kidney function were collected from the hospital information system using a pre-defined proforma. Ethical approval and patient consent was obtained. All biopsies were reviewed by

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a single pathologist. As per the department protocol, patients were started on prednisolone (1 mg/kg) body weight for 2 weeks. If there was a treatment response, a rapid steroid taper was done over 2-4 weeks. In case of unresponsiveness, full-dose steroids were continued for another 2 weeks and were tapered over the next 2-4 weeks, cumulating an entire 6-8 week steroid course. All patients were started on anti-peptic ulcer prophylaxis along with steroids.

### Definitions

Renal recovery was assessed after 3 months. Complete recovery (CR) was defined as the return of serum creatinine to <15% of the values before diagnosis at the end of 3 months. For patients without baseline creatinine before diagnosis, an eGFR >60 mL/min/1.73m<sup>2</sup> at 3 months was considered as CR. Partial recovery (PR) was defined as an eGFR between 60-15 mL/min/1.73m<sup>2</sup>, with at least 25% improvement in serum creatinine from the peak values documented during the AIN. Non-recovery (NR) was defined as the presence of dialysis dependency or eGFR <15 mL/min/1.73m<sup>2</sup> or <25% improvement in serum creatinine from the peak values documented during the disease.

### Statistical analysis

The categorical variables were expressed as percentages, and continuous variables were expressed as mean with standard deviation (SD) or median with interquartile range (IQR). The association between two categorical variables was tested using the chi-squared or Fisher's exact test. Continuous variables were compared using the Student's T-test, Mann-Whitney U test, ANOVA, and Kruskal Wallis test, depending on the data distribution and the number of groups. A 5% level of significance was decided. The analysis was done using SPSS v 26 by IBM Inc.

### Results

A total of 55 patients with biopsy-proven AIN, having a minimum of 3-month follow-up data, were included. AIN accounted for 1.6% of all kidney biopsies during the study period. Six patients with biopsy-proven AIN were excluded from the study due to incomplete 3-month follow-up data. The predominant etiology was drugs (24; 44%), followed by envenomation (15; 29%) [Figure 1]. The most frequent offending agents were multiple drug combinations, including non-steroidal anti-inflammatory agents, proton pump inhibitors, and antibiotics. The list of drugs responsible for AIN have been listed in Table 1. Envenomation-induced AIN referred to snake venom in 10 patients, and bees or wasps in six. The immunological causes were Sjögren syndrome (n=2), Systemic lupus erythematosus (SLE) (n=1), and Tubulointerstitial Nephritis and Uveitis syndrome (TINU) syndrome (n=1). The patient with SLE presented as granulomatous AIN initially, without any glomerular or vascular lesions, and had a CR with corticosteroid therapy. Anticancer drugs, lenvatinib and gefitinib, were responsible for AIN in two patients.

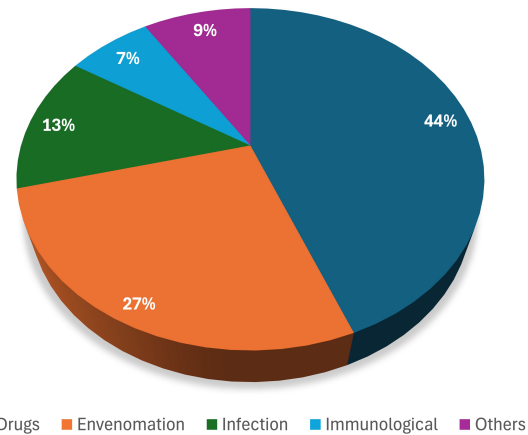


Figure 1: Causes of acute interstitial nephritis.

The median age was 46 years (IQR 32, 54.3), with 32 (58.2%) males. The age range was 12-68 years. There were 17 (31%) patients >50 years old and 7 (12.7%) >60 years of age. No patient had hypertension; only one had diabetes at baseline, but there were no changes suggestive of diabetic kidney disease in the biopsy.

The time between AKI documentation and AIN diagnosis was 16 days (IQR 7,30). The median creatinine was 3.04 mg/dL (IQR 2;5.42). Dialysis-requiring AKI was present in 19 patients (34.5%); of those, seven were due to drugs, eight were due to envenomation, and four were due to

Table 1: Drugs causing AIN

Drug	Number of AIN cases
Multiple drugs (NSAID/PPI/Antibiotics)	8
Non-steroidal analgesic agents	6
Rifampicin	4
Antibiotics	1
Anticancer drugs	2
Other agents	3

NSAIDs: Non-steroidal anti-inflammatory drugs, PPI: Proton pump inhibitors, AIN: Acute interstitial nephritis

Table 2: Clinical and laboratory parameters at presentation

Parameter	Value
Fever	11 (20%)
Arthralgia	4 (7.3%)
Need for renal replacement therapy	19 (34.5%)
Hemoglobin (g/dL)	10.10 ± 2.5
Total count (cells × 10 <sup>3</sup> /mL)	9.8 (7.2,15)
Platelets (cells × 10 <sup>3</sup> /mL)	243 (130,347)
Albumin (g/dL)	3.44±0.8
Eosinophilia	11 (20%)
Oliguria	20 (36.4%)
Albuminuria	35 (62%)
Nephrotic range proteinuria	6 (10.9%)
Eosinophiluria	6 (10.5%)
RBC in urine	27 (48%)
WBCs in urine	27 (49.1%)

infections. Systemic features like fever and arthralgia were uncommon; skin rashes were not reported. The clinical features of the presentation have been listed in Table 2.

### Kidney biopsy findings

The kidney biopsy findings have been given in Table 3. Lymphocytic cells, eosinophils, and plasma cells were the most common infiltrates. The reported proportion of interstitial fibrosis varied from 5-45%, and tubular atrophy varied from 5-45%. The majority (~87%) of the patients had negative immunofluorescence (IF). Out of the 4 patients with immunological causes, only one patient with SLE had IgG 3+, IgA3+, C31+, κ3+, λ3+, and c1q1+. Other IF-positive biopsies showed nonspecific IF findings. The causes of granulomatous AIN were drugs in two, SLE in one, and an unidentified etiology in one. In these patients, tuberculosis was ruled out using a tissue TB PCR. There were no significant differences between drug (n=24) and venom-induced AIN (n=15), with respect to tubular atrophy (p=0.70), interstitial fibrosis (p=0.62), glomerulosclerosis (p=0.27), and acute tubular necrosis (ATN) (p=0.07). The predominant infiltrates in drug-induced AIN were purely lymphocytic in 79.2%, whereas in envenomation-induced AIN, 56.25% of patients had lymphocytic infiltration alone in the interstitium, and the rest were mixed infiltrates (p=0.52)

### Renal recovery

The median eGFR of the cohort after 3 months was 35 mL/min/1.73m<sup>2</sup> (IQR 13.6, 71.4). CR was seen in 16 patients (29%), PR in 10 (18%), and NR in 29 (53%). Patient with AIN due to envenomation and immunological causes were more likely to have a favorable response to corticosteroid therapy compared to other etiologies. The need for dialysis was not associated with the recovery status. Among the 19 (34.5%) patients requiring dialysis at admission, four had a CR, six had PR, and nine had NR (P = 0.545). Underlying chronicity was associated with a NR/PR. The characteristics of the patients with CR and NR have been given in Table 4.

**Table 3: Histopathological parameters in kidney biopsy**

Parameter	Value
Lymphocytic infiltrates alone	36 (65%)
Lymphocytic infiltrates + plasma cells	9 (16%)
Lymphocytic infiltrates + eosinophils	8 (15%)
Interstitial fibrosis	12 (22%)
Mild (<25%)	10
Moderate (26% -50%)	2
Severe (> 50%)	0
Tubular atrophy	40 (73%)
Mild (<25%)	29
Moderate (26% -50%)	11
Severe (> 50%)	0
Glomerulosclerosis	24 (49%)
0-25%	15
25-50%	7
>50%	5
Granuloma	4 (7%)

**Table 4: Patient characteristics and renal recovery at 3 months**

Parameter	Nonrecovery (n=29)	Complete/Partial recovery (n=26)	p value
Age (years)	47 ± 13.13	40.5 ± 14.3	0.09
Male sex	19 (65.5%)	13 (50%)	0.24
Duration of AKI	10 (7, 14)	10 (3.5, 30)	0.87
Hemoglobin (g/dL)	10.3 ± 2.62	9.9 ± 2.5	0.56
Albumin (g/dL)	3.4 ± 0.9	3.4 ± 0.8	0.99
Dialysis dependence at presentation	9 (31.03%)	10 (38.5%)	0.55
Creatinine at presentation (mg/dL)	2.7 (1.93, 11.32)	3.10 (2.00, 4.95)	0.56
Nephrotic range proteinuria	3 (10.3%)	3 (11.5%)	0.89
Etiology of AIN			
Drugs	16	8	0.04
Envenomation	5	10	
Immunological	0	4	
Infections	4	3	
Others	4	1	
Interstitial fibrosis	5	7	0.44
Nil	24	19	
Up to 25%	5	5	
25-50%	0	2	
Tubular atrophy	23 (79.3)	17 (65.4)	0.26
Nil	6	9	
Up to 25%	15	14	
25-50%	8	3	
Glomerulosclerosis	20 (68.9)	7 (26.9)	0.014
Nil	9	19	
Up to 25%	10	5	
25-50%	6	1	
>50%	4	1	
Lymphocytic infiltrates	22 (61.1%)	14 (38.9%)	0.29
Acute tubular necrosis	12 (41.4%)	14 (53.8%)	0.053

Among patients with drug-induced AIN, 16 had NR (66.6%), and in those with envenomation-induced AIN, five had NR (33.3%) (P value=0.12). Short-term steroid-related adverse events like hyperglycemia, acneiform eruptions, and gastrointestinal intolerance were documented in 6 (11%) patients who received corticosteroid therapy. This included hyperglycemia in two patients, which required treatment, acneiform eruptions in three patients, and gastrointestinal intolerance in one patient. No severe, life-threatening adverse events were documented.

### Discussion

The reported AIN prevalence varies from 1-3% of all kidney biopsies; with biopsies performed on clinical diagnosis of AKI or acute kidney disease (AKD), the AIN incidence increases to 5–27%.<sup>5</sup> By far, the most common etiologic agent of AIN is drugs. AIN incidence is believed to be increasing; a Spanish biopsy registry study reported a threefold increase in diagnosis from 1994 to 2009. In our center, AIN accounted for only 1.6% of kidney biopsies. This

underestimation might be due to various reasons, such as avoiding biopsy in patients with spontaneous reduction in creatinine or not getting a nephrology consult for those with mild renal impairment. There was a median 16-day gap between AKI onset and AIN diagnosis. This delay was primarily due to late referrals. In patients with snakebite, biopsy was done when the clinical picture didn't fit the recovery pattern of ATN. Given that some patients with AIN could also have shown spontaneous early recovery, it is possible that this condition was under diagnosed.

The most common clinical manifestations of AIN are AKI, microscopic hematuria, non-nephrotic proteinuria, and leukocyturia.<sup>6,7</sup> The reported prevalence of these symptoms in our study is similar to that reported in the literature. In recent years, AIN has shifted to an oligosymptomatic presentation with isolated symptomatic or asymptomatic renal dysfunction. The classic triad of fever, arthralgia, and rashes is present only in the minority; the diagnosis might likely be missed altogether in those with milder renal dysfunction. In the present series, we did not encounter patients with this classic triad. Most had no extrarenal symptoms, with fever present only in 20% and lower proportions with eosinophilia and arthralgia; skin rashes were not encountered. These figures are much lower compared to a previous report by Clarkson *et al.*, where fever was reported in 30%, rash in 21%, and eosinophilia in 36%.<sup>7</sup> A recent study from India reported some incidences of fever (26%) and eosinophilia (14%).<sup>8</sup>

The leading AIN causes reported in various studies include drugs, infections, and idiopathic and associated systemic diseases like sarcoidosis, SLE, Sjögren's syndrome, and IgG4 disease.<sup>9</sup> The etiology of AIN, as described in the Western literature, suggests drugs as the cause in >75%-90% of the cases. Most cases of drug-induced AIN reported in the literature are due to antimicrobial agents, proton pump inhibitors, and nonsteroidal anti-inflammatory drugs (NSAIDs).<sup>10</sup> Data on AIN from LMICs is limited. A recent study from India reported a lower proportion (45%) accounted for by drugs, with a relatively higher proportion (30%) contributed by infections.<sup>8</sup> The major cause in the present study was drugs (45%), and patients taking multiple drugs like NSAIDs or antibiotics and PPI simultaneously were found to be the common cause for drug-induced AIN (33.3%). It is uncertain whether PPI alone can cause kidney disease. Concomitant intake of other drugs like NSAIDs or antibiotics may also contribute to disease in such patients.<sup>11</sup>

Notably, envenoming was found to be a major cause of AIN, accounting for ~1/3 of the cases. In a recent study from South India, snake envenoming accounted for 5% of AIN. The higher proportions of envenoming-related AIN are possibly due to the center's location, which predominantly caters to the rural population engaged in agriculture-related activities. AIN following envenomation

is often overlooked due to the limited awareness about this entity; literature is often limited to case reports and small case series; data is even more limited with bee/wasp stings.<sup>12</sup> AIN might reflect the effect of venom per se, antivenom, or even an allergic response to the multiple drugs, including antibiotics and analgesics, administered to these patients. Envenoming-related AIN presents as severe kidney failure persisting for weeks, often requiring dialysis, even after resolution of all symptoms of AIN. A previous study from the same center found that 5.7% of patients who developed AKI following snake envenoming had AIN. Identifying AIN after envenomation is important due to the reversible nature following corticosteroid administration, even after an apparent delay of 4-6 weeks. The reported response rate varies from 20%-80%. In the present study, 2/3 of envenomation-related AIN showed a favorable response to steroids.<sup>3,13,14</sup>

In the present study, 53% did not recover kidney function despite corticosteroid therapy. Even though there are initial improvements in GFR and dialysis independence, a proportion of patients with AIN might progress to varying degrees of CKD in the long term. Despite the immunological nature of the insult, drug-induced AIN does not often respond well to immunosuppression. Residual renal damage is common in >2/3 of patients; those who show rapid improvements in the initial 6-8 weeks are reported to have better long-term kidney function.<sup>15</sup>

Most available data about AIN management are from retrospective studies. It has been suggested that steroids may hasten dialysis independence but may not affect the GFR in the long term. Clarkson *et al.* reported that the majority with AIN have residual kidney damage on follow-up; administration of corticosteroids had no impact on short-term recovery or long-term kidney function.<sup>7</sup> However, there was a considerable delay (>3 weeks) between the onset of kidney failure and steroid initiation in the study. However, Gonzalez *et al.* reported complete recovery of kidney function in 54% of patients who received steroids as against 33% recovery among those who did not; institution of steroids within 7 days of withdrawal of the offending drug was associated with better prognosis.<sup>16</sup> In the present study, the majority of patients presented in the third week, and steroids were given once the biopsy confirmed AIN diagnosis, possibly accounting for suboptimal responses. A recent study from India has reported 80% recovery; however, the data on steroid responsiveness is not given. Even though pre-existing CKD was not documented in any of the patients, underlying chronicity in the biopsy was associated with poor outcomes. The presence of glomerulosclerosis in 27 patients (49.1%) is likely due to the underlying chronicity, probably age-related (around 31% of our study population was >50 years), as the glomerulosclerosis in most of the patients was mild (<25%). Although none of the patients

had documented pre-existing CKD, the possibility of underlying subclinical kidney damage cannot be ruled out. Our center caters to a geographical area endemic of CKDu, which further supports this consideration. Studies have shown that underlying chronicity was associated with nonrecovery.<sup>17</sup> We also observed that envenomation and immunological causes of AIN had better outcomes compared to drug-induced AIN, whereas with drug-induced AIN, only 50% showed a CR.

In conclusion, AIN in the present series was mainly drug-induced and secondary to envenomation, a finding not reported in previous literature. This might represent the etiologic spectrum differences between LMICs and HICs. The overall prognosis does not appear favorable despite receiving corticosteroids, with around half of the patients not recovering kidney function.

**Conflicts of interest:** There are no conflicts of interest.

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