AJKD

Original Investigation

# Biopsy-Proven Acute Interstitial Nephritis, 1993-2011: A Case Series

*Angela K. Muriithi, MBChB, MPH,[1] Nelson Leung, MD,[1] Anthony M. Valeri, MD,[2] Lynn D. Cornell, MD,[3] Sanjeev Sethi, MD, PhD,[3] Mary E. Fidler, MD,[3] and Samih H. Nasr, MD[3]*

**Background:** Acute interstitial nephritis (AIN) is an important cause of acute kidney injury, especially in hospitalized patients. The cause and outcome of AIN, particularly that due to drugs, is changing with prevalent medication use. The effectiveness of steroids for treatment of AIN is debated.

**Study Design:** Case series.

**Setting & Participants:** 133 patients with biopsy-proven AIN from 1993 through 2011 at a single center.

**Outcomes:** Recovery of kidney function by 6 months, either complete, partial, or none. Complete recovery was defined as improvement in serum creatinine level to within 25% of baseline (or $<$1.4 mg/dL), and partial recovery, as a $\geq$50% decrease in serum creatinine level from its peak value but not reaching within 25% of its baseline value.

**Results:** Causes of AIN included drugs (70%), autoimmune diseases (20%), and infections (4%). Drug-induced AIN was due to antibiotics in 49%, proton pump inhibitors (PPIs) in 14%, and nonsteroidal anti-inflammatory drugs (NSAIDs) in 11%. Overall, the top 3 drug causes were omeprazole (12%), amoxicillin (8%), and ciprofloxacin (8%). Patients with drug-induced compared to non-drug-induced AIN were older and had higher baseline kidney function, but more severe acute kidney injury. Patients with PPI-induced AIN were older, were less symptomatic, and had longer durations of drug exposure and longer delays in getting kidney biopsy and steroids than for antibiotic-induced or NSAID-induced AIN. At 6 months postbiopsy, 49% of patients with drug-induced AIN treated with steroids achieved complete recovery; 39%, partial recovery; and 12%, no recovery. Correlates of poor recovery included a longer duration of drug exposure (15 vs 30 vs 130 days for complete, partial, and no recovery, respectively; $P = 0.04$) and longer delay in starting steroid therapy (8 vs 11 vs 35 days, respectively; $P = 0.05$).

**Limitations:** Retrospective study, selection bias in patients who had kidney biopsy, single-center experience.

**Conclusions:** The cause of AIN may be shifting; PPIs are emerging as an important contributor to this disease. Delays in discontinuation of the culprit drug and in initiating steroid treatment adversely affect recovery of kidney function.

*Am J Kidney Dis.* ■(■):■-■. 

***INDEX WORDS:*** Acute interstitial nephritis (AIN); etiology of AIN; drug-induced AIN; steroid treatment of AIN; kidney biopsy; renal failure; proton pump inhibitor (PPI); case series; prognosis.

Interstitial inflammation was described first by Biermer[1] in 1860 and was defined as the distinct entity acute interstitial nephritis (AIN) in 1898 by Councilman.[2,3] Most of these early reported cases occurred in infectious diseases of children, particularly scarlet fever and diphtheria. The kidneys in these patients either contained the infectious agents, "infectious interstitial nephritis," or were sterile, "reactive interstitial nephritis."[2,3] Following the sharp decline in prevalence of infectious diseases in the 20th century and introduction of antibiotics for medical use in the 1940s, antibiotics became the most common cause of AIN. AIN was first noted as a complication of sulfonamides in the 1940s,[4] then methicillin and penicillin in the 1960s.[5] Since then, all classes of antibiotics have been implicated in its cause. In addition to antibiotics, nonsteroidal anti-inflammatory drugs (NSAIDs) have been a major cause of AIN[6-10] and surpassed antibiotics as the leading cause in some studies.[11] More recently, proton pump inhibitors (PPIs) increasingly have been reported to be a cause of AIN.[12-16] Other established causes of AIN include autoimmune diseases such as sarcoidosis, Sjögren syndrome, and the recently described entity of immunoglobulin G4 (IgG4)-related disease.[17] In a small percentage of cases, no obvious cause can be identified.

It has been noted that the prognosis of AIN is influenced by its cause. In the study by Schwarz et al[8] of 64 patients with biopsy-proven AIN, idiopathic and

*From the [1]Division of Nephrology and Hypertension, Mayo Clinic, Rochester, MN; [2]Division of Nephrology, Columbia University, College of Physicians and Surgeons, New York, NY; and [3]Division of Anatomic Pathology, Department of Laboratory Medicine and Pathology, Mayo Clinic, Rochester, MN.*

*Received October 2, 2013. Accepted in revised form April 18, 2014.*

*Address correspondence to Angela K. Muriithi, MBChB, MPH, Mayo Clinic, 200 First St SW, Rochester MN 55905. E-mail: muriithi.angela@mayo.edu or kagwiria76@yahoo.com*



*0272-6386/$36.00*

*http://dx.doi.org/10.1053/j.ajkd.2014.04.027*

infection-related AIN always were reversible, whereas drug-induced AIN was more likely to cause permanent damage, especially if NSAID related. The role of steroids in the treatment in drug-induced AIN remains to be established. In the study of 60 patients with drug-induced AIN reported by Clarkson et al,[11] there was no beneficial effect of steroids on the rate or extent of recovery of kidney function. In contrast, in the study by Gonzalez et al[18] of 61 patients, steroid therapy correlated with a lower final serum creatinine level. Furthermore, in the Gonzalez et al[18] study, an interval longer than 1 week between drug withdrawal and onset of steroid treatment correlated with an increased risk of incomplete recovery of kidney function.

In this study of 133 patients with biopsy-proven AIN, which to our knowledge represents the largest single-center series to date, we provide a current perspective on its causes, clinical features, laboratory findings, outcome according to cause, and prognostic indicators. We also evaluate the role of steroids in its management.

## METHODS

### Study Population

Retrospective review of all native kidney biopsies evaluated in the Renal Pathology Laboratory at Mayo Clinic, Rochester, from 1993 through 2011 identified 133 Mayo Clinic patients with AIN without concurrent glomerulonephritis. We excluded patients younger than 18 years, patients with glomerulonephritis or primary vascular disease, and those with transplant biopsies, as well as outside institution referrals.

### Pathologic Studies

A pathologic diagnosis of AIN required the presence of prominent interstitial inflammation in the nonfibrotic cortex and tubulitis. Standard processing of kidney biopsy specimens included light microscopy, immunofluorescence, and electron microscopy. For light microscopy, all cases were stained with hematoxylin and eosin, periodic acid–Schiff, Masson trichrome, and Jones methenamine silver.

### Clinical Data

The records of all patients were reviewed for the following information: causative agent, demographic and clinical data, kidney disease outcome, therapy for AIN (specifically steroid treatment), delays to steroid treatment, and total duration of treatment. The cause of AIN was determined according to the most probable cause by temporal association as determined by treating physicians. In most patients, the indication for biopsy was acute kidney injury (AKI), either with previously normal kidney function or previous chronic kidney disease (CKD) of any stage as defined by NKF-KDOQI (National Kidney Foundation–Kidney Disease Outcomes Quality Initiative) guidelines.[19] AKI Network (AKIN) stage of kidney injury was defined according to AKIN criteria.[20] Estimated glomerular filtration rate (eGFR) was calculated by the CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) equation and expressed as milliliters per minute per 1.73 $m^2$. Leukocytosis was defined as leukocytes $> 10.5 \times 10^9$/L, eosinophilia as eosinophils $> 0.5 \times 10^9$/L, and eosinophiluria as urine eosinophils $> 1\%$. Proteinuria was expressed as protein to osmolality ratio, which was the measure available in all patients, and ratio $> 0.15$ ($>150$ mg/d) was considered positive.

### Outcomes

Recovery of kidney function was based on the last serum creatinine measurement available within 6 months. We defined complete recovery as improvement in serum creatinine level to within 25% of its baseline (or to $<1.4$ mg/dL if its baseline was not available); partial recovery as a $\geq 50\%$ decrease in serum creatinine level from its peak value, but not reaching within 25% of its baseline value; and no recovery as failure to meet criteria for complete or partial recovery or remaining on renal replacement therapy. For outcomes beyond 6 months, we defined normal kidney function as final serum creatinine level $< 1.4$ mg/dL, progressive CKD as serum creatinine level $\geq 1.4$ mg/dL or end-stage renal disease (ESRD) if the patient remained on dialysis therapy or received a kidney transplant.

### Statistical Analysis

Results were expressed as median (with interquartile range) for continuous variables and number affected/total (percentage) for categorical variables. Mean values were reported occasionally if the data were normally distributed. Comparison between groups was done using $\chi^2$ test for categorical variables (or Fisher exact test when appropriate). For continuous variables for which normal distribution could be assumed, comparisons were made using analysis of variance; when normal distribution could not be assumed, we used nonparametric Mann-Whitney or Kruskal-Wallis test. Statistical significance was defined as $P < 0.05$. For the 3-group comparisons, exact statistical methods were used except when large sample size calculations allowed the Monte Carlo approximation to be used instead. If the $P$ value was $\leq 0.10$, we explored the relationships further using paired tests and adjusting for multiple comparisons. Categorical variables were compared using Fisher-Freeman-Halton exact test, except for ordinal variables (such as recovery outcome [complete vs partial vs none], tubular atrophy and interstitial fibrosis score, and AKIN score) when the Kruskal-Wallis test (for singly ordered contingency tables) or Jonckheere-Terpstra test (for doubly ordered contingency tables) was used. Multivariable analysis was performed to test the influence of different clinical and histologic parameters on recovery of kidney function at 6 months. Statistical analysis was performed using JMP, version 9 (SAS Institute Inc); SPSS for Windows, version 17 (SPSS Inc); and StatXact for Windows, version 9 (Cytel Corp). The study was approved by the Mayo Clinic Institutional Review Board.

## RESULTS

### Baseline Clinical and Demographic Data

Table 1 lists demographic and clinical characteristics of all 133 patients with AIN and compares drug-induced AIN to AIN from other causes. Most patients (58%) were hospitalized and developed AKI during the course of this hospitalization. Baseline serum creatinine levels (median, 1.1 mg/dL) were available for 109 patients, and 48 (44%) patients had CKD as defined by baseline eGFR $< 60$ mL/min/1.73 $m^2$. Prior to biopsy, AIN was suspected in only 55% of cases. Close to half the patients had pyuria and about one-third had hematuria or eosinophiluria as tested using Hansel stain. White and red blood cell casts were rare, encountered in only 3% and 1% of patients, respectively. Only 3 (0.2%) patients had completely