Acute kidney injury in interstitial nephritis

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Purpose of review
The purpose of this review is to describe the most common causes of acute interstitial nephritis (AIN), the diagnostic work-up and the therapeutic management.

Recent findings
Several case series and registries have found an increasing incidence of AIN, especially among older patients. Drug-induced AIN still represents the most common cause. Early withdrawal of the culprit drug together with corticosteroid therapy remain the mainstay of treatment, although recent studies have shown that prolonged treatment beyond 8 weeks does not further improve kidney function recovery.

Summary
AIN is a common cause of acute kidney injury, and therefore, physicians should suspect this entity especially in patients exposed to multiple medications. While immune-allergic reaction to numerous drugs is the most common cause of AIN, other underlying systemic diseases may also be involved, and therefore, every patient should undergo a complete diagnostic evaluation. Kidney biopsy provides the definitive diagnosis of AIN, and certain histologic features may help to identify the underlying condition. In drug-induced AIN, an early discontinuation of the culprit drug is the mainstay of therapy, and unless a rapid recovery of kidney function is observed, a course of glucocorticoid therapy should be initiated.

Keywords
acute interstitial nephritis, corticosteroids, kidney biopsy

INTRODUCTION

Acute kidney injury (AKI) is a growing problem among hospitalized patients and in ICUs, representing a significant contributor to morbidity and mortality [1,2]. Rapid identification of this complication, and early intervention of underlying conditions are essential to prevent the development of established chronic kidney disease. Prerenal dysfunction and acute tubular necrosis are common causes of AKI among ICU patients, although a number of common underlying clinical characteristics, such as hypoalbuminemia, reduced muscle mass and polymedication may also predispose them to acute interstitial nephritis (AIN) [3,4]. Hypoalbuminemia may increase the unbound fraction of the drug, which can expose cells to higher concentrations [5]. In addition, reduced muscle mass (with reduced total body water) may result in higher dosing and potential serum toxic concentrations [5]. When concomitant acute hepatic failure develops, impaired metabolism of drugs can also contribute to the above mechanisms.

AIN is a renal lesion characterized by the presence of inflammatory infiltrates, edema and tubulitis within the interstitium compartment, mostly associated with kidney function impairment [3].

Although the true incidence of the disease is difficult to determine, AIN is found in 5–27% of kidney biopsies performed for AKI [3,6–8], representing the third most common cause of AKI in hospitalized patients [9].

Several case series and registries have found an increasing incidence of AIN, especially among older patients [6,7,10]. However, it remains unclear whether this increase is due to a truly higher incidence or an improved detection and policy of kidney biopsy indications [11].

Drug-induced AIN may also contribute for this increased trend, with NSAIDs, proton-pump inhibitors (PPI) and antibiotics being the most common offending medications. Furthermore, the increased

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KEY POINTS

- AIN is a common cause of acute kidney injury. Thus, clinicians should suspect this entity especially in polymedicated patients.
- Medication is the most common cause of AIN, but other underlying systemic diseases may also be responsible, and therefore, a complete diagnostic work-up should be performed in every case.
- Very few specific blood tests are useful for the diagnosis of AIN and therefore, the definitive diagnosis requires a kidney biopsy.
- In drug-induced AIN, several observational studies have found that early administration of corticosteroids (<5 days after diagnosis) is associated with a better recovery of kidney function.

prescription of immune checkpoint inhibitors (ICPI) among cancer patients has also resulted in higher incidence of AKI and particularly AIN. The paucity of symptoms, especially in older patients may delay the diagnosis, which in turn may negatively impact on renal survival.

In the last years, significant advances in the understanding of the causes and pathogenic mechanisms of AIN have been reported. This review aims to update current knowledge and scientific studies addressing this issue.

CAUSE

Drug-induced

The most common causes of AIN are drug-induced, associated with infectious or systemic diseases and idiopathic forms [6]. Although immune allergic reaction to drugs account for more than two-thirds of AIN cases [9,12], the identification of the causative drug is often challenging, especially in patients exposed to polypharmacy. In fact, in a recent case series of drug-induced AIN, the culprit drug could not be clearly identified in nearly 30% of cases [13▪▪].

Numerous drugs have been incriminated in AIN [8], and in short, almost any drug should be considered as suspected causative agent of an AIN [6].

NSAIDs are commonly implicated in the development of AIN in both children and adults. Fewer extra-renal manifestations at the time of diagnosis, and longer latency periods since the exposure are peculiar features of NSAIDs compared with other common drug-induced AIN [12,14]. In addition, NSAIDs-induced AIN can also be associated with nephrotic syndrome when concomitant minimal change disease is present [15]. The exact mechanisms underlying this form of the disease are poorly understood; however, it is possible that the systemic release of cytokines and inflammatory factors by activated cells could alter the permselectivity of the glomerular filtration barrier [15].

Antibiotics (including both beta and nonbeta lactams) are also frequently implicated in AIN [8]. Hypersensitivity syndrome with fever, rash or eosinophilia is found in a large percentage of these cases (>75%) [12]. Fluorquinolones and especially ciprofloxacin, are among the most common causative antibiotics [12], with characteristic delayed onset of clinical manifestations, making its diagnosis a challenging task [16].

In recent years, significant epidemiological changes have taken place in AIN, due to the emergence of novel causative drugs such as PPI, 5-aminosalicylates or newer anticancer therapies [5,6,17,18▪,19].

PPIs are among the most widely used medications worldwide, and often taken over-the-counter [6,17]. According to different case series, PPIs were found to be responsible for AIN in 18–64% of the cases [20–22], especially in older patients [20]. Indeed, a case–control epidemiological study found that current PPI users more than 60 years old were at higher risk of AIN compared with younger current users [23].

The clinical presentation of PPI-induced AIN is often nonspecific including malaise or low-grade fever, with the classical triad of fever, rash and eosinophilia found in less than 10% of the cases [6]. The severity of AKI in this setting may be lower as compared with other drug-induced AIN, but the longer duration of the exposure due to its delayed diagnosis, may hamper the recovery of kidney function [20].

ICPI such as ipilimumab, nivolumab or pembrolizumab may induce AKI in around 1–29% of the cases, although the true incidence may be underestimated [24,25]. However, while AIN is a potential cause of AKI in cancer patients treated with ICPI, other causes may also be responsible. The reported interval between drug initiation and the onset of renal abnormalities ranges from 1 to 24 months [18▪,24,26▪,27], and extrarenal manifestations such as hypophysitis or colitis may precede AKI [18▪].

In addition, the drug reaction with eosinophilia and systemic symptoms (DRESS syndrome), a drug-induced hypersensitivity reaction characterized by fever, rash, eosinophilia and multiple organ involvement, can also be associated with AIN in 10–30% of cases [28]. Allopurinol, anticonvulsant

drugs [6] and antibiotics [29] are the drugs most frequently involved in this syndrome.

Infections

Both viral (including HIV, cytomegalovirus, Epstein–Barr virus and BK virus), and bacterial infections (including Brucella, Salmonella, Campylobacter or Mycoplasma, among others), can precipitate an AIN [30]. Although the exact pathogenic mechanism has not been clearly elucidated, direct cytopathic effects of microorganisms or the release of proinflammatory cytokines in the setting of infection could potentially explain the inflammatory kidney damage [6,31].

In addition, recent studies suggest that tuberculosis (TB)-related kidney disease could be evolving into an AIN type pattern [32].

Systemic diseases and other causes of acute interstitial nephritis

Several autoimmune diseases may cause AIN, including systemic lupus erythematous, Sjögren syndrome, scleroderma, tubulointerstitial nephritis and uveitis syndrome, IgG4-related disease and vasculitis [33▪]. These disorders are more common in younger patients, and they are usually accompanied by overt extra-renal manifestations, which in turn, can be of huge help in elucidating the diagnosis [6]. AIN in the setting of systemic diseases may occasionally recur, thus posing a therapeutic challenge for the clinician [6].

Acute infiltrates tend to progress to interstitial fibrosis, and varying degrees of chronic interstitial nephritis are usually observed in the kidney biopsies of these patients [33▪].

Other relevant pathological processes associated with AIN are AIN secondary to antitubular basement membrane (TBM) antibodies with or without concurrent antiglomerular basement membrane antibodies [34], and isolated light-chain mediated AIN with or without tubulopathy in the setting of monoclonal gammopathies [35].

Finally, early lesions of AIN have also been detected in the so-called interstitial nephritis in agricultural communities or Mesoamerican nephropathy [36▪▪], whose underlying pathogenic mechanisms still remains poorly understood.

PATHOGENESIS

Drug-induced, the most common cause of AIN is characterized by a dose-independent idiosyncratic drug hypersensitivity reaction that typically appears 7–10 days after exposure of the culprit drug [9].

Several potential mechanisms have been suggested to explain this type of AIN which are represented in Fig. 1 (reviewed in detail by Raghavan *et al.* [9,37▪]):

(1) A drug hapten may bind to the TBM, initiating an immune response [37▪].
(2) A drug-derived antigen released in the circulation with similar structure to a TBM component may trigger an immune response against TBM [37▪].
(3) Drug-derived antigen trapped within interstitium may elicit in-situ immune response [37▪].
(4) Drug-derived immune-complexes may become trapped in the interstitial space leading to an inflammatory response [37▪].

In addition, other complex necroinflammatory pathways have also been implicated in recent studies, triggering inflammation and self-perpetuating a cascade of tissue injury [37▪,38–40].

Recent advances in cancer immunotherapies such as ICPIs and chimeric antigen receptor T cells, have also led to an emerging incidence of drug-related nephrotoxicities [18▪,19,41,42▪], through an increased immune intolerance to both endogenous and drug-derived antigens [42▪].

The pathogenesis of AIN in the context of systemic diseases is heterogeneous, involving both production of autoantibodies, deposition of immune-complexes within the interstitium and activation of inflammatory pathways [43].

CLINICAL PRESENTATION

In the majority of cases, symptoms associated with AIN are nonspecific (malaise, nausea–vomiting or flank pain). The classical triad of AIN, consistent of fever, rash and eosinophilia, is observed more frequently in drug-related hypersensitivity reactions, especially when beta-lactam antibiotics are involved.

Low-grade or intermittent fever can develop, but may also be absent in AIN caused by some drugs [12]. Skin rash is typically maculopapular or morbilliform, although diffuse erythroderma or toxic epidermal necrolysis can also develop [3,12].

However, according to recently reported large series of AIN, these symptoms and signs are present in less than 25% of cases [7,13▪▪,21,44,45▪▪]. Arthralgia is other symptom frequently reported in other series [46].

The most common renal manifestations of AIN is a nonoliguric AKI with slow increase in serum creatinine, although rapidly progressive forms may also be seen [12]. Arterial hypertension or edema is less frequently observed [12].

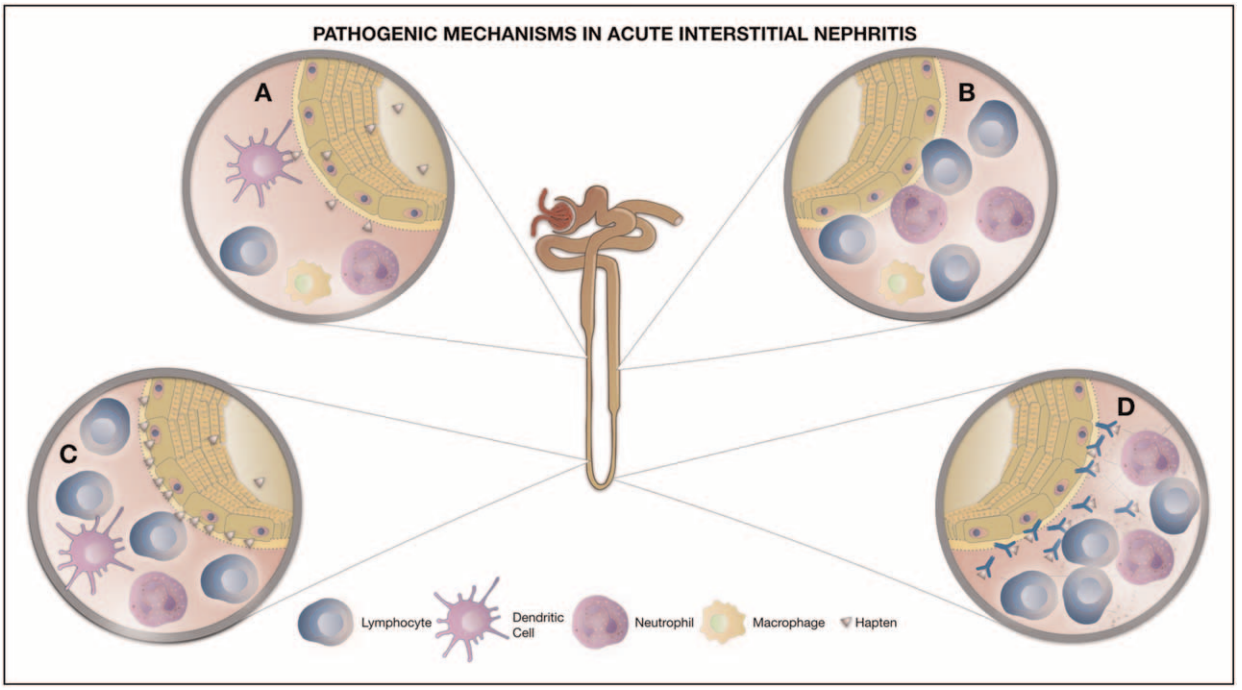

FIGURE 1. (a) Drug hapten may bind to the tubular basement membrane, initiating an immune response; (b) drug-derived antigen released in the circulation with similar structure to a tubular basement membrane component may trigger an immune response against tubular basement membrane; (c) drug-derived antigen trapped within interstitium may elicit in-situ immune response; (d) drug-derived immune-complexes may become trapped in the interstitial space leading to an inflammatory response.

DIAGNOSIS

Laboratory

AKI develops in almost all patients with AIN and consistently, increased serum creatinine and blood urea nitrogen levels should confirm this diagnosis [12].

Very few specific blood tests are useful for the diagnosis of AIN. Eosinophilia, when present, could give rise to the suspicion of AIN-related immune allergic disease [47]. However, eosinophilia may also occur in other clinical conditions such as cholesterol emboli syndrome, vasculitis and malignancy among others, and therefore, these other processes should be considered in the differential diagnosis, particularly in older patients [3,48].

A complete diagnostic work-up should be performed in every case of AIN, to rule out underlying infectious or systemic diseases, including hepatitis B, C and HIV serology, antinuclear antibodies, anti-neutrophil cytoplasmic antibodies, serum complement, anti-RO/SSa and anti-LA/SSb, angiotensin-converting enzyme, serum electrophoresis and immunofixation. In addition, these tests should be completed with urine cultures and Ziehl–Neelsen in selected cases.

Urinalysis may reveal eosinophiluria, defined as percentage of eosinophils greater than 1% of total urinary white cells count, although several studies have questioned the reliability of this test for the diagnosis of AIN [47,48].

Leukocyturia is a very common feature, often accompanied by leukocyte casts [3]. In fact, approximately 80% of patients with AIN may have a dipstick-positive leukocyte esterase, which is a surrogate marker for urinary leukocytes [47].

Another very frequent finding is microscopic hematuria, which may be present in up to 50% of the cases, although red blood cell casts are rare [3,13▪▪].

Urinalysis may also show varying degrees of proteinuria, usually nonnephrotic range, consistent with tubular proteinuria, although nephrotic range proteinuria has also been described [3,13▪▪,48].

Furthermore, a panel of urinary biomarkers, including monocyte chemotactic peptide-1 and neutrophil gelatinase-associated lipocalin, have also been tested in AIN, though these findings have not yet been translated into clinical practice [49]. Recent studies have reported the potential role of other biomarkers such as urine TNF-α and IL-9 in the differentiation between AIN from acute tubular injury [50▪].

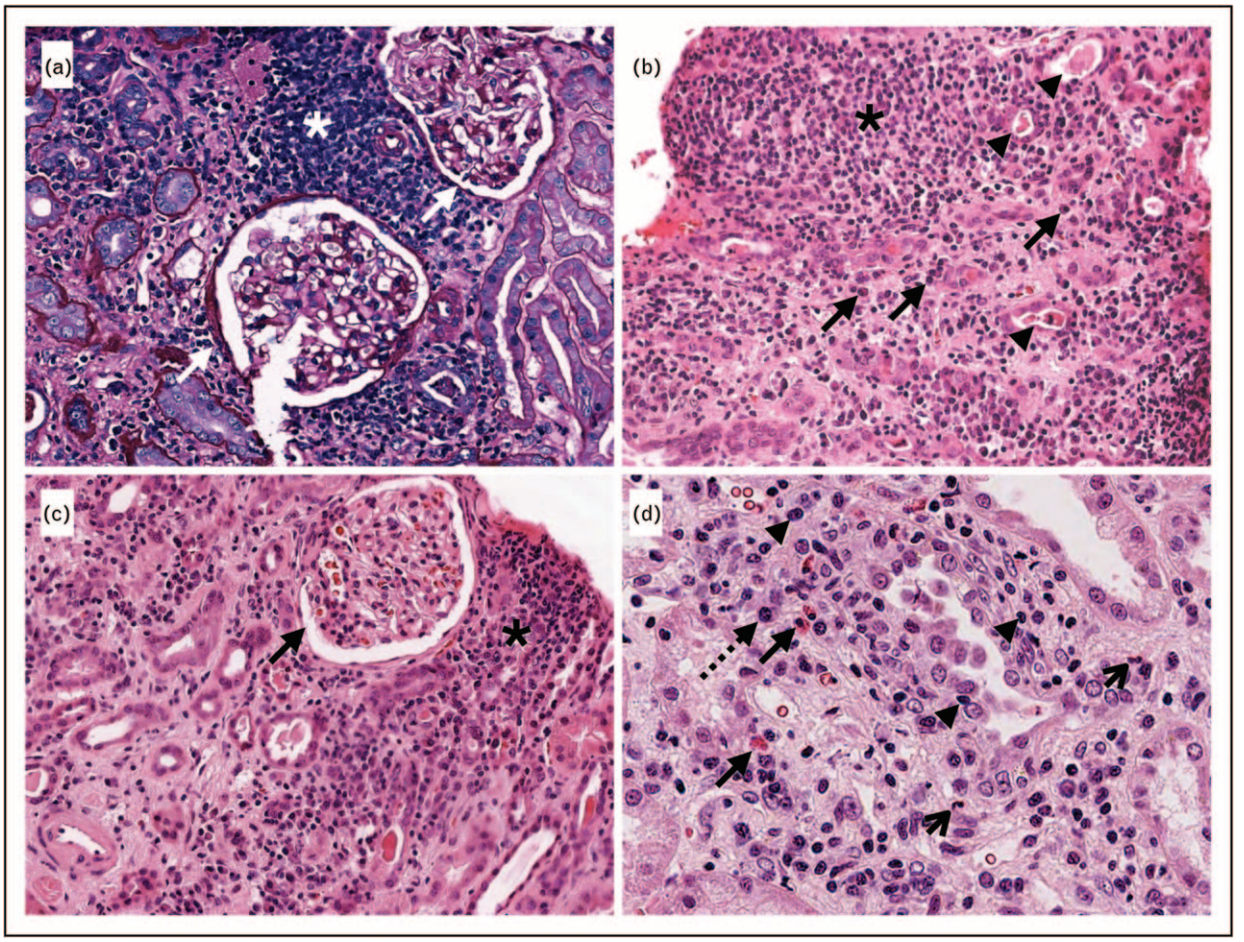

FIGURE 2. (a) Periodic acid–Schiff staining showing an inflammatory infiltrate predominantly composed of lymphocytes (*), with no significant glomerular abnormalities on light microscopy; (b) hematoxylin and eosin staining of renal tissue showing a lymphocytic infiltrate (*) with plasma cells (arrows) and hyaline casts (arrowheads); (c) lymphocytic inflammatory infiltrate with no significant glomerular lesions; (d) hematoxylin and eosin staining showing a mixed inflammatory infiltrate composed of lymphocytes (arrowheads), eosinophils (thick arrows), neutrophils (thin arrows) and plasma cells (dashed arrow).

Histopathology

Definitive diagnosis of AIN requires a kidney biopsy [3,11,12].

The characteristic interstitial infiltrate is composed of lymphocytes and monocytes, accompanied by variable number of eosinophils, plasma cells and neutrophils [48] (Fig. 2). A predominant eosinophilic infiltration may point toward a drug-induced AIN, whereas neutrophilic infiltration is suggestive of bacterial infection [48]. In addition, interstitial edema is often present earlier in the course of the disease.

The invasion of TBM by inflammatory cells (primarily lymphocytes) leads to the classic lesion of tubulitis [12].

Some characteristic histologic features such as granuloma may be observed in some patients with AIN [3].

Granulomatous forms of AIN are a rare condition that can be related with the exposition of some drugs such as vancomycin, ciprofloxacin, penicillin or cephalosporins, but it may also be caused by granulomatous systemic diseases, such as sarcoidosis, TB or other granuloma-forming conditions [31].

Renal imaging techniques

Several imaging modalities are available for the evaluation of the kidneys and urinary tract in AKI. While none of these techniques can replace the diagnostic information of a kidney biopsy, some specific findings have been associated with AIN.

For instance, gallium-67 scintigraphy has been proposed as a safe technique that may aid in the diagnosis of AIN [51]. Gallium-67 binds to lactoferrin, which is released by leukocytes within the interstitium, and therefore in the setting of AIN a gallium enhancement and positive test may be detected [48]. However, the main limitation of this technique

is its low specificity, because in addition to AIN, other inflammatory conditions such as pyelonephritis, atheroembolism or glomerulopathies can also yield positive results.

Furthermore, the potential role of positron emission test scanning has also been evaluated in the diagnosis of AIN [52].

MANAGEMENT AND PROGNOSIS

The therapeutic management will depend on the underlying causative condition. In drug-induced AIN, an early identification and discontinuation of the potential offending agent is the mainstay of therapy. However, in clinical practice this can be difficult, particularly in patients taking multiple medications [12]. Some clinical or laboratory manifestations, together with timing of exposure may point to a likely culprit drug [12].

The likelihood of spontaneous recovery of kidney function after discontinuation of the causative agent will depend on the duration of the exposure [12]. Although the efficacy of immunosuppression in AIN has not been evaluated in randomized controlled trials, several observational studies have found that early treatment with corticosteroids is associated with a better recovery of kidney function [7,13▪▪,44,53].

In a recent multicenter study including 182 patients with biopsy proven drug-induced AIN treated with corticosteroids, 41% of the patients recovered more than 75% of kidney function after 6 months, whereas only 13% recovered less than 25% of baseline kidney function [13▪▪]. The mean dose of corticosteroids was 0.8 ± 0.2 mg/kg/day, and no significant differences were observed between patients who received or not initial intravenous pulses [13▪▪]. In multivariate analysis, the main determinants of incomplete recovery of kidney function were the degree of interstitial fibrosis in kidney biopsy and the delay in the initiation of corticosteroid therapy [13▪▪]. In addition, another remarkable finding was that high-dose corticosteroid therapy for longer than 3 weeks or a tapering phase beyond 5 weeks was not associated with better renal outcomes, further increasing the risk for adverse effects of immunosuppression.

These observational studies are subject to limitations (particularly selection biases), however, weighing the benefits and risks of corticosteroid therapy we favor an early administration of corticosteroids (<5 days after diagnosis) unless rapid renal function recovery after drug withdrawal in mild cases [5], with the rationale of improving the interstitial infiltrates and avoiding the development of subsequent fibrosis.

One possible therapeutic regimen would be as follows: intravenous pulses of methylprednisolone, 125–250 mg/day for 3 consecutive days; oral prednisone, 0.5–1 mg/kg/day from the fourth day, up to 1–2 weeks; prednisone tapering for 4–6 weeks. However, if kidney function does not improve after 2 weeks of treatment, corticosteroid therapy should be discontinued to avoid side effects.

Finally, AIN in the setting of infections or systemic diseases require antimicrobial therapy or more targeted immunosuppressive regimens, respectively [3,33▪].

The reported prognosis of AIN is heterogeneous. According to the latest case series, recovery of kidney function is often incomplete in drug-induced AIN, ranging from 40 to 50% of the cases [7,13▪▪,21,44,53]. The prognosis of AIN secondary to other pathological processes is unknown or not well described.

CONCLUSION

AIN is a common cause of AKI. Clinicians should be aware of the possibility of a drug-induced AIN particularly in patients exposed to multiple medications. However, while medication is the most common cause of AIN, other underlying systemic diseases may also be responsible, and therefore, a complete diagnostic work-up should be performed in every case. Randomized trials in AIN are lacking, but several observational studies have found a beneficial effect of corticosteroids in drug-induced AIN, especially when they are administered earlier in the course of the disease.

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Conflicts of interest

There are no conflicts of interest.

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