Management of drug-associated acute interstitial nephritis

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Drug-associated acute interstitial nephritis (AIN) is characterized by acute or sub-acute loss of kidney function, interstitial infiltrates, edema, and tubulitis on kidney biopsy, with a relative sparing of the glomerulus and vasculature.\textsuperscript{1} Estimates indicate that AIN is the primary finding on 2-5\% of all native kidney biopsies. In those biopsied for acute kidney dysfunction, the frequency of AIN is closer to 10-30\%, although the true burden of AIN likely remains under-estimated.\textsuperscript{1} Due to procedural risk, biopsies are often deferred in favor of empiric discontinuation of the suspected offending agent. Several AIN etiologies have been identified, but the majority of cases (60-70\%) have been linked to drugs and toxins.

\textit{Pathophysiology and presentation}

Drug-associated AIN is thought to be a cell-mediated immune response, akin to a type 4 (delayed-type) hypersensitivity reaction.\textsuperscript{2} Mechanistic explanations for AIN include that drugs could act as haptens to modify the endogenous response to native renal proteins or induce an auto-immune reaction to the tubular basement membrane through molecular mimicry. Drugs could also rarely lead to systemic immune-activation that contributes to deposition or sequestration of immune complexes in the renal interstitium.\textsuperscript{2,3} As early as 7 days after drug exposure, the early inflammatory lesions in AIN can begin to evolve into irreversible interstitial fibrosis. This likely explains why, even with best available management, only 40-50\% of patients with AIN experience complete renal recovery.\textsuperscript{4}

As more and diverse cases of drug-associated AIN have been reported, it is apparent that the ‘classic triad’ of extra-renal manifestations which include fever, rash, and eosinophilia, only occur in about 10\% of patients.\textsuperscript{5,6} Rather, drug-associated AIN has a highly variable presentation. In 133 cases of biopsy-confirmed AIN, 95 of which were
drug-related, fever, rash, and eosinophilia individually occurred in 20-23% of patients. Microscopic hematuria, sterile pyuria, and non-nephrotic range proteinuria were present in 34%, 47%, and 91% of patients, respectively. Importantly, eosinophiluria was only present in 38% of drug-associated AIN cases. Recently, Moledina, et al. identified urinary TNF-α and IL-9 as independently predictive of AIN. After accounting for the clinician’s pre-biopsy suspicion of AIN, as well as standard available laboratory markers, urinary TNF-α and IL-9 significantly increased AIN prediction model performance (AUC = 0.84). While many questions remain, these tools represent an exciting new non-invasive diagnostic approach to increase the probability of detecting AIN. Ideally, such biomarkers could sufficiently increase the post-test probability of AIN such that a kidney biopsy may be avoided.

Drug causes
Several drugs and drug classes have been associated with AIN (Table 1). Beta-lactam antibiotics, including pencillins and cephalosporins, are among the leading etiologies for drug-associated AIN. Time to onset of beta-lactam AIN is typically over days to a few weeks, and it is often accompanied by extra-renal manifestations of hypersensitivity to the beta-lactam (such as a rash). Other non-beta-lactam antibiotics implicated in cases of AIN include sulfonamides, rifampin and ciprofloxacin.

Non-steroidal anti-inflammatory drugs (NSAIDs) and proton-pump inhibitors (PPIs) account for the bulk of the remaining drug-associated AIN cases. NSAIDs elicit nephrotoxicity through several mechanisms. Indirect nephrotoxicity may result from altered intraglomerular hemodynamics. Direct nephrotoxicity most commonly presents as AIN, but more rarely can also include minimal change disease, glomerulopathies, and papillary necrosis. With PPIs, the primary pattern of nephrotoxicity is AIN.
Epidemiologic studies indicate a 1.3- to 2-fold greater risk of AKI and chronic kidney disease (CKD) in patients treated with PPIs, not observed in comparator patients treated with histamine$_2$-receptor antagonists (H2RA).\textsuperscript{9} It is possible, if not probable, that many cases of CKD detected in PPI treated patients may reflect under-recognized and undertreated AIN. Unlike beta-lactams, the time to onset for these associations is often more delayed, over a matter of months. This delay may reflect slowed time to AIN detection, unrecognized over-the-counter use, or a different underlying pathophysiology altogether. It does appear that these cases have a lower incidence of systemic manifestations of hypersensitivity, less frequent eosinophilic interstitial infiltration, and a greater risk for interstitial fibrosis, perhaps secondary to the delayed recognition.

To date, these three major drug classes (antibiotics, NSAIDs, and PPIs) accounted for 80-90\% of the reported cases of drug-associated AIN. However, increasingly a new class of medications, immune checkpoint inhibitors, has gained attention as a cause of AIN. These drugs disinhibit the immune system, and, through T-lymphocyte activity, facilitate the recognition and eradication of cancer cells. Unfortunately, this unbridled immune response can also result in auto-immune toxicity directed at previously healthy host tissue, including in the kidney. The time course of AIN from checkpoint inhibitors may be from 1 to 8 months after drug initiation, but may extend to 1-2 months after drug discontinuation due to the long half-life of these agents and their sustained impact on the immune system.\textsuperscript{10} As the indications, number and diversity of drugs, and patient populations exposed to these treatments expand, immune checkpoint inhibitor-associated AIN will likely become more common.

Management
The cornerstones of drug-associated AIN management include: 1) early identification, 2) withdrawal of the suspected offending agent, 3) consideration for immunomodulatory therapy, and 4) secondary prevention.

Clinicians can contribute to early identification of drug-associated AIN by dispelling myths about required findings (e.g. insensitivity of the ‘classic triad’), avoiding over-reliance on non-definitive tests (e.g. urinary eosinophils), and early engagement of an interprofessional team. Nephrologists should evaluate patient history, clinical and laboratory data, and determine if advanced diagnostics are warranted. Clinical pharmacists should conduct a detailed review of the medication profile to identify the most likely offending agent(s).

Once a suspected offending agent is identified, the next step is drug withdrawal. Given that delayed intervention may allow irreversible interstitial fibrosis from the AIN to develop, it is essential to take early action to minimize exposure to the drug of concern. If the underlying condition warrants ongoing therapy, alternatives should be vetted by the interprofessional team. As an example, for a patient with gastroesophageal reflux disease who develops AIN from omeprazole, it would be reasonable to explore candidacy for dietary and lifestyle modifications, or use of a lower risk class of drugs (e.g. H2RAs). In cases where the medication cannot be safely withdrawn or substituted, it is unclear whether desensitization could be used to decrease the incidence or severity of AIN. To our knowledge this has not been studied.

Once AIN is identified, and the suspected drug is withdrawn, the next step is to consider an immunomodulatory agent. Few clinical trials are available to guide this aspect of AIN care; observational studies, case series and case reports define the field. While the
literature is somewhat inconsistent, it does appear that corticosteroids favorably impact renal recovery in drug-associated AIN.\textsuperscript{5,6,11,12}

Earlier time to corticosteroid initiation seems to favorably affect treatment response. In 61 biopsy-proven cases of drug-associated AIN, an interval of less than 7-days from drug withdrawal to corticosteroid administration and a lesser degree of interstitial fibrosis each predicted steroid responsiveness.\textsuperscript{6} These findings were replicated in an independent cohort.\textsuperscript{11} For individuals within 7-14 days of drug withdrawal without evidence of renal recovery, and with limited interstitial fibrosis on biopsy, corticosteroids could be trialed.\textsuperscript{12,13}

Dose and duration of corticosteroid therapy varies across studies. Most reports indicate an initial dose of 0.5-1mg/kg/day prednisone equivalent, which may be preceded by a “pulse dose” of 250-500mg/day of methylprednisolone for 2-4 days. A prospective randomized trial of 31 patients with drug-associated AIN compared the use of 1mg/kg/day prednisone equivalent with or without an initial bolus of 30mg/kg methylprednisolone (maximum 1g). Patients randomized to the pulse dose arm demonstrated a slightly greater improvement in kidney function by 1 week, but by weeks 2 and 3 the degree of recovery from baseline was similar between groups.\textsuperscript{13} In a multicenter cohort of 182 cases of steroid-treated drug-associated AIN, no benefit was observed with the use of pulse dose steroids, or extended steroid courses. While these data have limitations, if steroids are to be used, a reasonable approach could include initiation of 1mg/kg/day (maximum 60mg/day) of prednisone with repeat kidney function monitoring after 1-3 weeks. In responders, therapy could be tapered slowly over 2-6 weeks. In non-responders, corticosteroids could be discontinued more rapidly. Throughout therapy, symptoms of possible corticosteroid toxicity should be monitored for
including hyperglycemia, neuropsychiatric effects, new infections including *Pneumocystis jirovecii* pneumonia (PCP), and muscle weakness. In certain circumstances proactive preventative therapy (e.g. insulin, PCP prophylaxis) may be indicated.

In patients unable to receive corticosteroids or with relapsed or refractory AIN, alternative immunomodulatory therapies may be trialed. In 8 patients treated with corticosteroids for at least 6-months for AIN who were unable to discontinue therapy, mycophenolate mofetil (MMF) 500-1000mg twice daily led to a successful steroid withdrawal in all patients and at least partial recovery in 6 of 8. The T-cell depleting agent antithymocyte globulin was successfully used in one case of refractory AIN. Until additional data is available, these agents should be reserved for use in only rare circumstances.

Finally, in patients with drug-associated AIN, attention should be paid to secondary prevention. Key elements of secondary prevention should include 1) documentation of the drug intolerance/allergy in the electronic health record, 2) enhanced kidney monitoring during the at-risk and recovery period, and 3) follow-up care for chronic kidney disease if needed.
Table 1. Select agents with reported risk of drug-associated AIN

| Drug type/class          | Select agents                                                                 |
|--------------------------|-------------------------------------------------------------------------------|
| **Antimicrobials**       |                                                                               |
| Beta-lactam antibacterials| Penicillins (e.g., methicillin, nafcillin, amoxicillin)                       |
| Cephalosporins           |                                                                               |
| Other antimicrobials     | Sulfonamides (e.g., sulfamethoxazole/trimethoprim)                            |
|                         | Rifampin                                                                      |
|                         | Fluoroquinolones (e.g., ciprofloxacin)                                       |
|                         | Vancomycin                                                                    |
|                         | Acyclovir                                                                     |
|                         | Anti-retroviral agents (e.g., abacavir, indinavir)                             |
| **Anti-inflammatory**    |                                                                               |
|                         | NSAIDs (e.g., ibuprofen, nabumetone)                                          |
|                         | COX-2 Inhibitors (e.g., celecoxib)                                            |
|                         | 5-ASA derivatives (e.g., sulfasalazine, mesalamine)                           |
| **Acid-suppressive therapy** | PPIs (e.g., omeprazole, lansoprazole)                                       |
| **Immune checkpoint inhibitors** | Anti-PD1 antibody (e.g., pembrolizumab, nivolumab) | Anti-PD-L1 antibody (e.g., durvalumab) |
|                         | Anti-CTLA-4 antibody (e.g., ipilimumab)                                       |
| **Anti-convulsants**     | Phenytoin                                                                     |
|                         | Carbamazepine                                                                 |
|                         | Phenobarbital                                                                 |
| **Others**              | Allopurinol                                                                   |
|                         | Furosemide                                                                   |

NSAIDs: Nonsteroidal anti-inflammatory drugs; COX-2 inhibitors: cyclooxygenase-2 inhibitors; 5-ASA: 5-aminosalicylic acid derivatives; Anti-PD1 antibody: Anti-programmed cell death-1 (PD-1) antibody; Anti-PD-L1: Anti-programmed cell death ligand-1; Anti-CTLA-4 antibody: Anti-cytotoxic T lymphocyte-associated antigen 4
Disclosures
Dr. Barreto reports Advisory Board from FAST Biomedical outside the submitted work. Dr. Rule has nothing to disclose.

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