DRUG-INDUCED ACUTE TUBULOINTERSTITIAL NEPHRITIS

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Rezumat
Nefritele tubulointerstțiale alergic medicamentoase sunt afecțiuni tot mai frecvente în practica curentă ca urmare a accesului crescut al pacienților la o varietate de medicamente. Tabloul clinico-biologic asociază injurie renală acută cu fenomene de hipersensibilitate. Considerate clasic reversibile după sistarea medicamentului încriminat, nefritele tubulointerstțiale alergic medicamentoase și-au modificat în ultimele decenii caracterele evolutive, chiar sub tratament. Articolul de față prezintă caracteristicile clinico-biologice, terapeutice și evolutive ale nefritelor tubulointerstțiale alergic medicamentoase.

Cuvinte cheie: nefrite tubulointerstțiale acute; medicamente; injuria acută a rinichiului.

Abstract
Nowadays, incidence of drug-induced acute tubulointerstitial nephritis is on the rise due to increased access of the patients to a variety of both prescribed and over-the-counter drugs. Acute kidney injury and hypersensitivity manifestations are the main features of acute tubulointerstitial nephritis. Classically considered reversible after prompt withdrawal of the offending medication, recent decades revealed potential for evolution to chronic kidney disease. This article presents the challenges in the diagnosis and treatment and also evolutive features of allergic acute tubulointerstitial nephritis induced by drugs.

Keywords: acute tubulointerstitial nephritis, medication, hypersensitivity, acute kidney injury.
Introduction

The offer of drugs on the pharmaceutical market is constantly growing. The diversity of the drug supply covers a wide range of conditions from common intercurrent diseases such as colds to advanced stages of cancer.

A considerable number of medications can be purchased by the patients without physicians' prescription (over-the-counter). The kidney, a richly vascularized organ and equipped with a urine concentration system, is highly susceptible to a myriad of drug-induced side effects. If some of these adverse reactions can be considered iatrogenic (eg acute tubular necrosis after gentamicin) or "accidents" (eg contrast nephropathy after iodate contrast agent absolutely necessary to be used) being dose-dependent, allergic drug-induced acute tubulointerstitial nephritis (DI-ATIN) are part of the renal side effects difficult to prevent.

More than 150 drugs are reported to induce DI-ATIN, but the most involved are therapeutic classes recommended in current practice in all specialties: antibiotics, nonsteroidal anti-inflammatory drugs (NSAIDs) and proton pump inhibitors. The classic clinical-biological picture of DI-ATIN is characterized by the association of acute kidney injury (AKI) with allergic phenomena occurring a few days after the administration of a drug. Unfortunately, in current practice, the typical clinical picture is rarely present, often these conditions being classified as AKI of unknown cause.

Epidemiology, etiology, risk factors

Acute tubulointerstitial nephritis (ATIN) represent the third leading cause of AKI after prerenal azotemia and acute tubular necrosis. The exact incidence of ATIN is probably underestimated, because the definitive diagnosis is established by renal biopsy which is not performed, for various reasons, in all cases. From the reports of different national registries of renal biopsy, the prevalence of bioptic detection of ATIN varies between 1 and 10% of total biopsies performed for various indications and between 6.5 and 35% of biopsied cases to elucidate the cause of AKI.

Depending the cause, ATIN can be classified as drug-induced, infectious-associated, associated with systemic diseases or idiopathic; over 70% of cases are attributed to drugs. The frequency of DI-ATIN is higher in developed countries due to increased access to a wide range of drugs. Over 150 drugs have been reported in the literature as potential inducers of ATIN (Table 1). The list is constantly growing by the introduction, in recent decades, of various alternatives for conditions considered classically without therapeutic resources, such as immune checkpoint inhibitors used now successfully for advanced neoplasm. However, despite the diversification of drug offer on the market, the most involved offending drugs are the same classes (obviously enriched with new molecules) as 40 years ago: antibiotics and...
**Table 1.** Drugs that can induce acute allergic tubulo-interstitial nephritis

Legend: PD-1, programmed cell death protein-1; PD-L1, programmed death ligand 1; CTLA-4, cytotoxic T-lymphocyte antigen-4;

| Category                        | Drugs                                                                 |
|---------------------------------|----------------------------------------------------------------------|
| Antibiotics                     | β-Lactam (penicillin, cephalosporins)                                |
|                                 | Fluoroquinolones (ciprofloxacin)                                    |
|                                 | Sulfonamides (sulfamethoxazole/trimethoprim, nitrofurantoin)         |
|                                 | Rifampicin                                                          |
|                                 | Macrolides (clarithromycin, telithromycin)                           |
|                                 | Vancomycin, etc.                                                    |
| Non-steroidal anti-inflammatory drugs | All agents, including aspirin, including selective COX-2 inhibitors |
| Antisecretory agents            | Proton pump inhibitors: omeprazole, lansoprazole, pantoprazole, esomeprazole |
|                                 | H2-receptor antagonists: cimetidine, famotidine, ranitidine         |
| 5-aminosalicylates              | Sulfasalazine, mesalazine                                           |
| Diuretics                       | Furosemide, bumetanide, thiazides                                   |
| Immune check point inhibitors   | PD-1/PD-L1 inhibitors (nivolumab, pembrolizumab, cemiplimab, atezolizumab) |
|                                 | CTLA-4 inhibitors (ipilimumab, tremelimumab)                        |
| Angiogenesis inhibitors         | Tyrosine kinase inhibitors (sorafenib, sunitanib)                   |
| Others                          | Antiviral drugs (Aciclovir, Indinavir); Antiepileptics (phenytoin, phenobarbital, carbamazepine), Allopurinol, Amlodipine, Captopril, etc. |
NSAIDs\(^{17}\). In addition, increased number of ATIN after proton pump inhibitors are reported\(^ {15,18,19}\). Also, comparing to the 80’ reports\(^ {20}\), there are described ATIN after 5-aminosalicylates and new chemotherapeutic agents\(^ {10,21-23}\).

Except avoidance of polypharmacy, there is no prevention for DI-ATIN because the mechanism of this condition is allergic, so unpredictable. A higher frequency of DI-ATIN is reported in the literature in the elderly, but this does not seem to be related to age-specific immune changes, but to the increased number of drugs that the elderly take\(^ {24}\).

**Pathogenesis**

The pathogenic mechanism of NTIAM is allergic, most often involving cellular immunity\(^ {12,14,25}\) in the form of T-cell-mediated type-4 delayed hypersensitivity reaction. Drugs can act through different mechanisms\(^ {5,14,26}\):

- by acting as hapten, which is binding to a protein component of the tubular basement membrane (TBM), turning it into a neo-antigen;
- through mimicry: resemblance to an antigen in TBM or interstitium, thus inducing a cross-immune response;
- by acting as a “planted” antigen in TBM or in the interstitium with production of antibodies against it.

There are also described cases in which humoral immune response is involved: the drug induces production of circulating antibodies, and the circulating immune complexes are subsequently deposited in the interstitium.

**Clinic and biologic manifestations**

Histological findings in DI-ATIN are represented by diffuse or focal interstitial inflammatory infiltrate\(^ {14,27}\), consisting mainly of T-type lymphocytes, monocytes, macrophages, sometimes eosinophils and even neutrophils. Occasionally, granulomatous infiltrate with giant cells can be noticed.

The manifestations of ATIN are the result of the extension of the inflammatory infiltrate and of the interstitial edema to the adjacent tubules that present inflammatory lesions (appearance of tubulitis) or even of necrosis with variable extension.

Most often no glomerular lesions are present, and if they do occur (most often in ATIN after NSAIDs), they are usually in the form of minimal changes disease, which appear normal on examination with light microscope\(^ {14}\).

The classic clinical picture of DI-ATIN was first described after methicillin administration\(^ {5,28}\) and consists in the acute onset, a few days after the administration of a drug, of oliguric AKI associated with the classical triad: fever, maculopapular rash and eosinophilia. Other nonspecific manifestations may be present, such as chills, arthralgias, myalgias, dull low back pain, nausea, asthenia and general malaise.

Edema and hypertension are absent. Urine exam shows tubulointerstitial-type changes:
low urine density; tubular proteinuria with low molecular weight proteins; microscopic hematuria, with isomorphic red blood cells and usually without erythrocyte casts; leukocyturia with white cells casts and, specifically, increased eosinophiluria. Clinic and biologic manifestations are dose-independent and recur if the same drug or even a related drug is administered \(^{(28,30)}\).

Nowadays, the classic presentation is rarely seen. The interval between drug administration and onset of symptoms can vary from 1 day (typically for rifampicin, especially after re-administration) to a few days (typically for methicillin, amoxicillin), a few weeks (immune checkpoint inhibitors) or even months (for NSAIDs or proton pump inhibitors), which makes it difficult to establish a cause-effect relationship between AKI and the culprit drug \(^{(25,31-33)}\).

Both the classic triad fever-rash-eosinophilia and each of its components are quite rare today.

A frequently cited meta-analysis in the literature shows that out of 128 patients diagnosed with ATIN of whom 70% had DI-ATIN, the rash was present in only 14.8%, fever in 27.3%, eosinophilia in 23.3 %, and the entire triad in only 10% of patients \(^{(34)}\). There are also cases that show no signs of hypersensitivity \(^{(35)}\), many being considered AKI of unknown cause.

Regarding urinary findings, here too the profile of abnormalities can often be nonspecific for ATIN. Thus, in 50% of cases, AKI manifests with preserved diuresis; hematuria is present in less than half of patients \(^{(36)}\). Changes in fractional urinary excretion of sodium and urea can be both prerenal AKI-type and intrinsic AKI-type \(^{(14,37)}\). Eosinophiluria (more than 1% of leukocytes in the urine), considered classically highly suggestive for DI-ATIN, is not routinely searched because it requires special staining that is not widely available. Eosinophilia can also occur in AKI from other causes: thromboembolic kidney disease, acute tubular necrosis, etc. \(^{(38,39)}\). Proteinuria may be of nephrotic range, especially in NSAIDs-induced ATIN \(^{(30)}\).

Except kidney biopsy, there are no laboratory or imaging tests that would provide definitive diagnosis in DI-ATIN. Renal ultrasound is useful to rule out an obstructive AKI, as the kidneys often look normal or are slightly enlarged due to interstitial edema \(^{(8,40)}\). Imaging the kidney with \(^{67}\)Gallium scan shows diffuse increase uptake by the kidneys, but similar changes may occur in other types of AKI or in glomerular diseases \(^{(14,41-43)}\).

Although it provides the definitive diagnosis, kidney biopsy is often not routinely performed; in the presence of high clinical suspicion and rapid improvement after cessation of the offending drug, biopsy is often no longer necessary. However, in cases where there are several potentially responsible drugs, when kidney function does not recover after stopping the drug or after starting glucocorticoid treatment, biopsy is recommended \(^{(30)}\). Biopsy not only establishes the etiology of AKI, but is particularly useful for the detection of interstitial fibrosis and its extension, a situation that indicates the evolution towards chronicity and the uselessness of continuing corticosteroid treatment \(^{(30)}\).

**Evolution and prognosis**

Classically, DI-ATIN was considered completely reversible after discontinuation of the drug associated or not with corticosteroid treatment \(^{(30,34)}\).

Nowadays, there is evidence of the potential for chronicity of this condition, probably as a result of increased number of potentially offending drugs and also as a result of polypharmacy. Complete recovery of renal function after DI-ATIN is cited in about 60-65% of patients, while incomplete recovery occurs in 10-20% of patients and lack of recovery with chronic dialysis dependence in 5-10% \(^{(12,44)}\).

The risk of chronicity is higher in patients with severe forms of AKI requiring renal
replacement therapy, prolonged AKI, more than 3 weeks or NSAIDs-induced AKI\(^{(38,45)}\). Histologic markers suggestive for evolution toward chronic kidney disease are presence of extensive interstitial fibrosis and tubular atrophy\(^{(30,36)}\).

**Treatment of drug-induced acute allergic tubulointerstitial nephritis**

Stopping the potentially responsible drug is the main measure and sometimes it is sufficient for the recovery of renal function\(^{(12)}\). In patients with multiple potentially offending drugs, it is recommended sequential discontinuation and renal biopsy as soon as possible, in the absence of contraindications\(^{(30)}\).

In severe forms of AKI necessitating dialysis, it is advisable to discontinue all drugs at risk, unless one of them is absolutely necessary for a severe disease\(^{(30)}\). Lack of recovery of renal function within a few days of discontinuation of the drug requires treatment with corticosteroids. Usually short courses of orally prednisone 1 mg/kg/day are administered for 1-2 weeks until renal function begin to recover, then the doses are progressively decreased in a few weeks. The use of intravenous methylprednisolone as pulse therapy 500 mg -1g/day, 3 consecutive days before oral prednisone may be required in severe cases of AKI requiring dialysis.

The decision to initiate corticosteroid therapy and perform a biopsy should be made rapidly, within a few days in severe cases of AKI, due to the risk of chronicity\(^{(12,44)}\). In case of lack of response to corticosteroid therapy initiated without histological confirmation, renal biopsy is essential; corticoids do not alter histologic findings of DI-ATIN.

There are reports in the literature on the use of other immunosuppressive treatments (mycophenolate mofetil, cyclosporine, cyclophosphamide) in DI-ATIN that do not respond to corticosteroids and in which biopsy shows acute inflammatory infiltrate, but these include a small number of patients and experience is limited\(^{(47)}\). These alternatives are cited especially in NSAIDS-induced ATIN which usually has a poor response to corticoids or requires long-term corticotherapy with related specific side effects.

**Particular forms of DI-ATIN**

**ATIN to proton pump inhibitors**

Proton pump inhibitors (PPIs) are frequently recommended in long-term regimens by physicians of various specialties, often to counteract the possible gastric side effects of other drugs, but they are also administered without prescription by patients\(^{(48)}\). They are drugs that generally have few side effects\(^{(48)}\). PPIs-induced ATIN occurs in less than 1% of patients using PPIs, but due to the fact that they are the most widely used class of drugs in current practice, they are listed as the third leading cause of DI-ATIN.

The first cited in this class was omeprazole\(^{(49)}\), but afterwards other PPIs were reported: lanzoprazole\(^{(50)}\), esomeprazole\(^{(51)}\), rabepra-
zole\textsuperscript{52}, pantoprazole\textsuperscript{53}. The clinical presentation of PPIs-induced ATIN is often atypical: AKI, usually without accompanied systemic hypersensitivity symptoms, has a subacute or progressive onset after a time interval that may vary between a few days and several months after administration of PPIs\textsuperscript{54,55}. It is cited higher incidence in the elderly\textsuperscript{15,17,30,56}, increased risk of incomplete recovery of renal function\textsuperscript{57} and progression to chronicity\textsuperscript{54}, even with prompt corticosteroid treatment applied after biopsy confirmation. Eosinophilia is usually seen\textsuperscript{58}, but other specific manifestations of ATIN are inconsistent\textsuperscript{59}, so many cases are classified as AKI of unknown cause until a biopsy is obtained. In some non-Caucasian races, a genetic predisposition for PPIs-induced ATIN has been described\textsuperscript{60}; because PPIs are metabolized by the cytochrome P450 enzyme system, patients with CYT P450 genetic polymorphism appear to be at risk for ATIN due to the interstitial accumulation of PPIs and/or their metabolites where they elicit an immune-mediated inflammatory response\textsuperscript{19}.\!

**ATIN after rifampicin**

Rifampicin-induced ATIN usually occurs in re-treatment regimens, being less frequently cited during continuous treatment\textsuperscript{14,29,30}. The clinical picture is characterized by a severe, oliguric AKI, often requiring dialysis therapy\textsuperscript{61}, but with good recovery under treatment\textsuperscript{62}. AKI associates fever and digestive symptoms (nausea, vomiting, diarrhea, abdominal cramps); manifestation of hypersensitivity (skin rash, eosinophilia) are rarely noticed\textsuperscript{14,62}. Characteristic features associated with AKI are hemolytic anemia, thrombocytopenia and acute hepatitis\textsuperscript{14}. Anti-rifampicin antibodies are detected in the serum and can be deposited in the glomerulus, interstitium or intrarenal vessels\textsuperscript{63}; therefore, rifampicin-induced ATIN should be differentiated by biopsy from other types of rifampicin-induced AKI such as glomerulonephritis or acute tubular necrosis\textsuperscript{29,64}. In most cases, the presence of clinical and laboratory signs of interstitial involvement are sufficient to establish the diagnosis of DI-ATIN; biopsy is performed in cases with significant proteinuria or if renal function does not recover after rifampicin discontinuation\textsuperscript{63}. Histologically, rifampicin-induced ATIN typically associates severe tubular lesions in addition to interstitial inflammatory infiltrate\textsuperscript{65}. Interstitial deposition of antirifampicin antibodies is not found in the case of ATIN occurred during continuous treatment with rifampicin, which shows that, in these cases, tubulointerstitial impairment is produced by a cellular immune mechanism\textsuperscript{14}.\!

**NSAIDs-induced ATIN**

NSAIDs-induced ATIN may occur after any class of NSAIDs, including selective COX2 inhibitors or topic preparations\textsuperscript{30,66-69}. The interstitial accumulation of arachidonic acid metabolites causes immune-mediated stimulation of T lymphocytes which explains both predominance of T-type lymphocytes in the inflammatory infiltrate and the concomitant glomerular involvement\textsuperscript{70}; granulomatous infiltrates are frequently described\textsuperscript{71}. NSAID-induced ATIN should be differentiated from other forms of AKI secondary to NSAID, especially AKI produced by hemodynamic mechanism\textsuperscript{14,70}. NSAIDs-induced ATIN may occur after several months of NSAIDs use\textsuperscript{14,72}; recurrence after re-administration of the same drug or a related drug from the same class is reported\textsuperscript{73,74}. In most cases, NSAIDs-induced ATIN associate nephrotic syndrome in context of minimal lesions or membranous glomerulopathy\textsuperscript{30,66,75,76}. The clinical picture rarely includes manifestations of hypersensitivity, usually isolated, but nephrotic edema is almost present. AKI remits in many cases spontaneously after discontinuation of NSAIDs usually slowly, within a few weeks\textsuperscript{14,30,77}. However, in about 25% of cases,
recover of renal function is incomplete and corticosteroid treatment is not as effective as in other DI-ATIN.

Conclusions

Drug-induced acute tubulointerstitial nephritis represent common causes of acute renal injury. Given the immunoallergic nature of these conditions, there are no prophylaxis measures except to avoiding polypharmacy. Suspicion is crucial for diagnosis because clinical manifestations and laboratory abnormalities are often atypical. Renal biopsy provides a definite diagnosis, but is not performed in all cases. Discontinuation of the offending drug with or without short course of corticosteroids are required to be applied promptly, because, although considered classically reversible, there is evidence that acute allergic nephritis induced by drugs bear a considerable risk of chronicity.

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