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EDUCATIONAL REVIEW

Tubulointerstitial nephritis: diagnosis, treatment, and monitoring

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Abstract Tubulointerstitial nephritis (TIN) is a frequent cause of acute kidney injury (AKI) that can lead to chronic kidney disease (CKD). TIN is associated with an immune-mediated infiltration of the kidney interstitium by inflammatory cells, which may progress to fibrosis. Patients often present with nonspecific symptoms, which can lead to delayed diagnosis and treatment of the disease. Etiology can be drug-induced, infectious, idiopathic, genetic, or related to a systemic inflammatory condition such as tubulointerstitial nephritis and uveitis (TINU) syndrome, inflammatory bowel disease, or immunoglobulin G4 (IgG4)-associated immune complex multiorgan autoimmune disease (MAD). It is imperative to have a high clinical suspicion for TIN in order to remove potential offending agents and treat any associated systemic diseases. Treatment is ultimately dependent on underlying etiology. While there are no randomized controlled clinical trials to assess treatment choice and efficacy in TIN, corticosteroids have been a mainstay of therapy, and recent studies have suggested a possible role for mycophenolate mofetil. Urinary biomarkers such as alpha1- and beta2-microglobulin may help diagnose and monitor disease activity in TIN. Screening for TIN should be implemented in children with inflammatory bowel disease, uveitis, or IgG4-associated MAD.

Key summary points

1. Tubulointerstitial nephritis is often diagnosed late, so clinical suspicion is necessary for early identification and possible intervention (or removal of the offending agent).
2. Presenting signs and symptoms of TIN can include nonspecific systemic symptoms (fatigue, weight loss, headache, flank pain), fever, rash, eosinophilia/eosinophiluria, and evidence of elevated creatinine and Fanconi's syndrome (glucosuria, aminoaciduria, acidosis).
3. Etiology of TIN can be drug-induced, infectious, idiopathic, genetic, or related to a systemic inflammatory condition such as tubulointerstitial nephritis and uveitis (TINU) syndrome or inflammatory bowel disease (IBD)
4. Treatment is based on etiology; aside from removal of offending agents, the mainstay of therapy is corticosteroids and, less often, mycophenolate mofetil.
5. Urinary biomarkers such as alpha1-microglobulin (A1M) and beta2-microglobulin (B2M) may help diagnose and monitor disease activity in TIN.

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Introduction

Tubulointerstitial nephritis (TIN) is a well-described entity, although it often has a delayed diagnosis given its nonspecific presenting signs and symptoms. TIN can be categorized based on underlying etiology, histology, or duration (acute versus chronic). This review focuses on common etiologies of TIN and developments in genetic discoveries and novel biomarkers to aid in its diagnosis, prognosis, and treatment.

Definition

TIN is characterized by an immune-mediated infiltration of the kidney interstitium by inflammatory cells, leading to nonoliguric or oliguric acute kidney injury (AKI) [1–4]. Less frequently, the interstitial inflammation can lead to chronic changes, with subsequent development of chronic kidney disease (CKD) [5]. Numerous genetic and environmental factors can cause or contribute to TIN development. Particular aspects of histologic diagnosis (i.e., granulomas) or associated systemic disease can aid in identification of underlying etiology. TIN accounts for 2 % of native renal biopsies [6] and up to 27 % of cases of unexplained kidney disease in adult patients [3]. In children, TIN (both acute and chronic) accounts for 1–7 % of the histological diagnoses in renal biopsies [7, 8].

Etiology

TIN has multiple etiologies, including drug-related, infectious, systemic, autoimmune, genetic, and idiopathic [1, 3, 9, 10]:

1. Drug-related
    (a) Antimicrobials
    (b) NSAIDs (nonsteriodal anti-inflammatories)
    (c) Other
2. Infectious
    (a) Viral: cytomegalovirus, hepatitis, HIV, Epstein-Barr virus, hantavirus, polyomavirus
    (b) Bacterial: salmonella, streptococcus, yersinia, brucella, leptospirosis
    (c) Fungal: histoplasmosis
    (d) Parasitic: leishmania, toxoplasma
    (e) Localized TIN with acute pyelonephritis
3. Immune-mediated: sarcoidosis, SLE, Sjögren's disease, IBD
4. Idiopathic
5. TINU
6. Granulomatous TIN
    (a) Medications
    (b) Sarcoidosis
    (c) Tuberculosis
    (d) Bacterial/fungal infections
    (e) TINU
    (f) Granulomatosis with polyangiitis

The most common cause of TIN is related to medication or drug exposure [2–4, 11]. Many medications have been implicated, with beta-lactam antibiotics and nonsteroidal anti-inflammatory (NSAID) drugs being the most common (Table 1).

Presentation related to rifampin use is unique and can be accompanied by sudden onset of symptoms and renal biopsy findings ranging from classic acute TIN to acute tubular necrosis [12–14]. Overall, drug-induced TIN has been noted in 7–27 % of adult patients with unexplained nonoliguric or oliguric AKI [15]. Infectious causes of TIN include viral, bacterial, fungal, and parasitic [16–18]. TIN has been reported as the third leading cause of graft dysfunction in renal transplant patients [19]. In immunosuppressed renal transplant recipients, it is primarily related to infectious causes, including polyoma virus or cytomegalovirus, and can lead to increased risk of subsequent rejection [19–22]. TIN associated with polyoma virus infection has been reported in association with primary immunodeficiency [23]. Bone marrow transplant recipients are at risk for necrotizing TIN caused by adenovirus [24–26], and patients with HIV-associated nephropathy can have a component of TIN [27]. Epstein-Barr infections have been associated with TIN with uveitis (TINU) syndrome in children and adults [28, 29]. Among other infections associated with TIN are *Mycoplasma pneumoniae*, *Yersinia pseudotuberculosis*, and *Leptospira shermani* [30–33]. TIN has been described in association with systemic inflammatory conditions, such as inflammatory bowel disease (IBD), TINU syndrome, sarcoidosis, systemic lupus erythematosus (SLE), and Sjögren's disease. Immunoglobulin G4 (IgG4)-associated immune complex multiorgan autoimmune disease (MAD) has also been linked with TIN development, with IgG4-positive plasma-cell interstitial infiltrates and C3 deposition [34]. Autoimmune pancreatitis is in the spectrum of IgG4-associated MAD, where TIN is part of the disease manifestation [35–37]. In IgG4-associated conditions, hypocomplementemia and C3 interstitial deposition are frequently observed in addition to elevated serum levels of IgG and IgE. By contrast, hypocomplementemic immune-complex-mediated TIN described in the setting of advanced

Table 1 Medications implicated in tubulointerstitial nephritis (TIN)

Antimicrobials	NSAIDs	Diuretics	Neuropsychiatric	Other
Beta-lactams	Ibuprofen	Furosemide	Carbamezepine	Allopurinol
Cephalosporins	Ketorolac	Thiazide diuretics	Lamotrigine	Azathioprine
Sulfonamides		Triamterene	Levetiracetam	Antiepileptics
Macrolides		Amiloride	Phenytoin	Proton-pump inhibitors
Gentamicin		Tienilic acid	Lithium	Alendronate
Nitrofurantoin				Chlorpropamide
Clotrimazole				Captopril
Doxycycline				Sulfasalazine
Rifampin				
Ethambutol				
Isoniazid				
Vancomycin				
Ciprofloxacin				
Acyclovir				
Indinavir				

NSAIDs Nonsteroidal anti-inflammatories

renal failure, eosinophilia, eosinophiluria, and lymphopenia and characterized by near-pure plasma-cell interstitial infiltrates was unaccompanied by any extrarenal manifestations [38]. Despite severe hypocomplementemia, C3, C4, or C1q complement was absent from tubulointerstitial immune complex deposits [38]. TIN has also been described in patients with antitubular basement membrane antibodies [39]. Often, TIN is underrecognized in these inflammatory conditions and diagnosed later in the disease course.

Several genetic factors have been associated with development of TIN. TIN antigen (TIN-ag) is an extracellular matrix basement membrane protein and a target antigen in antitubular basement membrane antibody-mediated TIN [40]. Deletion of the TIN-ag gene *hTIN-ag* localized on chromosome 6 leads to disruption of the structure and function of tubulointerstitial epithelium and basement membrane [41]. Additionally, Kidney Disease Improving Global Outcomes (KDIGO) released a consensus report describing autosomal dominant tubulointerstitial kidney disease [16]. Thus far, four causal genes, *Uromodulin*, *Renin*, *Hepatocyte nuclear factor 1B*, and *Mucin-1* have been identified [42]. These are a group of disorders that lead to progressive tubulointerstitial fibrosis, a chronic form of TIN that inevitably leads to end-stage renal disease.

Pathophysiology

Acute interstitial inflammatory reactions are associated with damage to the tubulointerstitium, leading to AKI associated with TIN [4]. The high metabolic demand of the tubulointerstitium makes it particularly susceptible to injury because the inflammation and associated edema compromise renal blood flow, causing a decrease in glomerular filtration rate (GFR) [5]. In some situations, damage may lead to fibrosis (see below).

Interstitial edema and infiltration of lymphocytes and plasma cells, as well as poor tubular function in acute TIN, causes a decrease in GFR. In chronic TIN, fibrosis of the interstitium (as opposed to edema) causes the decrease in GFR [5, 43]. If prolonged, acute interstitial inflammatory reactions can lead to accumulation of extracellular matrix that causes irreversible impairment of renal function with interstitial fibrosis and tubular atrophy [4, 15]. Initially, macrophages may help repair acute injury, but eventually can contribute to inflammation and production of fibrogenic cytokines [5]. Studies have shown that the cytokine transforming growth factor-beta (TGF-β) may mediate profibrotic responses in the tubulointerstitium [5, 44]. Tubular damage can decrease the number of functional nephrons, eventually resulting in hyperfiltration and burnout of the remaining nephrons, leading to CKD [5].

The pathophysiology of drug-induced TIN is thought to be immune mediated and related to an allergic reaction. There are five concepts that support this view:

1. TIN only occurs in a small proportion of individuals taking a certain medication.
2. There is no dose dependence.
3. Patients develop systemic manifestations of a hypersensitivity reaction.
4. TIN can recur after re-exposure to the drug.
5. Eosinophils are often present on renal biopsy [4, 11].

This process likely involves cellular immunity, as there are seldom immune deposits noted by immunofluorescence on renal biopsies in patients with TIN [4].

Pathology

Regardless of underlying etiology, TIN is characterized histopathologically by tubulointerstitial inflammatory cell infiltrate (primarily lymphocytic and eosinophilic) and interstitial edema [6] (Fig. 1). When a significant number of eosinophils are present, drug-induced TIN needs to be considered, but neither the presence nor absence of eosinophils is absolutely diagnostic [15]. NSAID-induced TIN is less likely to be associated with eosinophils on renal biopsy, likely due to the antiinflammatory properties of NSAIDs. A higher density of neutrophils and plasma cells are suggestive of bacterial etiology [15].

Granulomatous TIN

Inflammatory cells infiltrating the tubulointerstitium can form granulomas, which are usually scarce and nonnecrotic with few multinucleate giant cells [4, 45] (Fig. 1c). By contrast, necrotic granulomas are commonly seen in TIN associated with bacterial (tuberculosis) or fungal infections [9]. The presence of granulomas on renal biopsy defines granulomatous TIN, which is relatively rare, with renal biopsy incidence of 0.5 % [11]. With time, the granulomas are often replaced by fibrosis, but despite varying histopathology, a diagnosis of granulomatous TIN does not necessarily correlate with poor prognosis [45, 46]. The underlying etiology for granulomatous TIN is similar to TIN, although sarcoidosis, TINU syndrome, and certain drug-related cases are more common. Systemic diseases such as Crohn's disease have also been implicated, although rare [10]. One study reported that the underlying etiology of granulomatous TIN was not found in 50 % of patients [46]. Interestingly, granulomatous TIN has been described in renal transplant recipients and was hypothesized to result from infections, which are more common in this patient population because of the use of immunosuppressive agents [9, 47].

Clinical presentation

A challenging feature of TIN is the nonspecific symptomatic presentation, which often leads to delayed diagnosis that may portend worse outcomes. Classically, presentation is thought to be associated with a hypersensitivity reaction, including rash, arthralgia, and fever, but as few as 5–10 % of patients present with all of these findings [3, 11]. In a comprehensive study of acute TIN, at presentation, 15 % of patients had rash, 27.3 % had fever, 23 % had eosinophilia, and only 10 % had all three [3]. The tubulointerstitial infiltrate of inflammatory cells can cause edema and painful stretching of the renal capsule, leading to abdominal, flank, or loin pain [6]. Thus, the kidneys in TIN are typically of normal size or enlarged with increased cortical echogenicity, as seen on ultrasound. If drug related, TIN can manifest in most cases between 1 and 3 weeks after exposure to the medication [9], with an average presentation of about 10 days after exposure [4]—except for rifampin exposure, when presentation may be much faster, as described above. Presence of extrarenal manifestations may be helpful in identifying a risk for TIN. A renal biopsy is the only definitive diagnostic modality that can confirm TIN suspected on clinical grounds. A renal biopsy should be considered with severe renal dysfunction, lack of identifiable offending agent, lack of renal recovery, uncommon features of TIN, or prior to initiation of treatment [1], but otherwise, TIN remains a clinical diagnosis. Tubulointerstitial dysfunction should be suspected in patients who develop hyperkalemic, hyperchloremic metabolic acidosis that is out of proportion to renal dysfunction [11]. Most patients are initially noted to have AKI (elevated BUN and/or creatinine) with further workup revealing TIN. Tubular dysfunction can manifest as Fanconi syndrome, so patients may present with electrolyte abnormalities (as above), metabolic acidosis, and elevated fractional excretion of sodium, glycosuria, and aminoaciduria. Additionally, eosinophilia, pyuria, hematuria, eosinophiluria, and mild proteinuria are present in a

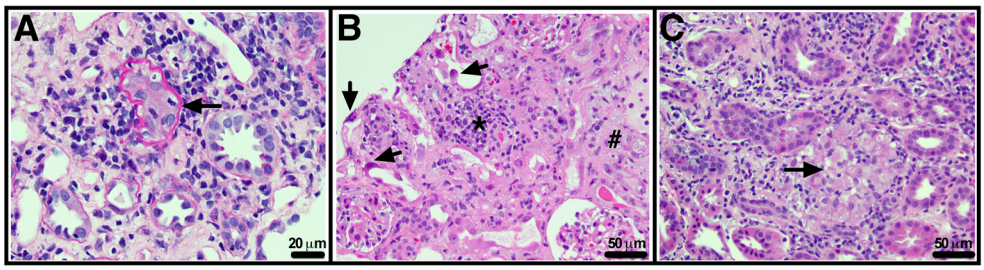

Fig. 1 Renal histopathology in tubulointerstitial nephritis (TIN). **a** TIN with predominantly lymphocytic infiltrate associated with tubular damage and tubulitis (*arrow*). Periodic acid Schiff stain, original magnification × 400. **b** Acute drug-induced tubular injury, in this case secondary to cidofovir. There is interstitial infiltrate (*), edema (#), and marked tubular regenerative changes (*arrows*). Glomeruli show little change. Hematoxylin and eosin (H&E) stain, original magnification × 200. **c** Granulomatous tubulointerstitial nephritis (*arrow*), in this case likely secondary to lamotrigine. H&E stain, original magnification × 200

variable number of cases [2, 6].Presenting signs and symptoms are as follows [11, 48]:

1. Symptoms
   (a) Fatigue
   (b) Anorexia, weight loss
   (c) Headache
   (d) Flank pain
   (e) Arthralgias
   (f) Myalgias
2. Signs
   (a) Fever
   (b) Skin rash
   (c) Costovertebral angle tenderness
3. Laboratory findings
   (a) Blood studies: renal failure, anemia, eosinophilia
   (b) Urine studies: sterile pyuria, Proteinuria, Eosinophiluria, white blood cell casts, micro/macroscopic hematuria (rare)

The differential diagnosis of both acute and chronic TIN is broad. Chronic TIN may manifest similarly to obstructive nephropathy; chronic pyelonephritis; papillary necrosis; tubulopathies including Fanconi syndrome, progressive interstitial fibrosis, or Balkan endemic nephropathy (BEN); Chinese herb nephropathy; and radiation nephritis [43, 49, 50]. Acute TIN has a differential diagnosis that could include acute glomerulonephritis, pyelonephritis, atheroembolic disease, or any cause of AKI (acute tubular necrosis, prerenal azotemia, urinary obstruction, or drug-induced AKI).

While eosinophiluria can be helpful in TIN diagnosis, it is neither sensitive nor specific. Eosinophiluria can also be seen with cystitis, prostatitis, pyelonephritis, atheroembolic renal disease, acute tubular necrosis and rapidly progressive glomerulonephritis [11]. In a study evaluating drug-induced TIN, of those patients with biopsy-confirmed TIN, 67 % had eosinophiluria and 33 % did not; 13 % without TIN had eosinophiluria [4].

Tubulointerstitial nephritis and uveitis syndrome (TINU) syndrome

TINU is a rare disorder, with only 133 cases reported in the literature by 2001 [51]. TINU accounts for <2 % of cases of uveitis [1, 52, 53]. The median age at presentation is 15 years, and the female to male ratio is 3:1 [53, 54]. Diagnosis requires the presence of both TIN and uveitis and is suggested by abnormal renal function, abnormal urinalysis, photophobia, eye pain and redness, eyelid edema, rapidly progressive loss of vision, and symptoms of systemic illness, including weight loss, fever, and fatigue [3, 51, 53]. In addition to the aforementioned eye symptoms, conjunctival and perilimbal injection are present, and pupils can be small with sluggish or no light reaction. The ophthalmologic examination reveals anterior chamber cells and flare, hypopyon, keratic nongranulomatous precipitates, vitreous humor cells, intraretinal hemorrhages or retinal vascular sheathing, cotton wool spots, dilated retinal vessels, and retinal edema (Fig. 2). If there is a prolonged inflammatory process, anterior (iridocorneal) or posterior (iridolenticular) synechiae may develop. Anterior uveitis (Fig. 2a) is present in 80 % of cases of TINU, while posterior and panuveitis (Fig. 2b and c) are less common [51, 55]. Ocular changes are bilateral in about 80 % of cases [56]. Uveitis generally occurs after onset of TIN (60 % of cases) but may be present between 1 month before and 3 months after the onset of TIN [3, 53]. In general, the course and severity of uveitis does not correlate with that of TIN [53, 54, 57–60].

Recurrence of uveitis occurs in ~40 % of patients with TINU, and relapses tend to be more severe than the initial episode. Younger patients are more likely to develop a chronic course of uveitis lasting >3 months [53, 54, 58, 59, 61, 62]. Intraocular complications occur in ~20 % of TINU patients and include posterior synechiae, optic disc swelling, cataracts, elevated intraocular pressure, or chorioretinal scarring (Fig. 2). Importantly, some complications, particularly cataracts and elevated intraocular pressure, are strongly associated with the use of systemic corticosteroids (see below). TINU syndrome remains a diagnosis of exclusion [54, 61, 63, 64]. Sarcoidosis and Sjögren's disease are in the differential diagnosis of TINU, although, median age and type of nephritis and uveitis differ.

In general, renal prognosis is good in the majority of treated patients with TINU [51]. While uveitis is more difficult to control, it carries a fairly good prognosis for visual acuity that rarely decreases below 20/40, with no reported cases of permanent vision loss [3, 55, 65]. Up to 50 % of TINU patients present with no ocular symptoms [55], emphasizing the critical need for uveitis screening in patients with TIN. This is particularly important in patients who do not have medication-induced or systemic-disease-associated TIN. Conversely, TINU may be underdiagnosed in patients presenting with idiopathic uveitis [51], also highlighting the importance of screening uveitis patients for TIN. Recently, human leukocyte antigen (HLA)-DR and -DQ alleles have been identified and associated with TINU and are considered risk alleles [65]. DNA typing for these alleles may be particularly useful in screening pediatric patients with idiopathic panuveitis (as opposed to anterior uveitis), which can aid in the diagnosis of TINU [65].

TIN associated with inflammatory bowel disease (IBD)

IBD has been associated with a variety of renal and urologic complications that occur in up to 23 % of patients [10]. TIN

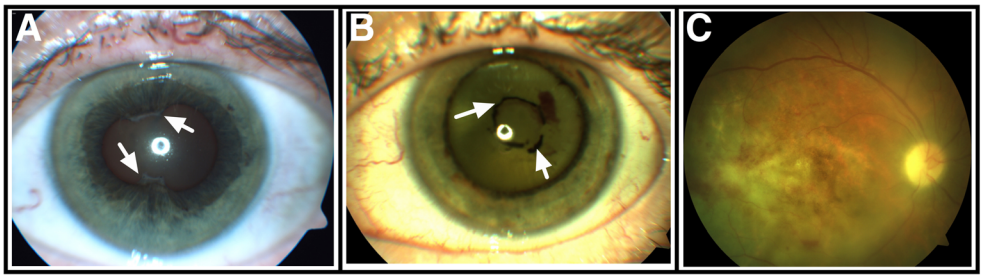

Fig. 2 Ophthalmologic findings in tubulointerstitial nephritis with uveitis (TINU). **a** Anterior uveitis complicated by posterior (iridolenticular) synechiae (*arrows*). **b** Panuveitis with endothelial precipitates and chronic anterior synechiae (*arrows*). **c** Fundus photograph of a patient with panuveitis demonstrating retinal infiltrates

has a strong association with IBD [66]. Other renal conditions in IBD patients include nephrolithiasis/urolithiasis, fistulas, glomerulonephritis, and renal amyloidosis [10, 67]. These manifestations may be secondary to systemic inflammation, susceptibility to autoimmunity, nutritional deficits, medication use, genetic predisposition, and infectious agents [66, 68]. One study reviewing renal biopsies in adults with IBD showed that TIN was present in 19 % of kidney biopsies [66]. Of those, 44 % were acute, 25 % were chronic, and 31 % were granulomatous TIN [66]. Mesalamine, used in the treatment of IBD, is a well-known medication associated with TIN [10, 11, 67, 68], but it has been clearly demonstrated that TIN can occur independently of medication use in IBD.

Inflammation and disease activity in IBD has been associated with low-molecular-weight (LMW) proteinuria [10, 67], adding to the utility of urinary biomarkers for monitoring disease activity and screening for TIN in IBD patients. Studies have shown an association between IBD activity and elevated urinary beta2-microglobulin (B2M) [69], alpha1-microglobulin (A1M) [70], or N-acetyl-beta-D-glucosaminidase (NAG) [71]. By contrast, other studies have found no such correlation [72, 73]. One study showed that elevated urinary A1M was associated with TIN and tubular damage, but this was independent of IBD activity [74]. A possible explanation for such discrepancy in correlating urinary biomarkers with disease activity is the timing of TIN diagnosis. For example, in IBD patients who do not have routine urinary studies, TIN may be diagnosed late when irreversible renal damage might have already occurred, leading to CKD [68, 75]. The above studies indicate that routine screening for TIN should be implemented in patients with IBD. This may be particularly important in patients receiving mesalamine given that associated TIN may be severe, chronic, and progressive if not detected early [66].

Treatment

Treatment for TIN remains influenced by clinicians' prior experience with the disease and is only supported by several small studies and case reports with conflicting results. There are no randomized, controlled, prospective studies, and corticosteroids are the mainstay of treatment although no consensus has been established regarding therapy duration or dose. It has been theorized that early steroid treatment could prevent fibrosis by decreasing inflammatory infiltrates [76], but this has not yet been proven. Treatment is primarily guided by underlying pathophysiology, if it can be determined. For example, drug-induced TIN may recover spontaneously with cessation of the offending medication, particularly if identified early [2]. Aside from treating obvious sources of infection, other treatment options for infection-related TIN have not been well-described, although in transplant patients, immunosuppressive medication can be decreased [16] or Cidofovir used in polyoma-virus-associated infections [77]. Since medication-related acute TIN usually resolves after discontinuation of the offending drug, we recommend that the first line of treatment for antibiotic-related acute TIN is antibiotic medication discontinuation while the infection is treated with an alternative agent. The need for additional medications, such as corticosteroids, should be assessed based on the subsequent clinical course. On the opposite end of the spectrum, systemic rheumatologic and inflammatory conditions associated with TIN (including TINU) are more often treated with corticosteroids or with other agents based on the systemic disease [36, 38, 78].

A retrospective study of 60 adults with acute TIN with a variety of underlying etiologies showed no difference in outcome when comparing treatment with corticosteroids to supportive care alone when assessing serum creatinine at 1, 6, and 12 months' follow-up or dialysis independence [6]. Conversely, a more recent prospective study assessing pediatric patients with idiopathic TIN or TINU showed that corticosteroids sped up recovery of TIN, particularly in patients with more severe disease [79]. Notably, though, renal function did not differ significantly at 6-months' follow-up. The study suggested that because TIN may be self-limiting, treatment may be delayed by 2 weeks in uncomplicated cases [79]. One multicenter retrospective study in adult patients with drug-induced TIN showed that steroid treatment, particularly if started early, may decrease the risk of incomplete renal recovery [76]. Results demonstrated that patients not treated with corticosteroids were more likely to have a higher final serum creatinine and had a higher likelihood of needing chronic dialysis. The most

prominent difference between patients who did and did not regain renal function was the time between removal of the offending medication and initiation of corticosteroid treatment [76].

In granulomatous TIN, one small retrospective study suggested that treatment with corticosteroids is associated with a better prognosis, irrespective of degree of tubulointerstitial fibrosis or inflammation on biopsy [46]. Another report stated that findings of mild tubulointerstitial fibrosis were associated with a better response to steroid therapy in granulomatous TIN [9]. The IgG4-associated TIN is characterized by good response to corticosteroids [36].

Aside from steroid therapy, mycophenolate mofetil (MMF) has been proposed as a possible treatment option in TIN. A retrospective chart review assessing a small group of adult patients with acute TIN showed that MMF was well tolerated and may be a useful therapy for steroid-resistant TIN or in patients with contraindications to steroid therapy [78].

In TINU, the treatment of anterior uveitis includes topical corticosteroids and cycloplegic agents and is effective in ~50 % of patients [54, 62, 79, 80]. However, most patients (80 %) are treated with systemic corticosteroids because of TIN. In patients who do not respond to systemic corticosteroids or who demonstrate ocular or systemic toxicity from these medications, immunomodulatory agents such as methotrexate, cyclosporine A, azathioprine, and MMF have been used to treat the uveitis [54, 59, 62]. While interstitial nephritis in TINU may resolve, uveitis requires long-term ophthalmologic care.

Monitoring

Aside from following renal function and electrolytes, clinicians often have a difficult time monitoring TIN, particularly in chronic cases. Serum C3 and C4 complement, IgG isotypes, and IgE levels can help identify patients with IgG4-associated immune-complex-mediated TIN variants. Urinary biomarkers have been proposed as a way of identifying and prognosticating TIN. BEN provides an example of a chronic, progressive TIN that predominantly affects the proximal tubule and serves as a useful model for testing biomarkers [81]. LMW proteinuria is suggestive of tubulointerstitial disease and possible fibrosis [79]. B2M and A1M are both LMW proteins that are normally freely filtered through the glomerulus and reabsorbed by cells in the proximal tubule [79, 82]. When renal tubules are damaged or dysfunctional, there is increased urinary excretion of LMW proteins. One study of urinary biomarkers in patients with BEN concluded that B2M had higher sensitivity and specificity than A1M in differentiating healthy controls from patients with BEN [82]. A study assessing the utility of A1M as a marker for chronic TIN showed that increased urinary ratios of A1M/albumin or A1M/protein in a 24-h urine collection showed an appropriate relationship with chronic TIN, and helped to differentiate it from healthy controls and those with glomerulonephritis [43]. Another study analyzed 61 urinary proteins present in patients with BEN, finding that A1M and B2M were consistently found in larger amounts in patients with BEN compared with healthy controls and patients with prerenal AKI [81]. Additionally, in comparing BEN with glomerulonephritis, elevated B2M was the most accurate biomarker for identifying BEN as opposed to glomerulonephritis [81]. Urinary B2M has also been proposed as a screening measure for individuals with uveitis to help detect TINU syndrome [51]. One study revealed that when using both serum creatinine and urinary B2M levels in patients with uveitis, there is a positive predictive value of 100 % and negative predictive value of 97 % when assessing for associated TIN [56]. At this time, compared with other urinary biomarkers, B2M and A1M are most commonly used for testing for tubular damage. B2M is degraded in urine when pH falls <6, while A1M remains stable [82]. A Finnish study of pediatric patients with TIN showed that patients with elevated and prolonged urinary LMW protein excretion (B2M and A1M) had an associated decrease in measured GFR when compared with those with normal urinary LMW protein excretion [79]. Another group studying urinary biomarkers concluded that urinary monocyte chemotactic peptide-1 (MCP-1) levels showed a close correlation with interstitial inflammation and edema in patients with drug-induced TIN [83]. Eventually, MCP-1 may be used to help differentiate TIN from ATN but is not yet commercially available. Taken together, the above studies demonstrate that measurement of urinary LMW protein excretion may be a feasible tool by which to monitor progression of tubulointerstitial disease in patients with TIN.

Chronic TIN

While some episodes of acute TIN are reversible (particularly if an offending medication is discontinued), others may progress into chronic TIN. The likelihood is increased with systemic inflammatory or rheumatologic diseases and delayed removal of the causative medication in drug-induced TIN [11], including analgesic and lithium nephropathy [84]. In one retrospective study of biopsies from adult patients with TIN, the median percentage of interstitial fibrosis was 30 % and median glomerulosclerosis 8 % [6], which indicates chronic change. In an Italian registry of renal biopsies, children with CKD most frequently had chronic interstitial diseases, which included juvenile nephronophthisis, chronic TIN, and reflux nephropathy [7]. Rarer causes of chronic TIN in children are heavy metal exposure [85] and neoplasia [86, 87]. As mentioned previously, TIN-ag is an integral component of the renal tubular basement membrane. Defects in this membrane observed in juvenile nephronophthisis have been associated with abnormalities in TIN-ag synthesis, which can eventually lead to renal failure [41]. Ongoing detection of

LMW proteins in the urine may be signs of ongoing renal tubulointerstitial inflammation or fibrosis, or both, which again supports the use of these biomarkers in follow-up of patients with TIN [79]. Chronic TIN rarely results from bacterial infections alone [88].

Prognosis

Prognosis primarily depends upon the cause of TIN, in combination with therapy for systemic diseases, timing of therapy, previous renal function, and removal of any known offending agents. Chronicity portends a worse outcome, and detection of fibrosis on renal biopsy is a marker of irreversible change. Early identification of TIN can often improve renal outcomes. Prolonged LMW proteinuria is a marker for poorer prognosis and decreased GFR [79]. In a review of adults with TIN, 64 % made a full recovery, while 23 % had partial recovery and 13 % remained on renal replacement therapy [3].

Conclusion

In summary, TIN is an underrecognized disease that often presents with nonspecific symptoms. A high clinical suspicion and particular attention to extrarenal manifestations and thorough review of potential risk factors are needed for accurate identification and diagnosis. It is most important to remove any potential offending agent and treat associated systemic disease to help preserve or recover renal function. Monitoring for TIN in patients with uveitis or IBD could be a useful tool for early diagnosis and treatment. While there are promising urinary biomarkers to diagnose and prognosticate TIN, A1M and B2M are the most promising for clinical use. Treatment is based on underlying pathophysiology, and use of corticosteroids remains poorly supported by clinical trials. Randomized controlled prospective trials are needed to best assess prognosis and therapy.

Questions (answers appear following the reference list)

1. Tubulointerstitial dysfunction is often accompanied by electrolyte abnormalities that include:

   A. Hyperkalemia, hyperchloremia, and metabolic acidosis
   B. Hyperkalemia, hyponatremia, and metabolic acidosis
   C. Hypokalemia, hypernatremia, and metabolic alkalosis
   D. Hypokalemia, hyperchloremia, and metabolic acidosis

2. What is the most common type of uveitis present in patients with TINU syndrome?

   A. Anterior uveitis
   B. Posterior uveitis
   C. Intermediate uveitis
   D. Panuveitis

3. The most common underlying etiology of TIN is

   A. TINU syndrome
   B. Inflammatory bowel disease
   C. Drug induced
   D. Infection

4. Regarding drug-induced TIN, which of the following is false?

   A. TIN can recur after re-exposure to the drug
   B. Eosinophils are a predominant finding on renal biopsy
   C. NSAIDs are a common cause for drug-induced TIN
   D. The risk for drug-induced TIN increases with increasing dose of the drug

5. Which of the following is a low-molecular-weight protein that can be used as a urinary biomarker for diagnosing and monitoring TIN?

   A. Beta2-microglobulin (B2M)
   B. Monocyte chemotactic peptide-1 (MCP-1)
   C. TIN antigen
   D. Mucin-1

Compliance with ethical standards

Conflict of interest The authors declare no conflict of interest.

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Answers

1. A
2. A
3. C
4. D
5. A