Tubulointerstitial Nephritis in Children

42

Priya S. Verghese, Kera E. Luckritz, and Allison A. Eddy

Introduction and Historical Perspective

An estimated 85% of the kidney consists of tubules and their surrounding interstitial space. Given their preeminence, it is crucial to understand the contribution of the tubulointerstitium in all renal disease processes. Despite its anatomical dominance, current understanding of the role of the interstitium in both primary and secondary disease processes remains incomplete.

The term acute interstitial nephritis (AIN) was coined by Councilman in 1898 when he provided the first and now classic description of the histopathologic changes following an investigation of autopsy specimens from patients with diphtheria, scarlet fever and other infectious diseases [1, 2]. Primary AIN is typically an immunologically-mediated disease characterized by tubular injury and interstitial inflammation, with relative sparing of the glomeruli and vessels, initiated by drugs, infections or other causes mentioned in detail in section "Etiology" [3]. Councilman's early description still has merit, though it may be more accurate to categorize the disease process as acute tubulointerstitial nephritis (TIN) since the renal tubules are also involved in all cases, both clinically and histopathologically.

In the pre-antibiotic era, systemic infections were the most common cause of tubulointerstitial disease. Today, a drug hypersensitivity reaction is a more common inciting event. Ironically many of these drugs were developed to treat the infectious disorders that had often been implicated as causes of AIN. In kidney transplant allografts, TIN can occur due to drugs, but also due to infections such as BK polyomavirus and adenovirus [4, 5] that often necessitate drastic reduction in immunosuppression to enable viral clearance.

Progressive chronic kidney disease (CKD), irrespective of the primary disease process, is characterized by significant chronic TIN indicating that TIN is a spectrum of pathologies, ranging from acute and reversible nephritis to chronic and

Priya S. Verghese, Kera E. Luckritz and Allison A. Eddy contributed equally with all other contributors.

P. S. Verghese
Ann & Robert H. Lurie Children's Hospital, Northwestern University Feinberg School of Medicine, Chicago, IL, USA
e-mail: pverghese@luriechildrens.org

K. E. Luckritz
C.S. Mott Children's Hospital, University of Michigan Health System, Ann Arbor, MI, USA
e-mail: keral@med.umich.edu

A. A. Eddy (✉)
Department of Pediatrics, University of British Columbia, Vancouver, BC, Canada

BC Children's Hospital, Vancouver, BC, Canada
e-mail: allison.eddy@cw.bc.ca; allison.eddy@ubc.ca

F. Schaefer, L. A. Greenbaum (eds.), *Pediatric Kidney Disease*,
https://doi.org/10.1007/978-3-031-11665-0_42

irreversible disease with fibrosis. For each individual patient, it is critical to try to identify and discontinue the offending toxin or agent before acute injury progresses to the chronic stage.

Epidemiology

Acute injury to the interstitium and the surrounding tubules is an important cause of renal dysfunction, currently accounting for 5–27% of kidney biopsies performed for acute kidney injury [6–9]. Reliable data on the incidence and prevalence of TIN are lacking, especially in the pediatric population. Within available biopsy registries, TIN represents approximately 1–3% of all biopsy diagnoses [7, 10]. Often the diagnosis is made clinically without performing a renal biopsy to confirm the diagnosis. Furthermore, it is likely that many cases are self-limited and remain clinically silent. Thus, the estimated numbers are likely conservative and lower than the true incidence. The incidence of TIN in kidney transplant allografts is also unknown [4, 5].

Histology and Pathogenesis

By definition, TIN is characterized by interstitial cellular infiltrates, usually sparing the vessels and glomeruli (Fig. 42.1a), although it is noted that severe primary glomerular injury rarely occurs without concurrent tubulointerstitial injury. Tubular cell damage may be manifest as epithelial proliferation and/or tubular dilatation. Intratubular cast deposition is often present as well [11]. Interstitial fibrosis and tubular atrophy, often accompanied by the persistent mononuclear cell infiltrate [11], can be representative of chronic TIN. The infiltrate is composed predominantly of T cells with some macrophages and plasma cells [6, 11, 12]. An impressive number of eosinophils may be present and suggests a drug-induced etiology (Fig. 42.1d). These lymphohematopoietic cells are a rich source of cytokines that contribute to kidney injury. Granuloma formation is a feature of biopsies in 6% of the patients and can occur in any form of AIN; granulomas are considered common in drug-induced TIN, infection-associated TIN and renal vasculitis

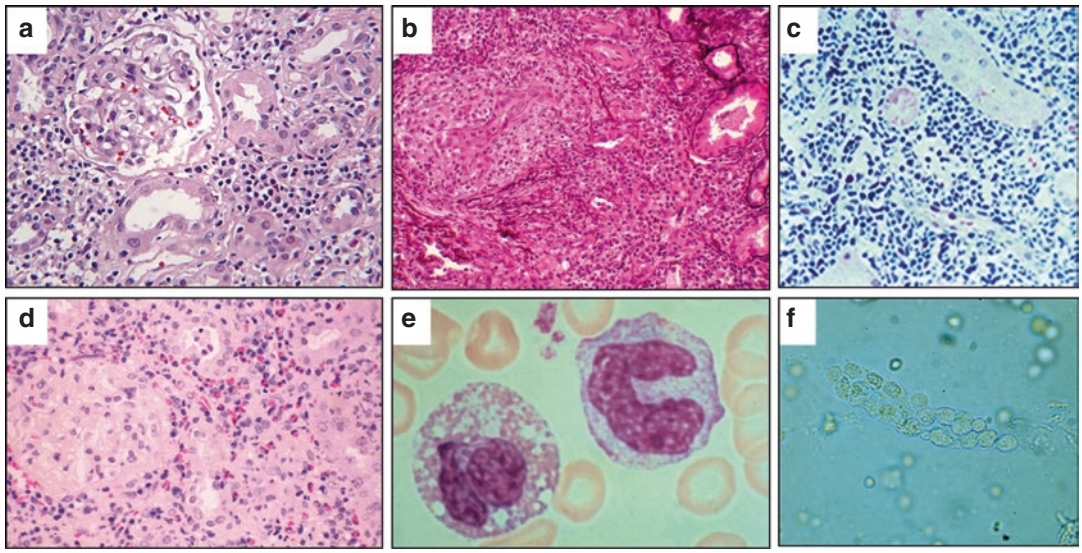

Fig. 42.1 Histological and urinary sediment features of acute tubulointerstitial nephritis (TIN). Histological photomicrographs illustrate an interstitial infiltrate of mononuclear cells, interstitial edema and tubular dilatation in acute TIN (**a**); acute TIN with granuloma formation (**b**); TIN characterized by an infiltrate of monomorphic interstitial mononuclear cell due to lymphoma (**c**); acute drug-induced TIN with numerous polymorphonuclear eosinophils (**d**). Examination of the urinary sediment may show eosinophils in drug-induced TIN (**e**), white blood cells and while blood cell casts (**f**)

[13] (Fig. 42.1b). Some studies have suggested that the degree of tubulointerstitial inflammation may be predictive of renal functional outcome, even in primary glomerular diseases [3, 8, 14, 15]. However, other studies have suggested the extent of chronic changes such as tubular atrophy on the initial biopsy are more predictive of long-term outcomes [8, 16]. Interestingly, in kidney transplant allografts, inflammation in areas of interstitial fibrosis is associated with decreased graft survival with or without concurrent evidence of rejection [17], once again supporting the prior theory that the degree of inflammation is more predictive of long-term outcomes.

In primary TIN, immunofluorescence staining for antibodies and complement proteins are typically negative. Occasionally, linear or granular deposits of IgG or IgM may be present along the tubular basement membranes [3]. Electron microscopy may reveal loss of continuity of basement membranes as well as thickened and multilaminated areas indicative of chronic damage [3].

These histopathologic findings, together with the apparent clinical response to corticosteroid therapy, supports a role for immune-mediated pathogenic mechanisms. Though the specific mechanisms remain unclear, an important role of chemokines and other inflammatory mediators is presumed [18]. A reliable animal model that faithfully mimics human acute drug or infection associated TIN is not available to elucidate specific pathways. Animal studies have shown that three endogenous kidney antigens (uromodulin, megalin, and a tubular basement membrane glycoprotein named TIN antigen) can elicit TIN, but the relevance of these findings to human acute TIN is unknown [9]. Isolated case reports describe autoantibodies to aquaporin 2 and HOXB7 [19], mitochondrial M2 protein [20] and two unidentified brush border antigens [21]. Current concepts suggest that an antigen, be it a hapten derived from a drug or microbe, can mimic a yet-to-be identified antigen normally present in renal tubules. When this antigen is presented to T-helper cells, an immune response is triggered. Macrophage and natural killer cell recruitment and activation follows. Evidence of a primary pathogenic role of T cells is supported by a study that demonstrated the presence of drug-specific sensitized T cells in the peripheral blood of patients with acute drug-induced TIN [22]. Four non-mutually exclusive theories of immune pathogenesis have been proposed [23]. (1) A component of the drug may be trapped along the tubular basement membrane (TBM) where it acts as a hapten, becoming the target of immune attack by sensitized T-cells, or less commonly, antibody producing B-cells. (2) A component of the circulating drug may be recognized as a foreign antigen that triggers an immune response. The antigen may be structurally similar (molecular "mimic") to a normal component of the tubulointerstitium (endogenous antigen) that becomes a target of the immune attack. (3) A drug-derived antigen may first be trapped "in situ" in the tubulointerstitium where immunologically reactive cells and/or antibodies are recruited. (4) Circulating antibodies generated against a drug-derived antigen may form immune complexes within the circulation that are subsequently trapped within the tubulointerstitium and initiate inflammation. Similar theories of pathogenesis have been proposed for "reactive" acute TIN triggered by an infectious agent.

A related drug-induced hypersensitivity syndrome is DRESS (drug reaction with eosinophilia and systemic symptoms), which is more common in adults than children. DRESS is characterized by a severe rash and visceral involvement that includes TIN in 10–30% of cases [24].

There is an animal model of anti-tubular basement membrane disease that has been well-characterized and thought to be mediated by an immune response to an endogenous TBM antigen [25]. However, human anti-TBM nephritis is distinctly rare; it is most commonly encountered in association with anti-GBM disease. Of interest, a patient harboring a deletion in the gene that encodes the human TIN antigen has been reported with CKD [26]. Three patients with autoimmune polyendocrine syndrome type 1 developed end-stage kidney disease (ESKD) due to TIN associated with autoantibodies to aquaporin 2 and HOXB7 [19]. Despite several studies, it is not clear that specific phenotyping studies of the infiltrating interstitial cells can differentiate the

antigenic trigger. The one exception is TIN due to lymphoma/lymphoproliferative disease where a single monomorphic cellular population invades the interstitium (Fig. 42.1c). The kidney is the most common solid organ to be infiltrated (60–90%) in patients with hematological malignancies [27].

Overlooked for many years, it is increasingly appreciated that many drug-induced nephrotoxic reactions triggered by tubular epithelial cell damage are associated with significant interstitial inflammation that also contributes to renal functional impairment. Recent studies have elucidated mechanisms that define "necroinflammation", which is distinct from the hypersensitivity-type responses that cause acute TIN (Fig. 42.2). Necroinflammation is defined pathologically as a pattern of injury associated with an auto-amplification loop that is triggered by a specific form of cell death called necroptosis—characterized by the release of intracellular debris into the interstitial space. This "debris" includes "danger-associated molecular patterns" or DAMPS that bind to unique pattern recognition receptors; an interstitial inflammatory response ensues. It is curious that a few drugs such as vancomycin [29], ciprofloxacin [30] and non-steroidal anti-inflammatory drugs are able to initiate either response. The nephrotoxic effects of some drugs are linked with intratubular crystal or cast formation that trigger necroinflammation (Fig. 42.2).

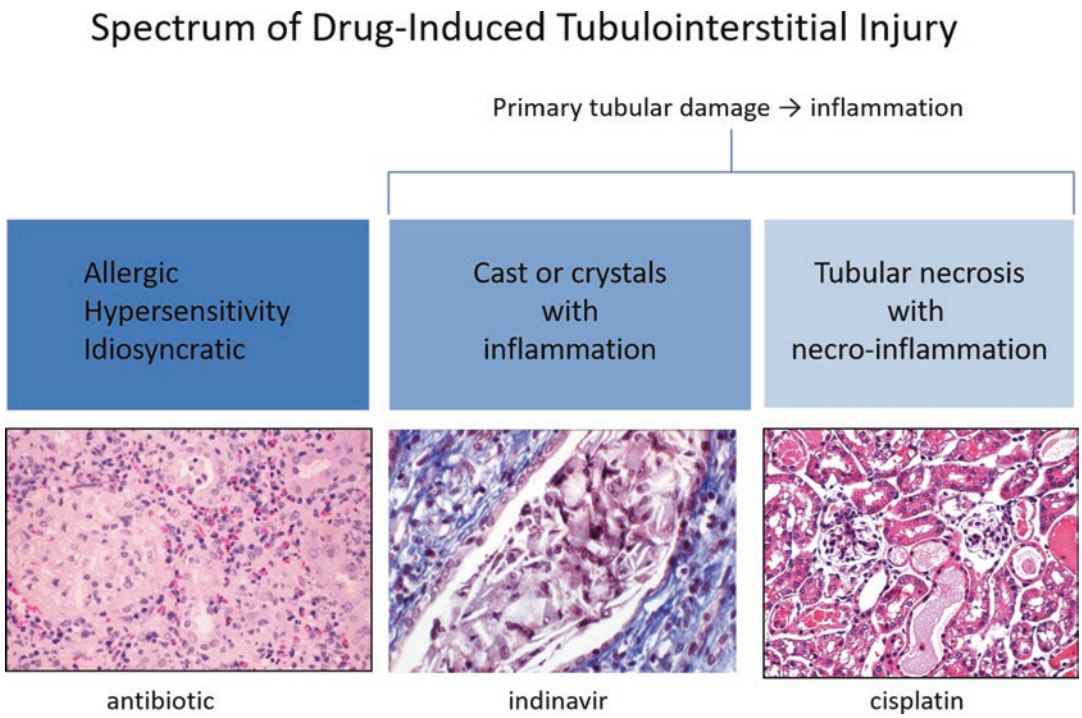

Fig. 42.2 Mechanisms of drug-induced TIN. Classical acute TIN results from an idiosyncratic allergic reaction with a primary interstitial inflammatory response (left). The nephrotoxic effects of some drugs such as indinavir are linked with intratubular crystal or cast formation, which causes tubular injury followed by interstitial inflammation (middle). Necroinflammation is a more recently recognized mechanism of tubular injury that can be initiated by drugs and is characterized by an auto-amplification loop of interstitial inflammation (right). Tubular death is caused by a specific mechanism called necroptosis, characterized by the release of intracellular debris into the interstitial space that activates unique pro-inflammatory signaling pathways. (The indinavir photomicrograph was reproduced from Fogo et al. [28] with copyright permission. The cisplatin photomicrograph was provided by Dr. Prasad Devarajan, University of Cincinnati College of Medicine)

In kidney transplant allografts, viral TIN secondary to BK polyomavirus or adenovirus is likely secondary to viral transmission via the donor organ [31].

Clinical Findings

When TIN was originally described, it was typically associated with systemic signs of inflammation. A "classic" triad of fever, eosinophilia and rash was observed in a third of the patients with methicillin-induced TIN. Recently, based on European studies of children with severe biopsy-confirmed TIN, clinical manifestations are frequently encountered but heterogenous and often non-specific [6, 8, 32–34]. When TIN occurs as a manifestation of a multi-system disease process, associated systemic symptoms may be present.

The classical clinical presentation of drug-induced TIN is acute kidney injury that begins after exposure to the offending drug. The kinetics of the onset of TIN varies depending upon the exposure history. Symptoms typically begin 3–5 days after re-exposure to the inciting drug, with a mean of 10 days until diagnosis, while it may take several weeks for the symptoms to develop with first-time drug exposure. The TIN risk is not dose-dependent, an observation that supports the theory that the pathogenesis of this disease is a 'hypersensitivity-type' immunological reaction. TIN recurrence following drug re-challenge also supports this hypothesis. Extra-renal symptoms and signs of hypersensitivity, including low-grade fever, a maculopapular rash and mild arthralgias, are more common in TIN associated with infectious and autoimmune diseases. Today, hypersensitivity symptoms are rare in drug-induced TIN and their presence does not exclude the possibility of drug-induced nephrotoxicity and/or acute tubular necrosis (ATN) rather than TIN as the primary kidney lesion. Nonspecific symptoms due to acute kidney injury including anorexia, nausea, vomiting and malaise were frequently reported in a significant number of the 106 children with a biopsy confirmed diagnoses of TIN [mean/median age ranged from 11.6–14 years; 22% males] published in five separate European studies (Table 42.1) [6, 8, 32–34]. Unlike limited studies in North America, however, a significant number of these children had tubulointerstitial nephritis and uveitis (TINU) syndrome. Kidney interstitial edema may cause renal enlargement and capsular swelling, thought to be the cause of flank pain that is present in some patients with AIN (33–79% of children as reported in the European studies) [6, 8, 32–34]. Adults (121 cases with 91% drug-induced TIN) [9, 35, 36] had similar clinical features as pediatric TIN patients, but with an increased reporting of skin rash and arthralgia.

Antimicrobials and non-steroidal anti-inflammatory drugs (NSAIDS) are most frequently suspected as the cause of drug-induced TIN, but the list of potential offending pharmacological agents is endless (Table 42.2). The risk of acute TIN is very low for an individual drug, despite a long list of single published case reports. The hallmark of TIN is an acute decline in renal function as evidenced by the rise in serum creatinine. This may be the only laboratory abnormality [3]. Acute TIN may also present as one of several more complex clinical scenarios:

1. Acute kidney injury. The absence of hypertension, significant albuminuria and red blood cell casts are clues to a diagnosis of TIN rather than glomerular or vascular disease, though in a given patient clinical manifestations may overlap considerably. Recent exposure to a potentially offending agent, significant pyuria in the absence of bacteriuria, a good urine output and evidence of tubular dysfunction suggest a diagnosis of TIN. Distinguishing between acute TIN and ATN may be challenging, although the presence of many renal tubular cells and muddy brown casts in the urine sediment is more suggestive of a diagnosis of ATN.
2. Chronic renal failure. When evaluating a new patient, the diagnostic challenge may be differentiating acute from chronic TIN. Small kidneys with increased echogenicity and anemia suggest a long-standing process. Many of the causes of chronic TIN in the pediatric population are associated with extra-renal

Table 42.1 Clinical features of TIN in pediatric patients

First author	Howell [32]	Jahnukainen [8]	Taktak [34]	Clavé [6]	Roy [33]	
Year	2016	2011	2015	2017	2020	
Country	England (GOSH)	Finland	Turkey	France	England (Liverpool)	
N	27	26	19	25	10	Extrapolated total
Years	1990–2012	1995–2007	1999–2014	2006–2016	2007–2014	
Anorexia	81%	54%		28%	Yes	43/78 = 55%
Vomiting	59%	35%	27%		70%	37/82 = 9%
Nausea	48%		21%			4/46 = 9%
Fever	41%	92%		28%	30%	45/88 = 51%
Loin/abdominal pain	33%	46%	79%	44%	Yes	47/97 = 48%
Uveitis	65%	46%	5%	28%	60%	43/107 = 41%
Initial creatinine[a] (μmol/L)	263	253	188	183	303	–
Follow up duration (months)	21	35	6	12	18.5	–
Abnormal renal function at last follow up (μmol/L)	56% have eGFR <80 mL/min/1.73 m^2	15% have eGFR <80 mL/min/1.73 m^2	Mean creatinine 49 μmol/L (35–73)	40% have eGFR <80 mL/min/1.73 m^2	50% have eGFR <80 mL/min/1.73 m^2	34/88 = 39%[b]
Proportion treated with steroids	96%	88%	32%	72%	80%	82/107 = 77%

[a] Median values reported (except for Taktak study in which mean value is reported)

[b] Taktak study excluded (follow-up renal functional data not provided)

Table 42.2 Drugs most commonly reported to cause acute TIN

Antimicrobials	Analgesics and narcotics	Diuretics	Others
Beta-lactams Methicillin Ampicillin Penicillin Oxacillin Nafcillin Amoxicillin Cephalosporins Sulfonamides Macrolides Erythromycin Clarithromycin Other antibiotics Colistin Rifampin Polymyxin Ethambutol Tetracycline Vancomycin [37] Linezolid [38] Ciprofloxacin Isoniazid Piperacillin-Tazobactam Clindamycin [39] Fluoroquinolone Anti-virals Acyclovir Indinavir Tenofovir Alpha-interferon Direct-acting antiviral agents for hepatitis C [40]	NSAIDs 5-Amino-salicylic acid [41] Mesalazine [42, 43] COX-2 inhibitors Acetaminophen *Drugs of Abuse* Cocaine [54–57] Synthetic cannabinoids [58] Anabolic steroids [59] Inhaled solvents/toluene [60–63]	Furosemide Thiazides Triamterene *Biologics* Nivolumab (anti-PD1) Vedolizumab [64] Pembrolixumab (anti-PD1) [65] Infliximab Adalimumab (anti-TNF) Atezolizumab (anti-PD-L1) Bortezomib [66]	Allopurinol Azathioprine [40] Ifosfamide H2 blocker Ranitidine PPIs Omeprazole Lansoprazole Pantoprazole [44] Antihypertensives Amlodipine Diltiazem Captopril Valsartan [45] Nifedipine [46] Anti-epileptics Carbamazepine Phenytoin Levetiracetam Clozapine [47] Miscellaneous Apixaban [48] Cetirizine Clozapine Ergotamine Etanercept Glucosamine [49] Immune checkpoint inhibitors [50, 51] Isotretinoin [52] IVIG [53] Lenalidomide Exenatide Mercury Rosuvastatin Warfarin Zoledronate

Citations are selected from recent publications. Unreferenced medications were cited in prior editions of this chapter
Abbreviations: *NSAID* non-steroidal anti-inflammatory drug, *COX-2* cyclo-oxygenase-2, *PPI* proton pump inhibitor

manifestations such as cystinosis, certain inborn errors of metabolism, and inflammatory bowel disease (IBD). More recently, chronic TIN has become a major cause of CKD in agricultural communities and is thought to be associated with heavy metal and/or pesticide exposure.

3. Tubulopathy. Patients may come to medical attention due to signs and symptoms of tubular dysfunction. The specific manifestations of tubular cell injury/dysfunction vary depending on the primary site of injury. Proximal tubular injury may cause Fanconi's syndrome with glucosuria, proteinuria, and phosphaturia, or it may present as a proximal renal tubular acidosis (RTA). Distal tubular cell injury may manifest as acidosis and hyperkalemia (type 4 RTA) while collecting duct damage typically results in a urinary concentrating defect (nephrogenic diabetes insipidus) (Fig. 42.3). Tubular cell injury may also manifest as potassium wasting. The pediatric case series by Howell et al. reported 7/10 with potassium wasting, 8/13 with reduced phosphate reabsorption and 7/16 with metabolic acidosis [32].

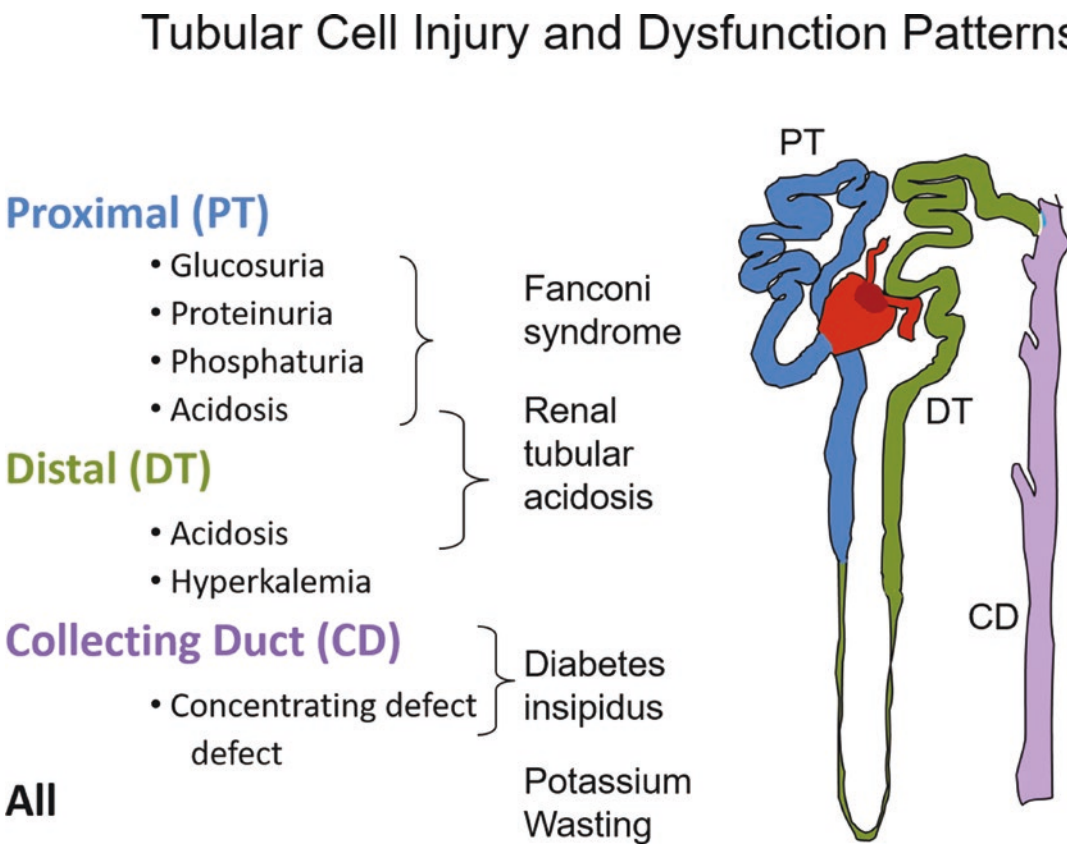

Fig. 42.3 Variable patterns of renal tubular functional defects present in patients with TIN, depending on which nephron segments (proximal, distal or collecting ducts) are injured because of the primary disease process and/or the associated interstitial inflammation

Diagnosis

Often diagnosed clinically, the sensitivity and specificity of the non-invasive diagnostic studies that are performed to diagnose TIN are poor.

Urinary Sediment

The urinary sediment often shows red cells, white cells and white cell casts (Fig. 42.1f) [3]. Sterile pyuria may or may not be associated with eosinophiluria. Urinary eosinophils (Fig. 42.1e) were once considered helpful, but more recent studies and a review of published data by Lusica et al. [67] conclude that urinary eosinophil counts lack adequate sensitivity or specificity. It is also important to remember that a bland urinary sediment does not exclude the diagnosis of acute TIN [15]. Proteinuria may be present, but is typically less than 1 g/24 h. Nephrotic range proteinuria is rare except in NSAID-induced TIN, where it is thought to be mediated by cytokine-induced glomerular injury.

Low Molecular Weight Proteinuria

Beta 2-microglobulin is a low molecular weight (~12 kDa) protein used in the evaluation of the

re-absorptive capacity of the proximal kidney tubule. Its daily production is constant and its clearance is almost exclusively by glomerular filtration followed by 99.9% reabsorption by the proximal tubule. Therefore, urinary beta 2-microglobulin levels are often elevated in patients with proximal tubular dysfunction, as frequently observed in TIN; an elevated urinary beta 2-microglobulin/creatinine ratio can help support a diagnosis of TIN [8]. Recent studies suggest that quantitative assessment of other low molecular weight urinary proteins such as α1 microglobulin, retinol binding globulin and vitamin D binding protein may also be informative [68, 69].

Blood Work

In the five most recent pediatric retrospective case series of biopsy-confirmed acute kidney injury due to TIN, the initial serum creatine (median in 4 series, mean in 1 series) ranged from 183 to 303 μmol/L (2.1–3.4 mg/dL). Anemia and elevated serum inflammatory markers (C-reactive protein and erythrocyte sedimentation rate) are common in patients with severe disease [6, 8, 32–34] (Table 42.1). Peripheral eosinophilia may be present in patients with TIN; and was described frequently in the era of methicillin-induced TIN.

Urinary TIN Biomarkers

There is considerable interest in the use of biomarkers to both differentiate causes of kidney disease non-invasively and to follow the disease course. A recent study of adult patients undergoing a kidney biopsy reported that patients with AIN have significantly higher urinary TNF-alpha and IL-9 levels than those with other causes of acute kidney injury [70]. Other promising urinary biomarkers include kidney injury molecule-1 (KIM-1) [71], N-acetyl-beta-D-glucosaminidase (NAG), complement C5b-9 [72] and increased urinary magnesium excretion [73].

Radiology

The renal ultrasound usually demonstrates increased echogenicity, often associated with an increased renal bipolar length, but these findings are non-specific [2, 3]. Gallium scanning has been proposed to differentiate between acute TIN and ATN, but the findings are often non-conclusive and the study is rarely performed now [2].

Biopsy

Since none of the non-invasive studies are both specific and sensitive for TIN, kidney biopsy remains the only definitive diagnostic study. For details on biopsy findings, see the section "Histology".

Causes, Treatment and Outcomes

The causes of TIN are numerous, but can be broadly divided into acute and chronic disorders, though there may be considerable overlap for any single etiology. Most of the larger case series have been conducted in adults and conclude that the majority (approximately 70%) are drug-related, followed by infections (16%) [12, 74]. In the five pediatric case series published since 2010 ($n = 106$ cases), 39% were due to drugs, followed by 36% due to TINU (5% in the adult series) and 17% associated with infections [6, 8, 32–34]. In a systematic review of 592 published TINU cases, it was reported that the median age was 17 years (interquartile range 13–46); 51% were under the age of 18 years [75]. The most common causes of acute TIN in pediatric patients are summarized in Fig. 42.4 and discussed in more detail in the following sections and Tables 42.2, 42.3 and 42.4.

Drugs

In the current era, drugs clearly surpass infections as the most commonly implicated cause of

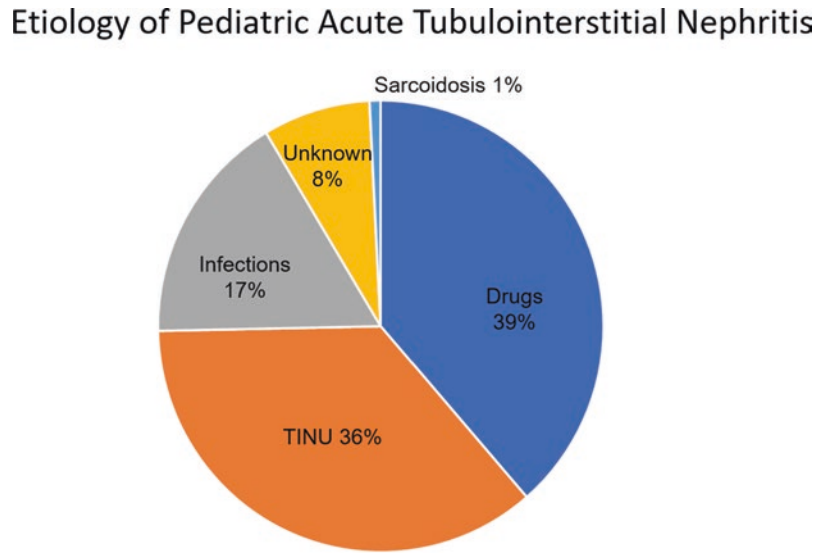

Fig. 42.4 Causes of pediatric acute TIN. Data are based on five European pediatric case series published since 2010, that also from the basis for Table 42.1. (n = 106 individual patients; etiology counted twice for 8 patients in the series by Howell et al. who had TINU plus a secondary etiology identified) [6, 8, 32–34]

acute TIN. In the adult literature, where there are more data, 35% are caused by PPIs, 35% by antibiotics and 20% by NSAIDS [78]. However, the list of potentially causative agents is extensive, expanding, and variable over time as drug prescribing practices change (Table 42.2).

Methicillin was long considered the prototypical cause of drug-induced TIN, as first reported in 1968 [79]. In fact, due to its infamy, its use has declined worldwide and it is no longer available in most countries. Methicillin and other beta-lactam antibiotics (penicillins and cephalosporins) are still more commonly associated with systemic signs of hypersensitivity, including the classic triad of rash, fever, and eosinophilia than any other group of drugs.

Rifampin has frequently been implicated as a cause of acute TIN. Affected patients fall into two groups: (1) Patients who receive short duration therapy with rifampin and (2) patients who have had prior or intermittent exposure to the drug. The first group typically lacks anti-rifampin antibodies and the onset of clinical symptoms is insidious. The second group may develop antibodies and clinical symptoms often begin abruptly [23]. Associated with certain agents such as rifampin and allopurinol, hemolysis or hepatitis may also be present [23].

NSAID-induced TIN may be associated with nephrotic syndrome in as many as 70% of the cases [23]. It is reported to occur more frequently in older patients, but it is unclear whether this is due to under-reporting in pediatrics, lower exposure rates or other factors. In NSAID-induced TIN, hematuria is almost always microscopic and extra-renal symptoms such as fever and rash occur in less than 10% of the patients [23]. The degree of interstitial inflammation is often less with NSAID-induced TIN. In addition to the classic TIN accompanied by "minimal change" glomerular disease, NSAIDs can also cause membranous nephropathy. Therefore, all patients with nephrotic syndrome associated with NSAID use should undergo a diagnostic renal biopsy [80].

The epidemiology of drug-induced TIN has changed significantly in the past two decades, especially following the first published report of PPI-induced TIN in 1992 [81]. In adults taking PPIs, a three times increased risk of developing TIN [82], a four times increased risk of acute kidney injury and a 20% increased risk for CKD [83] were reported. A meta-analysis also identified a 1.2 increased risk of CKD among PPI users, but no increased risk among H2 receptor antagonists [84]. Additionally, there is evidence that the duration of exposure to PPI is associated with increased risk and progression of CKD [85]. As newer therapies and drugs are introduced, one must maintain a high index of suspicion for drugs

Table 42.3 Infectious causes of acute TIN

Bacteria
Brucella
Campylobacter
Corynebacterium diphtheria
E. coli
Enterococcus
Legionella
Leptospira
Mycobacteria
Mycoplasma
Salmonella
Staphylococci
Streptococci
Syphilis
Yersinia
Viruses
Adenovirus [76]
BK polyoma
Cytomegalovirus
Epstein Barr virus
Hantavirus
Hepatitis A
Herpes simplex
Human immunodeficiency virus [77]
Influenza H1N1
Mumps
Rubeola
SARS-COV-2
Fungi
Cryptococcus
Histoplasmosis
Parasites
Babesiosis
Encephalitozoon cuniculi
Hydatid Disease
Leishmaniasis
Toxoplasmosis
Rickettsia
R. diaporica
R. rickettsii

Table 42.4 Causes of acute tubulointerstitial nephritis in the pediatric age-group (drugs and infections excluded)

Autoimmune disorders with TIN as typical renal manifestation
Tubulointerstitial nephritis and uveitis syndrome (TINU)
Sjögren's syndrome
Sarcoidosis
Anti-TBM nephritis (rare)
Autoimmune disorders with TIN usually associated with glomerular disease
Systemic lupus erythematosus
ANCA+ vasculitis
Many types of primary glomerulonephritis
Autoimmune disorders with TIN as rare manifestation
Inflammatory bowel disease
Ankylosing spondylitis
Malignant infiltration
Lymphoma
Leukemia
Other
Amanita mushrooms
Sickle cell nephropathy
Snake bites
Wasp and hornet stings (usually multiple)
Radiation nephritis
Renal allograft rejection
Xanthogranulomatous pyelonephritis
Idiopathic

as a cause of acute renal dysfunction without relying on the presence of the historically "classical" clinical features [86]. Future pharmacogenomic studies may identify patients at higher risk of TIN in association with the use of specific medications. One study failed to show that individuals with the CYP2C19 slower metabolizer genotype were at increased risk of omeprazole-induced AIN [87].

The primary treatment of drug-induced TIN is to identify and stop the offending agent. The immunologic trigger must be removed, particularly since persistent tubulointerstitial injury can progress to chronic irreversible damage. Early removal of the offending agent alone frequently leads to complete reversal of renal injury. Kidney biopsies are not performed and additional therapy is not required, if the drug exposure time was short and renal function improves quickly. After drug-induced acute TIN, the mean recovery time to the nadir creatinine is 1.5 months [23]. There are an increasing number of long-term follow-up studies in adults reporting an increased risk of CKD after PPI-induced TIN [85, 88].

Therapy with corticosteroids has been used for several decades to treat severe acute drug-induced TIN, but indications for treatment and evidence of efficacy are problematic due to the lack of prospective randomized controlled clinical trials. Earlier case series have suggested faster

rates of renal recovery with steroids, but their benefit to long-term kidney function is still debated. A systematic review of all studies published between 1975 and 2016 concluded: (1) Findings suggest that the evidence for the use of corticosteroids in the treatment of drug-induced AIN remains uncertain, (2) Given the shortage of proven treatments for drug-induced AIN to ameliorate the burden and consequences of acute kidney injury, suitably designed studies should be prioritized [89]. In the interim, there is a growing consensus of expert opinions that a course of corticosteroids is reasonable to treat acute kidney injury secondary to biopsy-proven acute TIN (in the absence of significant tubular atrophy and interstitial fibrosis) when kidney function does not improve within 3–6 days after the offending drug is withdrawn [90]. Studies by Gonzales et al. [36] and Fernandez-Juarez et al. [91] report worse renal functional outcome if treatment is delayed for more than a few weeks after the diagnosis is made (Fig. 42.5).

While older studies may have argued against the use of routine corticosteroids for severe drug-induced TIN, there are several possible explanations for a lack of glucocorticoid efficacy in

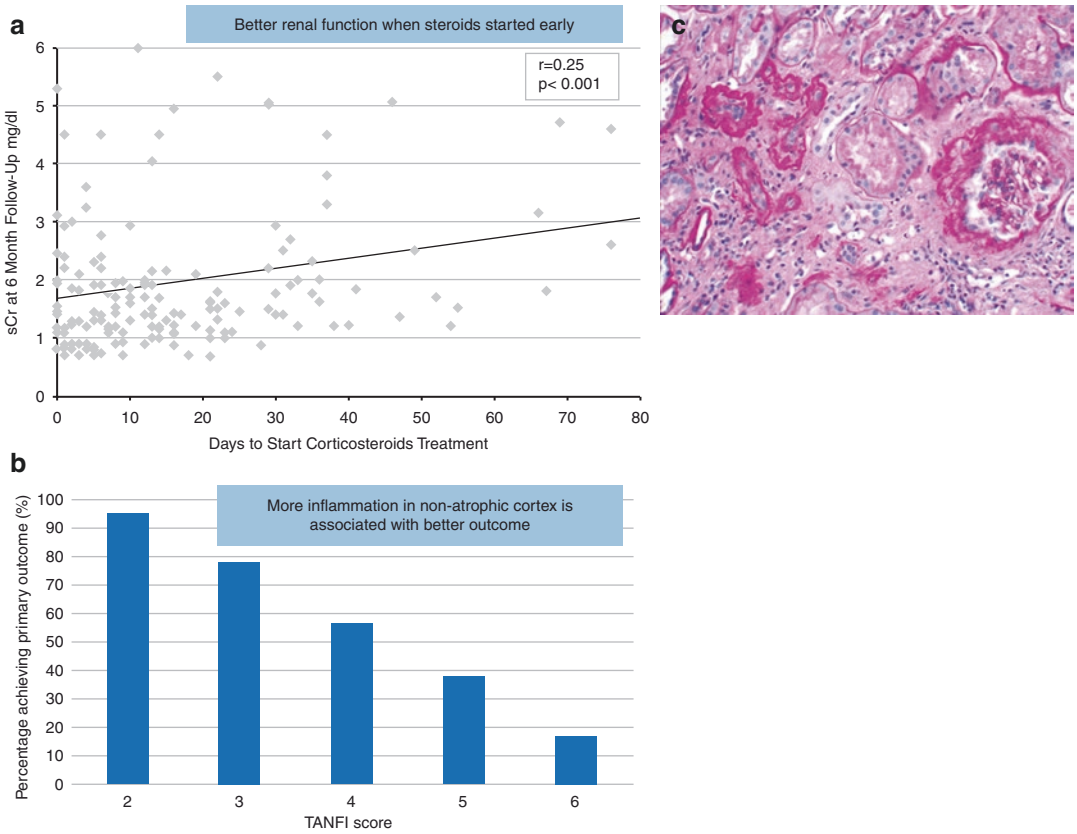

Fig. 42.5 Prognostic impact of early steroid initiation, and degree of tubulointerstitial inflammation and fibrosis/tubular atrophy on TIN outcomes. In a study of 182 adults with severe drug-induced TIN treated in Spain (mean peak creatinine 504 ± 309 μmol/L), the serum creatinine level 6 months after diagnosis was better when corticosteroid treatment was started early [91] (**a**). A kidney injury chronicity score applied to 120 adult kidney biopsies with primary acute TIN reported better clinical outcomes (50% reduction in serum creatinine or eGFR greater than 60 mL/min/1.73 m^2 at 1 year) in patients with low cortical tubular atrophy and with higher interstitial inflammation in non-fibrotic cortex scores. These data were combined into a single score called TANFI, calculated as the tubular atrophy score pulse the inverse of the non-fibrotic cortex with inflammation [92] (**b**). Representative photomicrograph of renal biopsy illustrating the features of chronic TIN—tubular atrophy, thickened tubular basement membranes and an expanded interstitial space occupied by scar tissue (**c**). (**a**, **b** were originally published in *Histopathology* and *CJASN*, respectively, and are reproduced with copyright permission)

earlier studies, including a bias towards treating the patients with worse disease, the possibility that a significant proportion of the patients had NSAID-associated TIN, which appears to be less likely to respond to glucocorticoid therapy, and the negative impact of delayed therapy onset [9, 23, 35]. Future studies will also need to control for the degree of chronic damage as quantified on the kidney biopsy (tubular atrophy and interstitial fibrosis), which negatively impacts reversibility and long-term prognosis [92]. When indicated, the leading experts recommend treating acute drug-induced TIN with prednisone 1 mg/kg/day for 2–4 weeks, followed by tapering to discontinuation over 3–4 weeks. The retrospective study by Fernandez-Juraz et al. with 182 adults from 13 centers in Spain reported that using high dose corticosteroids for longer than 3 weeks and total therapy duration longer than 8 weeks has a non-significant effect on renal recovery and may increase the risk for adverse steroid therapy effects [91]. Data on the use of immunosuppressive agents such as mycophenolate mofetil are too sparse to draw any conclusions.

While the serum creatinine at the time of biopsy is a poor prognostic indicator [36], evidence is emerging to suggest that patients with acute systemic inflammation (elevated ESR and CRP) [93] and low chronicity scores on biopsy [92] have better renal function outcome (Fig. 42.5).

Drugs have also been implicated in unusual cases of TIN. For example, anti-carbonic anhydrase II antibodies were detected in a patient with TIN associated with the use of famotidine [94].

Tubulointerstitial Nephritis with Uveitis

An association between TIN and anterior uveitis, occasionally associated with bone marrow granulomas, was first reported in 1975 and called TINU [95]. While anterior uveitis is more common, posterior uveitis can also occur. When first described, there was a female predominance; recent studies also indicate that 65% are female. The median age of onset is 17 years (55% are under 18 years of age) [75]. TINU is a syndrome of multiple etiologies. Though often idiopathic and presumed to be autoimmune in pathogenesis, it is important to search for evidence of the known causes of TIN with uveitis that are summarized in Fig. 42.6. It is speculated that disease pathogenesis involves an immunological response triggered by a recent drug exposure (often an

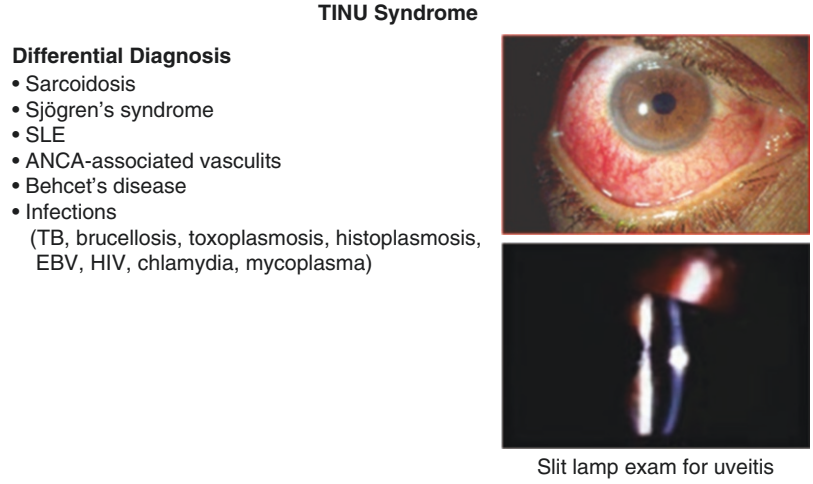

Fig. 42.6 Tubulointerstitial nephritis with uveitis syndrome (TINU). While often idiopathic, the known secondary causes of TINU listed in this figure should be considered in the differential diagnosis as specific therapy is available for many of them. The ocular photomicrographs, taken from patients with acute uveitis, serve as a reminder of the importance of performing a slit lamp examination as part of the evaluation of a patient with suspected acute TIN of unknown etiology

antimicrobial agent), an infection or an unknown agent. The systematic review of 592 cases, reported an association with drugs in 21%, infections in 6% and no identified trigger in 63% [75]. Some patients have serum auto-antibodies such as antinuclear antibodies, rheumatoid factor, antineutrophil cytoplasmic antibodies and/or anticardiolipin antibodies. One study posits that modified C-reactive protein might be a target antigen [96]. Some patients have associated autoimmune diseases such as hyperthyroidism [97], hyperparathyroidism, or rheumatoid arthritis. Patients may also have a history of recent insect bites [98].

The report of TINU in monozygotic male twins separated in onset by 2 years suggests the possibility of a genetic predisposition to the syndrome [99], as does a report in 1994 of identical female twins with the onset of TINU syndrome 1 year apart [100]. However, the lack of reports of multiple affected family members and the lack of geographic clustering questions the influence of environment and genetic factors. Reviewed by Cline and Vanguri [101], several small studies (2–20 patients from several countries), have suggested different HLA associations (especially some DRB1* alleles), but ethnic diversity among the cohorts prevents broader extrapolation of the findings.

Several of the non-specific symptoms associated with TIN may be present in patients with TINU syndrome. These include fever, weight loss, fatigue, malaise, loss of appetite, weakness, asthenia, abdominal or flank pain, arthralgias and myalgias. Less commonly, headache, polyuria, lymphadenopathy, edema, pharyngitis or rash may occur. The ocular manifestations commonly include eye pain and redness (77%), decreased visual acuity (20%) and photophobia (14%) [98], but recent studies have suggested that up to 58% of patients with TINU have reported no ocular symptoms despite slit-lamp confirmation of uveitis, making it critical that patients with acute TIN undergo regular eye examinations [8]. Onset of uveitis varies from several weeks before the onset of renal involvement, concurrent with the TIN, or up to 15 months after the onset of TIN. The systematic review by Regusci et al. reported the onset of uveitis after renal involvement in 52% of the patients [75]. Both recurrent acute and chronic uveitis are commonly described. The timing of uveitis recurrence has varied from 3 months after steroid tapering to 2 years after the first episode. The renal and ocular manifestations of TINU have also been reported to recur years after initial presentation, even after transplantation, further supporting a role for systemic immunological factors in the disease pathogenesis [102].

Laboratory findings may include elevated serum creatinine, evidence of tubular dysfunction, anemia, slightly abnormal liver function tests, eosinophilia, hypergammaglobulinemia and elevated erythrocyte sedimentation rate. A variety of serological markers have been reported without evidence of the associated diseases in 15% of patients (such as SLE, ANCA-associated vasculitis, anti-phospholipid syndrome, rheumatoid arthritis). However, definitive diagnosis requires a renal biopsy and a formal ophthalmologic slit-lamp examination to diagnose uveitis. Bone marrow and lymph node granulomas have been reported, but these studies are rarely performed now that TINU syndrome has become recognized as a distinct clinical entity.

The tubulointerstitial disease is self-limited in most patients, but there are reports of individuals progressing to ESKD [8, 102]. In the 2021 systematic review, 11% of the patients under 18 years had CKD at a median follow-up of 18 months [75]. The ocular disease usually requires treatment, with both topical and systemic steroids. There are anecdotal reports of utilizing other immunomodulatory therapies in the treatment of recalcitrant eye disease. While the acute eye disease usually improves, recurrences, complications, and chronic ocular disease are not uncommon. Most of the long-term complications of TINU have been ocular, estimated to occur in 20% of patients. These include posterior synechiae, optic disc swelling, cystoid macular edema, chorio-retinal scar formation, cataracts and glaucoma [95, 98]. Fortunately, the risk of visual loss appears low. Due to the morbidity associated with the ocular manifestations, early detection by slit lamp examination is essential.

Infections

Numerous infectious agents have been implicated in the pathogenesis of TIN, both acute and chronic. TIN was first recognized as a unique clinical entity in 1860 in a patient with scarlet fever. However, it was several decades later before Councilman introduced the term "interstitial nephritis" and described the histologic lesions. To quote his landmark paper "Acute interstitial lesions of the kidneys have been considered as common in scarlet fever, and are regarded by some authors as constituting the most frequent pathological alteration of the kidney in this disease. This has also been described in diphtheria and in other infectious diseases" [1]. The 1939–1945 era saw the eradication of serious and fatal streptococcal infections due to the introduction of antibiotics. In the current era, the infections implicated as causes of TIN vary from Councilman's time due to childhood immunizations and the use of effective antibiotics. In fact, since 1960 antibiotics rather than infections are a more common cause of acute TIN (Table 42.3, Fig. 42.4).

The infectious microorganisms may directly invade the renal parenchyma to cause a specific form of TIN (pyelonephritis). TIN is the most frequent renal biopsy finding in patients with renal tuberculosis [103]. Rare infectious processes may induce emphysematous or necrotizing interstitial parenchymal lesions [104, 105]. However, the traditional form of acute TIN is associated with infection at an extrarenal site and the tubulointerstitial inflammation is thought to represent a secondary or "reactive" immunological response to the infection. In the latter, the infectious agent is not cultured from the kidney or urine and cytokines derived from inflammatory cells are key kidney disease mediators.

When a renal biopsy is performed in a patient with pyelonephritis (not typically required or recommended), the interstitial lesion is often localized to a single pyramid and characterized by neutrophil predominance. In contrast, "reactive" TIN associated with a systemic infection is characterized histologically as either patchy or diffuse lesions that are associated with interstitial edema and a predominance of mononuclear cells. The pathogenic microbial antigens that initiate the immune response to cause TIN are largely unknown. One exception is leptospirosis, where an isolated outer membrane protein has been shown to interact in vitro with Toll-like receptor 2 to stimulate synthesis of inflammatory cytokines, chemokines and collagen by renal tubules [106]. The primary therapeutic measure is to treat the infection, preferably with non-nephrotoxic antimicrobials.

Viral infections are an important cause of TIN. Epstein-Barr virus (EBV) may have a pathogenetic role in certain forms of "idiopathic" TIN based on the detection of EBV genome in the proximal tubules in one case series [107]. HIV-1-assocated nephropathy is typically characterized by significant glomerular pathology, but coexistent TIN is common and more severe than observed in other primary glomerular disorders. This is likely related to the ability of HIV-1 to infect and damage tubular cells [108]. In a kidney biopsy series of 222 HIV-infected patients, 27% had TIN as the predominant lesion [77]. However, in at least half of the latter patient group, the concurrent use of nephrotoxic agents such as antiretroviral drugs may have contributed to the TIN. TIN has also been reported as a feature of the immune reconstitution syndrome in the HIV-infected population [109].

BK polyomavirus is an important cause of TIN in immunocompromised patients, especially following kidney transplantation, though it has been reported in other transplants recipients as well and rarely in children with a lymphoid malignancy [4, 110–112]. Adenovirus DNA has also been identified in a few kidney allografts with granulomatous TIN [5, 76]. Many other viruses listed in Table 42.3 have been associated with reported cases of TIN.

Granulomatous Interstitial Nephritis

TIN may be associated with the presence of granulomas on renal biopsy (Fig. 42.1b). Granulomatous TIN is found in approximately 6% of renal biopsies with TIN [13]. The differential

diagnosis of this histologically distinct variant includes drug-induced TIN (~25% of cases), infectious causes (tuberculosis, brucellosis, histoplasmosis, adenovirus, fungal), ANCA-associated vasculitis, sarcoidosis, TINU syndrome, multiple myeloma, IBD [113] and other dysproteinemias; it may be idiopathic in as many as 50% of the patients [114]. While TIN has been reported in up to 20% of renal biopsies performed in patients with IBD [41], granulomatous TIN is exceptionally rare and limited to a few IBD case reports [115].

Additionally, there is the frequent challenge of distinguishing between drug-induced AIN associated with IBD treatment and extra-intestinal manifestations of IBD primary disease. There are reports of biopsy proven AIN in IBD patients before they have started IBD treatment, suggesting a pathogenesis distinct from drug-induced AIN [116].

There are several systemic diseases that may cause acute TIN even in the pediatric age group (Table 42.4). A few of the more common examples are discussed briefly in the next sections.

Sarcoidosis

Sarcoidosis is a multisystem disease characterized by non-caseating granuloma formation in various organs, including the kidney. While the exact incidence of granulomatous TIN among patients with sarcoidosis is unknown, studies have cited an incidence up to 30% [114]. Although histologic evidence of renal involvement is said to be common in sarcoidosis, isolated renal sarcoidosis is rare [117, 118].

Patients with sarcoidosis tend to avidly absorb dietary calcium, leading to hypercalciuria and, less commonly, hypercalcemia. The clinical manifestations of calcium hyperabsorption may be silent or may cause nephrolithiasis, nephrocalcinosis, renal insufficiency or polyuria. Nephrocalcinosis is the most common cause of chronic renal failure in sarcoidosis [119]. Polyuria may be the result of hypercalcemia and hypercalciuria that decreases tubular responsiveness to antidiuretic hormone, or it may be a manifestation of diabetes insipidus or primary polydipsia as a consequence of granulomatous infiltration of the hypothalamus. It is important to recognize that the abnormalities in calcium metabolism can occur in other chronic granulomatous diseases due to increased calcitriol produced by activated mononuclear cells [120].

The urinary manifestations of sarcoid granulomatous TIN are similar to other forms of chronic TIN, often associated with a bland urine sediment, sterile pyuria and/or mild proteinuria. The serum creatinine is usually normal and CKD is rare. The renal biopsy findings may include TIN with mononuclear cell infiltration and non-caseating granulomas in the interstitium [121]. When glomerular disease is present, it is most frequently membranous nephropathy; however, granulomatous TIN is present in 2/3 of the cases with glomerular disease [122]. Chronic injury, manifest as interstitial fibrosis and tubular damage, is common in the primary sarcoidosis-associated glomerulopathies.

Corticosteroids remain the treatment of choice, with slowly tapered protocols to prevent disease recurrence [122–125]. While there are currently no large trials of therapeutic protocols for renal sarcoidosis, there are reports of tumor necrosis factor-α blocking agents improving renal function, supporting the theory that TNF-α may play a pathogenetic role [119, 126]. In the rare patient who develops ESKD, it is usually due to hypercalcemia and hypercalciuria rather than TIN [119]. Renal sarcoidosis has been reported to recur in approximately 15% of renal allografts [127, 128].

Sjögren's Syndrome

Sjögren's syndrome is classically described as a sicca syndrome that occurs as a consequence of lymphocytic (mainly activated CD4+ cells and B cells) and plasmacytic infiltrates in the exocrine glands, especially the salivary, parotid and lacrimal glands. This causes dry mouth and dry eyes. These sicca symptoms are less common in children; recurrent parotitis is a common presenting symptom [129]. The pathogenic immune process may also affect non-exocrine organs, including the skin, lung, gastrointestinal tract, central and peripheral nervous systems, musculoskeletal sys-

tem and the kidney. The most common renal manifestation is TIN with associated tubular dysfunction (Fanconi syndrome); glomerular disease has also been reported [130–132]. Though the presence of renal disease in patients with Sjögren's syndrome was first reported in the 1960s, its prevalence and primary pathogenesis remain ill-defined. In the literature, the frequency of renal abnormalities varies widely from 16% to 67% [130, 133]. The diagnosis of idiopathic Sjögren's syndrome is based on clinical and/or histopathological evidence of ocular, oral or salivary involvement and the presence of anti-Ro/SSA and/or anti-La/SSB auto-antibodies. Symptoms due to renal disease, such as polyuria and renal tubular acidosis, may precede sicca syndrome-related symptoms [133]. TIN is the most common renal finding in Sjögren's syndrome and carries the best prognosis [134], although one case series reported four patients with isolated TIN and primary Sjogren's disease that progressed to ESKD [131]. While steroids remain the mainstay of therapy for the renal manifestations, other medications such as rituximab have shown improvement in the extrarenal manifestations [131, 132, 135, 136].

Other Systemic Autoimmune Diseases

Renal involvement is common when systemic lupus erythematosus begins in the pediatric age group: 20–80% within a year of diagnosis and 48–100% at some point during the course of the disease [137]. Isolated TIN associated with tubular basement membrane (TBM) immune deposits can occur, but is extremely rare. Conversely, focal or diffuse interstitial inflammation in association with glomerular disease is relatively common and does not typically show a clear association with TBM immune deposits and the presence of TIN is not considered in the primary classification of lupus nephritis (Classes 1–VI) [138]. The severity of interstitial inflammation and, in particular, its association with tubular atrophy and interstitial fibrosis, are strong predictors of renal outcome [139].

The majority of pediatric patients with ANCA-associated systemic vasculitis have renal involvement (75–88%) [140]. TIN is typically present in association with focal necrotizing glomerulonephritis, though isolated cases of TIN have been reported [141]. The "signature" interstitial granuloma is only present in 6–12% of renal biopsies performed in patients with granulomatosis with polyangiitis [142].

Over the past decade, an increasing number of adults have been diagnosed with TIN due to an autoimmune multisystem disease referred to as IgG4-related disease [143], but there are very few published pediatric cases [144]. It is noted that IgG4+ cells can be detected in other forms of TIN [145]. Other causes of primary TIN include IBD [115, 116] and ankylosing spondylitis [113, 146]. In a study of native kidney biopsies performed in Finland, 13.3% of the patients with TIN had IBD [147]. Both IBD and some of the drug treatments (5-aminosalicylic acid, infliximab, vedolizumab) have been implicated as TIN triggers. Since many patients with systemic autoimmune disorders have complicated medical courses, it is always important to consider alternative causes for their TIN such as drugs and infection.

TIN has been reported in young boys with immunodysregulation, polyendocrinopathy. Enteropathy X-linked (IPEX), a rare genetic disease caused by an inherited mutation in the gene encoding forkhead box P3 (FOXP3) [148].

Xanthogranulomatous TIN

Xanthogranulomatous pyelonephritis (XGP) is a rare entity usually occurring in the fifth or sixth decade of life, though neonatal and childhood cases have been reported [149–151]. In a review of 66 children who underwent nephrectomy in Ireland between 1963 and 2016 for XPN, the median age was 4.84 years (range 1.1–14.8 years) [151]. It is a chronic destructive granulomatous inflammation of the renal parenchyma first described in 1916 by Schlagenhaufer in association with *Escherichia coli* and *Proteus mirabilis* urinary tract infections [152]. The exact etiology

remains unknown, but it is thought to be a result of chronic obstruction with persistent urinary infection [150, 153]. The disease may be mistaken for malignancy, with the consequence that diagnosis is often made on histology after nephrectomy. Medical management of the suppurative infection is possible when an early diagnosis is made, but this is unusual. Nephrectomy is not uncommon due to irreversible parenchymal destruction [154, 155].

Idiopathic TIN

Approximately 8–10% of cases of acute TIN remain idiopathic [6–8, 12, 32–34]. This diagnosis can only be made after all other possible causes have been eliminated by a thorough history, clinical examination, and relevant laboratory investigations.

Chronic Interstitial Nephritis

Epidemiology

The exact incidence and prevalence of primary chronic TIN is poorly documented. This topic is complicated by the fact that chronic interstitial changes typify virtually all chronic renal disorders that eventually progress to CKD stage 5.

Pathology

The early phase of chronic TIN shares histopathologic features with acute TIN, including interstitial inflammation and tubular cell activation. However, as the disease progresses, interstitial fibrosis and chronic tubular injury (dilated tubules with/without cast formation, atrophied tubules and thickened tubular basement membrane) appear (Fig. 42.5) [156, 157]. In the advanced stages, glomerulosclerosis may occur as a secondary consequence of the tubular damage or periglomerular interstitial fibrosis. For all chronic kidneys diseases, whether initially a glomerular or tubulointerstitial disorder, interstitial fibrosis severity is a strong predictor of renal functional loss and risk of progressive renal disease, as illustrated by a recent study of 1022 patients with IgA nephropathy [158].

Clinical Findings

The clinical findings in chronic TIN are similar to those in acute TIN, but tend to be more subtle and often go undetected until the patient develops signs and symptoms due to chronic renal insufficiency. Compared to chronic glomerular disease, in patients with chronic TIN hypertension is less common, daily protein excretion rates rarely exceeds 1.5 g/day and anemia may be disproportionately worse than the degree of renal functional impairment due to the loss of erythropoietin-producing cells in the peritubular interstitium. Bone disease may also be more prominent as a result of chronic phosphate wasting due to proximal tubular dysfunction.

Etiology

As in acute TIN, there are numerous causes of chronic TIN. In addition to diseases that may progress from acute TIN to chronic TIN, several diseases more typically present as chronic TIN. In the pediatric population, the causes of chronic TIN that are not sequelae of acute TIN can be broadly grouped into the following categories that are also summarized in Table 42.5; many are reviewed in greater detail in other chapters.

Genetic Kidney Diseases, especially the ciliopathies (nephronophthisis) and polycystic kidney disease, are associated with significant tubular damage and interstitial inflammation and fibrosis. Another group of inherited diseases that are increasingly recognized since first reported in 2002 are now classified as autosomal dominant tubulointerstitial kidney disease (ADTKD) [159]. They are rare diseases that are largely undetected in childhood, as the kidney disease is typically silent until clinical manifestations of chronic renal failure develop. Some patients provide a history of polyuria and/or enuresis due to a uri-

Table 42.5 Common causes of chronic TIN in childhood and adolescence

Category	Specific entity
Persistent TIN	All categories (late diagnosis)
Inherited kidney disease	Autosomal Dominant Tubulointerstitial Kidney Diseases (ADTKD) (*UMOD*, *MUC1*, *REN* and other less common gene mutations)
	Karyomegalic TIN (*FAN1* mutation)
	Nephronophthisis (ciliopathies)
	Polycystic kidney diseases
Inherited metabolic disease	Cystinosis
	Oxalosis
	Methylmalonic acidemia
	Mitochondrial cytopathies
	Adenine phosphoribosyltransferase (APRT) deficiency
Acquired metabolic disease	Nephrocalcinosis
	Uric acid-induced injury
	Potassium deficiency (anorexia nervosa)
Chronic nephrotoxicity	Chronic interstitial nephritis in agricultural communities (CINAC)
	Heavy metals (lead, cadmium)
	Calcineurin inhibitors
	Analgesic nephropathy
	Chinese herbs (Aristolochia fangchi)
	Chemotherapy (cisplatinum, isophosphamide)
Structural renal disease	Dysplasia
	Obstruction
	Reflux

nary concentrating defect. The first cases reported were caused by autosomal dominant mutations in *UMOD*, the gene that encodes the kidney-specific protein uromodulin (also known as Tamm-Horsfall protein). Patients often present with symptoms of gout between 15 and 40 years of age due to hyperuricemia (present in ~70% of affected patients) [160]. Stage 5 CKD due to chronic TIN develops between ages 30–60 years; the rate of progression may be decreased in the hyperuricemic patients with the use of allopurinol. Mutations in the *MUC1* gene, which encodes the glycoprotein mucin-1, were first reported in 2013. Mutations in *UMOD* and *MUCI* are the most prevalent etiologies of ADTKD [161]. It is estimated that ~50% of the ADTKD patients currently lack a genetic diagnosis [160]. Eight mutations have been reported in the *REN* gene that encodes prorenin [162, 163]. These patients may develop transient childhood anemia, have a tendency for hyperkalemia, defective urinary concentration and gout. Additional diseases have been classified as ADTKD, although the kidney phenotype may include features in addition to chronic TIN. These include patients with mutations in the genes *HNF1B* encoding hepatocyte nuclear factor 1 beta, and *SEC61A1* that encodes the alpha 1 subunit of SEC61 [161].

There is another rare genetic disease that resembles nephronophthisis histologically except for the presence of hyperchromatic and abnormally enlarged tubular epithelial cell nuclei that causes ESKD in the third or fourth decade of life. It was first recognized as a distinct entity and named karyomegalic interstitial nephritis (KIN) in 1979 [164]. In 2012 Zhou et al. [165] identified an autosomal recessive mutation in *FAN1* as a cause of TIN.

Other causes of chronic TIN include:

1. ***Congenital anomalies of the kidney and urinary tract.***
2. ***Inborn error of metabolism***, including cystinosis, oxalosis, methylmalonic acidemia, the mitochondrial cytopathies, adenine phosphoribosyltransferase (APRT) deficiency.
3. ***Chronic nephrotoxin exposure***, especially the calcineurin inhibitors, lithium, heavy met-

als (cadmium, mercury, and lead), chemotherapeutic agents (cisplatinum, ifosfamide), antimicrobials (amphotericin B, antiretroviral drugs), NSAIDs and certain Chinese herbs.

4. ***Chronic interstitial nephritis in agricultural communities (CINAC)***. This disease entity is increasing in endemic areas of the world, characterized as agricultural communities in hot tropical communities (patients in Sri Lanka and Central America are best studied) [166]. While male agricultural workers in the 20s to 40s age group are most frequently reported, it has also been reported in women, and markers of kidney damage can be found in children [167]. Histopathologically CINAC is a chronic TIN. The etiology is unclear and likely multifactorial. A recent kidney biopsy study by Vervaet et al. [168] reported abnormal proximal tubular lysosomes; by electron microscopy they contained electron-dense aggregates suggestive of a toxin-associate proximal tubulopathy. Several toxic agrochemicals and pesticides have been identified as candidates, but definitive proof of their role is still lacking. Exposure might be direct or may occur from contaminated water consumption or by inhalation. Heat stress and recurrent dehydration may be a contributing factor.
5. *Chronic allograft nephropathy.*

Treatment and Prognosis

Treatment of chronic TIN is based on the treatment of the primary disease process. In addition, there is increasing evidence that correction of anemia, reduction of proteinuria and suppression of inflammation may also slow the rate of the kidney disease progression [156]. Angiotensin converting-enzyme inhibitors and angiotensin receptor type 1 blockers are being used with increasing frequency for a variety of chronic renal diseases, especially when associated with hypertension and/or proteinuria. It is believed that in addition to decreasing intraglomerular pressure, these drugs reduce proteinuria and may also have an anti-fibrotic role related to angiotensin II blockade [169].

Outcomes

Patients with chronic TIN and CKD stage III (GFR 30–59 mL/min/1.73 m^2) or stage IV (GFR between 15 and 29 mL/min/1.73 m^2) are destined to progress to ESKD (GFR < 15 mL/min/1.73 m^2). Numerous comorbid factors correlate with a faster rate of renal functional decline, including hypertension, high-grade proteinuria, diabetes, smoking, obesity, dyslipidemia and anemia [12, 96].

While definitive therapy may not be available for the primary disease process that is responsible for chronic TIN, many of these comorbidities can be addressed therapeutically to preserve residual nephrons and slow the rate of CKD progression. Landmark studies by Risdon and Shainuck, more than half a century ago, highlighted the central importance of chronic TIN, assessed as the degree of tubular atrophy and interstitial fibrosis, to renal functional outcomes irrespective of the primary etiology of the CKD. Since then, advances in the field of cellular and molecular biology and genome sciences have utilized animal models and human kidney tissue biorepositories to decipher fundamental mechanisms that cause the chronic TIN component in human CKD. A major priority for ongoing and future studies is the identification of new therapeutic targets, development of safe therapeutic agents based on these "candidate" targets and subsequent randomized prospective clinical trials to establish their efficacy in patients with CKD. Analogous to current cancer treatment protocols, a multi-agent approach will almost certainly be necessary, taking into consideration specific genetic and molecular disease markers that get us closer to personalized medicine. Based on the current state of knowledge, several interrelated pathogenic pathways are potentially amenable to drug therapies [157]:

1. Preserving tubular epithelial cell integrity (and thus intact nephrons) by minimizing tubular injury/death/senescence and enhancing the repair of damaged tubules. Reactivating key kidney developmental pathways has been promising in experimental models. Permanent

tubular loss is a key predictor of irreversible CKD.
2. Blocking the numbers and/or function of a unique population of interstitial myofibroblasts that are the primary source of the scar-forming extracellular matrix proteins.
3. Regulating the interstitial cell inflammatory response that has multiple consequences—some harmful and others healing. The role of macrophages appears to be particularly important.
4. Disrupting the vicious circle of hypoxia and oxidant stress that develops at least in part because of the lack of preservation of a healthy interstitial capillary network vital for adequate kidney oxygenation.
5. Reducing the progressive accumulation of extracellular matrix proteins in the interstitium. Despite the identification of several matrix-degrading proteases in kidneys, there is still no convincing evidence that renal fibrosis can be reversed in humans. Effective therapies will need to target the extracellular matrix production pathways.

Further laboratory and clinical studies are needed to identify new evidence-based therapeutic options to improve long-term outcomes for patients with chronic TIN.

References

1. Councilman WT. Acute interstitial nephritis. J Exp Med. 1898; https://doi.org/10.1084/jem.3.4-5.393.
2. Kodner CM, Kudrimoti A. Diagnosis and management of acute interstitial nephritis. Am Fam Physician. 2003;67(12):2527–34.
3. Michel DM, Kelly CJ. Acute interstitial nephritis. J Am Soc Nephrol. 1998; https://doi.org/10.5005/jp/books/12074_52.
4. Hirsch HH, Vincenti F, Friman S, Tuncer M, Citterio F, Wiecek A, Scheuermann EH, Klinger M, Russ G, Pescovitz MD, Prestele H. Polyomavirus BK replication in de novo kidney transplant patients receiving tacrolimus or cyclosporine: a prospective, randomized, multicenter study. Am J Transplant. 2013;13(1):136–45. https://doi.org/10.1111/j.1600-6143.2012.04320.x.
5. Moreira LC, Rocha J, Silva M, Silva J, Almeida M, Pedroso S, Vizcaíno R, Martins LS, Dias L, Henriques AC, Cabrita A. Adenovirus infection-a rare cause of interstitial nephritis in kidney transplant. Nefrologia. 2019;39(1):106–7. https://doi.org/10.1016/j.nefro.2018.06.001.
6. Clavé S, Rousset-Rouvière C, Daniel L, Tsimaratos M. Acute tubulointerstitial nephritis in children and chronic kidney disease. Arch Pediatr. 2019;26(5):290–4. https://doi.org/10.1016/j.arcped.2019.05.002.
7. Goicoechea M, Rivera F, López-Gómez JM. Increased prevalence of acute tubulointerstitial nephritis. Nephrol Dial Transplant. 2013; https://doi.org/10.1093/ndt/gfs143.
8. Jahnukainen T, Ala-Houhala M, Karikoski R, Kataja J, Saarela V, Nuutinen M. Clinical outcome and occurrence of uveitis in children with idiopathic tubulointerstitial nephritis. Pediatr Nephrol. 2011; https://doi.org/10.1007/s00467-010-1698-4.
9. Praga M, González E. Acute interstitial nephritis. Kidney Int. 2012; https://doi.org/10.1038/ki.2010.89.
10. Lanewala A, Mubarak M, Akhter F, Aziz S, Bhatti S, Kazi JI. Pattern of pediatric renal disease observed in native renal biopsies in Pakistan. J Nephrol. 2009;22(6):739–46.
11. Braden GL, O'Shea MH, Mulhern JG. Tubulointerstitial diseases. Am J Kidney Dis. 2005; https://doi.org/10.1053/j.ajkd.2005.03.024.
12. Baker RJ, Pusey CD. The changing profile of acute tubulointerstitial nephritis. Nephrol Dial Transplant. 2004; https://doi.org/10.1093/ndt/gfg464.
13. Viero RM, Cavallo T. Granulomatous interstitial nephritis. Hum Pathol. 1995; https://doi.org/10.1016/0046-8177(95)90300-3.
14. Cameron JS. Tubular and interstitial factors in the progression of glomerulonephritis. Pediatr Nephrol. 1992; https://doi.org/10.1007/BF00878382.
15. Ulinski T, Sellier-Leclerc AL, Tudorache E, Bensman A, Aoun B. Acute tubulointerstitial nephritis. Pediatr Nephrol. 2012; https://doi.org/10.1007/s00467-011-1915-9.
16. Buysen JGM, Houthoff HJ, Krediet RT, Arisz L. Acute interstitial nephritis: a clinical and morphological study in 27 patients. Nephrol Dial Transplant. 1990; https://doi.org/10.1093/ndt/5.2.94.
17. Halloran PF, Matas A, Kasiske BL, Madill-Thomsen KS, Mackova M, Famulski KS. Molecular phenotype of kidney transplant indication biopsies with inflammation in scarred areas. Am J Transplant. 2019;19(5):1356–70. https://doi.org/10.1111/ajt.15178.
18. Harris DCH. Tubulointerstitial renal disease. Curr Opin Nephrol Hypertension. 2001; https://doi.org/10.1097/00041552-200105000-00003.
19. Landegren N, Pourmousa Lindberg M, Skov J, Hallgren Å, Eriksson D, Lisberg Toft-Bertelsen T, MacAulay N, Hagforsen E, Räisänen-Sokolowski A, Saha H, Nilsson T, Nordmark G, Ohlsson S, Gustafsson J, Husebye ES, Larsson E, Anderson MS, Perheentupa J, Rorsman F, et al. Autoantibodies

targeting a collecting duct-specific water channel in tubulointerstitial nephritis. J Am Soc Nephrol. 2016;27(10):3220–8. https://doi.org/10.1681/ASN.2015101126.
20. Nakamori A, Akagaki F, Yamaguchi Y, Sugiura T. Relapsing tubulointerstitial nephritis with anti-mitochondrial M2 antibody accompanied by pulmonary involvement. Intern Med (Tokyo, Japan). 2020;59(9):1179–87. https://doi.org/10.2169/internalmedicine.4048-19.
21. Rosales IA, Collins AB, do Carmo PAS, Tolkoff-Rubin N, Smith RN, Colvin RB. Immune complex tubulointerstitial nephritis due to autoantibodies to the proximal tubule brush border. J Am Soc Nephrol. 2016;27(2):380–4. https://doi.org/10.1681/ASN.2015030334.
22. Spanou Z, Keller M, Britschgi M, Yawalkar N, Fehr T, Neuweiler J, Gugger M, Mohaupt M, Pichler WJ. Involvement of drug-specific t cells in acute drug-induced interstitial nephritis. J Am Soc Nephrol. 2006; https://doi.org/10.1681/ASN.2006050418.
23. Rossert J. Drug-induced acute interstitial nephritis. Kidney Int. 2001; https://doi.org/10.1046/j.1523-1755.2001.060002804.x.
24. Metterle L, Hatch L, Seminario-Vidal L. Pediatric drug reaction with eosinophilia and systemic symptoms: a systematic review of the literature. Pediatr Dermatol. 2020;37(1):124–9. https://doi.org/10.1111/pde.14044.
25. Heeger PS, Smoyer WE, Saad T, Albert S, Kelly CJ, Neilson EG. Molecular analysis of the helper T cell response in murine interstitial nephritis. T cells recognizing an immunodominant epitope use multiple T cell receptor Vβ genes with similarities across CDR3. J Clin Investig. 1994; https://doi.org/10.1172/jci117563.
26. Takemura Y, Koshimichi M, Sugimoto K, Yanagida H, Fujita S, Miyazawa T, Miyazaki K, Okada M, Takemura T. A tubulointerstitial nephritis antigen gene defect causes childhood-onset chronic renal failure. Pediatr Nephrol. 2010; https://doi.org/10.1007/s00467-010-1463-8.
27. Luciano RL, Brewster UC. Kidney involvement in leukemia and lymphoma. Adv Chronic Kidney Dis. 2014; https://doi.org/10.1053/j.ackd.2013.07.004.
28. Fogo AB, Lusco MA, Najafian B, Alpers CE. AJKD atlas of renal pathology: indinavir nephrotoxicity. Am J Kidney Dis. 2017;69(1):e3.
29. Madigan LM, Fox LP. Vancomycin-associated drug-induced hypersensitivity syndrome. J Am Acad Dermatol. 2019;81(1):123–8. https://doi.org/10.1016/j.jaad.2019.02.002.
30. Goli R, Mukku KK, Raju SB, Uppin MS. Acute ciprofloxacin-induced crystal nephropathy with granulomatous interstitial nephritis. Indian J Nephrol. 2017;27(3):231–3. https://doi.org/10.4103/0971-4065.200522.
31. Verghese PS, Schmeling DO, Filtz EA, Matas AJ, Balfour HH. The impact of recipient BKV shedding before transplant on BKV viruria, DNAemia, and nephropathy post-transplant: a prospective study. Pediatr Transplant. 2017;21(5) https://doi.org/10.1111/petr.12942.
32. Howell M, Sebire NJ, Marks SD, Tullus K. Biopsy-proven paediatric tubulointerstitial nephritis. Pediatr Nephrol. 2016;31(10):1625–30. https://doi.org/10.1007/s00467-016-3374-9.
33. Roy S, Awogbemi T, Holt RCL. Acute tubulointerstitial nephritis in children—a retrospective case series in a UK tertiary paediatric centre. BMC Nephrol. 2020;21(1):17. https://doi.org/10.1186/s12882-020-1681-7.
34. Taktak A, Uncu N, Acar B, Çaycı Ş, Ensari A, Gür G, Köksoy A, Çakar N. Acute tubulointerstitial nephritis: a case series and long-term renal outcomes. Turk J Pediatr. 2015;57(6):566–71.
35. Clarkson MR, Giblin L, O'Connell FP, O'Kelly P, Walshe JJ, Conlon P, O'Meara Y, Dormon A, Campbell E, Donohoe J. Acute interstitial nephritis: clinical features and response to corticosteroid therapy. Nephrol Dial Transplant. 2004; https://doi.org/10.1093/ndt/gfh485.
36. González E, Gutiérrez E, Galeano C, Chevia C, De Sequera P, Bernis C, Parra EG, Delgado R, Sanz M, Ortiz M, Goicoechea M, Quereda C, Olea T, Bouarich H, Hernández Y, Segovia B, Praga M. Early steroid treatment improves the recovery of renal function in patients with drug-induced acute interstitial nephritis. Kidney Int. 2008; https://doi.org/10.1038/sj.ki.5002776.
37. Minhas JS, Wickner PG, Long AA, Banerji A, Blumenthal KG. Immune-mediated reactions to vancomycin: a systematic case review and analysis. Ann Allergy Asthma Immunol. 2016;116(6):544–53. https://doi.org/10.1016/j.anai.2016.03.030.
38. Nayak S, Nandwani A, Rastogi A, Gupta V. Acute interstitial nephritis and drug rash with secondary to Linezolid. Indian J Nephrol. 2012; https://doi.org/10.4103/0971-4065.103918.
39. Xie H, Chen H, Hu Y, Xu S, He Q, Liu J, Hu W, Liu Z. Clindamycin-induced acute kidney injury: large biopsy case series. Am J Nephrol. 2013; https://doi.org/10.1159/000354088.
40. Duque JC, Dejman A, Venkat V, Hernandez M, Roth D, Ladino MA. Acute interstitial nephritis following treatment with direct-acting antiviral agents in hepatitis C virus-infected patients: a case series. Clin Nephrol. 2021;95(1):22–7. https://doi.org/10.5414/CN110276.
41. Ambruzs JM, Walker PD, Larsen CP. The histopathologic spectrum of kidney biopsies in patients with inflammatory bowel disease. Clin J Am Soc Nephrol. 2014;9(2):265–70. https://doi.org/10.2215/CJN.04660513.
42. Skalova S, Dedek P, Pozler O, Podhola M. Mesalazine-induced interstitial nephritis. Ren Fail. 2009; https://doi.org/10.1080/08860220802595922.
43. Vasanth P, Parmley M, Torrealba J, Hamdi T. Interstitial nephritis in a patient with inflamma-

tory bowel disease. Case Rep Nephrol. 2016;2016:4260365. https://doi.org/10.1155/2016/4260365.
44. Al-Aly Z, Maddukuri G, Xie Y. Proton pump inhibitors and the kidney: implications of current evidence for clinical practice and when and how to deprescribe. Am J Kidney Dis. 2020;75(4):497–507. https://doi.org/10.1053/j.ajkd.2019.07.012.
45. Chen T, Xu P-C, Hu S-Y, Yan T-K, Jiang J-Q, Jia J-Y, Wei L, Shang W-Y. Severe acute interstitial nephritis induced by valsartan: a case report. Medicine. 2019b;98(6):e14428. https://doi.org/10.1097/MD.0000000000014428.
46. Golbin L, Dolley-Hitze T, Lorcy N, Rioux-Leclercq N, Vigneau C. Drug-induced acute interstitial nephritis with nifedipine. Case Rep Nephrol. 2016;2016:1971465. https://doi.org/10.1155/2016/1971465.
47. Lally J, Al Kalbani H, Krivoy A, Murphy KC, Gaughran F, MacCabe JH. Hepatitis, interstitial nephritis, and pancreatitis in association with clozapine treatment: a systematic review of case series and reports. J Clin Psychopharmacol. 2018;38(5):520–7. https://doi.org/10.1097/JCP.0000000000000922.
48. Abdulhadi B, Mulki R, Goyal A, Rangaswami J. Novel oral anticoagulant and kidney injury: apixaban-related acute interstitial nephritis. BMJ Case Rep. 2017; https://doi.org/10.1136/bcr-2017-221641.
49. Gueye S, Saint-Cricq M, Coulibaly M, Goumri N, Guilbeau-Frugier C, Quentin H, Ged E, Sidi Aly A, Rostaing L. Chronic tubulointerstitial nephropathy induced by glucosamine: a case report and literature review. Clin Nephrol. 2016;86(2):106–10. https://doi.org/10.5414/cn108781.
50. Manohar S, Albright RC. Interstitial nephritis in immune checkpoint inhibitor therapy. Kidney Int. 2019;96(1):252. https://doi.org/10.1016/j.kint.2018.11.009.
51. Shingarev R, Glezerman IG. Kidney complications of immune checkpoint inhibitors: a review. Am J Kidney Dis. 2019;74(4):529–37. https://doi.org/10.1053/j.ajkd.2019.03.433.
52. Kaya Aksoy G, Koyun M, Akkaya B, Comak E, Gemici A, Akman S. Eosinophilic tubulointerstitial nephritis on treatment with isotretinoin. Eur J Pediatr. 2016;175(12):2005–6. https://doi.org/10.1007/s00431-016-2778-7.
53. Sugimoto K, Nishi H, Miyazawa T, Wada N, Izu A, Enya T, Okada M, Takemura T. Tubulointerstitial nephritis complicating IVIG therapy for X-linked agammaglobulinemia. BMC Nephrol. 2014;15:109. https://doi.org/10.1186/1471-2369-15-109.
54. Bahaa Aldeen M, Talibmamury N, Alalusi S, Nadham O, Omer AR, Smalligan RD. When coke is not hydrating: cocaine-induced acute interstitial nephritis. J Investig Med High Impact Case Rep. 2014;2(3):2324709614551557. https://doi.org/10.1177/2324709614551557.
55. Decelle L, Cosyns JP, Georges B, Jadoul M, Lefebvre C. Acute interstitial nephritis after cocaine sniffing. Clin Nephrol. 2007;67(2):105–8. https://doi.org/10.5414/cnp67105.
56. Inayat F, Bokhari SRA, Roberts L, Rosen RM. Cocaine-induced acute interstitial nephritis: a comparative review of 7 cases. J Investig Med High Impact Case Rep. 2020;8:2324709620932450. https://doi.org/10.1177/2324709620932450.
57. Wojciechowski D, Kallakury B, Nouri P. A case of cocaine-induced acute interstitial nephritis. Am J Kidney Dis. 2008; https://doi.org/10.1053/j.ajkd.2008.03.018.
58. Riederer AM, Campleman SL, Carlson RG, Boyer EW, Manini AF, Wax PM, Brent JA, Toxicology Investigators Consortium (ToxIC). Acute poisonings from synthetic cannabinoids—50 U.S. Toxicology Investigators Consortium Registry sites, 2010–2015. MMWR Morb Mortal Wkly Rep. 2016;65(27):692–5. https://doi.org/10.15585/mmwr.mm6527a2.
59. Daher EF, Silva Júnior GB, Queiroz AL, Ramos LMA, Santos SQ, Barreto DMS, Guimarães AAC, Barbosa CA, Franco LM, Patrocínio RMSV. Acute kidney injury due to anabolic steroid and vitamin supplement abuse: report of two cases and a literature review. Int Urol Nephrol. 2009;41(3):717–23. https://doi.org/10.1007/s11255-009-9571-8.
60. Gupta RK, van der Meulen J, Johny KV. Oliguric acute renal failure due to glue-sniffing. Case report. Scand J Urol Nephrol. 1991;25(3):247–50. https://doi.org/10.3109/00365599109107958.
61. Nanavati A, Herlitz LC. Tubulointerstitial injury and drugs of abuse. Adv Chronic Kidney Dis. 2017;24(2):80–5. https://doi.org/10.1053/j.ackd.2016.09.008.
62. Patel R, Benjamin J. Renal disease associated with toluene inhalation. J Toxicol Clin Toxicol. 1986;24(3):213–23. https://doi.org/10.3109/15563658608990459.
63. Taverner D, Harrison DJ, Bell GM. Acute renal failure due to interstitial nephritis induced by "glue-sniffing" with subsequent recovery. Scott Med J. 1988;33(2):246–7. https://doi.org/10.1177/003693308803300208.
64. Bailly E, Von Tokarski F, Beau-Salinas F, Picon L, Miquelestorena-Standley E, Rousseau G, Jonville-Bera A-P, Halimi J-M. Interstitial nephritis secondary to vedolizumab treatment in Crohn disease and safe rechallenge using steroids: a case report. Am J Kidney Dis. 2018;71(1):142–5. https://doi.org/10.1053/j.ajkd.2017.08.008.
65. Escandon J, Peacock S, Trabolsi A, Thomas DB, Layka A, Lutzky J. Interstitial nephritis in melanoma patients secondary to PD-1 checkpoint inhibitor. J Immunother Cancer. 2017;5:3. https://doi.org/10.1186/s40425-016-0205-2.
66. Cheungpasitporn W, Leung N, Rajkumar SV, Cornell LD, Sethi S, Angioi A, Fervenza FC. Bortezomib-induced acute interstitial nephritis. Nephrol Dial Transplant. 2015;30(7):1225–9. https://doi.org/10.1093/ndt/gfv222.

67. Lusica M, Rondon-Berrios H, Feldman L. Urine eosinophils for acute interstitial nephritis. J Hosp Med. 2017;12(5):343–5. https://doi.org/10.12788/jhm.2737.
68. Mirković K, Doorenbos CRC, Dam WA, Lambers Heerspink HJ, Slagman MCJ, Nauta FL, Kramer AB, Gansevoort RT, van den Born J, Navis G, de Borst MH. Urinary vitamin D binding protein: a potential novel marker of renal interstitial inflammation and fibrosis. PLoS One. 2013; https://doi.org/10.1371/journal.pone.0055887.
69. Robles NR, Lopez-Gomez J, Garcia-Pino G, Ferreira F, Alvarado R, Sanchez-Casado E, Cubero JJ. Use of α1-microglobulin for diagnosing chronic interstitial nephropathy. Clin Exp Med. 2014; https://doi.org/10.1007/s10238-013-0242-9.
70. Moledina DG, Wilson FP, Pober JS, Perazella MA, Singh N, Luciano RL, Obeid W, Lin H, Kuperman M, Moeckel GW, Kashgarian M, Cantley LG, Parikh CR. Urine TNF-α and IL-9 for clinical diagnosis of acute interstitial nephritis. JCI Insight. 2019;4(10):e127456. https://doi.org/10.1172/jci.insight.127456.
71. Zhang Y, Li A, Wen J, Zhen J, Hao Q, Zhang Y, Hu Z, Xiao X. Kidney injury molecule-1 level is associated with the severity of renal interstitial injury and prognosis in adult Henoch-Schönlein purpura nephritis. Arch Med Res. 2017;48(5):449–58. https://doi.org/10.1016/j.arcmed.2017.10.005.
72. Zhao W-T, Huang J-W, Sun P-P, Su T, Tang J-W, Wang S-X, Liu G, Yang L. Diagnostic roles of urinary kidney injury molecule 1 and soluble C5b-9 in acute tubulointerstitial nephritis. Am J Physiol Renal Physiol. 2019;317(3):F584–92. https://doi.org/10.1152/ajprenal.00176.2019.
73. Noiri C, Shimizu T, Takayanagi K, Tayama Y, Iwashita T, Okazaki S, Hatano M, Matsumura O, Kato H, Matsuda A, Mitarai T, Hasegawa H. Clinical significance of fractional magnesium excretion (FEMg) as a predictor of interstitial nephropathy and its correlation with conventional parameters. Clin Exp Nephrol. 2015;19(6):1071–8. https://doi.org/10.1007/s10157-015-1099-x.
74. Perazella MA, Markowitz GS. Drug-induced acute interstitial nephritis. Nat Rev Nephrol. 2010; https://doi.org/10.1038/nrneph.2010.71.
75. Regusci A, Lava SAG, Milani GP, Bianchetti MG, Simonetti GD, Vanoni F. Tubulointerstitial nephritis and uveitis syndrome: a systematic review. Nephrol Dial Transplant. 2021; https://doi.org/10.1093/ndt/gfab030.
76. Storsley L, Gibson IW. Adenovirus interstitial nephritis and rejection in an allograft. J Am Soc Nephrol. 2011; https://doi.org/10.1681/ASN.2010090941.
77. Zaidan M, Lescure FX, Brochériou I, Dettwiler S, Guiard-Schmid JB, Pacanowski J, Rondeau E, Pialoux G, Girard PM, Ronco P, Plaisie E. Tubulointerstitial nephropathies in HIV-infected patients over the past 15 years: a clinico-pathological study. Clin J Am Soc Nephrol. 2013; https://doi.org/10.2215/CJN.10051012.
78. Valluri A, Hetherington L, Mcquarrie E, Fleming S, Kipgen D, Geddes CC, Mackinnon B, Bell S. Acute tubulointerstitial nephritis in Scotland. QJM. 2015;108(7):527–32. https://doi.org/10.1093/qjmed/hcu236.
79. Baldwin DS, Levine BB, McCluskey RT, Gallo GR. Renal failure and interstitial nephritis due to penicillin and methicillin. N Engl J Med. 1968; https://doi.org/10.1056/nejm196812052792302.
80. Nawaz FA, Larsen CP, Troxell ML. Membranous nephropathy and nonsteroidal anti-inflammatory agents. Am J Kidney Dis. 2013; https://doi.org/10.1053/j.ajkd.2013.03.045.
81. Ruffenach SJ, Siskind MS, Lien YHH. Acute interstitial nephritis due to omeprazole. Am J Med. 1992; https://doi.org/10.1016/0002-9343(92)90181-A.
82. Antoniou T, Macdonald EM, Hollands S, Gomes T, Mamdani MM, Garg AX, Paterson JM, Juurlink DN. Proton pump inhibitors and the risk of acute kidney injury in older patients: a population-based cohort study. CMAJ Open. 2015;3(2):E166–71. https://doi.org/10.9778/cmajo.20140074.
83. Hart E, Dunn TE, Feuerstein S, Jacobs DM. Proton pump inhibitors and risk of acute and chronic kidney disease: a retrospective cohort study. Pharmacotherapy. 2019;39(4):443–53. https://doi.org/10.1002/phar.2235.
84. Wijarnpreecha K, Thongprayoon C, Chesdachai S, Panjawatanana P, Ungprasert P, Cheungpasitporn W. Associations of proton-pump inhibitors and H2 receptor antagonists with chronic kidney disease: a meta-analysis. Dig Dis Sci. 2017;62(10):2821–7. https://doi.org/10.1007/s10620-017-4725-5.
85. Xie Y, Bowe B, Li T, Xian H, Balasubramanian S, Al-Aly Z. Proton pump inhibitors and risk of incident CKD and progression to ESRD. J Am Soc Nephrol. 2016;27(10):3153–63. https://doi.org/10.1681/ASN.2015121377.
86. Klassen S, Krepinsky JC, Prebtani APH. Pantoprazole-induced acute interstitial nephritis. CMAJ. 2013; https://doi.org/10.1503/cmaj.120954.
87. Helsby NA, Lo WY, Simpson IJ, Voss DM, Logan KE, Searle M, Schollum JBW, De Zoysa JR. Omeprazole-induced acute interstitial nephritis is not related to CYP2C19 genotype or CYP2C19 phenotype. Br J Clin Pharmacol. 2010; https://doi.org/10.1111/j.1365-2125.2010.03623.x.
88. Rodríguez-Poncelas A, Barceló MA, Saez M, Coll-de-Tuero G. Duration and dosing of Proton Pump Inhibitors associated with high incidence of chronic kidney disease in population-based cohort. PLoS One. 2018;13(10):e0204231. https://doi.org/10.1371/journal.pone.0204231.
89. Quinto LR, Sukkar L, Gallagher M. Effectiveness of corticosteroid compared with non-corticosteroid therapy for the treatment of drug-induced acute interstitial nephritis: a systematic review. Intern

Med J. 2019;49(5):562–9. https://doi.org/10.1111/imj.14081.
90. Moledina DG, Perazella MA. Drug-induced acute interstitial nephritis. Clin J Am Soc Nephrol. 2017; https://doi.org/10.2215/CJN.07630717.
91. Fernandez-Juarez G, Perez JV, Caravaca-Fontán F, Quintana L, Shabaka A, Rodriguez E, Gadola L, de Lorenzo A, Cobo MA, Oliet A, Sierra M, Cobelo C, Iglesias E, Blasco M, Galeano C, Cordon A, Oliva J, Praga M, Spanish Group for the Study of Glomerular Diseases (GLOSEN). Duration of treatment with corticosteroids and recovery of kidney function in acute interstitial nephritis. Clin J Am Soc Nephrol. 2018;13(12):1851–8. https://doi.org/10.2215/CJN.01390118.
92. Rankin AJ, Cannon E, Gillis K, Crosby J, Mark PB, Geddes CC, Fox JG, Mackinnon B, McQuarrie EP, Kipgen D. Predicting outcome in acute interstitial nephritis: a case-series examining the importance of histological parameters. Histopathology. 2020;76(5):698–706. https://doi.org/10.1111/his.14031.
93. Zheng X-Z, Gu Y-H, Su T, Zhou X-J, Huang J-W, Sun P-P, Jia Y, Xu D-M, Wang S-X, Liu G, Yang L. Elevation of erythrocyte sedimentation rate and C-reactive protein levels reflects renal interstitial inflammation in drug-induced acute tubulointerstitial nephritis. BMC Nephrol. 2020;21(1):514. https://doi.org/10.1186/s12882-020-02175-z.
94. Tojo A, Miyashita K, Kinugasa S, Takemura T, Goto A. Acute tubulointerstitial nephritis with an autoantibody response against carbonic anhydrase II. Am J Med Sci. 2013; https://doi.org/10.1097/MAJ.0b013e318272f1a6.
95. Dobrin RS, Vernier RL, Fish AJ. Acute eosinophilic interstitial nephritis and renal failure with bone marrow-lymph node granulomas and anterior uveitis. A new syndrome. Am J Med. 1975; https://doi.org/10.1016/0002-9343(75)90390-3.
96. Tan Y, Yu F, Qu Z, Su T, Xing GQ, Wu LH, Wang FM, Liu G, Yang L, Zhao MH. Modified C-reactive protein might be a target autoantigen of TINU syndrome. Clin J Am Soc Nephrol. 2011; https://doi.org/10.2215/CJN.09051209.
97. Yasuda K, Sasaki K, Yamato M, Rakugi H, Isaka Y, Hayashi T. Tubulointerstitial nephritis and uveitis syndrome with transient hyperthyroidism in an elderly patient. Clin Exp Nephrol. 2011; https://doi.org/10.1007/s10157-011-0505-2.
98. Mandeville JTH, Levinson RD, Holland GN. The tubulointerstitial nephritis and uveitis syndrome. Surv Ophthalmol. 2001; https://doi.org/10.1016/S0039-6257(01)00261-2.
99. Howarth L, Gilbert RD, Bass P, Deshpande PV. Tubulointerstitial nephritis and uveitis in monozygotic twin boys. Pediatr Nephrol. 2004; https://doi.org/10.1007/s00467-004-1518-9.
100. Gianviti A, Greco M, Barsotti P, Rizzoni G. Acute tubulointerstitial nephritis occurring with 1-year lapse in identical twins. Pediatr Nephrol. 1994; https://doi.org/10.1007/BF00856521.
101. Clive DM, Vanguri VK. The syndrome of tubulointerstitial nephritis with uveitis (TINU). Am J Kidney Dis. 2018;72(1):118–28. https://doi.org/10.1053/j.ajkd.2017.11.013.
102. Onyekpe I, Shenoy M, Denley H, Riad H, Webb NJA. Recurrent tubulointerstitial nephritis and uveitis syndrome in a renal transplant recipient. Nephrol Dial Transplant. 2011; https://doi.org/10.1093/ndt/gfr352.
103. Chapagain A, Dobbie H, Sheaff M, Yaqoob MM. Presentation, diagnosis, and treatment outcome of tuberculous-mediated tubulointerstitial nephritis. Kidney Int. 2011; https://doi.org/10.1038/ki.2010.482.
104. Alsaad KO, Tobar A, Belanger E, Ahmad M, Cattran DC, Herzenberg AM. Late-onset acute haemorrhagic necrotizing granulomatous adenovirus tubulointerstitial nephritis in a renal allograft. Nephrol Dial Transplant. 2007; https://doi.org/10.1093/ndt/gfl843.
105. Ubee SS, McGlynn L, Fordham M. Emphysematous pyelonephritis. BJU Int. 2011; https://doi.org/10.1111/j.1464-410X.2010.09660.x.
106. Tian YC, Chen YC, Hung CC, Chang CT, Wu MS, Phillips AO, Yang CW. Leptospiral outer membrane protein induces extracellular matrix accumulation through a TGF-β1/Smad-dependent pathway. J Am Soc Nephrol. 2006; https://doi.org/10.1681/ASN.2006020159.
107. Becker JL, Miller F, Nuovo GJ, Josepovitz C, Schubach WH, Nord EP. Epstein-Barr virus infection of renal proximal tubule cells: possible role in chronic interstitial nephritis. J Clin Investig. 1999; https://doi.org/10.1172/JCI7286.
108. Medapalli RK, He JC, Klotman PE. HIV-associated nephropathy: pathogenesis. Curr Opin Nephrol Hypertension. 2011; https://doi.org/10.1097/MNH.0b013e328345359a.
109. Martin-Blondel G, Debard A, Laurent C, Pugnet G, Modesto A, Massip P, Chauveau D, Marchou B. Mycobacterial-immune reconstitution inflammatory syndrome: a cause of acute interstitial nephritis during HIV infection. Nephrol Dial Transplant. 2011; https://doi.org/10.1093/ndt/gfr197.
110. Balba GP, Javaid B, Timpone JG. BK polyomavirus infection in the renal transplant recipient. Infect Dis Clin North Am. 2013; https://doi.org/10.1016/j.idc.2013.02.002.
111. Filler G, Licht C, Haig A. Native kidney BK virus nephropathy associated with acute lymphocytic leukemia. Pediatr Nephrol. 2013; https://doi.org/10.1007/s00467-013-2438-3.
112. Verghese PS, Finn LS, Englund JA, Sanders JE, Hingorani SR. BK nephropathy in pediatric hematopoietic stem cell transplant recipients. Pediatr Transplant. 2009;13(7):913–8. https://doi.org/10.1111/j.1399-3046.2008.01069.x.

113. Colvin RB, Traum AZ, Taheri D, Jafari M, Dolatkhah S. Granulomatous interstitial nephritis as a manifestation of Crohn disease. Arch Pathol Lab Med. 2014; https://doi.org/10.5858/arpa.2012-0224-CR.
114. Joss N, Morris S, Young B, Geddes C. Granulomatous interstitial nephritis. Clin J Am Soc Nephrol. 2007; https://doi.org/10.2215/CJN.01790506.
115. Timmermans SAMEG, Christiaans MHL, Abdul-Hamid MA, Stifft F, Damoiseaux JGMC, van Paassen P. Granulomatous interstitial nephritis and Crohn's disease. Clin Kidney J. 2016;9(4):556–9. https://doi.org/10.1093/ckj/sfw041.
116. Izzedine H, Simon J, Piette A-M, Lucsko M, Baumelou A, Charitanski D, Kernaonet E, Baglin A-C, Deray G, Beaufils H. Primary chronic interstitial nephritis in Crohn's disease. Gastroenterology. 2002;123(5):1436–40. https://doi.org/10.1053/gast.2002.36613.
117. Ghani AA, Al Waheeb S, Al Homoud E. Isolated sarcoid renal granulomatous tubulointerstitial disease. Saudi J Kidney Dis Transplant. 2011;22(6):1208–10.
118. Nagaraja P, Davies MR. Granulomatous interstitial nephritis causing acute renal failure: a rare presenting feature of sarcoidosis. QJM. 2014; https://doi.org/10.1093/qjmed/hcr263.
119. Thumfart J, Müller D, Rudolph B, Zimmering M, Querfeld U, Haffner D. Isolated sarcoid granulomatous interstitial nephritis responding to infliximab therapy. Am J Kidney Dis. 2005;45(2):411–4. https://doi.org/10.1053/j.ajkd.2004.10.011.
120. Inui N, Murayama A, Sasaki S, Suda T, Chida K, Kato S, Nakamura H. Correlation between 25-hydroxyvitamin D3 1α-hydroxylase gene expression in alveolar macrophages and the activity of sarcoidosis. Am J Med. 2001; https://doi.org/10.1016/S0002-9343(01)00724-0.
121. Nasr SH, Koscica J, Markowitz GS, D'Agati VD. Granulomatous interstitial nephritis. Am J Kidney Dis. 2003; https://doi.org/10.1053/ajkd.2003.50143.
122. Stehlé T, Joly D, Vanhille P, Boffa JJ, Rémy P, Mesnard L, Hoffmann M, Grimbert P, Choukroun G, Vrtovsnik F, Verine J, Desvaux D, Walker F, Lang P, Mahevas M, Sahali D, Audard V. Clinicopathological study of glomerular diseases associated with sarcoidosis: a multicenter study. Orphanet J Rare Dis. 2013; https://doi.org/10.1186/1750-1172-8-65.
123. Vorselaars AD, van Moorsel CH, Deneer VH, Grutters JC. Current therapy in sarcoidosis, the role of existing drugs and future medicine. Inflamm Allergy Drug Targets. 2013;12(6):369–77.
124. Correia FASC, Marchini GS, Torricelli FC, Danilovic A, Vicentini FC, Srougi M, Nahas WC, Mazzucchi E. Renal manifestations of sarcoidosis: from accurate diagnosis to specific treatment. Int Braz J Urol. 2020;46(1):15–25. https://doi.org/10.1590/S1677-5538.IBJU.2019.0042.
125. Zammouri A, Barbouch S, Najjar M, Aoudia R, Jaziri F, Kaaroud H, Hedri H, Abderrahim E, Goucha R, Hamida FB, Harzallah A, Abdallah TB. Tubulointerstitial nephritis due to sarcoidosis: clinical, laboratory, and histological features and outcome in a cohort of 24 patients. Saudi J Kidney Dis Transplant. 2019; https://doi.org/10.4103/1319-2442.275471.
126. Saha MK, Tarek H, Sagar V, Abraham P. Role of tumor necrosis factor inhibitor in granulomatous interstitial nephritis secondary to Crohn's disease. Int Urol Nephrol. 2014; https://doi.org/10.1007/s11255-012-0362-2.
127. Aouizerate J, Matignon M, Kamar N, Thervet E, Randoux C, Moulin B, Raffray L, Buchler M, Villar E, Mahevas M, Desvaux D, Dahan K, Diet C, Audard V, Lang P, Grimbert P. Renal transplantation in patients with sarcoidosis: a French multicenter study. Clin J Am Soc Nephrol. 2010; https://doi.org/10.2215/CJN.03970510.
128. Mann DM, Fyfe B, Osband AJ, Lebowitz J, Laskow DA, Jones J, Mann RA. Sarcoidosis within a renal allograft: a case report and review of the literature. Transplant Proc. 2013; https://doi.org/10.1016/j.transproceed.2012.11.008.
129. Igarashi T, Itoh Y, Shimizu A, Igarashi T, Yoshizaki K, Fukunaga Y. A case of juvenile Sjögren's syndrome with interstitial nephritis. J Nippon Med Sch. 2012; https://doi.org/10.1272/jnms.79.286.
130. Bossini N, Savoldi S, Franceschini F, Mombelloni S, Baronio M, Cavazzana I, Viola BF, Valzorio B, Mazzucchelli C, Cattaneo R, Scolari F, Maiorca R. Clinical and morphological features of kidney involvement in primary Sjögren's syndrome. Nephrol Dial Transplant. 2001; https://doi.org/10.1093/ndt/16.12.2328.
131. Jasiek M, Karras A, Le Guern V, Krastinova E, Mesbah R, Faguer S, Jourde-Chiche N, Fauchais A-L, Chiche L, Dernis E, Moulis G, Fraison J-B, Lazaro E, Jullien P, Hachulla E, Le Quellec A, Rémy P, Hummel A, Costedoat-Chalumeau N, Terrier B. A multicentre study of 95 biopsy-proven cases of renal disease in primary Sjögren's syndrome. Rheumatology (Oxford). 2017;56(3):362–70. https://doi.org/10.1093/rheumatology/kew376.
132. Maripuri S, Grande JP, Osborn TG, Fervenza FC, Matteson EL, Donadio JV, Hogan MC. Renal involvement in primary Sjögren's syndrome: a clinicopathologic study. Clin J Am Soc Nephrol. 2009; https://doi.org/10.2215/CJN.00980209.
133. Jain A, Srinivas BH, Emmanuel D, Jain VK, Parameshwaran S, Negi VS. Renal involvement in primary Sjogren's syndrome: a prospective cohort study. Rheumatol Int. 2018;38(12):2251–62. https://doi.org/10.1007/s00296-018-4118-x.
134. Goules AV, Tatouli IP, Moutsopoulos HM, Tzioufas AG. Clinically significant renal involvement in primary Sjögren's syndrome: clinical presentation and outcome. Arthritis Rheum. 2013; https://doi.org/10.1002/art.38100.
135. Kassan SS, Moutsopoulos HM. Clinical manifestations and early diagnosis of Sjögren syndrome.

Arch Intern Med. 2004; https://doi.org/10.1001/archinte.164.12.1275.
136. Pijpe J, Van Imhoff GW, Spijkervet FKL, Roodenburg JLN, Wolbink GJ, Mansour K, Vissink A, Kallenberg CGM, Bootsma H. Rituximab treatment in patients with primary Sjögren's syndrome: an open-label phase II study. Arthritis Rheum. 2005; https://doi.org/10.1002/art.21260.
137. Silverman E, Eddy A. Systemic erythematosus. In: Textbook of pediatric rheumatology. 6th ed. Amsterdam: Elsevier; 2011. p. 315–43.
138. Lan-Ting H, You-Ming C, Li-Xin W, Chen W, Xiao-Yan Z, Hong-Yan H. Clinicopathological factors for tubulointerstitial injury in lupus nephritis. Clin Rheumatol. 2020;39(5):1617–26. https://doi.org/10.1007/s10067-019-04909-3.
139. Yu F, Wu LH, Tan Y, Li LH, Wang CL, Wang WK, Qu Z, Chen MH, Gao JJ, Li ZY, Zheng X, Ao J, Zhu SN, Wang SX, Zhao MH, Zou WZ, Liu G. Tubulointerstitial lesions of patients with lupus nephritis classified by the 2003 International Society of Nephrology and Renal Pathology Society system. Kidney Int. 2010; https://doi.org/10.1038/ki.2010.13.
140. Cabral D, Benseler S. Granulomatous vasculitis, microscopic polyangiitis and primary angiitis of the central nervous system. In: Textbook of pediatric rheumatology. Amsterdam: Elsevier; 2011. https://doi.org/10.1016/B978-1-4160-6581-4.10034-2.
141. Plafkin C, Zhong W, Singh T. ANCA vasculitis presenting with acute interstitial nephritis without glomerular involvement. Clin Nephrol Case Stud. 2019;7:46–50. https://doi.org/10.5414/CNCS109805.
142. Javaud N, Belenfant X, Stirnemann J, Laederich J, Ziol M, Callard P, Ronco P, Rondeau E, Fain O. Renal granulomatoses: a retrospective study of 40 cases and review of the literature. Medicine. 2007;86(3):170–80. https://doi.org/10.1097/MD.0b013e3180699f55.
143. Mann S, Seidman MA, Barbour SJ, Levin A, Carruthers M, Chen LYC. Recognizing IgG4-related tubulointerstitial nephritis. Can J Kidney Health Dis. 2016;3:34. https://doi.org/10.1186/s40697-016-0126-5.
144. Şahin Akkelle B. IgG4 related disease in a 7 year old girl with multiple organ involvement: a rare presentation. Türk Pediatri Arşivi. 2019; https://doi.org/10.14744/TurkPediatriArs.2019.83435.
145. Houghton DC, Troxell ML. An abundance of IgG4 plasma cells is not specific for IgG4-related tubulointerstitial nephritis. Mod Pathol. 2011; https://doi.org/10.1038/modpathol.2011.101.
146. Wen YK. Tubulointerstitial nephritis and uveitis with Fanconi syndrome in a patient with ankylosing spondylitis. Clin Nephrol. 2009; https://doi.org/10.5414/cnp72315.
147. Pohjonen J, Nurmi R, Metso M, Oksanen P, Huhtala H, Pörsti I, Mustonen J, Kaukinen K, Mäkelä S. Inflammatory bowel disease in patients undergoing renal biopsies. Clin Kidney J. 2019;12(5):645–51. https://doi.org/10.1093/ckj/sfz004.
148. Sheikine Y, Woda CB, Lee PY, Chatila TA, Keles S, Charbonnier L-M, Schmidt B, Rosen S, Rodig NM. Renal involvement in the immunodysregulation, polyendocrinopathy, enteropathy, X-linked (IPEX) disorder. Pediatr Nephrol (Berlin, Germany). 2015;30(7):1197–202. https://doi.org/10.1007/s00467-015-3102-x.
149. Busto Castanon L, Gomez Castro A, Candal Alonso J, Gonzalez Martin M. Pielonefritis xantogranolomatosa (Y displasia quistica) en un recien nacido. Arch Esp Urol. 1980;(3):33, 303–314.
150. Li L, Parwani AV. Xanthogranulomatous pyelonephritis. Arch Pathol Lab Med. 2011; https://doi.org/10.2223/jped.692.
151. Stoica I, O'Kelly F, McDermott MB, Quinn FMJ. Xanthogranulomatous pyelonephritis in a paediatric cohort (1963–2016): outcomes from a large single-center series. J Pediatr Urol. 2018;14(2):169.e1–7. https://doi.org/10.1016/j.jpurol.2017.10.017.
152. Schlagenhaufer F. Uber eigentumliche staphylomykosen der Nieren und des pararenalen Bindegewebes. Frankf Zt Pathol. 1916;19:139–48.
153. Kim SW, Yoon BI, Ha US, Sohn DW, Cho YH. Xanthogranulomatous pyelonephritis: clinical experience with 21 cases. J Infect Chemother. 2013; https://doi.org/10.1007/s10156-013-0611-z.
154. Brown PS, Dodson M, Weintrub PS. Xanthogranulomatous pyelonephritis: report of nonsurgical management of a case and review of the literature. Clin Infect Dis. 1996; https://doi.org/10.1093/clinids/22.2.308.
155. Hughes PM, Gupta SC, Thomas NB. Xanthogranulomatous pyelonephritis in childhood. Clin Radiol. 1990;41(5):360–2. https://doi.org/10.1016/s0009-9260(05)81705-2.
156. Eddy A, Yamaguchi I. Chronic tubulointerstitial nephritis. In: Schrier's diseases of the kidney, vol. 2. 9th ed. Philadelphia, PA: Wolters Kluwer/Lippincott Williams & Wilkins; 2013. p. 1626–58.
157. Ruiz-Ortega M, Rayego-Mateos S, Lamas S, Ortiz A, Rodrigues-Diez RR. Targeting the progression of chronic kidney disease. Nat Rev Nephrol. 2020;16(5):269–88. https://doi.org/10.1038/s41581-019-0248-y.
158. Chen T, Li X, Li Y, Xia E, Qin Y, Liang S, Xu F, Liang D, Zeng C, Liu Z. Prediction and risk stratification of kidney outcomes in IgA nephropathy. Am J Kidney Dis. 2019a;74(3):300–9. https://doi.org/10.1053/j.ajkd.2019.02.016.
159. Eckardt K-U, Alper SL, Antignac C, Bleyer AJ, Chauveau D, Dahan K, Deltas C, Hosking A, Kmoch S, Rampoldi L, Wiesener M, Wolf MT, Devuyst O, Kidney Disease: Improving Global Outcomes. Autosomal dominant tubulointerstitial kidney disease: diagnosis, classification, and management—a KDIGO consensus report. Kidney

Int. 2015;88(4):676–83. https://doi.org/10.1038/ki.2015.28.
160. Olinger E, Hofmann P, Kidd K, Dufour I, Belge H, Schaeffer C, Kipp A, Bonny O, Deltas C, Demoulin N, Fehr T, Fuster DG, Gale DP, Goffin E, Hodaňová K, Huynh-Do U, Kistler A, Morelle J, Papagregoriou G, et al. Clinical and genetic spectra of autosomal dominant tubulointerstitial kidney disease due to mutations in UMOD and MUC1. Kidney Int. 2020;98(3):717–31. https://doi.org/10.1016/j.kint.2020.04.038.
161. Devuyst O, Olinger E, Weber S, Eckardt KU, Kmoch S, Rampoldi L, Bleyer AJ. Autosomal dominant tubulointerstitial kidney disease. Nat Rev Dis Primers. 2019; https://doi.org/10.1038/s41572-019-0109-9.
162. Schaeffer C, Olinger E. Clinical and genetic spectra of kidney disease caused by REN mutations. Kidney Int. 2020;98(6):1397–400. https://doi.org/10.1016/j.kint.2020.08.013.
163. Živná M, Kidd K, Zaidan M, Vyleťal P, Barešová V, Hodaňová K, Sovová J, Hartmannová H, Votruba M, Trešlová H, Jedličková I, Sikora J, Hůlková H, Robins V, Hnízda A, Živný J, Papagregoriou G, Mesnard L, Beck BB, et al. An international cohort study of autosomal dominant tubulointerstitial kidney disease due to REN mutations identifies distinct clinical subtypes. Kidney Int. 2020;98(6):1589–604. https://doi.org/10.1016/j.kint.2020.06.041.
164. Mihatsch MJ, Gudat F, Zollinger HU, Heierli C, Thölen H, Reutter FW. Systemic karyomegaly associated with chronic interstitial nephritis. A new disease entity? Clin Nephrol. 1979;12(2):54–62.
165. Zhou W, Otto EA, Cluckey A, Airik R, Hurd TW, Chaki M, Diaz K, Lach FP, Bennett GR, Gee HY, Ghosh AK, Natarajan S, Thongthip S, Veturi U, Allen SJ, Janssen S, Ramaswami G, Dixon J, Burkhalter F, et al. FAN1 mutations cause karyomegalic interstitial nephritis, linking chronic kidney failure to defective DNA damage repair. Nat Genet. 2012; https://doi.org/10.1038/ng.2347.
166. Jayasumana C, Orantes C, Herrera R, Almaguer M, Lopez L, Silva LC, Ordunez P, Siribaddana S, Gunatilake S, De Broe ME. Chronic interstitial nephritis in agricultural communities: a worldwide epidemic with social, occupational and environmental determinants. Nephrol Dial Transplant. 2017;32(2):234–41. https://doi.org/10.1093/ndt/gfw346.
167. Ramírez-Rubio O, Amador JJ, Kaufman JS, Weiner DE, Parikh CR, Khan U, McClean MD, Laws RL, López-Pilarte D, Friedman DJ, Kupferman J, Brooks DR. Urine biomarkers of kidney injury among adolescents in Nicaragua, a region affected by an epidemic of chronic kidney disease of unknown aetiology. Nephrol Dial Transplant. 2016;31(3):424–32. https://doi.org/10.1093/ndt/gfv292.
168. Vervaet BA, Nast CC, Jayasumana C, Schreurs G, Roels F, Herath C, Kojc N, Samaee V, Rodrigo S, Gowrishankar S, Mousson C, Dassanayake R, Orantes CM, Vuiblet V, Rigothier C, D'Haese PC, De Broe ME. Chronic interstitial nephritis in agricultural communities is a toxin-induced proximal tubular nephropathy. Kidney Int. 2020;97(2):350–69. https://doi.org/10.1016/j.kint.2019.11.009.
169. Rodríguez-Iturbe B, Johnson RJ, Herrera-Acosta J. Tubulointerstitial damage and progression of renal failure. Kidney Int. 2005; https://doi.org/10.1111/j.1523-1755.2005.09915.x.