



# BMJ Open Aetiology, course and treatment of acute tubulointerstitial nephritis in paediatric patients: a cross-sectional web-based survey

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## ABSTRACT

**Background** Acute tubulointerstitial nephritis (TIN) is a significant cause of acute renal failure in paediatric and adult patients. There are no large paediatric series focusing on the aetiology, treatment and courses of acute TIN.

**Patients, design and setting** We collected retrospective clinical data from paediatric patients with acute biopsy-proven TIN by means of an online survey. Members of four professional societies were invited to participate.

**Results** Thirty-nine physicians from 18 countries responded. 171 patients with acute TIN were included (54% female, median age 12 years). The most frequent causes were tubulointerstitial nephritis and uveitis syndrome in 31% and drug-induced TIN in 30% (the majority of these caused by non-steroidal anti-inflammatory drugs). In 28% of patients, no initiating noxae were identified (idiopathic TIN). Median estimated glomerular filtration rate (eGFR) rose significantly from 31 at time of renal biopsy to 86 mL/min/1.73 m<sup>2</sup> 3–6 months later ( $p < 0.001$ ). After 3–6 months, eGFR normalised in 41% of patients (eGFR  $\geq 90$  mL/min/1.73 m<sup>2</sup>), with only 3% having severe or end-stage impairment of renal function ( $< 30$  mL/min/1.73 m<sup>2</sup>). 80% of patients received corticosteroid therapy. Median eGFR after 3–6 months did not differ between steroid-treated and steroid-untreated patients. Other immunosuppressants were used in 18% ( $n=31$ ) of patients, 21 of whom received mycophenolate mofetil.

**Conclusions** Despite different aetiologies, acute paediatric TIN had a favourable outcome overall with 88% of patients showing no or mild impairment of eGFR after 3–6 months. Prospective randomised controlled trials are needed to evaluate the efficacy of glucocorticoid treatment in paediatric patients with acute TIN.

## INTRODUCTION

Acute tubulointerstitial nephritis (TIN) is a significant cause of acute renal failure in

## Strengths and limitations of this study

- Largest study on children with tubulointerstitial nephritis.
- Patients from all parts of the world included as a joint project of the most important societies for paediatric nephrology.
- Retrospective data collected in a survey.
- Short follow-up period.
- Detailed results of renal biopsy were not available.

paediatric and adult patients. TIN accounts for approximately 2%–3% of native renal biopsies.<sup>1–3</sup> In biopsies to evaluate acute renal failure of unknown origin, TIN represents about 13% of cases in adult patients.<sup>2,3</sup> Reliable data on the incidence and prevalence of paediatric TIN are lacking.

Renal histopathology in TIN is characterised by interstitial cellular infiltrates and oedema, but vessels and glomeruli are typically spared.<sup>4</sup> The inflammatory process may eventually lead to interstitial fibrosis and chronic kidney disease.<sup>5</sup>

Numerous causes of TIN are known, with drugs, especially non-steroidal anti-inflammatory drugs (NSAIDs), being the trigger in 60%–70% of cases<sup>6</sup>; however, the identity of the causative agent in cases of TIN is usually speculative. Other cases of TIN are related to infections or systemic diseases. In some cases, renal disease can be accompanied by uveal inflammation (tubulointerstitial nephritis with uveitis (TINU)).<sup>7,8</sup> Other TIN cases are presumed to be idiopathic.<sup>4</sup> Despite

the different aetiologies of TIN, a common immune-mediated pathogenic mechanism is assumed. Antigen-mediated cellular immune responses seem to play a key role in the pathogenesis of TIN.<sup>3,9</sup> It is also important to note that this is a very heterogeneous group of patients. While histopathology is similar, TIN due to sarcoidosis is probably biologically distinct entity from that due to antibiotics, recreational drugs, NSAIDs and infectious agents. Clinical symptoms of TIN are often non-specific and therefore may lead to delayed diagnosis and treatment.<sup>4,10</sup>

Corticosteroids are well established in the treatment of severe TIN, although prospective randomised controlled clinical trials assessing the indications and efficacy of corticosteroid treatment are not available. In adult patients, retrospective data indicated beneficial effects of corticosteroids on renal function recovery in drug-induced TIN.<sup>11–14</sup> However, results of other retrospective studies did not support the routine administration of corticosteroid therapy.<sup>1,15</sup> Results from a small prospective paediatric study showed an accelerated renal recovery with corticosteroid treatment.<sup>16</sup> There is very limited experience of the use of other immunosuppressive agents (eg, mycophenolate mofetil (MMF)) in patients with TIN. Moreover, there is no consensus on a standard therapeutic regimen (eg, intravenous vs oral administration, dosage and duration of therapy) in either children or adults.

In this study, we assessed the aetiology, therapy and clinical course of TIN in a large paediatric cohort with manifestation of acute TIN between 2007 and 2018. Data were collected retrospectively via a survey circulated to members of the German Society of Pediatric Nephrology (GPN), European Society of Pediatric Nephrology (ESPN), European Network of Rare Kidney Diseases (ERKnet) and Pediatric Nephrology Research Consortium (PNRC) based in the USA.

## PATIENTS AND METHODS

Members of GPN, ESPN, ERKNet and PNRC were invited to participate in the online survey. An email invitation with a summary of the project and a link to an online questionnaire service provider (<https://www.google.de/intl/de/forms/about/>) was sent to all mailing list contacts of GPN, ESPN, ERKNet and PNRC. The survey was launched in April 2018 and was closed in June 2019.

The data collection was retrospective and fully anonymised. Only patients with biopsy-proven TIN were included in the study. Further inclusion criteria were age between 0 and 18 years, and presentation of disease was between 2007 and 2018.

The questionnaire comprised 57 items. Answers were given as multiple choice or short free texts assessing the incidence, aetiology and course of acute TIN in children. 'Yes', 'no' and 'not assessed' were given as answer options for disease symptoms, urinary findings and biopsy results. Free-text answers were required for precise causative

factors for TIN (eg, drug name, pathogen, underlying systemic disease). The questionnaire is provided in the online supplemental material.

Creatinine-based 'Bedside Schwartz' formula (estimated glomerular filtration rate (eGFR)= $0.413 \times (\text{height}/\text{Scr})$ ) was used for eGFR.<sup>17</sup>

The responses were automatically collected in a database provided by the survey administration app. All statistical data analyses were performed in GraphPad Prism V.8 (<https://www.graphpad.com>). Continuous variables were expressed as median, and range as no normal distribution was assumed. Three different non-parametric tests were used for analysis of non-normally distributed variables: Mann-Whitney U test and Kruskal-Wallis test were used, respectively, to compare medians of two groups and three or more groups of variables not normally distributed; one sample Wilcoxon test was conducted for comparison of paired data. Statistical significance of dichotomous variables was measured by using the  $\chi^2$  test.  $P < 0.05$  was considered statistically significant.

## ETHICS APPROVAL

The study was approved by the council of the ESPN, GPN, ERKNet and PNRC. Requests for authorisation by the ethics committees of the other centres were not considered necessary because this was a survey that simply collected the experience and practices of the physicians, and it did not involve approaching patients directly or seeking any patient-specific data.

## Patient and public involvement

Patients and public were not involved in the design and conduct of this study.

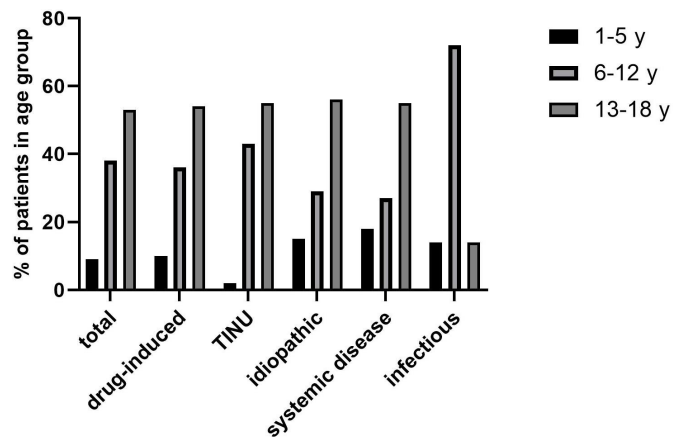
## RESULTS

Thirty-nine clinicians from 18 countries participated in the survey. One hundred and seventy-one patient cases were included in the final analysis. Patients originated from Northern Europe (n=41), Southern Europe (n=38), Western Europe (n=25), Eastern Europe (n=8), Western Asia (n=31), Southern Asia (n=1), Southeastern Asia (n=5) and Northern America (n=22).

Gender distribution was equal with 93 (54%) females and 78 males (46%). The median age (range) was 13 (1–17) years at diagnosis with the following age distribution: 1–5 years: 9% (16/171); 6–12 years: 38% (64/171); 13–18 years: 53% (91/171) (see [figure 1](#)).

## Aetiology

About one-third of TIN cases was drug related or induced by a toxic agent (30%, 52/171). TINU syndrome accounts for another third of included cases (31%, 53/171). Twenty-eight per cent (48/171) of cases were presumed to be idiopathic. Systemic diseases (7%, 11/171) and infections (4%, 7/171) were rare causes of acute interstitial nephritis (see [figure 2](#)). Infectious causes were most



**Figure 1** Age distribution of 171 patients with acute tubulointerstitial nephritis. TINU, tubulointerstitial nephritis with uveitis.

prevalent in patients aged 6–12 years. TIN from other causes was predominant in teenage patients (13–18 years) (see [figure 1](#)).

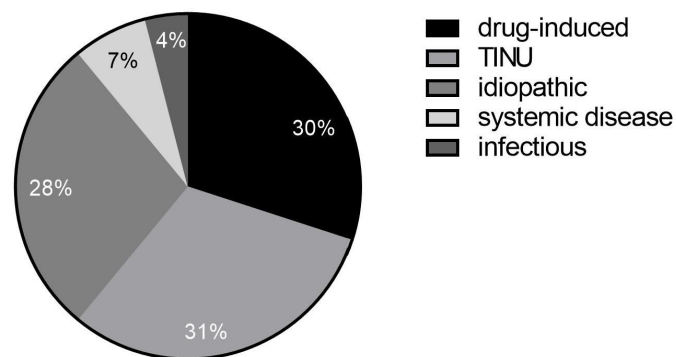
#### Drug-induced TIN

NSAIDs and antimicrobials were identified as the most common causative drugs and represented 79% (41/52) of drug-induced TIN cases. NSAIDs alone accounted for 48% (25/52) of drug-induced cases, while 10% (5/52) of patients received a combination of NSAIDs and antibiotics. Twenty-one per cent (11/52) of drug-induced cases were based on the administration of antimicrobial therapy (antiviral or antibacterial) without comedication. Other less frequent substances were identified in 21% (11/52) (see [table 1](#)).

Median age (13 years, range 1–17) and gender distribution (24/52=46% male, 28/52=54% female) did not differ from the total group.

#### TINU syndrome

TINU syndrome showed a slight predominance in females (58%=31/53 female, 42%=22/53 male) without statistical significance. Median age of onset was equal to the total group (13 years) with an age range between 5 and 17 years.



**Figure 2** Aetiology of acute tubulointerstitial nephritis in 171 paediatric patients. TINU, tubulointerstitial nephritis with uveitis.

**Table 1** Drugs and toxic agents as causes of tubulointerstitial nephritis (TIN) in 52 patients with acute TIN

NSAIDs (without comedication)	25	48%
Ibuprofen	6	
Flurbiprofen	3	
Morniflumate	3	
Ketoprofen	1	
Unspecified	12	
Antimicrobials	11	21%
Acyclovir	1	
Amoxicillin±clavulanic acid	3	
Trimethoprim/sulfamethoxazole	1	
Midecamycin	1	
Penicillin	2	
Unspecified	1	
Combination of antibiotics	2	
NSAIDs+antimicrobials	5	10%
Others	11	21%
Bee venom	2	
Herbal medicines	3	
Mesalazine	2	
Levetiracetam+oxcarbazepine	1	
Paracetamol+chlorphenamine maleate	1	
Hydrochlorothiazide	1	
Smoking	1	

NSAIDs, non-steroidal anti-inflammatory drugs.

#### Idiopathic TIN

In 28% (48/171) of cases no acute TIN trigger could be identified. Median age (range) was 13 years (3–16) with a balanced gender distribution of 50% (24/48) males and 50% (24/48) females.

#### TIN associated with systemic diseases

Median age (range) of onset was 14 years (1–17). Sixty-four per cent (7/11) were female and 36% (4/11) male patients. For a complete list of diagnoses see [box 1](#).

#### TIN associated with infections

Median age (range) was 11 years (1–15), and included four male (57%, 4/7) and three female patients (43%, 3/7). Adenovirus, BK polyoma virus, hepatitis C virus and rhinovirus were reported in one patient each. Three patients showed symptoms of upper respiratory tract infection without pathogen identification.

#### Clinical and urinary features

Clinical and urinary features in the patient cohort are summarised in [table 2](#). The most frequent clinical symptom at presentation of disease was fatigue in 70% (119/171) of patients, followed by vomiting or nausea in 49% (83/169; no data=2) and fever in 43% (73/171)

**Box 1** List of diagnoses in patients with systemic diseases as causes of acute tubulointerstitial nephritis (TIN). Two patients were diagnosed with Sjögren's syndrome, all other diagnoses were made in one patient each

Sarcoidosis.  
Sjögren's syndrome.  
Autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy type 1.  
Atypic haemolytic syndrome.  
Microscopic polyangiitis.  
Familial Mediterranean fever.  
Metabolic disease (undefined).  
Chronic osteomyelitis.  
Juvenile rheumatoid arthritis.  
B cell lymphoma.

of patients. Fourteen per cent (24/169; no data=2) of patients showed ocular symptoms at manifestation of disease, consistent with the diagnosis of TINU syndrome. In 22 of 24 patients with ocular symptoms TINU was diagnosed, and vice versa, 58% (31/53) of TINU patients had no ocular symptoms at onset of renal disease.

Polyuria, nocturia or enuresis (12 patients), weight loss (10 patients) and headache (seven patients) were the most frequent additional symptoms given in free-text answers.

### Histological findings

The most frequent histological findings were interstitial infiltration in 95% (162/170; no data=1) and interstitial oedema in 63% (106/167; no data=4) of patients. Interstitial granulomas were reported in 6% (11/171) of patients, among them drug-induced (four patients), idiopathic (four patients) and TINU cases (two patients) and one patient with sarcoidosis.

Interstitial fibrosis and tubular atrophy as markers of chronic renal damage were seen in 38% (64/170; no data=1) and 38% (65/171), respectively, whereas glomerulosclerosis was present in only 7% (12/171) of patients. Anonymised copies of original biopsy results were available in seven cases.

### Treatment

#### Corticosteroids

Eighty per cent of patients (137/171) were treated with corticosteroids (intravenous and/or oral); 20% (34/171) did not receive any corticosteroids. Forty per cent of patients received a combination of intravenous steroids followed by oral steroids. Details of corticosteroid treatment in the patient group are summarised in [table 3](#).

Ninety-six per cent (131/137) of steroid-treated patients received oral corticosteroids. Median duration of oral corticosteroid treatment was 90 days (4–1365). Forty-four per cent (60/137) of steroid-treated patients were

**Table 2** Clinical and urinary features at presentation in patients with acute tubulointerstitial nephritis (TIN)

Features		Number of patients	No data
<b>Clinical features</b>			
Fatigue	70%	119/171	0
Vomiting/nausea	49%	83/169	2
Fever	43%	73/171	0
Flank pain	33%	56/168	3
Arterial hypertension	22%	38/171	0
Oliguria/anuria	20%	35/171	0
Ocular symptoms	14%	24/169	2
Joint pain	14%	24/169	2
Exanthema	6%	11/171	0
<b>Urinary features</b>			
Tubular proteinuria	72%	79/109	62
Glucosuria	56%	80/143	28
Glomerular proteinuria, non-nephrotic range (<1000 mg/m <sup>2</sup> BSA/day in 24 hours urine collection or <2 g/g creatinine in spot urine sample)	53%	90/171	0
Microscopic haematuria	39%	66/170	1
Leukocyturia	29%	49/170	1
Glomerular proteinuria, nephrotic-range (>1000 mg/m <sup>2</sup> BSA/day in 24 hours urine collection or >2 g/g creatinine in spot urine sample)	11%	19/171	0
Urinary eosinophilia	9%	7/78	93
Macroscopic haematuria	8%	14/169	2

**Table 3** Details of corticosteroid treatment in 137 patients

Corticosteroid-treated patients	n=137 (± 100%)	Median dosage and range (in mg/kg/day)
<b>Route of administration</b>		
Oral CS, no intravenous CS	56%	
Intravenous CS, no oral CS	4%	
Oral+intravenous CS	40%	
<b>Substance</b>		
Oral prednisone	31%	1.03 (0.40–2.33)
Oral prednisolone	56%	1.00 (0.35–2.00)
Oral methylprednisolone	7%	0.97 (0.67–4.00)
Intravenous prednisolone	7%	6.94 (0.66–22.73)
Intravenous methylprednisolone	37%	10.81 (1.63–30.00)
Unknown oral CS	1%	–

CS, corticosteroids; IV, intravenous.

treated with intravenous corticosteroids with a median treatment duration (range) of 3 days (1–6).

Eighteen per cent (31/171) of all patients included in the study were treated with non-corticosteroid immunosuppressive drugs. Of these, all but one patient (patient with TIN as a complication of autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy (APECED) type 1) were additionally treated with corticosteroids (oral and/or intravenous). MMF was the most frequently used non-corticosteroid immunosuppressant in 12% (21/171) of all cases. Details of immunosuppressive treatment are given in [table 4](#).

#### Renal function and residual damage

Serum creatinine levels were collected at time of renal biopsy, 2 weeks and 3–6 months later. Renal function parameters at biopsy were available for all 171 patients, serum creatinine levels 2 weeks and 3–6 months after renal biopsy were given for 168 and 164 patients, respectively.

For all patients, median eGFR rose significantly from 31 (3–182) mL/min/1.73 m<sup>2</sup> at renal biopsy to 86 (7–169) mL/min/1.73 m<sup>2</sup> 3–6 months after renal biopsy (p<0.001). After 2 weeks, renal function had already significantly improved with a median eGFR of 67 mL/min/1.73 m<sup>2</sup> (5–167) (p<0.001) (see [figure 3A](#)). Significant improvement in renal function was detectable in every aetiological subgroup 2 weeks and 3–6 months after renal biopsy (see [figure 3B and C](#)). The median rise in eGFR was 22–96 mL/min/1.73 m<sup>2</sup> in drug-induced TIN, 36–85 mL/min/1.73 m<sup>2</sup> in TINU syndrome, 36–81 mL/min/1.73 m<sup>2</sup> in idiopathic TIN, 35–72 mL/min/1.73 m<sup>2</sup> in TIN associated with systemic diseases and 28–98 mL/min/1.73 m<sup>2</sup> in TIN associated with infections.

**Table 4** Immunosuppressants in 31 patients with acute tubulointerstitial nephritis (TIN)

Immunosuppressant	Indication (number of treated patients)	Total number of treated patients
Mycophenolate mofetil	Drug-induced TIN (3), TINU (11), idiopathic TIN (5), systemic disease (2)	21
Azathioprine	Drug-induced TIN (1), TINU (1), idiopathic TIN (3)	5
Cyclosporine	TINU (1), idiopathic TIN (2)	3
Methotrexate	TINU (2), systemic disease (1)	3
Cyclophosphamide	Idiopathic TIN (1), systemic disease (1)	2
Rituximab	Systemic disease	1
Eculizumab	Systemic disease	1
Hydroxychloroquine	Systemic disease	1

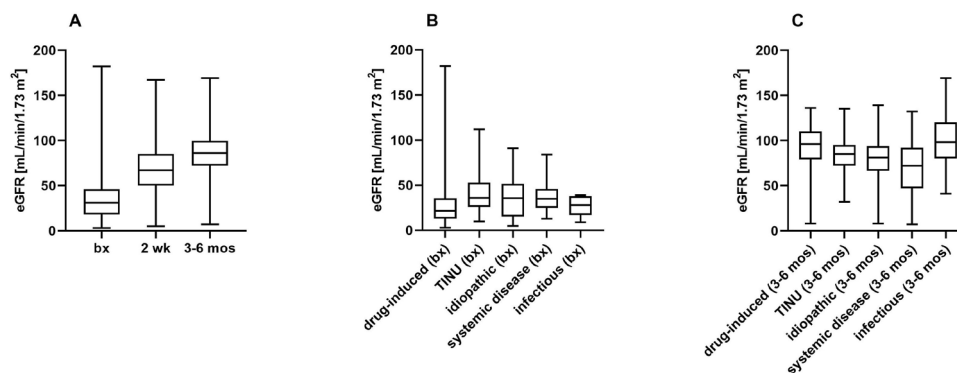
More than one medication was administered in several cases. TINU, tubulointerstitial nephritis with uveitis.

eGFR was normalised (>90 mL/min/1.73 m<sup>2</sup>) in 41% (67/164; no data=7) after 3–6 months, 59% (97/164) had an impaired eGFR (<90 mL/min/1.73 m<sup>2</sup>). Most patients (47%=77/164) showed a mild reduction in glomerular filtration rate (60–89 mL/min/1.73 m<sup>2</sup>), while a mild to moderate impairment (30–59 mL/min/1.73 m<sup>2</sup>) was present in 9% (14/164). Only 3% (6/164) had eGFR <30 mL/min/1.73 m<sup>2</sup> (see [table 5](#)).

Median eGFR after 3–6 months was 85 (8–168) mL/min/1.73 m<sup>2</sup> in the steroid group and 91 (7–135) mL/min/1.73 m<sup>2</sup> in the non-steroid group (p=0.10). Before initiation of treatment, steroid-treated patients had a significantly lower eGFR than patients who were not treated with steroids (30 mL/min/1.73 m<sup>2</sup> compared with 38 mL/min/1.73 m<sup>2</sup>) (p=0.03) (see [table 6](#)).

Seven per cent (12/171) needed renal replacement therapy either as haemodialysis (7/171) or peritoneal dialysis (5/171). Median duration (range) of renal replacement therapy was 6.5 (2–180) days. Seven (12/164; no data=7) of patients had glomerular proteinuria 3–6 months after renal biopsy and in 19% (32/164) urinalysis showed persistent tubular proteinuria. Mixed proteinuria (glomerular and tubular) was detected in 9% (14/164). The majority of patients (65%=106/164) had no residual proteinuria. The prevalence of proteinuria (glomerular and/or tubular) did not differ between steroid-treated and untreated patients (p=0.50).

Arterial hypertension treated with medication was present in 19% (32/171), 17% (28/171) needed one or two antihypertensive drugs, 2% (4/171) were treated with three or more antihypertensives. Most patients



**Figure 3** (A) Significant improvement of estimated glomerular filtration rate (eGFR) 2 weeks and 3–6 months after renal biopsy in patients with acute tubulointerstitial nephritis (TIN). (B and C) Significant improvement of GFR in all etiological subgroups with acute TIN. TINU, tubulointerstitial nephritis with uveitis.

(81%=139/171) did not need antihypertensive treatment. Significantly more steroid-treated patients than patients without steroid treatment needed antihypertensive treatment 3–6 months later (22% vs 6%,  $p=0.03$ ).

## DISCUSSION

The results of this survey shed some light on cause, clinical management and outcome of TIN in paediatric patients. To the best of our knowledge, our findings are from the largest paediatric TIN cohort to date.

The clinical presentation of TIN was unspecific with fatigue, vomiting or nausea and fever being the most frequent features. Only one patient of 171 (0.6%) showed the ‘classic’ triad of fever, arthralgia and skin rash or exanthema that dominated the clinical picture in early reports of mainly drug-induced cases. Actually, this symptom triad occurred in 5%–10% of patients in earlier reports.<sup>9 18</sup>

Drug-induced TIN is the underlying cause in 60%–70% of cases in adults.<sup>6 18</sup> In our cohort, drugs were responsible for only 30% of TIN cases. The fact that only biopsy-proven cases were included in our analysis might be responsible for a lower percentage of drug-induced cases since in clinical practice patients with typical clinical hallmarks of drug-induced TIN and mild to moderate renal failure do not always undergo renal biopsy. NSAIDs and antimicrobials are the most common culprits in drug-induced TIN.<sup>6 19</sup> Whether NSAIDs or antimicrobials are the leading class of drugs in the aetiology of TIN, however, is a matter of debate.<sup>1 11 20 21</sup> In our paediatric cohort, NSAIDs were identified as the leading cause in 48% of

patients with drug-induced TIN, and another 10% had a history of NSAIDs plus antimicrobial intake. Co-administration of two or more drugs can make it difficult to identify the culpable agent, but NSAIDs clearly represent the main cause for drug-induced TIN in our study, followed by antibiotics (21% of drug-induced cases). Although proton-pump inhibitors (PPIs) are a widely prescribed class of drugs and have been considered a relevant cause of acute TIN since the first published report of PPI-induced TIN in 1992,<sup>22–25</sup> no case of PPI-induced TIN was found in our cohort.

Remarkably, three patients had a history of herbal medicine intake. Aristolochic acid and other plant alkaloids have been identified as nephrotoxic ingredients in Chinese herbal medicine, and interstitial nephritis is one possible manifestation of its nephrotoxic capacity.<sup>26 27</sup> Furthermore, interstitial nephritis was triggered by bee stings in two patients. Acute kidney injury due to immune-mediated acute interstitial nephritis has been reported as a rare complication of Hymenoptera stings (bees and wasps) in a number of case reports or case series.<sup>28–30</sup> Another patient developed acute TIN after smoking a potentially nephrotoxic substance. A number of legal and illegal drugs should be taken into consideration as possible triggers of TIN, particularly in adolescents. For example, synthetic cannabinoids have become popular recreational drugs with  $\Delta 9$ -tetrahydrocannabinol-like effects that are solubilised, sprayed onto herbal mixtures and usually smoked. Renal manifestations of synthetic

**Table 5** Development of estimated glomerular filtration rate (eGFR) (mL/min/1.73 m<sup>2</sup>) 2 weeks and 3–6 months after diagnosis of acute tubulointerstitial nephritis (TIN)

	Number of patients	eGFR (mL/min/1.73 m <sup>2</sup> )				
		≥90	60–89	30–59	15–29	<15
Biopsy	171	3%	11%	40%	27%	19%
2 weeks	168	20%	42%	34%	2%	2%
3–6 months	164	41%	47%	9%	1%	2%

**Table 6** Development of estimated glomerular filtration rate (eGFR) in patients without corticosteroid treatment versus patients with corticosteroid treatment

	Corticosteroid treatment (n=137)	No corticosteroid treatment (n=34)	P value
Biopsy	30 (3–182)	38 (9–112)	0.03
2 weeks	67 (5–167)	67 (25–132)	0.86
3–6 months	85 (8–169)	91 (7–135)	0.10

Values for eGFR (mL/min/1.73 m<sup>2</sup>) are given as median with range.

cannabinoid use are acute tubular necrosis and acute interstitial nephritis.<sup>31</sup> Our results show that a variety of drugs, medications and toxic agents are involved in the pathogenesis of acute interstitial nephritis and should be considered as a potential aspect of the patient's medical history.

TIN was associated with systemic diseases in 7% of patients. In adults, systemic diseases underlie 10%–15% of cases.<sup>19</sup> Sjögren's syndrome and sarcoidosis are well described autoimmune disorders with TIN as typical renal manifestation. Interstitial nephritis is the prevalent renal finding in Sjögren's syndrome; 98% of patients with renal involvement show TIN in renal biopsy.<sup>32</sup> TIN associated with APECED type 1,<sup>33 34</sup> microscopic polyangiitis,<sup>35</sup> familial Mediterranean fever,<sup>36 37</sup> rheumatoid arthritis<sup>38</sup> and malignant infiltration<sup>39</sup> has been described in the literature. The case of a 17-year-old girl with atypical haemolytic uraemic syndrome and acute TIN included in our analysis has also been described by Basak *et al.*<sup>40</sup>

Infectious causes were found in 4% (in adults 5%–10%<sup>19</sup>). Only viral and no bacterial, fungal or parasitic pathogens were identified. Adenovirus, BK polyoma virus (both predominantly in renal transplant patients) and hepatitis C have been described as infectious causes of TIN.<sup>41–43</sup> Three patients had symptoms of upper respiratory tract infection without pathogen identification, and rhinovirus was identified in another patient. It remains unclear if a bacterial or viral pathogen was the unequivocal cause of TIN in these cases or if other underlying factors played a role in the pathogenesis (eg, intake of NSAIDs or antibiotics to treat respiratory symptoms). It has to be noted that all diagnoses were established by the participating physicians based on biopsy results and clinical findings.

TINU is thought to be a rare condition with an incidence of uveitis among TIN patients of less than 10%.<sup>18</sup> Jahnukainen *et al.*<sup>44</sup> reported that uveitis was diagnosed in 46% in a case series of 26 children with 'idiopathic TIN', supporting the assumption that the prevalence of uveitis among TIN patients is higher than previously assumed. In our study, 58% of TINU patients had no ocular symptoms at onset of renal disease. This is in line with previous reports that uveitis may evolve up to 14 months after the onset of TIN<sup>45 46</sup> and that a high percentage of TINU patients are ophthalmologically asymptomatic at the onset of renal symptoms.<sup>44</sup> Thorough ophthalmological examinations over months after the onset of TIN are necessary even in patients without ocular symptoms.<sup>44 46</sup> Our results support the rationale for this recommendation.

In our study, the overall renal outcome 3–6 months after diagnosis of TIN was favourable with a rise in median eGFR from 31 to 86 mL/min/1.73 m<sup>2</sup>. Only 2% (two patients with idiopathic TIN, one patient with drug-induced TIN and another patient with systemic disease) had eGFR <15 mL/min/1.73 m<sup>2</sup> (CKD 5).

The role of corticosteroids in the treatment of TIN has remained controversial. Available studies in adults are retrospective and not controlled and deliver partially

contradictory results.<sup>1 11–15</sup> A prospective paediatric study with 17 patients showed that prednisone speeds up renal recovery, but there was no significant difference in renal function between prednisone and control patients after 6 months' follow-up.<sup>16</sup>

In our study, renal function improved significantly after 2 weeks and showed further significant improvement 3–6 months after kidney biopsy. This development of eGFR was found in all aetiological subgroups. Corticosteroid treatment of TIN seems well established among paediatric nephrologists, since 80% of included patients received steroids. Whereas patients who were not treated with steroids had a significantly better median eGFR than patients who underwent steroid therapy at time of renal biopsy, there was no significant difference in eGFR 2 weeks and 3–6 months later and the rate of glomerular and/or tubular proteinuria 3–6 months later. However, we were not able to evaluate the efficacy of corticosteroid treatment of acute TIN since the number of patients was not equally distributed between the steroid-treated and untreated group (80% receiving steroid treatment) and long-term effects of corticosteroid treatment were not monitored. MMF is an additional treatment option in paediatric TIN patients with different etiological backgrounds but was exclusively used in combination with corticosteroids (the exception being one patient with APECED type 1 syndrome, treated with MMF and rituximab). MMF has been described as a successful therapeutic option for steroid-resistant or intolerant patients.<sup>47</sup>

### Strengths and limitations of our study

Our results are based on retrospective data collected in an online survey. This method of data collection requires concise and comprehensive questions but at the same time needs to be feasible and low threshold. We were not able to check the data for correctness but relied on the clinical data given by the participants.

Our follow-up period of 3–6 months is relatively short. In a larger and, at best, prospective study on paediatric TIN, we propose a follow-up period of at least 1 year. Biopsy results were not available as original copies apart from a few cases. Thus, we were not able to grade the degree of histological changes (eg, interstitial fibrosis). Ideally, all original biopsy samples should be re-evaluated by one pathologist. As many TIN patients with mild or moderate renal failure do not undergo kidney biopsy in all centres, severe cases were presumably over-represented in our study population.

The main strength of our study is the high number of patients and participating centres. It is the largest collection of children with TIN until now.

### Conclusion

Data from this large cohort suggest an overall positive outcome of biopsy-proven acute TIN in paediatric patients. Eighty-eight per cent of patients showed no or mild impairment of renal function 3–6 months after TIN was diagnosed. Prospective randomised controlled trials



are required to determine the efficacy of corticosteroids in the management of acute TIN in paediatric patients.

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