



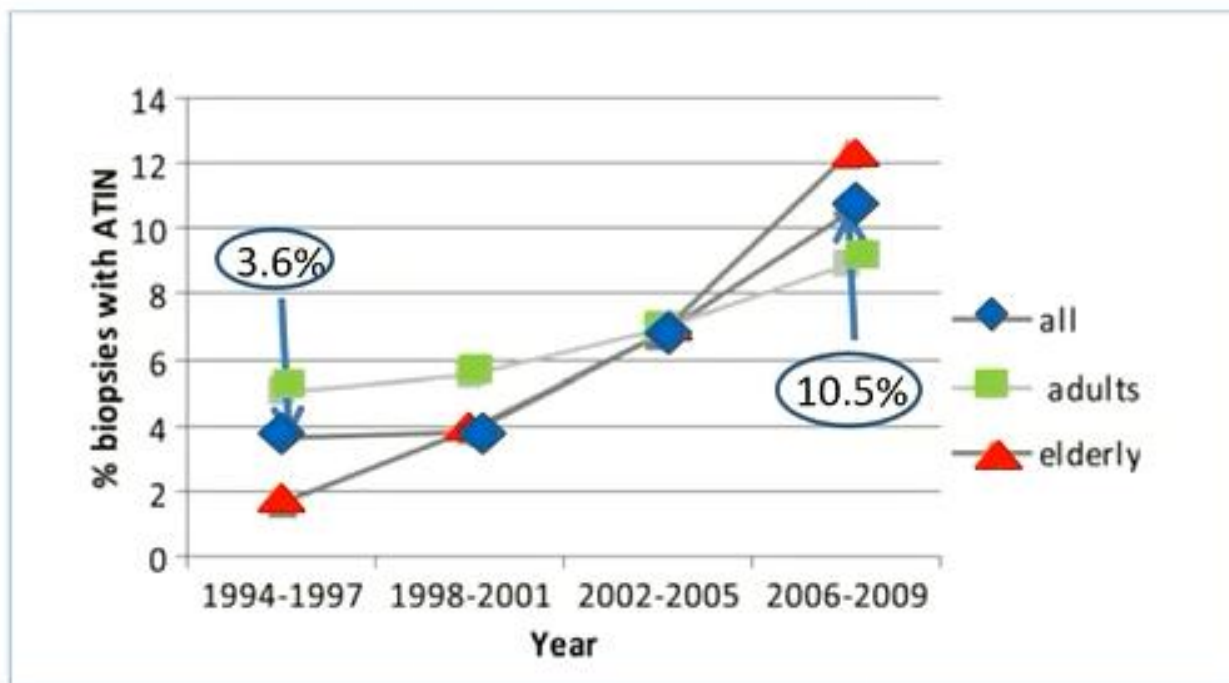
58<sup>TH</sup>  
ERA-EDTA  
CONGRESS  
BERLIN & VIRTUAL  
JUNE 5-8, 2021

## Immune-mediated Interstitial Nephritis

Gema Fernández Juárez  
Hospital Universitario Fundación Alcorcón. Madrid. Spain.

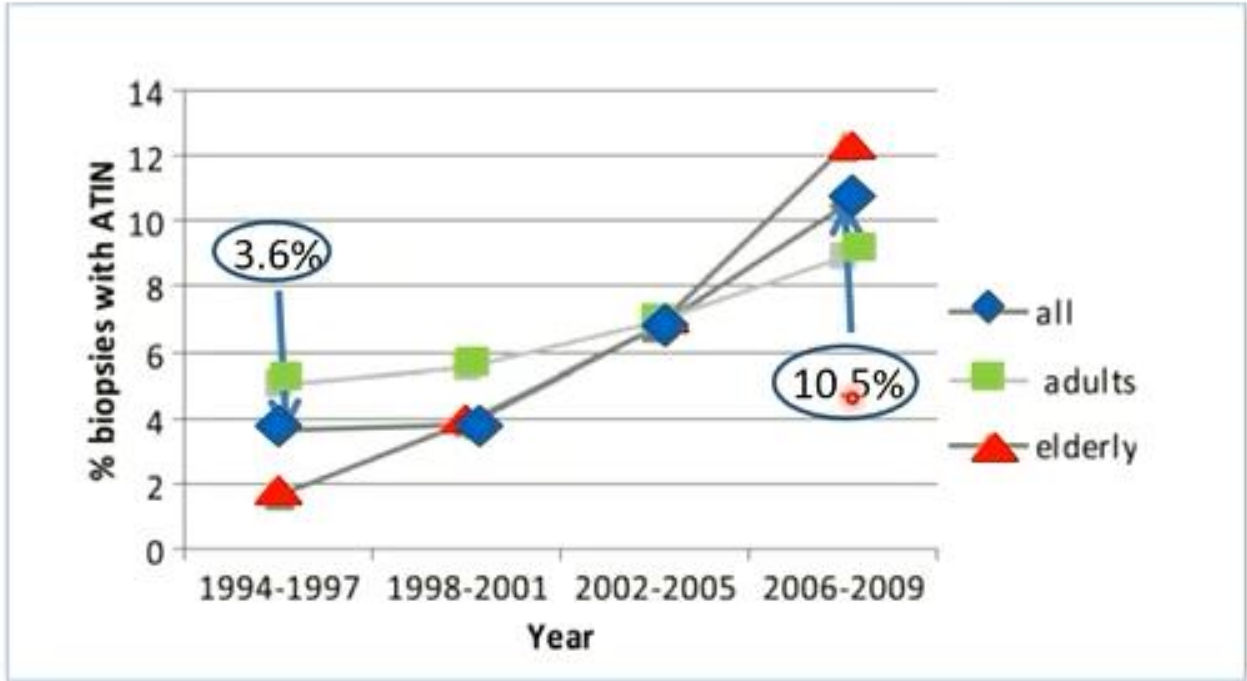


## Spanish Glomerular Disease Register



# Spanish Glomerular Disease Register

↑ Access to kidney biopsy  
Drug Sensibility  
Polydrugs



# RENAL FAILURE AND INTERSTITIAL NEPHRITIS DUE TO PENICILLIN AND METHICILLIN\*

DAVID S. BALDWIN, M.D., BERNARD B. LEVINE, M.D., ROBERT T. McCLUSKEY, M.D.,  
AND GLORIA R. GALLO, M.D.

THE NEW ENGLAND JOURNAL OF MEDICINE

Dec. 5, 1968

TABLE 1. Clinical Features in Seven Patients in Whom Nephropathy Due to Methicillin or Penicillin Developed.

PATIENT	SEX	AGE yr	DIAGNOSIS	DRUG	DOSAGE/DAY	DURATION OF DRUG TREATMENT days	FEVER	RASH days†	EOSINOPHILIA*
S.F.	M	47	Staphylococcal sepsis	Methicillin	6-20 gm	40	37-42	None	13-59 (38%)
L.C.	M	37	Osteomyelitis	Methicillin	24 gm	32	13-23	None	22-40 (25%)
W.K.	M	79	Staphylococcal sepsis	Methicillin	6-24 gm	44	31-37	44-51	26-50 (14%)
A.J.	F	57	Bacterial endocarditis	Methicillin	4-6 gm	19	13-24	None	13-24 (13%)
				Penicillin	20,000,000 units	17			
O.O.	M	54	Bacterial endocarditis	Penicillin	12,000,000-20,000,000 units	16	8-20	16-20	22-31 (5%)
M.L.	F	57	Bacterial endocarditis	Penicillin	30,000,000 units	42	21-27	30-35	23- (26%)
F.H.	F	70	Bacterial endocarditis	Penicillin	40,000,000-60,000,000 units	41	22-29	11-20	13-64 (44%)



## List of reponsible drugs

Drug	No. of Patients (%)
<u>Antibiotics</u>	47 (49)
Penicillins	19 (20)
Fluoroquinolones	13 (14)
Cephalosporins	5 (5)
Vancomycin	4 (4)
Sulfonamides	2 (2)
Rifampin	2 (2)
Imipenem	2 (2)
<u>PPIs</u>	13 (14)
Omeprazole	11 (12)
Esomeprazole	1 (1)
Rabeprazole	1 (1)
<u>NSAIDs</u>	10 (11)
Ibuprofen	5 (5)
Nabumetone	1 (1)
Salicylates	1 (1)
Celecoxib	1 (1)
Rofecoxib	1 (1)
Combination of NSAIDs	1 (1)
<u>Other drugs</u>	11 (11)
Allopurinol	2 (2)
Cimetidine	1 (1)
Creatine supplement	1 (1)
Hydrochlorothiazide	2 (2)
Lisinopril	1 (1)
Mesalamine	1 (1)
Olmesartan	1 (1)
Lenalidomide	1 (1)
Risedronate	1 (1)
<u>Multidrugs</u>	14 (15)
Combinations of antibiotics and other drugs	9 (10)
Combinations of other drugs	5 (5)



## Characteristics of each drug

Drug class	Associated clinical features
<b>Antibiotics</b>	
β-Lactams	Fever and rash, eosinophilia, eosinophiluria, and pyuria
Sulfonamides	Fever and rash, eosinophilia, eosinophiluria, and pyuria
Fluoroquinolones	Eosinophilia and pyuria
Rifampicin	Fever and rash, eosinophilia, eosinophiluria, and pyuria
Erythromycin	Inconsistent pyuria
Vancomycin	Inconsistent pyuria
Minocycline	NA
Ethambutol	NA
Chloramphenicol	NA
<b>Antiviral medications</b>	
Abacavir	Rash
Indinavir	Eosinophiluria, crystalluria
Atazanavir	Crystalluria
Aciclovir	Crystalluria
<b>Anticonvulsants</b>	
Phenytoin	Rash, Inconsistent pyuria
Carbamazepine	Inconsistent pyuria
Phenobarbital	Inconsistent pyuria

### Analgesics

NSAIDs      Edema and cognitive heart failure, hyponatremia and hyperkalemia, nephrotic syndrome

Selective COX-2 inhibitors      Edema and cognitive heart failure, hyponatremia and hyperkalemia, nephrotic syndrome

### Gastrointestinal medications

Proton pump inhibitors      Rare rash, Inconsistent pyuria

H<sub>2</sub> receptor antagonists      Rare rash, Inconsistent pyuria

### Other

5-Aminosalicylates      Rare rash, Inconsistent pyuria

Diuretics      Rare rash, Inconsistent pyuria, hyponatremia, and hypokalemia

Allopurinol      Rare rash (sometimes severe), inconsistent pyuria

Captopril      Rare rash, Inconsistent pyuria

Interferon      Rare rash, Inconsistent pyuria, and proteinuria

Ciclosporin      Rare rash, Inconsistent pyuria, and hypertension

Antiangiogenesis drugs      Rare rash, Inconsistent pyuria, hypertension, and proteinuria





## Characteristics of each drug

Drug class	Associated clinical features
<b>Antibiotics</b>	
β-Lactams	Fever and rash, eosinophilia, eosinophiluria, and pyuria
Sulfonamides	Fever and rash, eosinophilia, eosinophiluria, and pyuria
Fluoroquinolones	Eosinophilia and pyuria
Rifampicin	Fever and rash, eosinophilia, eosinophiluria, and pyuria
Erythromycin	Inconsistent pyuria
Vancomycin	Inconsistent pyuria
Minocycline	NA
Ethambutol	NA
Chloramphenicol	NA
<b>Antiviral medications</b>	
Abacavir	Rash
Indinavir	Eosinophiluria, crystalluria
Atazanavir	Crystalluria
Aciclovir	Crystalluria
<b>Anticonvulsants</b>	
Phenytoin	Rash, inconsistent pyuria
Carbamazepine	Inconsistent pyuria
Phenobarbital	Inconsistent pyuria

Drug class	Associated clinical features
<b>Analgesics</b>	
NSAIDs	Edema and cognitive heart failure, hyponatremia and hyperkalemia, nephrotic syndrome
Selective COX-2 Inhibitors	Edema and cognitive heart failure, hyponatremia and hyperkalemia, nephrotic syndrome
<b>Gastrointestinal medications</b>	
Proton pump inhibitors	Rare rash, inconsistent pyuria
H <sub>2</sub> receptor antagonists	Rare rash, inconsistent pyuria
<b>Other</b>	
5-Aminosalicylates	Rare rash, inconsistent pyuria
Diuretics	Rare rash, inconsistent pyuria, hyponatremia, and hypokalemia
Allopurinol	Rare rash (sometimes severe), inconsistent pyuria
Captopril	Rare rash, inconsistent pyuria
Interferon	Rare rash, inconsistent pyuria, and proteinuria
Ciclosporin	Rare rash, inconsistent pyuria, and hypertension
Antiangiogenesis drugs	Rare rash, inconsistent pyuria, hypertension, and proteinuria



## Proton Pump Inhibitors and Acute Interstitial Nephritis

**n=18**

PPI used	Age (y)/sex	Dose (mg/day)	Indications	Prior exposure duration (wk)
Esomeprazole	63/M	NA	GERD	6
Esomeprazole	63/F	NA	GERD	3
Esomeprazole	83/F	20	Dyspepsia	16
Omeprazole	77/M	20	Dyspepsia	4
Omeprazole	74/M	20	GERD	8
Omeprazole	78/M	40	GERD	16
Omeprazole	73/M	40	GERD	10
Omeprazole	89/F	40	GERD	NA
Omeprazole	49/F	20	Dysphagia	4
Omeprazole	72/F	20	GERD	24
Omeprazole	80/F	20	GERD	12
Omeprazole	65/F	20	GERD	6
Omeprazole	71/M	20	GERD	8
Omeprazole	74/F	20	GERD	8
Pantoprazole	77/M	80	GERD	8
Pantoprazole	79/F	40	Dyspepsia	12
Pantoprazole	80/F	NA	GERD	16
Rabeprazole	62/M	40	GERD	12





## Proton Pump Inhibitors and Acute Interstitial Nephritis

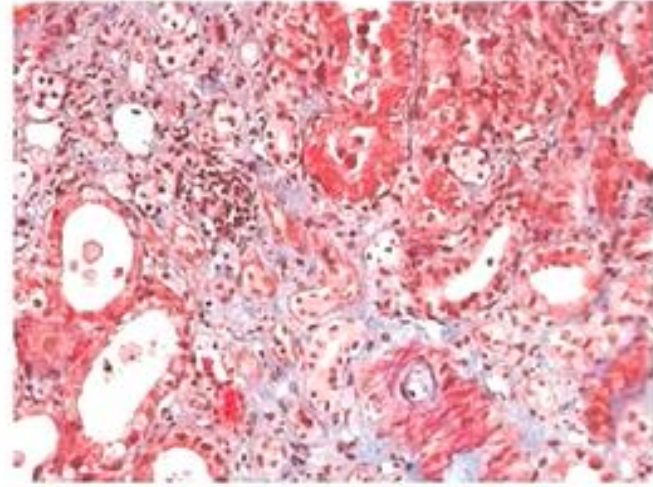
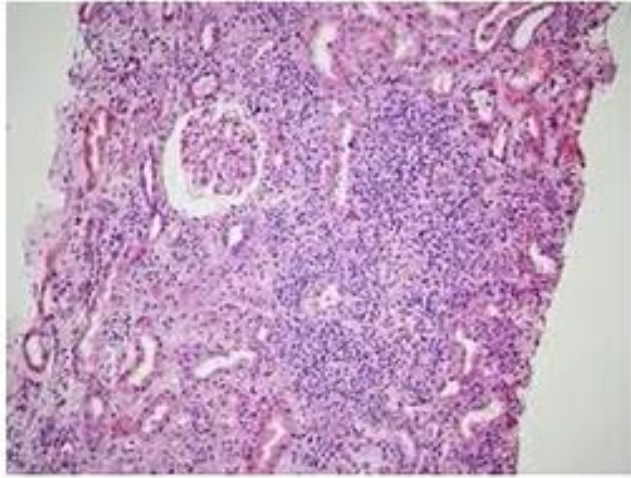
**n=18**

PPI used	Age (y)/sex	Dose (mg/day)	Indications	Prior exposure duration (wk)
Esomeprazole	63/M	NA	GERD	6
Esomeprazole	63/F	NA	GERD	3
Esomeprazole	83/F	20	Dyspepsia	16
Omeprazole	77/M	20	Dyspepsia	4
Omeprazole	74/M	20	GERD	8
Omeprazole	78/M	40	GERD	16
Omeprazole	73/M	40	GERD	10
Omeprazole	89/F	40	GERD	NA
Omeprazole	49/F	20	Dysphagia	4
Omeprazole	72/F	20	GERD	24
Omeprazole	80/F	20	GERD	12
Omeprazole	65/F	20	GERD	6
Omeprazole	71/M	20	GERD	8
Omeprazole	74/F	20	GERD	8
Pantoprazole	77/M	80	GERD	8
Pantoprazole	79/F	40	Dyspepsia	12
Pantoprazole	80/F	NA	GERD	16
Rabeprazole	62/M	40	GERD	12

Age (y)/sex	Symptoms/signs
63/M	Nausea, vomiting, weight loss, oliguria
63/F	Nausea, occasional vomiting
83/F	Unsteady, malaise
77/M	Confusion, lethargy, malaise, nausea, fever
74/M	Anorexia, nocturia, thirst, weight loss
78/M	Hematemesis, fever
73/M	Fatigue, lethargy
89/F <sup>a</sup>	NA
49/F	Fatigue, thirst
72/F	Fatigue
80/F	Fatigue, malaise
65/F	Backache, lethargy, nausea
71/M	Nausea, metallic taste in mouth, hypertension
74/F	Nocturia
77/M	Anorexia, lethargy, malaise, nausea, pruritis, weight loss
79/F	Fatigue, lethargy, thirst
80/F	Lethargy
62/M	Frequency, nausea

**No skin rash**





# Proton Pump Inhibitor Use and the Risk of Chronic Kidney Disease

Benjamin Lazarus, MBBS; Yuan Chen, MS; Francis P. Wilson, MD, MS; Yingying Sang, MS; Alex R. Chang, MD, MS; Josef Coresh, MD, PhD; Morgan E. Grams, MD, PhD

Table 2. Proton Pump Inhibitor Use and the Risk of Incident Chronic Kidney Disease<sup>a</sup>

Variable	Atherosclerosis Risk in Communities Study (n = 10 4820)		Geisinger Health System Replication Cohort (n = 248 751)	
	No. of Events	No. of Participants	No. of Events	No. of Participants
PPI users	56	322	1921	16 900
H <sub>2</sub> receptor antagonist users	158	956	1022	6640
Nonusers	1224	9204	27 204	225 221
<b>Association Between PPI Use and Incident CKD</b>	<b>Hazard Ratio (95% CI)</b>	<b>P Value</b>	<b>Hazard Ratio (95% CI)</b>	<b>P Value</b>
Unadjusted baseline PPI use vs no PPI use	1.45 (1.11-1.90)	.006	1.20 (1.15-1.26)	<.001
Baseline PPI use vs no PPI use	1.50 (1.14-1.96)	.003	1.17 (1.12-1.23)	<.001
Time-varying PPI ever use vs never PPI use	1.35 (1.17-1.55)	<.001	1.22 (1.19-1.25)	<.001
Baseline PPI use vs baseline H <sub>2</sub> receptor antagonist use	1.39 (1.01-1.91)	.05	1.29 (1.19-1.40)	<.001
Baseline PPI use vs propensity score-matched no PPI use	1.76 (1.13-2.74)	.01	1.16 (1.09-1.24)	<.001
Time-varying PPI ever use vs never PPI use, after excluding baseline PPI users	NA	NA	1.24 (1.20-1.28)	<.001
<b>Negative Control</b>				
Baseline H <sub>2</sub> receptor antagonist use vs no H <sub>2</sub> receptor antagonist use	1.15 (0.98-1.36)	.10	0.93 (0.88-0.99)	.03



# Proton Pump Inhibitor Use and the Risk of Chronic Kidney Disease

Benjamin Lazarus, MBBS; Yuan Chen, MS; Francis P. Wilson, MD, MS; Yingying Sang, MS; Alex R. Chang, MD, MS; Josef Coresh, MD, PhD; Morgan E. Grams, MD, PhD

**Table 2. Proton Pump Inhibitor Use and the Risk of Incident Chronic Kidney Disease<sup>a</sup>**

Variable	Atherosclerosis Risk in Communities Study (n = 10 4820)		Geisinger Health System Replication Cohort (n = 248 751)	
	No. of Events	No. of Participants	No. of Events	No. of Participants
PPI users	56	322	1921	16 900
H <sub>2</sub> receptor antagonist users	158	956	1022	6640
Nonusers	1224	9204	27 204	225 221
<b>Association Between PPI Use and Incident CKD</b>	<b>Hazard Ratio (95% CI)</b>	<b>P Value</b>	<b>Hazard Ratio (95% CI)</b>	<b>P Value</b>
Unadjusted baseline PPI use vs no PPI use	1.45 (1.11-1.90)	.006	1.20 (1.15-1.26)	<.001
Baseline PPI use vs no PPI use	1.50 (1.14-1.96)	.003	1.17 (1.12-1.23)	<.001
Time-varying PPI ever use vs never PPI use	1.35 (1.17-1.55)	<.001	1.22 (1.19-1.25)	<.001
Baseline PPI use vs baseline H <sub>2</sub> receptor antagonist use	1.39 (1.01-1.91)	.05	1.29 (1.19-1.40)	<.001
Baseline PPI use vs propensity score-matched no PPI use	1.76 (1.13-2.74)	.01	1.16 (1.09-1.24)	<.001
Time-varying PPI ever use vs never PPI use, after excluding baseline PPI users	NA	NA	1.24 (1.20-1.28)	<.001
<b>Negative Control</b>				
Baseline H <sub>2</sub> receptor antagonist use vs no H <sub>2</sub> receptor antagonist use	1.15 (0.98-1.36)	.10	0.93 (0.88-0.99)	.03

**10-year CKD risk of 1.7% to 3.3% attributable to prescription PPI use  
NNT 30 to 60**



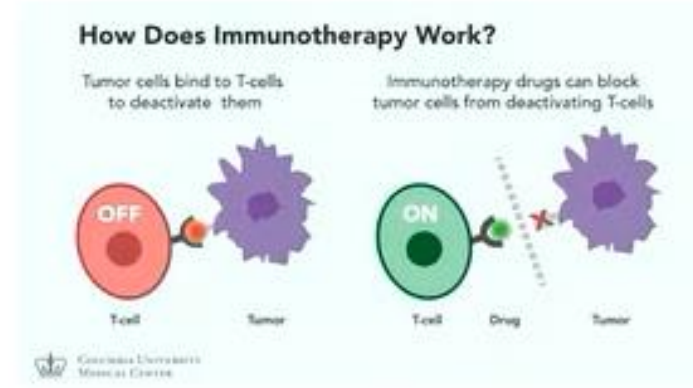


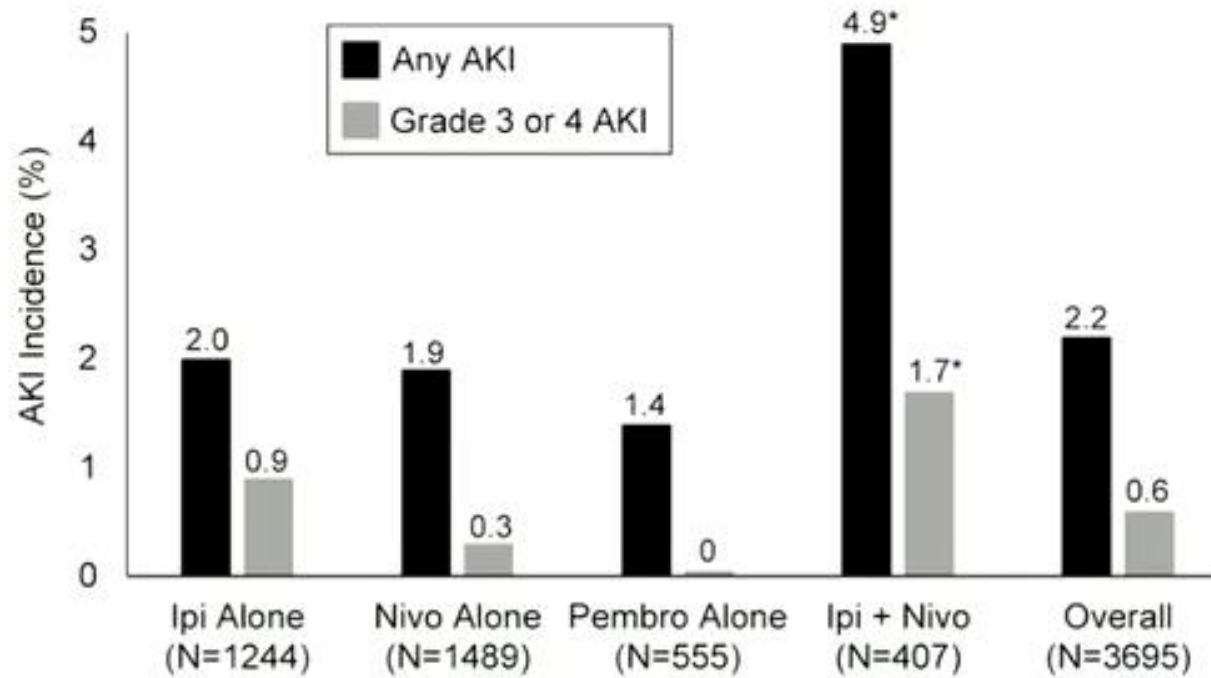
## Check point drugs

✓T4 (CTLA-4) → ipilimumab

✓(PD-1) → nivolumab, pembrolizumab

✓(PD-L1) → Atezolizumab y durvalumab





- The incidence of renal adverse events was reported to be relatively low (<1%) in randomized clinical trials of ICIs (ipilimumab, nivolumab, or pembrolizumab)
- The risk of renal events was reported to increase by 6% when ipilimumab and nivolumab were used in combination





Pt	Urine sediment <sup>a</sup>	Proteinuria (dipstick/UPCR)	Day of AKI <sup>b</sup>	Days since last dose of CPI	Eos	HTN <sup>c</sup>	Oliguria <sup>d</sup>	Kidney size (cm)	Peak SCr (mg/dl)	Requirement for RRT
1	5-10 WBCs <sup>e</sup> 2 RBCs	1+ / 0.6	54	54	No	No	No	R 12.8 L 13.8	6.2	No
2	2-3 WBCs 3-5 RBCs	Trace/NA	91	49	No	No	No	R 12.2 L 13.2	4.1	No
3	5-10 WBCs 0 RBCs 0-2 WBC casts	Trace/NA	69	14	No	No	No	R 11.6 L 12.6	9.7	3 HD treatments starting on day 130 No
4	16-34 WBCs	NA/NA	70	28	NA	No	No	R 13.0 L 13.0	3.6	No
5	5 WBCs <sup>e</sup> 1 RBC	Neg/0.26	245	63	No	No	No	R 13.2 L 13.0	2.9	No
6	0 WBC 0 RBC	Neg/0.74	183	36	No	Yes	Yes	R 10.9 L 13.5	11.7	HD-dependent starting on day 183 No
7	0 WBC <sup>e</sup> 0 RBC	Neg/NA	224	14	No	No	No	R 11.8 L 12.2	3.8	No
8	6-9 WBCs 0-3 RBCs	1+ / 0.98	154	7	No	No	Yes	R 12.8 L 11.8	5.6	HD-dependent starting on day 210 No
9	9 WBCs <sup>e</sup> 8 RBCs WBC casts	2+ / 0.12	42	21	No	Yes	No	R 12.4 L 13.0	7.3	No
10	3 WBCs <sup>e</sup> 3 RBCs WBC casts	1+ / 0.73	120	57	No	No	No	R 8.0 L 10.0	2.9	No
11	50-100 WBCs 0-2 RBCs	1+ / 0.18	60	18	14.7%	No	No	R 10.2 L 10.0	4.5	No
12	20-50 WBCs 0-2 RBCs	1+ / NA	21	21	No	No	No	NA	13.3	3 HD treatments starting on day 21 No
13	11-20 WBCs 0 RBCs	Neg/0.36	231	21	No	No	No	R 10.7 L 11.9	2.5	No
Median		0.48	91	21				R 12.0, L 12.8	4.5	
IQR		0.24-0.73	60-183	18-49				R 10.9-12.8 L 11.9-13.1	3.6-7.3	



## Treatment

- Early suspicion of the disease and early withdrawal of the responsible drug is the cornerstone of the treatment.



## Treatment

- Early suspicion of the disease and early withdrawal of the responsible drug is the cornerstone of the treatment.



In acute TIN induced by PPI, only in 25% of patients, the disease has been suspected before renal biopsy



## Treatment

- Early suspicion of the disease and early withdrawal of the responsible drug is the cornerstone of the treatment.



In acute TIN induced by PPI, only in 25% of patients, the disease has been suspected before renal biopsy



In 30 % of acute TIN we are not able to identify the responsible drugs (polipharmacy, ranged time from drugs to renal damage .....



# Prognosis

Characteristic	All Patients (N = 133)	Drug-Induced AIN (n = 95)	All Other Causes (n = 38)	P
Ultimate outcome at 6-mo F/U				0.2
Normal <sup>1</sup>	48/89 (54)	32/60 (53)	16/29 (55)	
Progressive CKD	37/89 (42)	24/60 (40)	13/29 (45)	
ESRD	4/89 (4)	4/60 (7)	0/29 (0)	

*American Journal Kidney Disease 2014*

## Drug induced TIN (n=182 pacientes)

- 74/182 patients (41%) recovered >75% baseline eGFR
- 84/182 patients (46%) recovered 75-25% baseline eGFR
- 24/182 patients (13%) recovered < 25% baseline eGFR
- 10/182 patients (5.5%) needed chronic dialysis

*Fernández-Juárez et al. Clin J Am Soc Nephrol 13:2018*

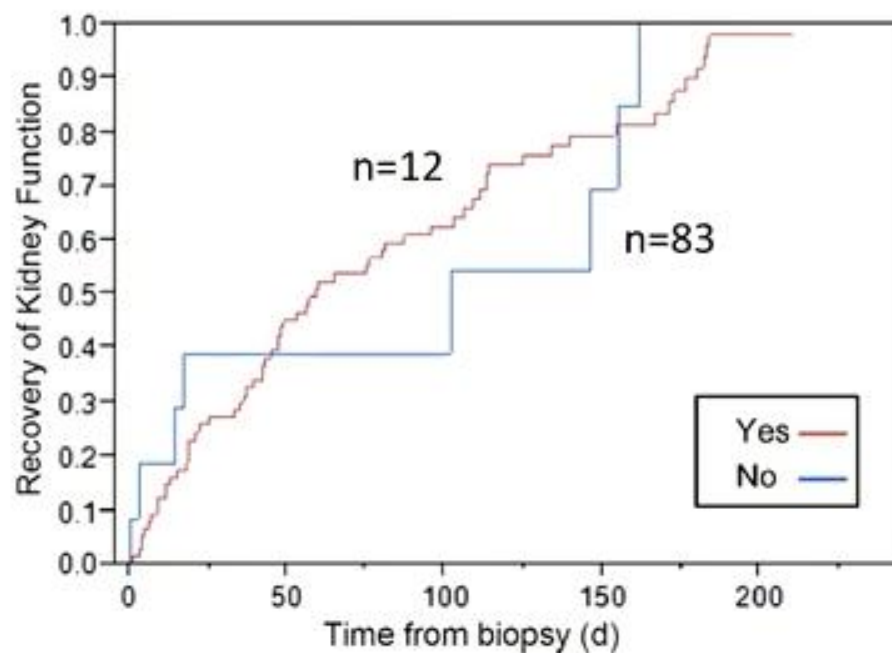


# Biopsy-Proven Acute Interstitial Nephritis, 1993-2011: A Case Series

Angela K. Muriithi, MBChB, MPH,<sup>1</sup> Nelson Leung, MD,<sup>1</sup> Anthony M. Valeri, MD,<sup>2</sup>  
Lynn D. Cornell, MD,<sup>3</sup> Sanjeev Sethi, MD, PhD,<sup>3</sup> Mary E. Fidler, MD,<sup>3</sup> and  
Samih H. Nasr, MD<sup>3</sup>

n=133 patients

n=95 (70%) induced by drugs



**Figure 2.** Survival analysis among patients with drug-induced acute interstitial nephritis (n = 95; 83 treated with steroids vs 12 not; log-rank  $P = 0.7$ ).

	Esteroides	
	Si	no
Cr peak (mg/dl)	4.5	3.5
Cr 6 month (mg/dl)	1.4	1.5

	Respuesta			p
	RC	RP	No	
Days to start corticosteroids treatment	8	11	35	< 0.05



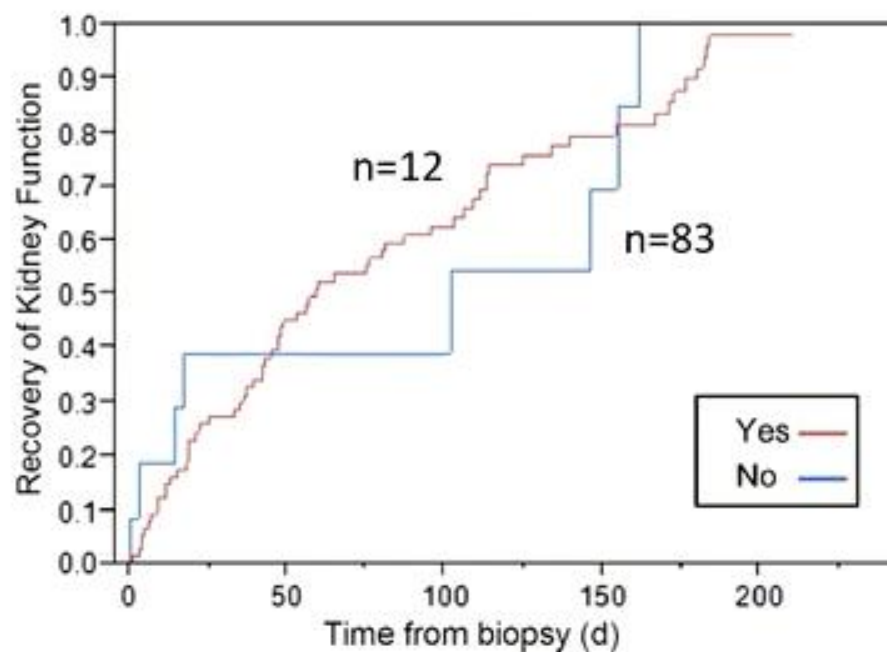


# Biopsy-Proven Acute Interstitial Nephritis, 1993-2011: A Case Series

Angela K. Muriithi, MBChB, MPH,<sup>1</sup> Nelson Leung, MD,<sup>1</sup> Anthony M. Valeri, MD,<sup>2</sup>  
Lynn D. Cornell, MD,<sup>3</sup> Sanjeev Sethi, MD, PhD,<sup>3</sup> Mary E. Fidler, MD,<sup>3</sup> and  
Samih H. Nasr, MD<sup>3</sup>

n=133 patients

n=95 (70%) induced by drugs



**Figure 2.** Survival analysis among patients with drug-induced acute interstitial nephritis (n = 95; 83 treated with steroids vs 12 not; log-rank  $P = 0.7$ ).

	Esteroides	
	Si	no
Cr peak (mg/dl)	4.5	3.5
Cr 6 month (mg/dl)	1.4	1.5

	Respuesta			p
	RC	RP	No	
Days to start corticosteroids treatment	8	11	35	< 0.05



**Table 3 | Characteristics of steroid-treated patients with a complete (Group 1a) or incomplete (Group 1b) recovery of baseline renal function**

	Group 1a (n=28)	Group 1b (n=24)	P-value
Age (years)	55 ± 18 (range 18–78)	60 ± 16 (range 18–81)	NS
Gender (M/F) (%)	61/39	62/38	NS
Baseline Scr (mg per 100ml)	1.07 ± 0.31 (range 0.6–1.9)	1.20 ± 0.4 (range 0.6–2.3)	NS
Baseline eGFR (ml per min per 1.73m <sup>2</sup> )	77 ± 29 (range 36–151)	65 ± 21 (range 35–106)	NS
Offending drug (antibiotics/NSAIDs/other) (%)	57/29/14	50/50/0	NS
Duration of the treatment (days)	11 ± 7 (range 3–35)	16 ± 16 (range 5–60)	NS
Highest Scr (mg per 100ml)	5.3 ± 3.5 (range 1.5–13.3)	6.4 ± 3.3 (range 2.9–12.7)	NS
Proteinuria (g/24h)	1.1 ± 1.4 (range 0–6)	0.9 ± 0.8 (range 0–3.4)	NS
Final Scr (mg per 100ml)	1.1 ± 0.26 (range 0.7–1.8)	3.23 ± 2.7 (range 1.5–12.7)	< 0.0001
Chronic dialysis	0	2 (8.3%)	NS
Interval between drug withdrawal and onset of corticosteroid treatment (days)	13 ± 10 (range 2–53)	34 ± 17 (range 3–68)	< 0.0001
Patients with an interval between drug withdrawal and onset of corticosteroid treatment < 7 days	10 (35.7%)	2 (8.3%)	< 0.05
Patients with an interval between drug withdrawal and onset of corticosteroid treatment < 15 days	19 (67.9%)	2 (8.3%)	< 0.05
Duration of steroid treatment (days)	75 ± 37 (range 20–180)	78 ± 42 (range 16–165)	NS
Follow-up (months)	16 ± 17 (range 6–60)	24 ± 20 (range 6–63)	NS

eGFR, estimated glomerular filtration rate; F, female; M, male; NS, not significant; NSAID, non-steroidal anti-inflammatory drug; Scr, serum creatinine.



# Duration of Treatment with Corticosteroids and Recovery of Kidney Function in Acute Interstitial Nephritis

Gema Fernandez-Juarez,<sup>1</sup> Javier Villacorta Perez,<sup>1</sup> Fernando Caravaca-Fontán,<sup>2</sup> Luis Quintana,<sup>3</sup> Amir Shabaka,<sup>4</sup> Eva Rodriguez,<sup>5</sup> Liliana Gadola,<sup>6</sup> Alberto de Lorenzo,<sup>7</sup> Maria Angeles Cobo,<sup>8</sup> Aniana Oliet,<sup>9</sup> Milagros Sierra,<sup>10</sup> Carmen Cobelo,<sup>11</sup> Elena Iglesias,<sup>12</sup> Miguel Blasco,<sup>3</sup> Cristina Galeano,<sup>13</sup> Alfredo Cordon,<sup>1</sup> Jesus Oliva,<sup>14</sup> and Manuel Praga,<sup>2</sup> on behalf of the Spanish Group for the Study of Glomerular Diseases (GLOSEN)

Variables	Global n=182	Complete Recovery n=75	Partial Recovery n=83	Nonrecovery n=24	P Value
Interval between D-AIN diagnosis and offending drug discontinuation, d <sup>a</sup>	6 (1-13)	5 (1-13)	6 (1-13)	11 (4-36)	0.1
Interval between D-AIN diagnosis and start of corticosteroids, d <sup>a</sup>	12 (4-22)	9 (2-17) <sup>b</sup>	12 (5-22) <sup>c</sup>	29/12-44)	0.008
Interval between D-AIN diagnosis and start of corticosteroids < 15 d	110 (61)	51 (70)	52 (63)	7 (29)	0.002
Interval between D-AIN diagnosis and start of corticosteroids < 21 d	129 (71)	60 (82)	60 (72)	9 (37)	<0.001
Intravenous pulse corticosteroids	88 (48)	33 (45)	46 (55)	9 (37)	0.23
Initial corticosteroid dose, mg/kg per day	0.8±0.2	0.8±0.2	0.83±0.17	0.9±0.2	0.8
Duration of high-dose corticosteroid treatment, wk <sup>a</sup>	2 (1-4)	2 (1-4)	2 (1-4)	1.5 (1-3)	0.8
Total duration of corticosteroid treatment <sup>a</sup>	9 (7-13)	9 (7-12.5)	9 (7-14)	9 (7-20)	0.6

Complete recovery: Scr at 6 months did not exceed baseline Scr by >25%. Partial recovery: Scr at 6 months exceeded baseline Scr by 25%–75%. Nonrecovery: Scr at 6 months exceeded baseline Scr by >75% or required maintenance dialysis. AIN, acute interstitial nephritis; D-AIN, drug-induced acute interstitial nephritis; Scr, serum creatinine.

<sup>a</sup>Median (interquartile range).

<sup>b</sup>P=0.0001 complete recovery versus partial recovery.

<sup>c</sup>P=0.001 partial recovery versus non-recovery.

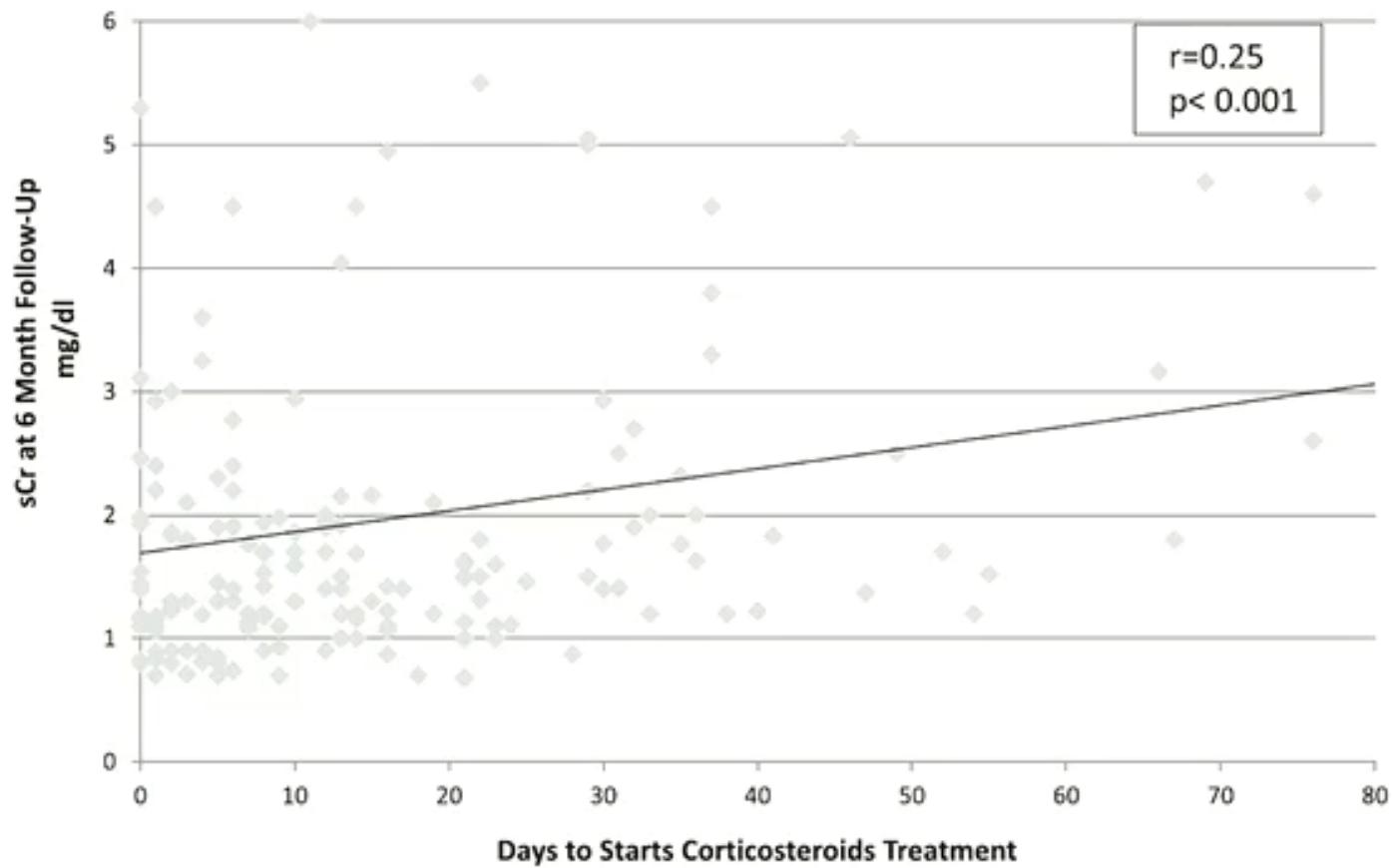


**Table 4. Univariable and multivariable analyses to study the involved factors in severe loss of kidney function after drug-induced AIN injury**

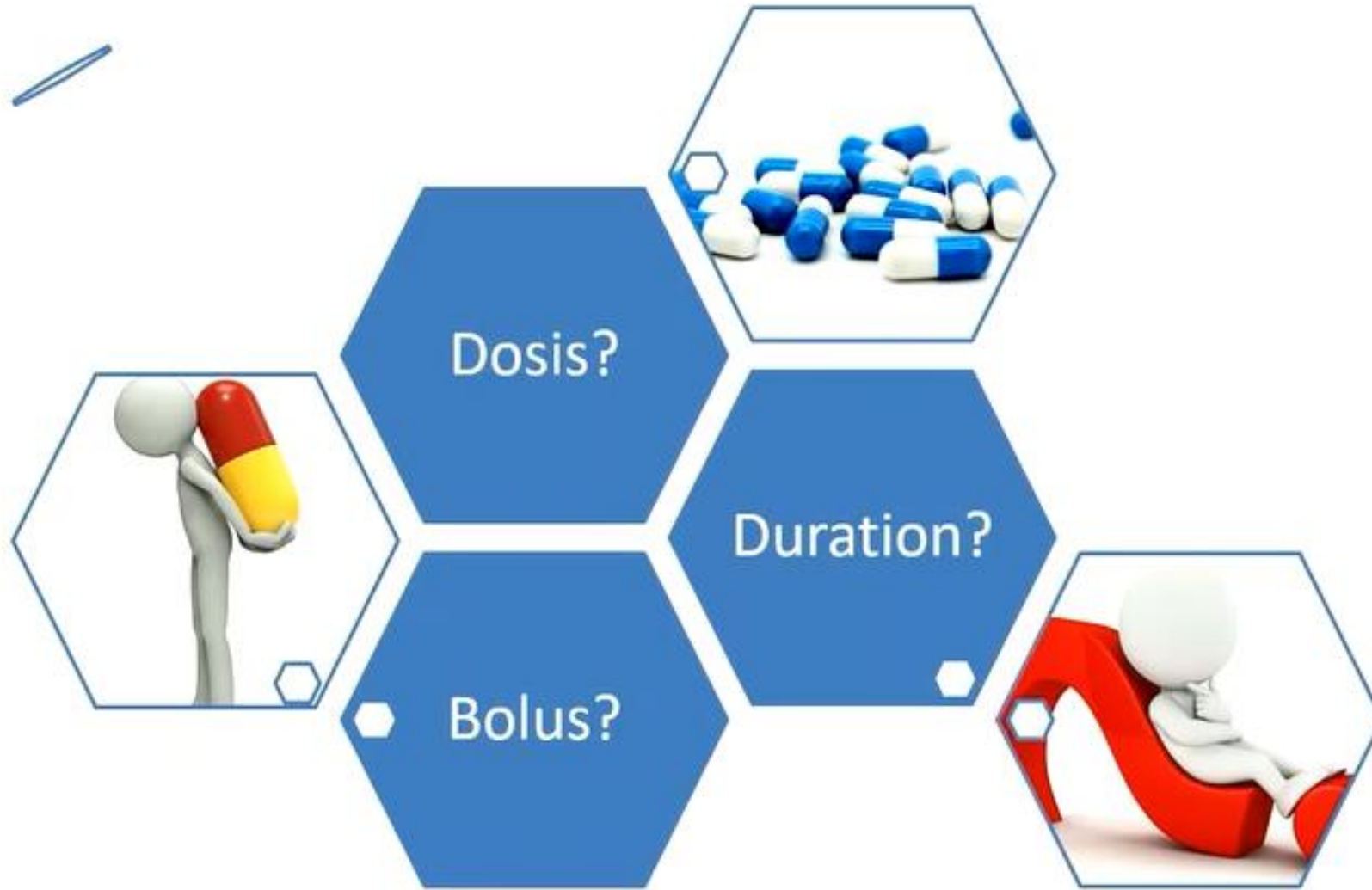
Variables	Univariable Model			Multivariable Model		
	OR	95% CI	P Value	OR	95% CI	P Value
Proteinuria, g/24 h	1.49	1.01 to 2.19	0.04	1.26	0.92 to 2.66	0.35
Acute dialysis	3.05	1.20 to 7.70	0.02	3.15	0.89 to 11.01	0.07
Interval between D-AIN detection and start of corticosteroids	1.02	1.00 to 1.04	0.006	1.02	1.00 to 1.04	0.03
Fibrosis in kidney biopsy specimen >50%	6.23	2.52 to 15.41	<0.001	8.68	2.7 to 27.4	<0.001
Age at onset, yr	1.00	0.97 to 1.03	0.99			
Baseline Scr, mg/dl	2.17	0.75 to 6.29	0.15			
Time to withdrawal of offending drug, d	0.99	0.98 to 1.02	0.1			
Time to kidney biopsy	1.02	1.00 to 1.04	0.04			
Bolus corticosteroids	0.61	0.25 to 1.45	0.25			
Total duration of corticosteroid treatment, wk	1.01	0.95 to 1.05	0.99			
Duration of corticosteroid treatment at high dose, wk	0.94	0.75 to 1.19	0.94			

AIN, acute interstitial nephritis; OR, odds ratio; 95% CI, 95% confidence interval; Scr, Serum creatinine; D-AIN, drug-induced acute interstitial nephritis.











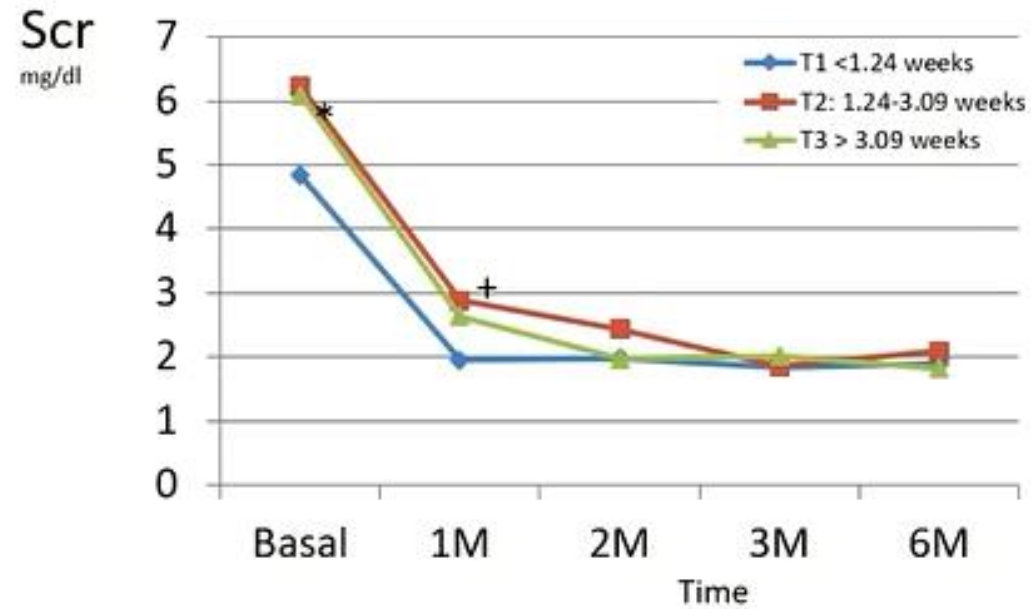
**Table 4.** Univariable and multivariable analyses to study the involved factors in severe loss of kidney function after drug-induced AIN injury

Variables	Univariable Model			Multivariable Model		
	OR	95% CI	P Value	OR	95% CI	P Value
Proteinuria, g/24 h	1.49	1.01 to 2.19	0.04	1.26	0.92 to 2.66	0.35
Acute dialysis	3.05	1.20 to 7.70	0.02	3.15	0.89 to 11.01	0.07
Interval between D-AIN detection and start of corticosteroids	1.02	1.00 to 1.04	0.006	1.02	1.00 to 1.04	0.03
Fibrosis in kidney biopsy specimen >50%	6.23	2.52 to 15.41	<0.001	8.68	2.7 to 27.4	<0.001
Age at onset, yr	1.00	0.97 to 1.03	0.99			
Baseline Scr, mg/dl	2.17	0.75 to 6.29	0.15			
Time to withdrawal of offending drug, d	0.99	0.98 to 1.02	0.1			
Time to kidney biopsy	1.02	1.00 to 1.04	0.04			
Bolus corticosteroids	0.61	0.25 to 1.45	0.25			
Total duration of corticosteroid treatment, wk	1.01	0.95 to 1.05	0.99			
Duration of corticosteroid treatment at high dose, wk	0.94	0.75 to 1.19	0.94			

AIN, acute interstitial nephritis; OR, odds ratio; 95% CI, 95% confidence interval; Scr, Serum creatinine; D-AIN, drug-induced acute interstitial nephritis.



## Evolution of serum creatinine according to the duration of high dose INITIAL steroids treatment divided by tertiles.

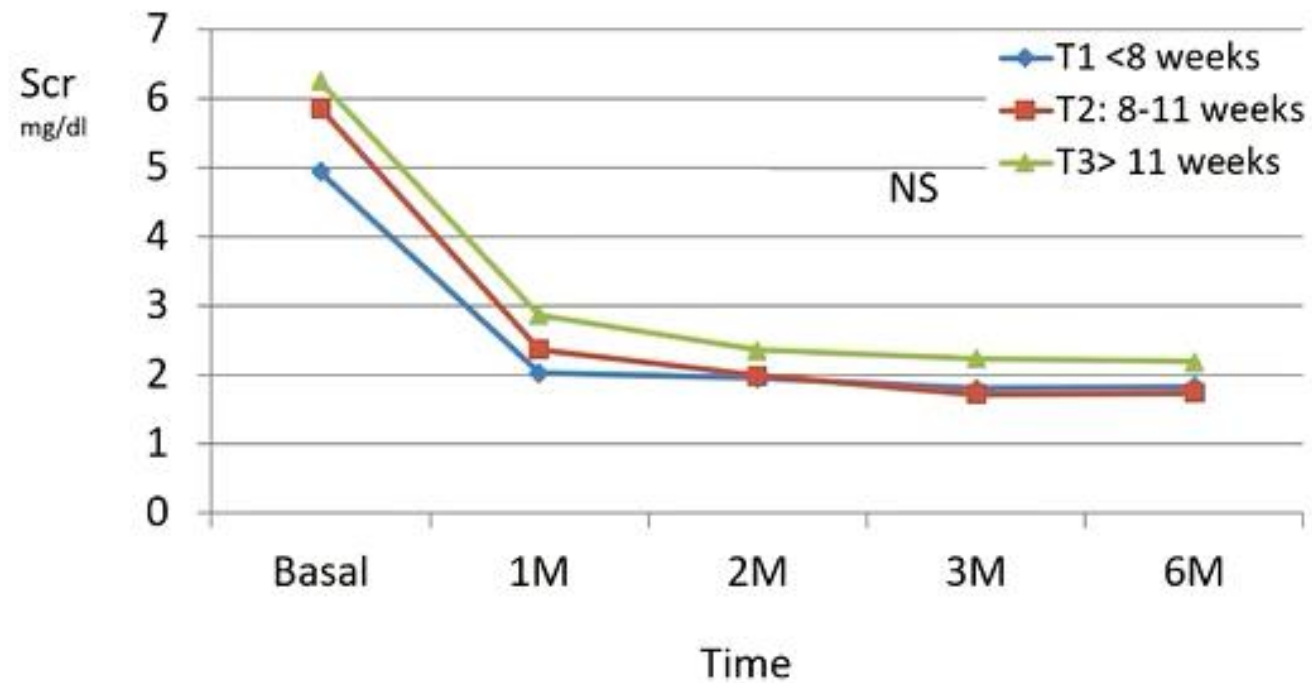


T1: High doses initial steroids treatment < 1.24 weeks, T2: High doses initial steroids treatment 1.24- 3.09 weeks, T3: High doses initial steroids treatment > 3.09 weeks.

- $p=0.05$  Baseline serum creatinine in T1 group vs T2-T3 group; +  $p= 0.003$  Serum creatinine at 1<sup>st</sup> month in T1 group vs T2-T3 group



## Changes in the Scr of patients according to the total duration of steroids treatment divided by tertiles



Fernández-Juárez et al. Clinical Journal of American Society of Nephrology  
In press 2018

t1: Total duration of steroids treatment < 8 weeks, T2: Total duration of steroids treatment 8-11 weeks, T3: Total duration of steroids treatment > 11 weeks. No statistical difference



# Mycophenolate Mofetil for the Treatment of Interstitial Nephritis

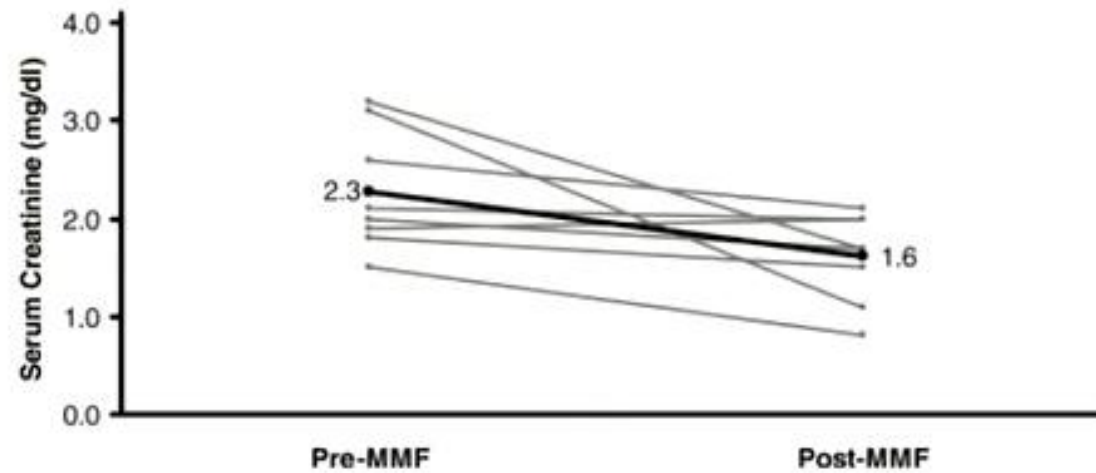
Dean C. Presdie,\* Glen S. Markowitz,<sup>†</sup> Jai Radhakrishnan,\* Thomas L. Nickolas,\*  
Vivette D. D'Agati,<sup>‡</sup> Joshua A. Schwimmer,<sup>\*†</sup> Mark Gardenswartz,<sup>‡</sup> Raquel Rosen,<sup>§</sup> and  
Gerald B. Appel\*

	Patient							
	1	2	3	4	5	6	7	8
Age (y)	67	53	61	60	63	65	54	57
Race	white	white	white	white	white	white	white	black
Gender	male	female	female	male	female	male	female	female
Presentation	ARF	ARF	ARF	ARF	ARF	ARF	ARF	ARF
Hypertension	yes	no	no	yes	yes	yes	no	yes
Creatinine (mg/dl)	3.2	1.5	2.0	2.1	3.1	1.9	1.8	2.6
GFR by MDRD (32) (ml/min)	35.8	38.0	36.0	49.5	20.8	47.0	48.0	22.5
24-h urine protein (g)	0.200	0.500	0.225	U	1.502	0.076	0.388	1.071
Presumed cause of AIN	ciprofloxacin	unknown	MCTD	pANCA	drug-induced	unknown	unknown	sarcoidosis
Renal biopsy findings	AIN with eosinophils	AIN	AIN	GIN	AIN with eosinophils	AIN	AIN	GIN
Treatment								
steroid courses	2	2	1	1	1	1	1	1
max MMF daily dose (mg)	1500	1500	2000	1000	1500	2000	1500	2000
MMF duration (mo)	32	23	29	24	25	13	34	14
Follow-up								
duration, after MMF (mo)	8	8	5	0	3	8	0	0
creatinine (mg/dl)	1.7	0.8	1.7	2.0	1.1	2.0	1.5	2.1



# Mycophenolate Mofetil for the Treatment of Interstitial Nephritis

Dean C. Preddie,\* Glen S. Markowitz,<sup>†</sup> Jai Radhakrishnan,\* Thomas L. Nickolas,\*  
Vivette D. D'Agati,<sup>†</sup> Joshua A. Schwimmer,\*<sup>‡</sup> Mark Gardenzwartz,<sup>‡</sup> Raquel Rosen,<sup>§</sup> and  
Gerald B. Appel\*

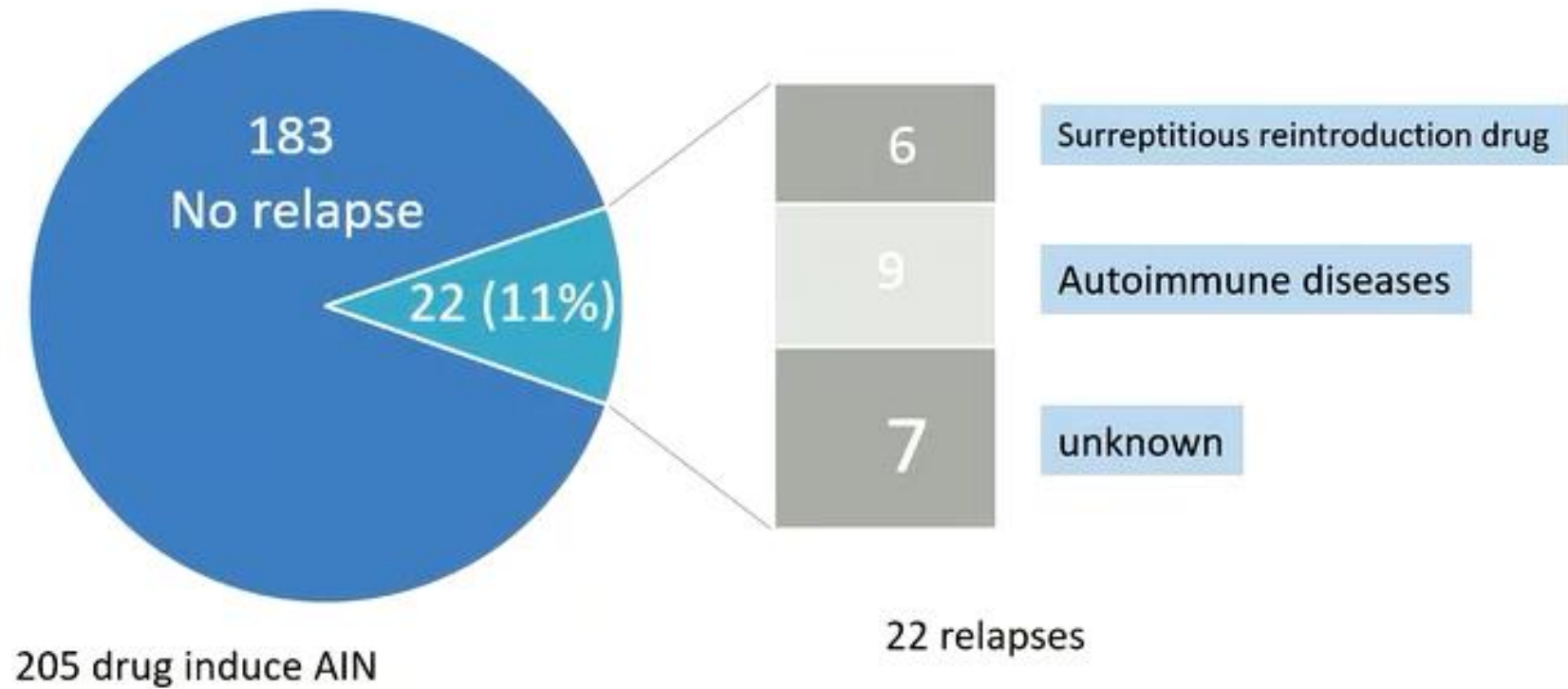


*Clin J Am Soc Nephrol* 1: 718–722, 2006.



## Recurrent acute interstitial nephritis: what lies beneath

Time to first recurrence was 111 days (IQR 67–248)

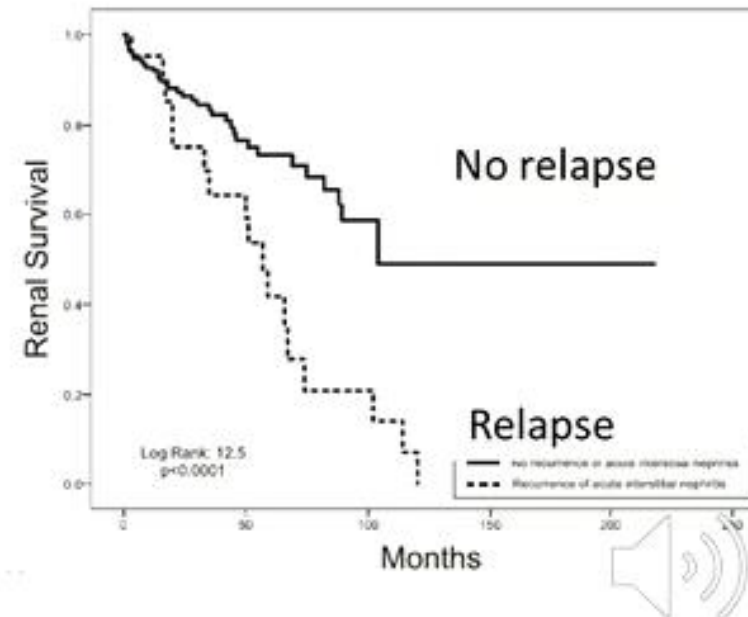


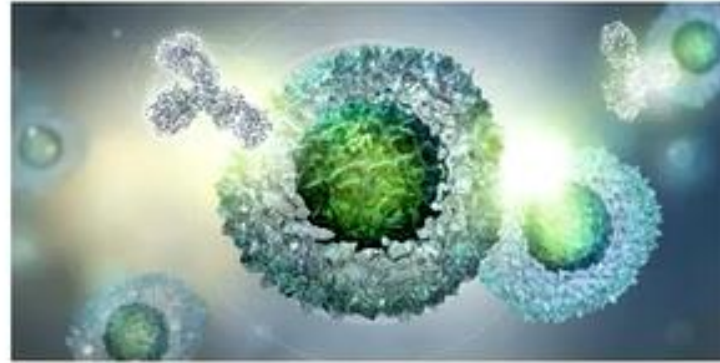


## Recurrent acute interstitial nephritis: what lies beneath

### Uncovered immunological diseases

- 2 patients (9%) sarcoidosis
- 3 patients (14%) S Sjögren
- 2 Patients (9%) light-chain-mediated AIN
- 2 patients (90%) AIN and uveitis syndrome (TNU)





Check point therapy → re-challenge ?



## Conclusions

1. Acute TIN should be considered in the differential diagnosis of all cases of acute kidney damage.
2. Withdrawal of the drug potentially responsible is an essential point of treatment
3. The beneficial effect of corticosteroids is optimal when they are started within the first 2 weeks of the injury, any benefit being doubtful if started beyond 4 weeks.
4. Full-doses Corticosteroids should be discontinued as soon as renal function recovers or after completing 3 weeks of treatment. Extending the treatment beyond that point or for more than 5 weeks, has not been shown to improve renal prognosis, but simply to increase the associated side effects .
5. When identification of responsible drug is unclear, immunological etiologies should be ruled out
6. Dealing with a disorder like drug-induced acute TIN, which is so prevalent and has such severe repercussions, we need to seek biomarkers to help with early diagnosis and to conduct clinical trials to help to optimise the current treatment regimen

