

Drug induced

AIN

Anjali Gupta

History

1792 – Admiral Jones Autopsy Specimen

1800 – Autopsy lesions referred as productive/
pyelonephritis

1898 – Councilman description of AIN

1914- Volhard included AIN in classification of renal
disease

1946- More et al described lesions secondary to drugs

1953- Spuhler described analgesic nephropathy

Histology

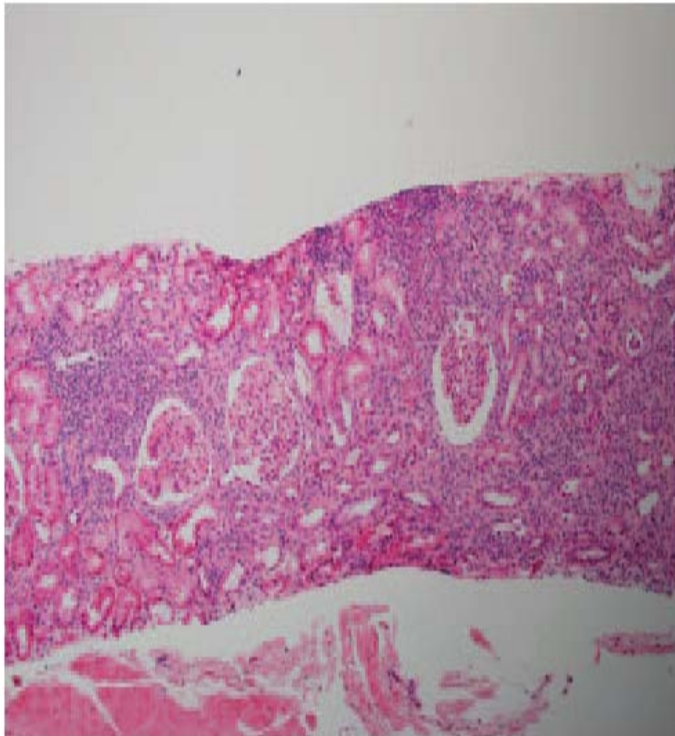


Figure 1 | Interstitial inflammatory infiltrates in a case of drug-induced acute interstitial nephritis (AIN; hematoxylin and eosin original magnification $\times 10$).



Figure 2 | Extensive interstitial fibrosis (green areas) in a renal biopsy obtained 4 weeks after the onset of acute interstitial nephritis (AIN; Masson original magnification $\times 10$).

Diffuse vs Patchy involvement

Kidney International (2010) 77, 956–961

Etiology of AIN

Table 1 | Etiology of biopsy-proven AIN

Drugs (> 75% of AIN)	Antibiotics: ampicillin, cephalosporins, ciprofloxacin, cloxacillin, methicillin, penicillin, rifampicin, sulfonamides, vancomycin. NSAIDs Other: allopurinol, acyclovir, famotidine, furosemide, omeprazole, phenytoin
Infections (5–10%)	Bacteria: <i>Brucella</i> , <i>Campylobacter</i> , <i>Escherichia coli</i> , <i>Legionella</i> , <i>Salmonella</i> , <i>Streptococcus</i> , <i>Staphylococcus</i> , <i>Yersinia</i> Viruses: cytomegalovirus, Epstein–Barr, hantavirus, human immunodeficiency virus, polyomavirus Other: <i>Leptospira</i> , <i>Mycobacterium tuberculosis</i> , <i>Mycoplasma</i> , <i>Rickettsia</i> , <i>Schistosoma</i> , <i>Toxoplasma</i>
Idiopathic (5–10%)	Anti-TBM TINU
Associated with systemic diseases (10–15%)	Sarcoidosis, Sjögren, systemic lupus erythematosus

AIN

- ❖ AIN accounts for 7 to 15% cases of AKI. In one case series as high as 27%.

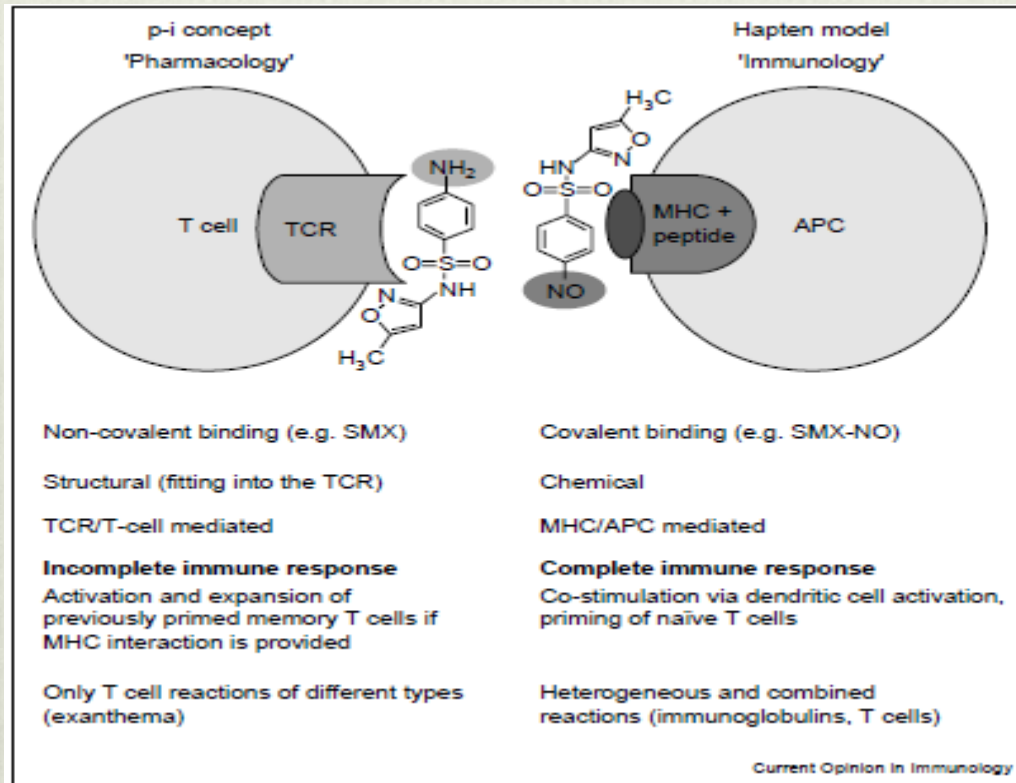
Farrington K, Levison DA, Greenwood RN, Cattell WR, Baker LR. Renal biopsy in patients with unexplained renal impairment and normal kidney size. Q J Med 1989; 70: 221–233

- ❖ In one case series only 40% of pt had a S cr <1.2 and 68% had <1.7 *Kidney Int 2001*

Pathogenesis

- ❖ In 1974, Border et al showed that methicillin molecules acts as hapten and binds to TBM, leading to production of anti –TBM ab. *N Engl J Med 1974; 291:381-384*
- ❖ Its now recognized it's a T cell mediated immune reaction .
- ❖ Recent studies by different groups have shown that patients with drug hypersensitivity harbor drug-specific T cells in their peripheral blood and also in affected tissues.

Drugs acting as Hapten

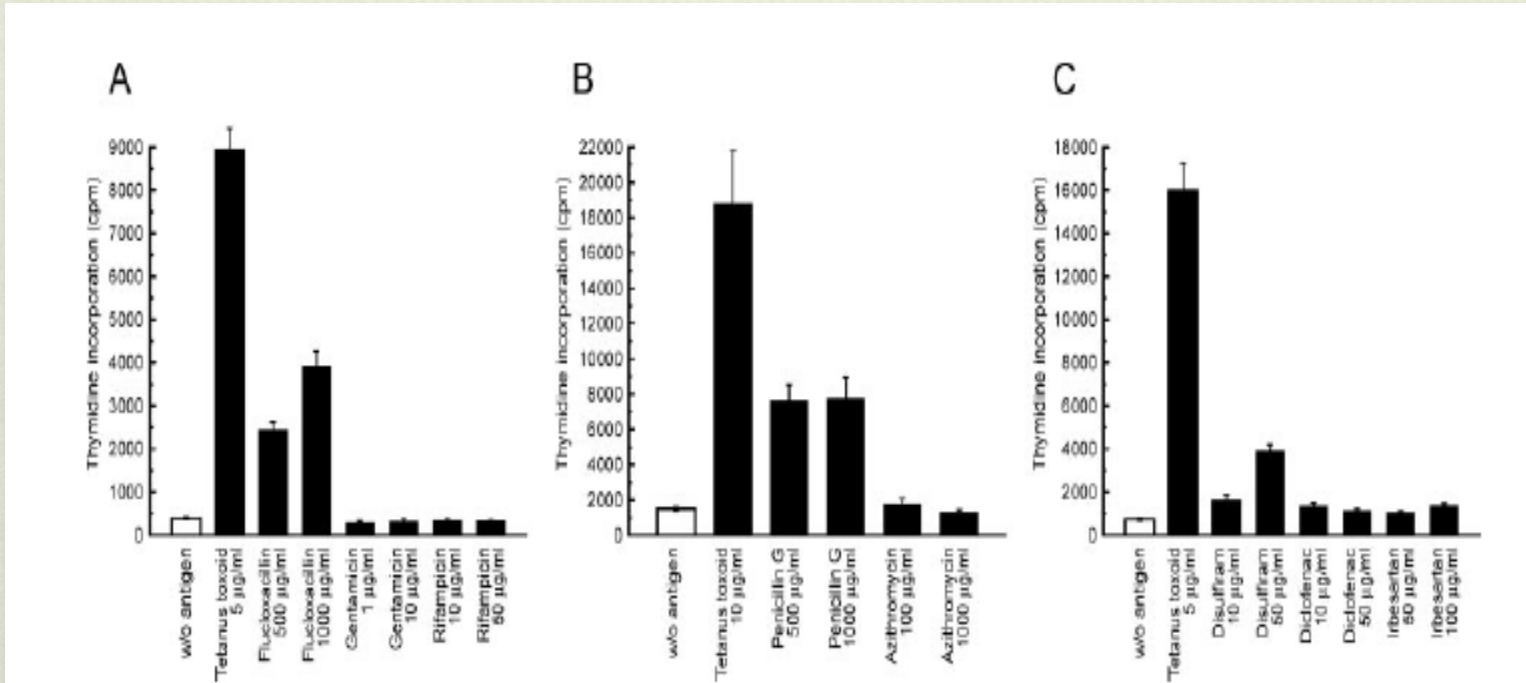


Involvement of Drug-Specific T Cells in Acute Drug-Induced Interstitial Nephritis

- ❖ To investigate the concept that drug-specific T cells are important in the development of DIN
- ❖ Lymphocyte transformation test was performed in 3 pt with DIN
 - p1 Flucloxacillin, gentamicin, rifamicin
 - p2 azithromycin, indomethacin, pcn, van
 - p3 diclofenanc, irbesartan, disulfiram

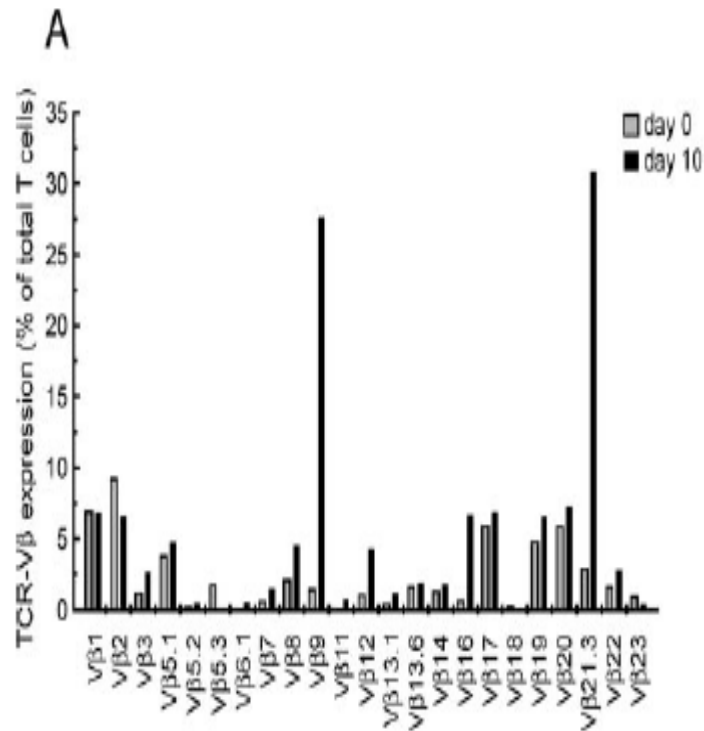
J Am Soc Nephrol 17: 2919–2927, 2006.

Lymphocyte Transformation Test



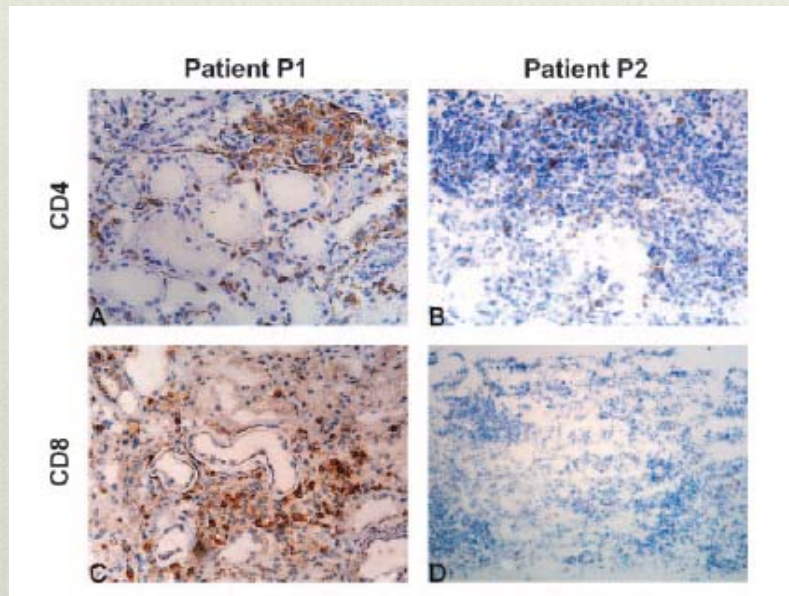
LTT were positive for one drug but negative for the other drugs to which the patients had been exposed .

Generation of Flucloxacillin –specific TCL



- ❖ PBMC + drug + IL2 incubated for 4 weeks
- ❖ TCR-V β accessed of stimulated and unstimulated cells
- ❖ Oligoclonal expansion of cells

Correlation of the in vitro analysis of PBMC with the type of renal inflammation



This T cell infiltration in patient P1 was composed mainly of CD4 T cells but a substantial amount of CD8 T cells were also seen.

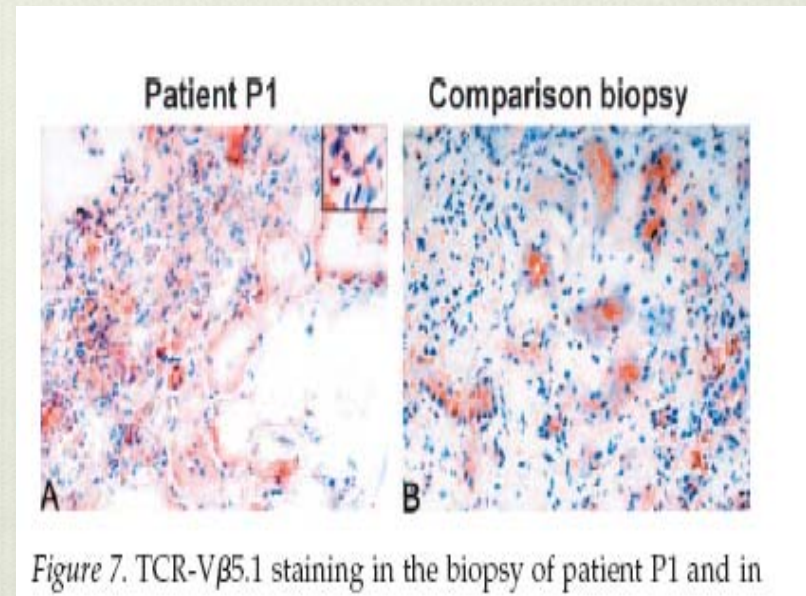
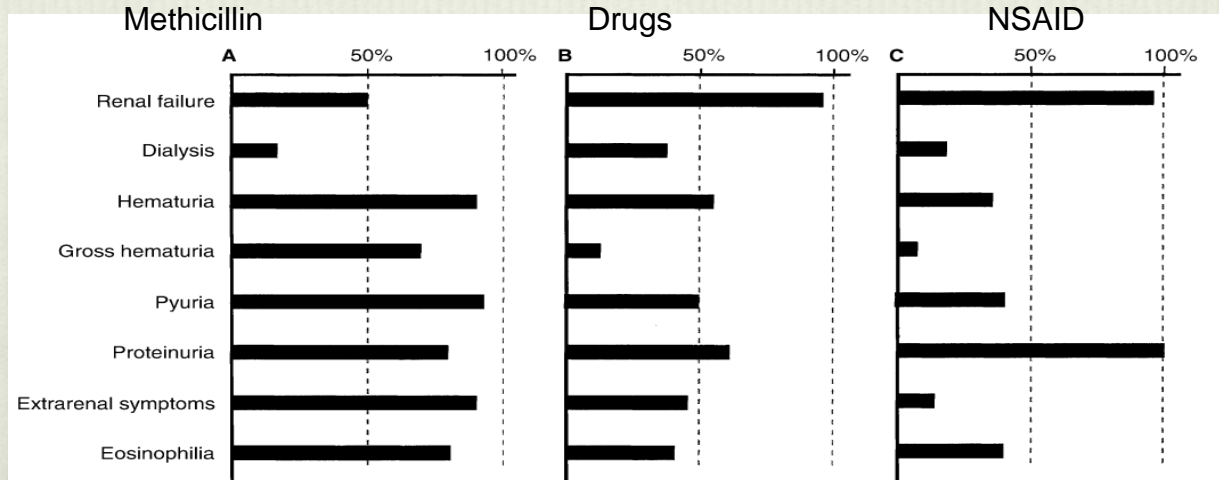


Figure 7. TCR-Vβ5.1 staining in the biopsy of patient P1 and in

The mean of TCR-V5.1 T cells was 120/mm² but only 27.2/mm² in the control patient whereas the total CD4 T cell count was comparable

Non invasive diagnostic test

❖ Clinical manifestations



❖ Gallium scan – Low sensitivity -50-60%

Koselj, M, Kveder, R, Bren, AF, Rott, T: Acute renal failure in patients with drug-induced acute interstitial nephritis. Ren Fail 1993 15:69–7

❖ Urinary Biomarkers ?

Pathological Significance of a Panel of Urinary Biomarkers in Patients with Drug-Induced Tubulointerstitial Nephritis

Clin J Am Soc of neph 5: 1954–1959, 2010

- ❖ Aim: To look for noninvasive markers that have close correlations with the pathologic lesions .
- ❖ Hypothesis: urinary levels of MCP-1, NGAL, 1-MG, and NAG are related to the amount of tubulointerstitial damage.
- ❖ 40 patients who were clinicopathologically diagnosed with DTIN from January 2001 to May 2008, were included in this study.

Urinary Biomarkers in DTIN

Table 1. Demographics and clinical characteristics of the subjects

	DTIN (n = 40)	Control (n = 20)
Age (years)	43.90 ± 13.42	43.5 ± 10.53
Gender (f/m)	29/11	14/6
Systolic BP (mmHg)	122.30 ± 16.23 ^a	109.25 ± 9.38
Diastolic BP (mmHg)	78.24 ± 11.32 ^a	62.1 ± 7.72
Hemoglobin (g/L)	106.46 ± 17.88 ^a	119.3 ± 8.02
umAlb (mg/L)	94.31 ± 88.13 ^b	1.27 ± 2.72
Scr (μmol/L)	202.56 ± 86.43 ^b	81.7 ± 20.35

Table 2. Comparison of urinary biomarkers in the subjects

	DTIN (n = 40)	Control (n = 20)
MCP-1(ng/mmol creatinine)	363.25 ± 495.53 ^a	8.83 ± 15.38
NGAL (μg/mmol creatinine)	233.39 ± 225.37 ^a	0.60 ± 0.75
a1-MG (mg/mmol creatinine)	31.86 ± 22.86 ^a	0.80 ± 0.53
NAG (u/nmol creatinine)	3.15 ± 2.10 ^a	0.72 ± 0.34

Values are expressed as means ± SD.

^aP < 0.01 versus control.

Urinary Biomarkers in DTIN

Table 3. Correlation between urinary biomarkers and tubulointerstitial lesions

Indexes	Urinary MCP-1		Urinary NGAL		Urinary α 1-MG		Urinary NAG	
	<i>r</i>	<i>P</i>	<i>r</i>	<i>P</i>	<i>r</i>	<i>P</i>	<i>r</i>	<i>P</i>
Interstitial edema	0.501	<0.001	0.370	0.011	0.458	0.003	0.278	0.061
Inflammation infiltration	0.768	<0.001	0.639	<0.001	0.557	<0.001	0.391	0.007
Tubular atrophy	0.563	<0.001	0.692	<0.001	0.641	<0.001	0.424	0.003
Interstitial fibrosis	-0.059	0.695	0.187	0.213	0.122	0.447	-0.123	0.414

Limitations

- ❖ Biomarkers are not specific for DAIN
- ❖ It was done in well screened pts, needs to be seen in other clinical settings
- ❖ Correlation between pathological finding and course/prognosis of AIN is not established

Is NSAID induced AIN
different??

NSAID induced renal disease

Glomerular and Interstitial Disease Induced by Nonsteroidal Anti-Inflammatory Drugs

Am Jr Nephrol: 1984

Table II. Clinical presentation of nonsteroidal anti-inflammatory drug-induced glomerular and interstitial disease¹

	Number	Age years	Drug exposure months	Peak serum creatinine mg/dl	Urinary protein g/24 h	Systemic hypersensitivity reaction ²
A) Nephrotic syndrome and renal failure [3, 8, 12, 16, 18, 52-57]	26	65 ± 1.98	5.7 ± 0.8	6.1 ± 0.65	13.2 ± 1.48	3
B) Nephrotic syndrome without renal failure [18, 54, 58, 59]	4	64.8 ± 5.1	11.3 ± 6.4	1.05 ± 0.12	7.35 ± 2.76	0
C) Renal failure without nephrotic syndrome ³ [13, 19, 60-63]	6	62.7 ± 9.7	1.2 ± 0.5	7.0 ± 1.3	-	4

Treatment

- ❖ Recent studies have shown that serum creatinine remains elevated in 40% of cases
- ❖ No RCT
 1. Few cases of AKI are biopsied of which few have AIN.
 2. Many cases of AIN are never biopsied
 3. Randomization to placebo or steroids?
- ❖ Discontinuation of the drug

Steroids in AIN

- ❖ Controversial
- ❖ No RCT
- ❖ Beneficial use of steroids was established by two small studies

1-Acute interstitial nephritis due to methicillin- 8 of the 14 patients treated with glucocorticoids recovered more quickly (9 versus 54 days) and had a lower final plasma creatinine concentration (1.4 versus 1.9) Am J Med 1978

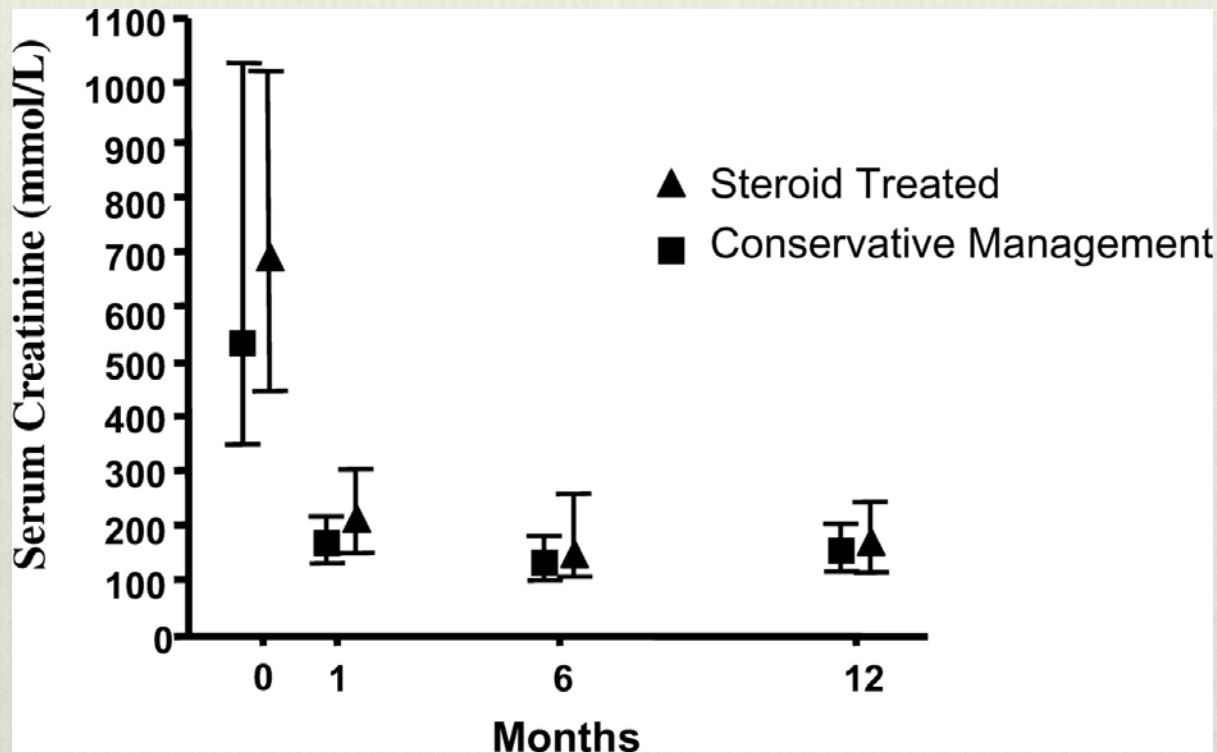
2- Acute interstitial nephritis: a clinical and morphological study in 27 patients . 10 of 27 pt were given steroids after worsening of kidney function inspite of drug withdrawal

Acute Interstitial Nephritis: Clinical features and response to corticosteroid therapy

Nephron Dialysis Transplant 2004

- ❖ Retrospective case series of 60 pts from a single centre
- ❖ NSAIDS were the causative agent in 44% of the cases
- ❖ 58% of pt needed RRT at some point and 7% reached ESRD
- ❖ 42 pt had complete follow up of which 60% received steroids
(both groups on an av had 40% (30-70%) interstitial fibrosis)
- ❖ On an average time to biopsy was 3 weeks and 4 weeks resp
- ❖ Subgroup analysis of NSAID associated 18 pts showed no difference

Effect of corticosteroid therapy compared with conservative management.



- 26 were treated conservatively and 16 were treated with steroids
- 2 differences btw the grp, av time to biopsy was 4 week in steroid gp as c/w 3 weeks in other
- Av Scr was higher in steroid treated gp. (700vs 545)

Conclusions

- ❖ Steroids failed to show benefit - *however significant sclerosis on biopsy , late onset of treatment ?*
- ❖ Pt did not recover completely, average cr at 1 year 1.6
- ❖ No difference noted in presentation, severity or response to steroids in NSAID subgroup

Early steroid treatment improves the recovery of renal function in patients with drug-induced acute interstitial nephritis

Table 2 | Characteristics of Group 1 (steroid treatment) and Group 2 (no steroid treatment)

	Group 1 (n=52)	Group 2 (n=9)	P-value
Age (years)	57.6 ± 17.5	58.1 ± 18	NS
Gender (M/F) (%)	61.5/38.5	77.8/22.2	NS
Baseline Scr (mg per 100 ml)	1.14 ± 0.4	1.13 ± 0.37	NS
Baseline eGFR (ml per min per 1.73 m ²)	71 ± 26	70 ± 25	NS
Offending drug (antibiotics/NSAIDs/others) (%)	53.8/34.6/11.5	66.7/33.3/0	NS
Duration of the treatment (days)	13.4 ± (r 3-60)	12.6 ± (range 4-30)	NS
Highest Scr (mg per 100 ml)	5.9 ± 3.4	4.9 ± 2.1	NS
Proteinuria (g/24 h)	1 ± 1.2 (range 0-6)	0.6 ± 0.6 (range 0-1.7)	NS
Complete recovery of renal function	28 (54%)	3 (33%)	NS
Chronic dialysis	2 (3.8 %)	4 (44.4 %)	<0.001
Final Scr (mg per 100 ml)	2.1 ± 2.1 (range 0.7-12.7)	3.7 ± 2.9 (range 0.7-8.9)	<0.05
Follow-up (months)	19 ± 19 (range 6-60)	18 ± 18 (range 6-56)	NS

- Final Scr was significantly lower in Group 1
- Pt on chronic dialysis 44.4 vs 3.8%
- No side effects attributable to steroid treatment were observed
- However small no of patients in group 2.

Complete vs Incomplete renal recovery

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

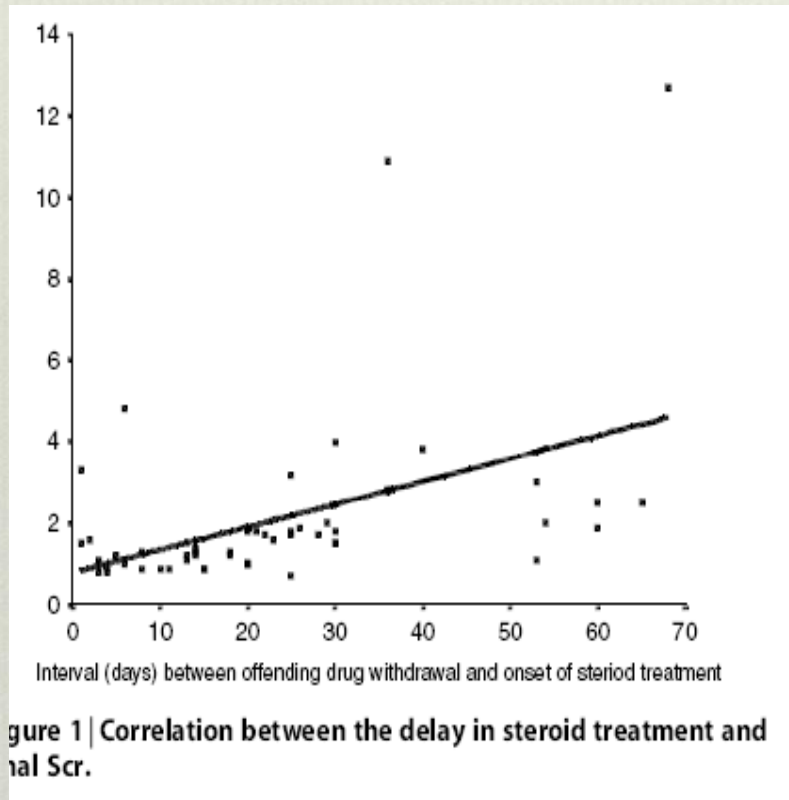
	Group 1a (n=28)	Group 1b (n=24)	P-value
Age (years)	55 ± 18 (range 18–78)	60 ± 16 (range 18–81)	NS
Gender (M/F) (%)	61/39	62/38	NS
Baseline Scr (mg per 100 ml)	1.07 ± 0.31 (range 0.6–1.9)	1.20 ± 0.4 (range 0.6–2.3)	NS
Baseline eGFR (ml per min per 1.73 m ²)	77 ± 29 (range 36–151)	65 ± 21 (range 35–106)	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 100 ml)	5.3 ± 3.5 (range 1.5–13.3)	6.4 ± 3.3 (range 2.9–12.7)	NS
Proteinuria (g/24 h)	1.1 ± 1.4 (range 0–6)	0.9 ± 0.8 (range 0–3.4)	NS
Final Scr (mg per 100 ml)	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.

Risk for incomplete recovery of renal function

Multiple logistic regression

- ❖ Interval longer than 7 days between drug withdrawal and onset of steroid treatment
(OR) 6.6 (CI) 1.3–33.6
- ❖ Severity of interstitial fibrosis
(OR) 14.5 (CI) 3.4–61



Interval between drug withdrawal and onset of steroid

Patients with DI-AIN due to NSAIDs treated with steroids

Table 5 | Patients with DI-AIN due to NSAIDs treated with steroids

	NSAIDs-Group 1a (n=9)	NSAIDs-Group 1b (n=11)	P-value
Age (years)	51 ± 24 (range 18-78)	61.2 ± 16 (range 24-81)	NS
Gender (M/F) (%)	66.7/33.3	45.5/54.4	NS
Baseline Scr (mg per 100 ml)	1 ± 0.39 (range 0.6-1.9)	1.1 ± 0.46 (range 0.6-2.3)	NS
Baseline eGFR (ml per min per 1.73m ²)	83 ± 37 (range 36-151)	70 ± 25 (range 35-106)	NS
Duration of NSAIDs treatment (days)	12.4 ± 10.9 (range 3-35)	25.4 ± 20.4 (range 7-60)	NS
Highest Scr (mg per 100 ml)	3.8 ± 1.7 (1.5-7.7)	5.2 ± 2.7 (range 3.1-12)	NS
Proteinuria (g/24 h)	1.8 ± 2.2 (range 0.33-6)	1.3 ± 1 (range 0.1-3.4)	NS
Final Scr (mg per 100 ml)	1.1 ± 0.3 (range 0.7-1.6)	2.4 ± 1 (range 1.6-4.8)	<0.0001
Chronic dialysis	0	1 (9.1 %)	NS
Interval between NSAIDs withdrawal and onset of corticosteroid treatment (days)	18.4 ± 16 (range 2-53)	31.4 ± 15 (range 6-60)	<0.05
Patients with an interval between NSAIDs withdrawal and onset of corticosteroid treatment <7 days	3 (33 %)	1 (9.1 %)	NS
Patients with an interval between NSAIDs withdrawal and onset of corticosteroid treatment <15days	5 (44 %)	1 (9.1 %)	<0.05
Duration of steroid treatment (days)	91.5 ± 49.9 (range 20-180)	75.4 ± 42 (range 30-180)	NS
Follow up (months)	30 ± 24.5 (range 6-60)	21.3 ± 17 (6-60)	NS

- 20 pt received steroids. Group 1a complete recovery as compared with group 1b incomplete recovery.
- 3 pt who did not receive steroids had a final Scr of 1.9 (BI0.7-1.3)

Conclusions

Table 4 | Histologic findings

	Group 1	Group 2	P-value	Group 1a	Group 1b	P-value
Interval between drug withdrawal and renal biopsy (days)	22 ± 17 (range 1-65)	26 ± 24 (range 7-75)	NS	13 ± 10 (range 1-53)	33 ± 17 (range 1-65)	<0.0001
<i>Interstitial fibrosis</i>						
Mild	32 (61.5%)	4 (44%)	NS	25 (89.3%)	7 (29.2%)	<0.0001
Moderate	14 (27%)	2 (22.2%)		3 (10.7%)	11 (45.8%)	
Severe	6 (11.5%)	3 (33%)		0	6 (25%)	

- ❖ Early steroid have a beneficial affect on outcome on AIN, early and complete recovery.
- ❖ NSAID induced AIN had similar response to steroids

Cellcept in AIN

- ❖ Scarce information exists on alternative treatments to steroids
- ❖ MMF was studied as an alternative treatment in steroid-resistant or steroid-dependent AIN or when steroids are contraindicated
- ❖ Small retrospective study involving 8 patients

Mycophenolate Mofetil for the Treatment of Interstitial Nephritis

Table 1. Clinical findings and outcomes^a

	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)	32	15	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

- ❖ 6 of the 8 patients had improvement in renal function, as evidenced by a decline in serum creatinine of at least 0.3 mg/dl.
- ❖ Mean follow up of 28 mo; range 14 to 40 mo
- ❖ 3 were still maintained on MMF and 5 were discontinued (1 died sec to MI)
- ❖ Limitations: small study, retrospective, unclear how much and how steroids were tapered

Thank you

