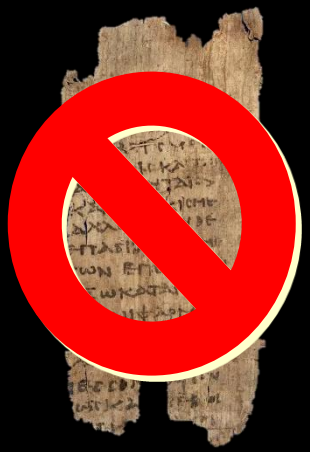
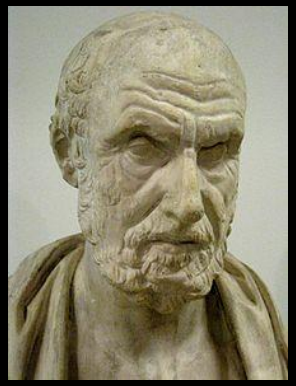
Drug Induced Nephrotoxicity

Warren Kupin MD,FACP
Professor of Medicine
Miami Transplant Institute
Katz Family Division of Nephrology and Hypertension
University of Miami Miller School of Medicine

"First Do No Harm" : Primum No Nocere

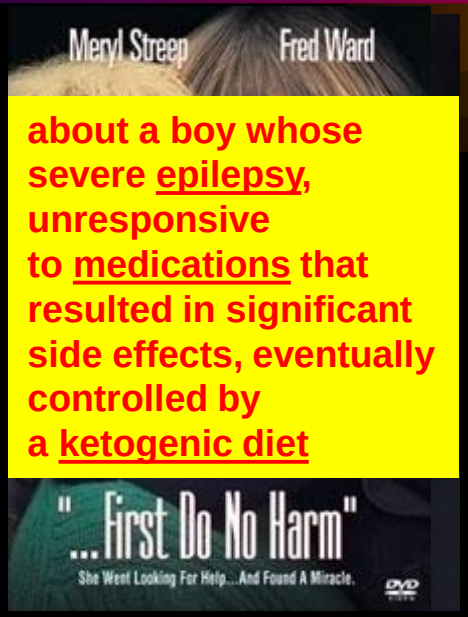
Hippocratic Oath ?



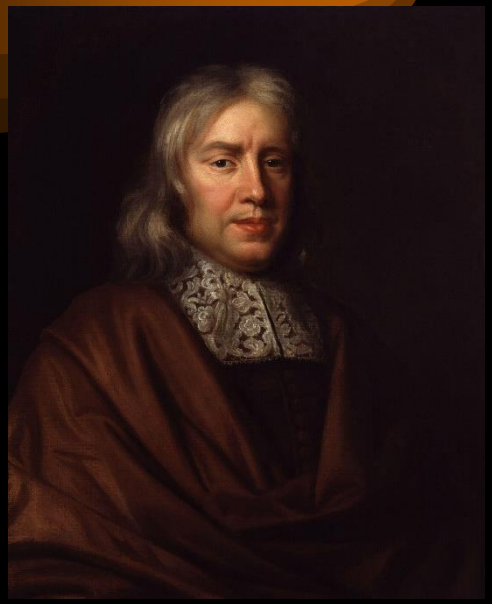


I will use treatment to help the sick according to my ability and judgment, but never with a view to injury

"The physician must ... have two special objects in view with regard to disease, namely, to do good or to do no harm"



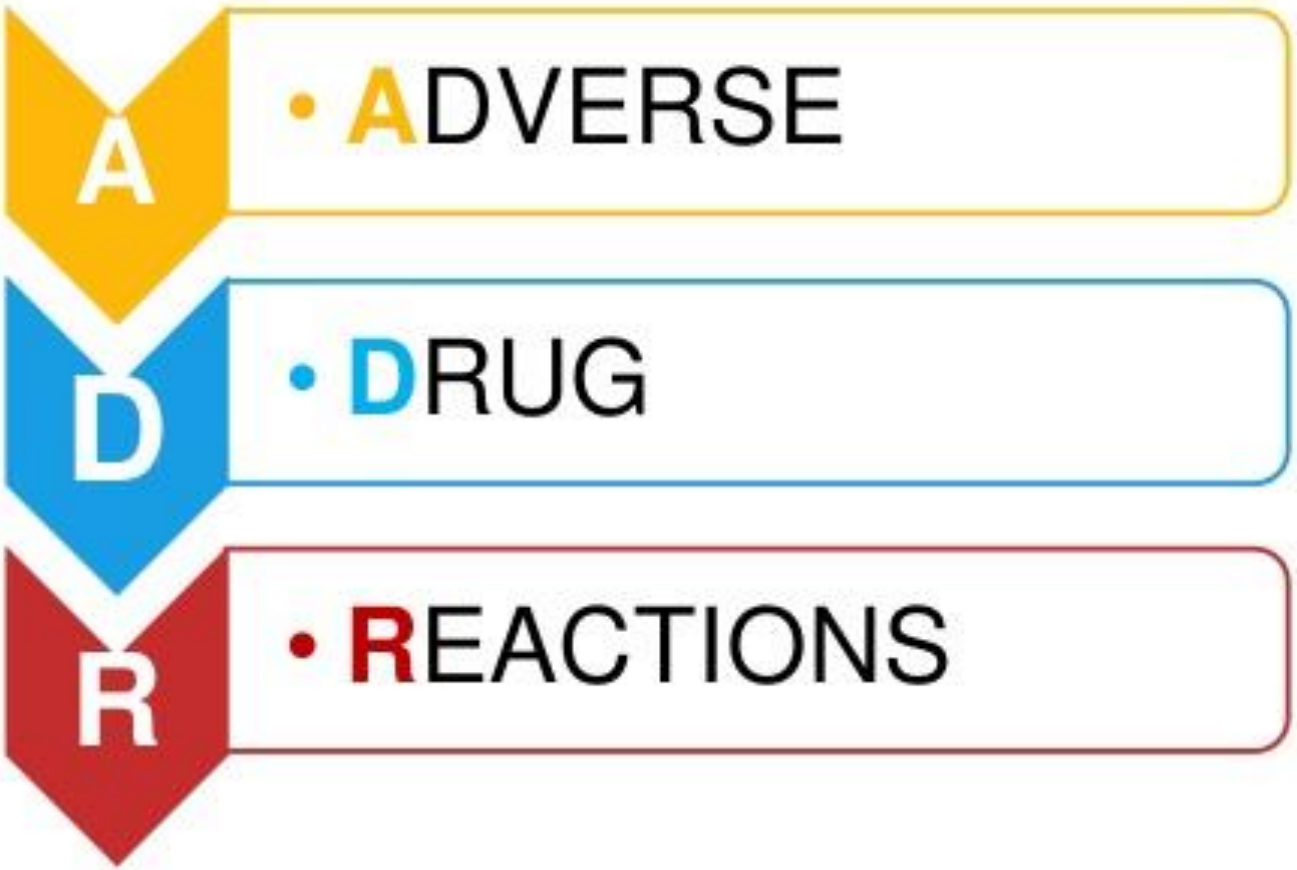
about a boy whose severe epilepsy, unresponsive to medications that resulted in significant side effects, eventually controlled by a ketogenic diet



Thomas Syndenham
The English Hippocrates

Described Syndenham's Chorea (St Vitus's Dance)

How Can A Physician do Harm ?



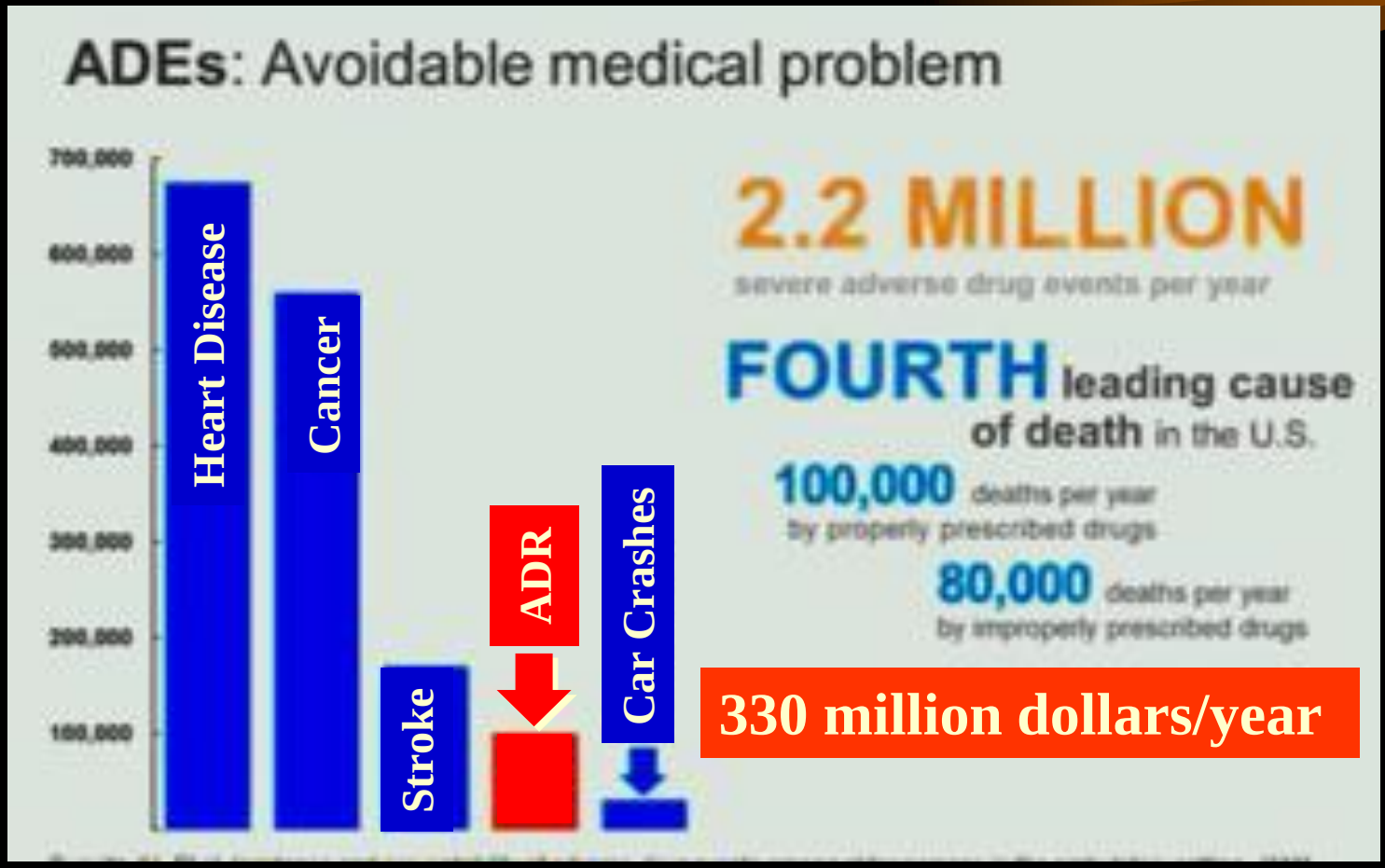
unwanted or harmful reaction experienced following the administration of a drug or combination of drugs under normal conditions of use

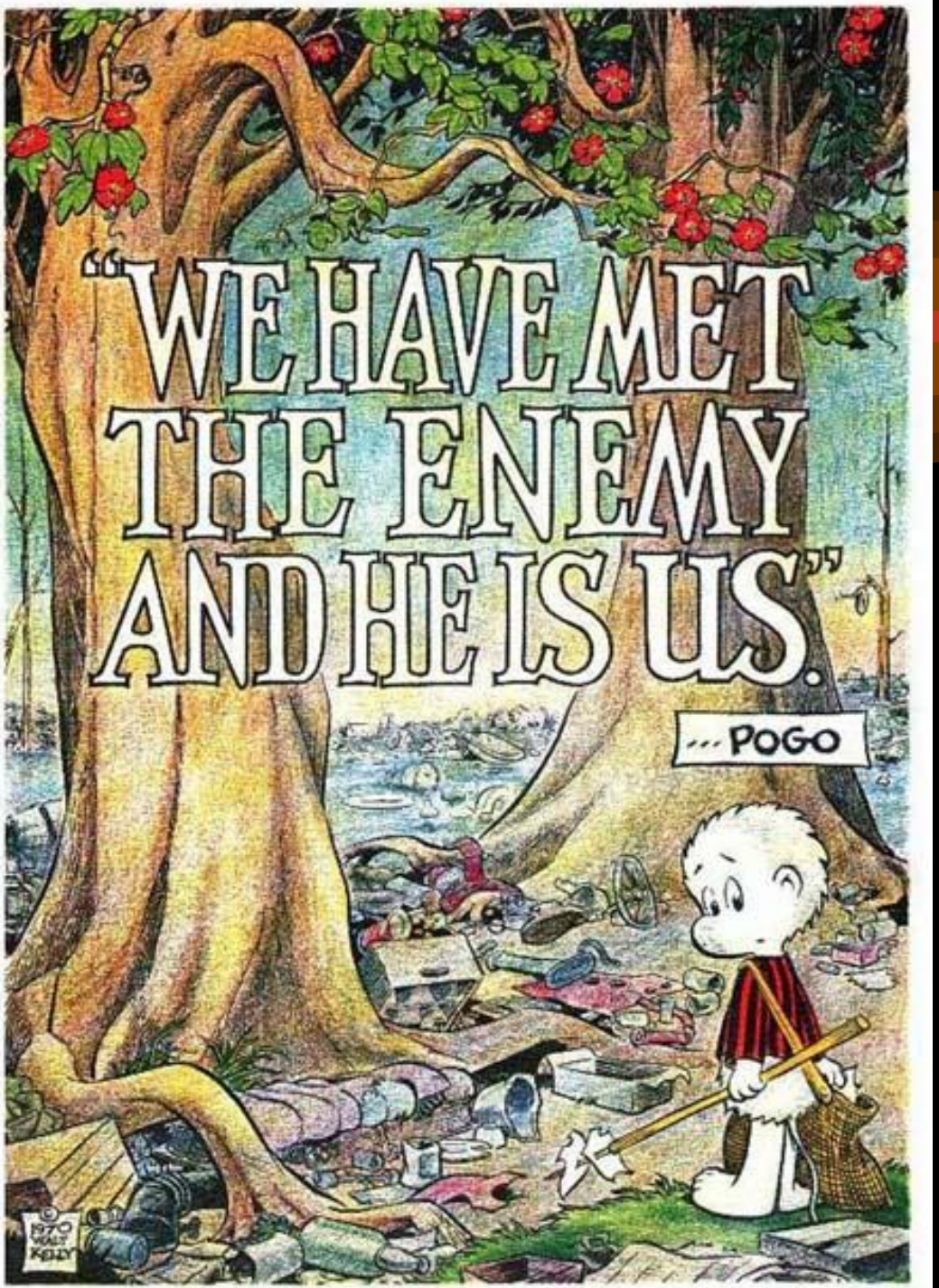
Adverse Drug Reactions

Direct Cause of 3 – 7 % of Hospitalizations

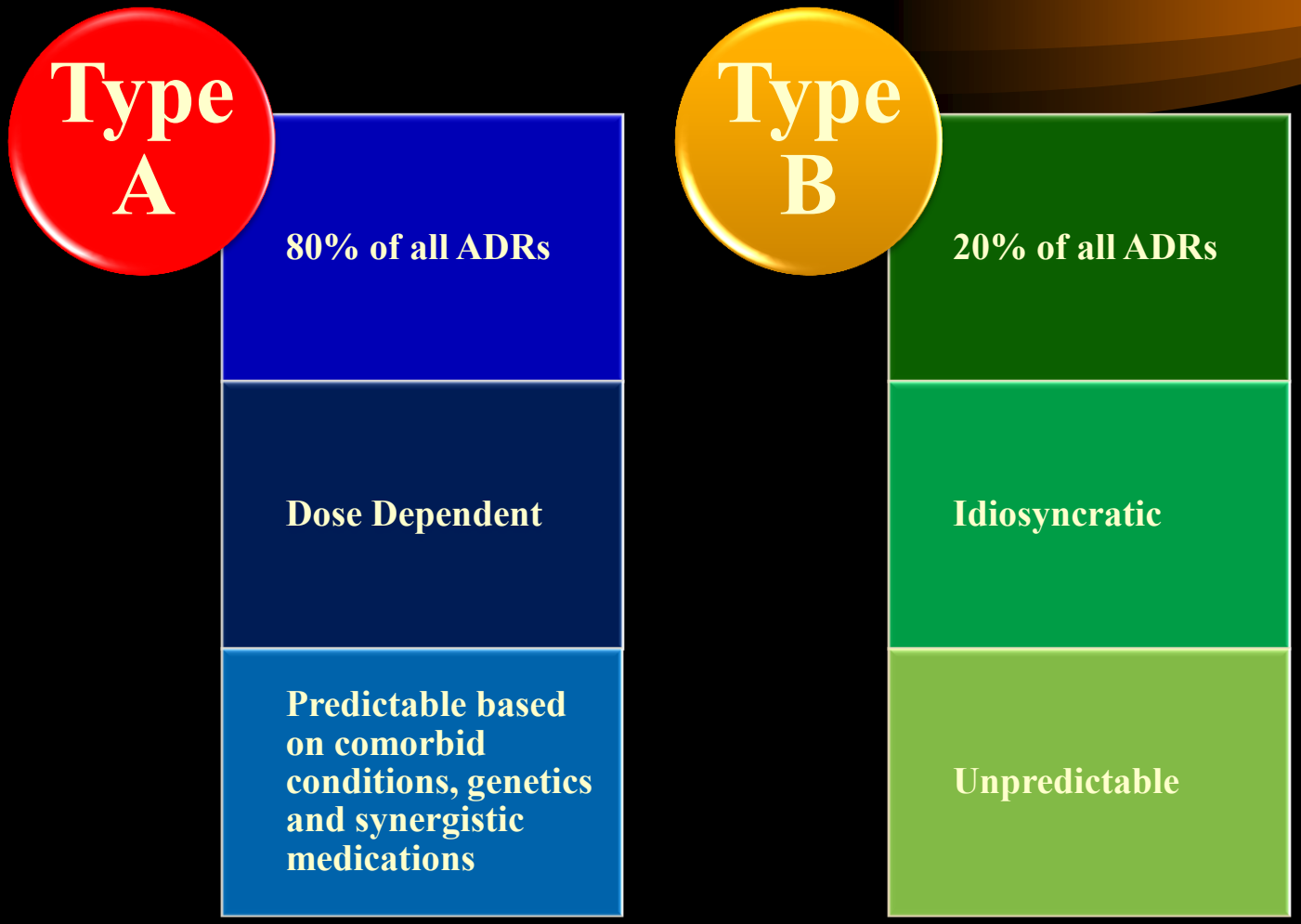
Occurs in 10 – 20% of Hospitalizations

Adverse Drug Reactions

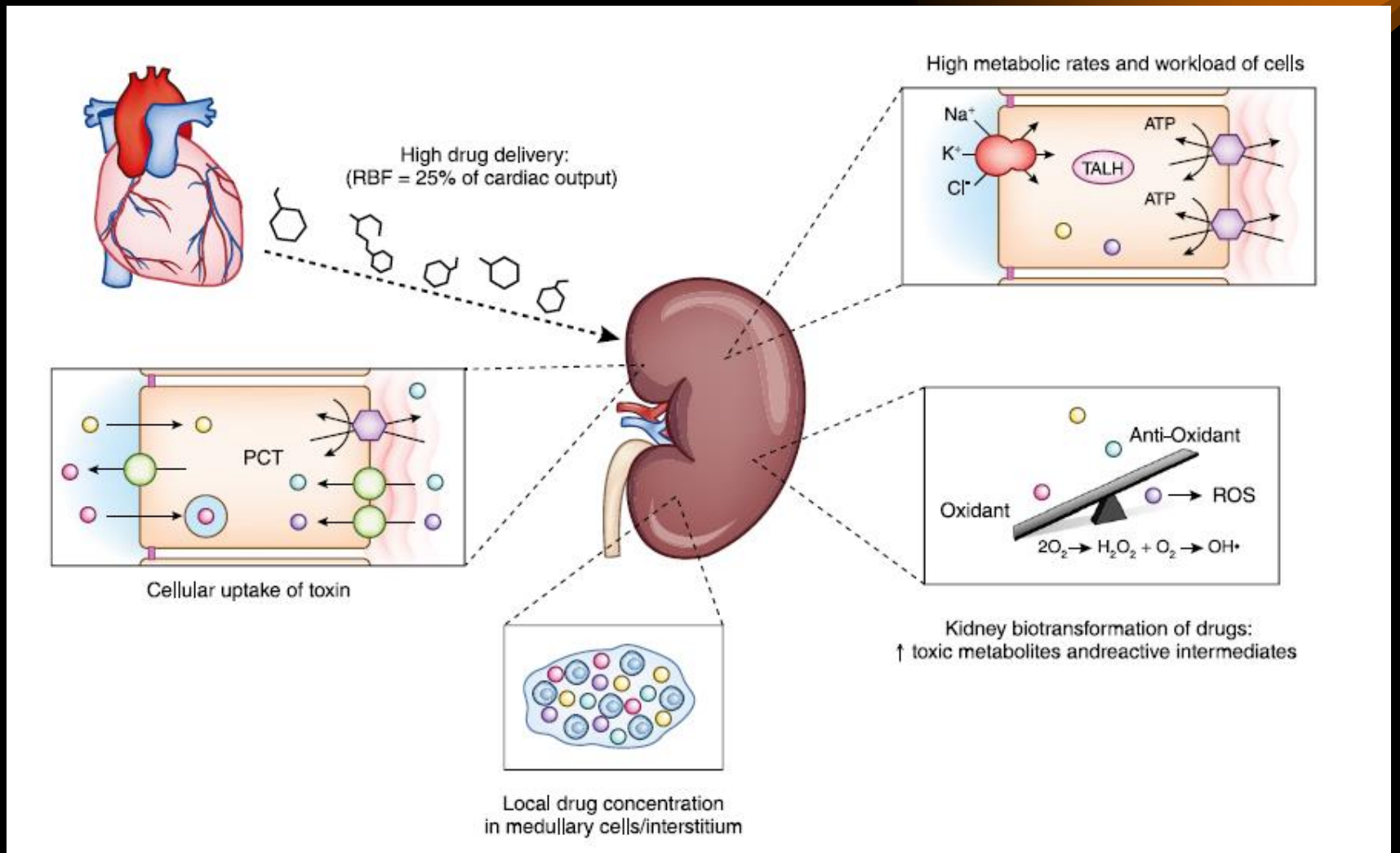



"WE HAVE MET THE ENEMY AND HE IS US."
...POGO
© 1970 WALT KELLY

Adverse Drug Reactions



The Kidney is at Increased of Nephrotoxicity Compared to other Organs



Prevalence of Drug Induced Nephrotoxicity as a Cause of Acute Kidney Injury (AKI)

16%
Pediatric AKI

20%
Adult AKI
(66% in the elderly)


Direct Tubular Injury
Impaired autoregulation
Interstitial Nephritis
Drug Nephrotoxicity
Injury to other organs leading to secondary AKI
Rhaddomyolysis / HRS
Increased Autoimmunity
Crystal Induced Obstruction

Renal Manifestations of Drug Induced Injury

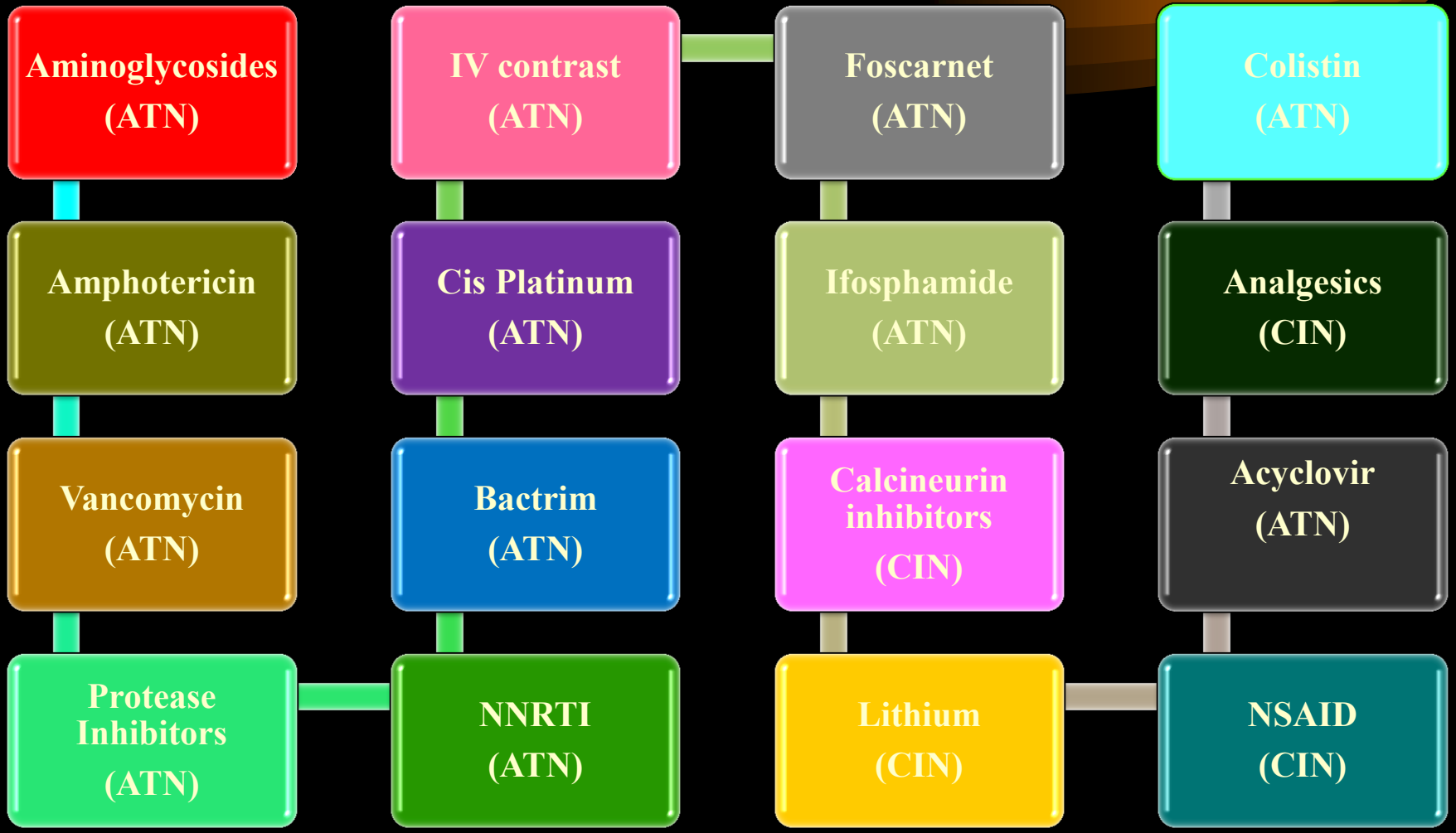
Type A ADR

- Acute or Chronic cellular injury
  - Acute Tubular Necrosis (ATN)
  - Chronic Interstitial Nephritis
- Crystal Induced Tubular Obstruction (AKI)

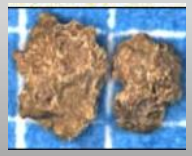
Type B ADR

- **Type I Hypersensitivity (no nephrotoxicity)**
- **Secondary renal injury due to idiosyncratic extra-renal complications**
  - **Rhabdomyolysis**
- **Type 4 Hypersensitivity**
  - **Acute Interstitial Nephritis**

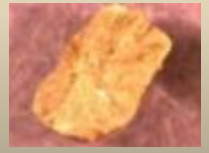
Examples of Type A Drug Nephrotoxicity



Typical Examples of Type A Drug Nephrotoxicity Crystal Induced AKI / Stones



Triamterene



Ciprofloxacin

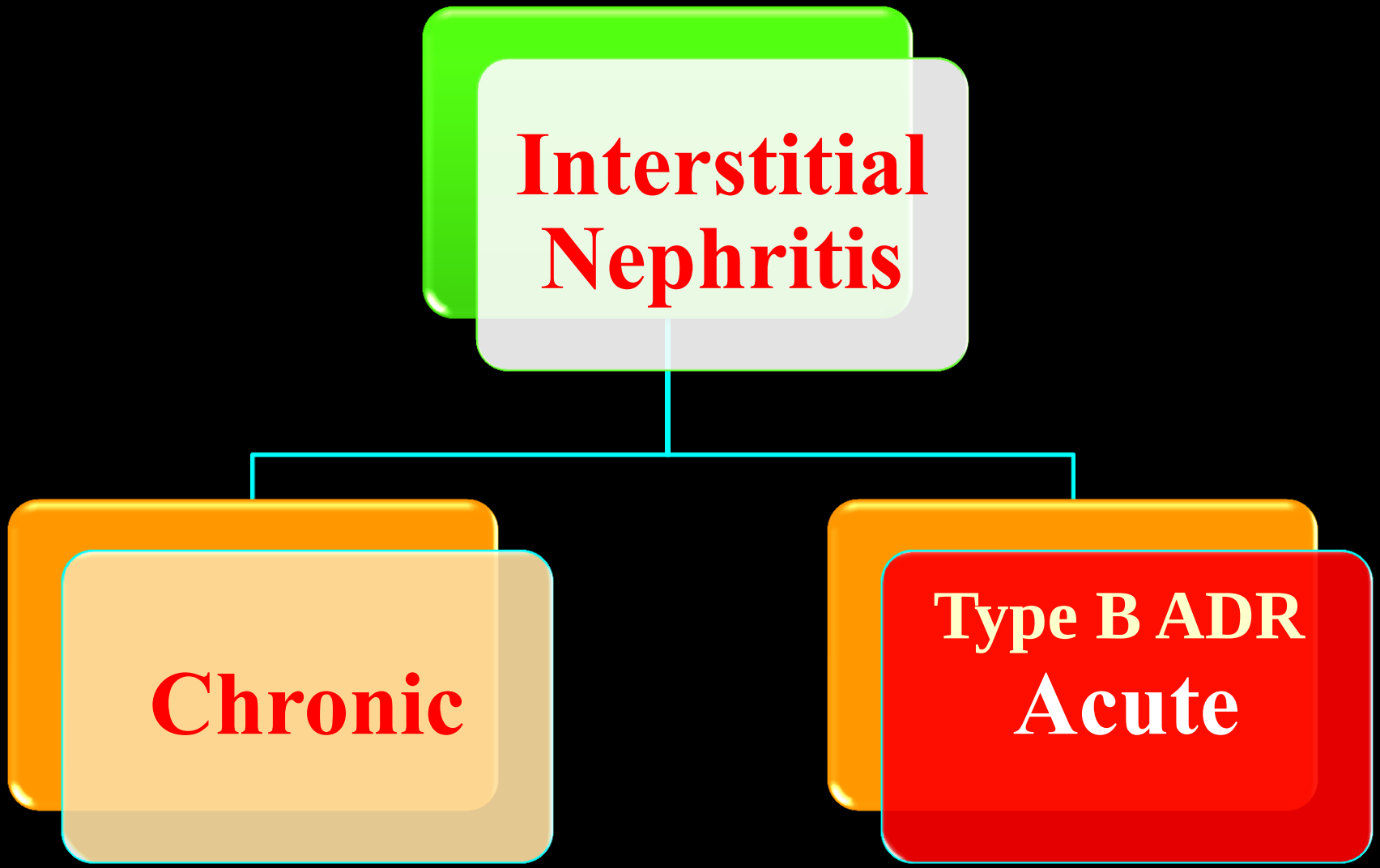
Protease Inhibitors

Allopurinol

CA Inhibitors

Guafenesin

Classification of Interstitial Nephritis



Examples of Drug Induced Nephrotoxicity

Type A

- 75 year old patient with MRSA Treated with IV Vancomycin
- Trough levels 15-20 mg/dl after 2 weeks of therapy
- Baseline creatinine 1.6 mg/dl (Stage 3 CKD secondary to Diabetes)
- Increased creatinine to 2.4 mg/dl
- Urine sediment : granular casts

Acute Tubular Necrosis ATN

Type B : Acute

- 55 year old woman started on Bactrim for a UTI
- 7 days later she developed a fever / rash and increased creatinine
- Urine sediment shows wbcs, rbcs, granular casts

Interstitial Nephritis

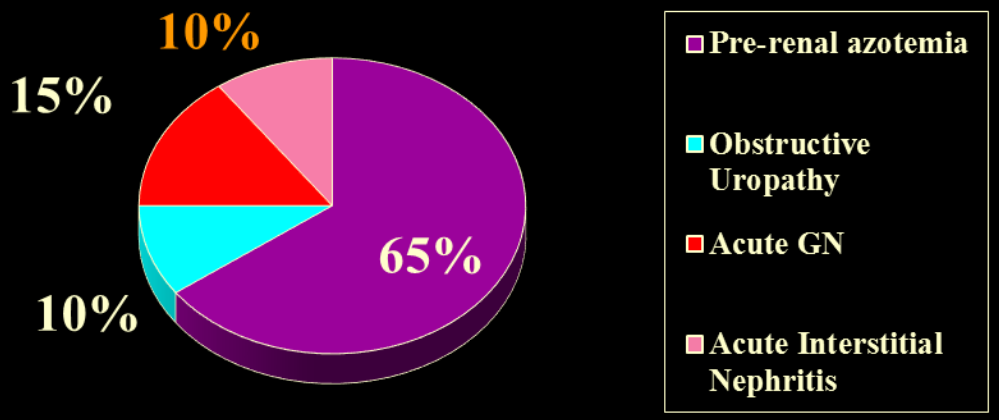
Type B : Subacute/Chronic

- 60 year old with GERD on PPI for 3 months
- Progressive rise of creatinine over weeks without any constitutional symptoms
- Urine sediment shows granular and waxy casts, wbcs, rbcs

Interstitial Nephritis

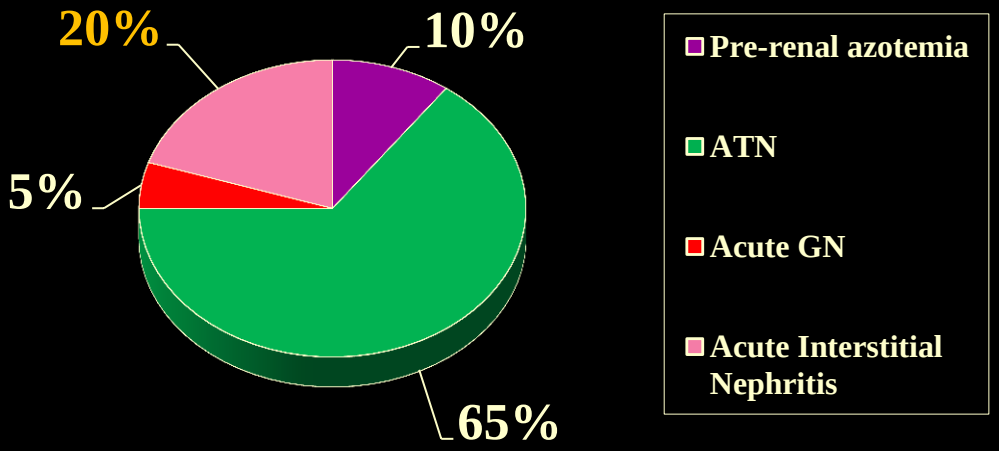
Etiology of AKI Differs by Location

Outpatient

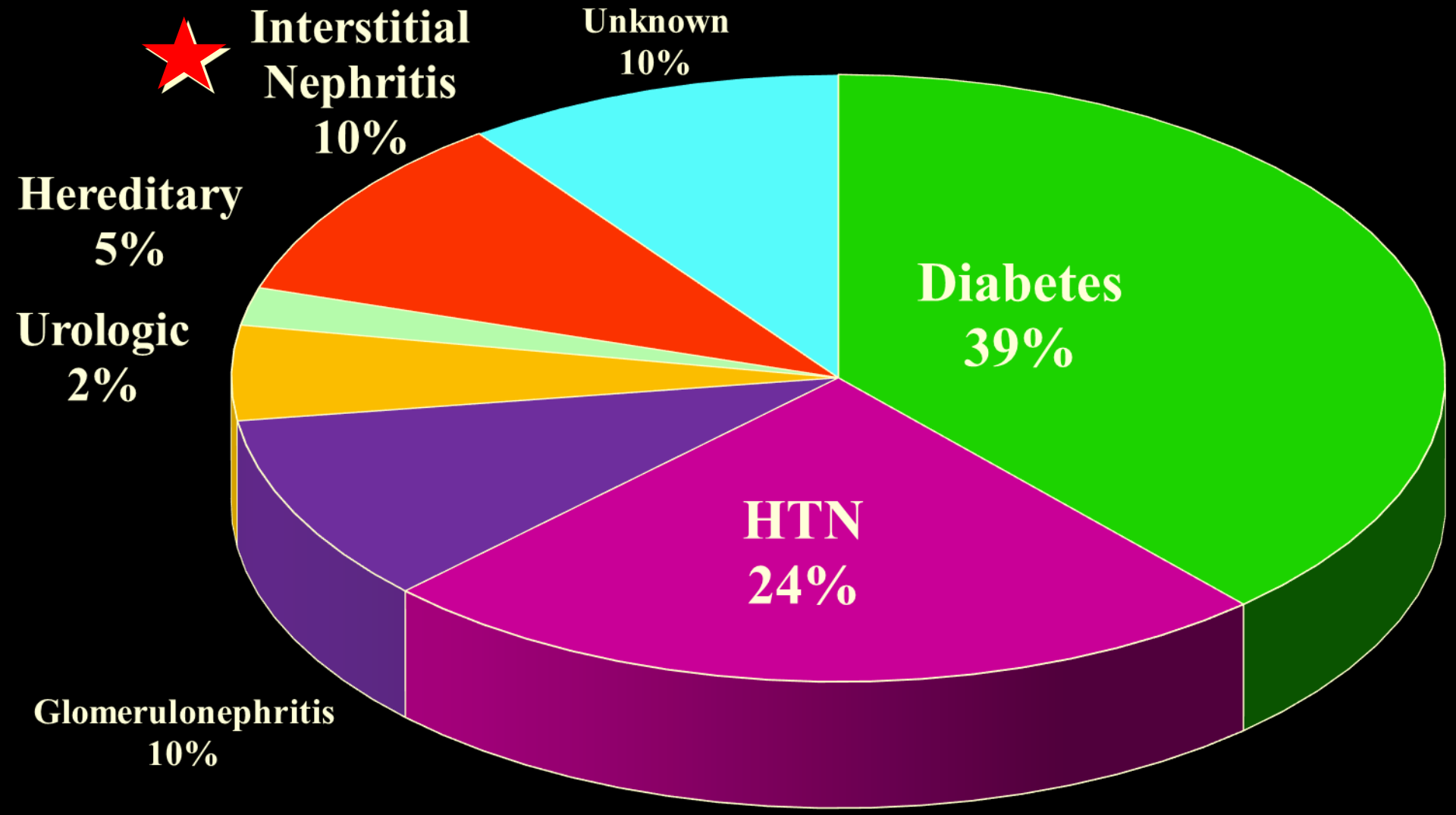


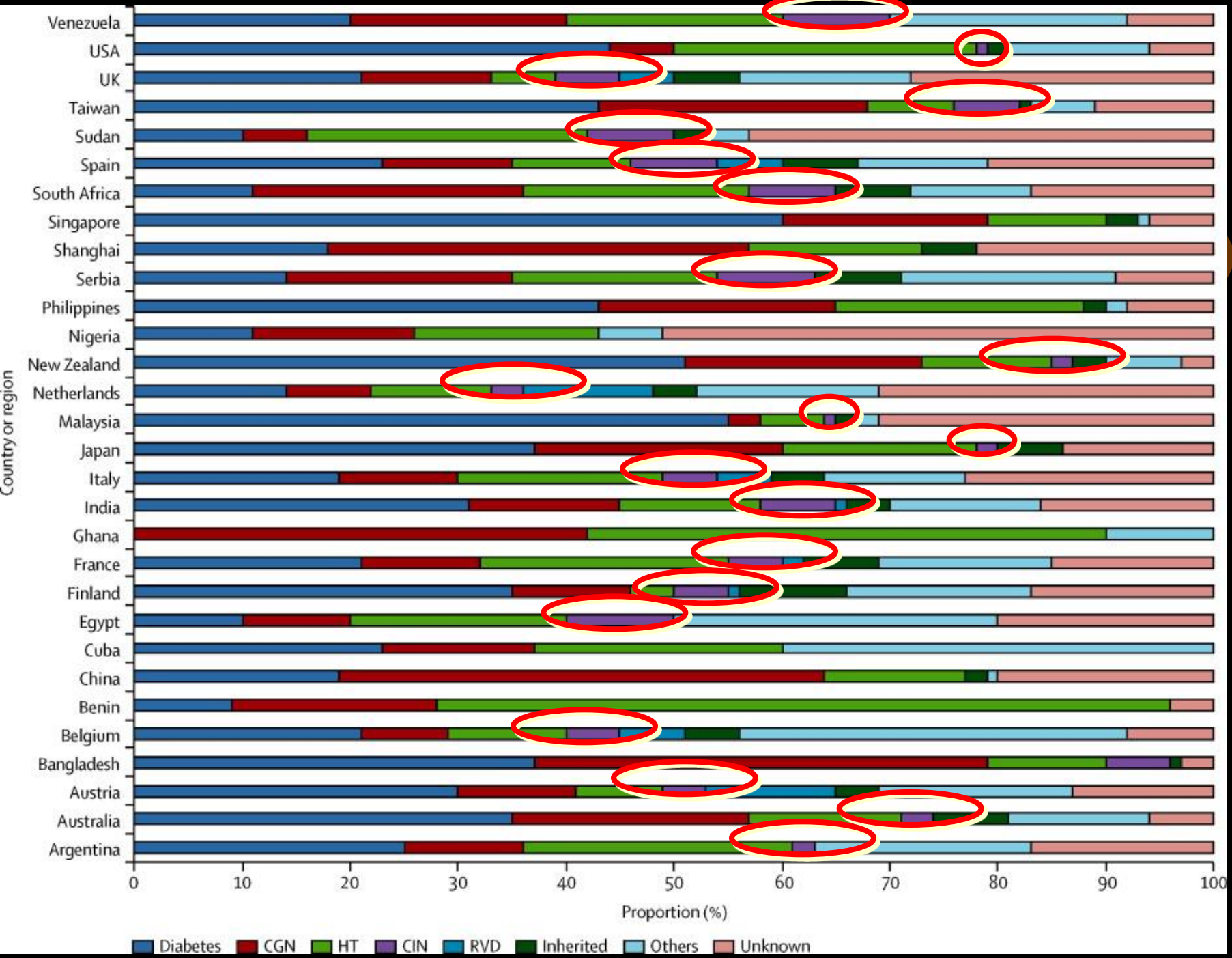
33,000 cases Annually

Inpatient



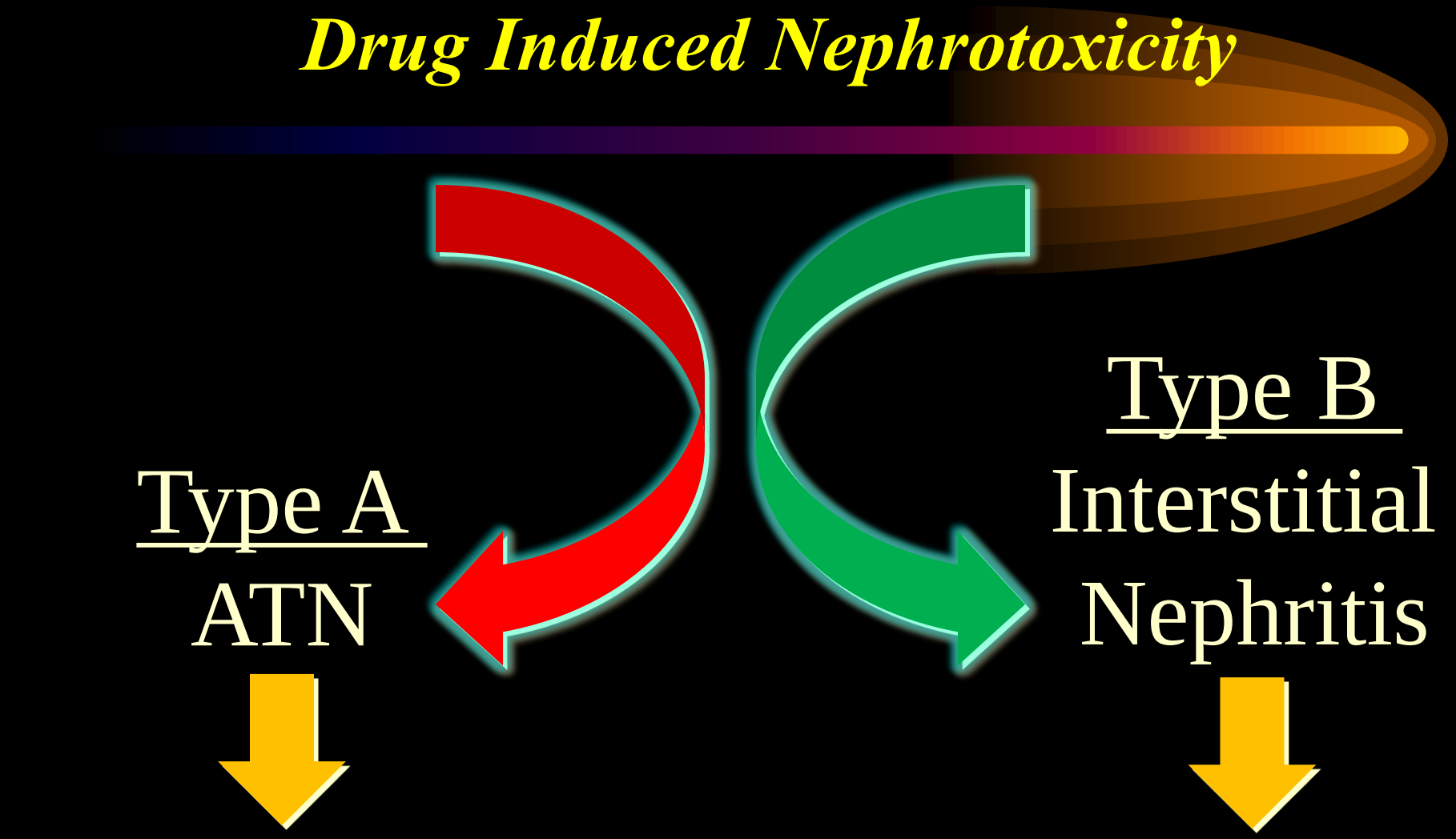
CKD in the U.S.
(23 million Patients)





Jha V, Garcia-Garcia G, Iseki K. Chronic kidney disease: global dimension and perspectives. Lancet 2013; 382:260–272.

Key Differential Diagnosis in Drug Induced Nephrotoxicity



Etiology of Chronic Interstitial Nephritis

Acute Interstitial Nephritis (AIN)

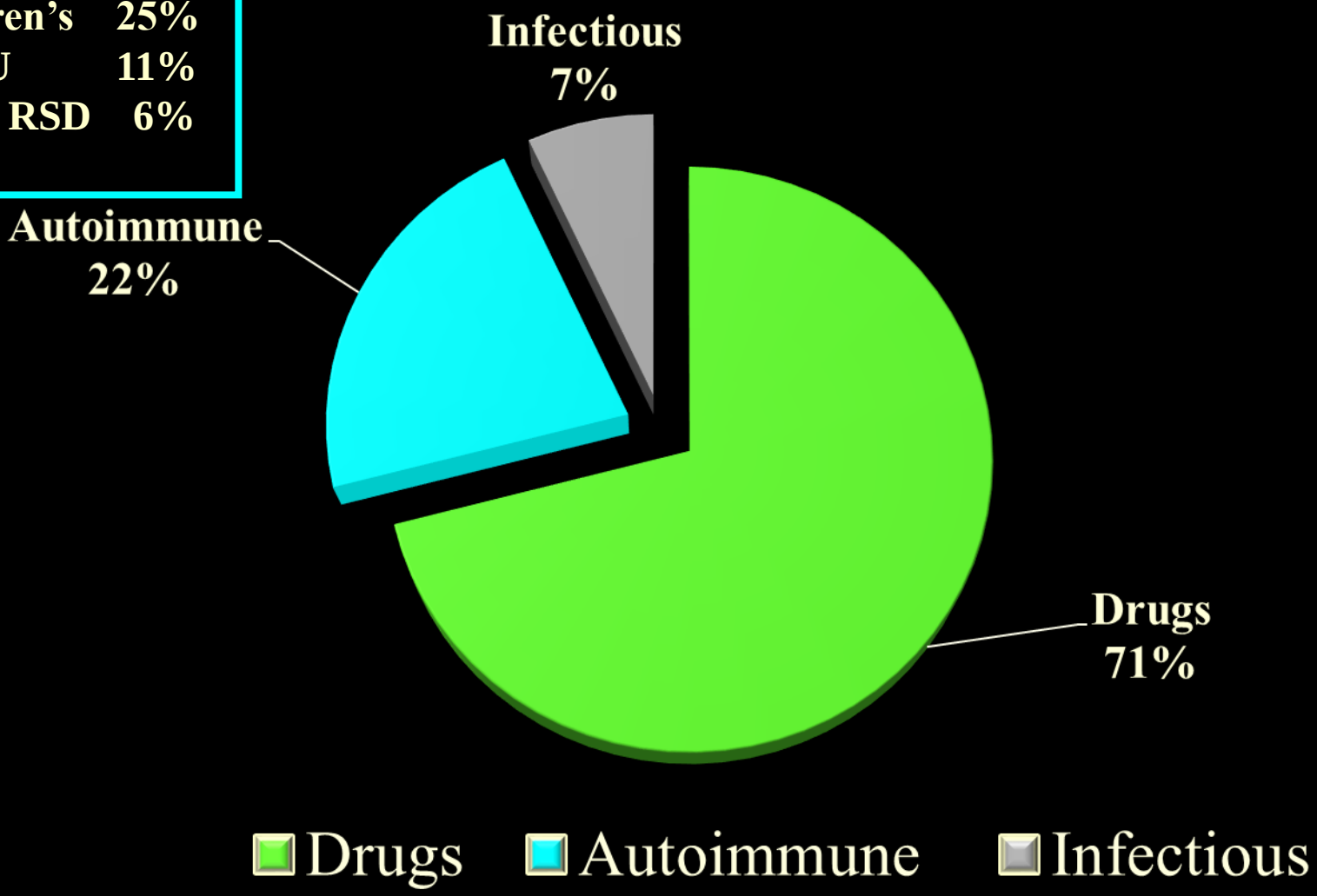
Inadequately Treated

Chronic Interstitial Nephritis (CIN) – CKD and ESRD

Muriithi AK . Am J Kidney Dis. 2014 Jun 11

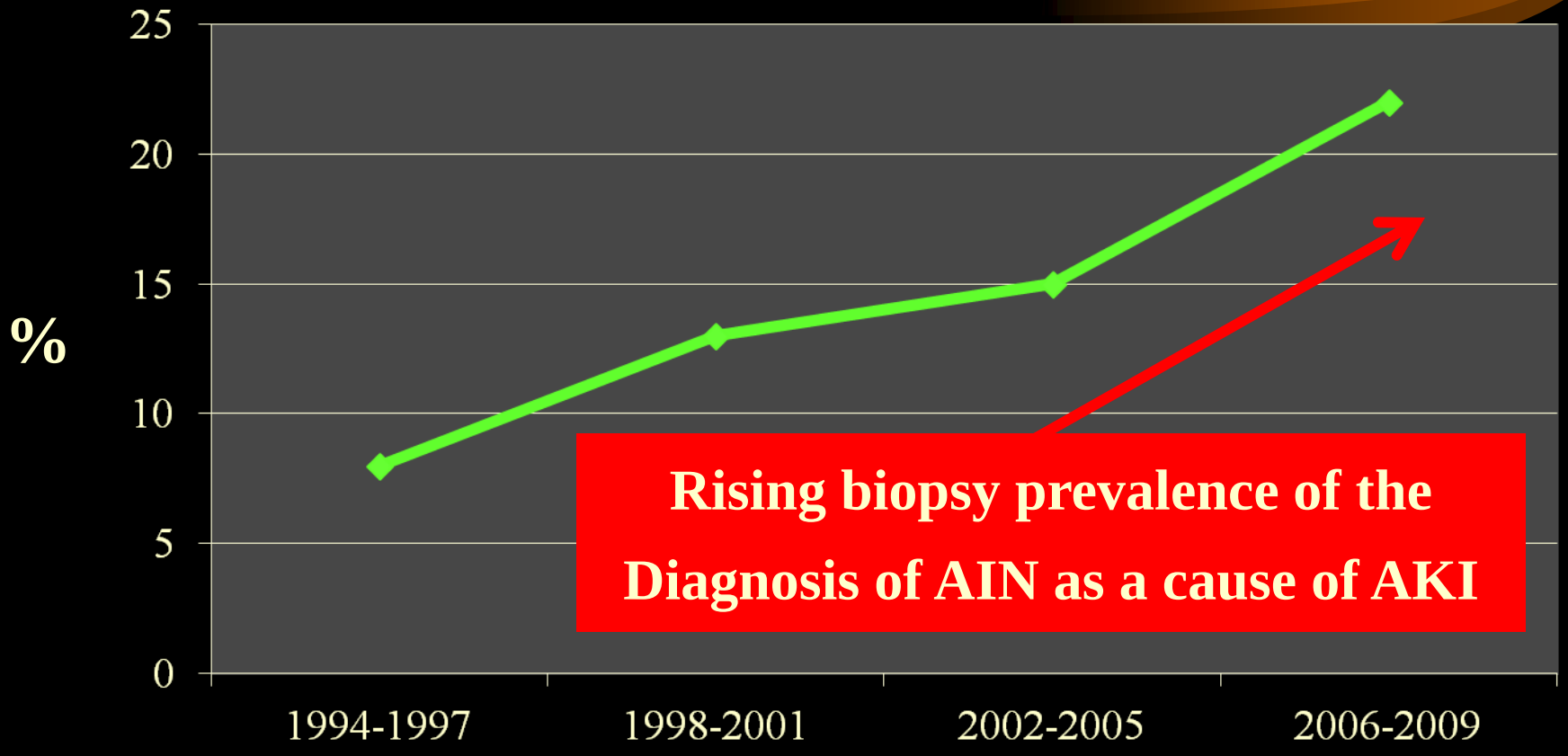
AIN Experience – 1998-2013

Sarcoid	50%
Sjogren's	25%
TINU	11%
IgG4 RSD	6%

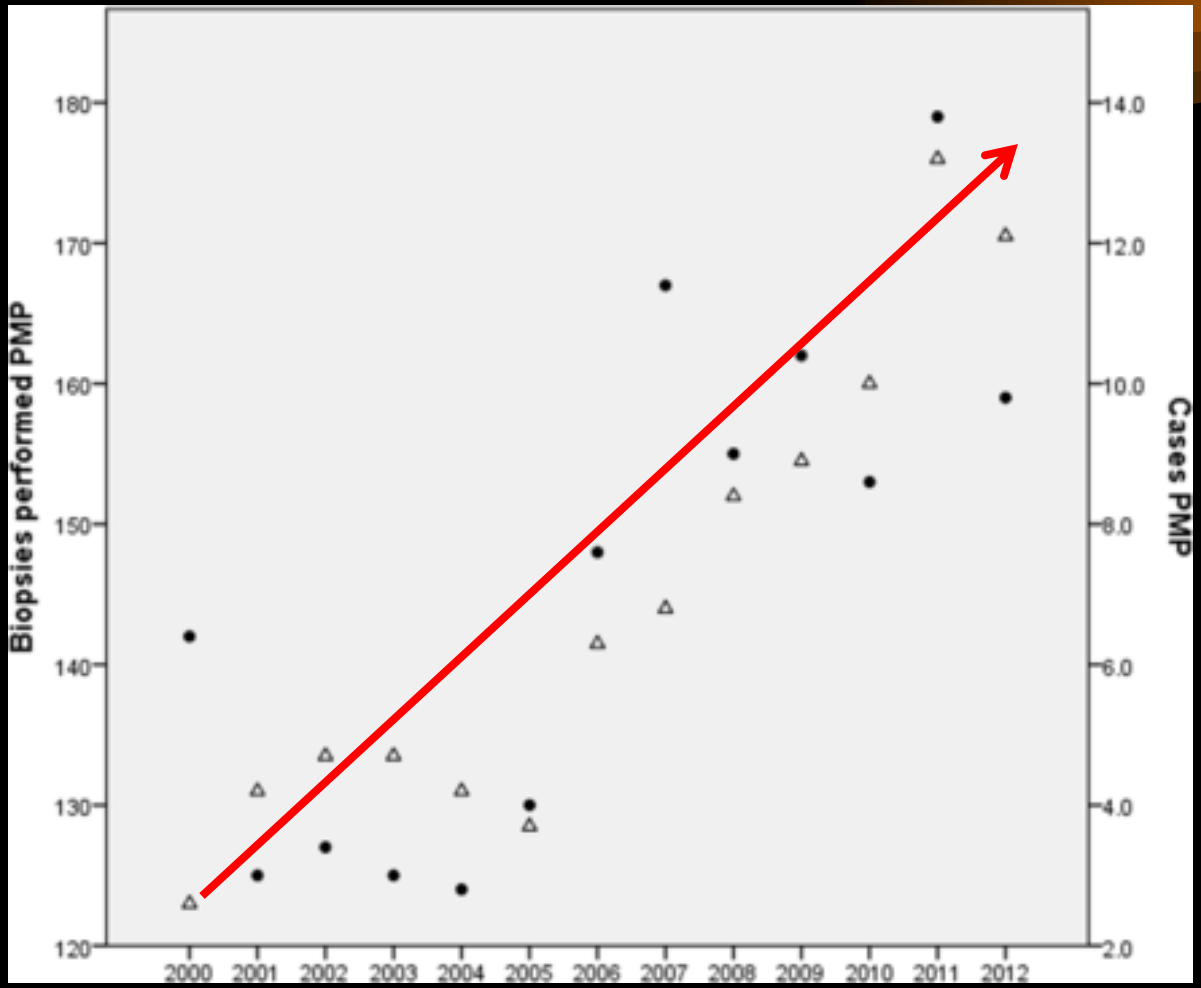


Goicoechea M.Nephrol Dial Transplant (2013) 28: 112–115

Increasing Prevalence of Interstitial Nephritis in Patients with AKI

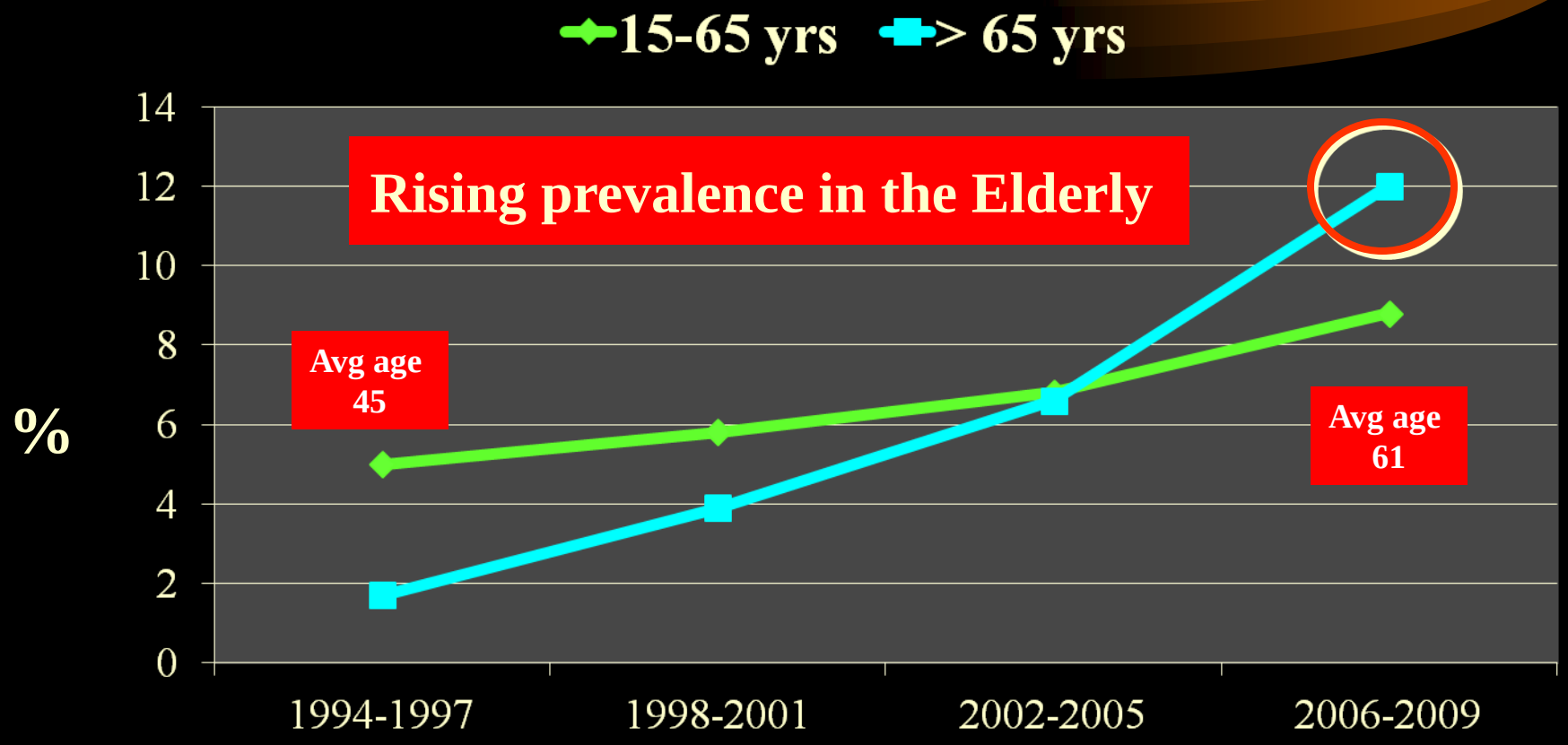


Increasing Incidence of AIN - UK

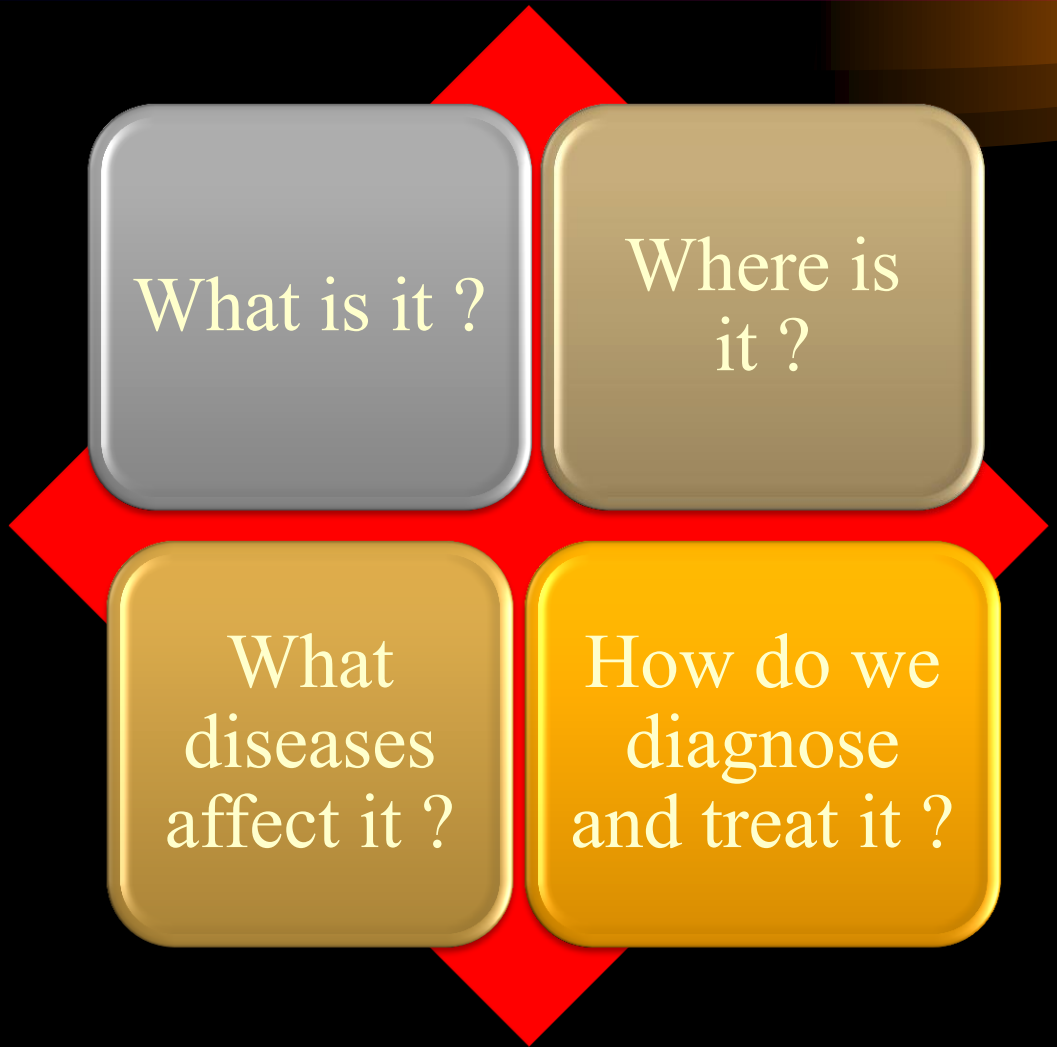


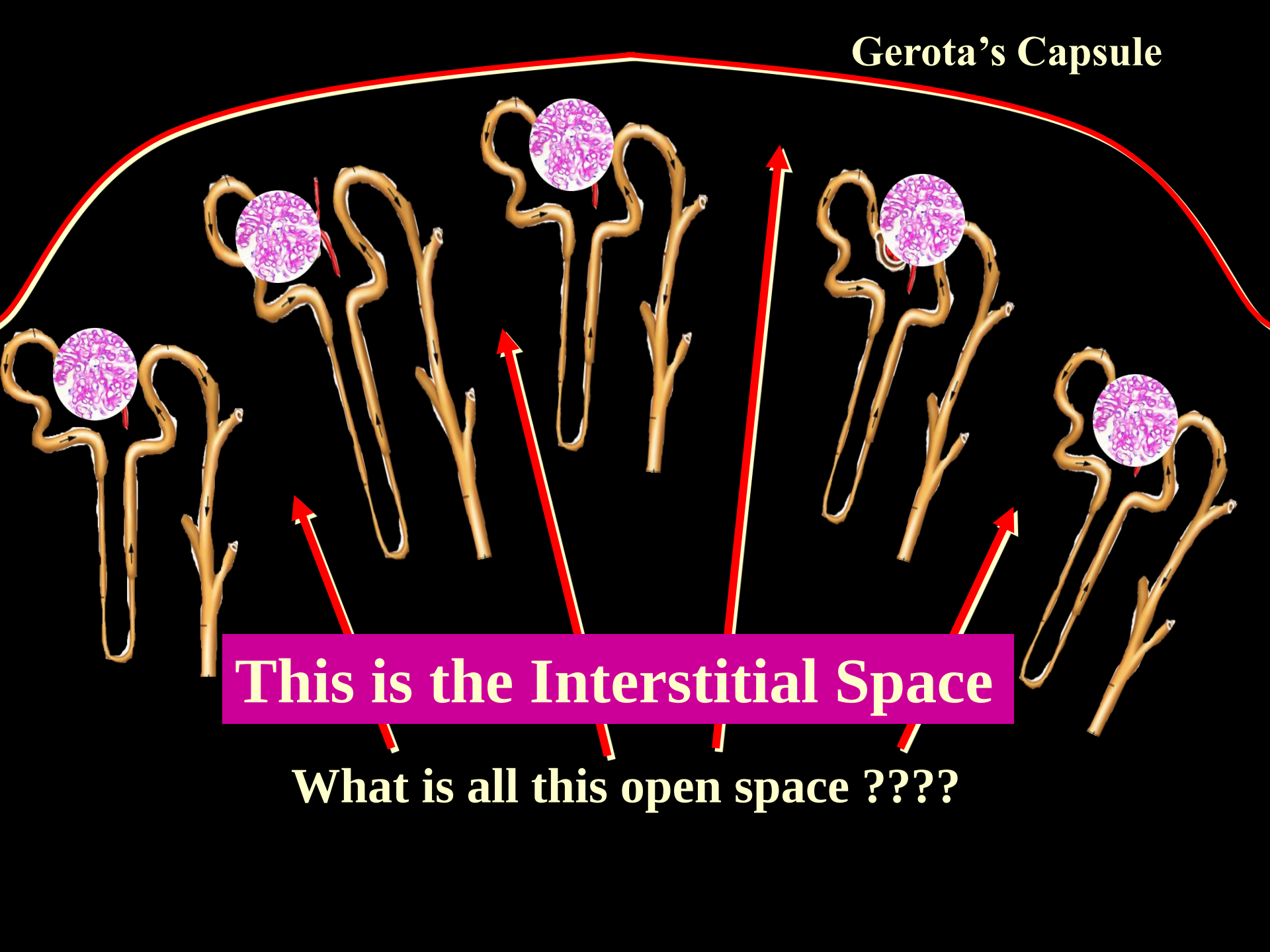
Goicoechea M.Nephrol Dial Transplant (2013) 28: 112–115

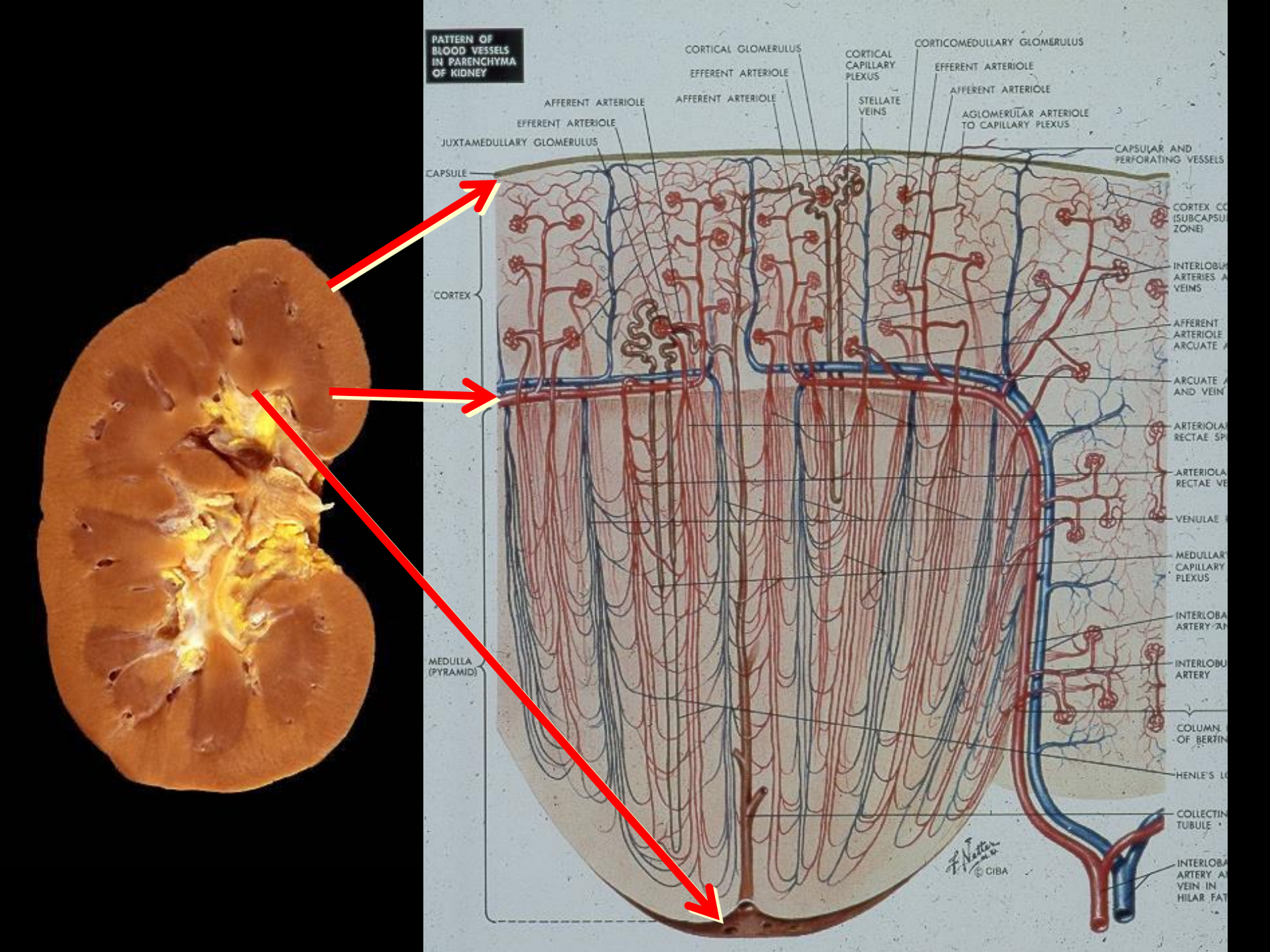
Increasing Prevalence of Interstitial Nephritis in all Kidney Biopsies



The Renal Interstitium

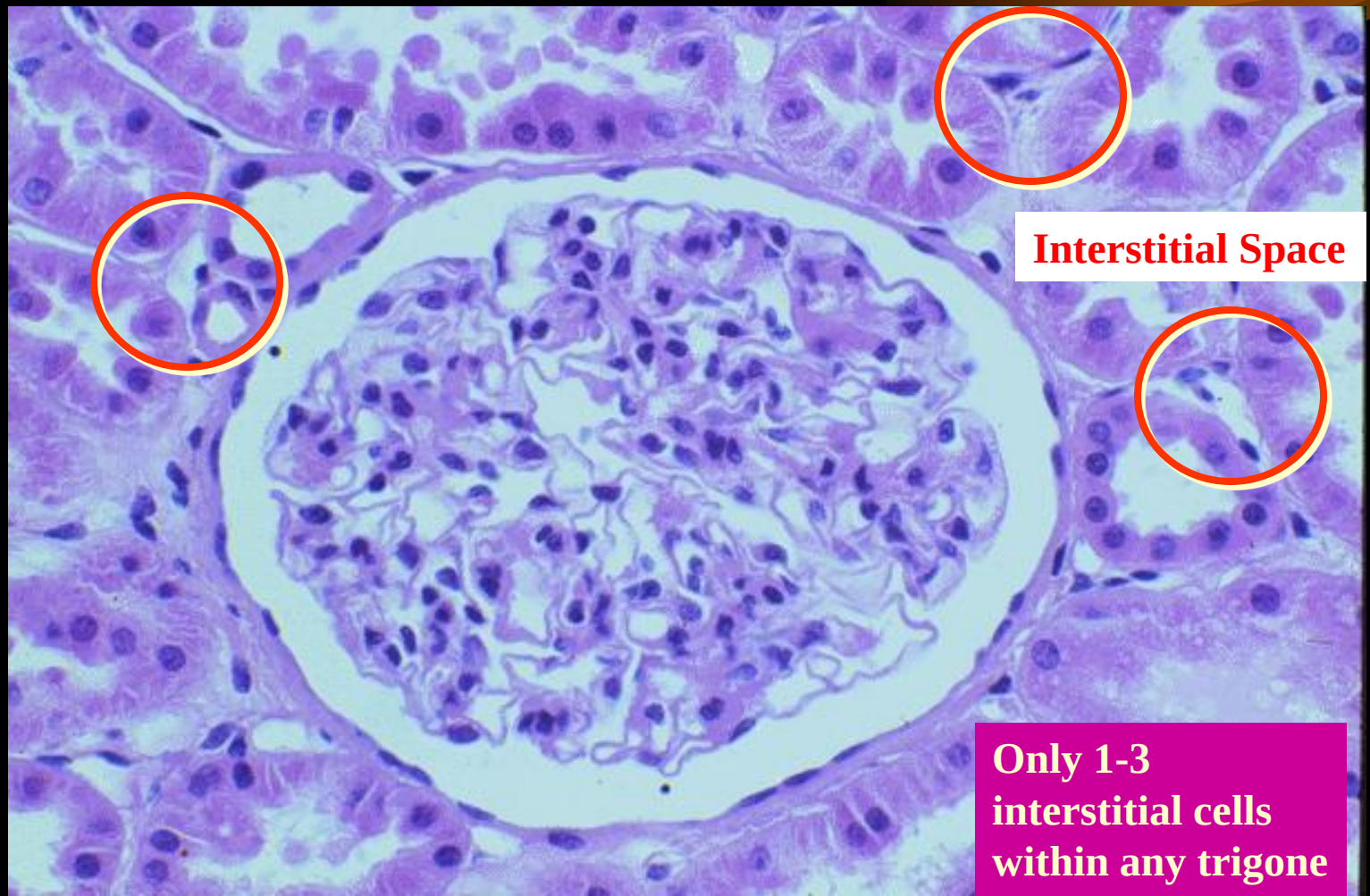



Gerota's Capsule
This is the Interstitial Space
What is all this open space ????


PATTERN OF BLOOD VESSELS IN PARENCHYMA OF KIDNEY
CORTICAL GLOMERULUS
EFFERENT ARTERIOLE
AFFERENT ARTERIOLE
CORTICAL CAPILLARY PLEXUS
CORTICOMEDULLARY GLOMERULUS
EFFERENT ARTERIOLE
AFFERENT ARTERIOLE
STELLATE VEINS
AGLOMERULAR ARTERIOLE TO CAPILLARY PLEXUS
AFFERENT ARTERIOLE
EFFERENT ARTERIOLE
JUXTAMEDULLARY GLOMERULUS
CAPSULE
CAPSULAR AND PERFORATING VESSELS
CORTEX
MEDULLA (PYRAMID)
VENULAE
HENLE'S
© CIBA

Normal Glomerulus and Tubules :

“Back to Back “ Tubular Arrangement



The Interstitium

Functional Characteristics

- **Structural support of the**
  - **Tubules**
  - **Vasculature**
- **Conduit for solute and oxygen transfer**
- **Production of cytokines**
- **Hormone production**
  - **Prostaglandins (medulla)**
  - **1-OH Hydroxylation of Vitamin D (proximal tubule)**
  - **Erythropoietin – cells around the peritubular capillaries**
  - **Renin**

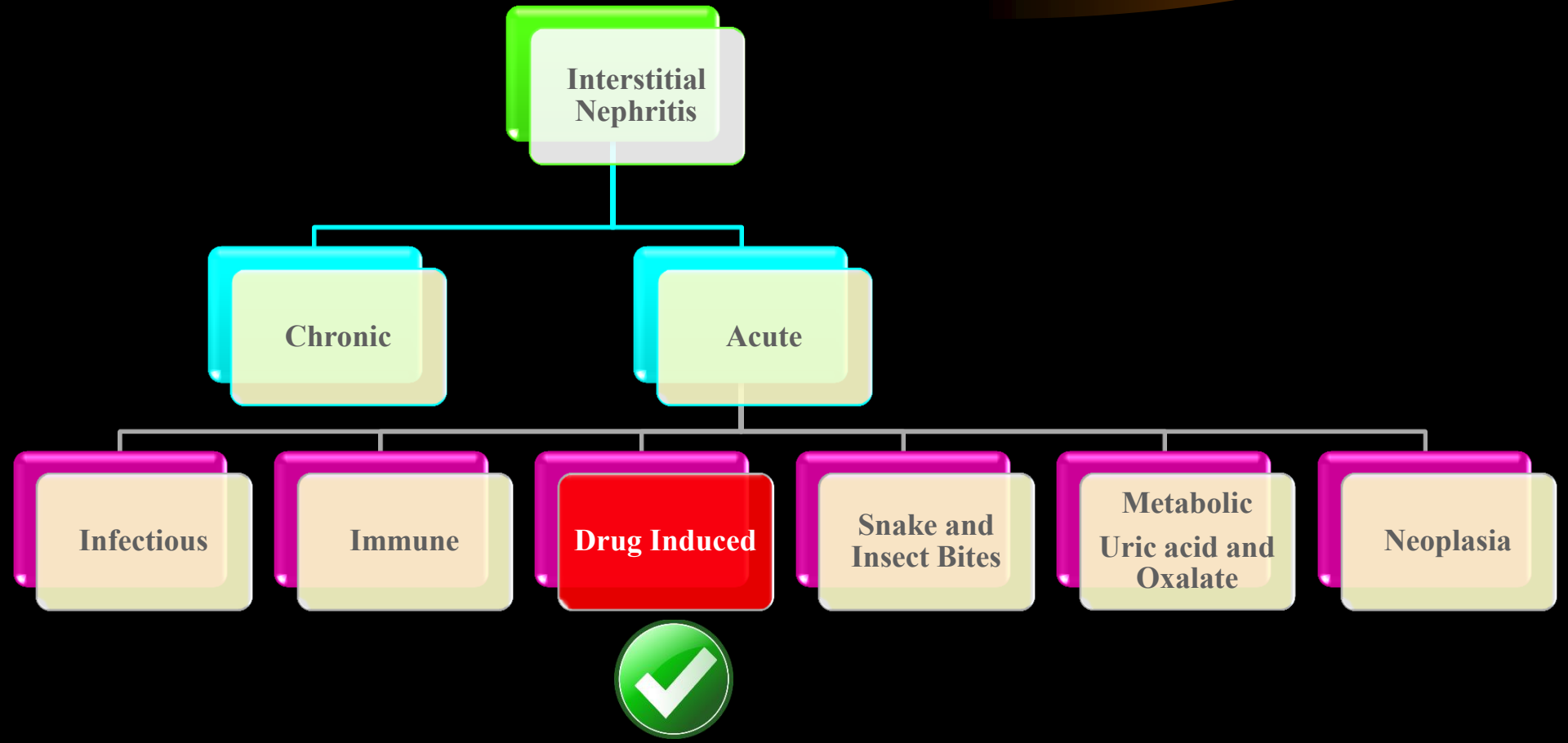
Caveat :
Tubular disorders are more likely associated with a higher risk of osteomalacia and anemia compared to Glomerular diseases for any given degree of renal dysfunction

The Interstitium

Renal Interstitial Cells

- **Cortex**
  - **Fibroblasts (Type I)**
    - **Fibronectin, Collagen I,III,VI , Proteoglycans**
    - **EPO production (peritubular capillary fibroblasts)**
  - **Mononuclear cells (MHC class II) - Myeloid origin / Dendritic**
- **Medulla**
  - **Fibroblasts**
  - **Mononuclear cells (MHC class II)**
  - **Pericytes**
  - **Lipid-laden cells (PG production)**
  - **Pluripotent stem cells (?)**

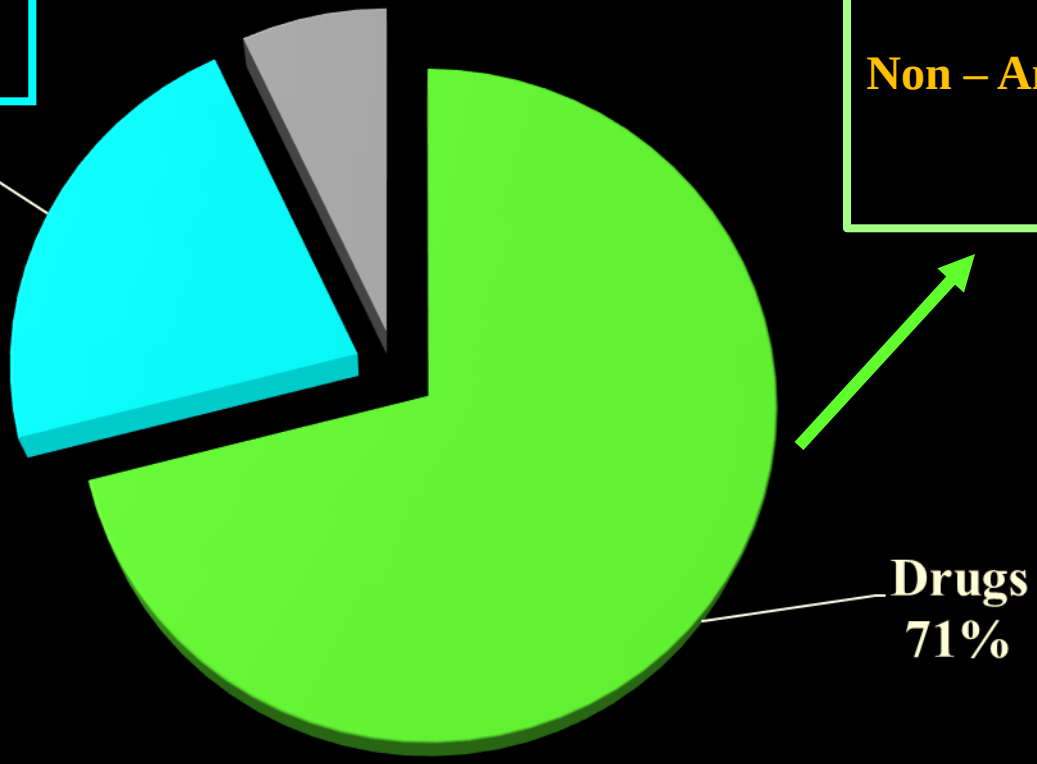
Classification of Interstitial Nephritis



Muriithi AK . Am J Kidney Dis. 2014 Jun 11

AIN Experience – 1998-2013

Sarcoid	50%
Sjogren's	25%
TINU	11%
IgG4 RSD	6%



Antibiotics	50%
Non – Antibiotics	50%
PPI	27%
NSAIDS	21%

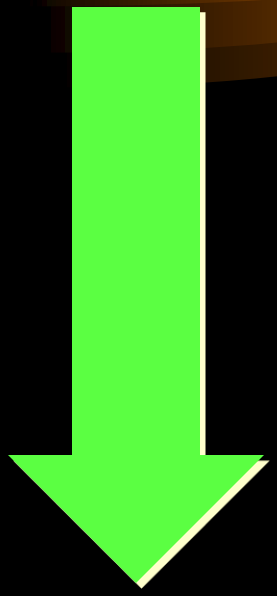
Acute Interstitial Nephritis
Common Drugs

- PPI – all classes of proton pump inhibitors
- NSAIDs
  - Both COX-1 and COX-2 inhibitors
- Allopurinol
- Ampicillin / PCN
- Cephalosporin
- Rifampin
- Sulfonamides
  - Furosemide
  - Bumetanide
  - Trimethoprim-Sulfamethoxazole
- Ciprofloxacin

Non-Abx Drugs

If you are sulfa allergic you may need to avoid all loop diuretics except Ethacrynic acid

Pathogenesis of Acute Interstitial Nephritis



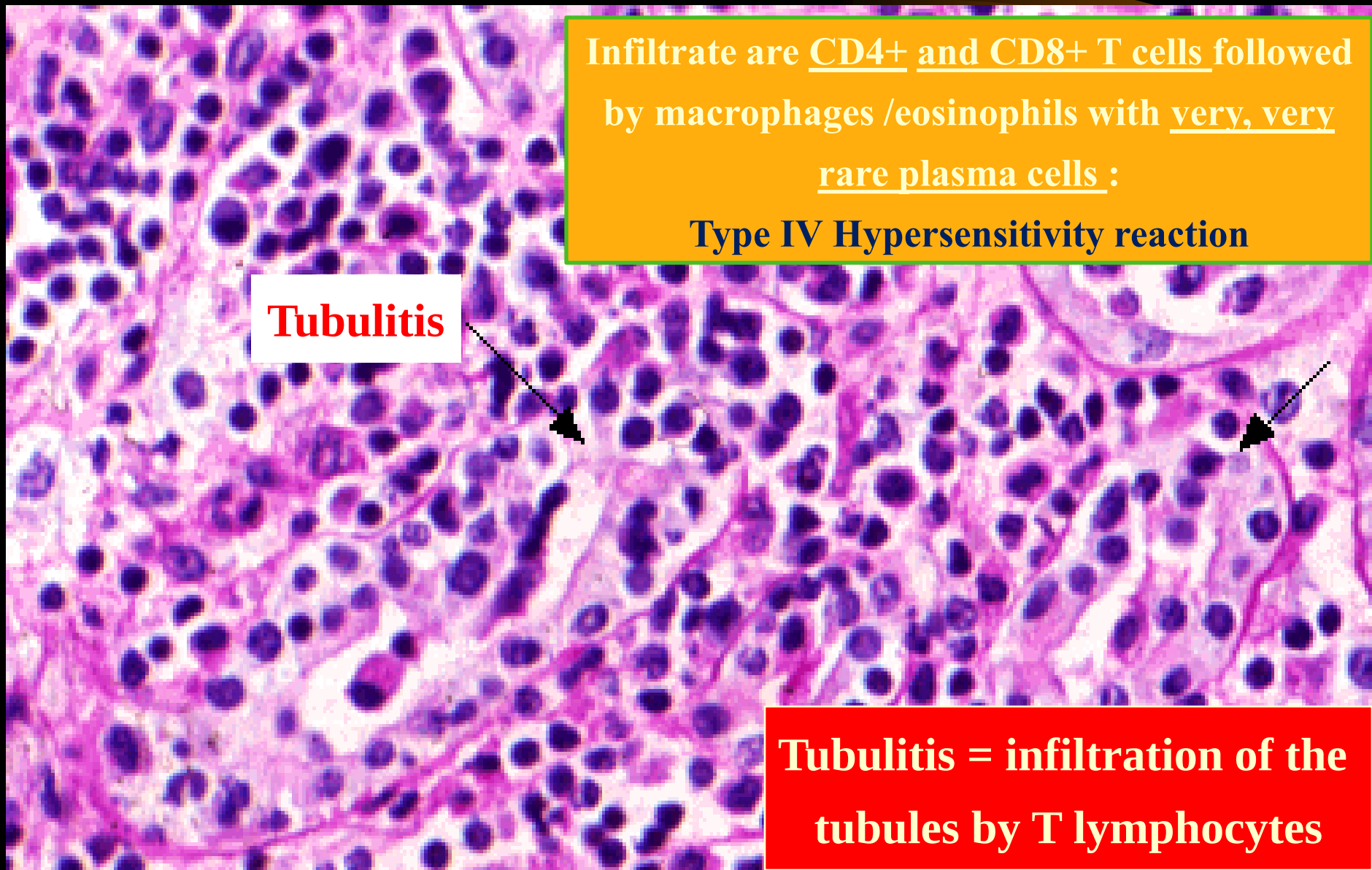
Type I Hypersensitivity Reaction
Immediate (minutes)
IgE
Systemic Vasoactive Mediators
Anaphylaxis

Type IV Hypersensitivity Reaction
Delayed (days-months)
Cell Mediated : T cells

Drug Induced Acute Allergic Interstitial Nephritis

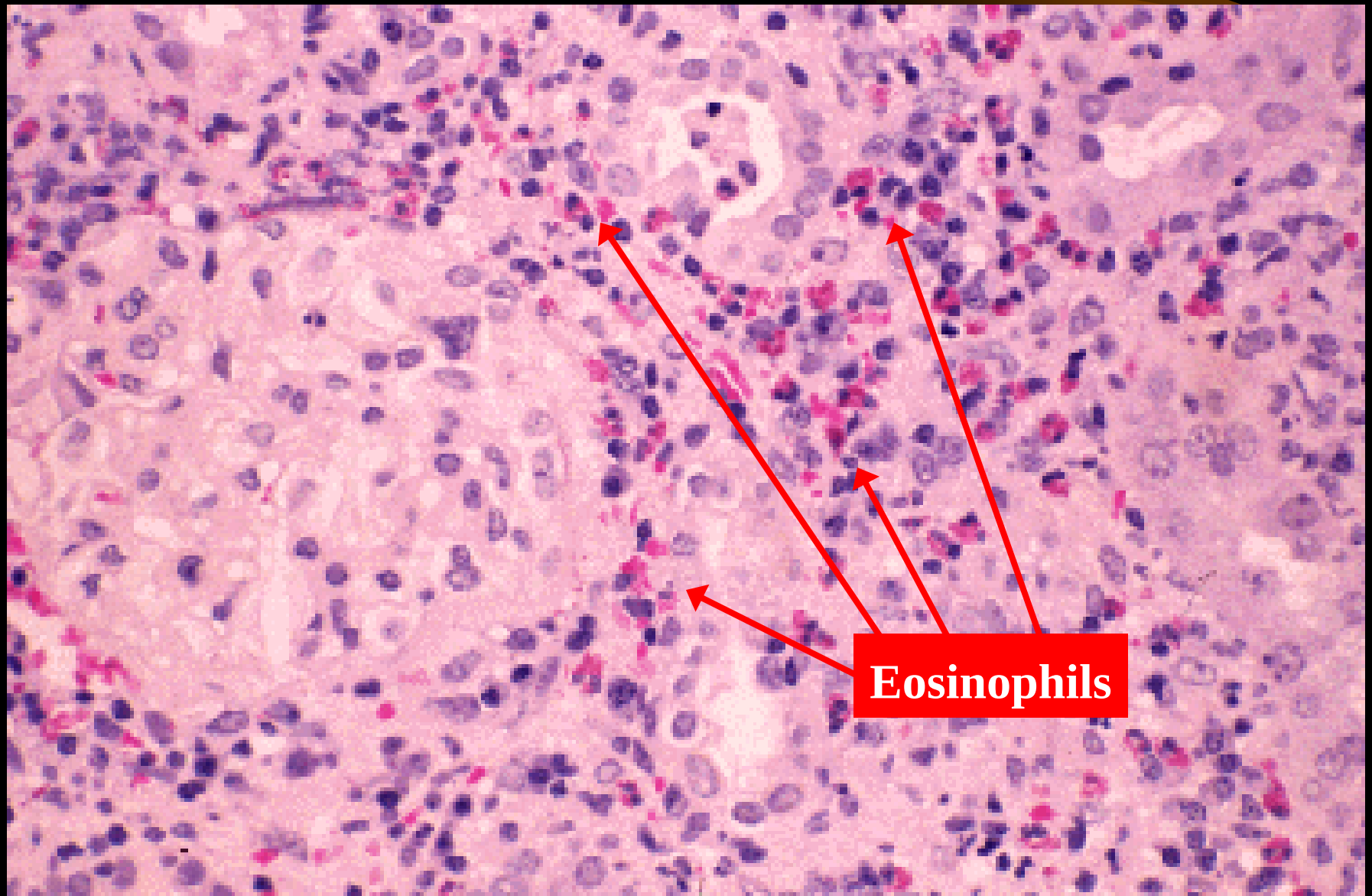
- Characterized by predominant involvement of the renal interstitial compartment by
  - Interstitial edema
  - Interstitial cellular infiltrate
    - T lymphocytes (70%- both CD4 and CD8)
    - Monocytes (15%)
    - Eosinophils (variable based on drug compound)
    - B cells (7%)
    - Neutrophils
    - Granuloma formation

Acute Interstitial Nephritis = ATN + Cellular Infiltrate

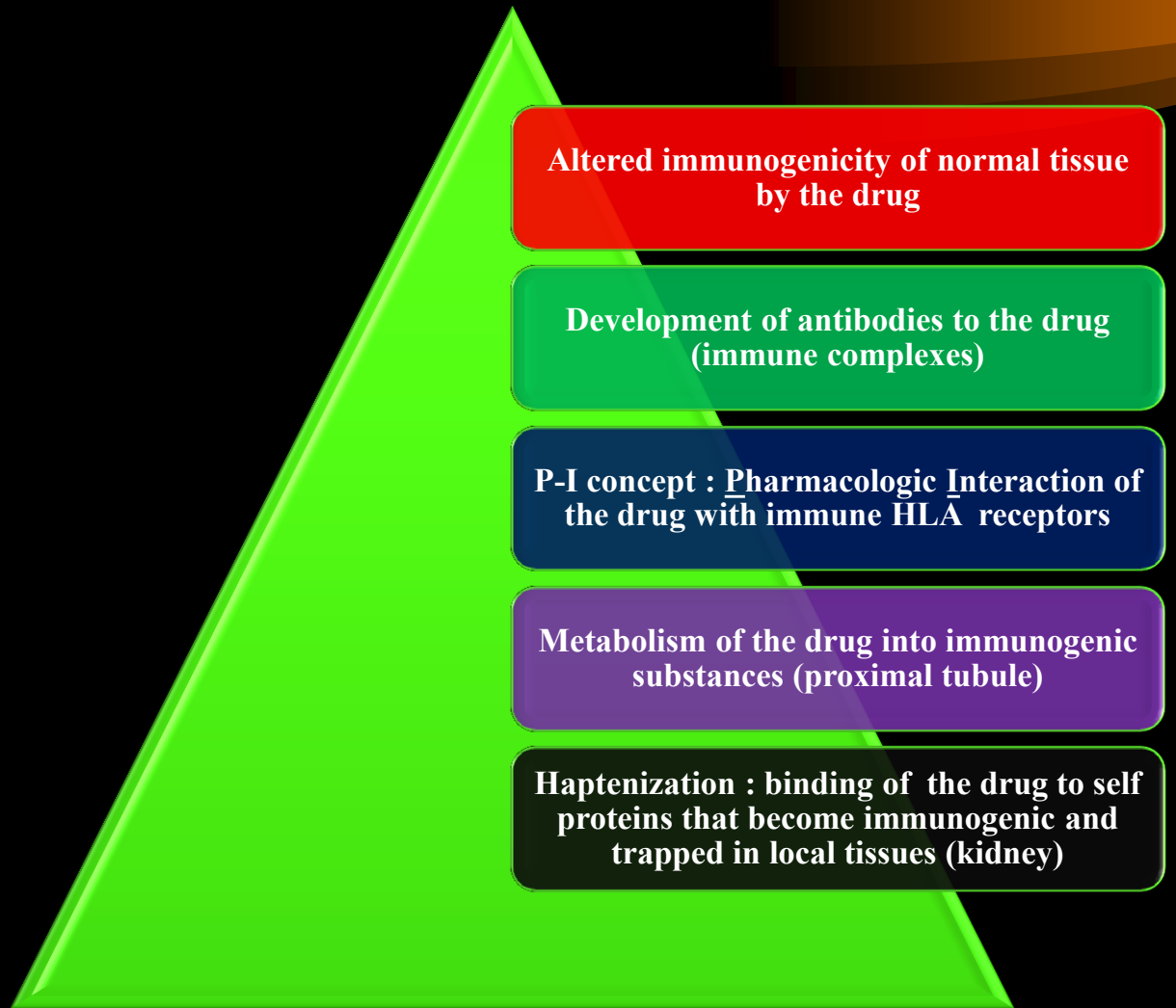


Acute Interstitial Nephritis

Tissue Eosinophils

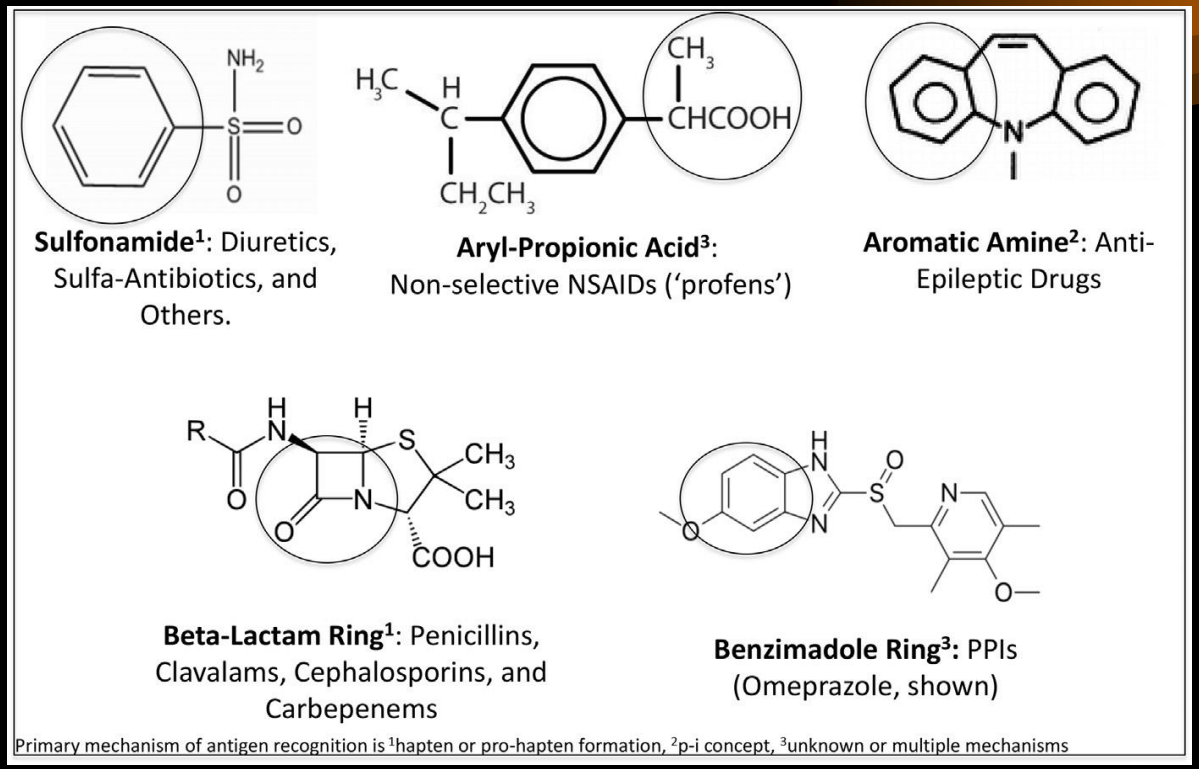


Adverse Drug Reaction (ADR) : Drug Hypersensitivity Reaction (DHR)



Raghavan R. Adv Chronic Kidney Dis. 2017;24(2):64-71

Drug Induced AIN : Structure Matters !



Sulfonamide[1]: Diuretics, Sulfa-Antibiotics, and Others.

Aryl-Propionic Acid[3]: Non-selective NSAIDs ('profens')

Aromatic Amine[2]: Anti-Epileptic Drugs

Beta-Lactam Ring[1]: Penicillins, Clavalams, Cephalosporins, and Carbepenems

Benzimadole Ring[3]: PPIs (Omeprazole, shown)

Primary mechanism of antigen recognition is [1]hapten or pro-hapten formation, [2]p-i concept, [3]unknown or multiple mechanisms

- **All drugs that share a common "backbone"**
- **or "core structure" elicit the same risk of AIN**

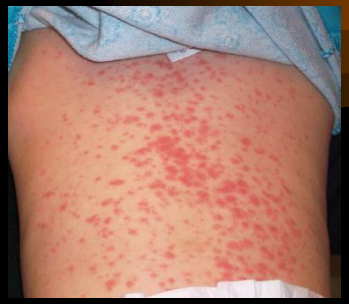
Acute Allergic Interstitial Nephritis

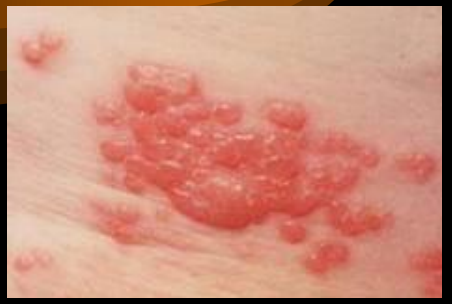
- Acute rise in creatinine temporally related to an offending drug
  - 5 - 7 Days to months
- Constellation of clinical findings include :
  - Fever (20%)
  - Rash (30%)
  - Eosinophilia (30%)

  } Present together in < 10%
  - Eosinophiluria
  - Non-nephrotic range proteinuria
    - < 2 gm
  - Combination of Type I, Type II and Type IV RTA
- Back (flank) pain secondary to distention of the renal capsule from cell infiltration and swelling – 30%

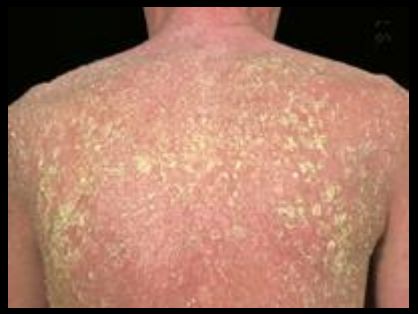
Types of Skin Rash seen in AIN

- **Maculopapular / Morbilliform**

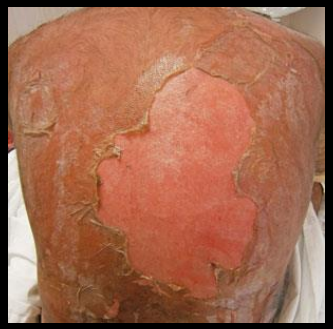




- **Diffuse Erythroderma (Exfoliative Dermatitis)**

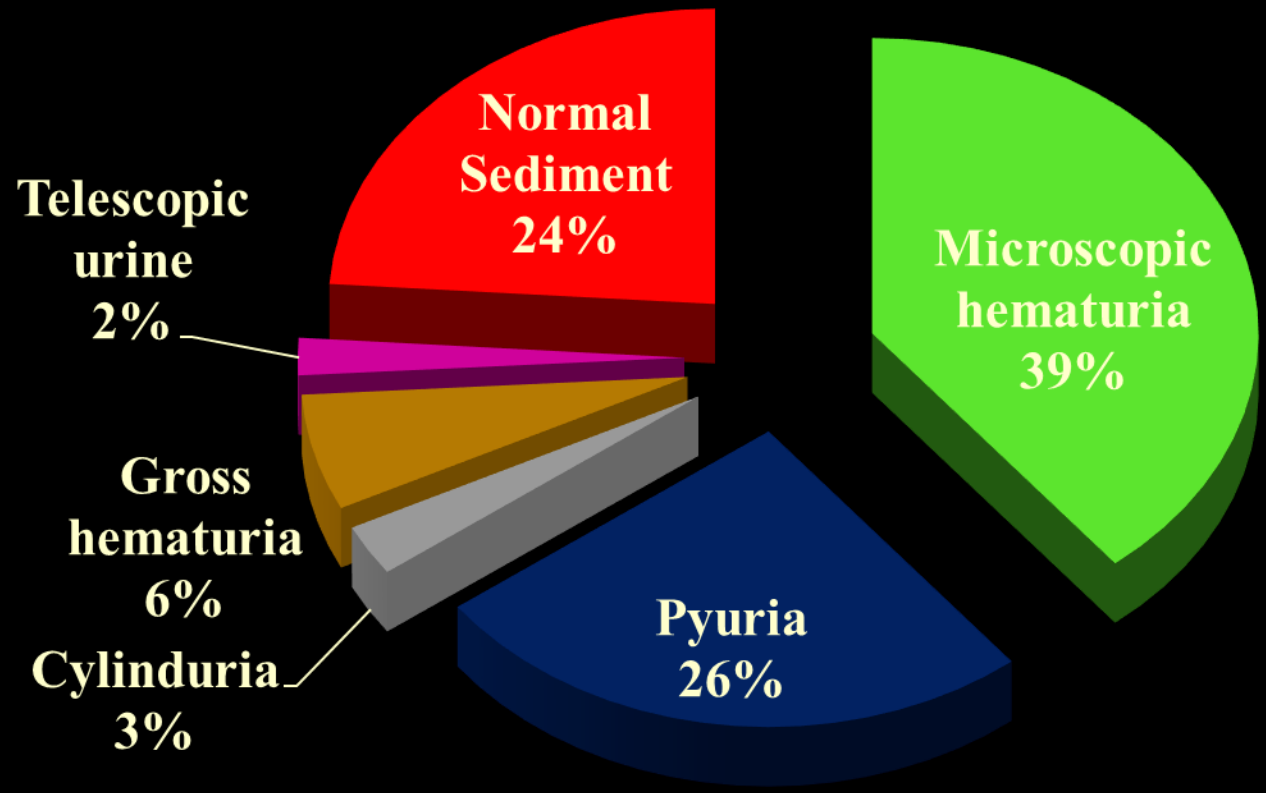


- **Toxic Epidermal Necrolysis**

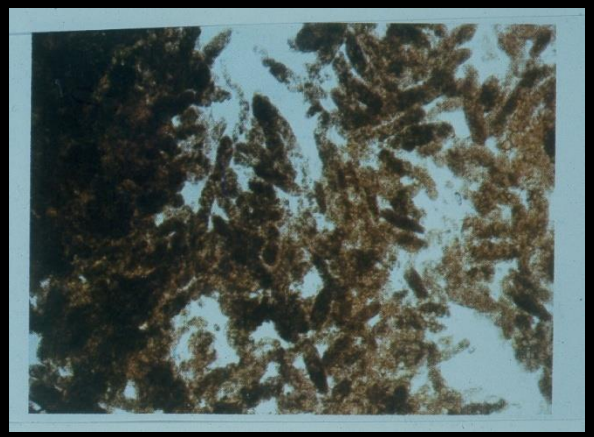


Goicoechea M.Nephrol Dial Transplant (2013) 28: 112–115

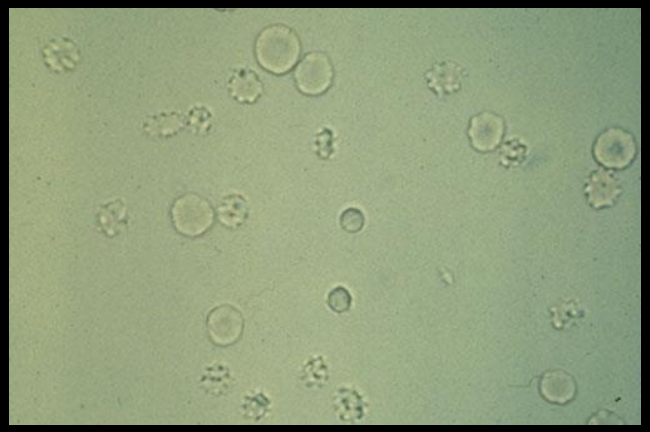
Urinalysis in AIN



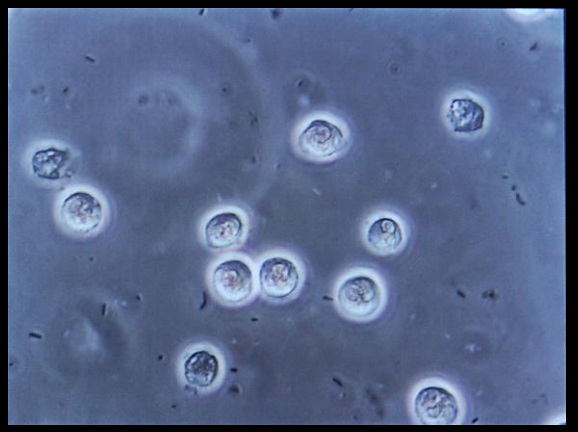
Urinalysis in AIN = Tubulo-Interstitial Nephritis (ATN + Inflammation)



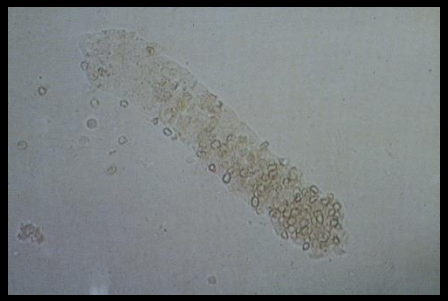
Granular Casts



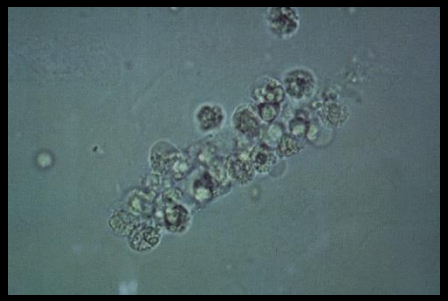
RBCs including Dysmorphic RBCs



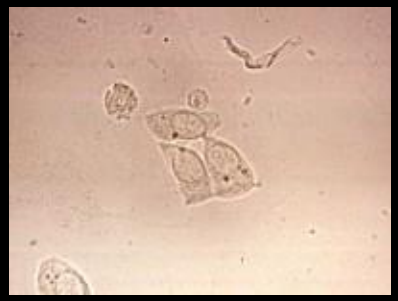
WBCs



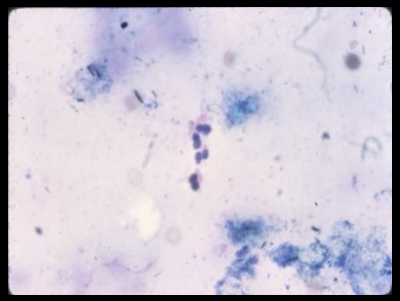
Rare RBC Casts



WBC Casts (50%)



Renal Tubular Epithelial cells

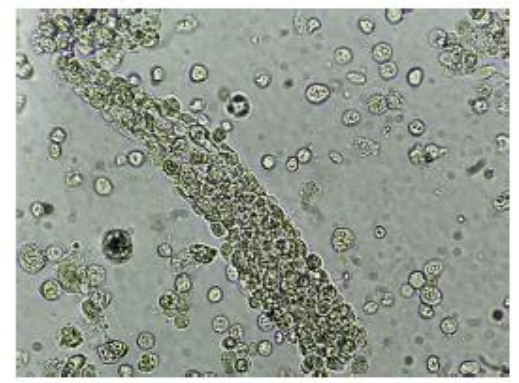


Eosinophils

Perazella M. Adv Chronic Kidney Dis. 2017;24(2):57-63

Urinalysis in AIN

Urine Dipstick/Urine Microscopy	Interstitial Nephritis	Nephritic Syndrome	Nephrotic Syndrome	Tubular Necrosis
Protein	0/+	++	++++	0/+
Blood/RBCs	0/+	++++	0	0
LE/WBCs	+++	0/+	0	0
RBC casts	0	++	0	0
WBC casts	+++	0	0	0
RTE cell casts, Granular casts	+	+	0	++++



- **Urinary WBCs are an under- appreciated manifestation of AIN**
- **Often confused with a UTI, the diagnosis of AIN may be delayed by prolonged antibiotic treatment even in the presence of a negative urine culture**
- **WBCs and WBC casts in the presence of AKI and a negative culture strongly suggests AIN**

Muriithi AK, J Am Soc Nephrol. 2013;8(11):1857-1862.

Differential Diagnosis of Eosinophiluria

- AIN
- Cholesterol emboli
- Acute / chronic cystitis
- UTI / prostatitis
- Transplant rejection

AIN

Sensitivity 36%

Specificity 68%

Hansel's Stain : Previously Recommended Predictor if

>1% of urinary wbcs are eosinophils

- **However based on this data**

urinary eosinophils should no longer be used as a biomarker for ATIN.

Imaging in AIN

U/S

- Increased echogenicity
- Increased size

Gallium

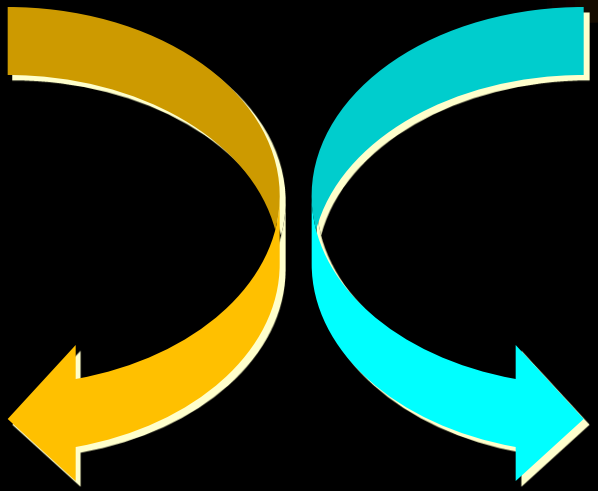
- 67gallium binds to lactoferrin, which is expressed on inflammatory cell surfaces and also released by leukocytes within the kidney interstitium
- Increased update

PET

- Uptake of 2-[18F] fluoro-2-deoxy-D-glucose by infiltrating inflammatory cells

Praga M. Kidney International (2010) 77, 956–961

Interstitial Nephritis : Proteinuria



Nephrotic Range Proteinuria

2.5%

Non Nephrotic Range Proteinuria

97.5%

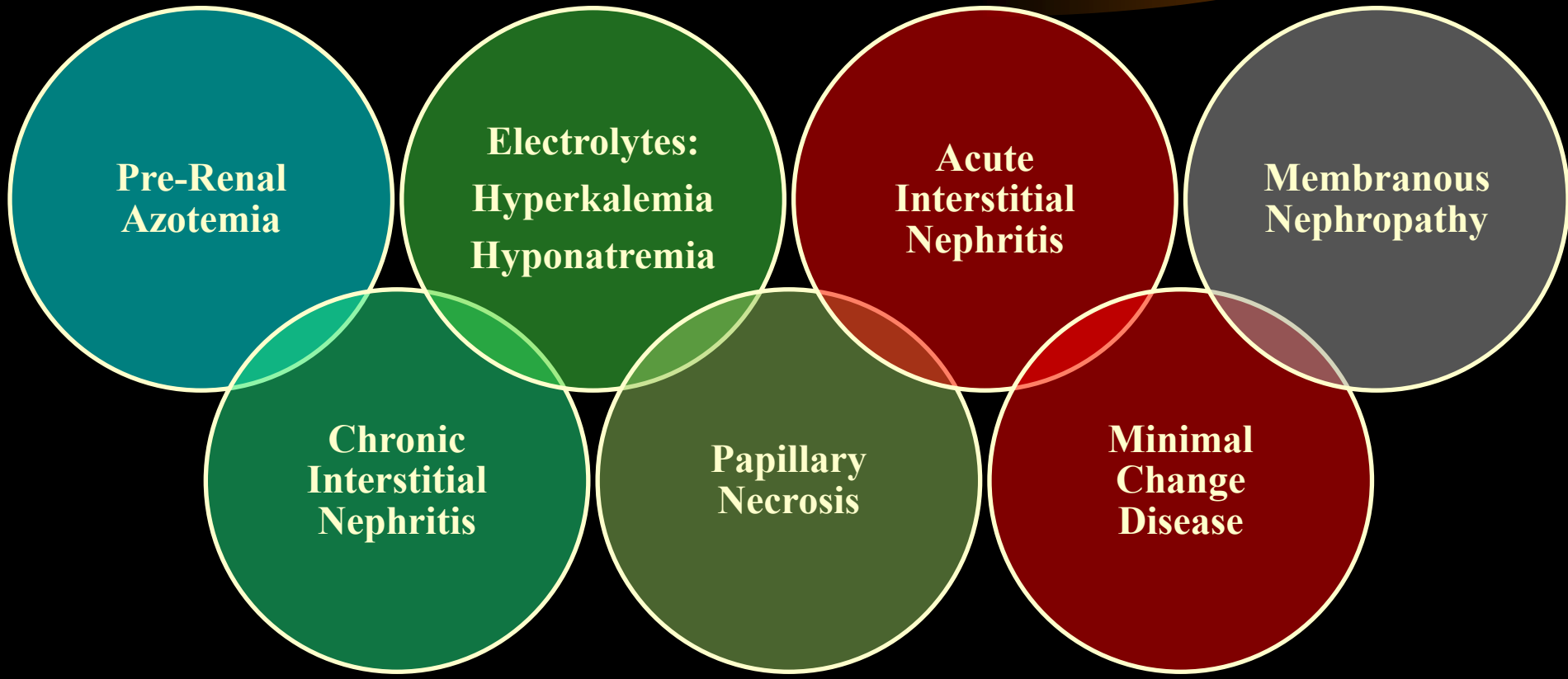
AIN and NSAID's

Lack the typical features of AIN

- **Prolonged use 3-6 months**
- **Absence of fever, rash, eosinophilia**
- **Lower concentration of infiltrating eosinophils on biopsy**

Association with Minimal Change or Membranous Nephropathy

The World of NSAID Induced Renal Disease



Drug Induced AIN and Nephrotic Syndrome

- **NSAIDs**
- **Interferon**

Differentiating ATN from AIN

	ATN	AIN
Time of onset	Days to weeks	Weeks to months
Kidney U/S	Normal	Large / Echogenic
Systemic Findings	None	Rash/fever
Eosinophilia/ Eosinophiluria	None	Occasional
Potassium	Elevated in proportion to GFR	Disproportionately elevated to GFR (Type IV RTA)
FENA	> 2%	> 2%
Acidosis	Anion Gap	Non Anion Gap
Urinalysis	Granular Casts Renal Tubular Cells	Granular Casts WBC casts WBCs, RBCs Rare RBC casts

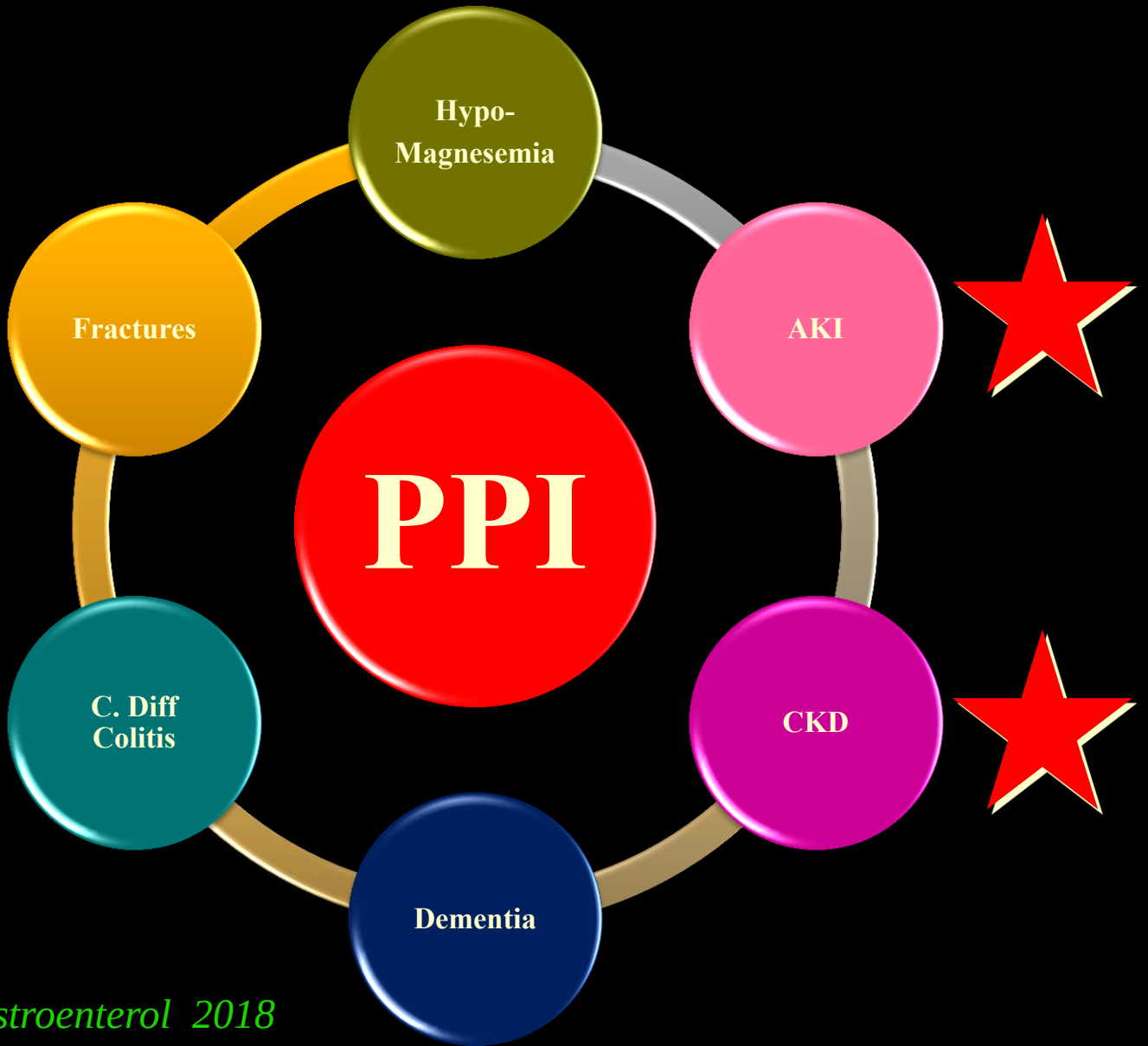
PPI use in the U.S.

15 million users a year
$10 Billion dollars

40-70% of these prescriptions have no appropriate indication
25% of Users can discontinue the medication with no relapse

JAMA Intern Med. 2016 Feb;176(2):238-46

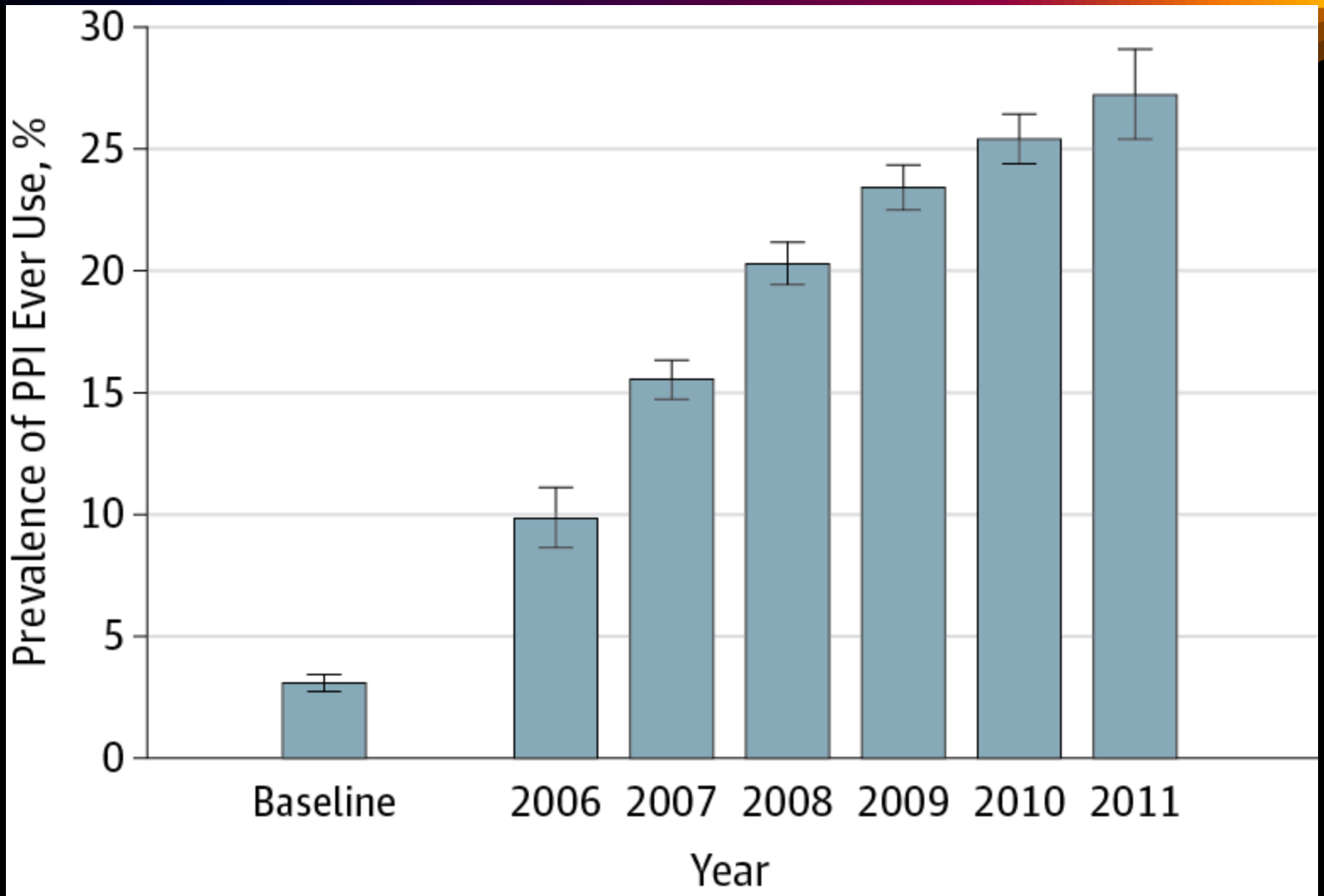
PPI Use and Systemic Complications : Causal Associations



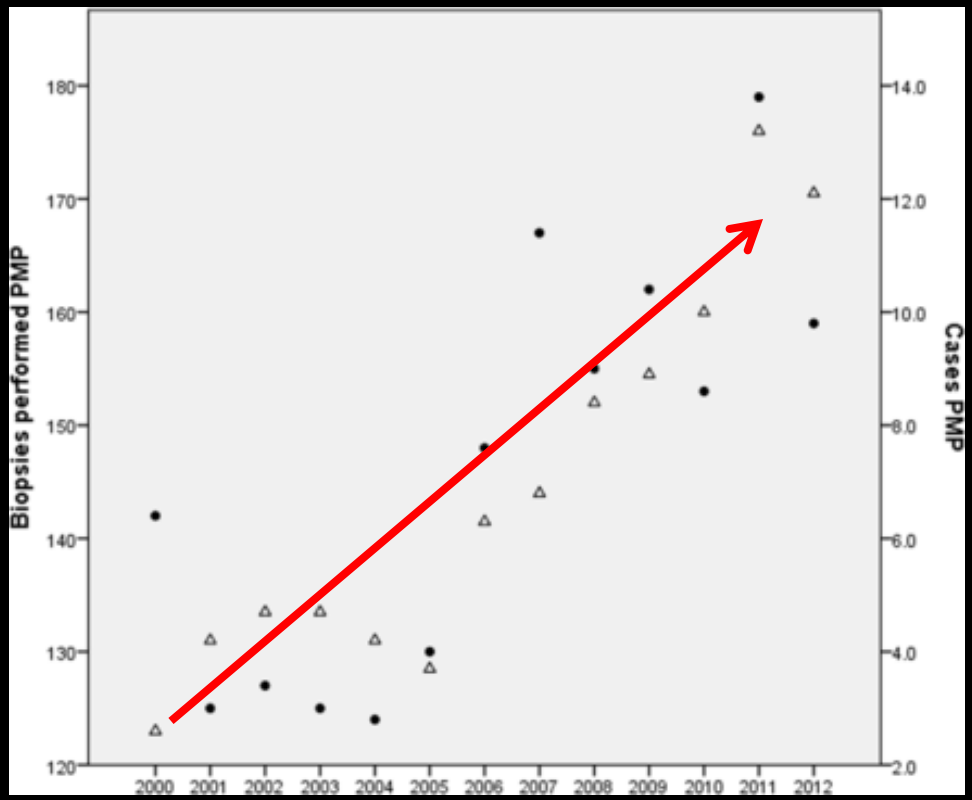
Kamal F, J Clin Gastroenterol 2018

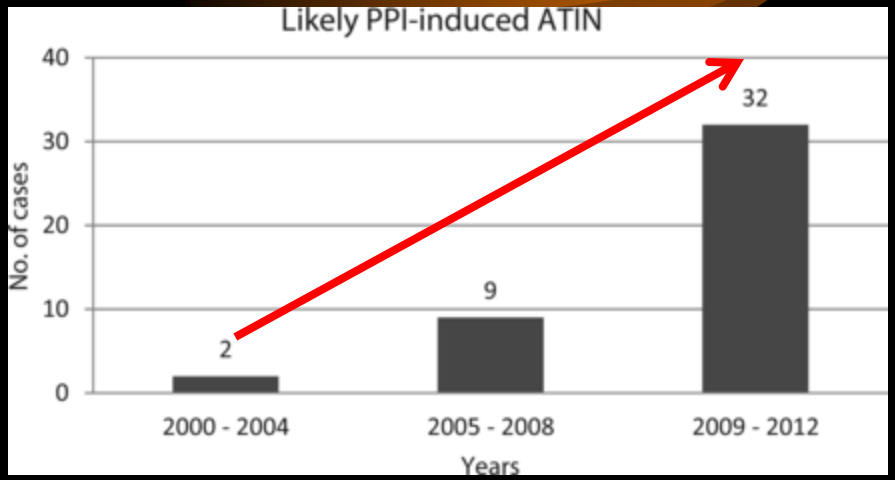
JAMA Intern Med. 2016 Feb;176(2):238-46

PPI use in the Atherosclerotic Risk Trial over 13 Years Followup



Increasing Incidence of AIN - UK



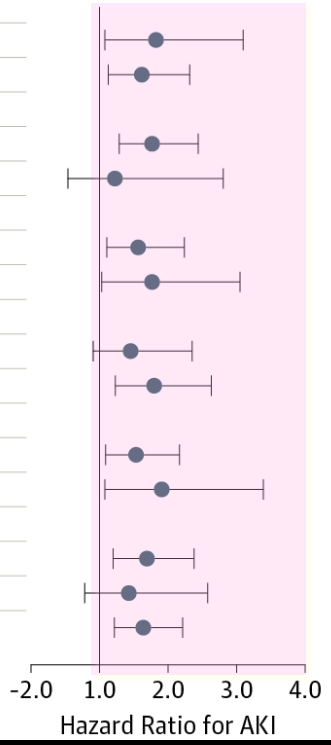


Etiology of AIN	
Antibiotics	35%
PPI	35%
NSAIDs	20%

Risk of AKI with PPI Use in 2 Major Population Studies

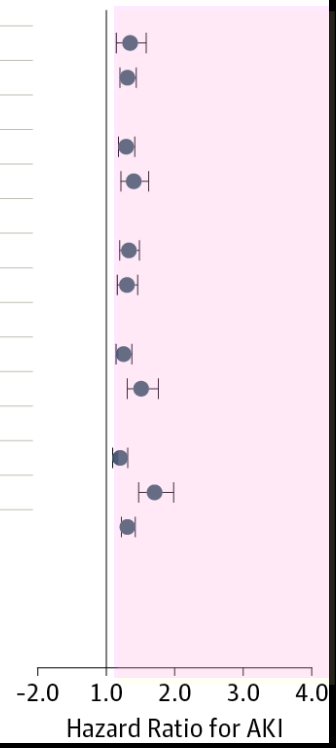
Atherosclerotic risk Trial

	Overall Population		Baseline PPI Users	
	No. of Events	No. of Participants	No. of Events	No. of Participants
Age				
Young	326	5617	15	174
Old	634	5528	32	184
Race				
White	1731	8768	41	309
Black	229	2377	6	49
Diabetes mellitus				
No	655	9316	33	300
Yes	305	1829	14	58
Sex				
Male	492	4891	18	151
Female	468	6254	29	207
ACE-I/ARB use				
No	734	9574	34	294
Yes	226	157	13	64
Diuretics use				
No	777	9903	36	294
Yes	183	1242	11	64
Overall	960	11 145	47	358



Geisinger Health System

	Overall Population		Baseline PPI Users	
	No. of Events	No. of Participants	No. of Events	No. of Participants
Age				
Young	2033	127 542	168	8518
Old	8143	121 209	560	8382
Diabetes mellitus				
No	7226	222 829	516	15 081
Yes	2950	25 922	212	1819
Sex				
Male	5804	108 070	384	7304
Female	4372	140 681	344	9596
ACE-I/ARB use				
No	8398	223 579	517	14 277
Yes	1778	25 172	211	2623
Diuretics use				
No	8568	226 879	512	14 569
Yes	1608	21 872	216	2331
Overall	10 176	248 751	728	16 900

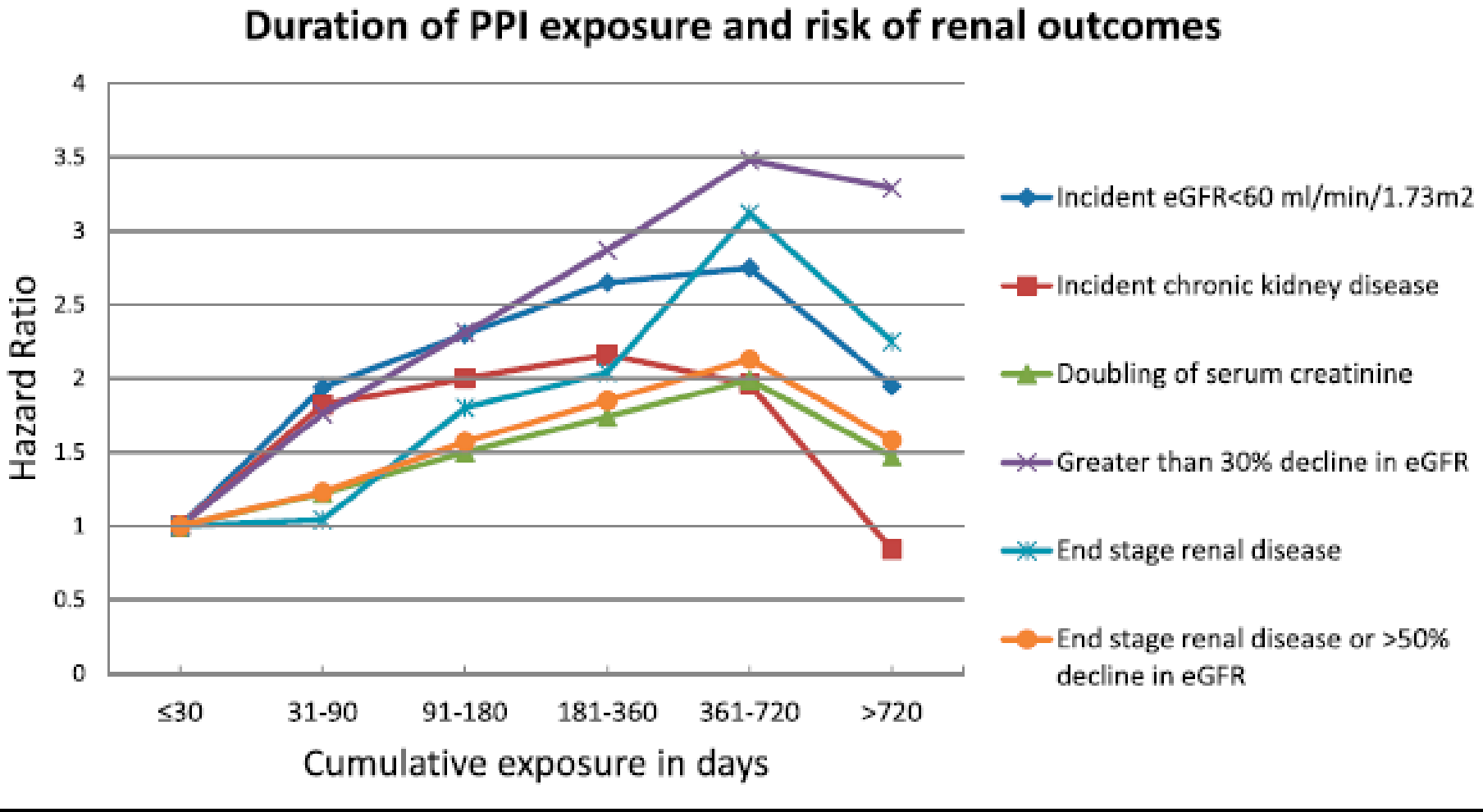


Increased Risk of 70% for AKI in PPI users

JAMA Intern Med. 2016 Feb;176(2):238-46

Xie Y.J Am Soc Nephrol 2016 April 14

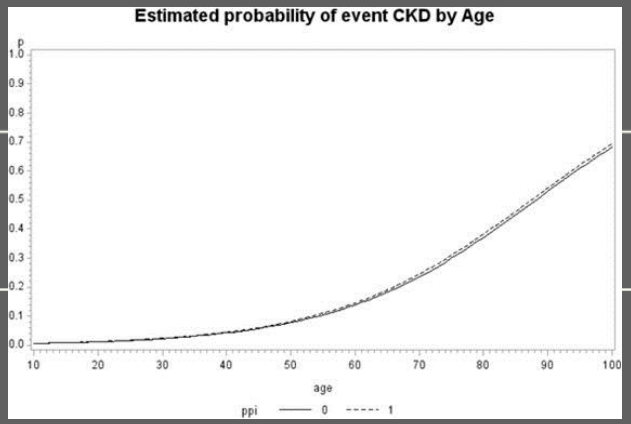
PPI Compared to H2 blockers and the risk of CKD : VA Study



Arora P, BMC Nephrology. 2016;17:112

Risk of CKD : VA Study

N = 23,000



OR

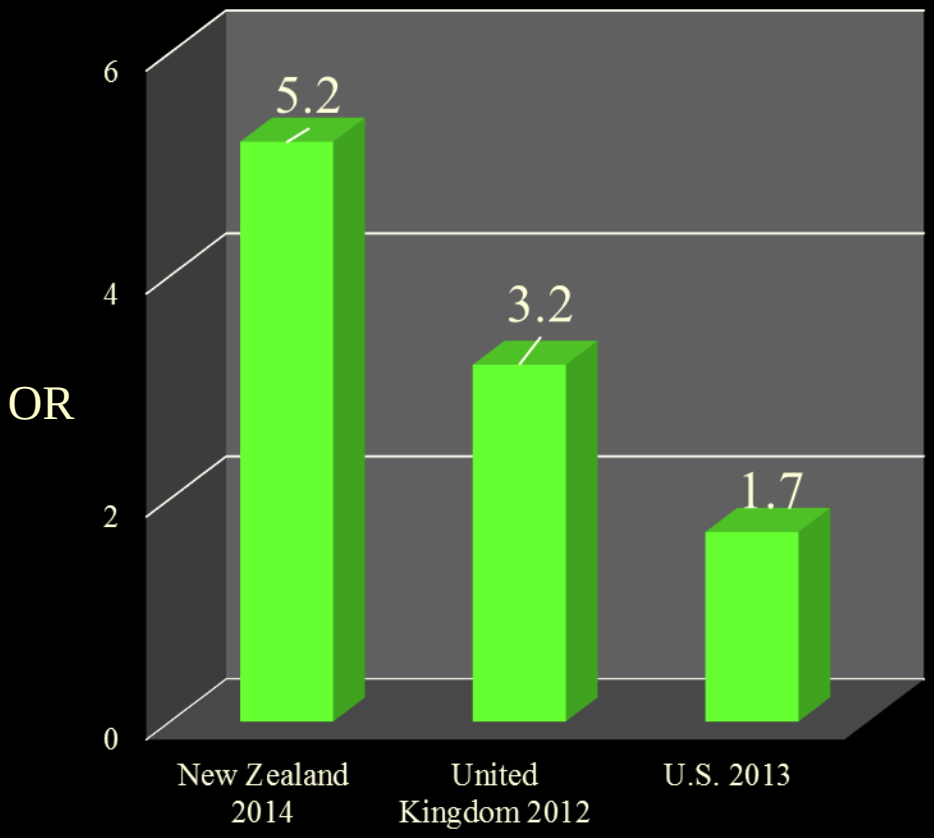
3
2.5
2
1.5
1
0.5
0

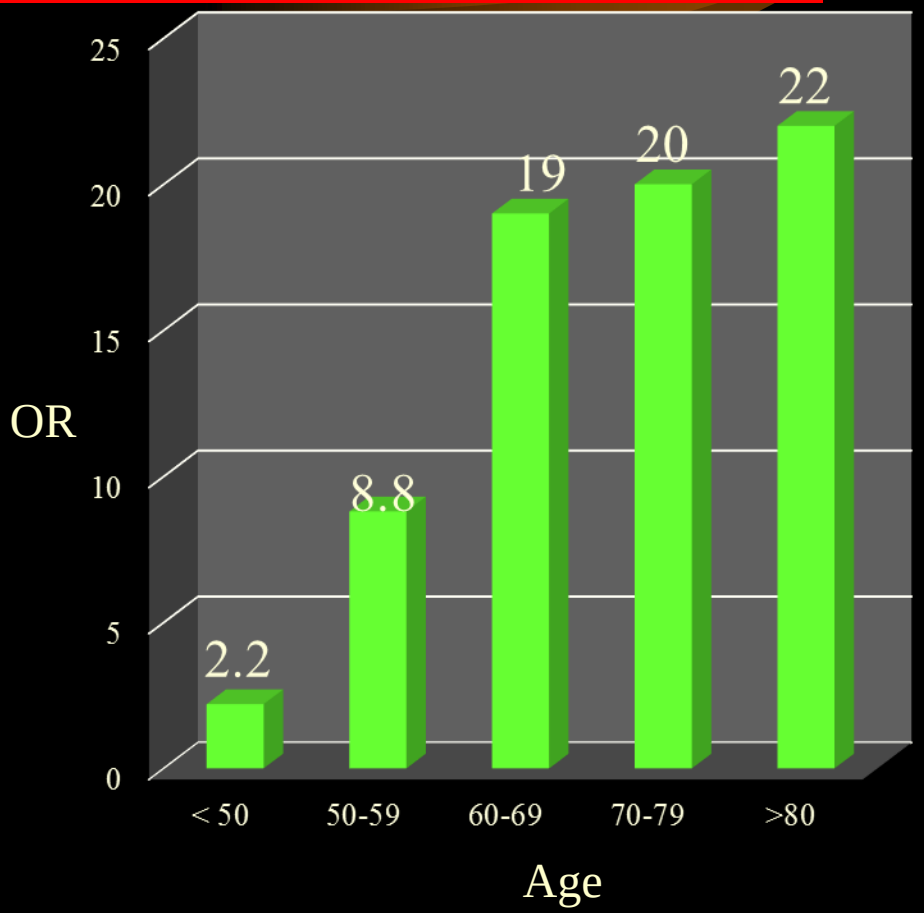
Diabetes	HTN	Male sex	PPI
2.43	1.68	1.34	1.1

Blank M. Kidney Intern March 2014

PPI and Allergic Interstitial Nephritis

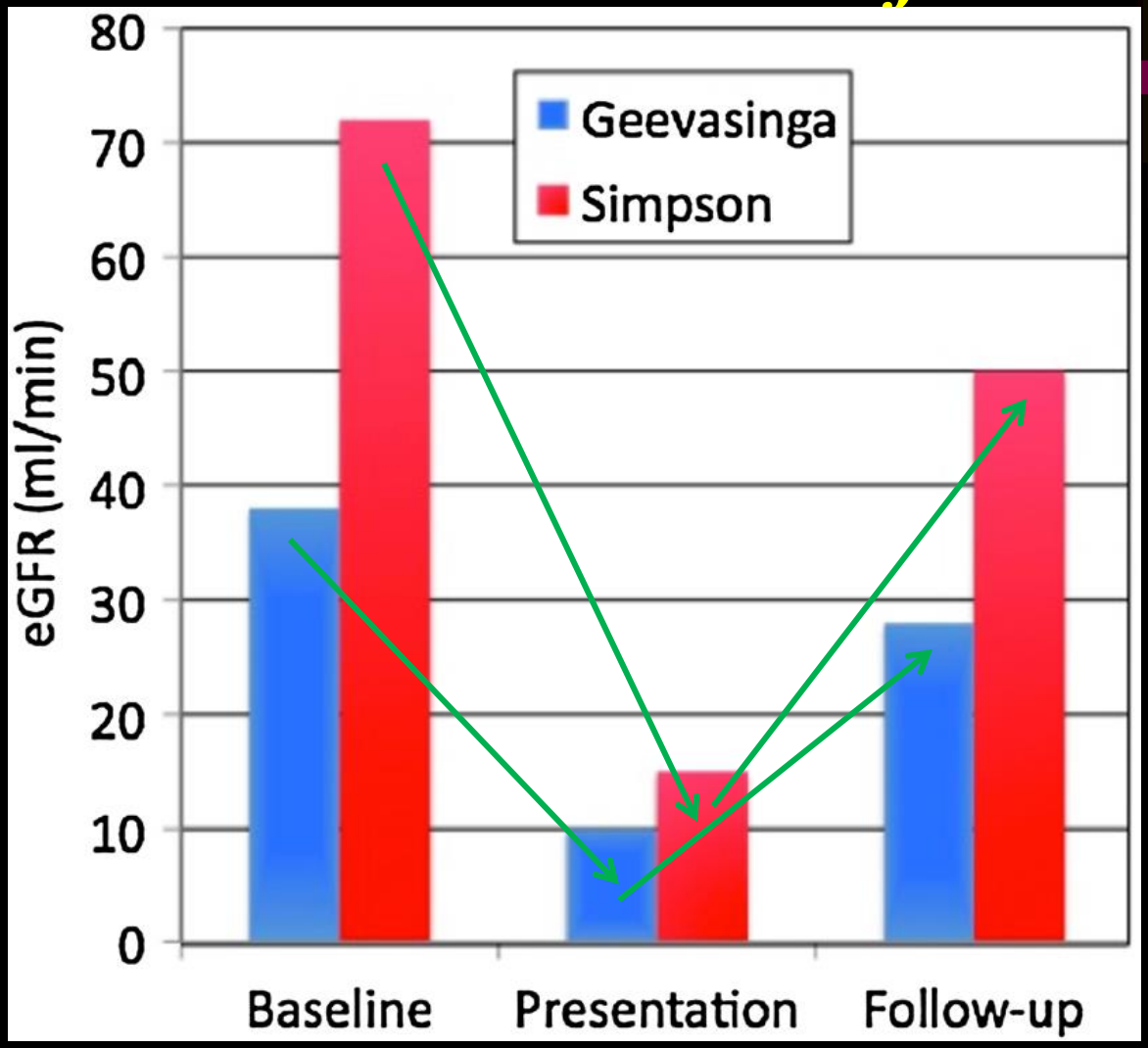
Any Patient on a PPI with AKI : Suspect the PPI !!!





Moledina DG. J Nephrol 2016 Apr 12

Persistent CKD after AKI from PPI



Conclusion

Patients with AKI from PPI often are left with persistent CKD due to delayed diagnosis

Sierra F. Alimentary Pharmacology & Therapeutics (2007) 26:545-553

Berney-Mayer L .Nephrology 19 (2014) 359–365

AIN & Proton Pump Inhibitors

- **Idiosyncratic (no relation to dose/duration)**
  - **All drug classes implicated**
- **Minimal systemic hypersensitivity reaction**
  - **Fever <50%**
  - **Rash <10%**
  - **Eosinophilia < 10%**

TH17/TH1 response >> TH2 response

(atypical of most cases of drug induced AIN)

- **Duration of PPI treatment prior to AIN**
  - **Mean 10 weeks (range 1 wk – 18 months)**
- **Path: AIN, tissue eosinophils seen in approx 80%**
- **Treatment often delayed**
  - **75% of cases have been left with Stage 3-4 CKD**

KI REPORTS
KIReports.org

Kidney Int Rep (2017) 2, 297–301;

REVIEW

Proton Pump Inhibitors and Kidney Disease—GI Upset for the Nephrologist?

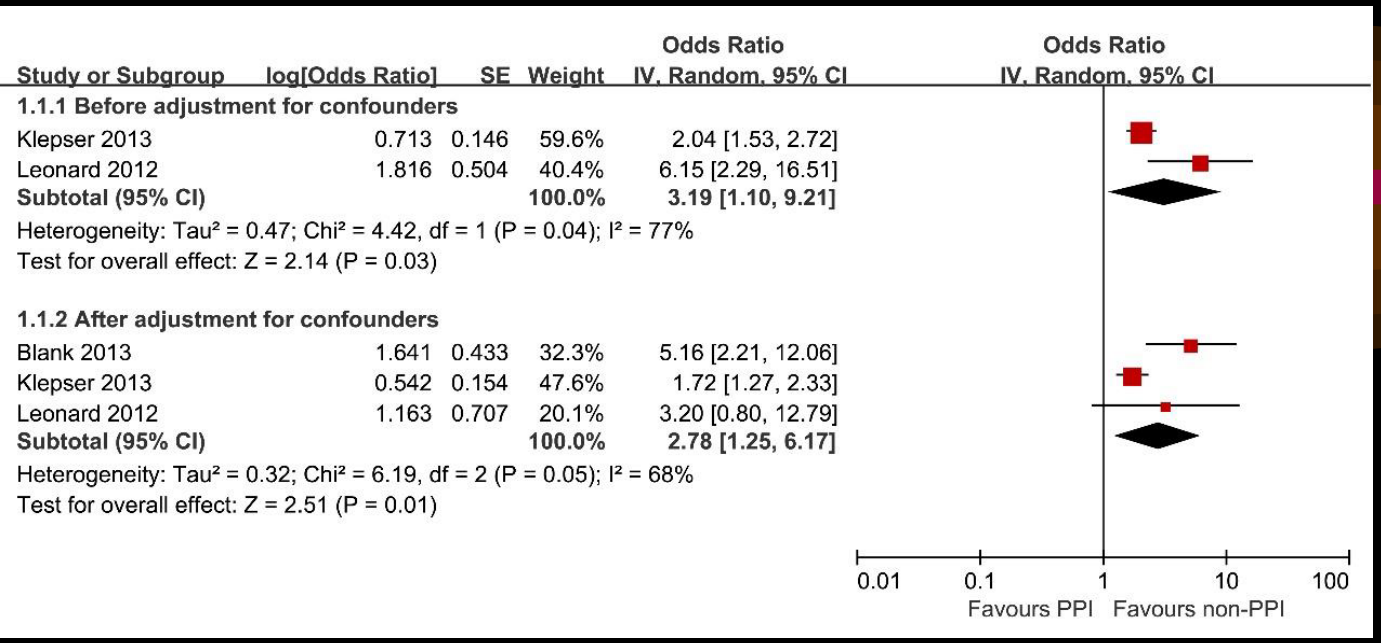
Stephanie M. Toth-Manikowski[1] and Morgan E. Grams[1,2]

[1]Department of Medicine, Johns Hopkins University, Baltimore, Maryland, USA; and [2]Department of Epidemiology, Johns Hopkins University Bloomberg School of Public Health, Baltimore, Maryland, USA

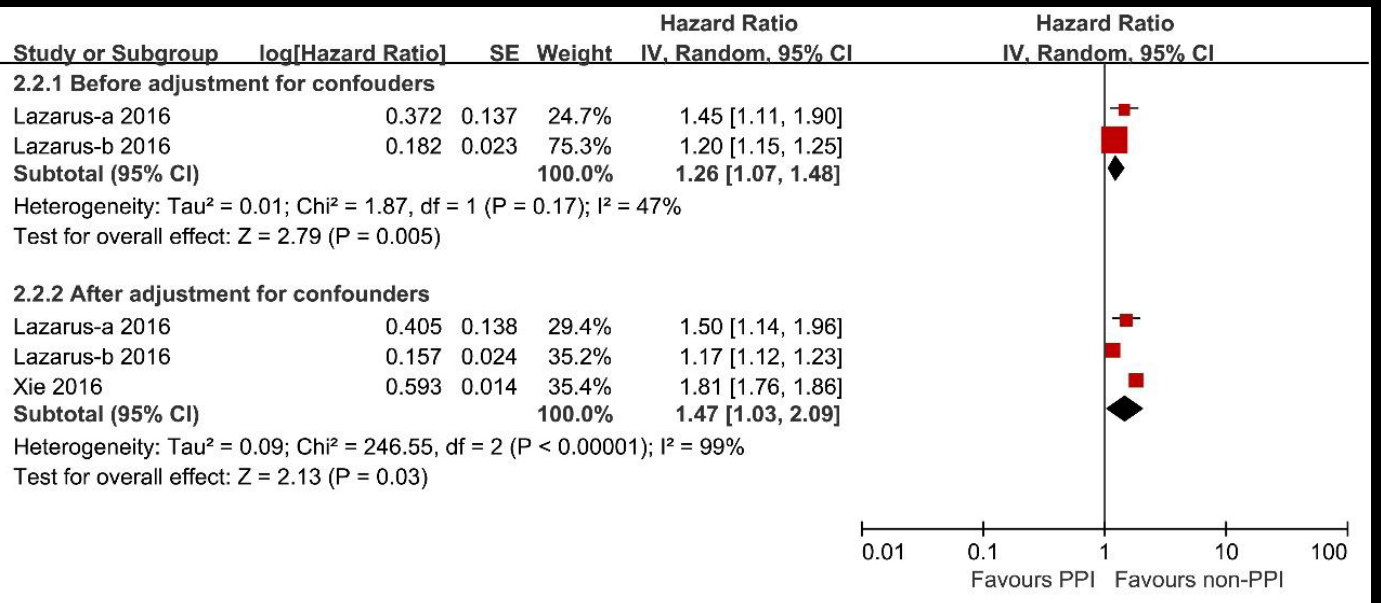
Author, year	Study design	Type of kidney injury evaluated	Reference group	Risk associations with PPI use
Geevasinga *et al.*, 2006[36]	Case series	AIN	NA	NA
Simpson *et al.*, 2006[37]	Case series	AIN	NA	NA
Leonard *et al.*, 2012[38]	Case-control	AIN	No PPI use	OR 3.20 (0.80–12.79)
Leonard *et al.*, 2012[38]	Case-control	AKI	No PPI use	OR 1.05 (0.97–1.14)
Klepser *et al.*, 2013[39]	Case-control	AKI	No PPI use	**OR 1.72 (1.27-232)**
Antoniou *et al.*, 2015[40]	Health system data	AKI	No PPI use	**HR 2.52 (2.27-2.79)**
Lazarus *et al.*, 2016[41]	Prospective cohort	AKI	No PPI use	**HR 1.64 (1.22-2.21)**
	Health system data		No PPI use	**HR 1.31 (1.22-1.42)**
	Prospective cohort	AKI	H_2RA use	**HR 1.58 (1.05-2.40)**
	Health system data		H_2RA use	**HR 1.31 (1.13-1.48)**
Lazarus *et al.*, 2016[41]	Prospective cohort	CKD	No PPI use	**HR 1.50 (1.14-1.96)**
	Health system data		No PPI use	**HR 1.17 (1.12-1.23)**
	Prospective cohort	CKD	H_2RA use	**HR 1.39 (1.01-1.91)**
	Health system data		H_2RA use	**HR 1.29 (1.19-1.40)**
Xie *et al.*, 2016[42]	Prospective cohort	CKD	H_2RA use	**HR 1.28 (1.23-1.34)**
Xie *et al.*, 2016[42]	Prospective cohort	ESRD	H_2RA use	**HR 1.96 (1.21-3.18)**
Peng *et al.*, 2016[43]	Case-control	ESRD	No PPI use	**OR 1.88 (1.71-2.06)**

Qie T. J gastroenterol April 12 2018

Risk of AIN/AKI and CIN/CKD with PPI

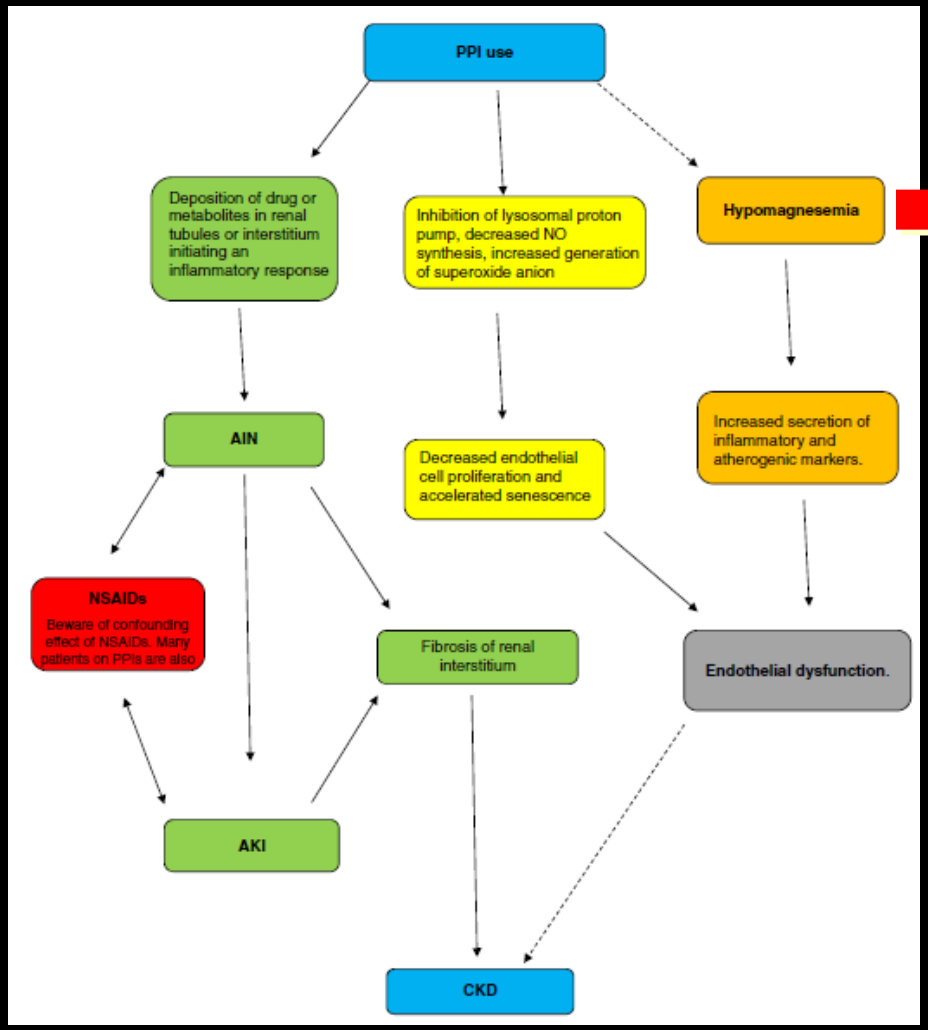


AKI
OR 2.78



CKD
OR 1.47

PPI Use and AKI / CKD: Mechanisms



The Atherosclerosis Risk in Communities (ARIC) study found that magnesium level of ≤ 0.7 mmol/L (≤1.8 mg/dL) was associated with incident CKD and endstage renal disease (ESRD)

5 – Aminosalicylates

- **AIN has been reported with all preparations used for inflammatory bowel disease**
  - **Asacol®**
  - **Pentasa®**
  - **Dipentum®**
  - **Colazal®**
- **idiosyncratic, non-dose-dependent reaction**
- **40% incidence of CKD as a result of delayed recognition and cessation of drug exposure**

HAART Related Nephropathy

- **Protease Inhibitors**
  - **Indinavir / Atazanavir**
    - **Crystalluria / AKI / Nephrolithiasis**
    - **Less frequent with other PI**
    - **Additional causes of crystalluria in HIV patients**
      - **Ciprofloxacin**
      - **Acyclovir**
      - **Sulfadiazine**
    - **Allergic Interstitial Nephritis**

AIN Secondary to Chemotherapy

Checkpoint Inhibitors

- pembrolizumab and nivolumab that target PD-1,atezolizumab, which is a PD-L1 inhibitor, and ipilimumab,which binds to CTLA-4.
- **Frequent autoimmune sequela**
- AIN develops 2 wks to 8 months AFTER initiation of therapy and 2 months after the last dose
- Steroid responsive

Ifosfamide

- Alkylating agent
- Predominant ATN with predilection for the proximal tubule – Fanconi's syndrome
- AIN reported in 30% of cases

Pemetrexed

- enzymes involved in DNA synthesis and is used in the treatment of mesothelioma and non-small cell lung cancer
- Antifolate
- Predilection for the proximal tubule

Intravesicle BCG

- live attenuated vaccine, is an established and effective treatment for noninvasive transitional cell carcinoma of the bladder
- Leads to Type IV hypersensitivity reaction and AIN

Tyrosine kinase inhibitors / Lenalidomide : occasional cases of AIN

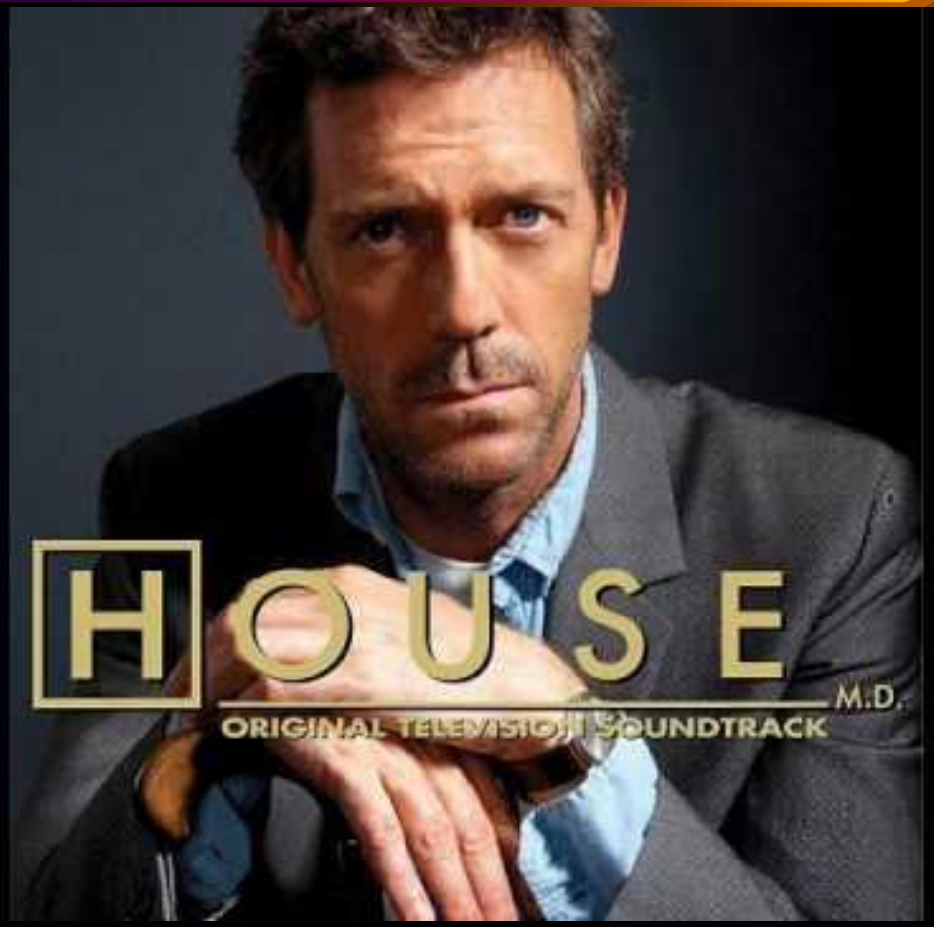
Nast C. Adv Chronic Kidney Dis. 2017;24(2):72-79

Buysen, JGM, Nephrol Dial Transplant 1990 5:94–99

Renal Biopsy for Drug Induced AIN

AKI Secondary to ATN

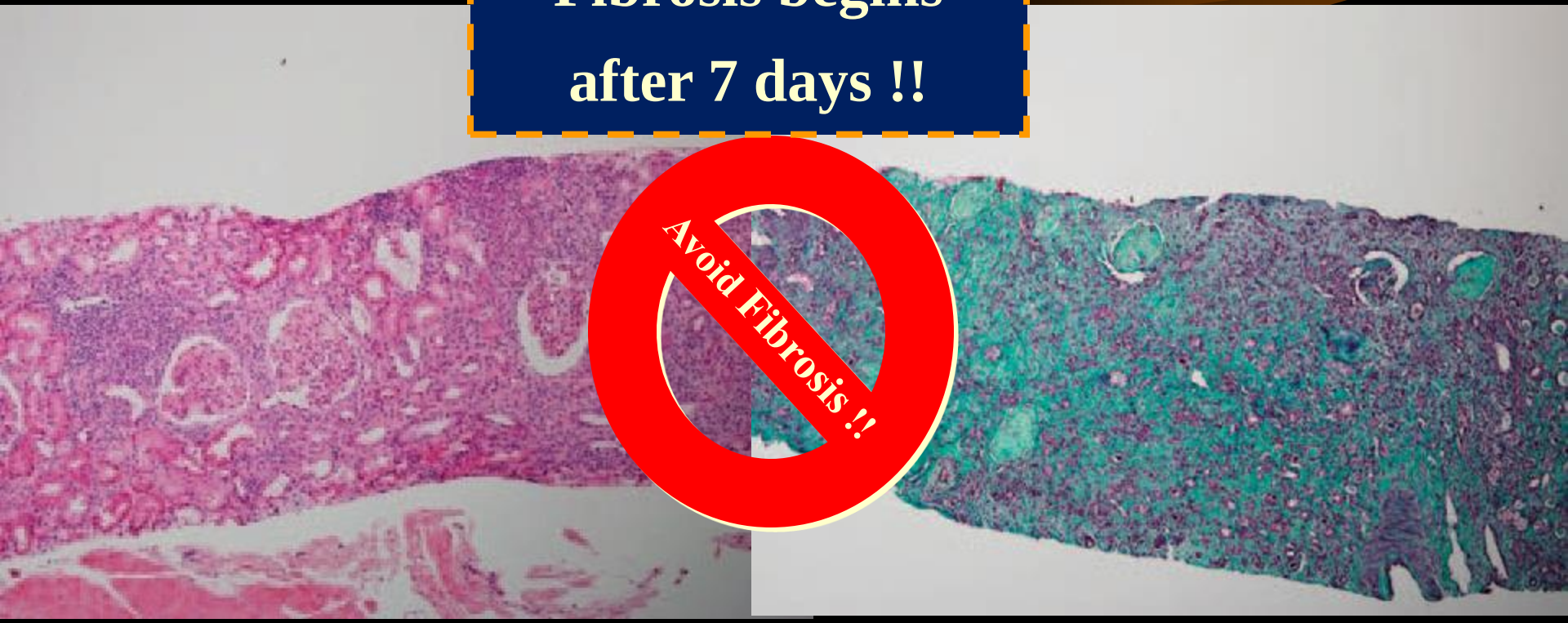
Suspected AIN



Praga M . Kidney Intern 2010 Jun;77(11):956-61

Goal of Therapy in AIN

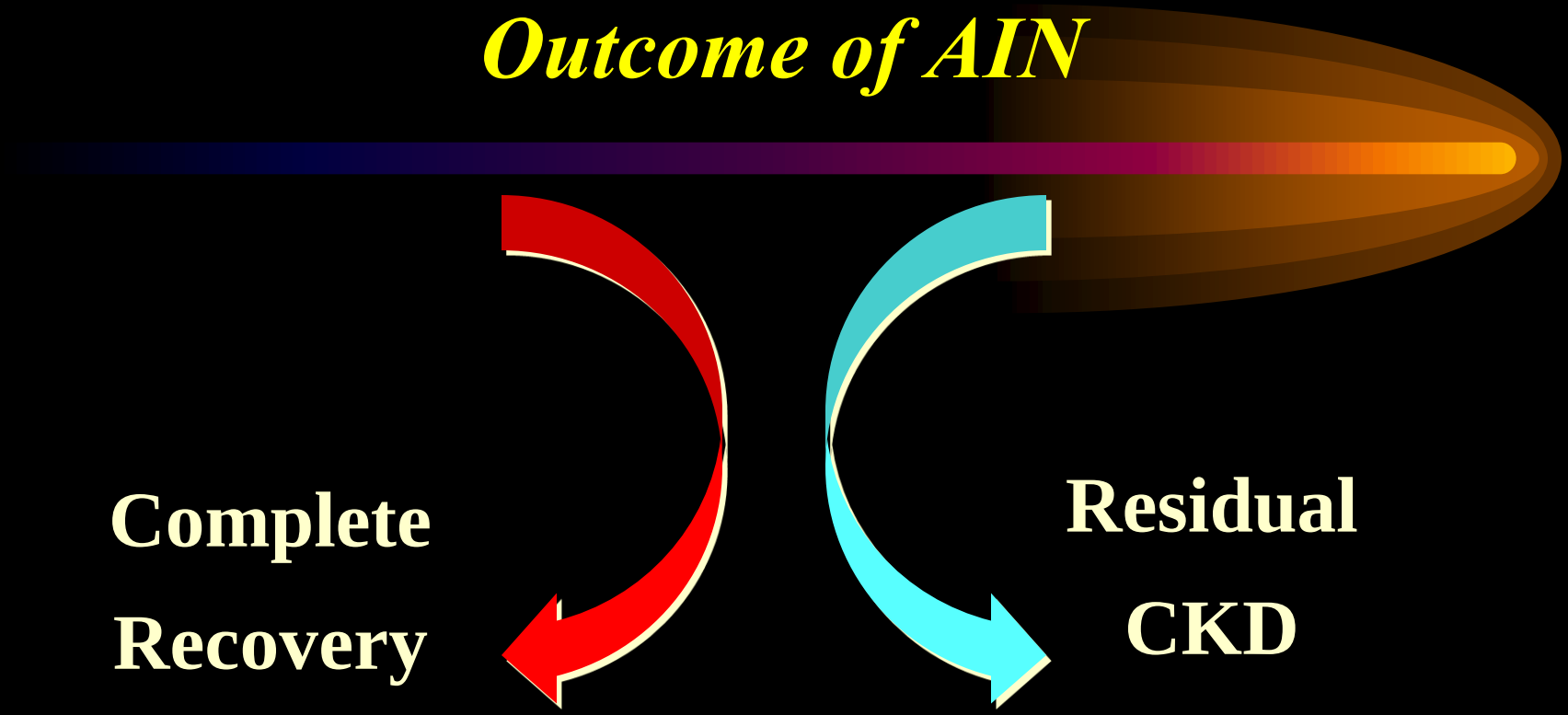
Fibrosis begins after 7 days !!



Trichrome stain often used to demonstrate Fibrosis

Clarkson MR.Nephrol Dial Transplant. 2004;19(11):2778
Baker RJ.Nephrol Dial Transplant. 2004;19(1):8
Bhaumik SK. Ren Fail. 1996;18(1):97

Outcome of AIN



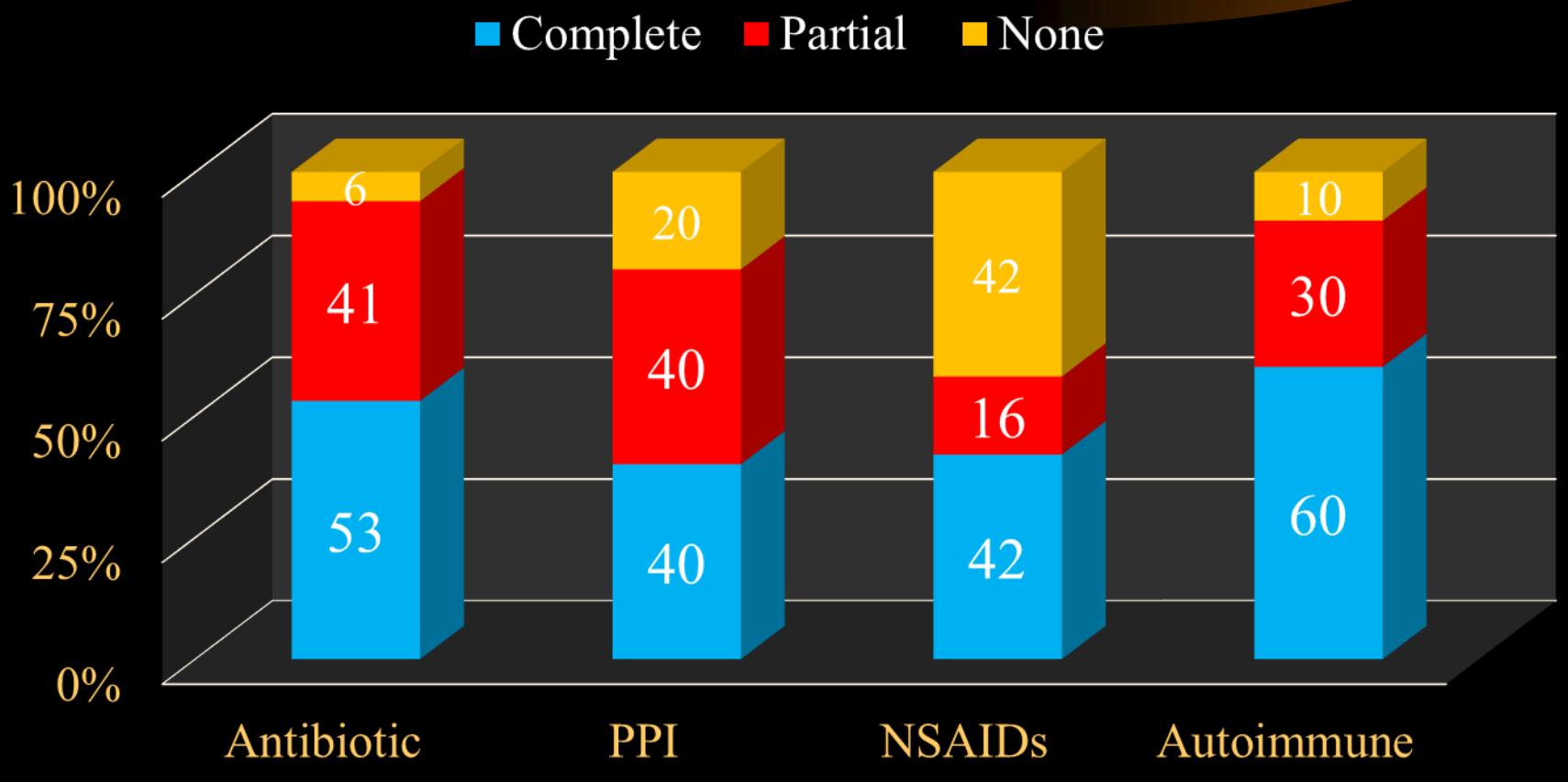
Complete Recovery 50%

Residual CKD 50%

10% ESRD

Muriithi AK . Am J Kidney Dis. 2014 Jun 11

Outcome of AIN based on Etiology



Early Steroid Rx improves Recovery of Renal function in drug induced AIN

	Std Rx - Recovery	
	Complete	Incomplete
Time from drug withdrawal to RX (days)	13 +/-10	34 +/-17
Interstitial Fibrosis		
Mild	89%	29%
Mod	11%	46%
Severe	0 %	25%

Gonzalez E, Gutierrrez E, Galeano C, et al. Kidney Int 73:940-6, 2008

Moledina D. Clin J Am Soc Nephrol 12: 2046–2049, 2017.

Drug Induced AIN : To Steroid or not to Steroid ?

Table 1. Studies examining corticosteroid therapy in acute interstitial nephritis

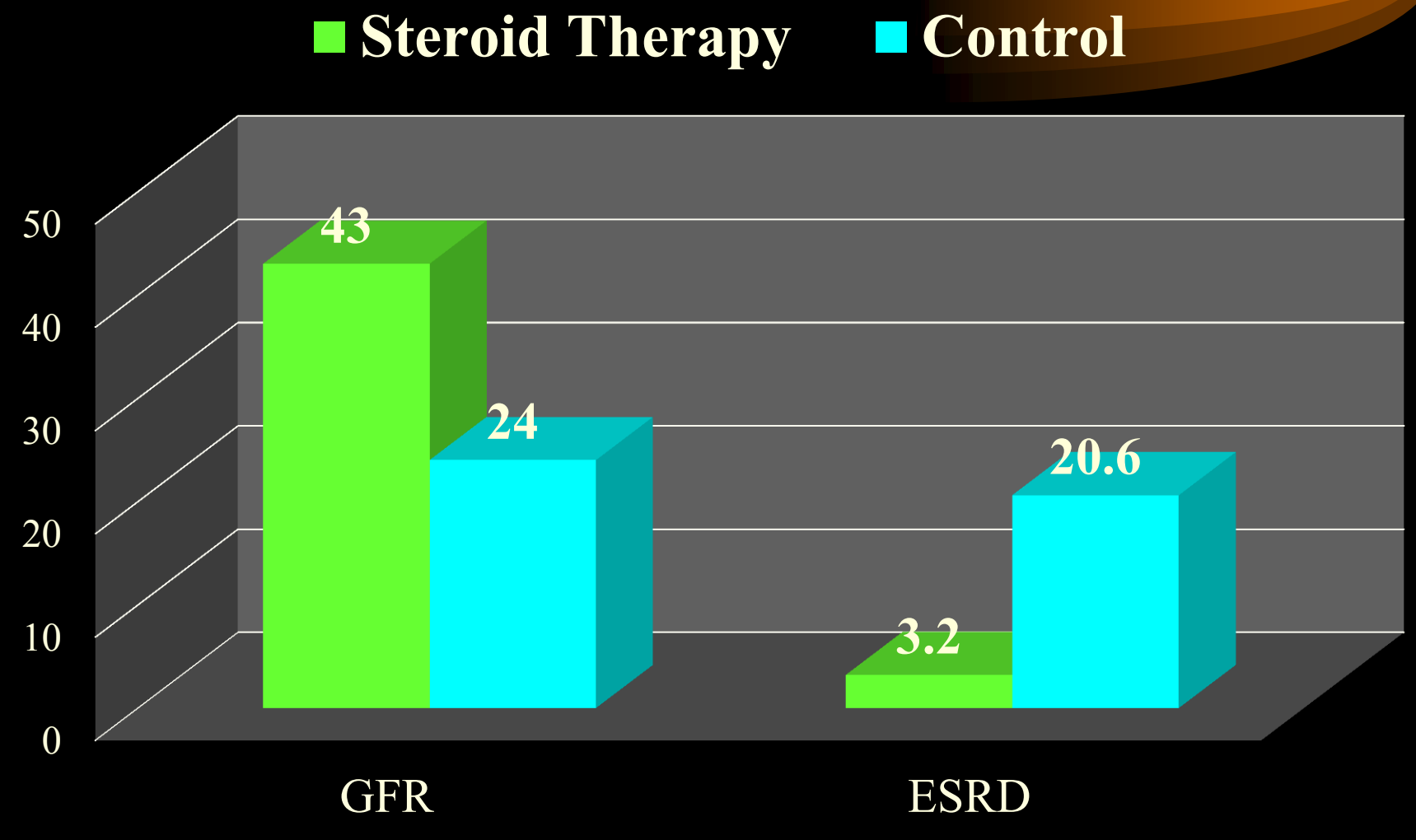
Author, Yr (ref)	Sample size		Peak SCr, mg/dl		Final SCr, mg/dl		Follow-Up, Mo	Comment
	Steroid	No Steroid	Steroid	No Steroid	Steroid	No Steroid		
Clarkson *et al.* 2004 (4)	26	16	7.9	6.1	1.6	1.6	12	Patients received steroids late after diagnosis (median delay >3 wk).
González *et al.* 2008 (5)	52	9	5.9	4.9	2.1	3.7	19	Steroid treated patients with complete recovery had shorter delay to steroids (13 d) as compared with those without complete recovery (34 d).
Raza *et al.* 2012 (7)	37	12	6.5	5.2	2.8	3.4	19	Improved GFR with steroid versus control ($P<0.05$). No difference in kidney outcomes on the basis of steroid timing.
Muriithi *et al.* 2014 (6)	83	12	3.0	4.5	1.4	1.5	6	Steroid-treated patients had superior kidney outcomes with early versus late steroid therapy.
Valluri *et al.* 2015 (8)	73	51	4.03	3.16	NR	NR	12	Worse kidney function in steroid-treated versus control at biopsy (SCr 4.2 versus 3.3 mg/dl). Steroid-treated patients had complete recovery (48%) versus control group (41%); final SCr not different at 1 yr.
Prendecki *et al.* 2016 (9)	158	29	20.5 ml/min (eGFR)	25 ml/min (eGFR)	43 ml/min (eGFR)	24 ml/min (eGFR)	24	Steroid-treated patient had better eGFR at 2 yr and less dialysis (5.1% versus 24.1%). Dose, duration, and time to steroid initiation were variable.

SCr, serum creatinine concentration; NR, not reported.

Overall patients receiving steroids have improved renal function at short and long term followup compared to patients without therapy

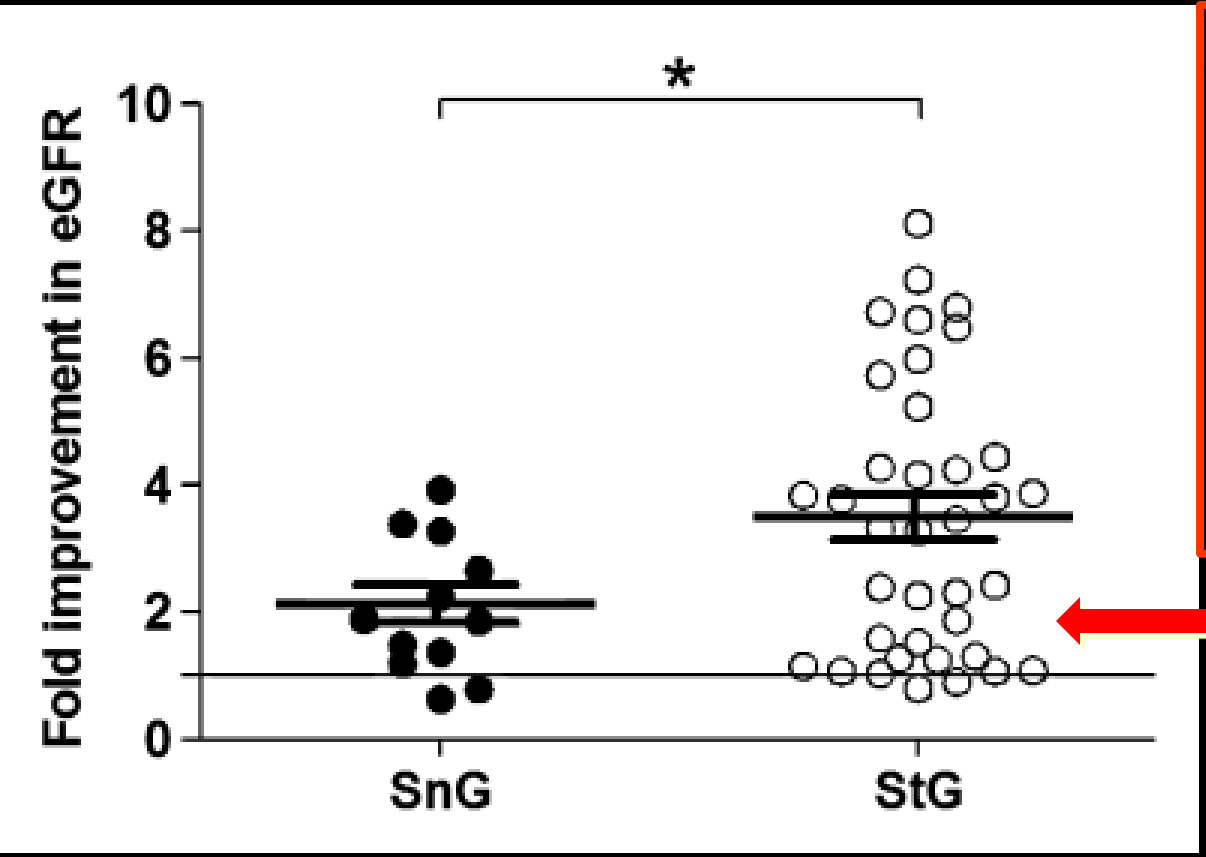
Prendecki M. Clin Kidney J. 2016;9(6):1-7.

Steroid Therapy for AIN
Significant Benefit on the Development of CKD



Devon R. Nephrology 17 (2012) 748–753

Improved Renal Outcome with Steroid Therapy in AIN

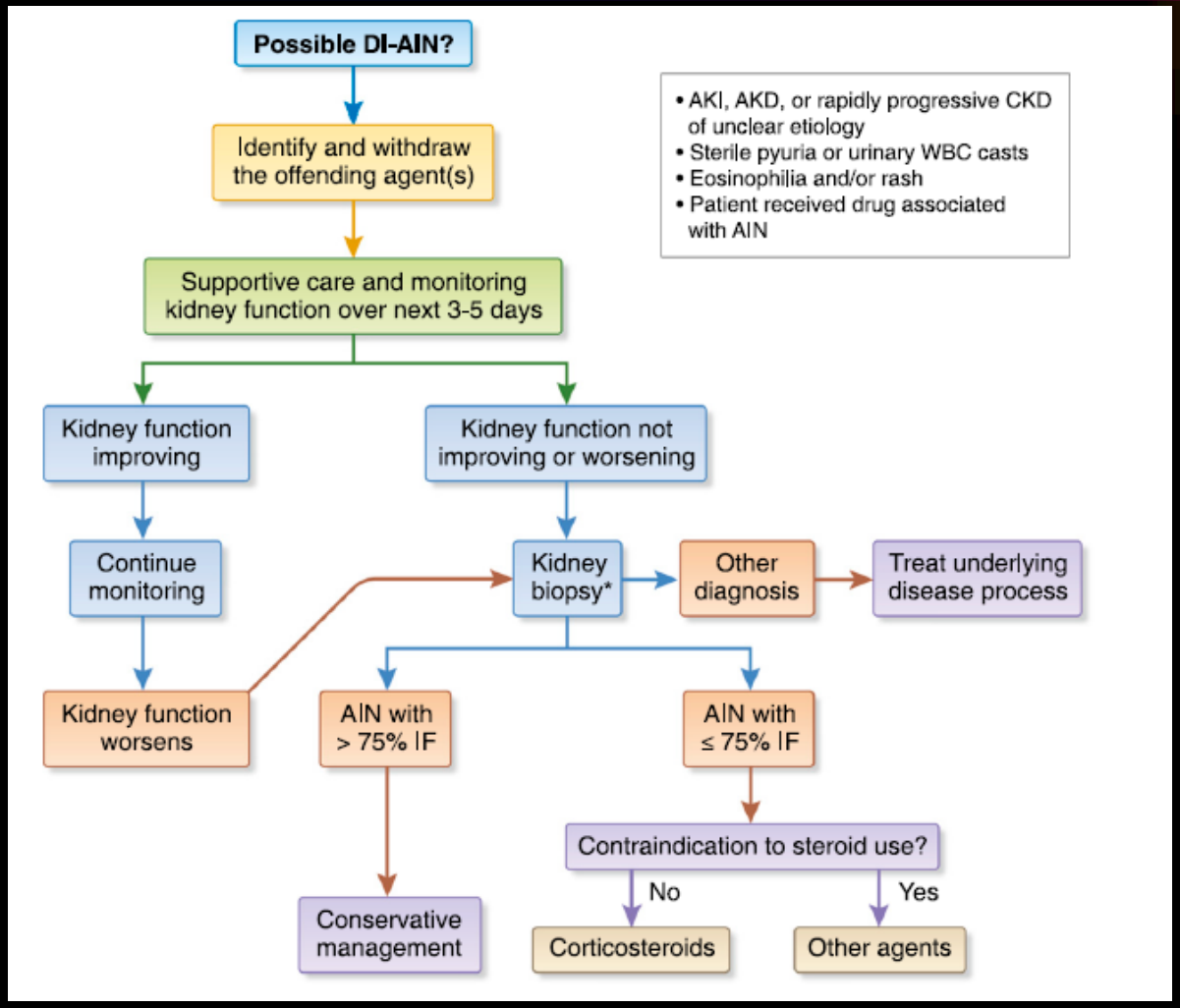


Steroid treated patients experienced a greater degree of renal recovery

Patients with AIN due to PPI had a lower response rate to steroids

Moledina D. Clin J Am Soc Nephrol 12: 2046–2049, 2017.

Drug Induced AIN: When to Biopsy ?



250–500mg intravenous methylprednisolone followed by 1 mg/kg per day of oral prednisone or 1 mg/kg per day of oral prednisone without intravenous therapy

Continue for 6 weeks – if no improvement – then discontinue

In steroid intolerant patients, mycophenolate mofetil can be considered

Treatment of Drug Induced AIN

Immediate discontinuation of the offending agent

No improvement within 5-7 days

or

Dialysis dependence

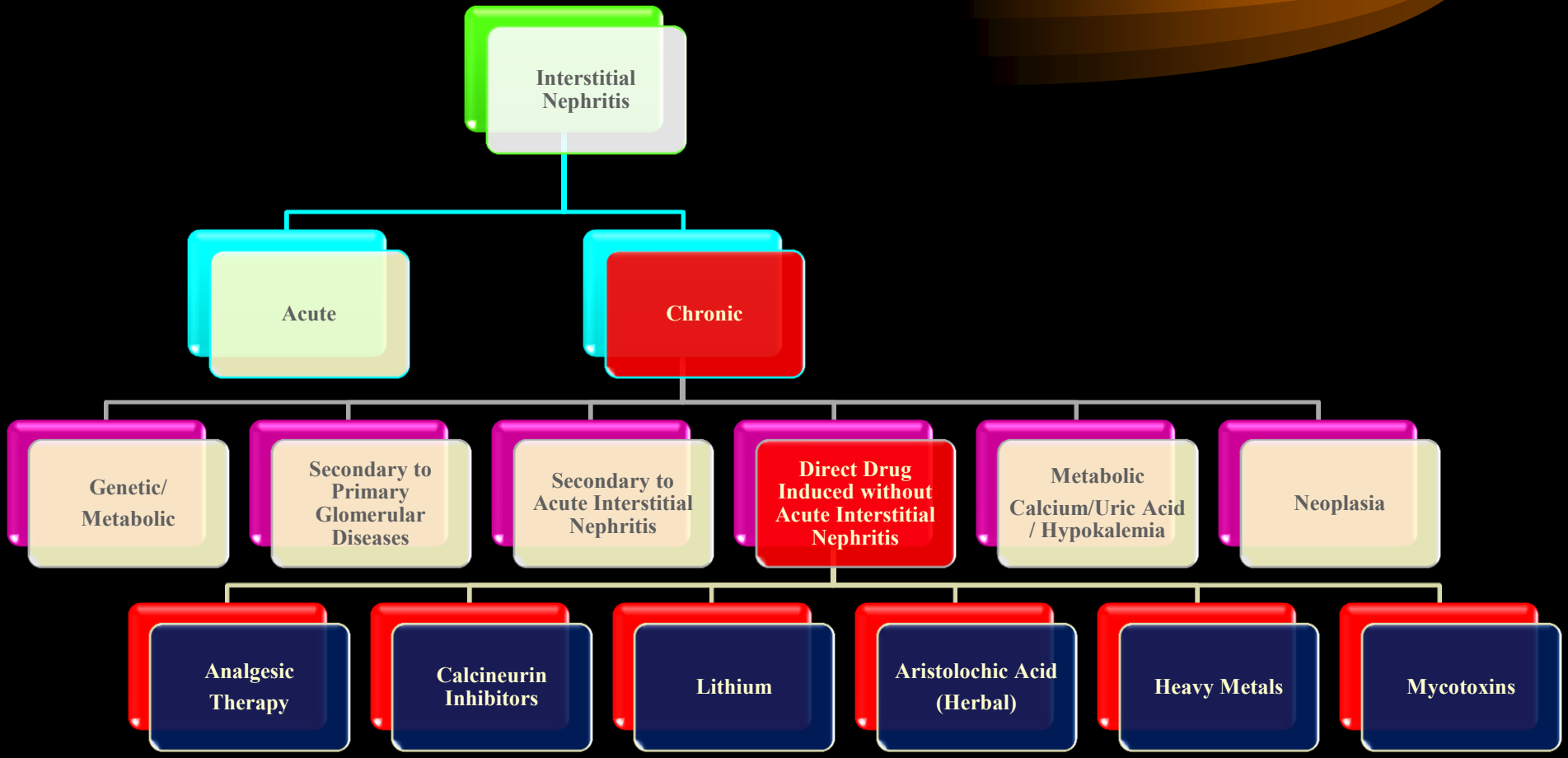
Glucocorticoid Therapy

Etiology of Chronic Interstitial Nephritis

Acute Interstitial Nephritis (AIN)

Chronic Interstitial Nephritis (CIN)

Classification of Interstitial Nephritis



Chronic Interstitial Nephritis : Analgesic Nephropathy

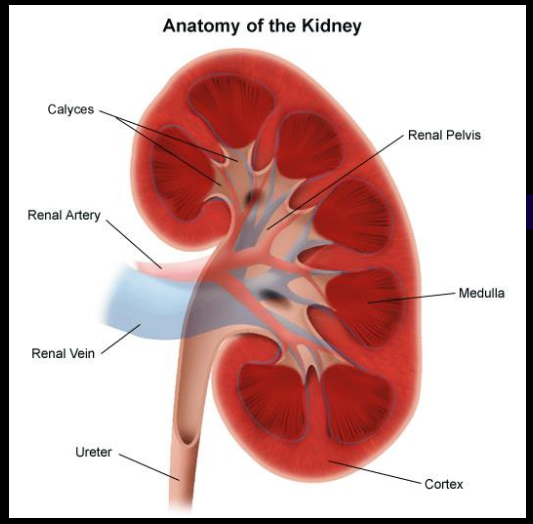
- **Most common drugs worldwide responsible for chronic interstitial fibrosis**
- **Primary analgesic use involves combination therapy of**
  - **Phenacetin ± Acetaminophen (metabolite)**

    And
  - **ASA or Caffeine**
  - **NSAIDS may be able to induce the same syndrome independently**

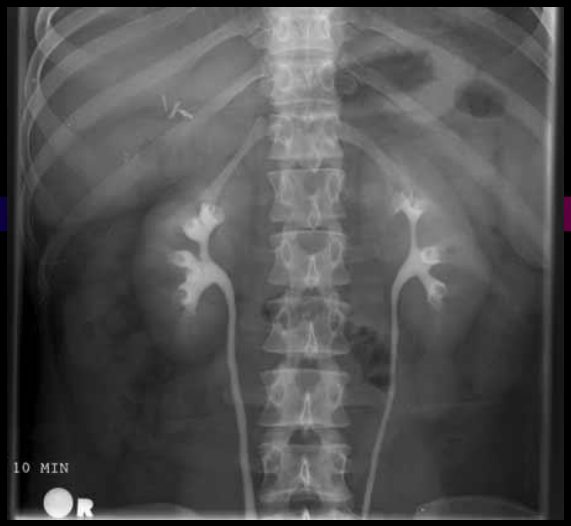
Chronic Interstitial Nephritis : Analgesic Nephropathy

- **Dose dependent**
  - **Years of chronic use**
  - **Cumulative dose of 3 kg of index compound**
  - **Daily ingestion of 1 g/day over 3 years**
- **Pathogenesis**
  - **Intra-renal conversion to reactive metabolites**
  - **Enhanced concentration in the medulla/papillae**

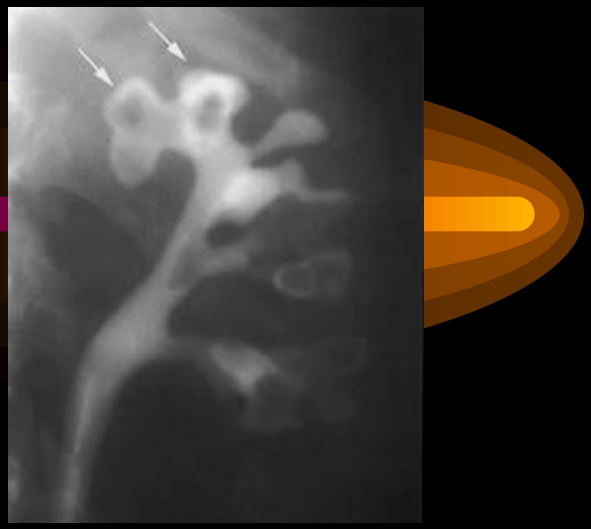
Normal



Normal



Papillary Necrosis

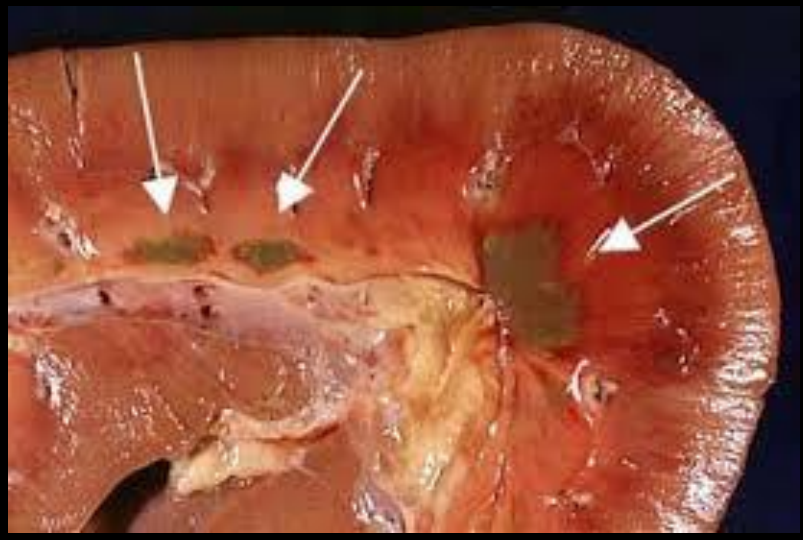


Papillary Necrosis

Blunting of the Calyces

Calcified Papillae

Small contracted kidneys




Papillary Necrosis

Presne C.Kidney Int. 2003;64(2):585
Juurlink Wn. J Am Geriatr Soc. 2004;52(5):794
Rej S. J Geriatr Psychiatry Neurol. 2012 Mar;25(1):51-61

Lithium and the Kidney

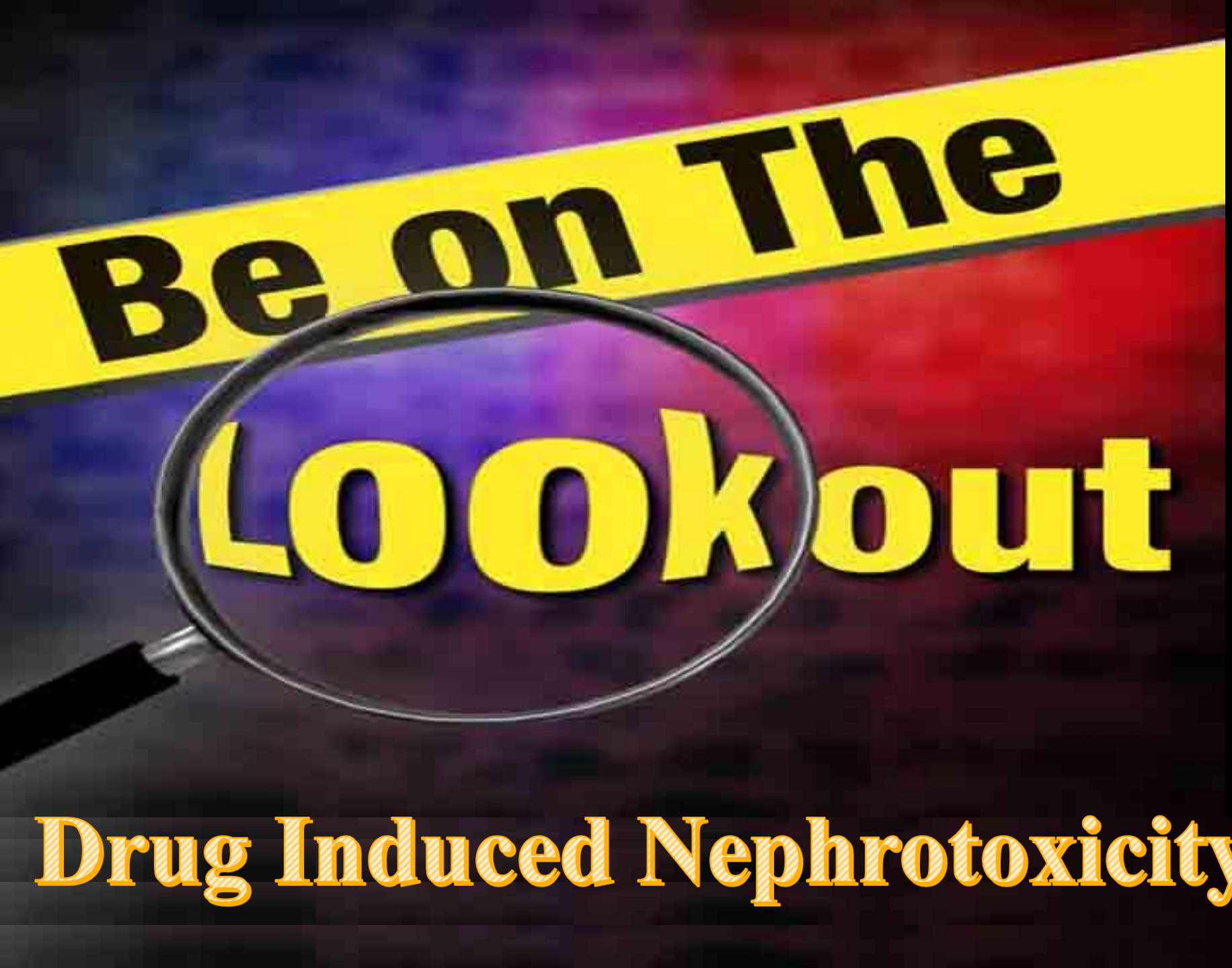
- **Nephrogenic DI (20-40%)**
- **Type I distal RTA**
- **Chronic Interstitial Nephritis (15-20%)** 
- **Hypercalcemia (Hyperparathyroidism – direct effect on the gland)**

Lithium enters the tubules through the Na channel of the collecting ducts (ENAC) in the principal cells

Prevention of nephrotoxicity can be accomplished with the concomitant use of amiloride

Summary : Drug Nephrotoxicity

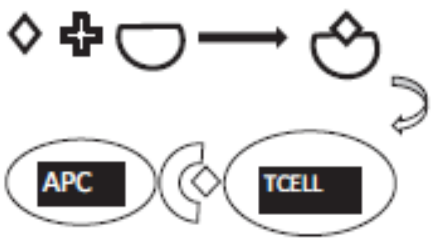
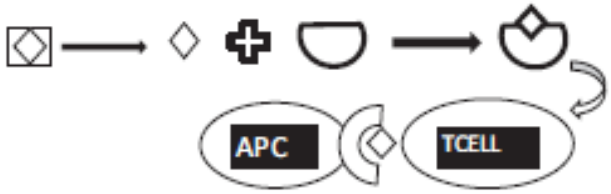
- Interstitial Nephritis is a Type B ADR represents an important cause of both AKI and CKD in the outpatient and inpatient population and is increasing in frequency
- AIN from PPI often leads to CKD as a result of delayed diagnosis and lacks the typical clinical presentation of AIN
- Early discontinuation of the offending drug and possibly the use of steroids may reduce the risk of CKD in drug induced AIN
- CIN often results from poorly treated AIN but also may develop directly without preceding AIN
- Analgesic Nephropathy and Lithium represent two typical causes of CIN
- Drug induced Nephrotoxicity represents a serious consequence of ADR : careful review of the medication list is essential in all patients with AKI or CKD



Drug Induced Nephrotoxicity

Raghavan R. Adv Chronic Kidney Dis. 2017;24(2):64-71

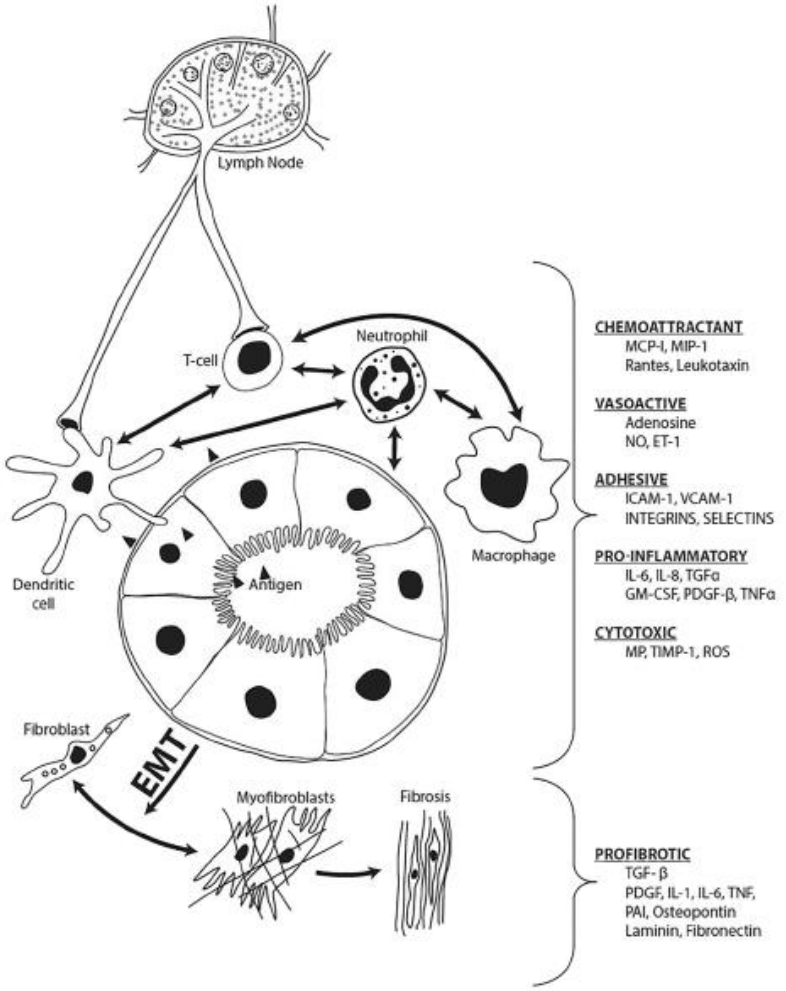
Mechanisms of Drug Induced AIN

Mechanism	Illustration	Published Drugs Linked to AIN
Hapten		Penicillins[1,46]: Amoxicillin, Ampicillin, Dicloxacillin, Oxacillin, Benzylpenicillin, Carbenicillin, Cloxacillin, Flucloxacillin, Methicillin, Piperacillin/Tazobactam Cephalosporins[1,46]: Cefaclor, Cefepime Cefamandole, Cefazolin, Cefoperazone, Cefotaxime, Cefotetan, Cefoxitin, Ceftriaxone, Cephalexin, Cephaloridine, Cephalothin, Cephradine NSAIDs Including Salicylates[1,47]: Aceclofenac, Alclofenac Aspirin, Diclofenac, Naproxen
Pro-hapten		Sulfonamide-Containing Drugs[1,8,48-50]: Celecoxib, Chlorthalidone, Chlorpropamide, Furosemide (Frusomide), Hydrochlorothiazide, Trimethoprim-sulfamethoxazole
p-i Concept		Other[1,6,7,51]: Carbamazepine (HLA-B*15:02), Allopurinol (HLA-B*58:01, HLA-B*58:01), Flucloxacillin (HLA-B*57:01)

Abbreviations: ◇, Drug (as hapten); ⊃, carrier protein; ⊠, nonreactive drug metabolized into a reactive compound that binds to specific proteins (haptenization); APC, antigen-presenting cell; ⊃, host-specific T-cell receptor; (MHC, major histocompatibility complex protein expressed by host.

Raghavan R. Adv Chronic Kidney Dis. 2017;24(2):64-71

Drug Induced – AIN : Major role of the Proximal Tubule



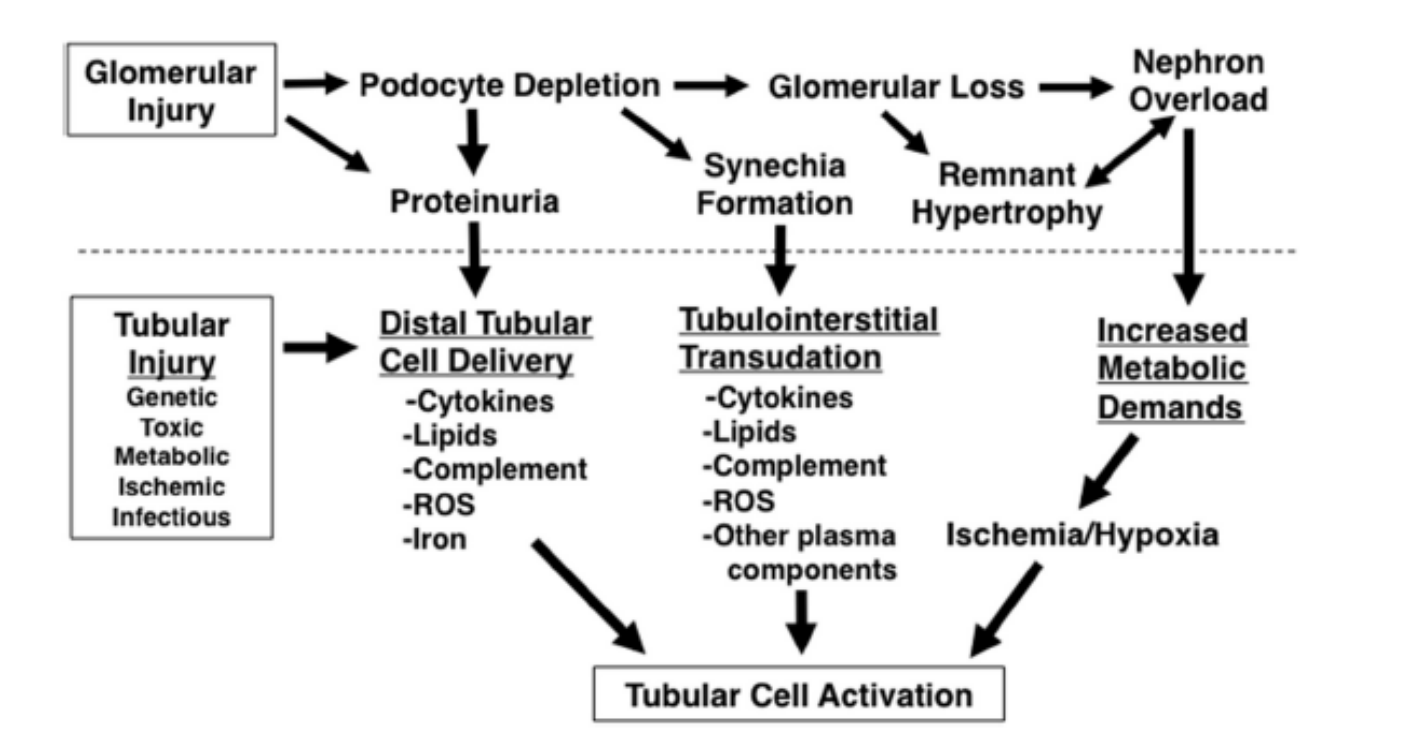
High blood flow of the kidney predisposed it to increase delivery of drugs

Filtration / secretion of the drug with subsequent absorption / metabolism by the proximal tubule

3 phases :
“antigen recognition” and presentation phase
an “integrative” or
regulatory (primarily cellular) phase an “effector”or mediator (primarily humoral) phase

Schnaper H.Adv Chronic Kidney Dis. 2017;24(2):107-116

Tubulointerstial Injury is the Final Common Pathway to CKD/ESRD in Glomerular and Interstitial Diseases



The mal-adaptive repair of injured proximal and distal tubular cells from any process leads to progressive interstitial fibrosis –

Caveat : The prognosis of any kidney disease is dependent on the degree of tubulointerstitial injury (not the degree of glomerular disease)

Location of Chemotherapy Induced Nephrotoxicity