ACUTE INTERSTITIAL NEPHRITIS

A chameleon in a globalized world

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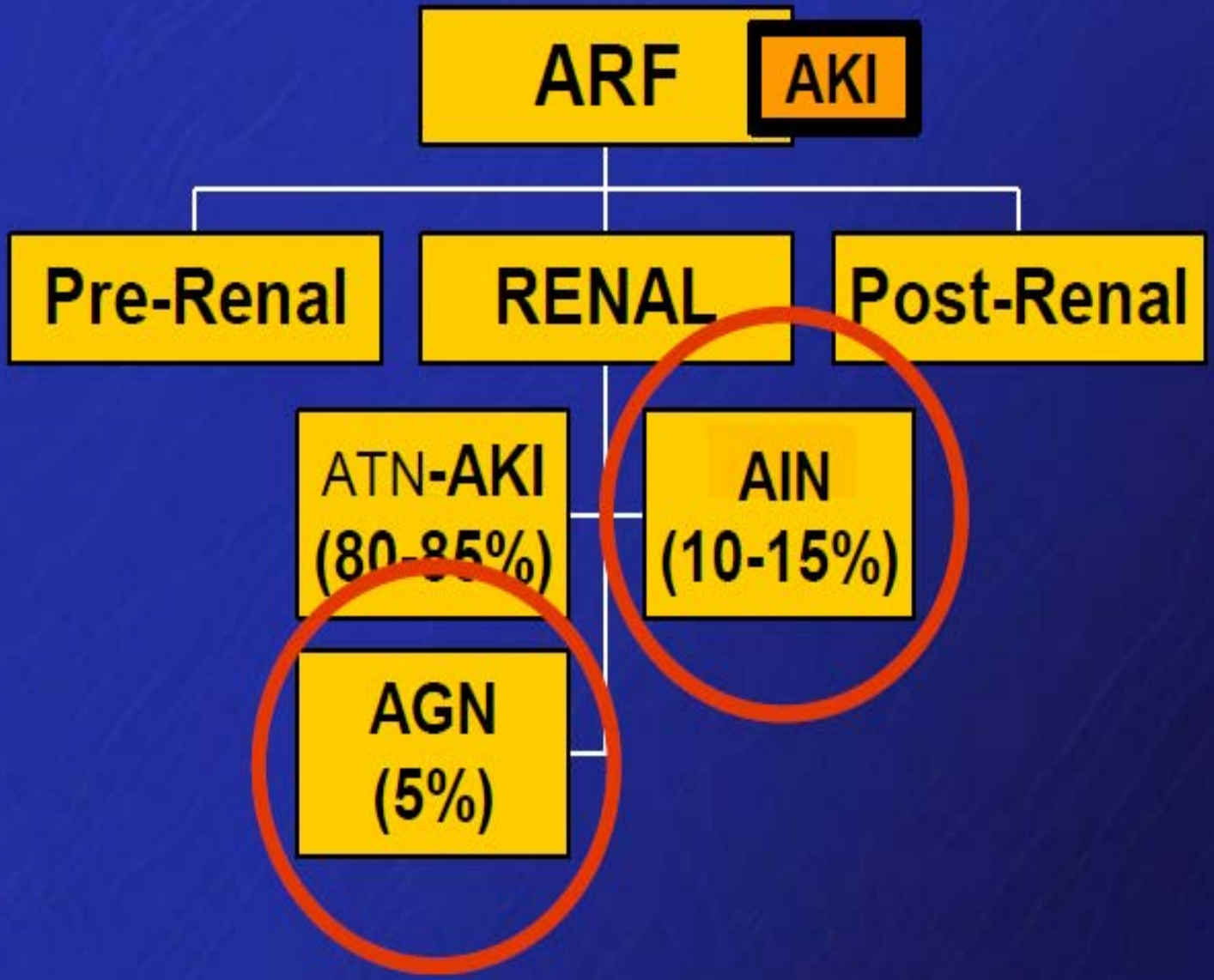
DEFINITION
AND PREVALENCE

- Acute interstitial nephritis (AIN) is a renal lesion characterized by an inflammatory infiltrate in the kidney interstitium

- Classically presents as acute renal failure (ARF) after the use of some offending drug or secondary to infection, autoimmune disorders or other systemic diseases



Garabed Eknoyan, MD

AIN is underrecognized and underdiagnosed cause of AKI

- 1-10% (average 2,8%) of all kidney biopsies
- 6.5-35% (average 13.5%) of biopsies in ARF

Raghavan R and Eknoyan G. Clinical Nephrology, 2014

Definitive diagnosis

- biopsy
- lab or clinical indentification of the causative factor

UNDERESTIMATED DUE TO...

- relatively low index of suspicion
- general reluctance to biopsy if laboratory abnormalities are minor and the symptoms subside after change of medications
- a confirmatory biopsy is often not done in older and frail patients

SNEAK PEEK OF ETIOLOGY

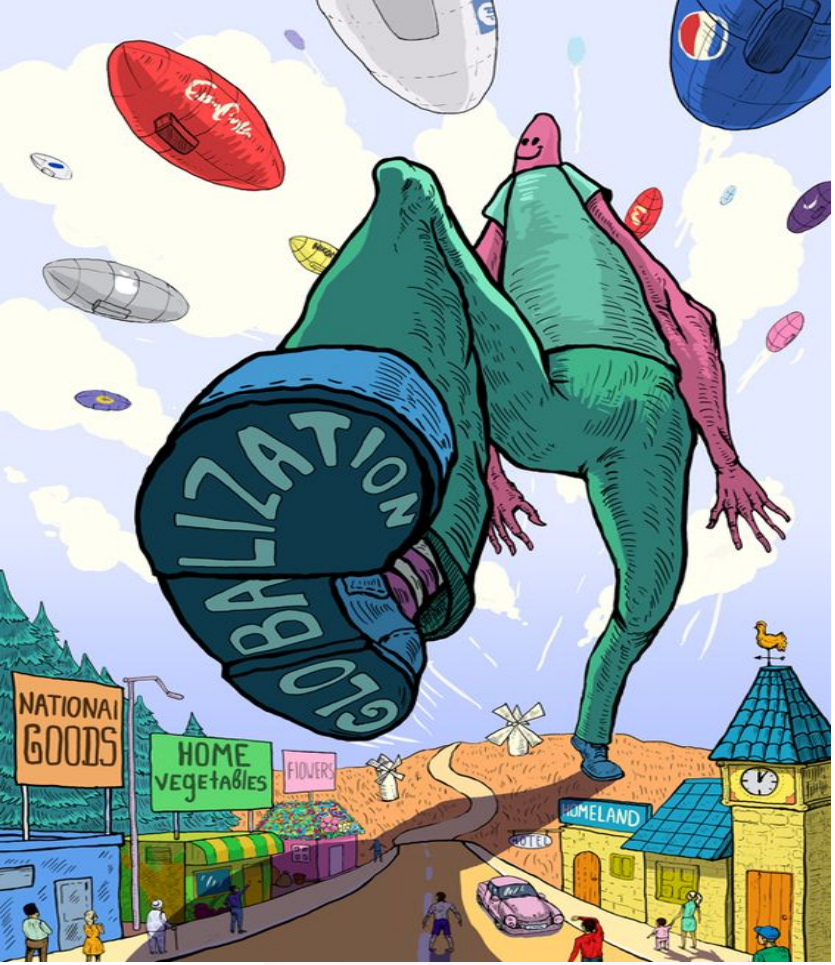
- most often **drugs**
- Less frequently **infection** or **sarcoidosis**
- **autoimmune disorders** or other **systemic disease**
- **infections** remote to the kidney (eg, *Legionella*, leptospirosis, and streptococcal organisms)
- and **tubulointerstitial nephritis with uveitis** (TINU) syndrome

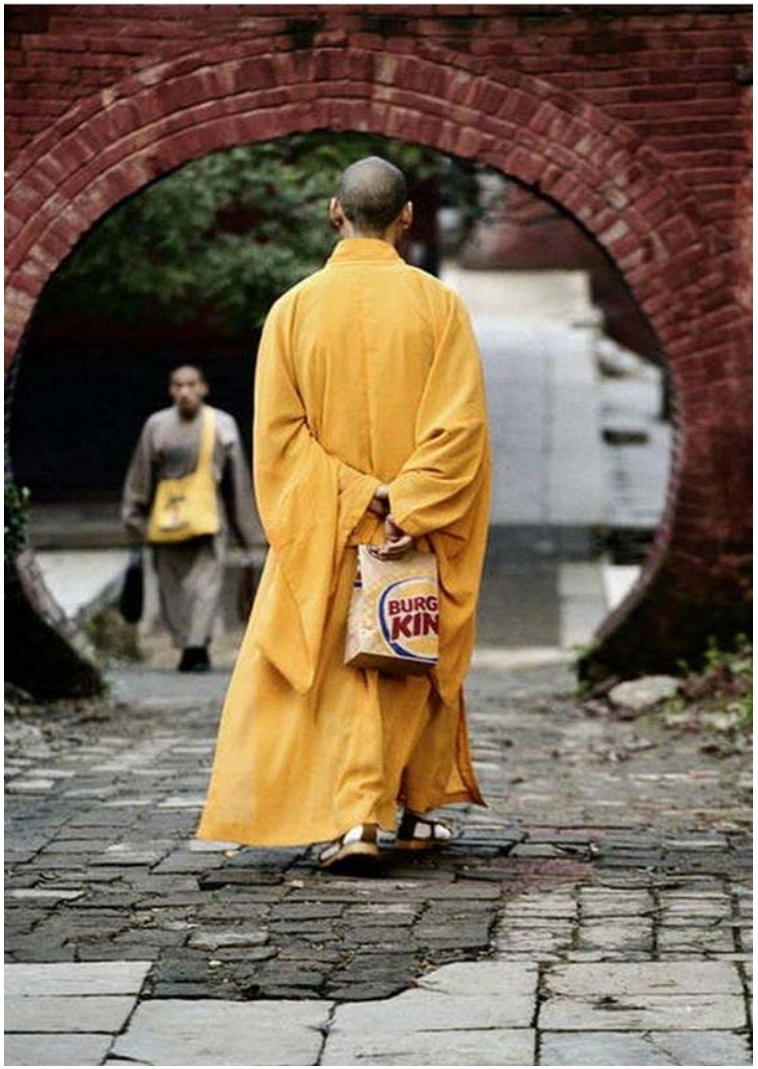
In developed world, drugs account for around 70% of all cases (150 different agents)

The remaining cases are due to infections, autoimmune diseases, and rarely idiopathic?

...geographycally dependand

Raghavan R and Eknoyan G. Clinical Nephrology, 2014

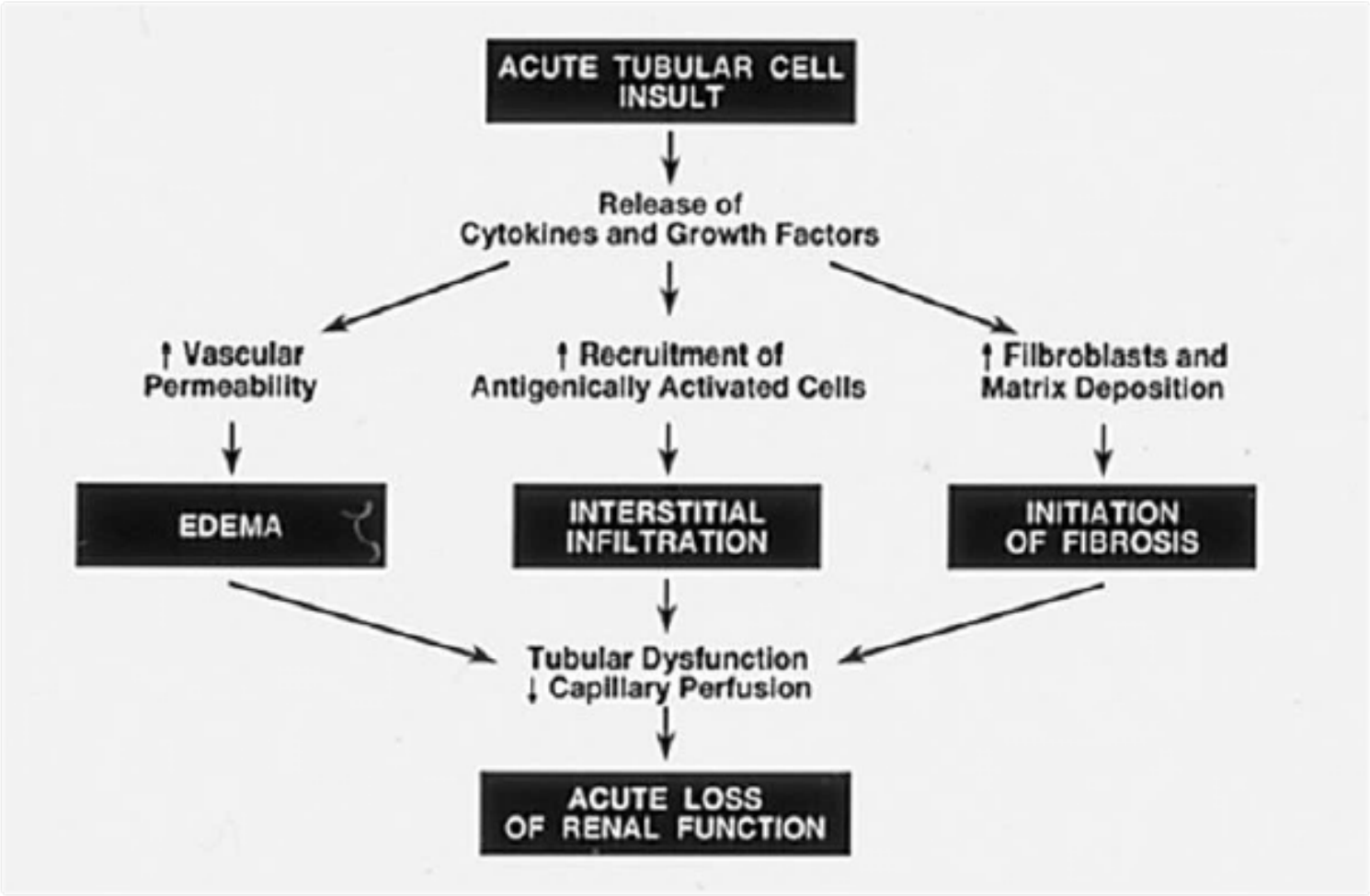

GLOBALIZATION
NATIONAL GOODS
HOME vegetables
FLOWERS
HOMELAND


BURG KIN

PATHOGENESIS

- The central component- altered tubular function

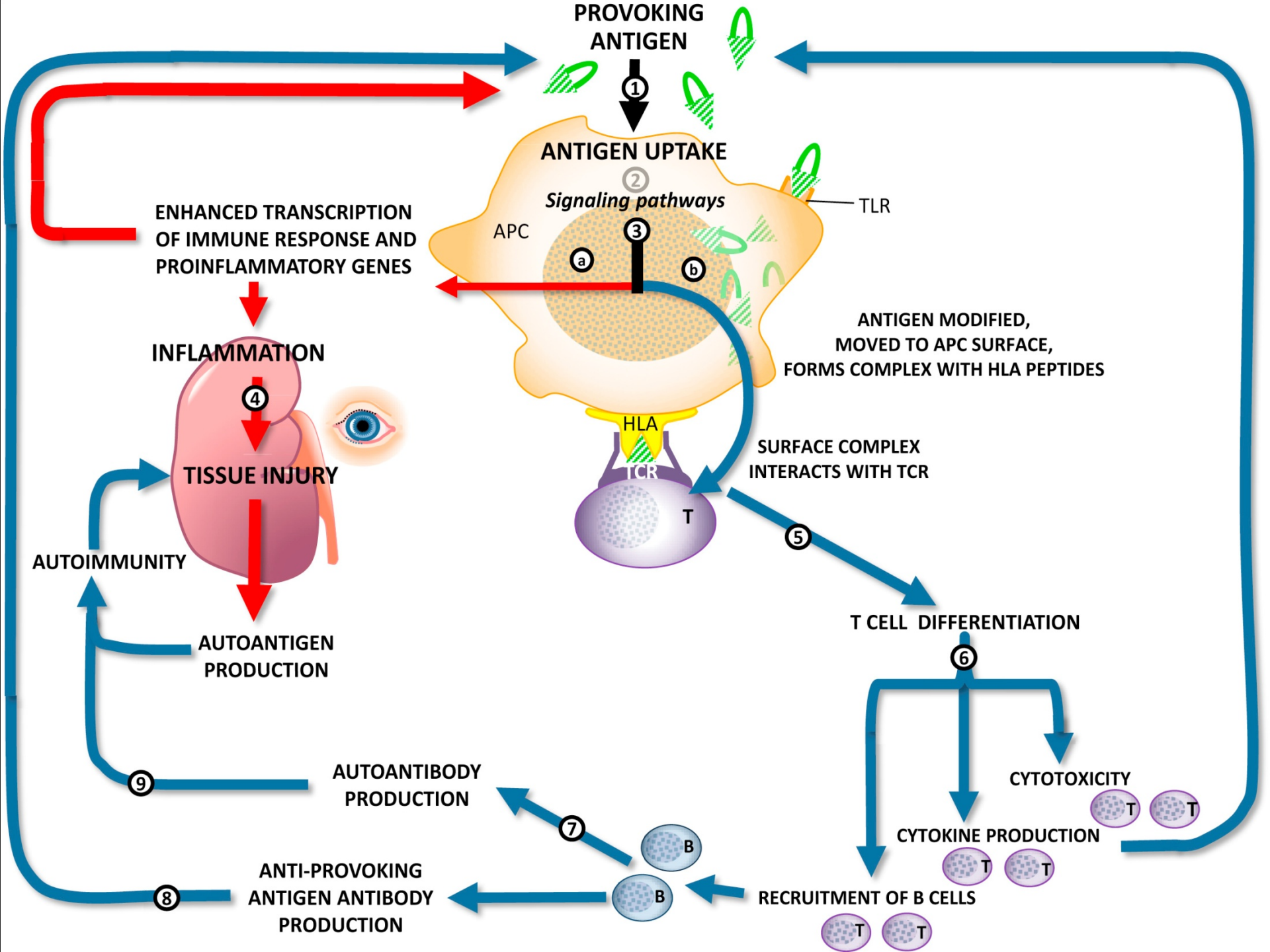
- It preceedes glomerular injury and decrements in filtration rate.


ACUTE TUBULAR CELL INSULT
Release of Cytokines and Growth Factors
↑ Vascular Permeability
↑ Recruitment of Antigenically Activated Cells
↑ Fibroblasts and Matrix Deposition
EDEMA
INTERSTITIAL INFILTRATION
INITIATION OF FIBROSIS
Tubular Dysfunction
↓ Capillary Perfusion
ACUTE LOSS OF RENAL FUNCTION

- **idiosyncratic delayed hypersensitivity** immune reactions to foreign antigens
  - occurs in only a small No of exposed individuals
  - not dose-related
  - other systemic manifestions of hypersensitititivity (fever, skin rash, eosinophilia, arthralgia)
  - reaction recurs on re-exposure to the same drug or one of its congeners.

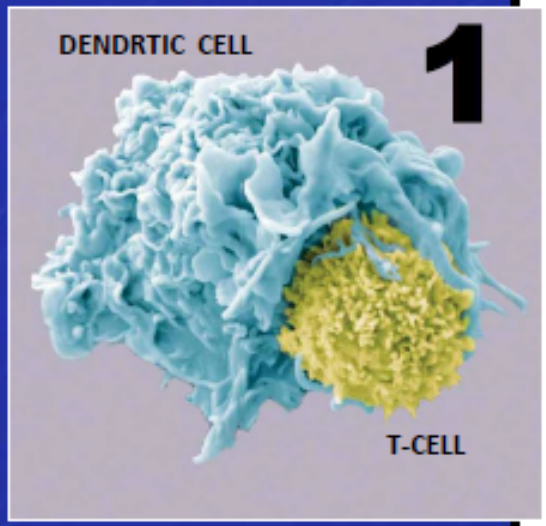
- **T cells central** pathogenetic role...

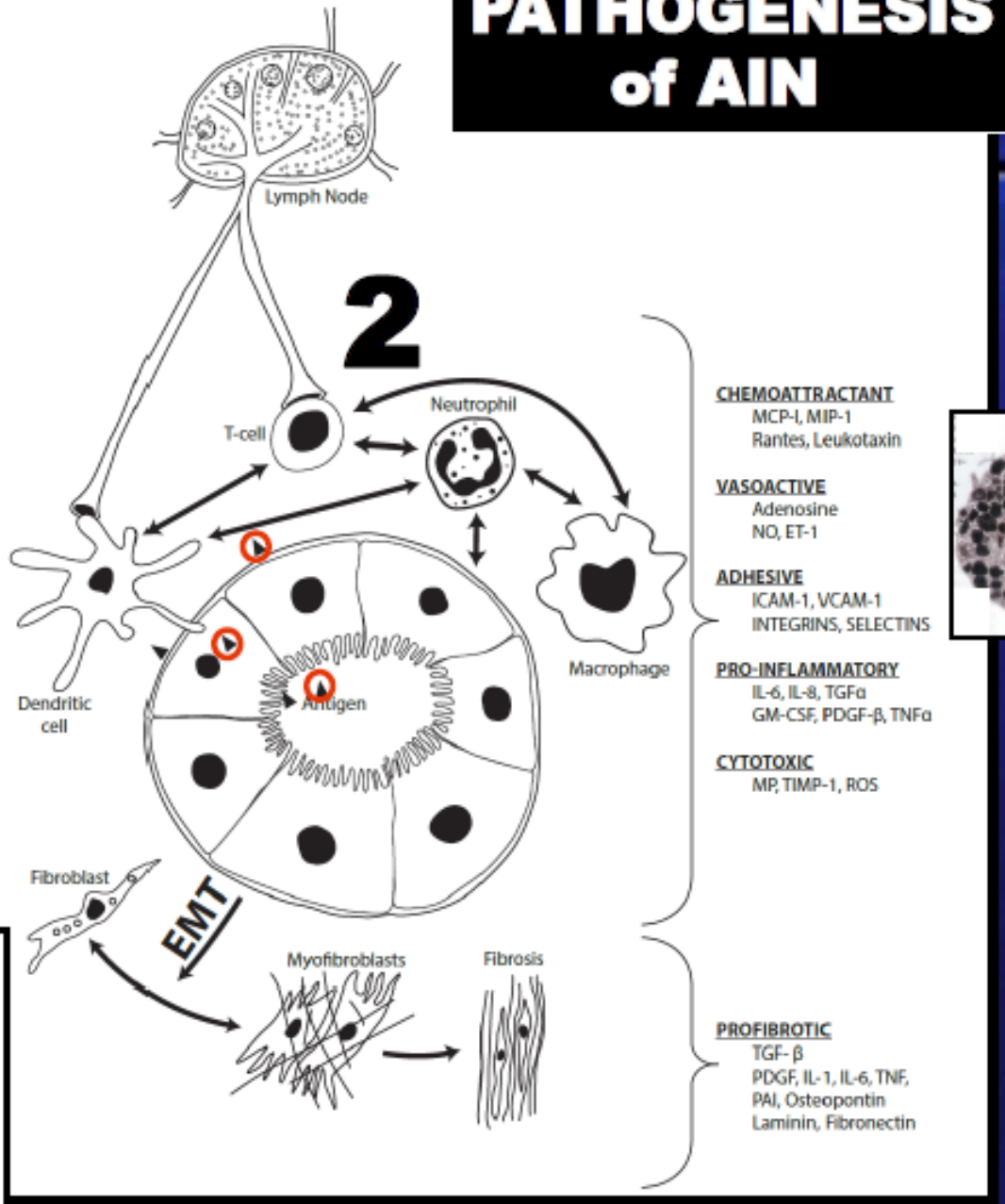
- **dysregulated immunologic resposes** that ensues Ag exposure
  - skin eruptions, eosinophylia, fever, hematologic abnoralities, and solid organ involvement (liver, lung, kidneys...)


PROVOKING ANTIGEN
1
ANTIGEN UPTAKE
2
Signaling pathways
TLR
APC
3
a
b
ENHANCED TRANSCRIPTION OF IMMUNE RESPONSE AND PROINFLAMMATORY GENES
ANTIGEN MODIFIED, MOVED TO APC SURFACE, FORMS COMPLEX WITH HLA PEPTIDES
INFLAMMATION
4
HLA
TCR
T
SURFACE COMPLEX INTERACTS WITH TCR
TISSUE INJURY
AUTOIMMUNITY
5
T CELL DIFFERENTIATION
6
AUTOANTIBODY PRODUCTION
9
AUTOANTIGEN PRODUCTION
CYTOTOXICITY
T
T
CYTOKINE PRODUCTION
T
T
7
B
ANTI-PROVOKING ANTIGEN ANTIBODY PRODUCTION
8
B
RECRUITMENT OF B CELLS
T
T

PATHOGENESIS of AIN

1. Activation
2. Signaling
3. Fibrogenic
4. Destructive





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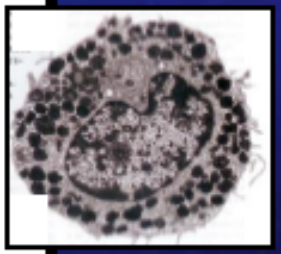
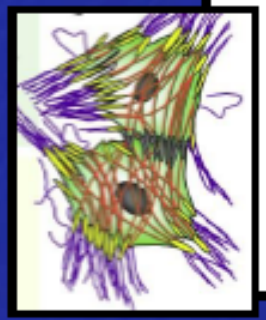


MACROPHAGE

4



MYOFIBROBLAST

Clin Nephrol 2014; 82:149-162

Garabed Eknoyan, MD

AIN – Outcomes

Recovery

GOOD

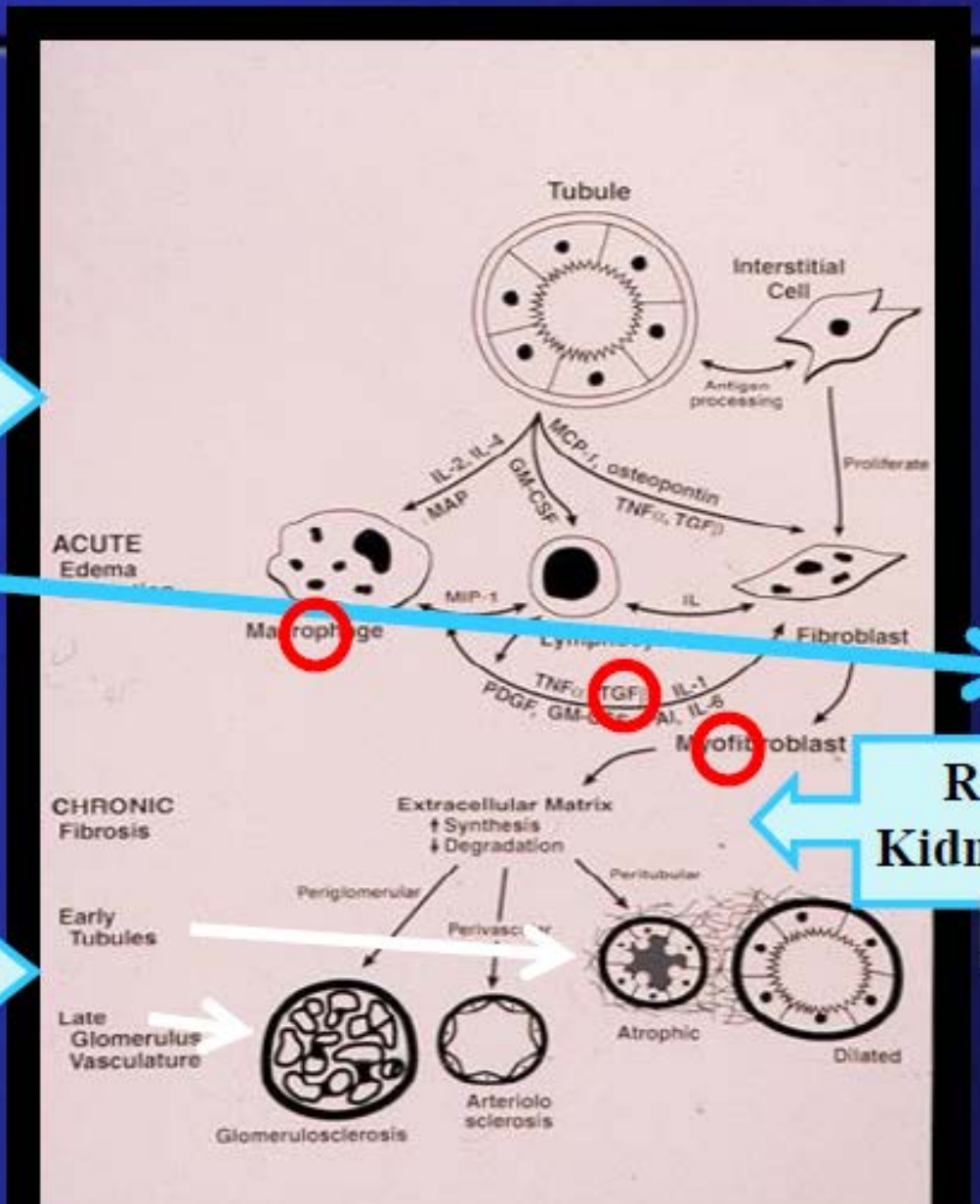
ACUTE
Edema
Infiltration
Tubular Injury

BAD

2

CHRONIC
Fibrosis
Tubular atrophy
and dilatation

ESRD



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Residual Kidney Injury

CKD

CORRELATES OF OUTCOME

- severity of pathology
- time to diagnosis (and treatment)
- kidney function (tubular and glomerular disfunction)

DIAGNOSIS

Differential
Structural
Laboratory
Clinical

	Acute Tubular Necrosis (ATN)	Acute Interstitial Nephritis (AIN)
Onset following injury	Hours to days	Days to weeks
Urine volume	Oliguria < 500 mL/d	Polyuria (> 2,000 mL/d)
Clinical features	Hemodynamic instability	Rash (25 – 40%), fever (35 – 70%), back pain (25 – 40%), arthralgia (25 – 40%)
Histology	Tubular epithelial cell injury	Interstitial cellular infiltrates, edema, tubulitis
Eosinophilia	Absent	Present (35 – 60%)
Tubular dysfunction†	Rare	Very common
FE_{Na}#	> 1%	> 1%
Urine microscopy	Epithelial cell and broad granular casts	Hematuria (70 – 90%), pyuria (75 – 85%), eosinophiliuria* (variable)
Treatment	Hemodynamic resuscitation, withdrawal of nephrotoxic agent, supportive care	Withdrawal of offending agent, supportive care, limited trial steroids
Prognosis	Recovery (65%), CKD (~ 35%)	Recovery (65%), CKD (~ 35%)

Clin Nephrol 2014; 82:149-162

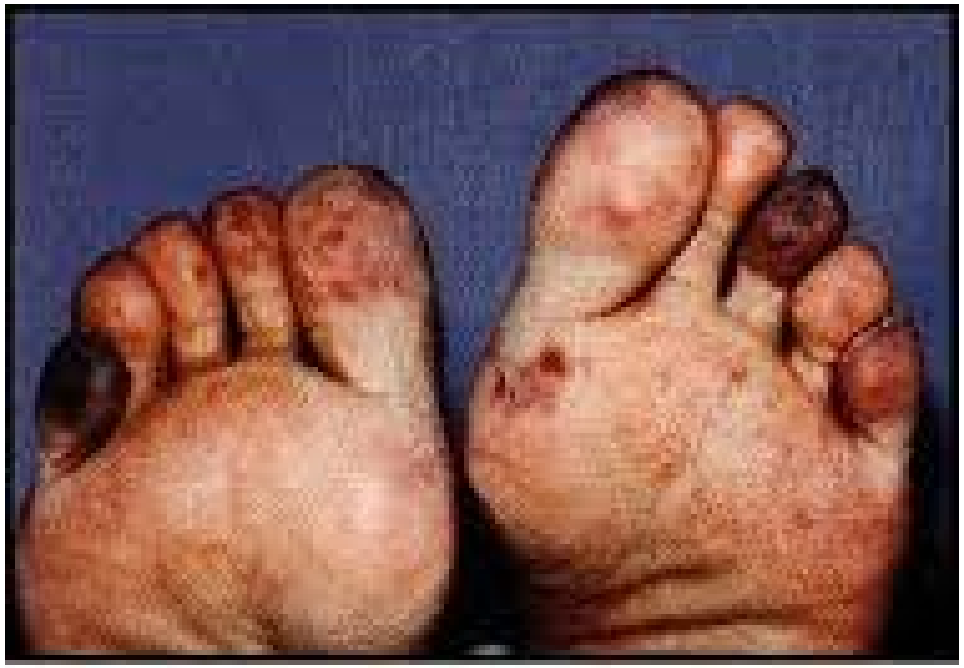
Differentiation from GN

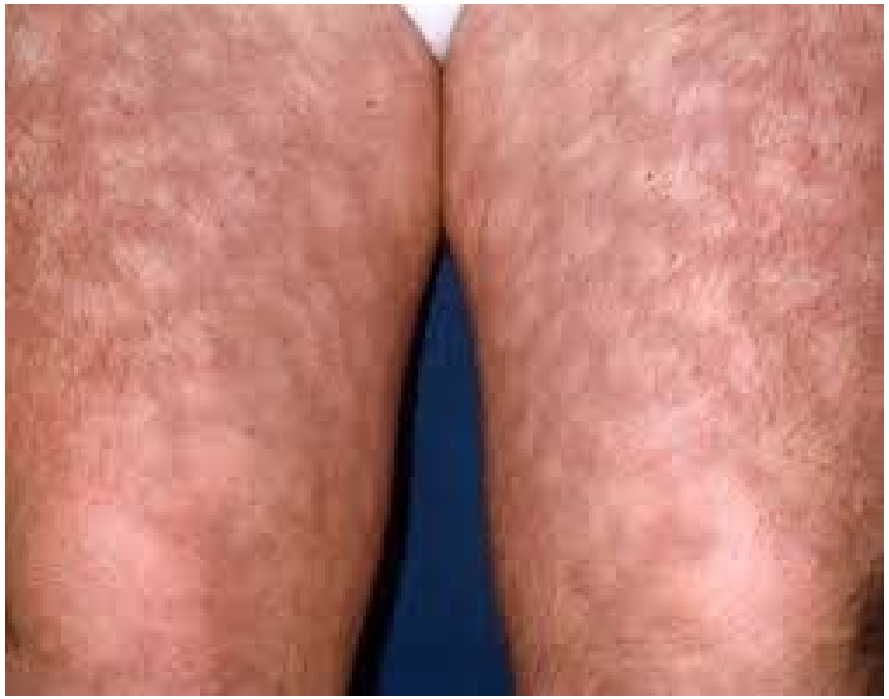
- GNF
  - hypertension
  - edema
  - oliguria

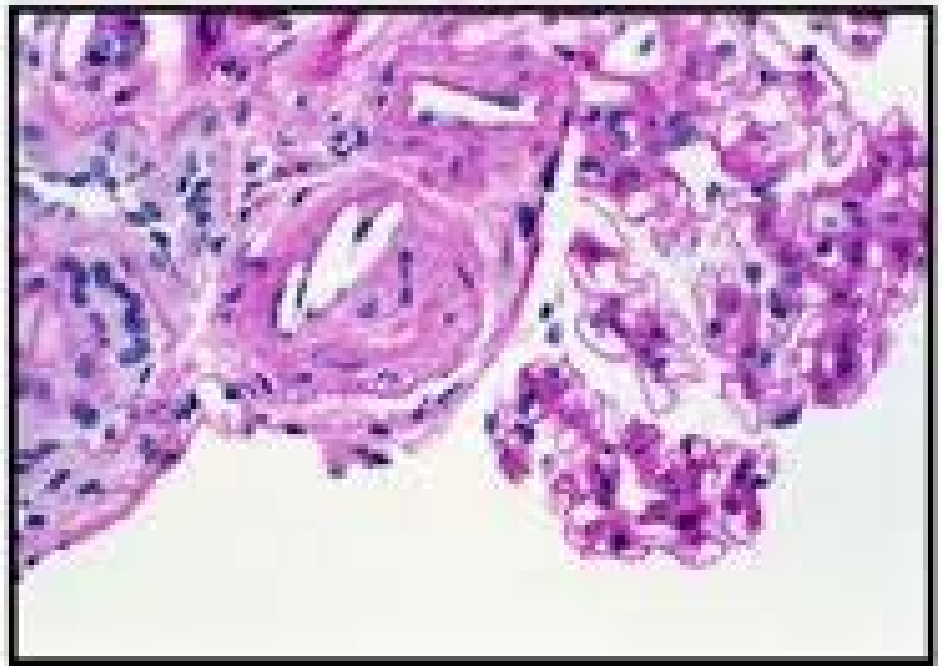
- AIN
  - subnephrotic proteinuria (nephrotic- NSAID)....
  - pyuria, hematuria, and white cell casts

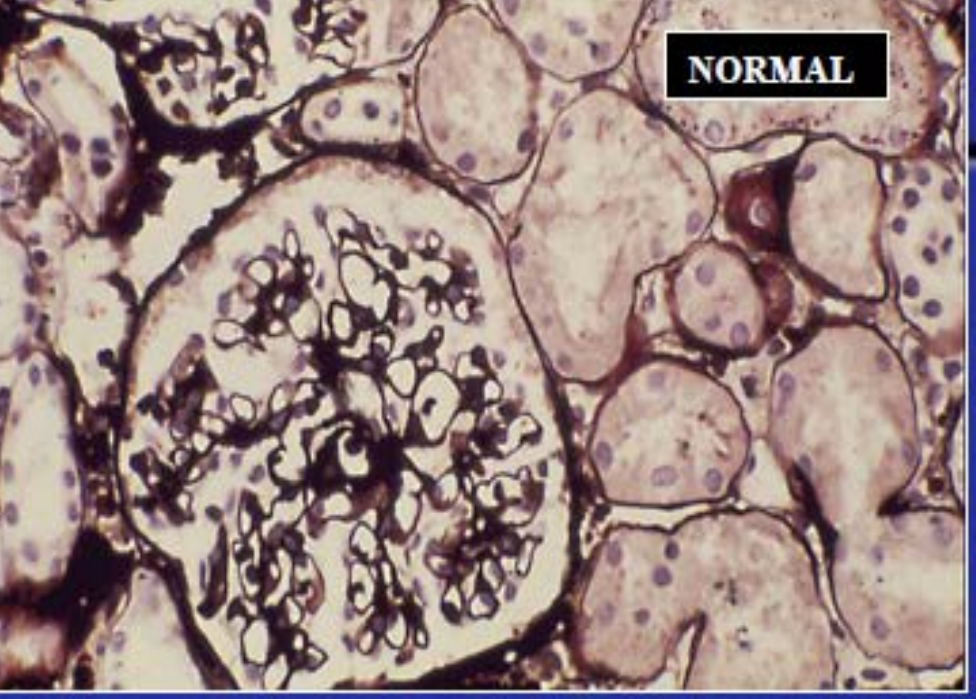
Differentiation from renal atheroemboli

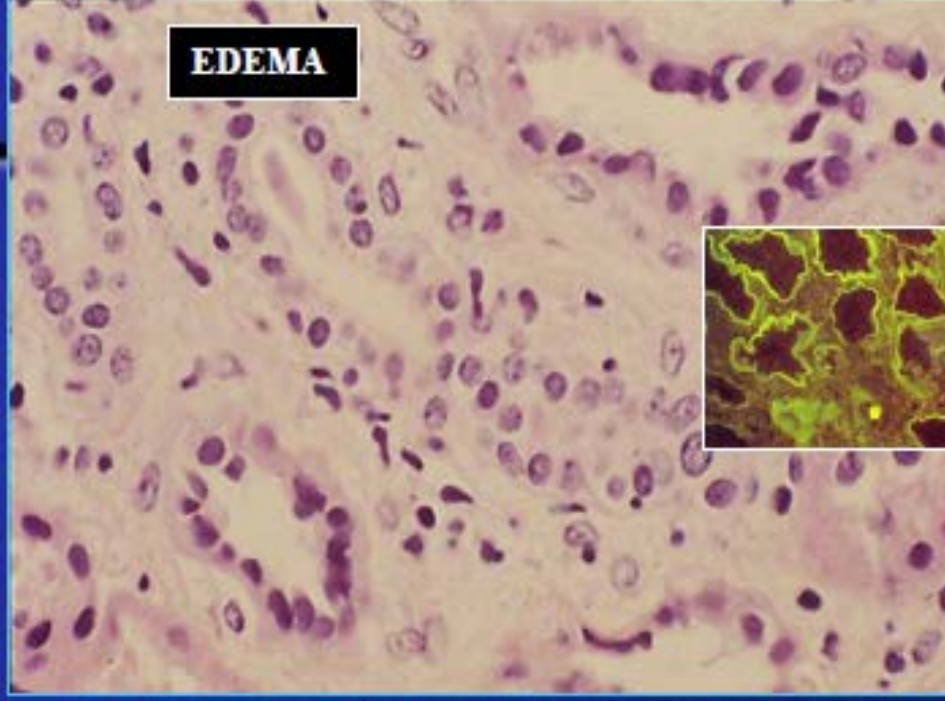
- predominance of white blood cells and white blood cell casts
- particularly among older patients
- may present with eosinophiluria, eosinophilia, and skin lesions
- commonly reticular (livedo reticularis) with digital infarcts
- majority preceded by an endovascular procedure

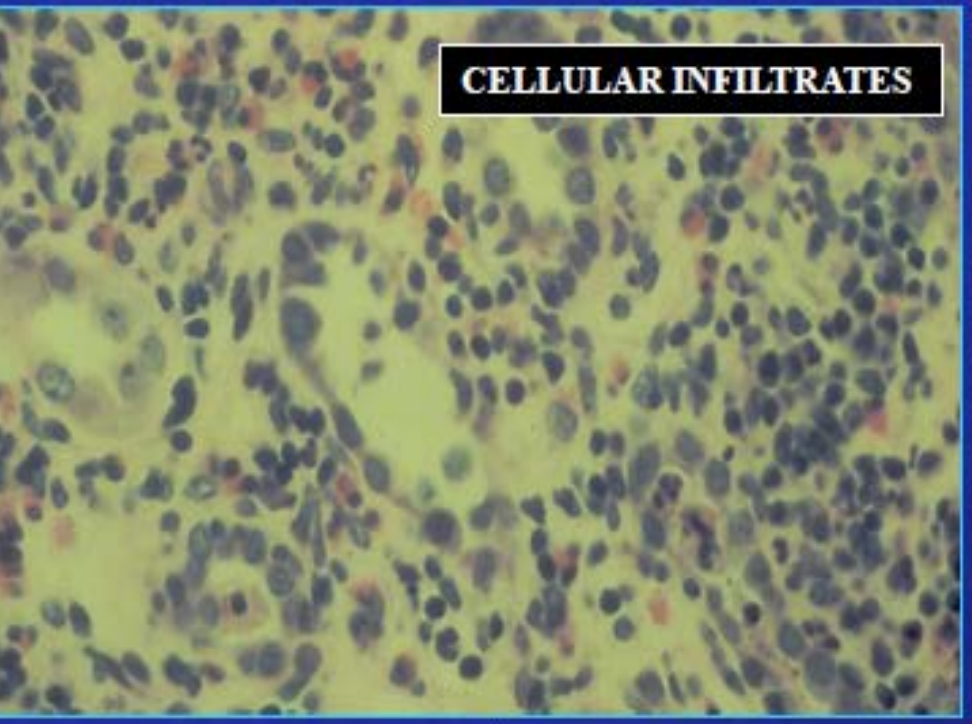


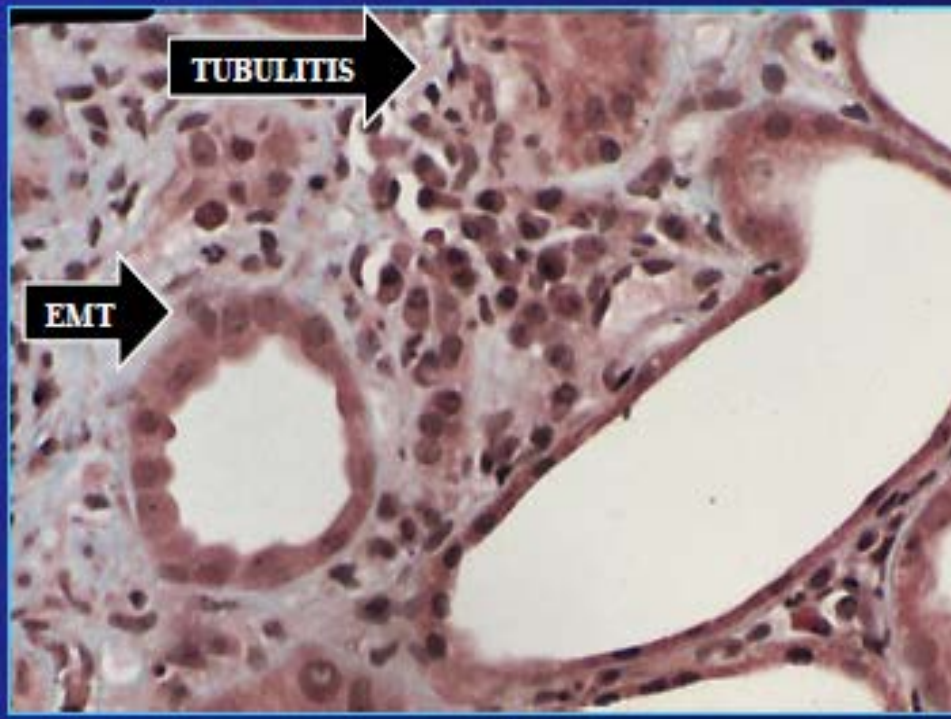




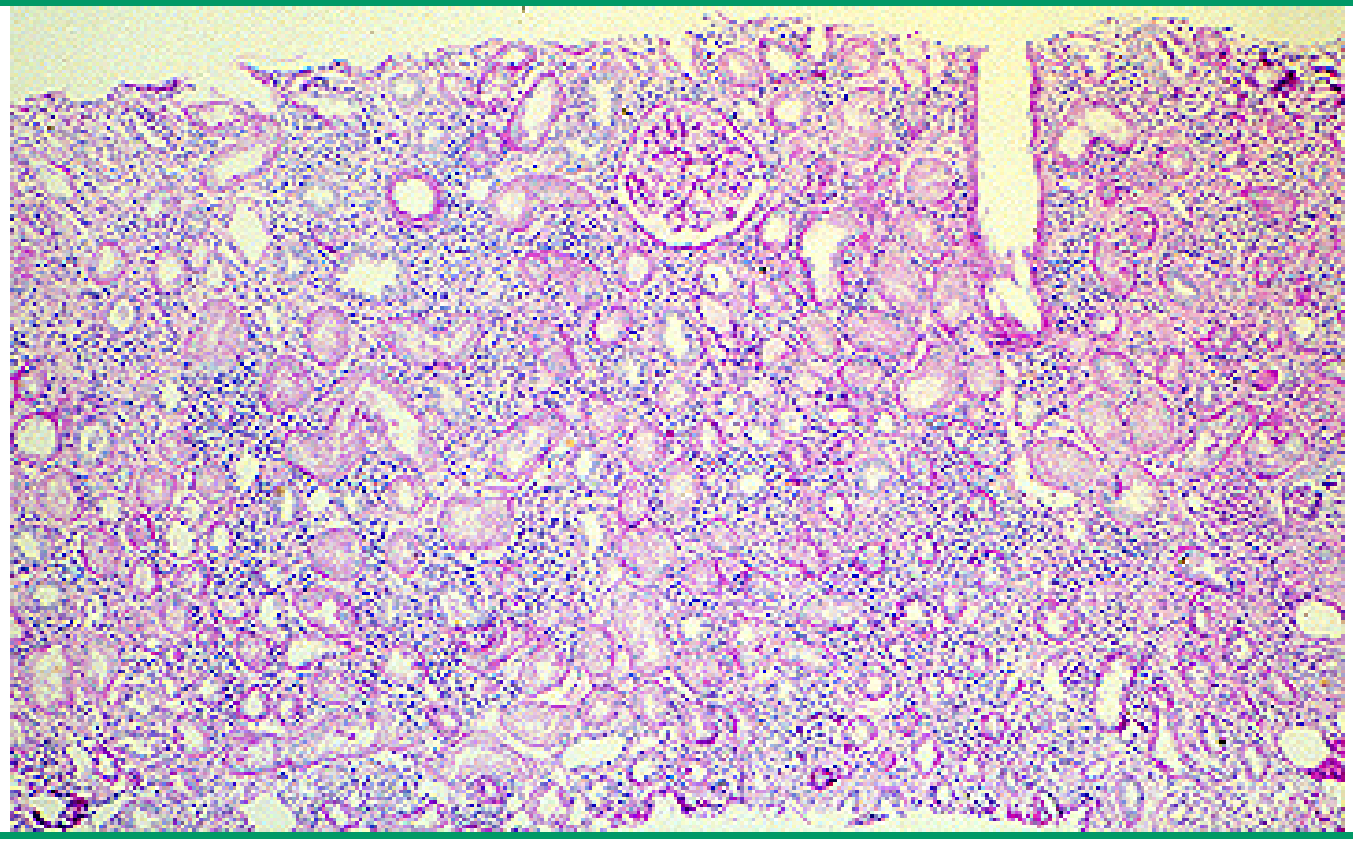

NORMAL


EDEMA


CELLULAR INFILTRATES


TUBULITIS
EMT

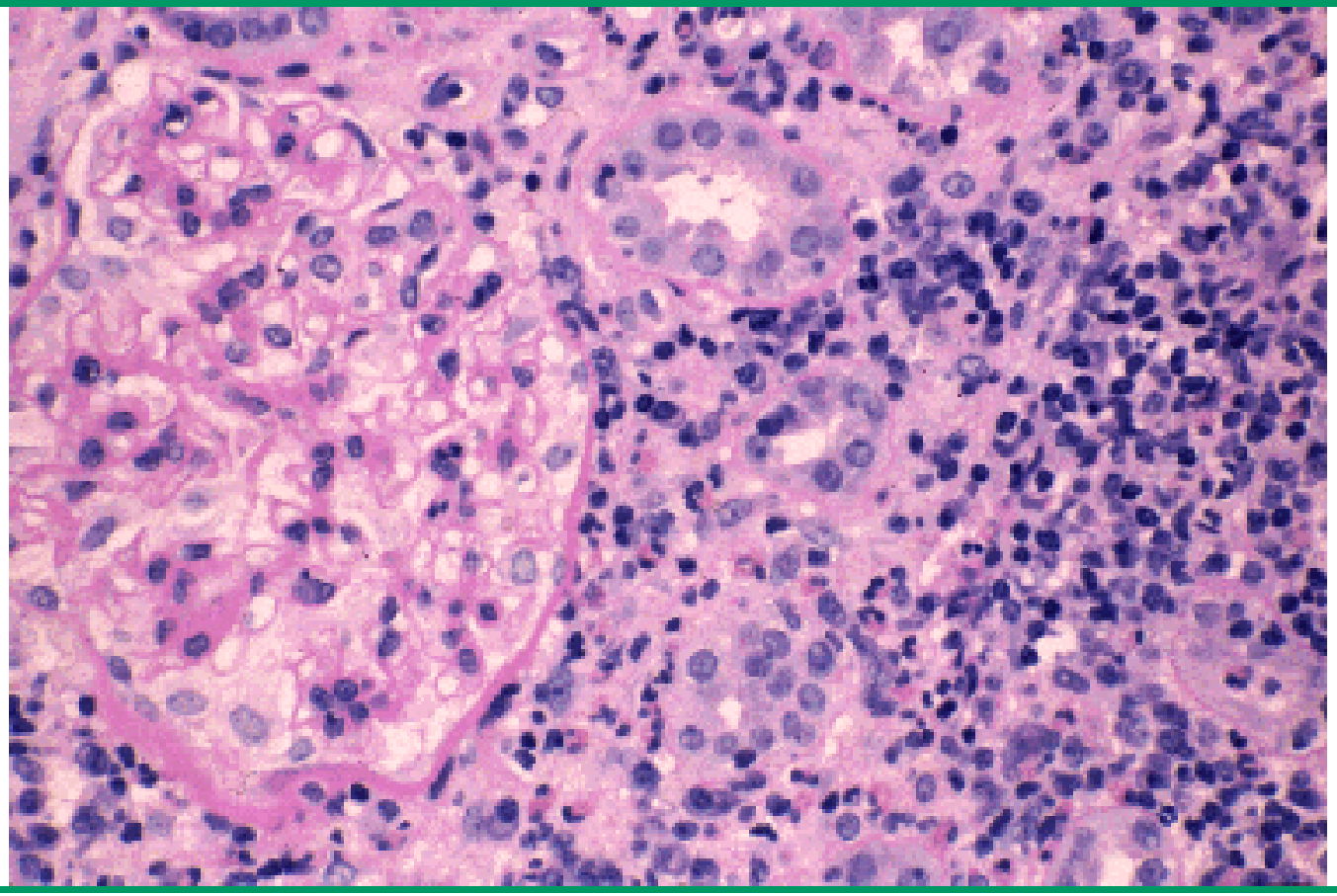
Low power light micrograph of kidney biopsy of a patient with severe acute interstitial nephritis



Low power view of severe acute interstitial nephritis showing diffuse interstitial inflammatory infiltrate. One normal glomerulus is present at the top of the slide.

Courtesy of Helmut Rennke, MD.

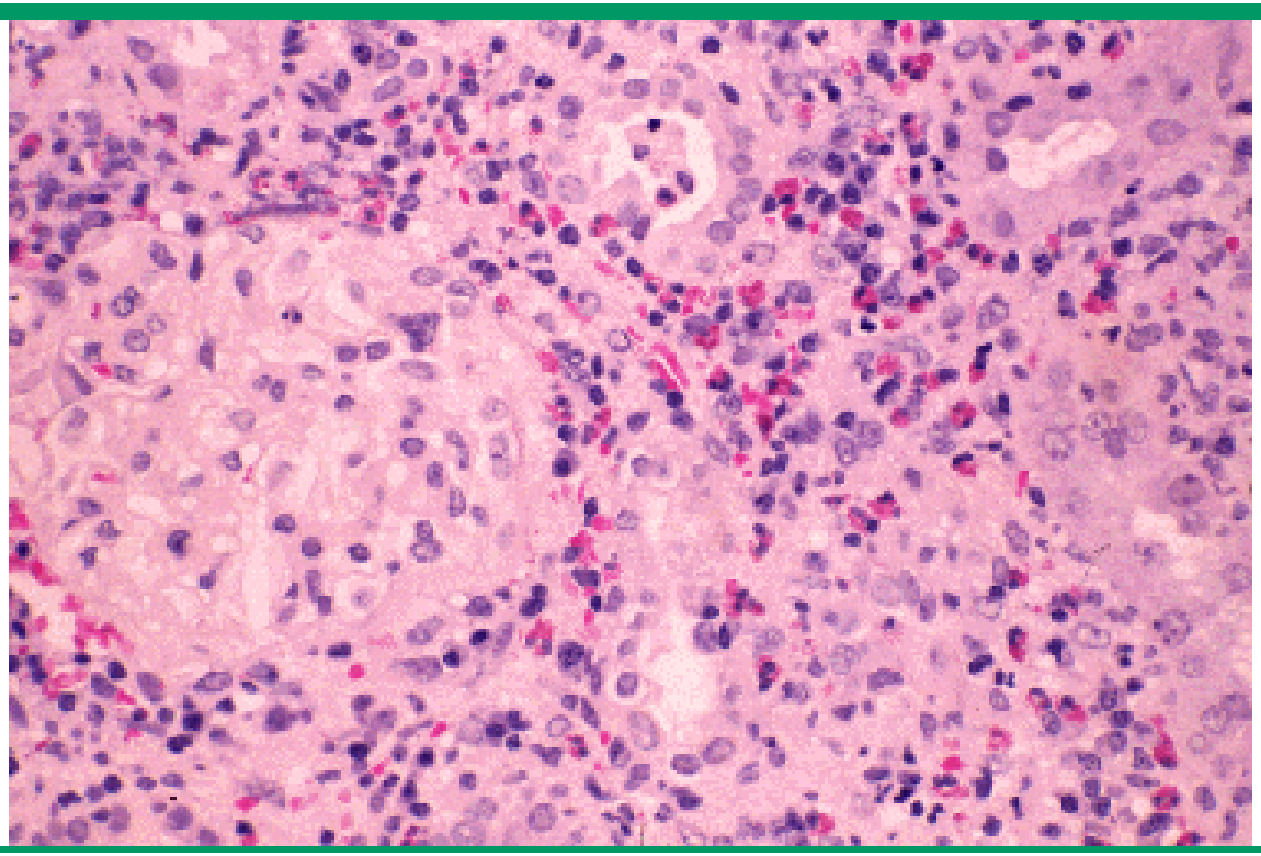
High power light micrograph of kidney biopsy of a patient with acute interstitial nephritis



High power light micrograph of acute interstitial nephritis showing diffuse interstitial infiltrate of inflammatory cells on the right and an uninvolved glomerulus on the left.

Courtesy of Helmut Rennke, MD.

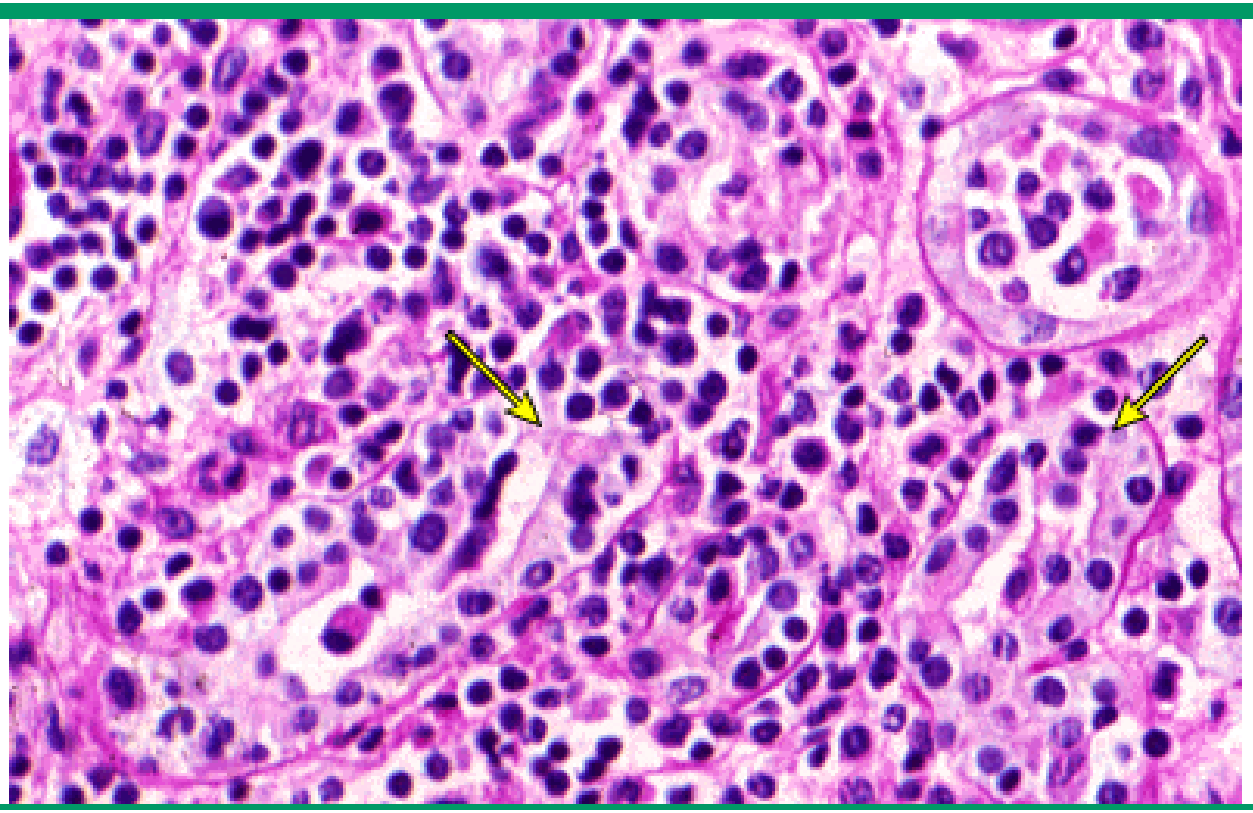
Light micrograph of kidney biopsy of a patient with acute interstitial nephritis showing eosinophils



Light micrograph with hematoxylin and eosin stain of acute interstitial nephritis showing diffuse interstitial infiltrate with many red-staining eosinophils. An uninvolved glomerulus is on the left.

Courtesy of Helmut Rennke, MD.

High power light micrograph of kidney biopsy of a patient with acute interstitial nephritis showing diffuse infiltration of mononuclear cells



High power light micrograph of interstitial nephritis showing diffuse interstitial infiltrate of mononuclear cells, many of which are actively invading the tubules leading to disruption of the tubular basement membranes (arrows). A white cell cast is present in the tubule in the upper right corner.

Courtesy of Helmut Rennke, MD.

Clinical and laboratory presentation

With AIN from any cause, patients may present with nonspecific signs and symptoms of acute renal dysfunction

- **Classical allergic-type reaction:**
- Rash – 15 % (25-40%)
- Fever – 27 % (35-40%?)
- Eosinophilia – 23 % (35-60%?)
- Triad of rash, fever, and eosinophilia – 10 %
- Arthralgias 45 % (25-40%)

- Flank pain 20-40%
- Hypertension 10-15%?

- **Symptoms related to the underlying disease** (infection or systemic condition)

- **Microbiologic features unique to different culprit organisms**

- **No radiographic findings diagnostic for AIN**

Raghavan R and Eknoyan G. Clinical Nephrology, 2014
Praga M and Appel G, UpToDate, 2018
Praga M and González E, Kidney Int 2010

Signs of **tubulointerstitial damage** (eg Fanconi sy, RTA) are present but **rarely dominate – only high clinical suspition** would point investigations at that direction

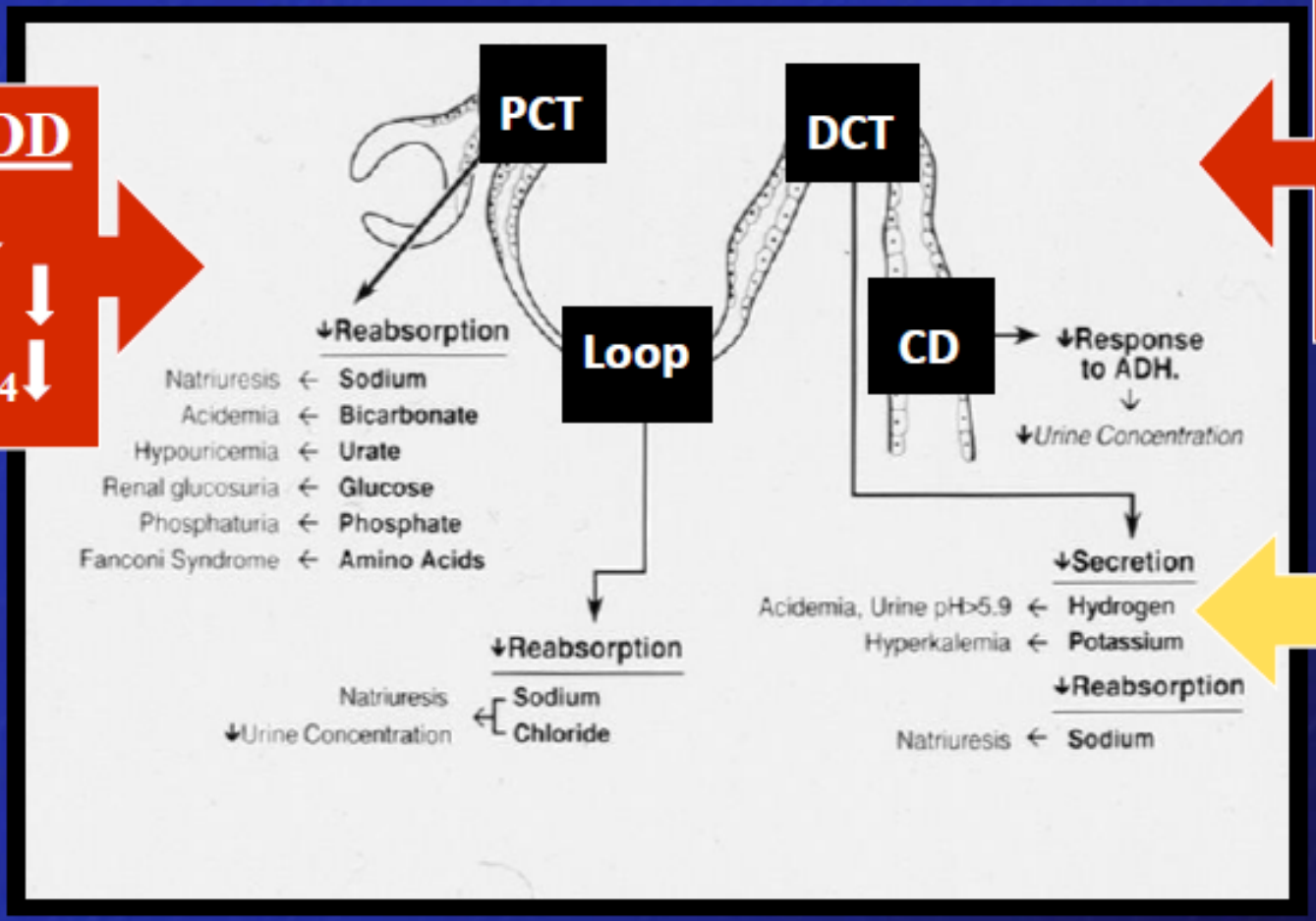
Neelakantappa K et al. Am J Kidney Dis, 1993

The early diagnosis of AIN by detecting tubular disfuncition is central for its diagnosis at potentialy reversible stage

Raghavan R and Eknoyan G. Clinical Nephrology, 2014

AIN is a disease of Tubular Dysfunction…

BLOOD
CO_2 ↓
Urate ↓
± PO_4 ↓



BLOOD
K^+ ↑
Disproportionate
CO_2 ↓

URINE
↑ VOLUME
↓ Sp. Gr.
Glucose ±
↑ FE_{Na}
pH > 5.9

Garabed Eknoyan, MD

Urinalysis

- Gross hematuria 5-20%
- Mircohematuria 70-90%
- Proteinuria (1-2 g) 70-85%
- Pyuria 70- >80%
- FENa >1% 100%
- Eosinophiluria (>1-5% of WBCs)- ?%
  - PP 38%, low sensitivity 60%, high specificitiy 85%

Wright. ArchINt Med, 1985; Hansel, NEJM, 1986; Hansel Arch Pathol Lab Med, 1989; Hansel,Clin Nephrol, 1994)

...neither necessary nor sufficient for the dg of AIN, and its ordering in the absence of pyuria is a total waste

Raghavan R and Eknoyan G. Clinical Nephrology, 2014

ETIOLOGY

- Drugs– 70 to 75 % (65-70%)
  – antibiotics 30 to 49 %
- Infections – 4 to 10 % (10-15%)
- Systemic disease – 10 to 20 % (10-15%)
- TINU syndrome – 5 to 10 % (Eknoyan)
- Idiopathic?! – ~ 15%

>150

Praga M and Appel G. UpToDate. 2017

Raghavan R and Eknoyan G. Clinical Nephrology, 2014

- **NSAIDs**, including selective (COX)-2 inhibitors
- **Penicillins and cephalosporins**
- **Rifampin**
- **Antimicrobial sulfonamides**, including TMP-SMX
- **Quinolones** (Ciprofloxacin)
- **Diuretics** (loop and thiazide)
- Cimetidine (only rare with other **H-2 blockers**)
- **Allopurinol**
- **PPIs** (omeprazole and lansoprazole)
- **Indinavir**
- **5-aminosalicylates** (eg, mesalamine)
- **checkpoint inhibitors** (ipilimumab, nivolumab, pembrolizumab, atezolizumab)

Michel DM et al. J Am Soc Nephrol 1998
Muriithi AK et al. Am J Kidney Dis 2014
Wang YC et al. Clin Nephrol 2009

Reported cases of Drug-induced AIN

DRUG	# of Cases	Principal agents
Antibiotics	> 50	Methicillin, Ciprofloxacin, Rifampin
NSAIDs	> 40	Propionic acid derivatives
Proton pump inhib. H_2 Antagonists	> 50	Omeprazole Cimetidine
Cancer drugs	> 20	Ifosfamide
Diuretics	> 10	HCTZ, Furosemide
Others	> 20	Allopurinol, 5-Aminosalicylic acid

Clin Nephrol 2014; 82:149-162

INFECTION

- *Legionella*,
- *Leptospira*,
- CMV, and
- *Streptococcus...*

  .... primarily invade remote organs but exerted an inflammatory response in the kidney

Ellis D et al. Pediatrics 1981

Dharmarajan TS et al. Int Urol Nephrol 1999

- More recent reports- identification of organism-specific antigens or DNA in kidney proximal tubule cells

Baksh FK et al. Am J Kidney Dis 2001

Granulomatous IN (GIN)

- 0.5–0.9% of native kidney biopsies

Shah S et al. Clinical Kidney Journal, 2015

- ~ 6% of all IN

Viero RM and Cavallo T. Hum Pathol 1995

- Etiology
  - infections (mycobacterial infection),
  - sarcoidosis,
  - drugs (AB and NSAID) and
  - idiopathic?
    - IBD, TINU, infections, GPA

- The etiology of GIN also has **geographic variations**.
- **Drugs**- the leading cause of GIN, equaling or exceeding sarcoidosis in **developed countries**
- **Infection** is a more likely etiology in **developing countries**

- One of the largest series of GIN from Glasgow
  - **drug**-induced **45%**
  - renal **sarcoidosis 29%** and
  - **idiopathic 10.5%**
  - **No case of infection**

Bijol V et al. Int J Surg Pathol 2006

- India
  - tuberculosis **53%**
  - **idiopathic 23.5%**
  - **sarcoidosis 18%** and
  - **fungal 5.9%** etiology

Agrawal TP et al, Clinical Kidney Journal, 2015

- Large series from South Africa
- 45 cases in HIV, 73% of whom had TBC

Nel D. Doctoral Thesis. Faculty of Health Sciences, University of Cape Town, Cape Town, 2014

- France in between regarding TBC and other causes

Mignon F et al. Adv Nephrol Necker Hosp 1984

Javaud N et al. Medicine (Baltimore) 2007

- In the renal allograft
  - Infections due to immunocompromised state (Mycobacteria and fungi-like candida) and AB
-

Meehan SM et al. Am J Kidney Dis, 2000

- Idiopathic?!- just our ignorance of all possible etiologies in globalised world or laziness for holistic approach to the patient

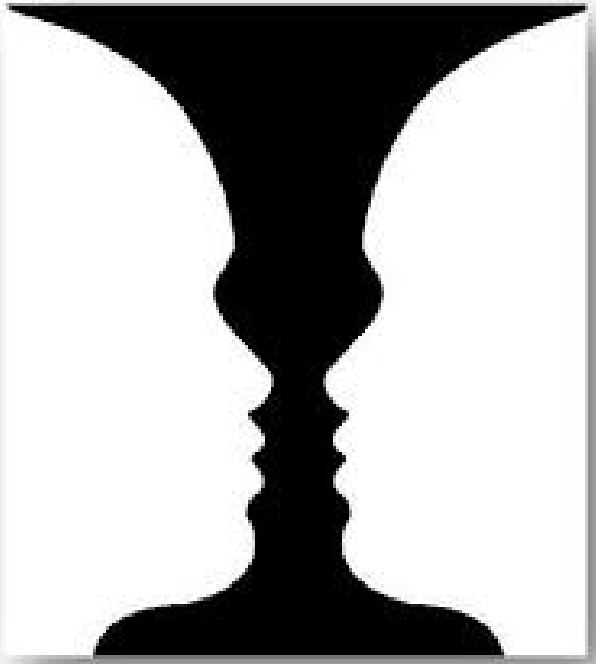
- AIN remains a cemeleon in a globalized world

- In order to target diagnostics into right direction, one should be aware of patterns of the disease worldwide.

“One only sees what one looks for.

One only looks for what one knows.”

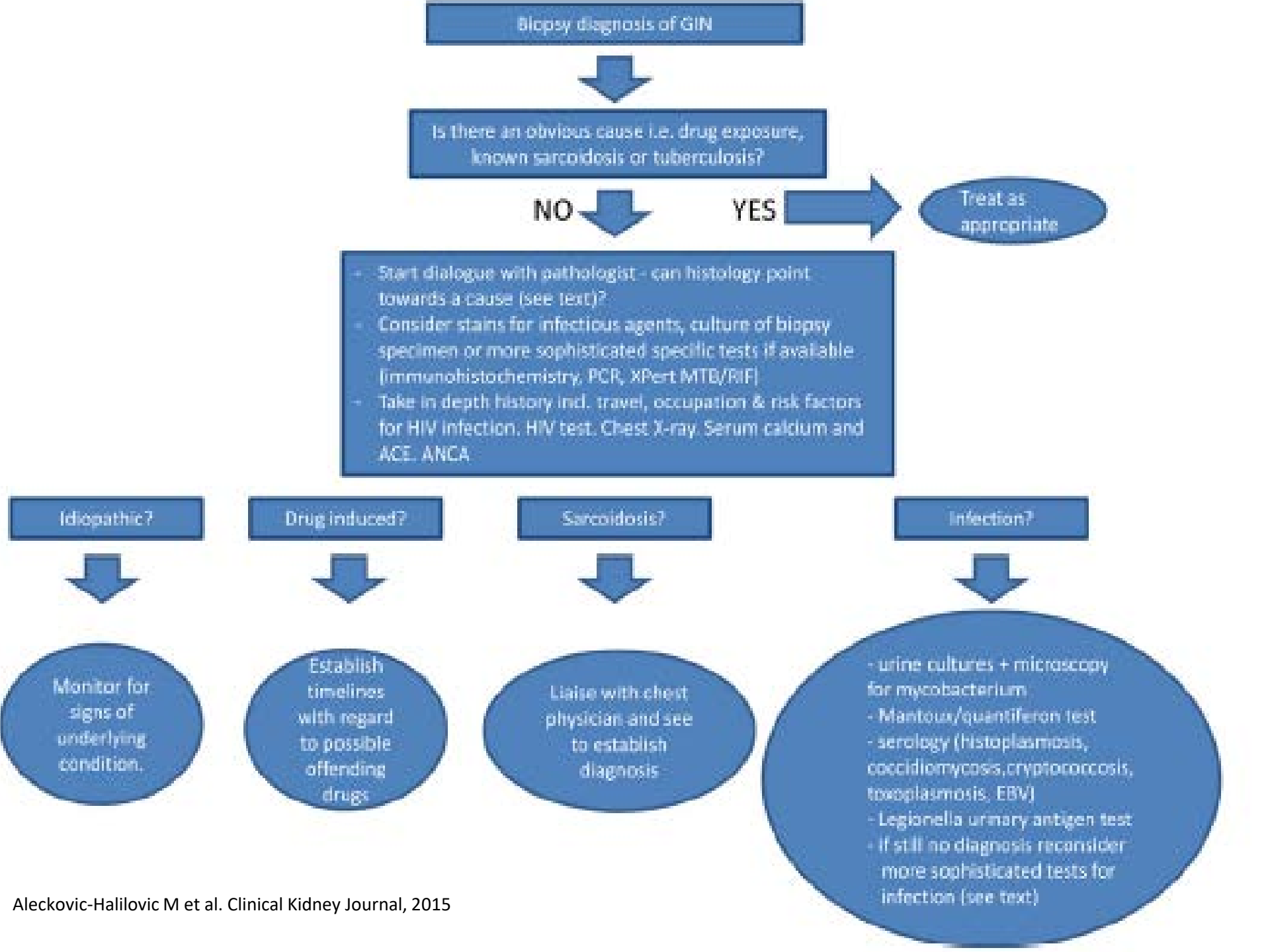
Johann Wolfgang von Goethe



- **The cause** of GIN has to be investigated as it has definite **therapeutic implications**.

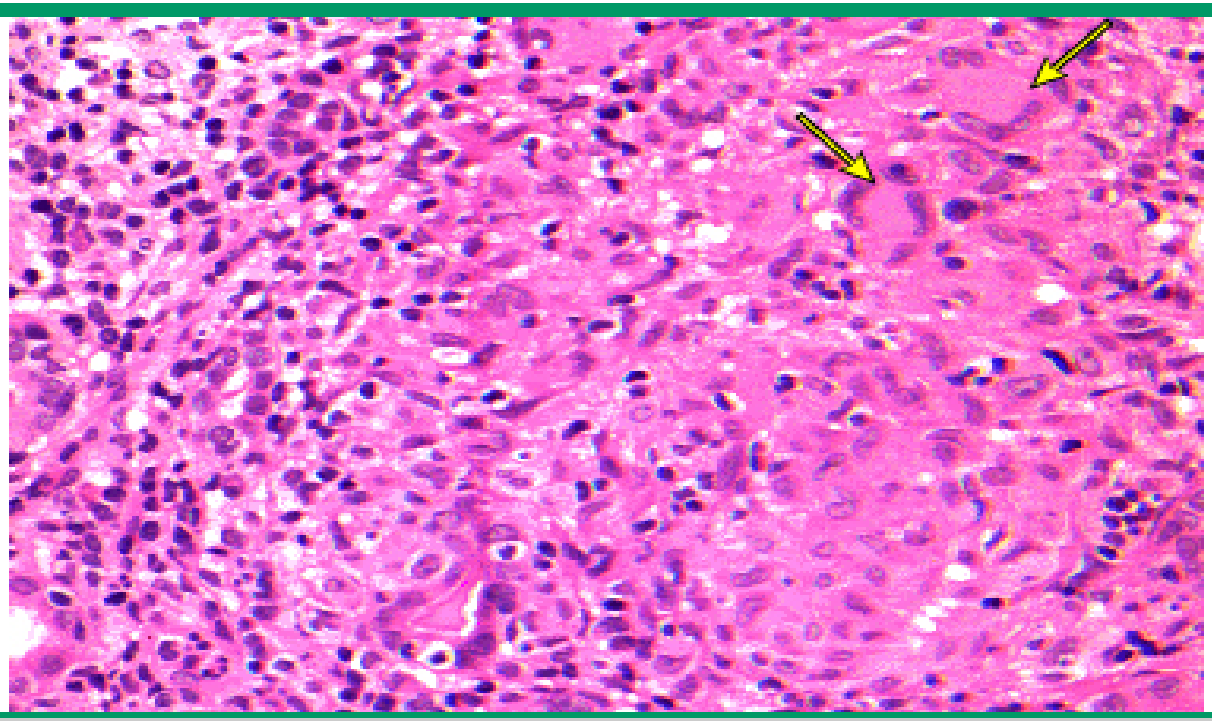
- Chronic GIN has a poor renal outcome

Chapagain A et al. Kidney Int, 2011



Aleckovic-Halilovic M et al. Clinical Kidney Journal, 2015

Light micrograph of kidney biopsy of a patient with granulomatous acute interstitial nephritis



Light micrograph shows granulomatous change in acute interstitial nephritis. The interstitial infiltrate is seen on the left, while the granuloma is on the right. The granuloma consists of both giant cells (arrows) and epithelioid cells with abundant cytoplasm, which has an amorphous red appearance. Although these findings are characteristic of sarcoid involvement in the kidney, they can be seen with any cause (drug or infection) of acute interstitial nephritis.

Courtesy of Helmut Rennke, MD.

Tuberculosis

- Tuberculosis (TB) is **underdiagnosed cause of severe TIN, leading to a delay of specific treatment and a poor renal outcome**.

Chapagain A et al. Kidney Int, 2011

- Hunt down TB in high-risk populations or in cases without corticosteroid response.

- In high-risk populations, a low threshold of suspicion might lead to timely diagnosis and initiation of treatment and preserving renal function.

- Renal involvement due to hematogenous spread from a primary focus (most common lungs)
- ...or immunological reaction
- Urogenital TB- second most common extrapulmonary site
  - Renal injury- urinary tract scarring, less commonly GNF or secondary amyloidosis
- GIN could be the sole manifestation
- Granulomas are not always detected- they are missed on biopsy or not formed (HIV, postpartum...)

Agrawal TP et al, CKJ, 2015

Chapagain A et al. Kidney Int, 2011

- Available tests have poor sensitivity and specificity.
- urine testing for acid fast bacilli and Ziehl-Neelsen staining of biopsies lack sensitivity

  Ball S et al. NDT, 1997
- culture time consuming and poor sensitivity in paucibacillary specimens
- ...even culture of renal biopsy mostly provide negative results

  Chapagain A et al. Kidney Int, 2011
- Nucleic acid amplification tests- high sensitivity and specificity
- PCR has shown poor sensitivity in paraffin-embedded extra-pulmonary samples (32% positive), probably due to a low burden of mycobacteria

  Alvarado-Esquivel C et al. BMC Clin Pathol 2009

  Eastwood JB et al. Kidney Int, 2011
- Histological findings in GIN, not specific, but may point us in the right direction

- TB interstitial nephritis with no extra-renal involvements- difficult to diagnose

- No evidence of pulmonary disease- PET/CT imaging for identifiying the sight and guiding biopsy for PHD, culture, PCR

Delafosse M et al. Severe TIN: tracking tuberculosis even in the absence of renal granuloma, CKJ, 2018

Systemic/autoimmune diseases

- **Sarcoidosis**
- **SLE**
- **Sjögren's syndrome**
- **granulomatosis with polyangiitis** (GPA)

- A subtypes of idiopatic AIN:
  - **TINU sy—** occasionally with systemic findings
  - **Hypocomplementemic interstitial nephritis**
    - **especially IgG4-positive-** lymphoplasmacytic infiltration of IgG4-positive plasma cells and small lymphocytes with development of a mass in the or diffuse enlargement of an organ

IgG4 disease

Main clinical phenotypes :

- pancreato-hepato-biliary disease,
- retroperitoneal fibrosis and/or aortitis,
- head- and neck-limited disease, and
- classic Mikulicz syndrome with systemic involvement.

IgG4 disease

- Kidneys involved in approximately 30 % of cases of IgG4-related disease

Stone JH et al, N Engl J Med,2012 and Saeki T et al, Kidney Int,2010

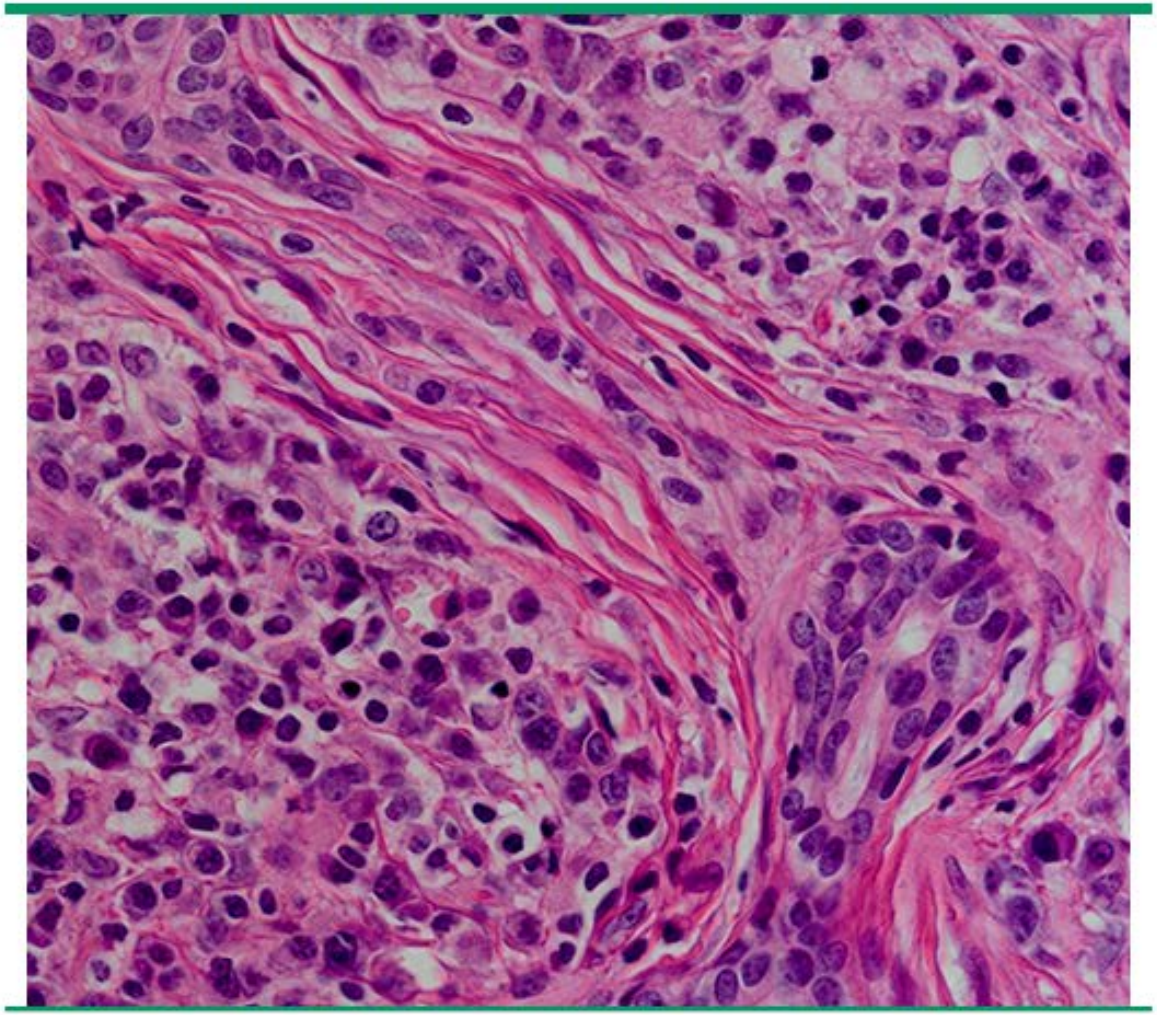
- TIN is the most commonly associated renal lesion, although glomerular lesions (mostly membranous nephropathy) have been reported

Cornell LD, Curr Opin Nephrol Hypertens, 2012

IgG4- diagnosis and differential

- biopsy of an involved organ whenever possible
- PH findings never diagnostic alone- interprete in the context of clinical, serologic, and radiologic data
- PH findings usually strikingly similar in different tissues
  - lymphoplasmacytic tissue infiltration of mainly IgG4-positive plasma cells and lymphocytes
  - fibrosis of stormiform features
  - obliterative phlebitis and modest tissue eosinophilia
- Serum IgG4 levels- significant aid but not diagnostic
- Blood plasmablasts- diagnostic, but not widely available
- Additional organ involvement should be identified

Lacrimal gland histopathology in IgG4-related disease

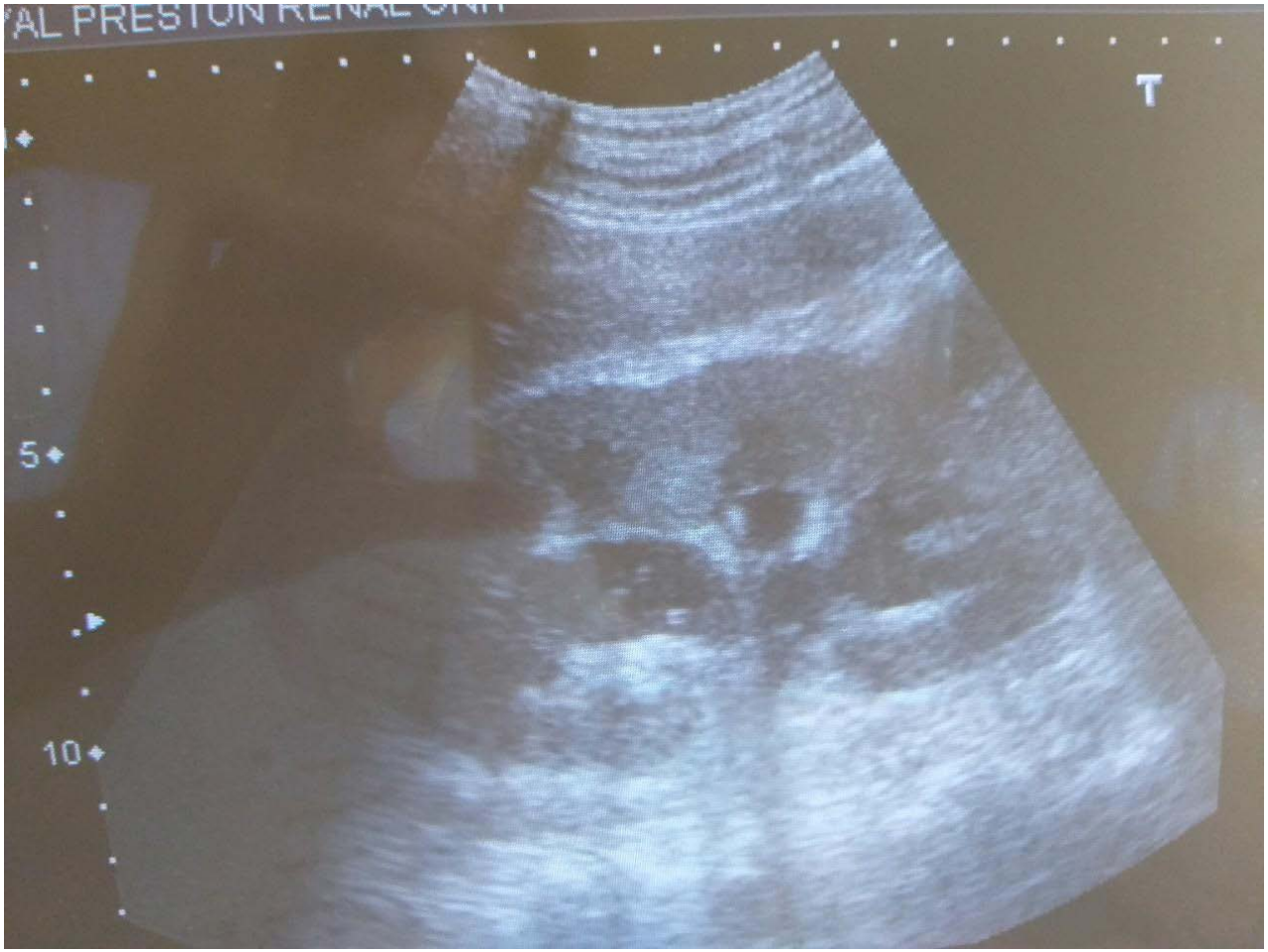


Lacrimal gland biopsy showing a lymphoplasmacytic infiltrate enmeshed within a stream of storiform fibrosis.

IgG4: immunoglobulin G4.

Courtesy of John H Stone, MD.

UpToDate®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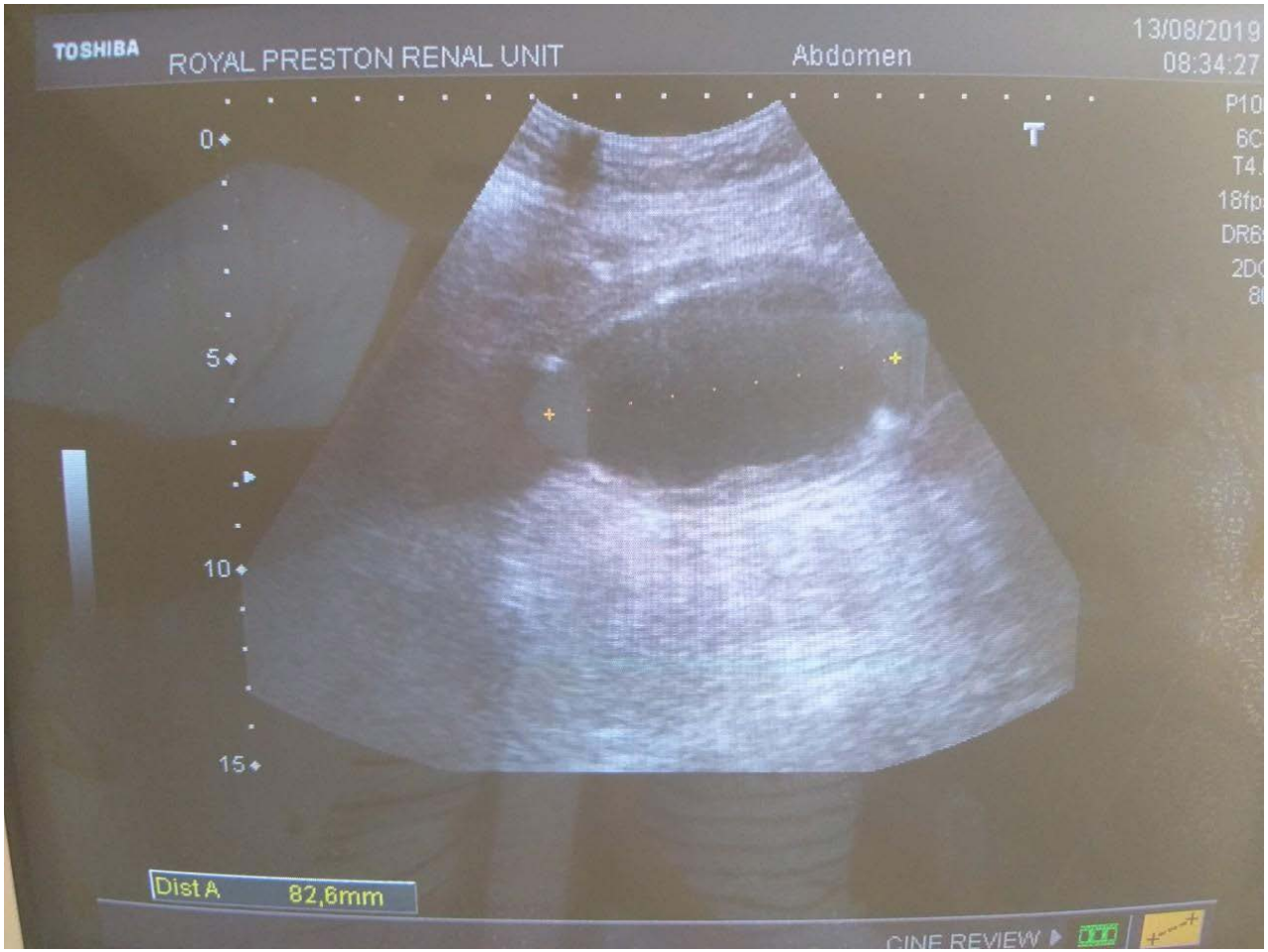
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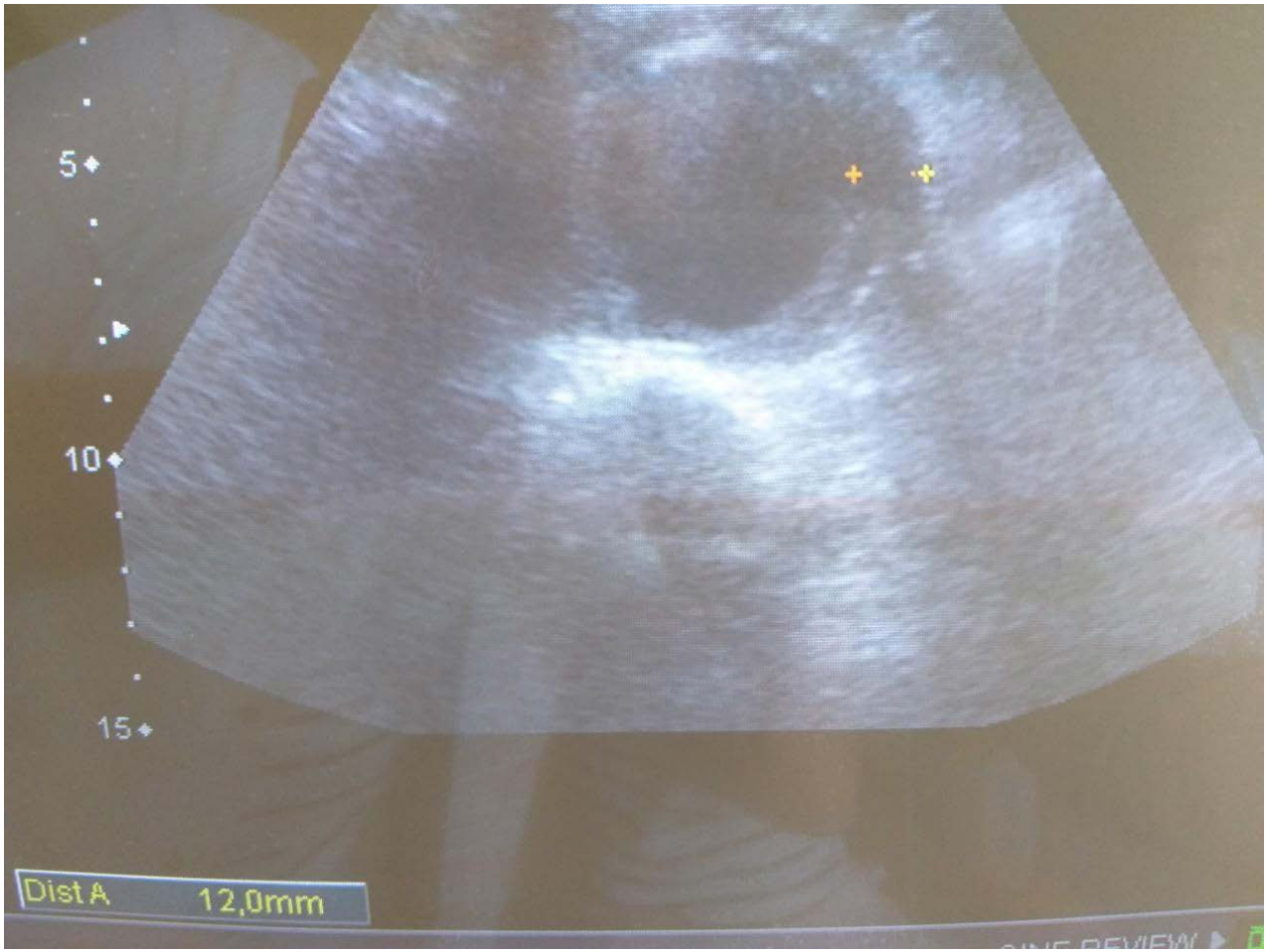
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IgG4- treatment and prognosis

- Glucocorticoids- prednisone (0.6 mg/kg/day), tapered to discontinuation over a two-months
- In patients resistant, dependent on or with contraindications to glucocorticoids – rituximab
- Spontaneous improvement can be seen
- Relapses are common

Inflammatory bowel disease and kidney

- intestinal permeability already increased in the earlier stages of CKD
  - promote deterioration in kidney function
  - promotes cardiovascular diseases

Rostoker G et al, Nephron 1993

- The linkage between the most common primary (IgAN) and the mucosa is well known

Coppo R. Nephrol Dial Transplant 2015

  - persistent proteinuria in patients with IgAN succesfully treated with targeted-release enteric budesonide

Fellstrom BC et al. Lancet 2017

Clinical Kidney Journal, 2019, 1–7
doi: 10.1093/ckj/sfz004
Original Article

ORIGINAL ARTICLE

Inflammatory bowel disease in patients undergoing renal biopsies

Jussi Pohjonen[1,2], Rakel Nurmi[1], Martti Metso[2], Pia Oksanen[3,4], Heini Huhtala[5], Ilkka Pörsti[2,4], Jukka Mustonen[2,4], Katri Kaukinen[1,2] and Satu Mäkelä[2,4]

- approximately **7-fold compared with the general population**
  - **20**-fold in patients with TIN
  - **8**-fold in patients with IgAN

- Renal findings did not associate with the activity IBD (more than half patients asymptomatic)

- Wheather a concomitant IBD truly affects the course of chronic kidney disease should be examined in further studies.

Extraintestinal manifestations (EIM) of IBD due to:

- systemic inflammation
- autoimmune susceptibility
- and/ or drug-related toxicities [1].

Timmermans S et al. Granulomatous interstitial nephritis and Crohn's disease. CKJ, 2016
Danese S et al. Extraintestinal manifestations in inflammatory bowel disease. World J Gastroenterol,

- 6–47% have EIMs- skin, eyes, joints and biliary tract
- up to 20% are renal or urinary manifestations
  - mostly urological complications (nephrolithiasis)
- parenchymal renal disease is rare, but may reveal a wide spectrum of pathologies of glomerular and tubulo-interstitial compartments

Danese S et al. World J Gastroenterol 2005

Rothfuss KS et al. World J Gastroenterol 2006

- GIN in IBD- extremely rare.
  - Only 12 patients (7 case reports) have been described in the English literature

Archimandritis AJ and Weetch MS. BMJ 1993
Polci R et al. Ren Fail 2012

- <1% of native renal biopsies

- ~5% of renal biopsies from IBD patients, mostly linked to current or recent past exposure to 5-aminosalicylic acid (5-ASA)- design precluded any conclusions regarding causal relationship

Ambruzs et al. Clin J Am Soc Nephrol 2014

- There are reports not associated with 5-ASA

Timmermans et al., Clinical Kidney Journal, 2016

- GIN is a genuine extraintestinal manifestation of Crohn's disease

- systemic immune dysregulation and T-cell activation against GI Ag and cross-reactivity with kidney

Timmermans S et al. Granulomatous interstitial nephritis and Crohn's disease, CKJ, 2016

- **The incidence of renal disease in IBD may have been underestimated**- renal impairment usualy with only **subtle urinary abnormalities**

- **renal function** should be **monitored in** all patients with **IBD** and that **a renal biopsy done when indicated**

- Corticosteroids effective, but **GIN in IBD can be challenging and sometimes more aggressive immunosuppressive regimen** (MMF, CNI) may be beneficial

TREATMENT

DISCONTINUATION OF POTENTIAL CAUSATIVE AGENT

SUPPORTIVE THERAPY

IMMUNOSUPPRESSIVE THERAPY if no improvement in kidney function by 3 do 7 days (or rapid deterioration)

Raghavan R and Eknoyan E. Clinical Nephrology, 2014
Kshirsagar AV and Falk R, UpToDate, 2017;
Gonzales et al. Kidney International 2008

INFORM PATIENT

- Renal biopsy
  - confirms AIN
  - excludes other diseases or
  - significant chronic damage (eg, marked interstitial fibrosis, tubular atrophy, and minimal or no acute inflammation)- immunosuppressive not indicated

- **An empiric trial** of glucocorticoid therapy is a **reasonable** alternative in patients with a strongly suggestive history of acute drug-induced AIN **when kidney biopsy is not feasible.**

Kshirsagar AV and Falk R, Treatment of acute interstitial nephritis, UpToDate, 2017

Glucocorticoids ineffective -possible explanations-

- patients treated with steroids had more severe disease
- a significant proportion NSAID-associated- less likely to respond to glucocorticoid therapy
- unrecognized underlying (infective) etiology

Other agents

- only in patients who have **biopsy-proven AIN** and:
- **glucocorticoid dependent**,
- glucocorticoid **resistant**
- **unable to tolerate** glucocorticoid therapy and

- mycophenolate mofetil (MMF)
- cyclosporine and
- anecdotal use of cyclophosphamide

Kshirsagar AV and Falk R, Treatment of acute interstitial nephritis, UpToDate, 2017

Therapy for infectious etiology

- Specific antimicrobial therapy
- The role of corticosteroids remains unclear in this setting
  - Neither the British nor the AmericanThoracic Society guidelines provide guidance for GIN due to TB
- Some authors favour TB therapy alone...

  Gupta P et al. Ren Fail 2014
- ...others combine with steroid treatment with careful risk assesment

  Chapagain A et al.Kidney Int 2011
- Granulomatous inflammation heals by fibrosis- concomitant use of steroids might reduce fibrosis
- In at risk patients (from endemic regions or immunosuppressed) presents with GIN, but TB tests remain negative or equivocal- consider at least tuberculostatic prophylaxis when embarking on steroid treatment

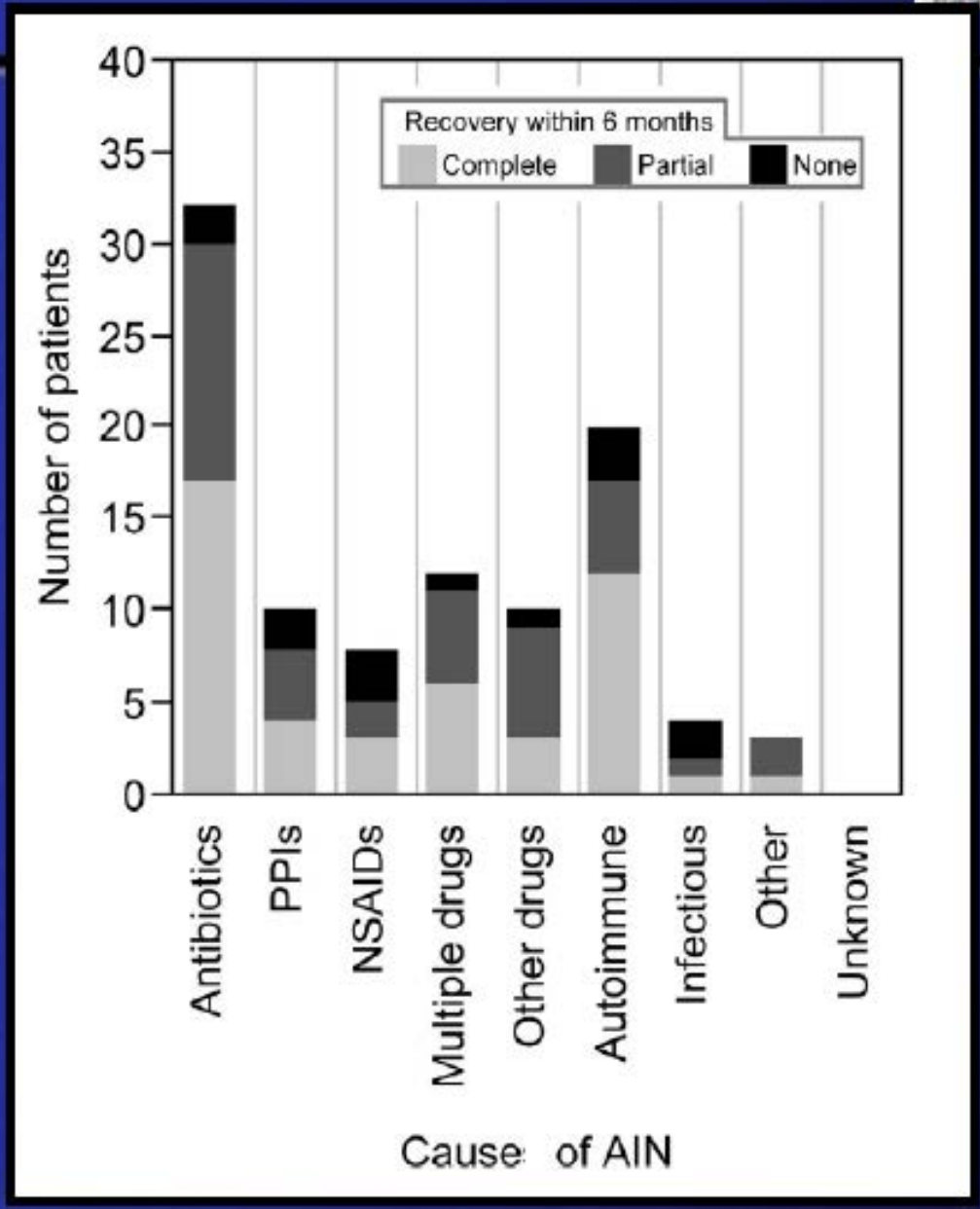
  Aleckovic-Halilovic M et al. Clinical Kidney Journal, 2015

PROGNOSIS

Negative indicators of recovery

- prolonged renal failure (greater than three weeks)
- AIN associated with NSAID use
- certain histologic findings (interstitial granulomas, interstitial fibrosis, and tubular atrophy)

AIN is a serious disease



AJKD 2014; 38:736-748

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

E González[1], E Gutiérrez[1], C Galeano[2], C Chevia[3], P de Sequera[4], C Bernis[5], EG Parra[6], R Delgado[7], M Sanz[8], M Ortiz[9], M Goicoechea[10], C Quereda[2], T Olea[3], H Bouarich[4], Y Hernández[5], B Segovia[1] and M Praga[1], for Grupo Madrileño De Nefritis Intersticiales

the latter (Table 3). In addition, we found a significant correlation between the delay in the onset of steroids and the final Scr (Figure 1), and that an interval longer than 7 days between drug withdrawal and onset of steroid treatment was the only clinical factor that significantly increased the risk of an incomplete recovery of renal function by multiple logistic regression analysis.

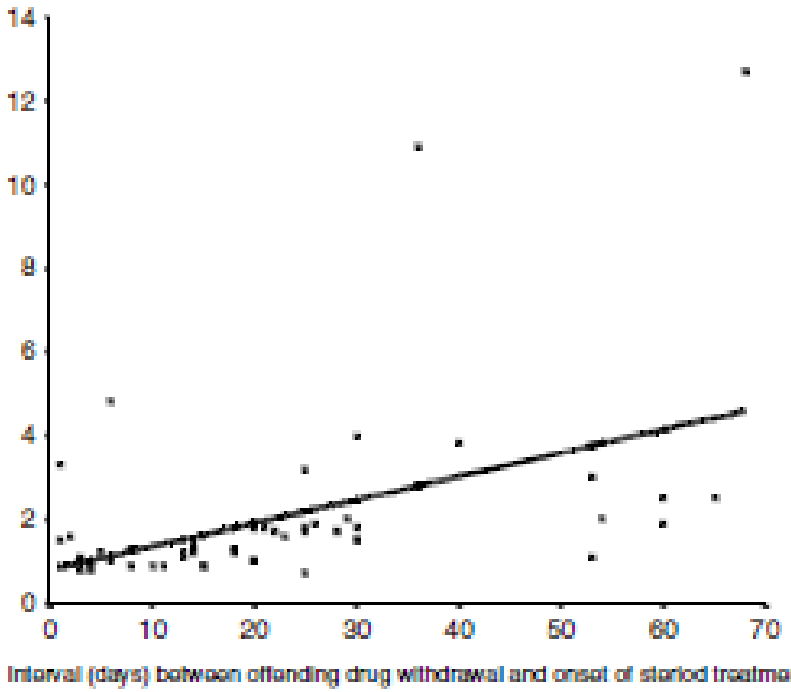


Figure 1 | Correlation between the delay in steroid treatment and final Scr.

Kidney International(2008)73, 940–946

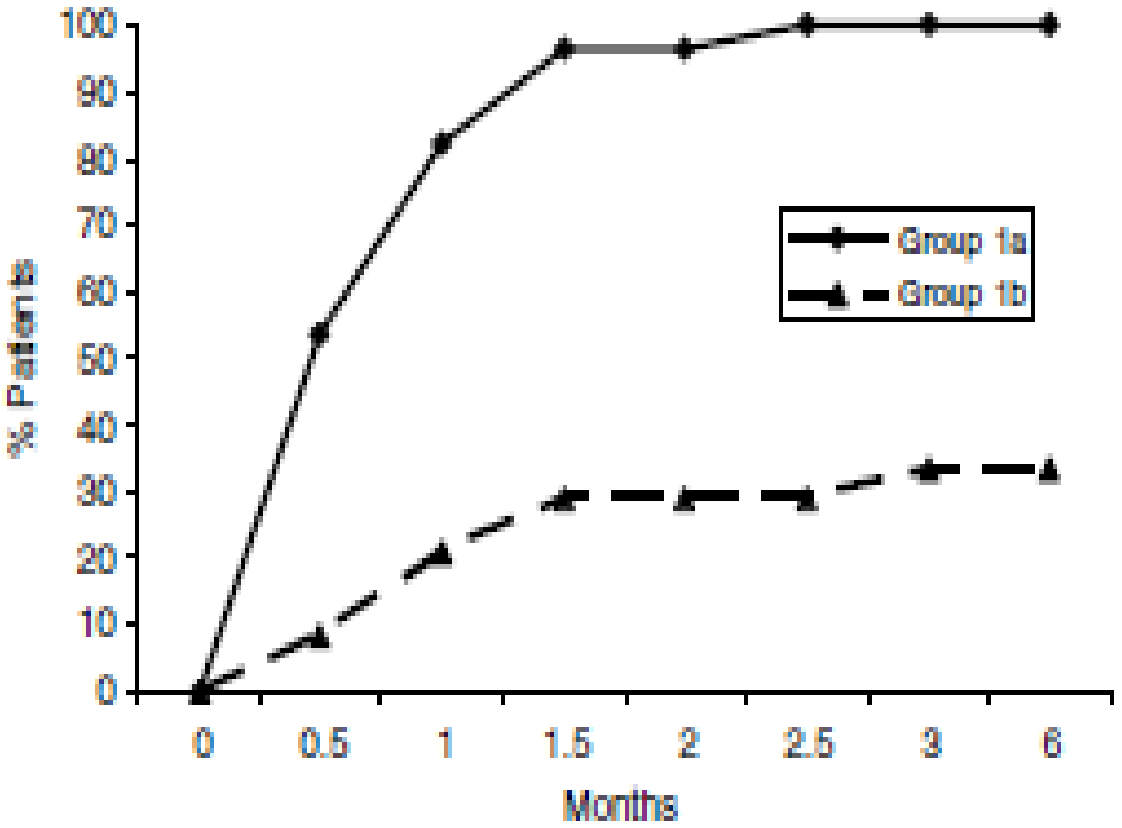
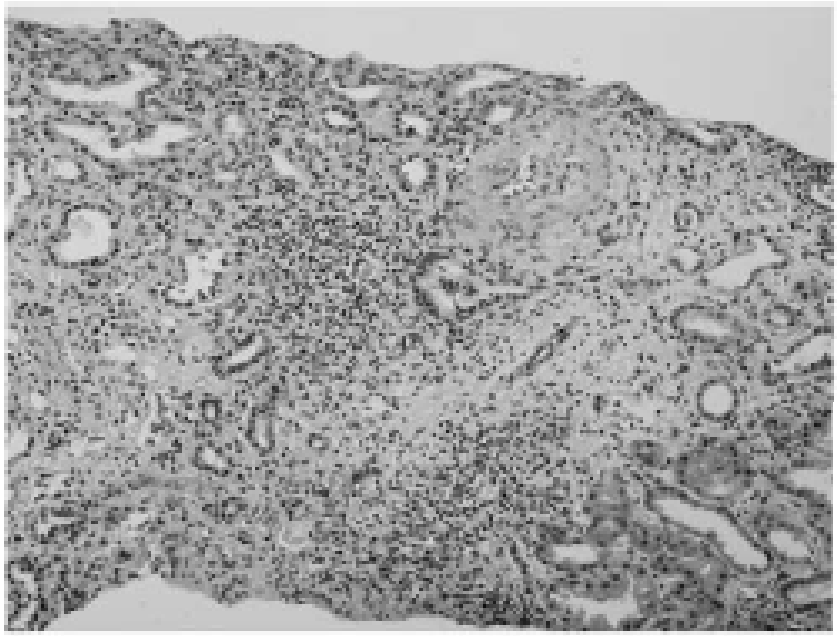


Figure 2 | Rate of renal function recovery, expressed by a >50% decrease of highest Scr, in Group 1a (final complete recovery of renal function) and Group 1b (incomplete recovery).

Kidney International(2008)73, 940–946



AIN and it demonstrates that interstitial cellularity is rapidly replaced (in the absence of steroid treatment) by extensive fibrosis in a few weeks.

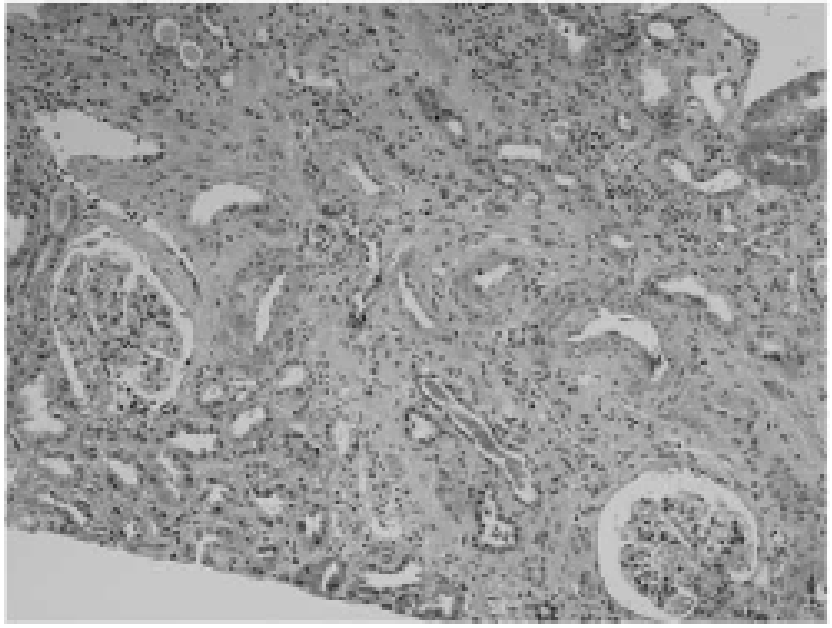


Figure 3 | Evolution of interstitial infiltrates. Dense interstitial cellular infiltrates in the first renal biopsy of a patient of Group 1b (top). In a second renal biopsy, obtained 33 days later, cellular infiltrates have been largely replaced by fibrotic areas in the interstitium (bottom).

Kidney International(2008)73, 940–946

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Therefore, our study strongly suggests that steroid treatment is indicated in DI-AIN and that it should be started immediately or soon after the diagnosis to avoid the risk of incomplete renal function recovery. No significant side effects attributable to steroids were observed, probably due to the short duration of the treatment (8–12 weeks).

Kidney International(2008)73, 940–946

Take home messages

- AIN is a disease of tubular dysfunction.
- AIN is NOT rare and is easy to detect: Urine analysis and BMP.
- AIN is a serious disease and a cause of CKD and ESRD.
- Early AIN detection is preventive translational medicine at its best.

WELCOME TO TUZLA AND COME AGAIN