Nephritis

Joe Ghata

ACP, 10/5/19

Disclaimers

Case 1

82 year old male with Alzheimer's Disease and with mitral valve endocarditis secondary to strep viridian is discharged to home on intravenous penicillin via an upper extremity central line. Three weeks later he presents with The central line sit is clear. On exam, he has a pruritic maculopapular rash on his legs and trunk. Vital signs are temperature 39.7 C, pulse of 90 beats/min, respirations 18/min, and blood pressure of 140/85 mm Hg. Labs reveal a WBC of 13,500/microliter, with 75% PMN, 8% lymphocytes, 4% monocytes and 13% eosinophils. Previous BUN/creatinine was 13/0.9, but now is 60/2.3. Electrolytes and complement levels are otherwise normal. Repeat blood and urine cultures are pending.

What is the most likely diagnosis?

A. Acute interstitial nephritis
B. Immunoglobin A Vasculitis (HSP nephritis)
C. Pyelonephritis
D. Acute tubular necrosis
E. Post-infectious Glomerulonephritis

Objectives

- History of Interstitial Nephritis
- Anatomy and Physiology of Kidney
- Acute Renal Pathophysiology Primer
- Types of Hypersensitivity Reactions
- Acute Interstitial Nephritis Diagnostics and Etiologies
- AIN Clinical Course and Treatment
- Take-Home Message

History of Nephritis

Milestones

- Before the 1800s, the kidney was considered a tubulosecretory organ.
- 1827 - report of dropsical albuminuric medical cases by Richard Bright.
- 1858 - Rudolph Virchow report of nephritis affecting tubules, interstitium, and vasculature.
- 1862 - First Case Report by Micheal Anton Biermer.
- 1869 - Edwin Klebs added glomerular nephritis.

VOLUME III JULY AND SEPTEMBER, 1898 NOS. 4 AND 5

THE JOURNAL

OF

EXPERIMENTAL MEDICINE

ACUTE INTERSTITIAL NEPHRITIS.

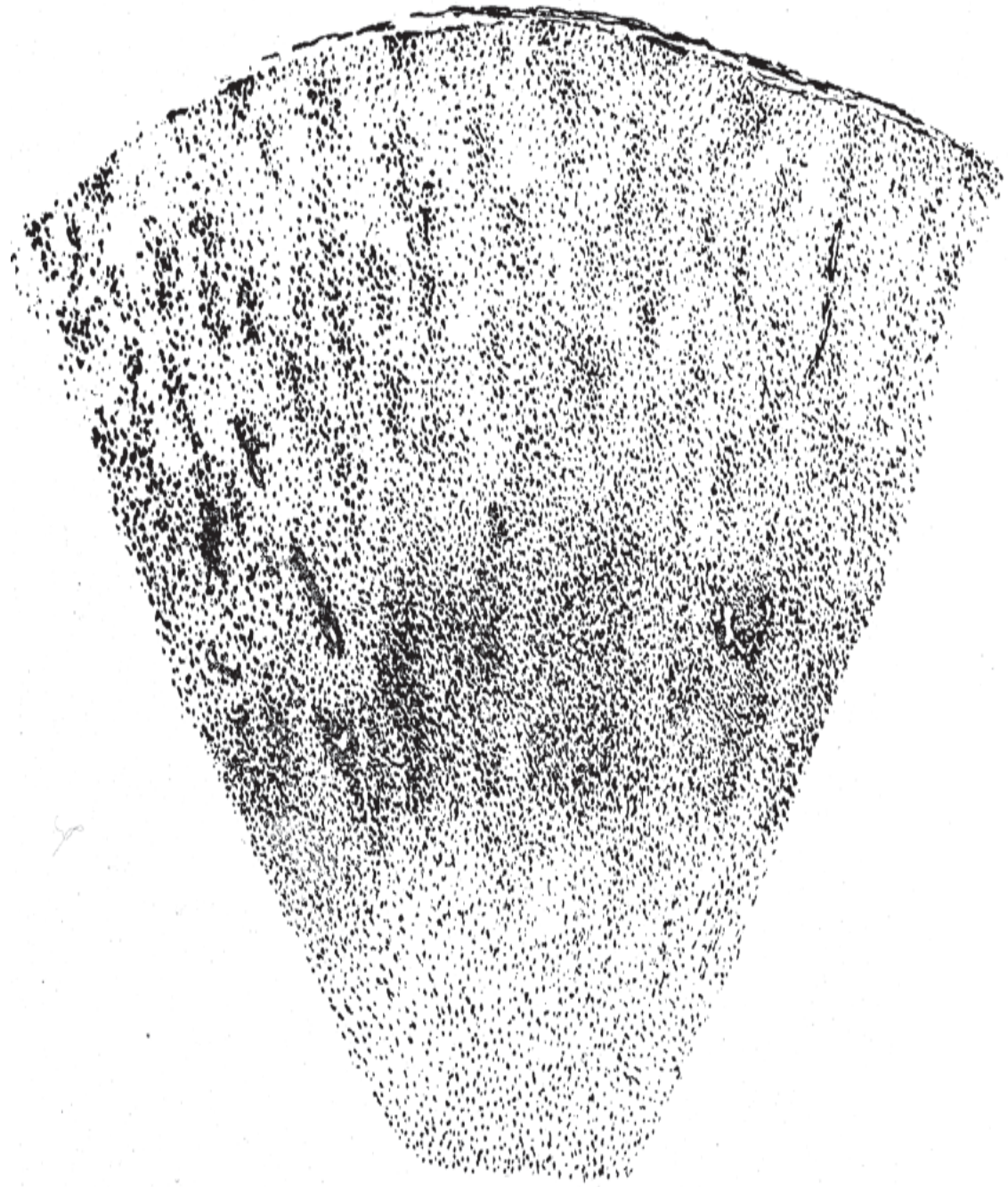
BY W. T. COUNCILMAN, M. D.

(From the Sears Pathological Laboratory of Harvard University.)

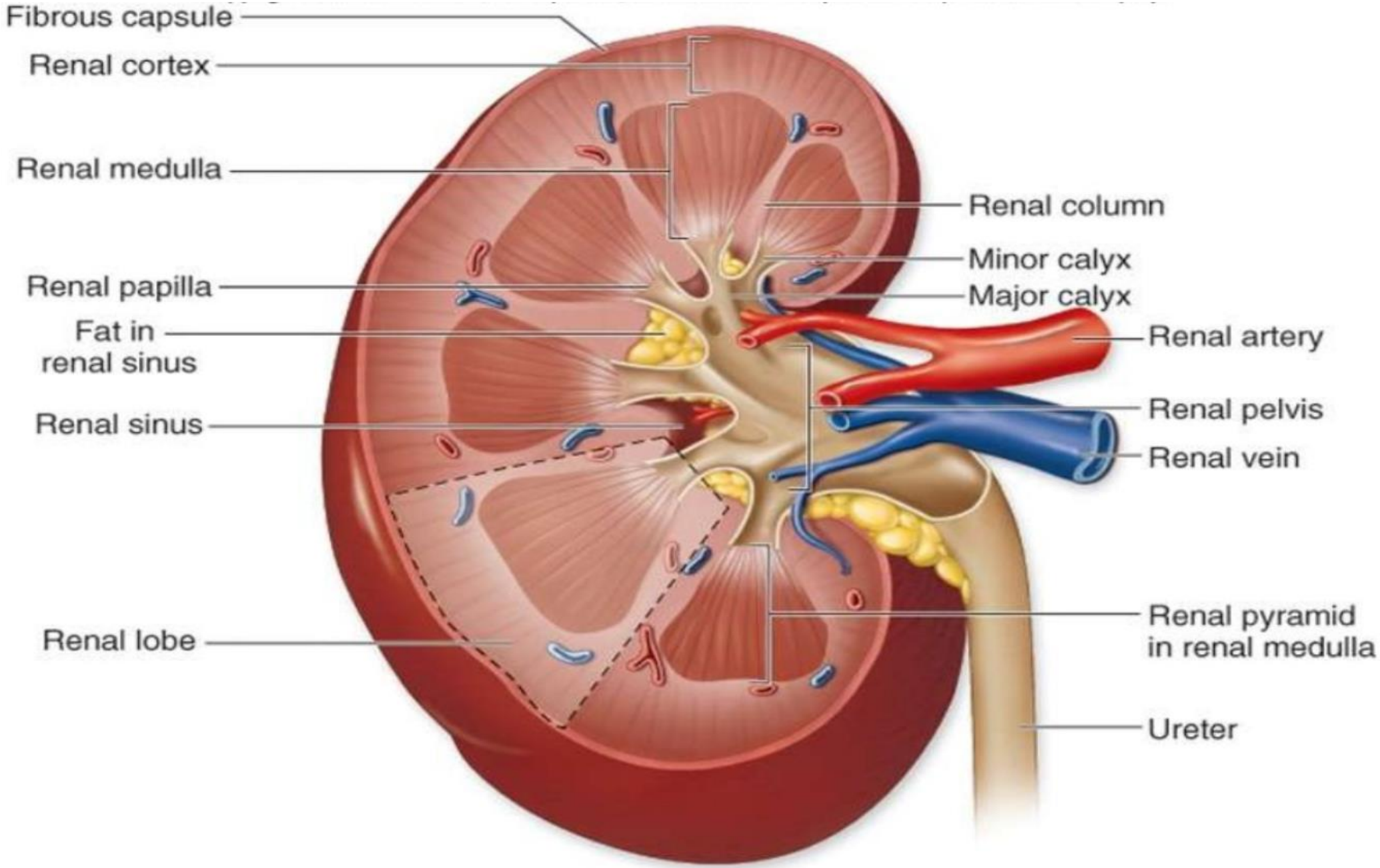
PLATES XXXVII AND XXXVIII.

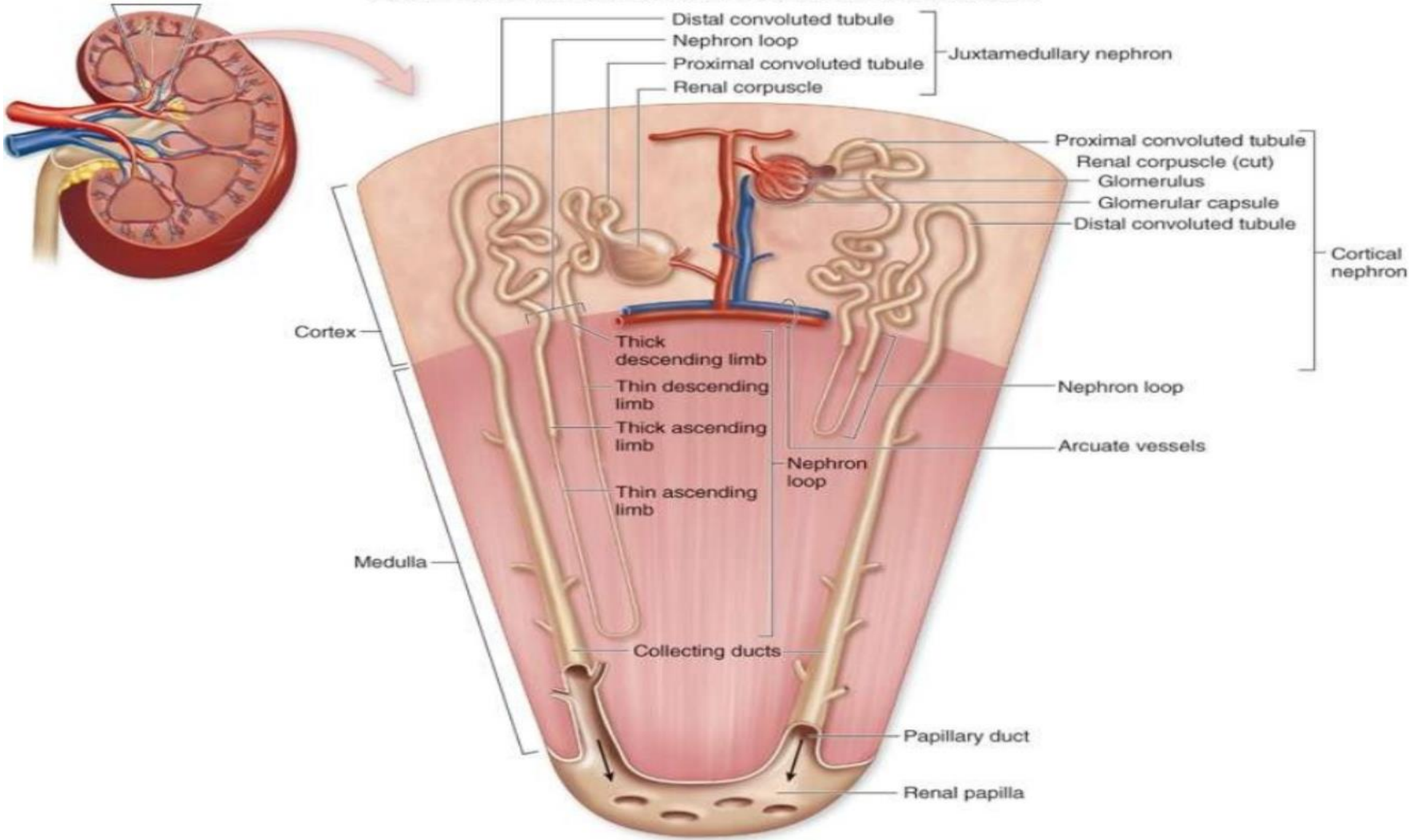
DEFINITION.—An acute inflammation of the kidney characterized by cellular and fluid exudation in the interstitial tissue, accompanied by, but not dependent on, degeneration of the epithelium; the exudation is not purulent in character, and the lesions may be both diffuse and focal.

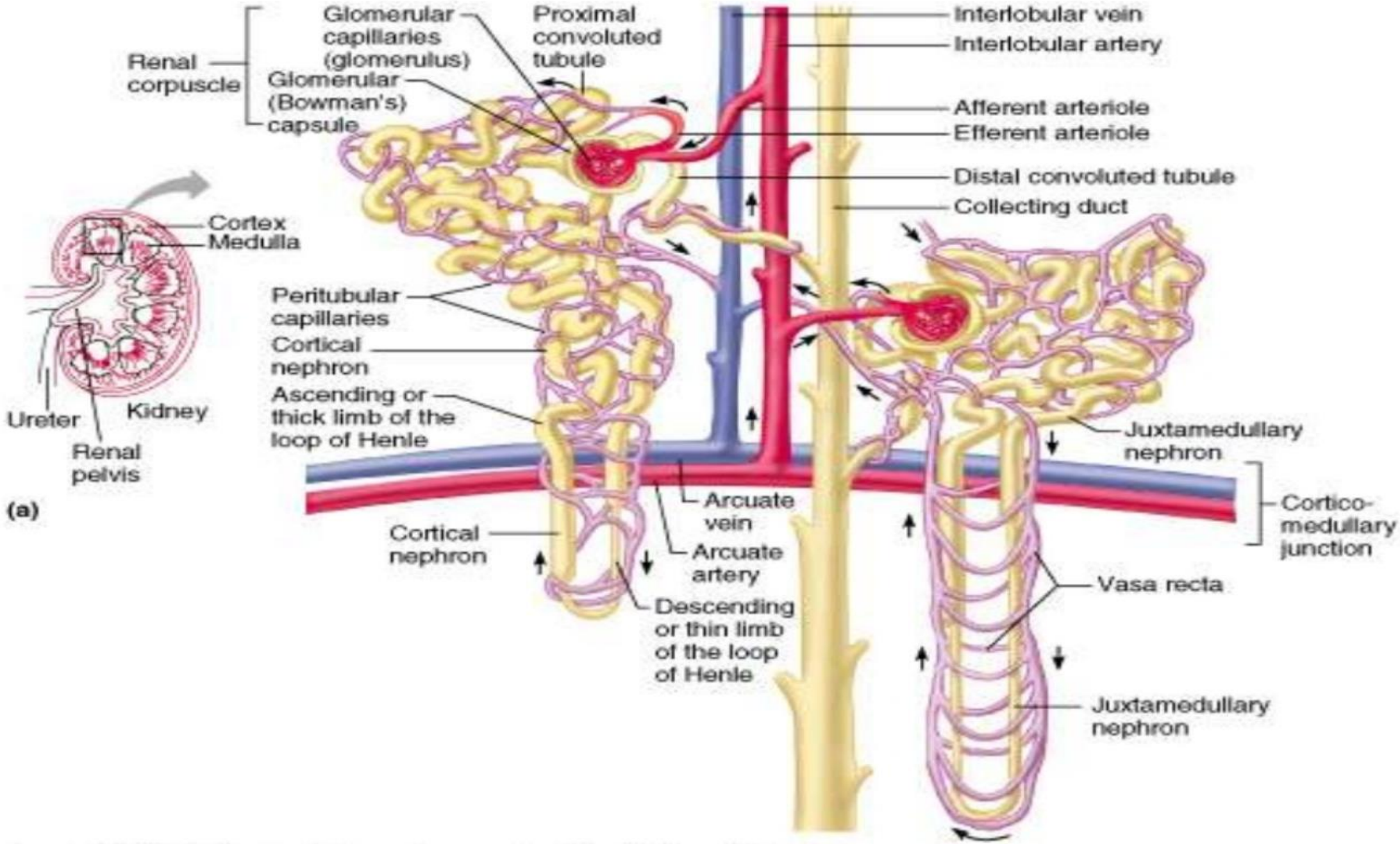
This condition was first described by Biermer (1). He found the kidneys of a child four and a half years old, who died of scarlet fever, greatly swollen, the surface pale, and on microscopical examination showing intense infiltration of the connective tissue with lymphoid cells. He considers the formation of lymphoid tissue here analogous to that found in typhoid fever. The cellular infiltration is more marked in the pyramids than in the cortex. E. Wagner (2) describes a similar case, in which,

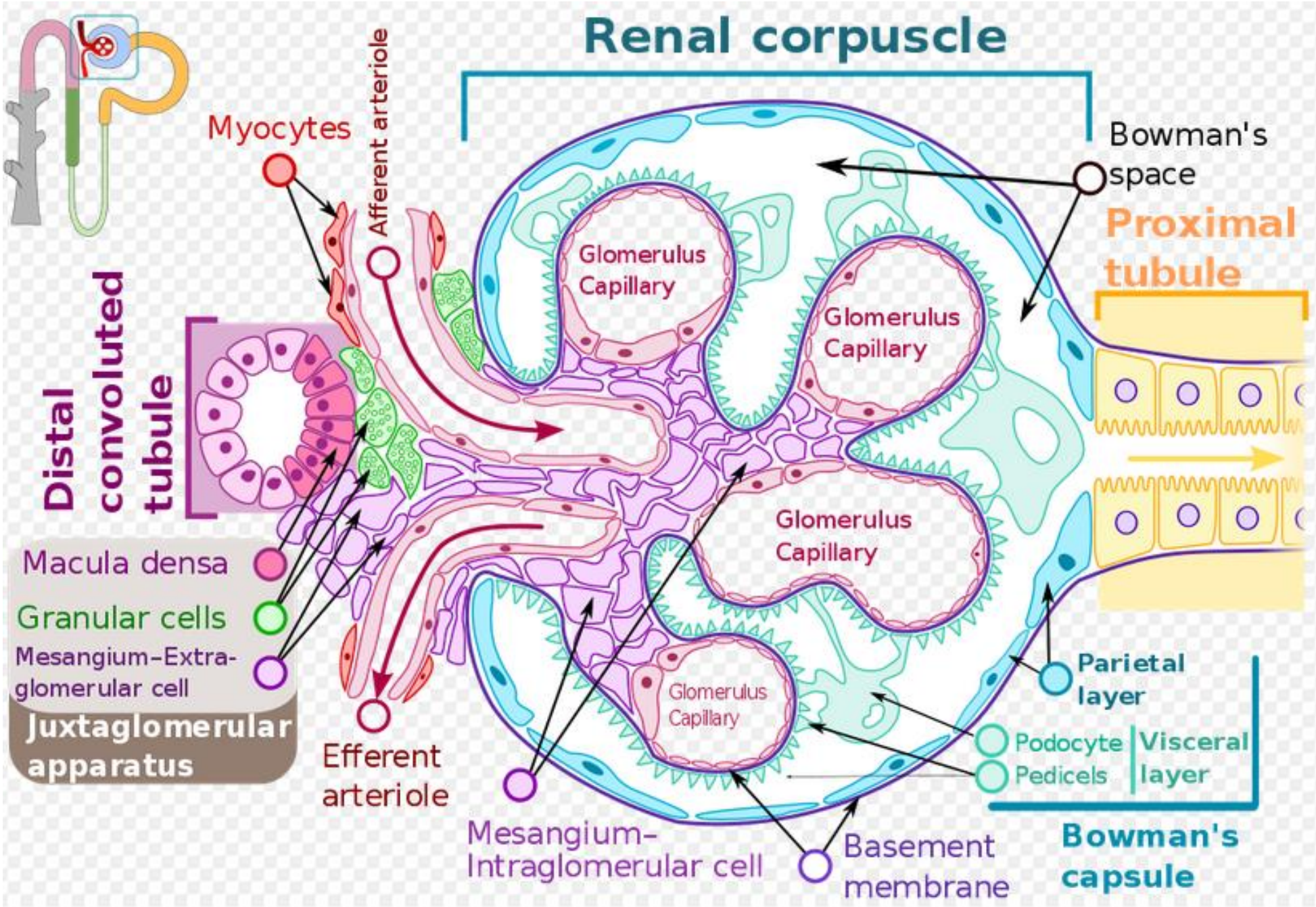


Anatomy and Physiology

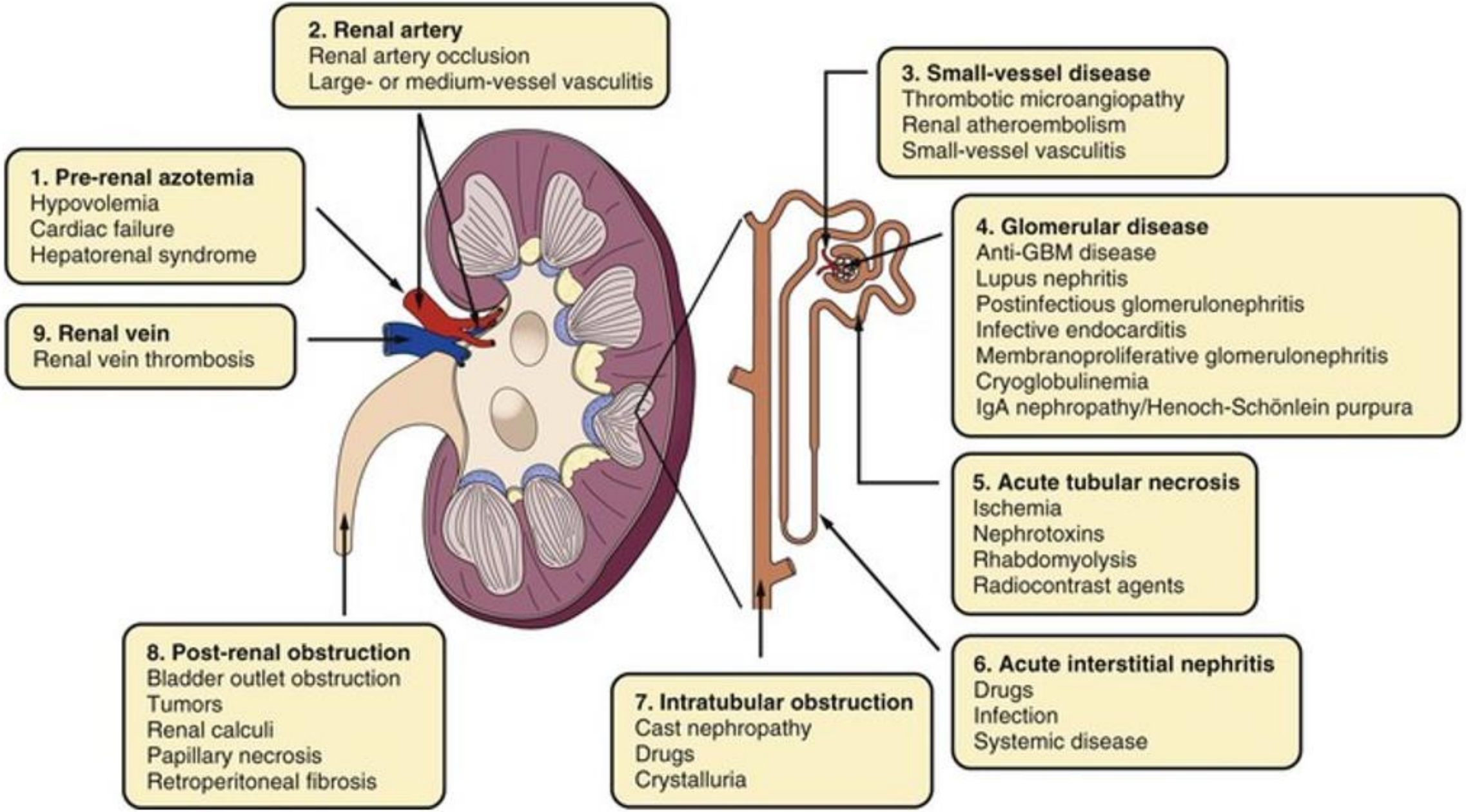

Fibrous capsule
Renal cortex
Renal medulla
Renal papilla
Fat in renal sinus
Renal sinus
Renal lobe
Renal column
Minor calyx
Major calyx
Renal artery
Renal pelvis
Renal vein
Renal pyramid in renal medulla
Ureter

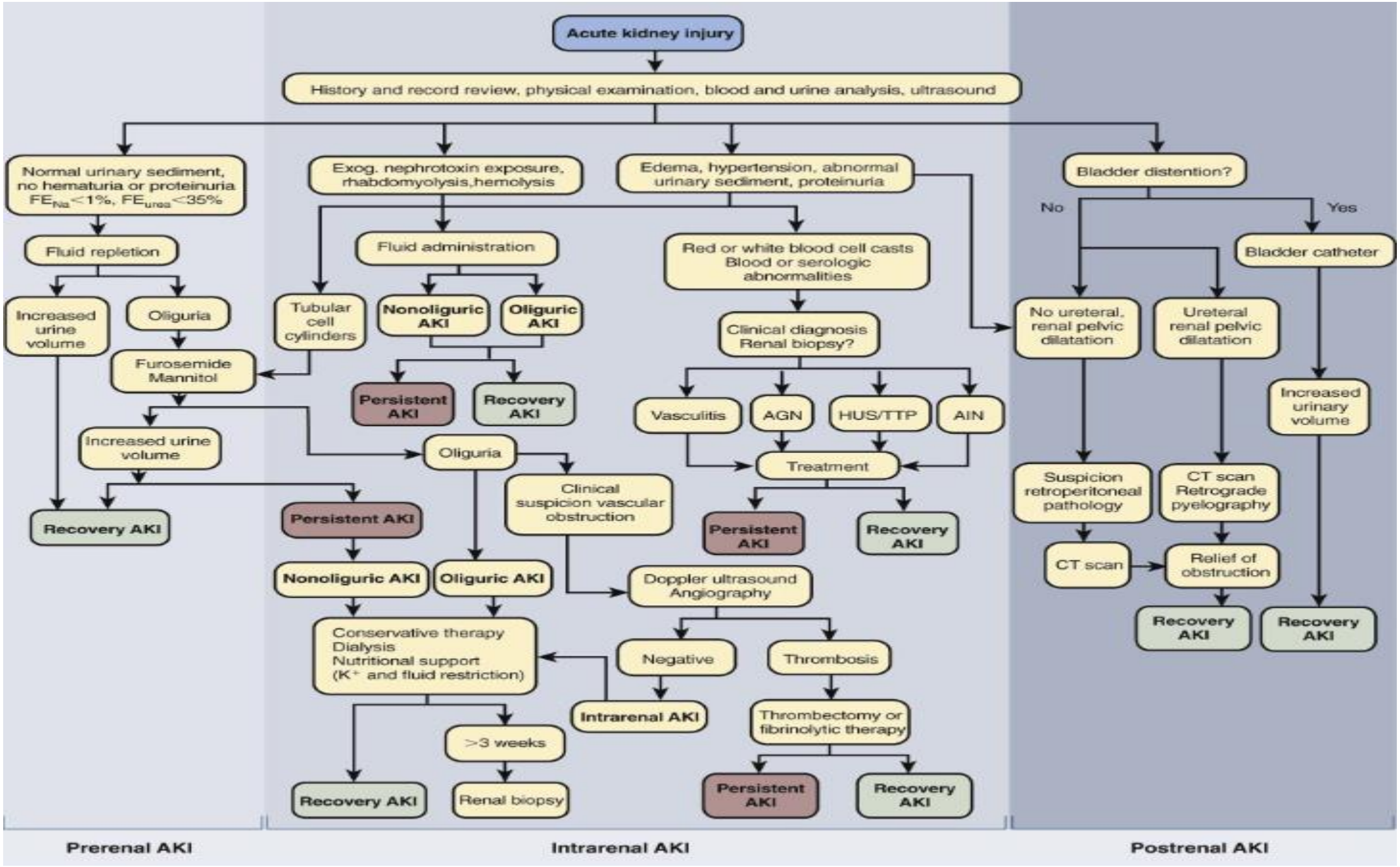

Distal convoluted tubule
Nephron loop
Proximal convoluted tubule
Renal corpuscle
Juxtamedullary nephron
Proximal convoluted tubule
Renal corpuscle (cut)
Glomerulus
Glomerular capsule
Distal convoluted tubule
Cortical nephron
Cortex
Thick descending limb
Thin descending limb
Thick ascending limb
Thin ascending limb
Nephron loop
Nephron loop
Arcuate vessels
Medulla
Collecting ducts
Papillary duct
Renal papilla

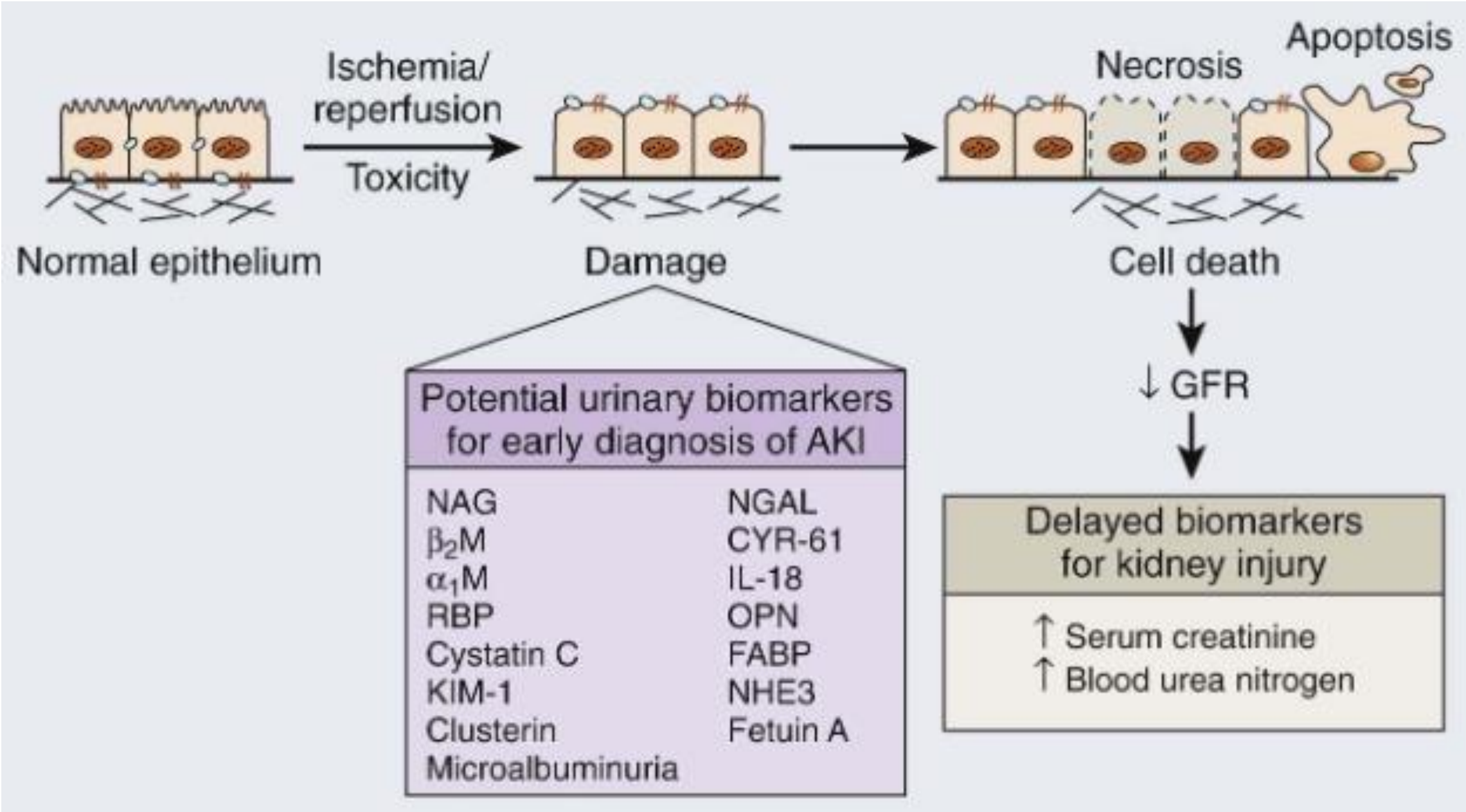

Renal corpuscle
Glomerular capillaries (glomerulus)
Glomerular (Bowman's) capsule
Proximal convoluted tubule
Interlobular vein
Interlobular artery
Afferent arteriole
Efferent arteriole
Distal convoluted tubule
Collecting duct
Cortex
Medulla
Ureter
Kidney
Renal pelvis
(a)
Peritubular capillaries
Cortical nephron
Ascending or thick limb of the loop of Henle
Juxtamedullary nephron
Cortico-medullary junction
Arcuate vein
Arcuate artery
Cortical nephron
Descending or thin limb of the loop of Henle
Vasa recta
Juxtamedullary nephron

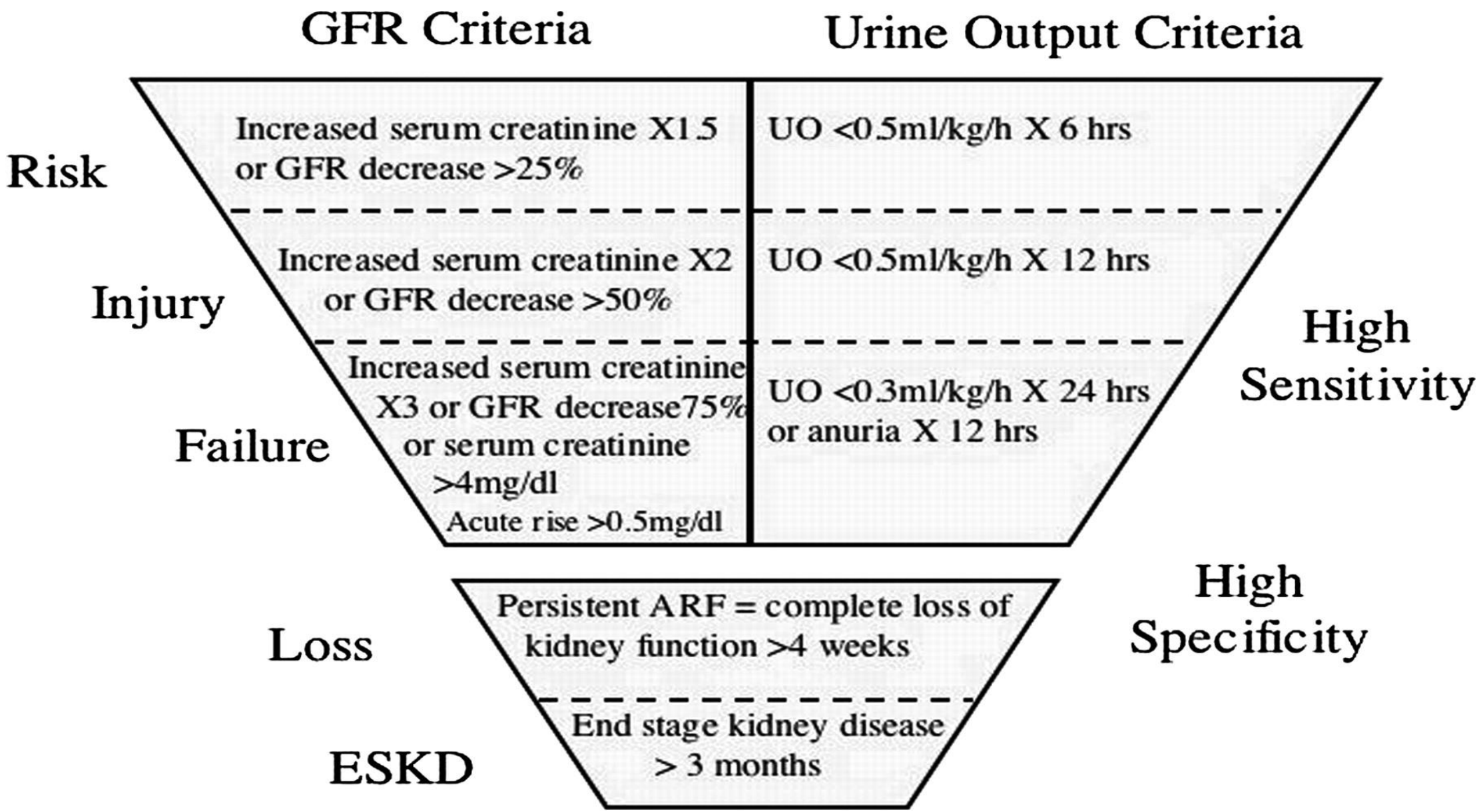

Renal corpuscle
Myocytes
Afferent arteriole
Bowman's space
Proximal tubule
Glomerulus Capillary
Glomerulus Capillary
Glomerulus Capillary
Glomerulus Capillary
Distal convoluted tubule
Macula densa
Granular cells
Mesangium–Extra-glomerular cell
Juxtaglomerular apparatus
Efferent arteriole
Mesangium–Intraglomerular cell
Basement membrane
Parietal layer
Podocyte Pedicels
Visceral layer
Bowman's capsule

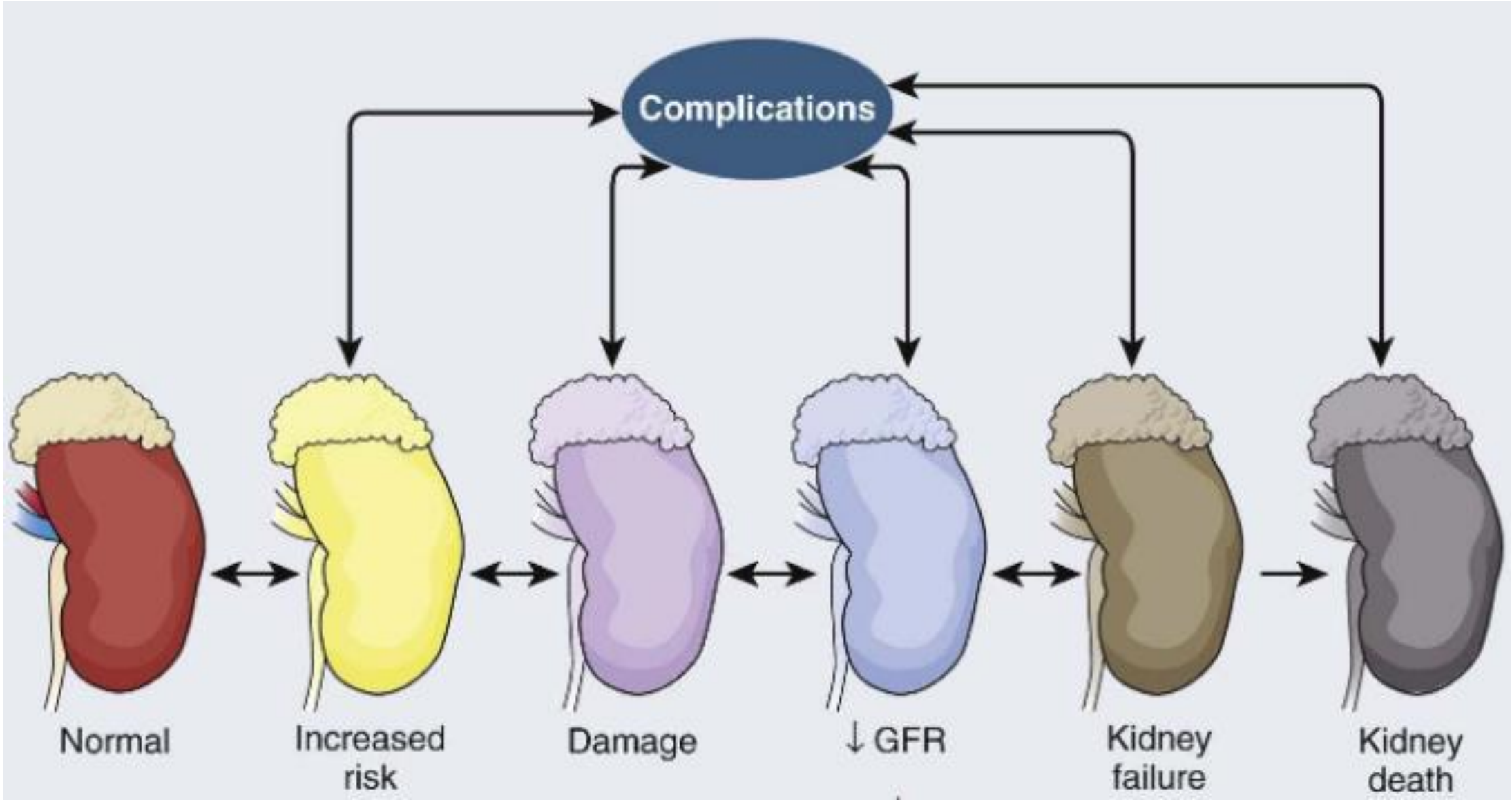
Acute Renal Failure


2. Renal artery
Renal artery occlusion
Large- or medium-vessel vasculitis
3. Small-vessel disease
Thrombotic microangiopathy
Renal atheroembolism
Small-vessel vasculitis
1. Pre-renal azotemia
Hypovolemia
Cardiac failure
Hepatorenal syndrome
4. Glomerular disease
Anti-GBM disease
Lupus nephritis
Postinfectious glomerulonephritis
Infective endocarditis
Membranoproliferative glomerulonephritis
Cryoglobulinemia
IgA nephropathy/Henoch-Schönlein purpura
9. Renal vein
Renal vein thrombosis
5. Acute tubular necrosis
Ischemia
Nephrotoxins
Rhabdomyolysis
Radiocontrast agents
8. Post-renal obstruction
Bladder outlet obstruction
Tumors
Renal calculi
Papillary necrosis
Retroperitoneal fibrosis
7. Intratubular obstruction
Cast nephropathy
Drugs
Crystalluria
6. Acute interstitial nephritis
Drugs
Infection
Systemic disease

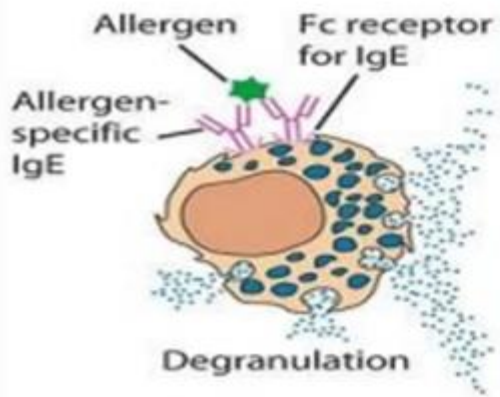
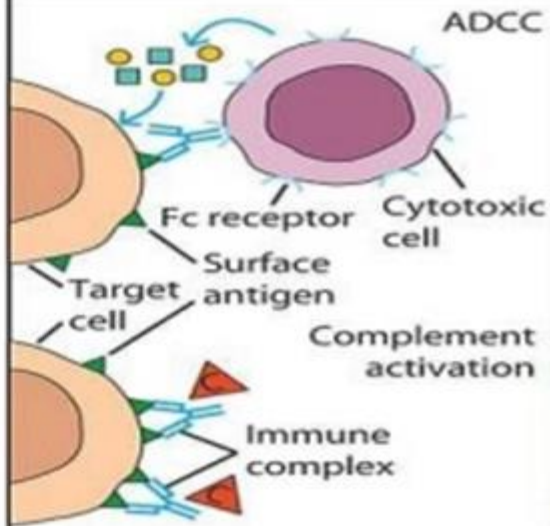
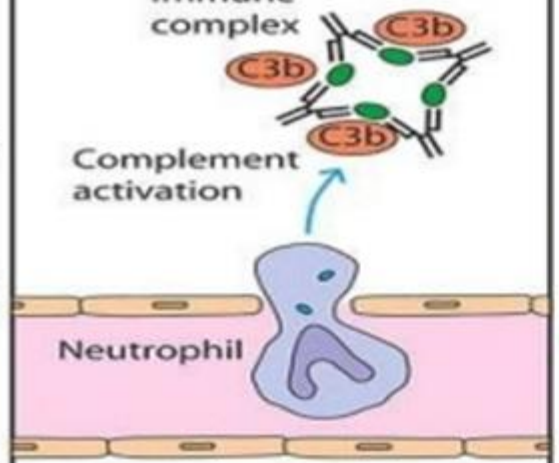
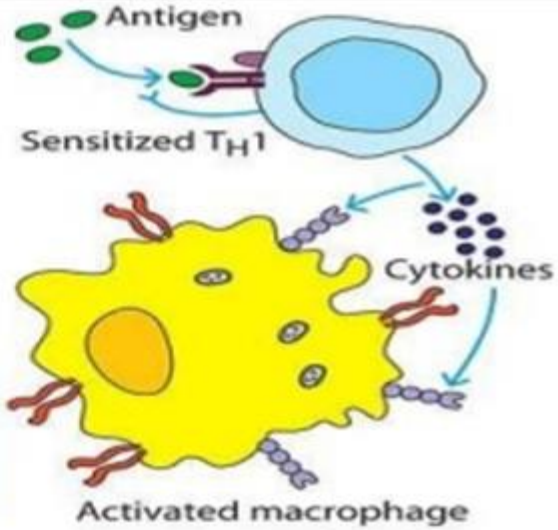

Acute kidney injury
History and record review, physical examination, blood and urine analysis, ultrasound
Normal urinary sediment, no hematuria or proteinuria FE_{Na}<1%, FE_{urea}<35%
Exog. nephrotoxin exposure, rhabdomyolysis,hemolysis
Edema, hypertension, abnormal urinary sediment, proteinuria
Bladder distention?
No
Yes
Fluid repletion
Fluid administration
Red or white blood cell casts Blood or serologic abnormalities
Bladder catheter
Increased urine volume
Oliguria
Tubular cell cylinders
Nonoliguric AKI
Oliguric AKI
No ureteral, renal pelvic dilatation
Ureteral renal pelvic dilatation
Furosemide Mannitol
Persistent AKI
Recovery AKI
Clinical diagnosis Renal biopsy?
Increased urinary volume
Vasculitis
AGN
HUS/TTP
AIN
Increased urine volume
Oliguria
Treatment
Suspicion retroperitoneal pathology
CT scan Retrograde pyelography
Recovery AKI
Persistent AKI
Clinical suspicion vascular obstruction
Recovery AKI
CT scan
Relief of obstruction
Nonoliguric AKI
Oliguric AKI
Doppler ultrasound Angiography
Conservative therapy Dialysis Nutritional support (K^+ and fluid restriction)
Negative
Thrombosis
Recovery AKI
Recovery AKI
Intrarenal AKI
Thrombectomy or fibrinolytic therapy
>3 weeks
Recovery AKI
Renal biopsy
Persistent AKI
Recovery AKI
Prerenal AKI
Intrarenal AKI
Postrenal AKI

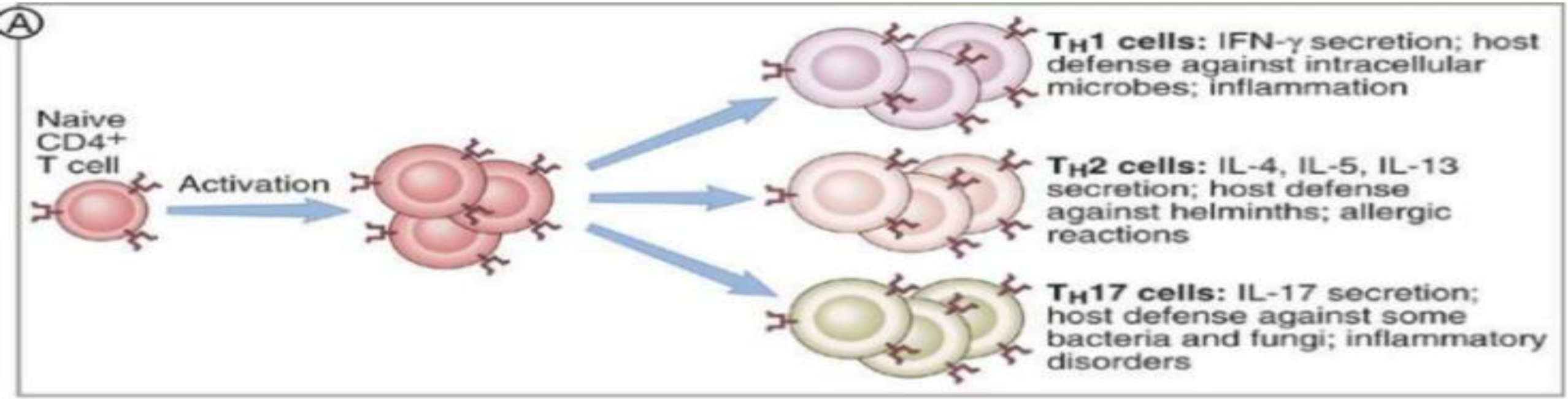

Ischemia/
reperfusion
Toxicity
Necrosis
Apoptosis
Normal epithelium
Damage
Cell death
↓ GFR
Potential urinary biomarkers for early diagnosis of AKI
NAG
β2M
α1M
RBP
Cystatin C
KIM-1
Clusterin
Microalbuminuria
NGAL
CYR-61
IL-18
OPN
FABP
NHE3
Fetuin A
Delayed biomarkers for kidney injury
↑ Serum creatinine
↑ Blood urea nitrogen


GFR Criteria
Urine Output Criteria
Risk
Increased serum creatinine X1.5
or GFR decrease >25%
UO <0.5ml/kg/h X 6 hrs
Injury
Increased serum creatinine X2
or GFR decrease >50%
UO <0.5ml/kg/h X 12 hrs
Failure
Increased serum creatinine
X3 or GFR decrease75%
or serum creatinine
>4mg/dl
Acute rise >0.5mg/dl
UO <0.3ml/kg/h X 24 hrs
or anuria X 12 hrs
High
Sensitivity
Loss
Persistent ARF = complete loss of
kidney function >4 weeks
ESKD
End stage kidney disease
> 3 months
High
Specificity


Complications
Normal
Increased risk
Damage
↓ GFR
Kidney failure
Kidney death

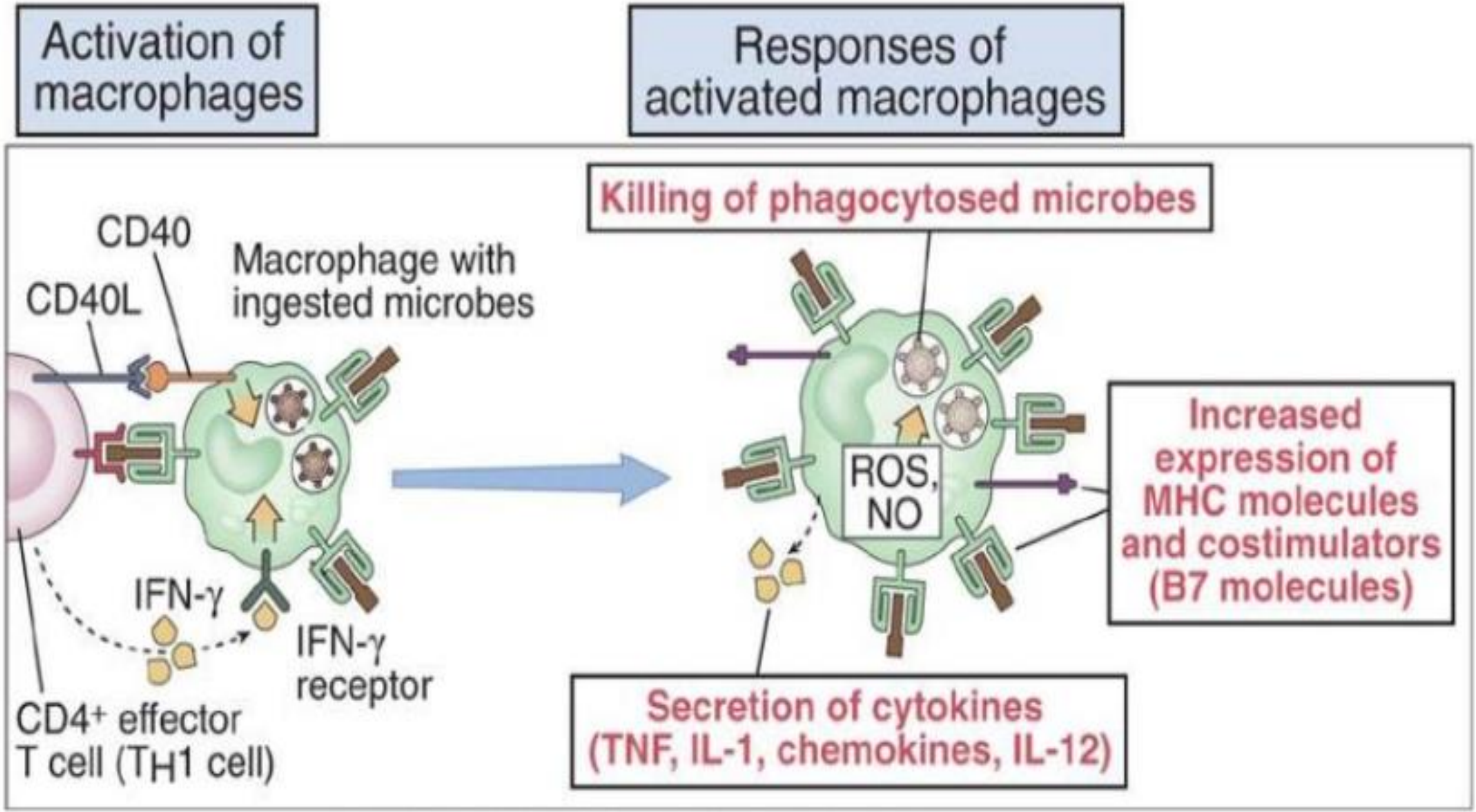
Hypersensitivity Reactions

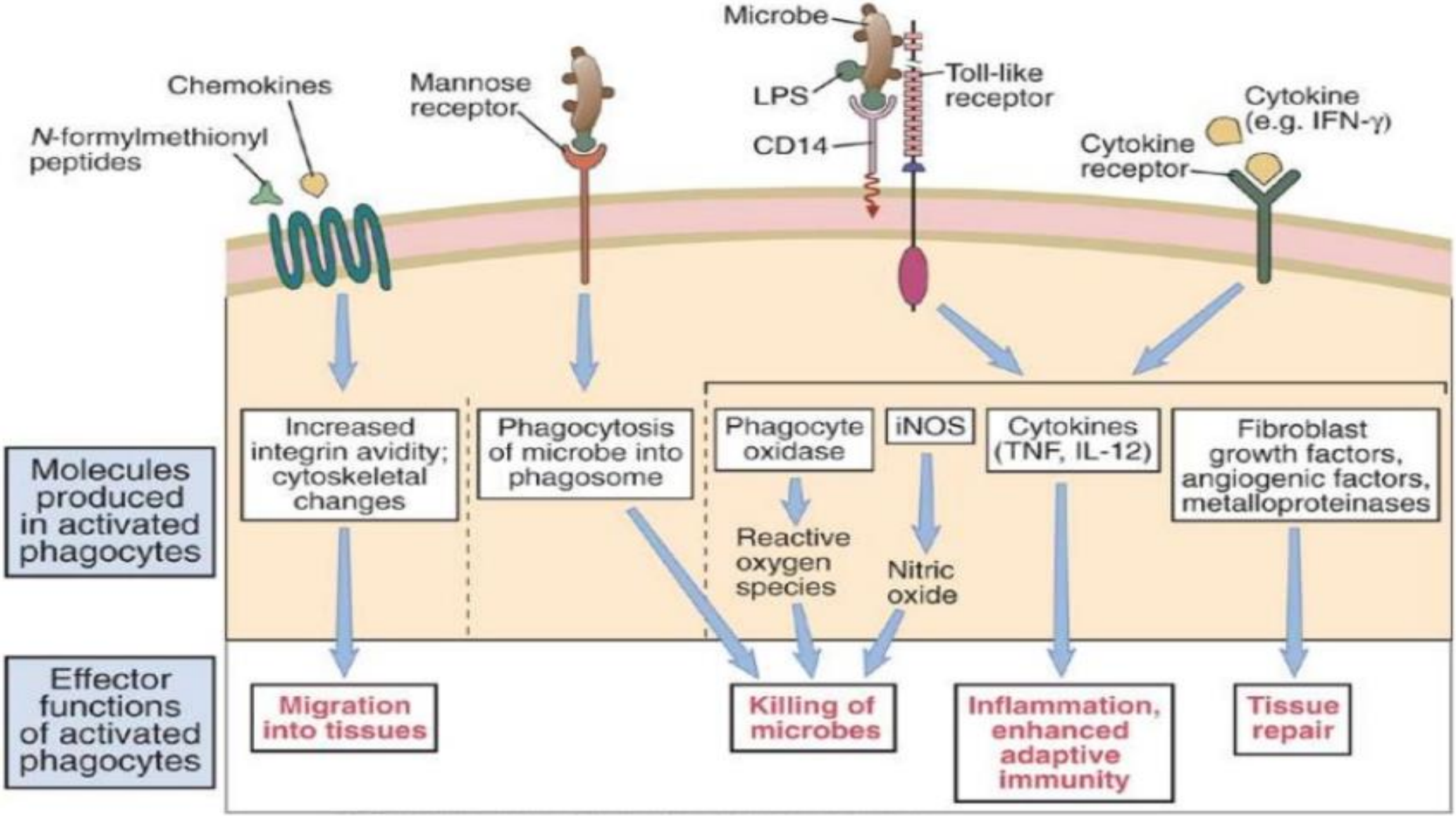
 **Type I**	 **Type II**	 **Type III**	 **Type IV**
IgE-Mediated Hypersensitivity	IgG-Mediated Cytotoxic Hypersensitivity	Immune Complex-Mediated Hypersensitivity	Cell-Mediated Hypersensitivity
Ag induces crosslinking of IgE bound to mast cells and basophils with release of vasoactive mediators	Ab directed against cell surface antigens meditates cell destruction via complement activation or ADCC	Ag-Ab complexes deposited in various tissues induce complement activation and an ensuing inflammatory response mediated by massive infiltration of neutrophils	Sensitized T_H1 cells release cytokines that activate macrophages or T_C cells which mediate direct cellular damage
Typical manifestations include systemic anaphylaxis and localized anaphylaxis such as hay fever, asthma, hives, food allergies, and eczema	Typical manifestations include blood transfusion reactions, erythroblastosis fetalis, and autoimmune hemolytic anemia	Typical manifestations include localized Arthus reaction and generalized reactions such as serum sickness, necrotizing vasculitis, glomerulnephritis, rheumatoid arthritis, and systemic lupus erythematosus	Typical manifestations include contact dermatitis, tubercular lesions and graft rejection

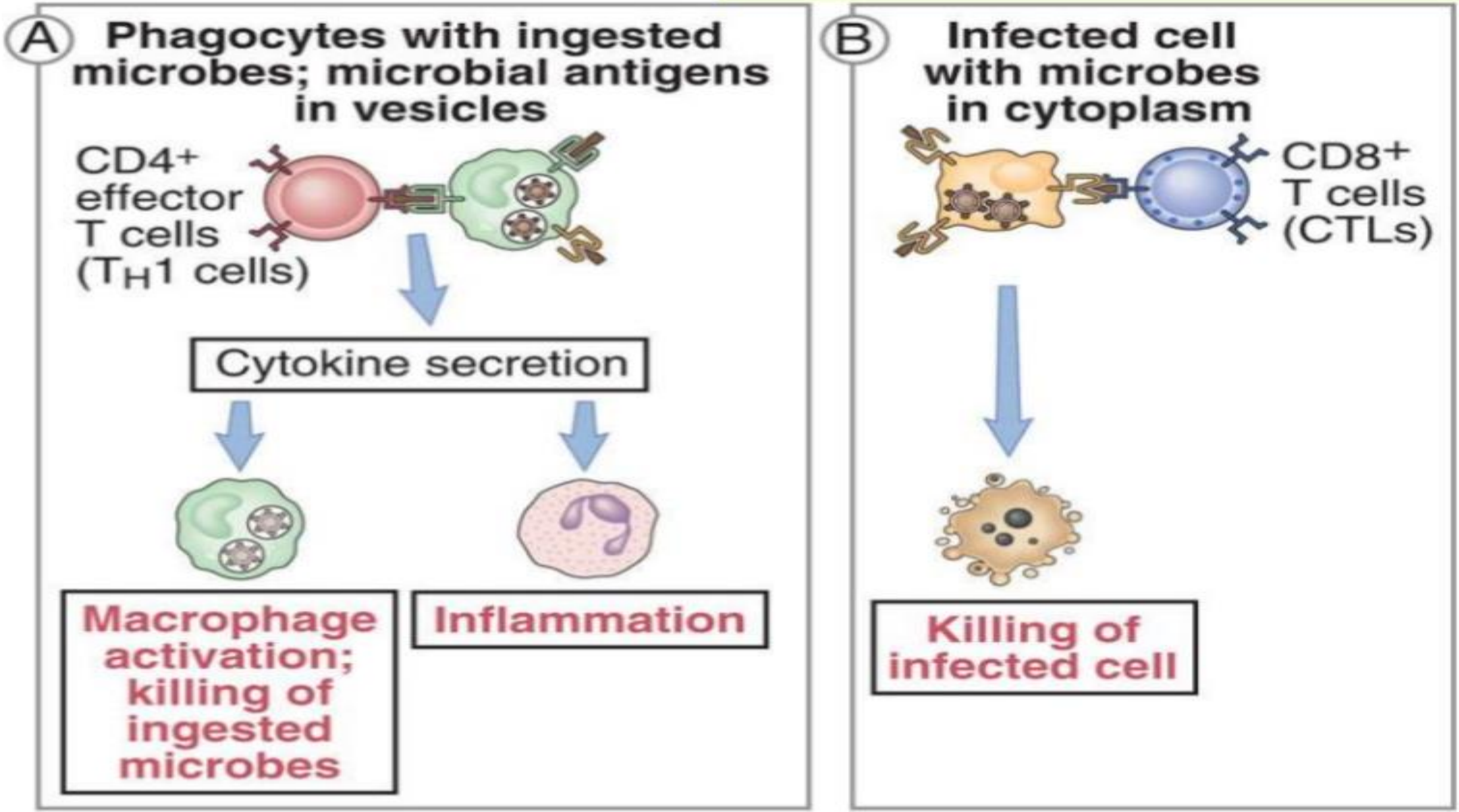


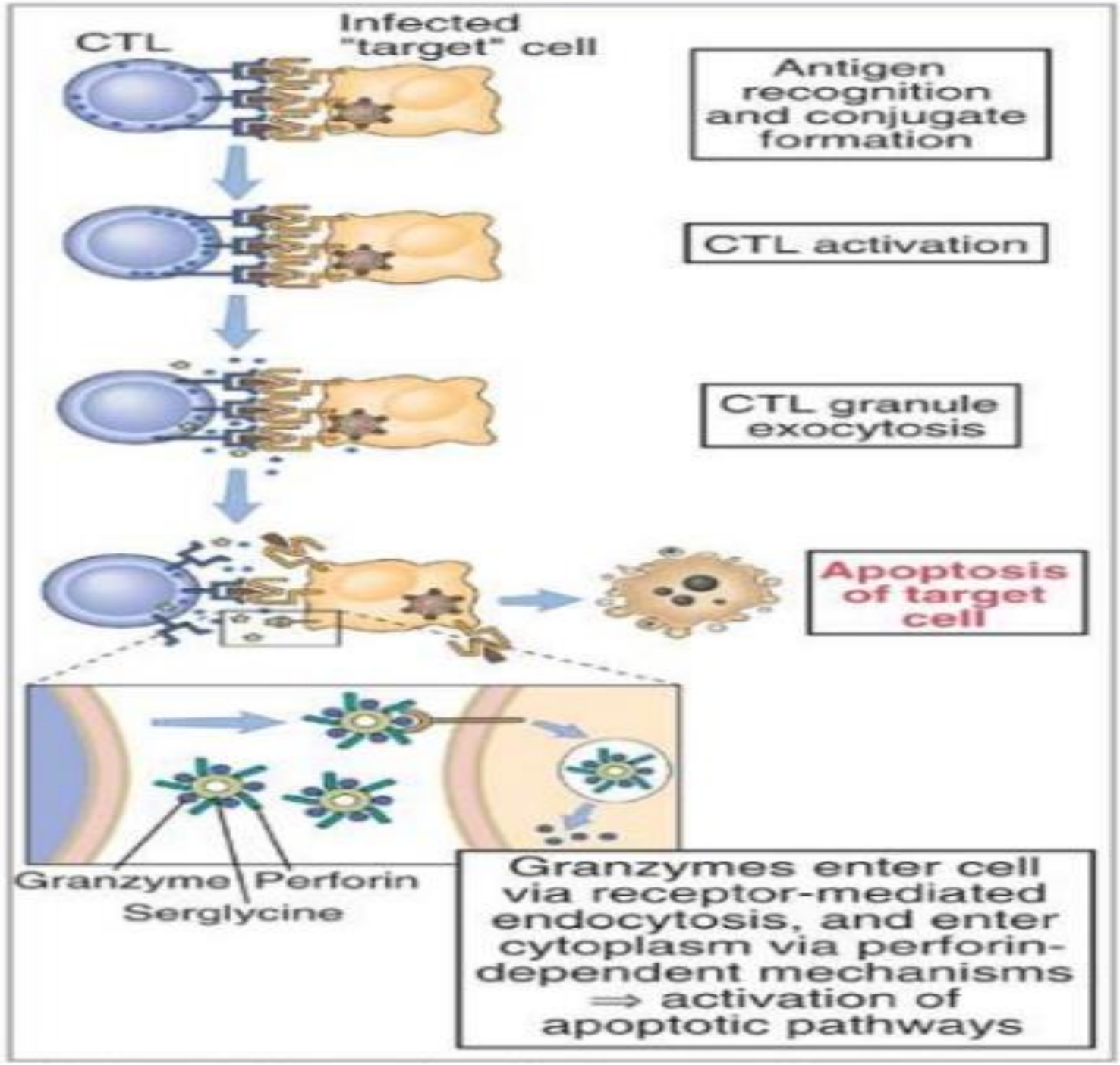
B

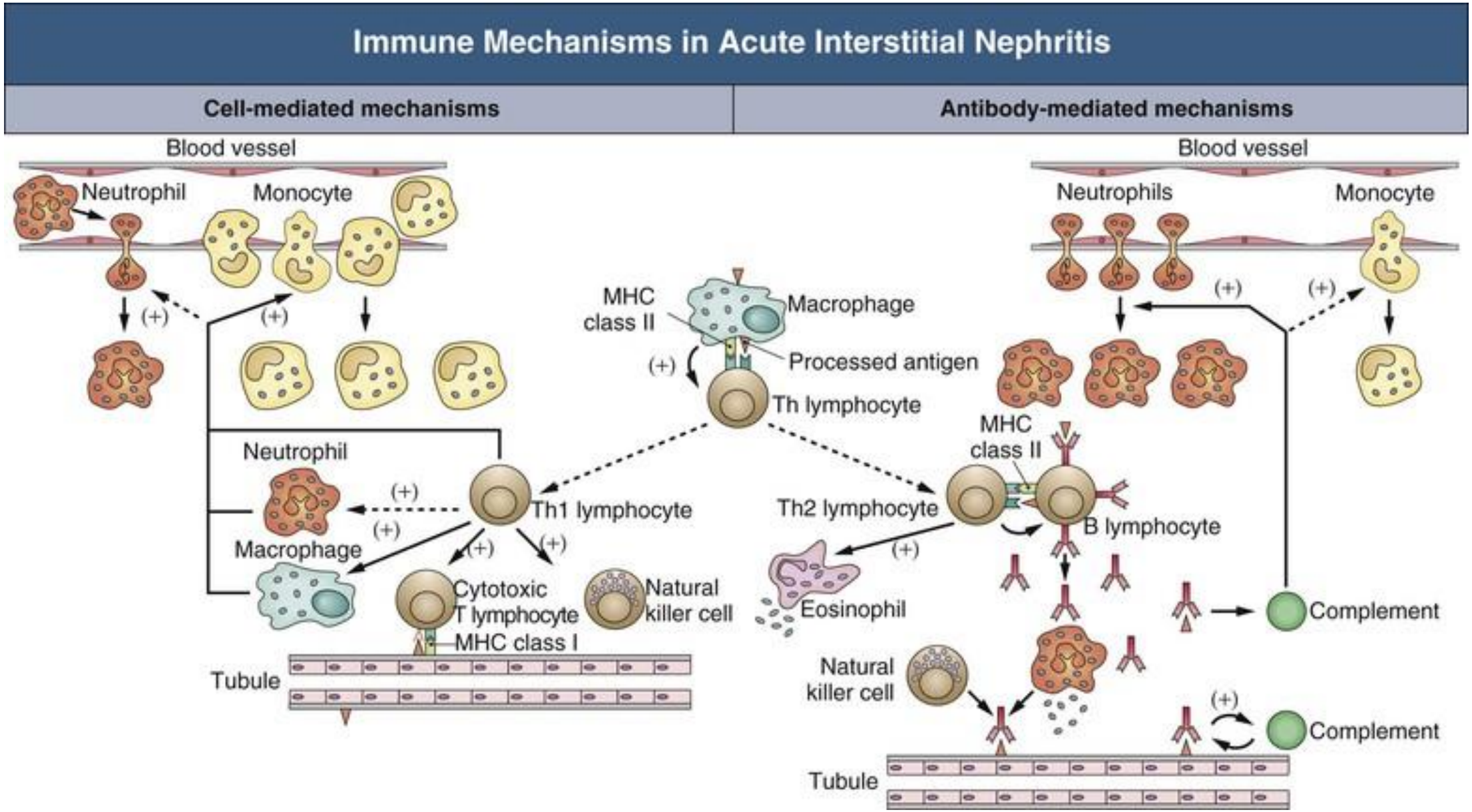
Property	T_H1	T_H2	T_H17
Principal cytokines produced	IFN-γ	IL-4, IL-5, IL-13	IL-17, IL-22
Antibody isotypes stimulated	Complement and Fc receptor-binding IgG subclasses such as IgG2a (mouse)	IgE; IgG1 (mouse), IgG4 (humans)	?
Macrophage activation	Classical (microbial killing)	Alternative (tissue repair)	?
Dominant leukocytes recruited	Monocytes	Eosinophils	Neutrophils, monocytes


Activation of macrophages
Responses of activated macrophages
CD40
CD40L
Macrophage with ingested microbes
IFN-γ
IFN-γ receptor
CD4+ effector T cell (TH1 cell)
Killing of phagocytosed microbes
ROS, NO
Increased expression of MHC molecules and costimulators (B7 molecules)
Secretion of cytokines (TNF, IL-1, chemokines, IL-12)


Microbe
Chemokines
Mannose receptor
LPS
Toll-like receptor
CD14
Cytokine (e.g. IFN-γ)
N-formylmethionyl peptides
Cytokine receptor
Molecules produced in activated phagocytes
Increased integrin avidity; cytoskeletal changes
Phagocytosis of microbe into phagosome
Phagocyte oxidase
iNOS
Cytokines (TNF, IL-12)
Fibroblast growth factors, angiogenic factors, metalloproteinases
Reactive oxygen species
Nitric oxide
Effector functions of activated phagocytes
Migration into tissues
Killing of microbes
Inflammation, enhanced adaptive immunity
Tissue repair


A
Phagocytes with ingested microbes; microbial antigens in vesicles
CD4+ effector T cells (T_H1 cells)
Cytokine secretion
Macrophage activation; killing of ingested microbes
Inflammation
B
Infected cell with microbes in cytoplasm
CD8+ T cells (CTLs)
Killing of infected cell


CTL
Infected "target" cell
Antigen recognition and conjugate formation
CTL activation
CTL granule exocytosis
Apoptosis of target cell
Granzyme
Perforin
Serglycine
Granzymes enter cell via receptor-mediated endocytosis, and enter cytoplasm via perforin-dependent mechanisms ⇒ activation of apoptotic pathways

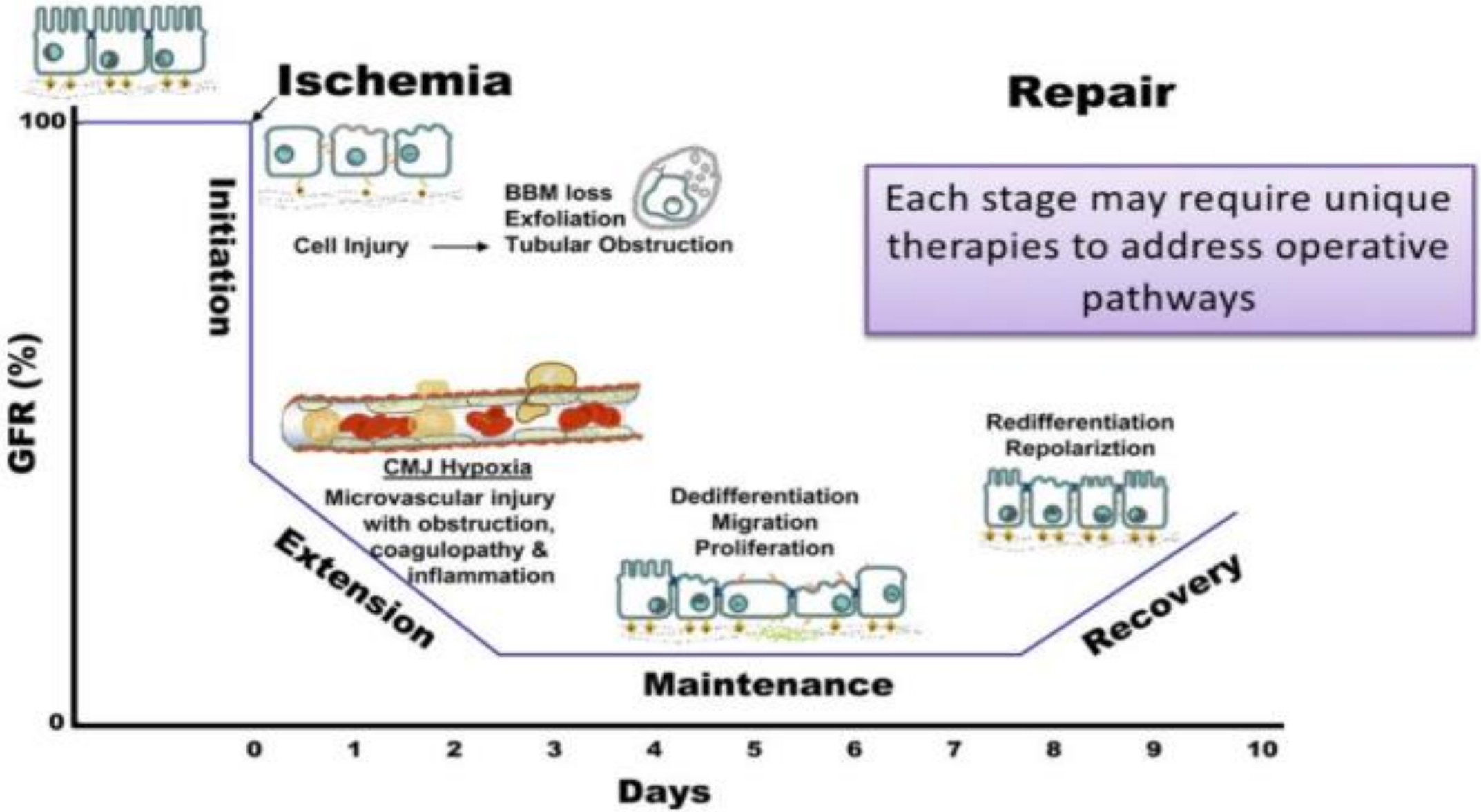

Immune Mechanisms in Acute Interstitial Nephritis
Cell-mediated mechanisms
Antibody-mediated mechanisms
Blood vessel
Neutrophil
Monocyte
(+)
MHC class II
Macrophage
Processed antigen
Th lymphocyte
Neutrophil
Th1 lymphocyte
Macrophage
Cytotoxic T lymphocyte
Natural killer cell
MHC class I
Tubule
Blood vessel
Neutrophils
Monocyte
MHC class II
Th2 lymphocyte
B lymphocyte
Eosinophil
Complement
Natural killer cell
Complement
Tubule

Acute Interstitial Nephritis

Acute Interstitial Nephritis

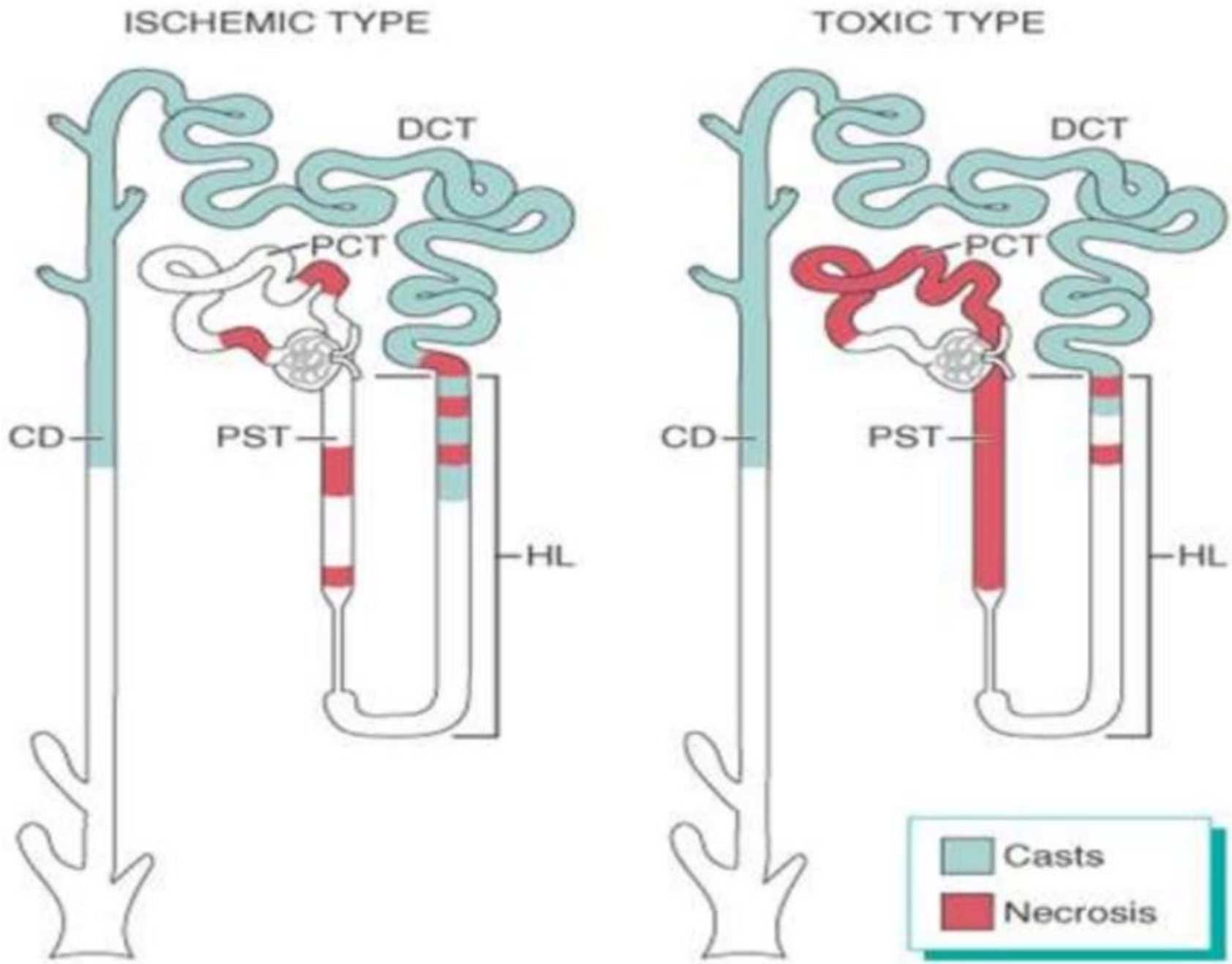
- A common cause of intrinsic AKI
  - Now, the second leading after ATN
- AIN may be more common in AKI since biopsies often not performed
  - 13-27% of biopsies for AKI (Farrington et al. The Quarterly journal of medicine 1989; Haas et al. American journal of kidney diseases 2000; Goicoechea et al. NDT 2013)
  - In elderly (> 65 yo): increasing biopsies in this age group with AKI (25-50%) (Moutzouris DA et al. Clin J Am Soc Nephrol 2009; Nair R et al. Am J Kidney Dis 2004)
    - AIN was seen in 19% of biopsies in a study in USA (Haas et al. American journal of kidney diseases 2000)
    - Nearly 8-fold increase in AIN in a study in Spain (Goicoechea et al. Nephrol Dial Transplant 2013)
  - 1% of “healthy” people biopsied for isolated proteinuria/hematuria
  - 1-15% of all biopsies in patients with renal disease

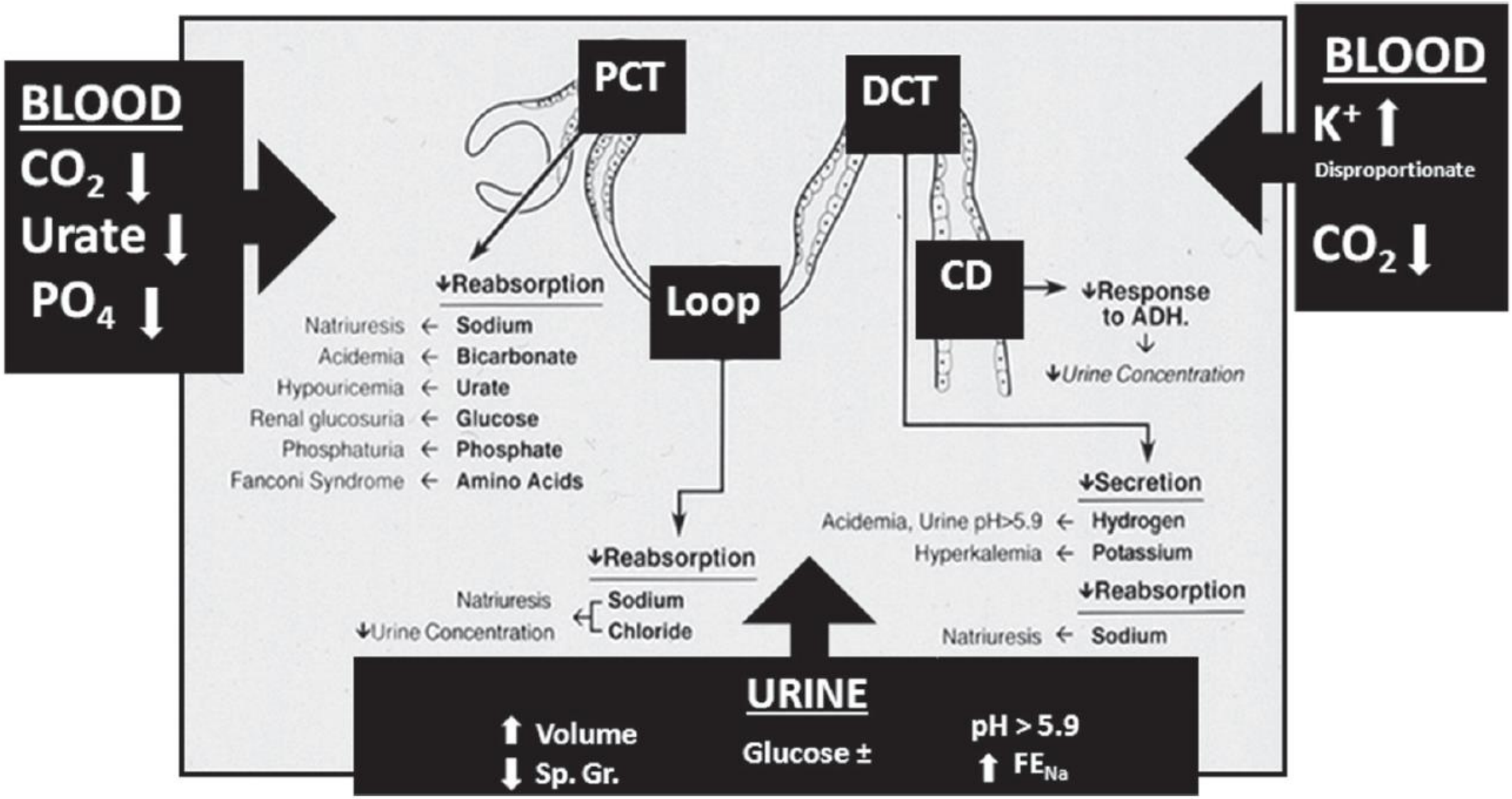
	Acute Tubular Necrosis	Acute Interstitial Nephritis
Onset following injury	Hours to days	Days to weeks
Urine volume	Oliguria < 500 mL/d	Polyuria (> 2,000 mL/d)
Clinical features	Hemodynamic instability	Rash (25 – 40%), fever (35 – 70%), back pain (25 – 40%), arthralgia (25 – 40%)
Histology	Tubular epithelial cell injury	Interstitial cellular infiltrates, edema, tubulitis
Eosinophilia	Absent	Present (35 – 60%)
Tubular dysfunction†	Rare	Very common
FE_{Na} #	> 1%	> 1%



Each stage may require unique therapies to address operative pathways

Adapted from Sutton TA et al. Kidney Int 2002; 62; 1539-1549


ISCHEMIC TYPE
DCT
PCT
CD
PST
HL
TOXIC TYPE
DCT
PCT
CD
PST
HL
Casts
Necrosis

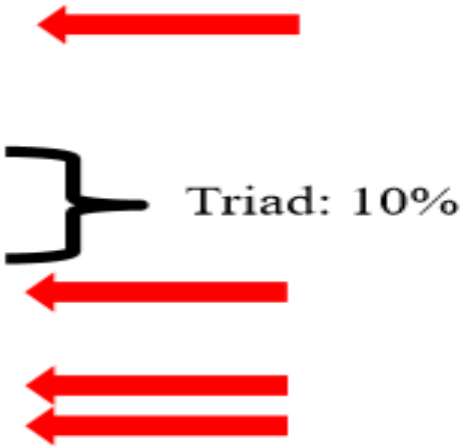

BLOOD
CO_2 ↓
Urate ↓
PO_4 ↓
PCT
DCT
Loop
CD
↓Reabsorption
Natriuresis ← Sodium
Acidemia ← Bicarbonate
Hypouricemia ← Urate
Renal glucosuria ← Glucose
Phosphaturia ← Phosphate
Fanconi Syndrome ← Amino Acids
↓Reabsorption
Natriuresis
↓Urine Concentration
Sodium
Chloride
↓Response to ADH.
↓
↓Urine Concentration
↓Secretion
Acidemia, Urine pH>5.9 ← Hydrogen
Hyperkalemia ← Potassium
↓Reabsorption
Natriuresis ← Sodium
BLOOD
K^+ ↑
Disproportionate
CO_2 ↓
URINE
↑ Volume
↓ Sp. Gr.
Glucose ±
pH > 5.9
↑ FE_{Na}

Clinical Presentation of AIN

Table 2 | Clinical and laboratory features at presentation in patients with AIN (pooled data from González *et al.*[18] and Clarkson *et al.*[19])

Features	
Acute renal failure	100%
Acute renal failure requiring dialysis	40%
Arthralgias[a]	45%
Fever	36%
Skin rash	22%
Eosinophilia (>500 eosinophils per mm^3)	35%
Microhematuria[b]	67%
Gross hematuria[b]	5%
Leukocyturia[b]	82%
Non-nephrotic proteinuria	93%
Nephrotic-range proteinuria	2.5%
Complete nephrotic syndrome	0.8%

[a]Data from Clarkson *et al.*[19]
[b]Data from González *et al.*[18]

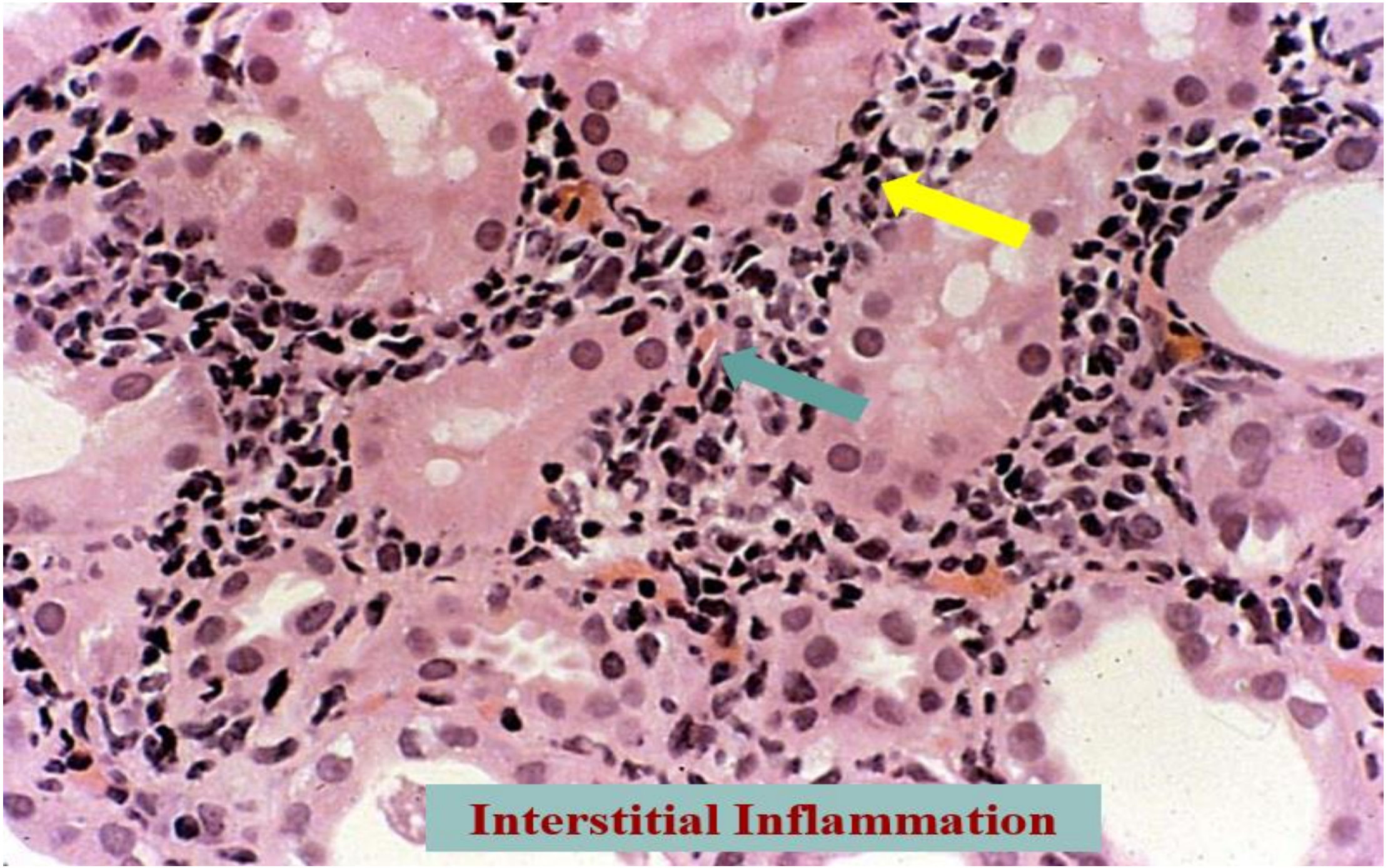


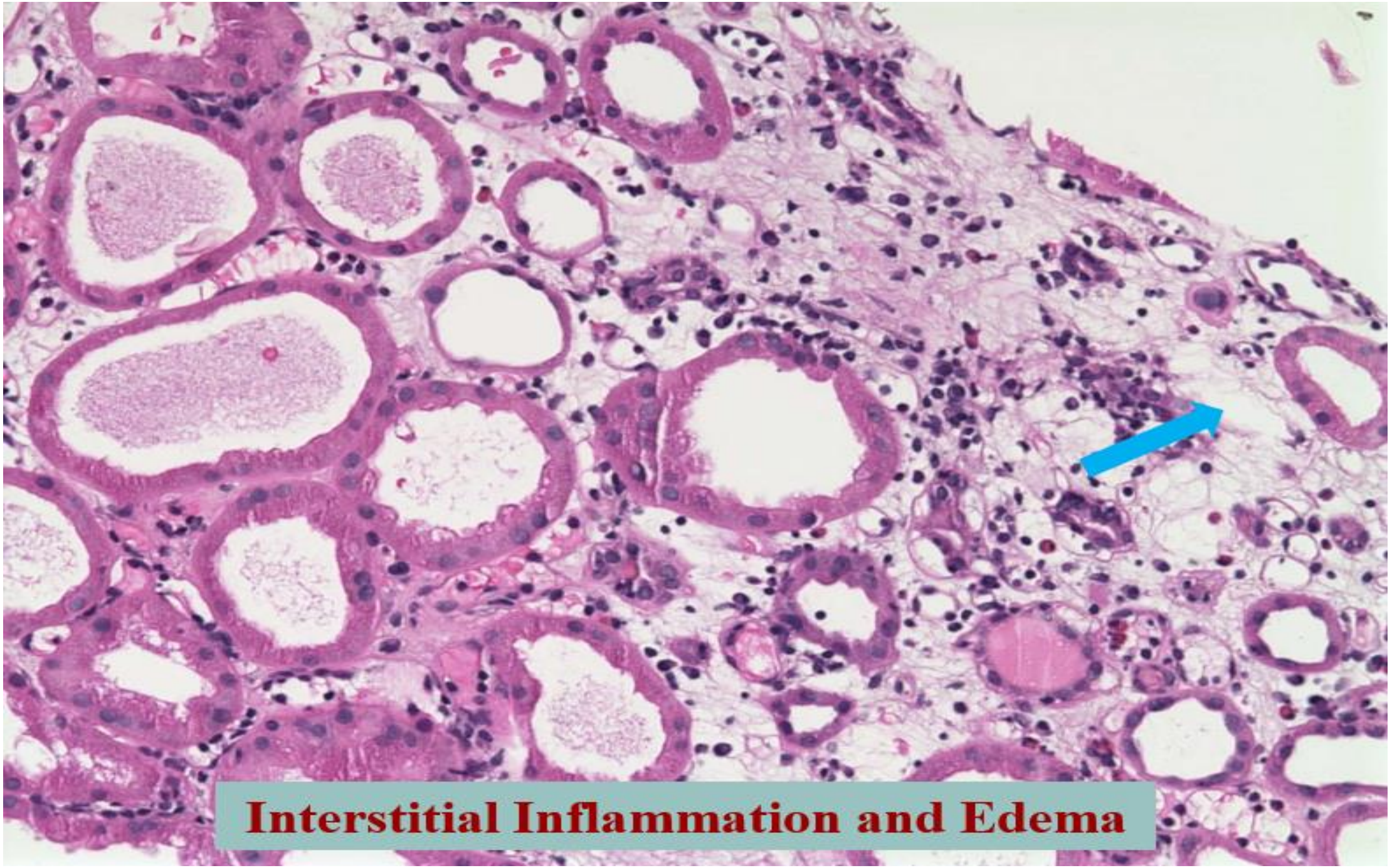
Praga and Gonzalez, *KI(2010) 77, 956–961*

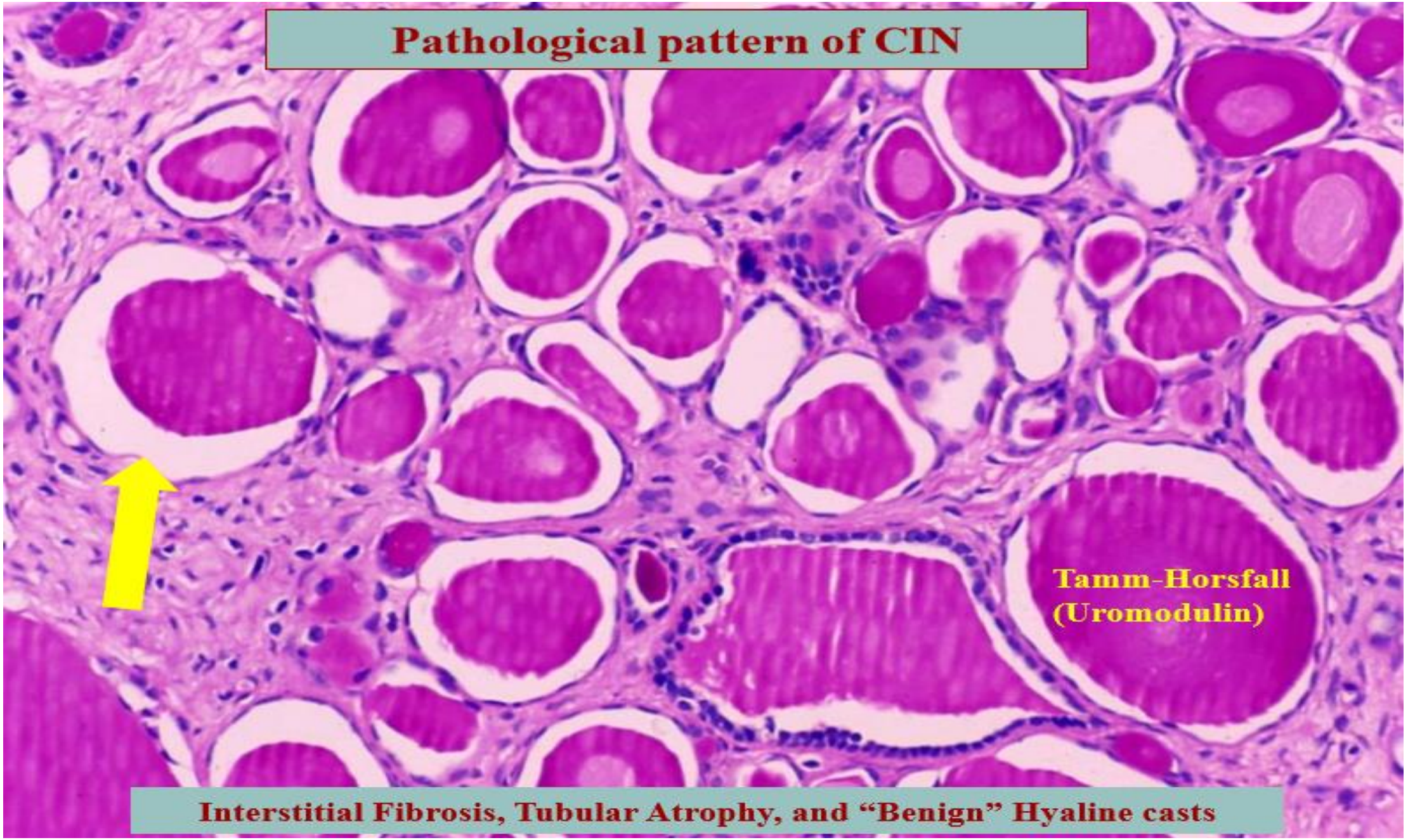
Diagnosis

- Renal biopsy remains the definitive diagnostic modality
  - Hallmark of AIN:
    - Inflammatory interstitial infiltrate of monocytes and lymphocytes (fewer eosinophils, plasma cells, and neutrophils)
    - Interstitial edema
    - Renal tubule separation
    - Tubulitis
    - Absence of glomerular or vascular pathology
  - Fibrotic changes may be seen as early as within 7-10 days
  - Granuloma patterns can occur and commonly are drug-related

Grad et al. NEJM 2010; Perazella et al. Nature reviews Nephrology 2010; Rossert et al. Floege J JR, Feehally J, ed. Comprehensive Clinical Nephrology 2010; Michel et al. JASN 1998


Interstitial Inflammation


Interstitial Inflammation and Edema


Pathological pattern of CIN
Tamm-Horsfall
(Uromodulin)
Interstitial Fibrosis, Tubular Atrophy, and "Benign" Hyaline casts

Types of TIN

- Primary TIN – limited to the tubulointerstitium, associated with drugs. Glomeruli and vessels are uninvolved.
- Secondary TIN – associated with a primary glomerular, vascular or systemic disease.
- Reactive TIN – inflammation from effects of systemic infection, where kidneys are usually sterile
- Idiopathic TIN – unknown pathology

Etiologies of AIN

- Drugs (Allergic interstitial nephritis) (70-75%)
  - Antibiotics: 30-50%
  - Mean delay between drug start date and AKI is 10 days
  - Latent period can be as short as 1 day with some antibiotics
- Systemic disease (10-20%)
  - Autoimmune diseases (Sarcoidosis, SLE, Sjögren's, ANCA)
  - Neoplastic (leukemias, lymphomas)
  - Acute allograft rejection
- Infections (bacterial, viral, parasitic) (5-10%)
- Idiopathic (5-10%)
  - Hypocomplementemic AIN with TBM Antibodies
  - IG4 related TINU

Drug Related Allergic Interstitial Nephritis

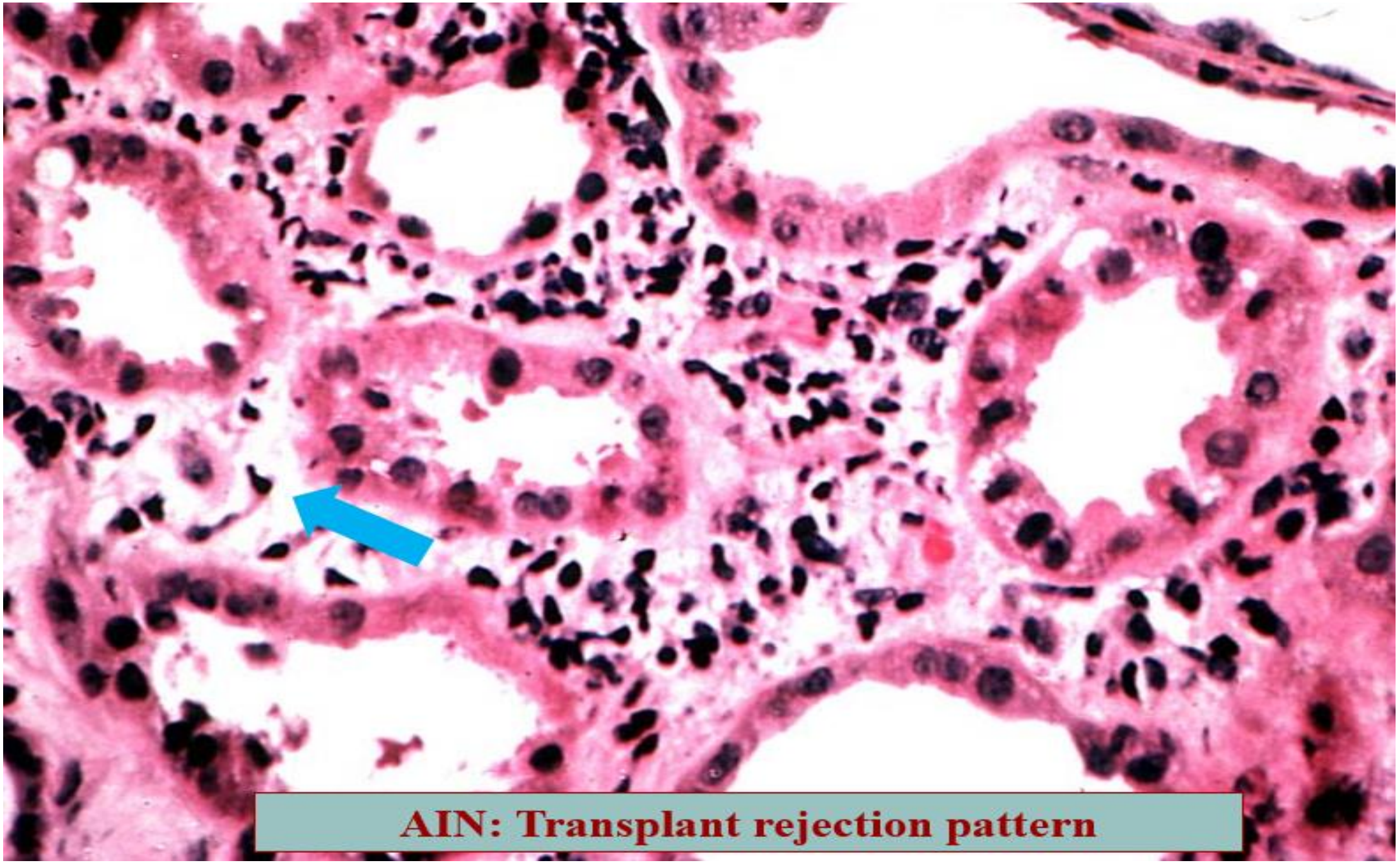
- **Antibiotics:** PCN, cephalosporins, ciprofloxacin, rifampin, sulfa, vanco, erythromycin, Sulfamethoxazole/Trimethoprim (bactrim), acyclovir, ethambutol (EMB)
- **Diuretics:** thiazides, furosemide, bumetanide, triamterene
- **NSAIDS** (including selective COX-2 inhibitor): pure interstitial nephritis (ISN) ± papillary necrosis/ minimal change nephropathy (MCN) + ISN (85%)
- **PPI** (omeprazole and lansoprazole)
- **H2 blockers** (cimetidine, ranitidine-rare)
- **Allopurinol**
- **Indinavir**
- **5-aminosalicylates (5-ASA)** (i.e. mesalamine)
- **Others**: phenobarbital, phenytoin, nitrofurantoin, IFN, IL-2, Angiotensin converting enzyme inhibitor (ACEI: i.e.captopril), checkpoint inhibitors

Case 2

- A 24 yo male with a hx for aplastic anemia s/p umbilical cord stem cell transplant c/b CMV viremia and EBV related post-stem cell PTLD of his lungs and intestinal tract treated with Rituximab; ESRD from TTP/HUS-induced chronic TMA on hemodialysis, who is postop day #4 s/p living unrelated kidney transplant.
- His U.O.P decreased from 750 cc/hr post-op to 20 cc/hr. His Cr increased to 5.5 after initially going down from 6.64 to 3.73 post-op.
- He was last dialyzed the day prior to transplantation without complication.

Case 2

- **Medications**: Valganciclovir (valcyte), tacrolimus, MMF, prednisone , labetalol, Amlodipine, Minoxidil, Sulfamethoxazole/Trimethoprim (bactrim)
- **PE:** Temp 99.4 BP 127/71 HR 118 RR 16, INS/OUTS: 2700/480, JVP ~ 12 cm, mild tenderness to palpation of LLQ at surgical site. trace lower extremity edema. foley draining dark yellow urine
- **Lab:** Urinalysis: 1.015/5.0, 2+ protein, 61 RBCs, 6 WBCs, Na 131, HCO3 18, Cr 5.5, BUN 84, WBC 10.5, Hb 10, Hct 29.6
- **Renal Biopsy:** Kidney allograft biopsy, 4 days post-transplantation:
  - Acute Interstitial Inflammation; The changes are most likely an expression of a acute interstitial nephritis. However, acute rejection could have resulted in similar changes

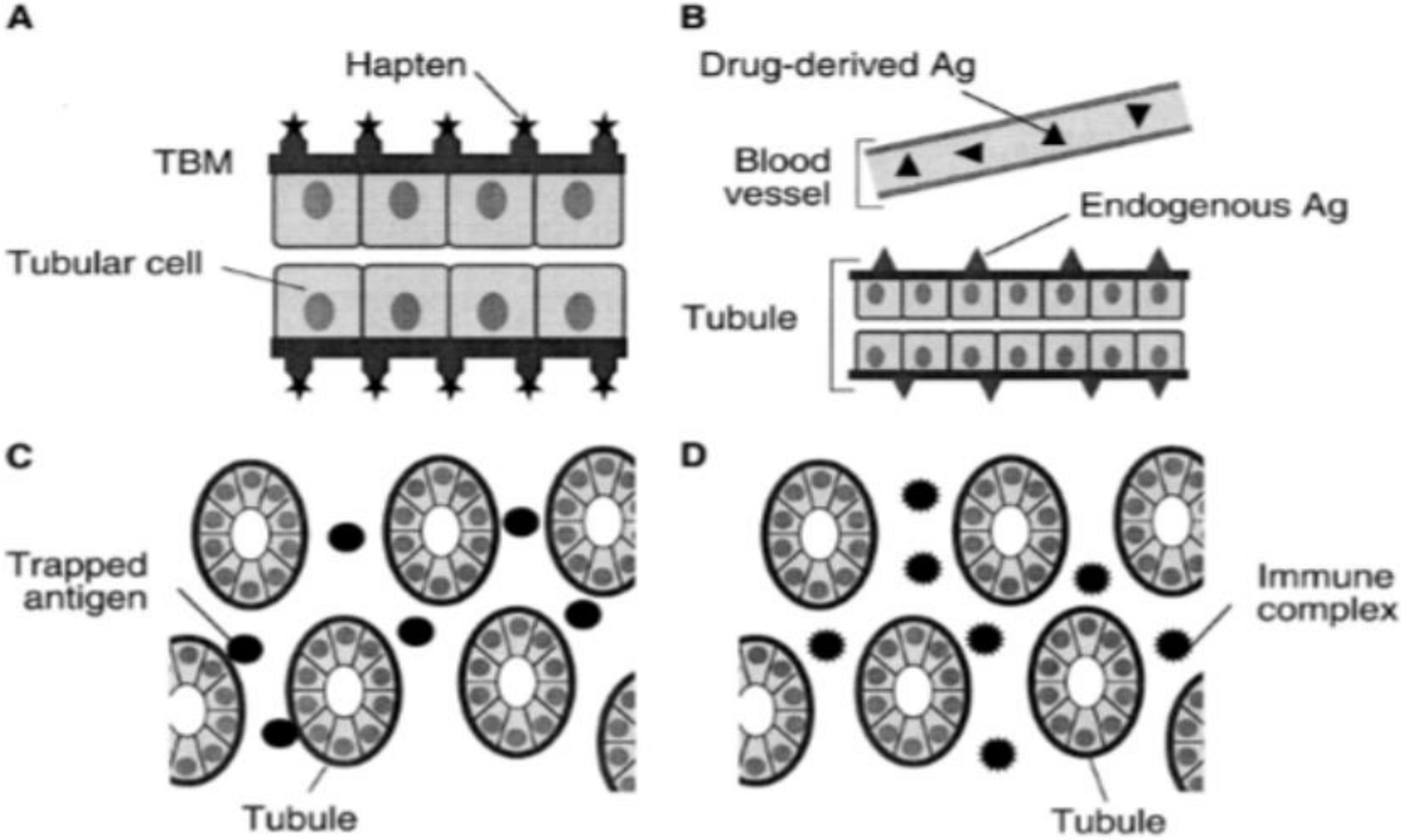

AIN: Transplant rejection pattern

Case 2 - Bactrim and DRAIN

- TMP-SMX is the standard PJP prophylaxis in transplantation.
- Josephson, et al. AJKD, 34(3): 540-548, September 1999
  - 6 patients with delayed graft function (DGF) and drug- induced interstitial nephritis
  - 5/6 occurred within 4 weeks of transplantation
- Garvey, et al. Clin Nephrol, 72(5): 331-336, November 2009
  - 11/109 (10.1%) biopsies performed for early allograft dysfunction
  - early allograft dysfunction defined as < 1 month
  - TMP-SMX stopped and creatinine immediately improved

Drug-induced Hypersensitivity Reaction Classification

Classification	Description
Type IVa	T helper 1 cell Interferon-γ/Interleukin-12 - Monocyte/macrophage stimulation - Synthesis of complement-fixing antibody and complement-mediated injury - Co-stimulation of pro-inflammatory responses (tumor necrosis factor, interleukin-12) -Co-stimulation of CD8 T-cell responses
Type IVb	T helper 2 cell Interleukin-4, interleukin-5, inerleukin-13 - B-cell production of IgE and IgG4 - Macrophage deactivation - Mast cell and eosinophil responses
Type IVc	Cytotoxic T cells - Injury via perforin/granzyme and Fas ligand-dependent processes
Type IVd	T cell (interleukin-8 and granulocyte monocyte-colony stimulating factor) - Neutrophil-mediated inflammation/'sterile polymorphonuclear-rich inflammation'


A
Hapten
TBM
Tubular cell
B
Drug-derived Ag
Blood vessel
Endogenous Ag
Tubule
C
Trapped antigen
Tubule
D
Immune complex
Tubule

Clinical Course of AIN

- Most resolve with removal of offending agent/ treatment of underlying infection
- 30-70% did not fully recovered their baseline renal function (Buysen et.al. NDT 1990; Rossert KI 2001; Galpin et.al. Am J Med 1978; Pusey et.al. Q J Med 1983; Kida et.al. Clin Nephrol 1984 ; Laberke et.al. Clin Nephrol 1980; Bhaumik et.al. Ren Fail 1996)
- Up to 1/3 may need dialysis
- Likelihood of recovery inversely proportional to degree of renal failure
  - Scattered infiltrates associated with better outcome (Buysen et.al. NDT 1990; Laberke et.al. Clin Nephrol 1980)
- 50% of idiopathic remain with some renal dysfunction

Treatment of AIN

- NSAID-induced AIN: withdraw of the offending drug
  - Addition of steroids does not change the clinical course (Porile et.al. j Clin Pharmacol 1990)
- Steroids: mainstay of treatment in idiopathic AIN, TINU and AIN associated with systemic diseases (Rossert KI 2001; Neilson KI 1989; Finkelberg et.al. NEJM 2006; Yoneda et.al. AJKD 2007)
- Cyclophosphamide; Cyclosporine: steroid-resistant idiopathic AIN (Zuliani et.al. Clin Nephrol 2005)
- Mycophenolate Mofetil (MMF): steroid dependent, resistant AIN; or unable to tolerate steroid therapy (Preddie et.al. Clin J Am Soc nephrol 2006)
- ? Plasmapheresis or cytotoxics: if strong anti-TBM Ab

Role of Steroids

- There are no prospective randomized controlled trials to date to assess the efficacy of steroids in treatment
- Some data suggest that corticosteroids helps improvement of renal function and prognosis (Rossert J. KI 2001; Galpin et al. Am J Med 1978; Handa SP CMAJ 1986; Buysen et al NDT 1990)
  - One series with Methicillin-induced AIN: 14 patients with average peak Cr of 8 mg/dL. 8 patients received glucocorticoids. These patients recovered more quickly (9 versus 54 days) and had a lower final Cr level (1.4 versus 1.9 mg/dL than the six who received no therapy
  - One series with biopsy-proven AIN: total of 27 patients (15 drug induced; 9 due to infection; 3 idiopathic)
    - The 10 patients who did not improve after stopping the drug or treatment of the infection were given glucocorticoids within 5 to 20 days of biopsy. 6 patients had normalized Cr within ~one month, and the remaining 4 had partial improvement in kidney function

Role of Steroids

- Retrospective studies: demonstrated conflicting results (Rosssert J KI 2001; Clarkson et.al NDT 2004; Schwartz et al Clin Nephrol 2000; Bhaumik et al Ren Fail 1996; Koseli et al Ren Fail 1993; Gonzalez E et.al KI 2008; Appel GB KI 2008; Muriithi et al Am J Kidney Dis 2014)
- Multi-center study with 61 patients: 52 patients (85%) received steroids vs 9 patients (15%) did not (Gonzalez, et al. Kidney International, 73:940-946, 2008)
  - Lower % of dialysis by 18 months (3.8 % vs. 44%)
  - Lower Cr level (2.1 vs 3.7 mg/dL)
  - Those received steroids < 7 days of stopping offending drug were more likely to recover kidney function (Odds ratio 6.6,95% CI 1.3-33.6)
- Single center study with 60 biopsy-proven AIN patients: 42 follow-up data, 25 (60%) received steroid treatment and 17 (40%) did not (Clarkson, et al. Nephrol Dial Transplant, 19:2778-2783, 2004)
  - no difference in Cr observed at 1, 6 and 12 months
- Another series with 95 biopsy-proven AIN: 83 patients received steroids and 12 did not (Muriithi et al Am J Kidney Dis 2014)
  - At six months, there was no difference in the probability of recovery of renal function between the group given steroids and the group not given steroids

KDOQI Guidelines

- Treat patients who do not have significant improvement in the Cr within 3-7 days after discontinuation of the offending agent
  - a renal biopsy is preferred
    - to confirm AIN
    - to exclude other possible diseases
    - Assess the present of interstitial nephritis with significant chronic damage (interstitial fibrosis, tubular atrophy, and minimal or no acute inflammation), in which case immunosuppressive therapy might not be indicated
- An empiric trial for patients with a strongly suggestive history of DRAIN when kidney biopsy is not feasible
- The optimal dose and duration of therapy are unclear
  - Administer prednisone at a dose of 1 mg/kg per day (max 40 to 60 mg) for 1-2 weeks with gradual taper for a total therapy duration of 2-3 months.
  - In more severe AKI, use IV methylprednisolone (0.5 to 1 g/day for three days)
  - The duration of steroids varies widely among the many (cohort) studies in the literature, from days to 12 weeks (Rossert J. KI 2001; Galpin et al. Am J Med 1978; Handa SP CMAJ 1986; Buysen et al NDT 1990)

Take-home Message

- ATN and AIN constitute 85% causes of intrinsic AKI
  - The remaining 15% have a high component of accompanying ATN and AIN
- The “triad” of AIN: fever, rash and eosinophilia
  - Only seen in ~ 10% of patients with AIN
  - Absence of “triad” does not r/o AIN
- Drugs are a common cause of AIN
  - Most of the Drug-Related AIN improve spontaneously after stopping the offending agent.
  - Clinical suspicion for drug-induced nephrotoxicity should be high
  - Delayed intervention results in poor renal outcomes
- Steroid remains as the mainstay treatment option for AIN
  - The optimal dose and duration are currently unclear