

# Acute Kidney Injury

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# Definition

Rapid decrease in GFR (minutes-days)



Metabolic waste rate of production > rate of excretion

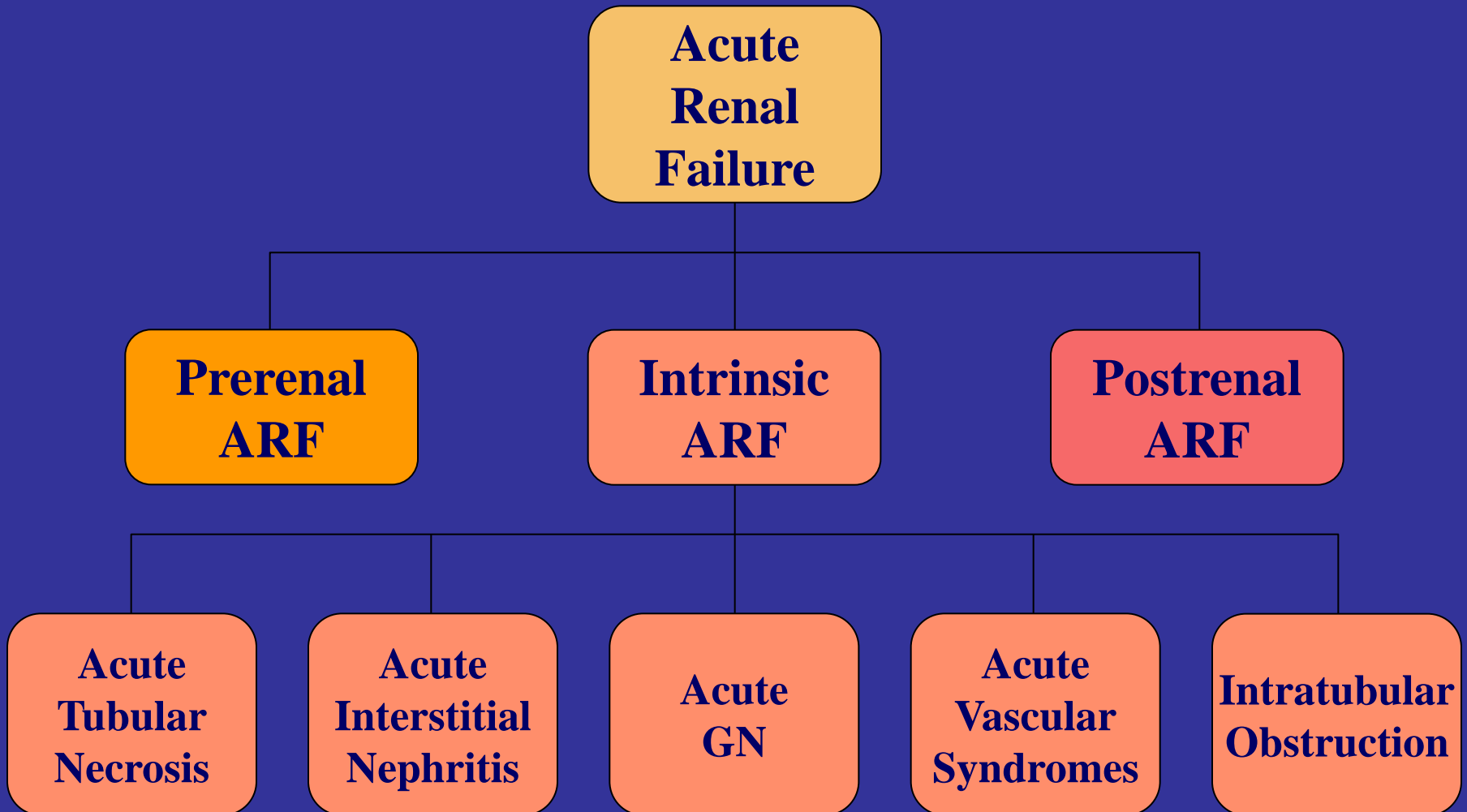


Rise in serum markers of renal function:  
urea and creatinine

# Manifestations

- Azotemia progressing to uremia
- Hyperkalemia
- Metabolic acidosis
- Volume overload
- Hyperphosphatemia
- Accumulation and toxicity of medications excreted by the kidney

# Classification of the Etiologies of Acute Renal Failure



# Prerenal Azotemia

- Functional response to renal hyperfusion
- Renal structure and microstructure are preserved
- Complete recovery may be seen in 1-2 days after relief of offending lesion (normal perfusion)

# Postrenal Azotemia

- Obstruction of the urinary tract
- Few microscopic changes initially,
  - Early hydronephrosis
  - Pelvic dilation
  - Distention or blunting of the renal papilla
- Or no microscopic changes
- Complete recovery may be seen in 1-2 days after relief of offending lesion (normal outflow)

# Intrinsic Renal Azotemia

- Parenchymal injury of the blood vessels, glomeruli, tubules, or interstitium
- Recovery may be prolonged

# Ischemic Acute Renal Failure: prerenal azotemia and acute tubular necrosis

- Prerenal azotemia and ATN account for more than half of the cases of ARF seen in hospitalized patients
- Often, the contribution of ischemia is unrecognized because the patient is normotensive



# Prerenal Acute Renal Failure: Clinical Presentation

- BUN:Creatinine ratio
  - > 20:1
- Urine indices
  - Oliguria
    - usually < 500 mL/24 hours; but may be non-oliguric
  - Elevated urine concentration
    - $U_{Osm} > 700$  mmol/L
    - specific gravity > 1.020
  - Evidence of high renal sodium avidity
    - $U_{Na} < 20$  mmol/L
    - $FE_{Na} < 0.01$
  - Inactive urine sediment

# Response to Hypoperfusion: Renin-Angiotensin System



## Proximal mechanism

Constricts efferent arteriole  
↑ glom. hydrostatic pressure  
& ↓ renal blood flow  
FF ↑ (FF=GFR/RPF)  
↑ Na reabsorption

## Distal mechanism

Stimulates zona glomerulosa  
to secrete aldosterone.  
↑ Na channels in distal &  
collecting tubules  
Stimulates Na-K-ATPase pump at  
basolateral membrane

# Role of Antidiuretic Hormone

- Synthesized in the hypothalamus
- Stored in posterior pituitary
- Release stimulated by
  - hyperosmolality (sensitive, 1% change stimulates release)
  - volume depletion (less sensitive – only released if enough change in volume to lower blood pressure; renin/sympathetic system will be stimulated first).
- Binds to V2 receptor on the basolateral membrane of the principal cells in the collecting tubules → apical membrane insertion of aquaporin-2 channels
- Binds to V1a receptors on the vascular smooth muscle cells

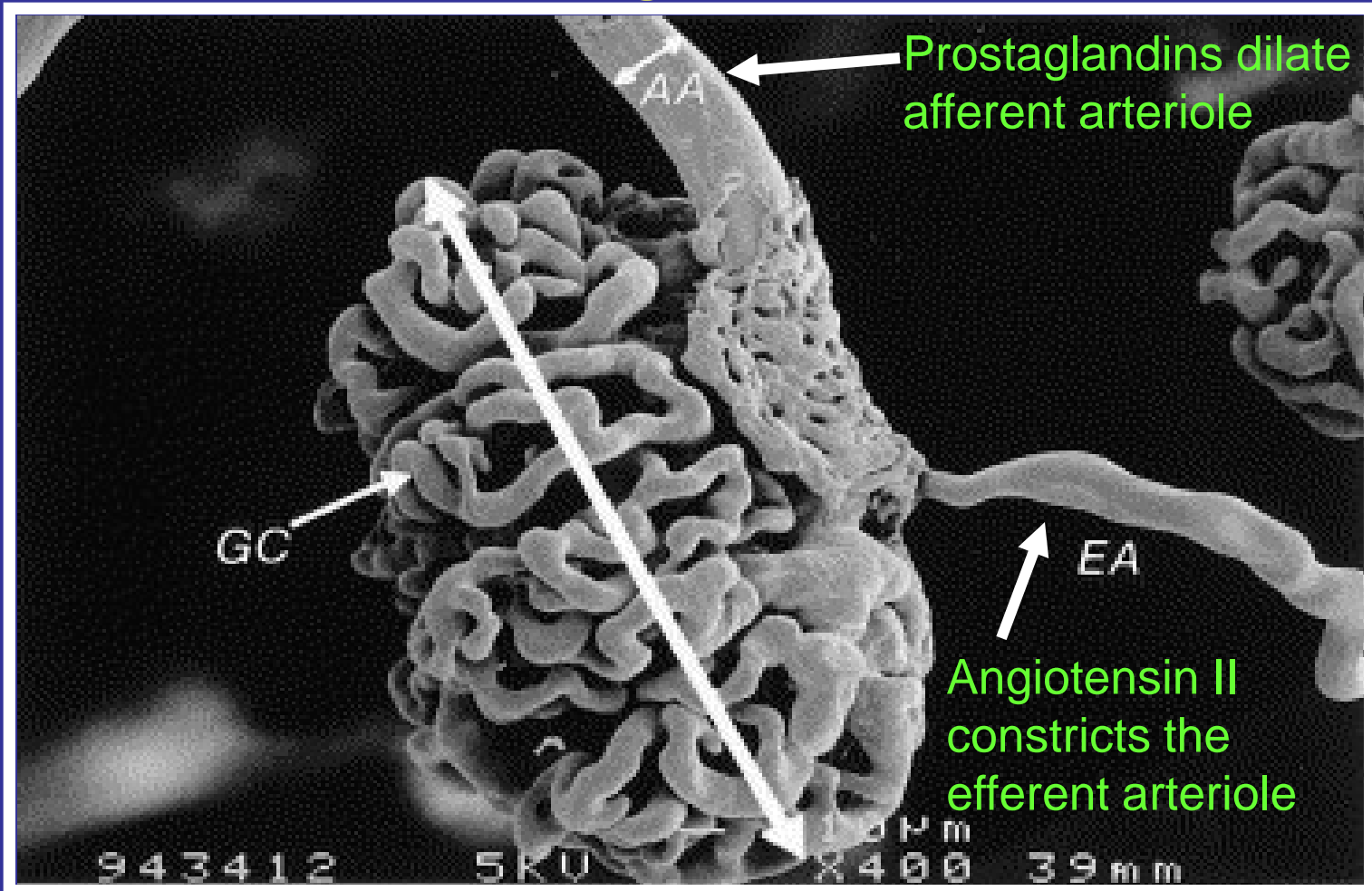
# Renal Nerves

- Sympathetic nerves directly increase afferent and efferent arterial tone
  - ↓ both RPF & GFR, favoring sodium retention
- Directly stimulate proximal tubules and thick ascending limb segments

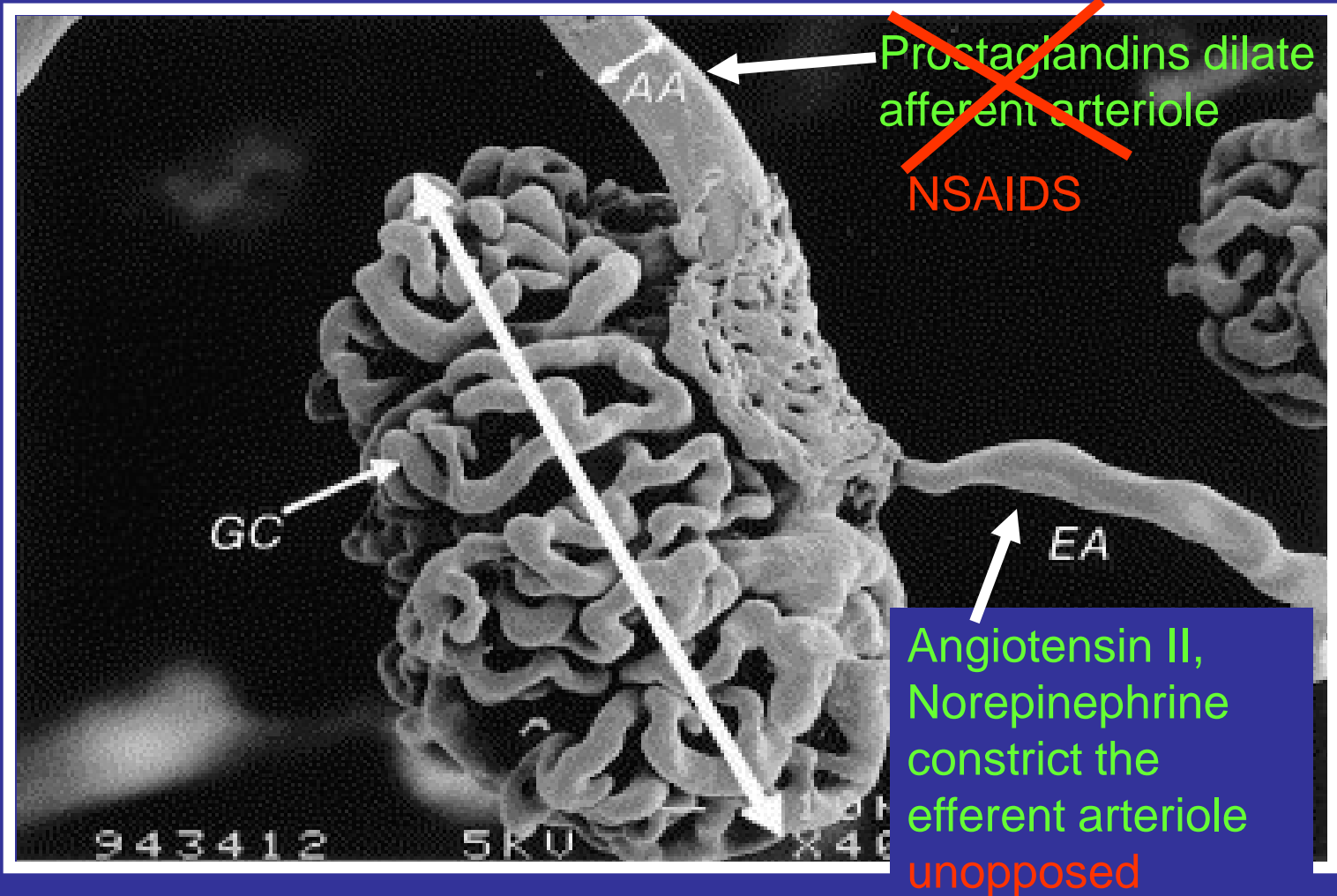
# Autoregulation

- Autoregulation can maintain GFR with SBP as low as 80.
- Glomerular capillary pressure regulated by resistances in afferent and efferent arterioles.
- Drop in renal artery pressure leads to prostaglandin mediated drop in afferent glomerular arteriolar resistance which sustains glomerular capillary pressure, the driving force of filtration.
- Angiotensin II increases efferent glomerular arteriolar resistance.

# Renal Response to Ischemia: autoregulation

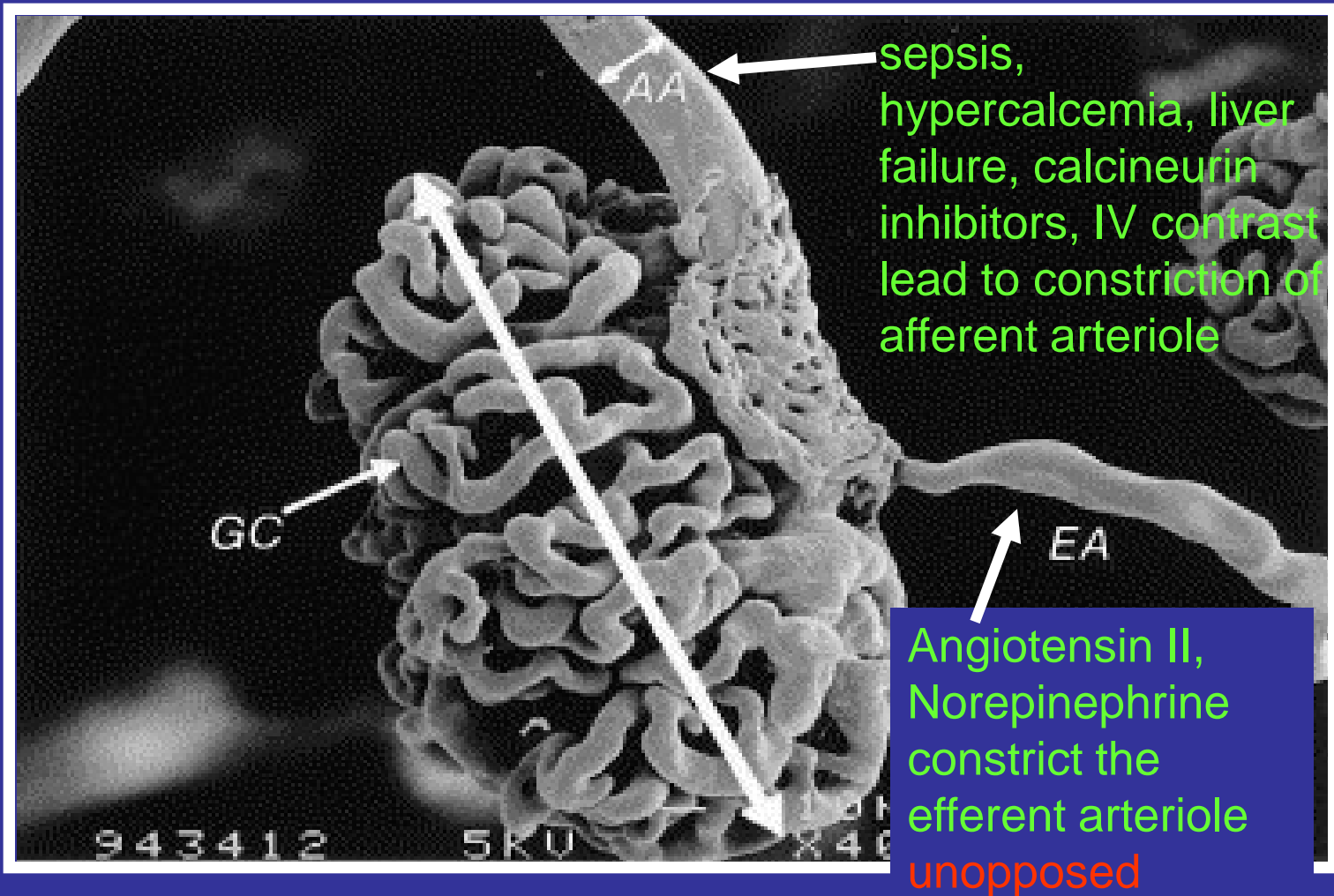


# Causes of Autoregulation Failure: NSAIDs



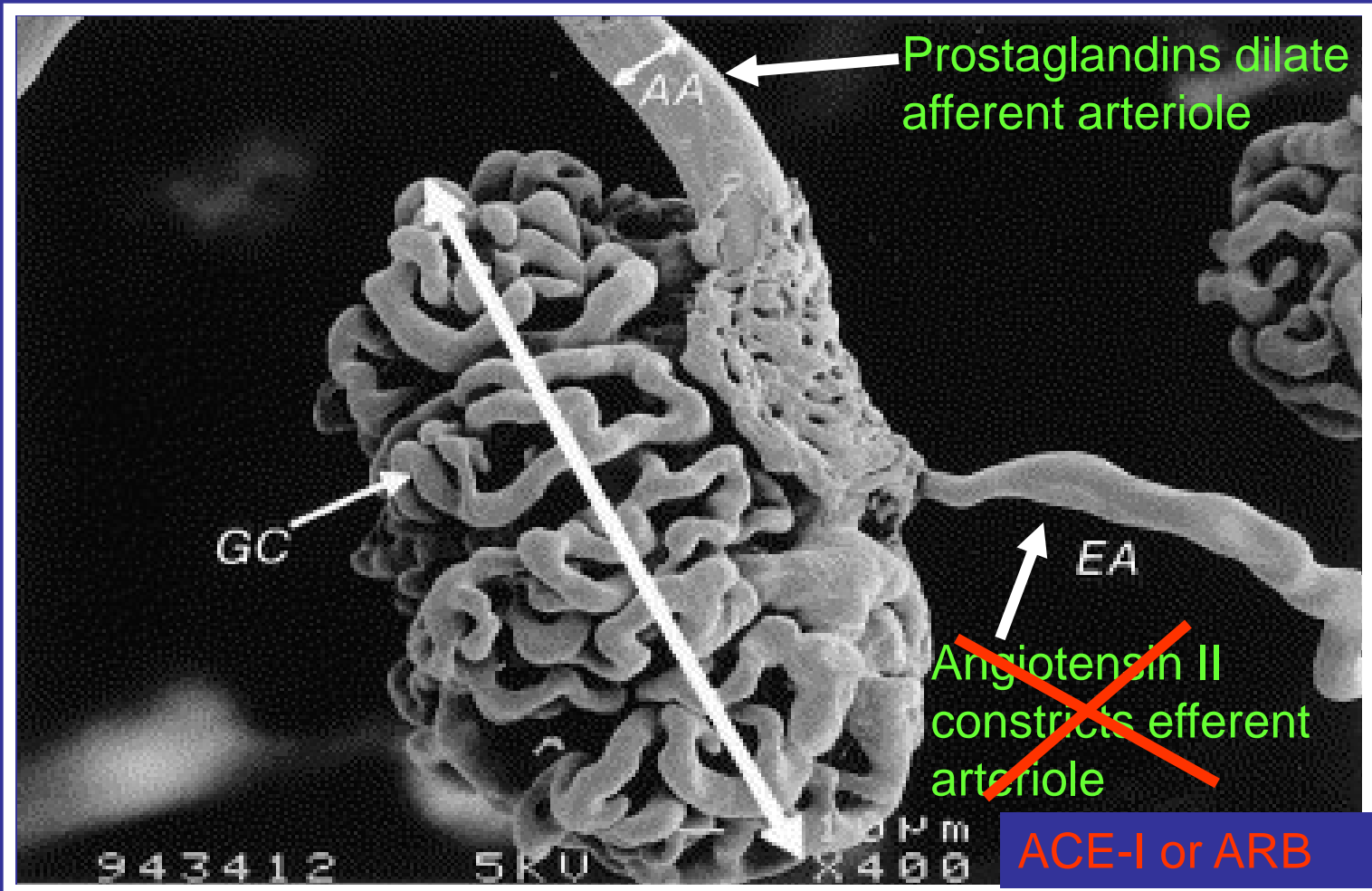
# Causes of Autoregulation Failure:

sepsis, ↑ca, liver failure, calcineurin inhibitors, radiocontrast





# Causes of Autoregulation Failure: ACE-I or ARB



# Normotensive Ischemic Acute Renal Failure

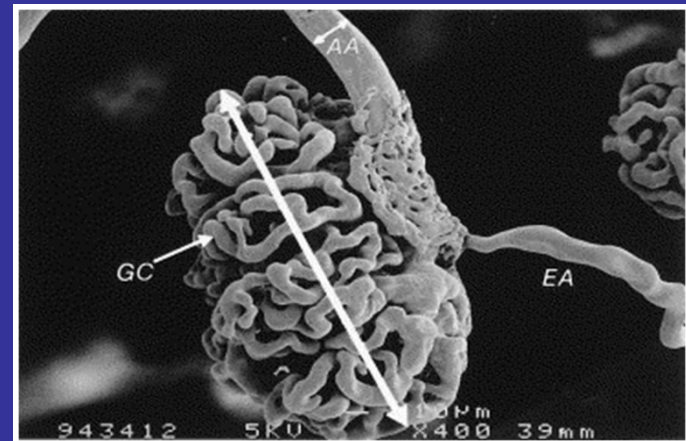
- Increased renal susceptibility to modest reductions in perfusion pressure
- Caused by failure to decrease afferent arteriolar resistance or failure to increase efferent arteriolar resistance

# Factors Increasing Susceptibility to Renal Hypoperfusion:

## Failure to Decrease Afferent Arteriolar Resistance

- Structural changes in small arteries/arterioles
  - Old age
  - Atherosclerosis
  - Chronic hypertension
  - Chronic kidney disease
  - Malignant hypertension
- Reduction in vasodilatory prostaglandins
  - NSAIDs
  - COX-2 inhibitors

- Afferent arteriolar constriction
  - Sepsis
  - Hypercalcemia
  - Hepatorenal syndrome
  - Cyclosporine or tacrolimus
  - Radiocontrast agents



# Factors Increasing Susceptibility to Renal Hypoperfusion

## Failure to Constrict Efferent Arteriole:

- ACE-I
- ARB

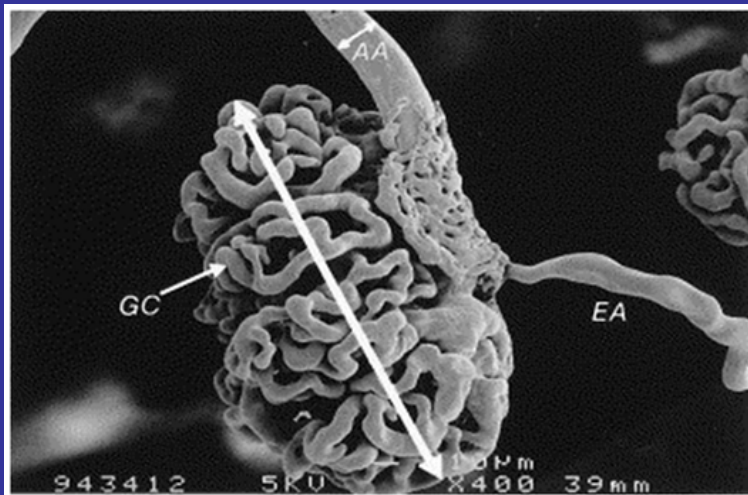


Image from Annals of Thoracic Surgery, 65:993-8, April 1998

## Structural changes

- Renal artery stenosis

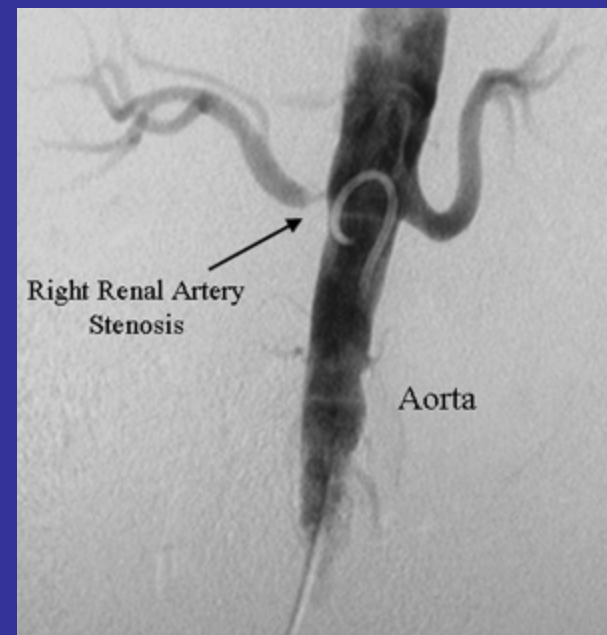


Image from VascularWeb.org

# When Autoregulation Fails...

Endogenous vasoconstrictors constrict afferent arterioles



Reduced glomerular capillary pressure



Reduced blood flow and perfusion to postglomerular capillary bed



Tubular ischemia

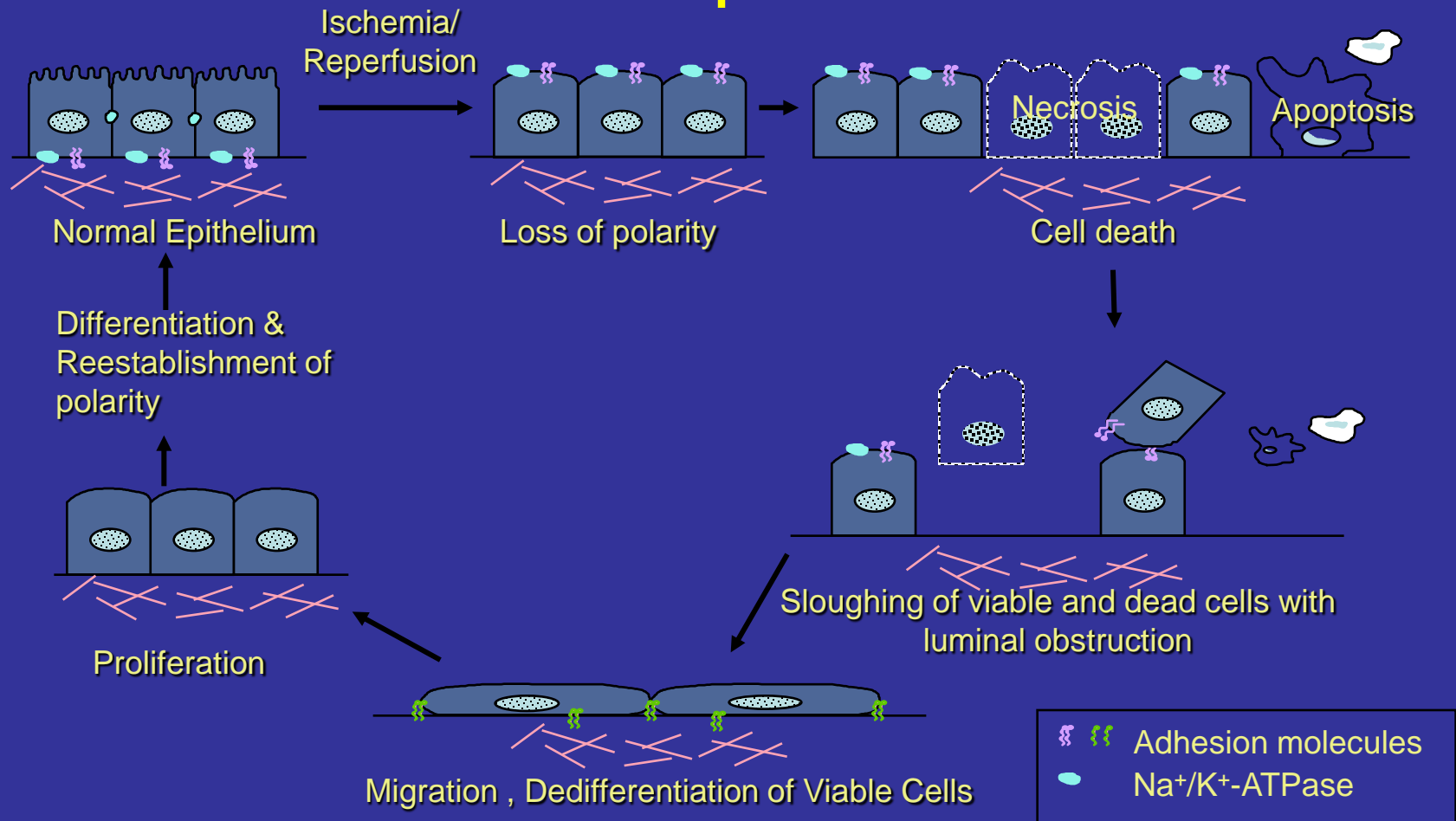


Acute tubular necrosis

# Acute Tubular Necrosis: causes

- Ischemic
  - prolonged prerenal azotemia
  - hypotension
  - hypovolemic shock
  - cardiopulmonary arrest
  - cardiopulmonary bypass
- Sepsis
- Nephrotoxic
  - drug-induced
    - radiocontrast agents
    - aminoglycosides
    - amphotericin B
    - cisplatin
    - acetaminophen
  - pigment nephropathy
    - hemoglobin
    - myoglobin

# Pathophysiology of ATN: Tubular Epithelial Cell Injury and Repair

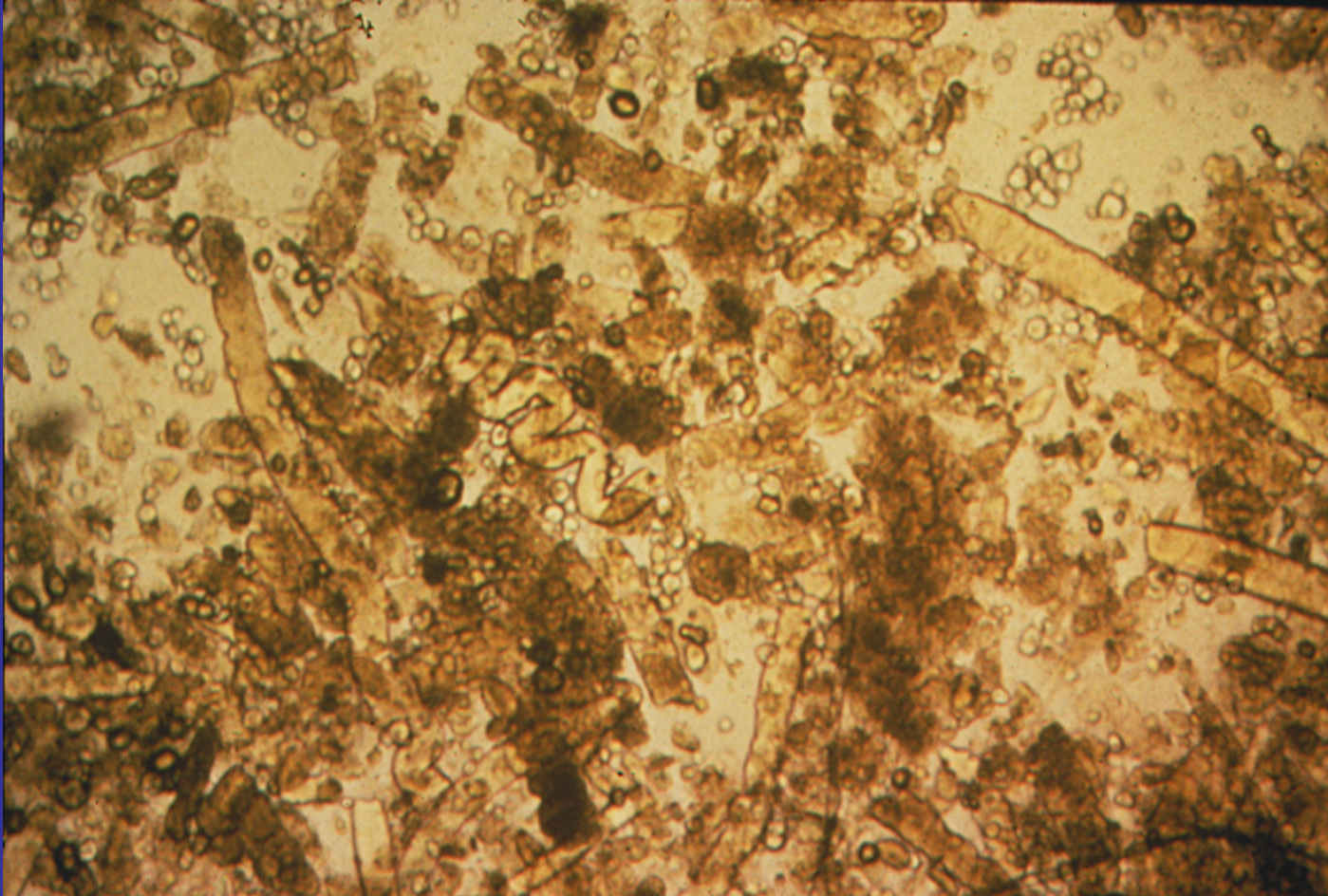


# Acute Tubular Necrosis: Clinical Presentation

- Urine indices
  - Urine volume
    - may be oliguric or non-oliguric
  - Isosthenuric urine concentration
    - $U_{\text{Osm}} \cong 300 \text{ mmol/L}$
    - specific gravity  $\cong 1.010$
  - Evidence of renal sodium wasting
    - $U_{\text{Na}} > 40 \text{ mmol/L}$
    - $FE_{\text{Na}} > 0.02$
  - Urine sediment
    - tubular epithelial cell casts
    - Pigmented or “muddy brown” granular casts

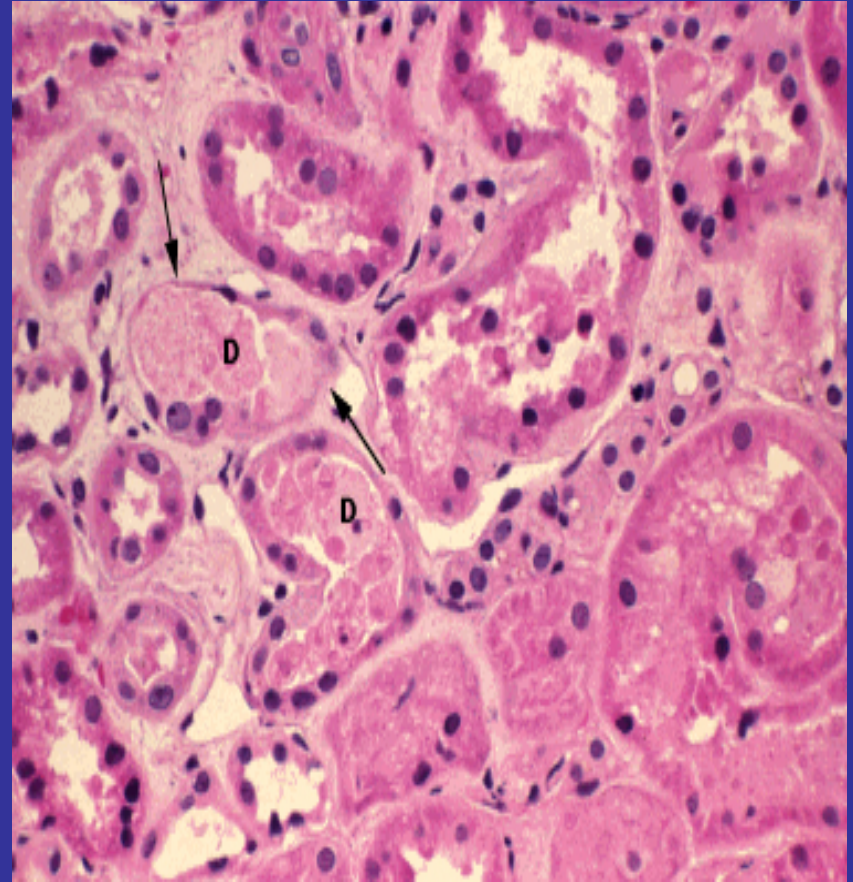


# Pigmented Granular Casts



# Acute Tubular Necrosis

- focal loss of tubular epithelial cells (arrows)
- partial occlusion of tubular lumens by cellular debris (D)



# Fractional Excretion of Sodium

- Enables us to determine the degree to which the tubules are functioning – i.e. capable of absorbing sodium
- Etiologies of a fractional excretion of sodium  $< 0.01$ 
  - normal renal function
  - prerenal azotemia
  - hepatorenal syndrome
  - early obstructive uropathy
  - contrast nephropathy
  - rhabdomyolysis
  - acute glomerulonephritis

# High Fractional Excretion of Sodium

- High FENa simply means tubules cannot absorb sodium.
- In ATN, the injured tubules cannot absorb sodium due
- Patient can still be prerenal and may not have ATN.
  - Diuretics (can check FEurea)
  - Chronic kidney disease
  - Preceding polyuria leading to loss of corticomedullary gradient

# Significance of the Fractional Excretion of Sodium: Prognosis

Low FeNa suggests that recovery can occur in hours to days

High FeNa (in the absence of diuretics or underlying CKD) suggests that recovery may be delayed – days to weeks after renal insult stops

# Management Ischemic ARF

Identify and deal with risk factors promptly

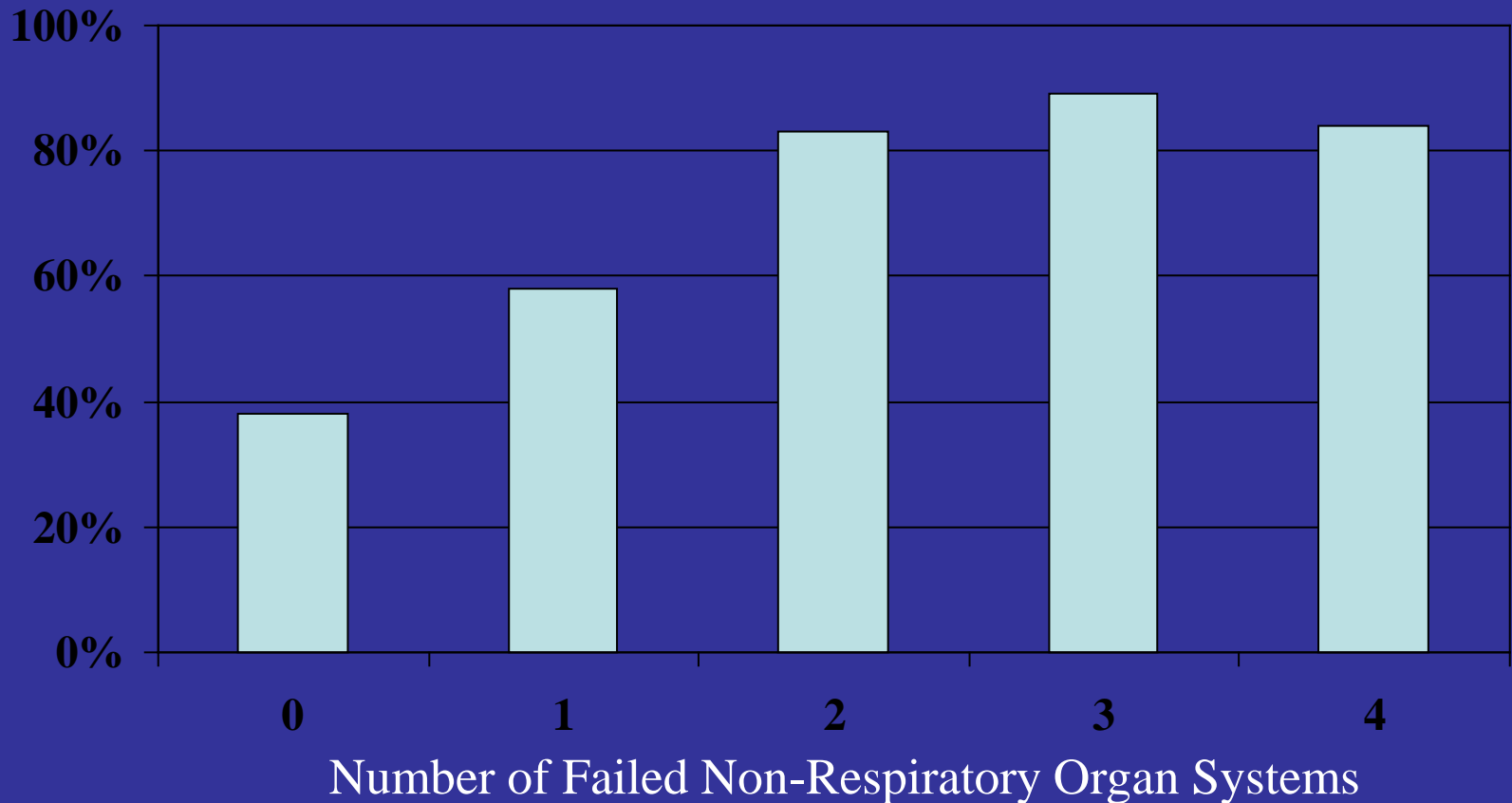
- Any BP on lower end of normal should be corrected
  - Correction of hypovolemia
  - Discontinuation of antihypertensives
  - Discontinuation of other meds that lower blood pressure (narcotics)
- Evaluate for occult infection
- Stop NSAIDs

Prompt intervention can reverse ARF and prevent ATN

# Acute Tubular Necrosis: Treatment

- Supportive therapy: avoid volume depletion, hypotension, nsaids, unnecessary anesthesia, surgery, or contrast
- Adjust doses of renally excreted medications
- Acute dialysis for:
  - volume overload
  - metabolic acidosis
  - hyperkalemia
  - uremic syndrome: pericarditis, encephalopathy

# Mortality in Acute Tubular Necrosis





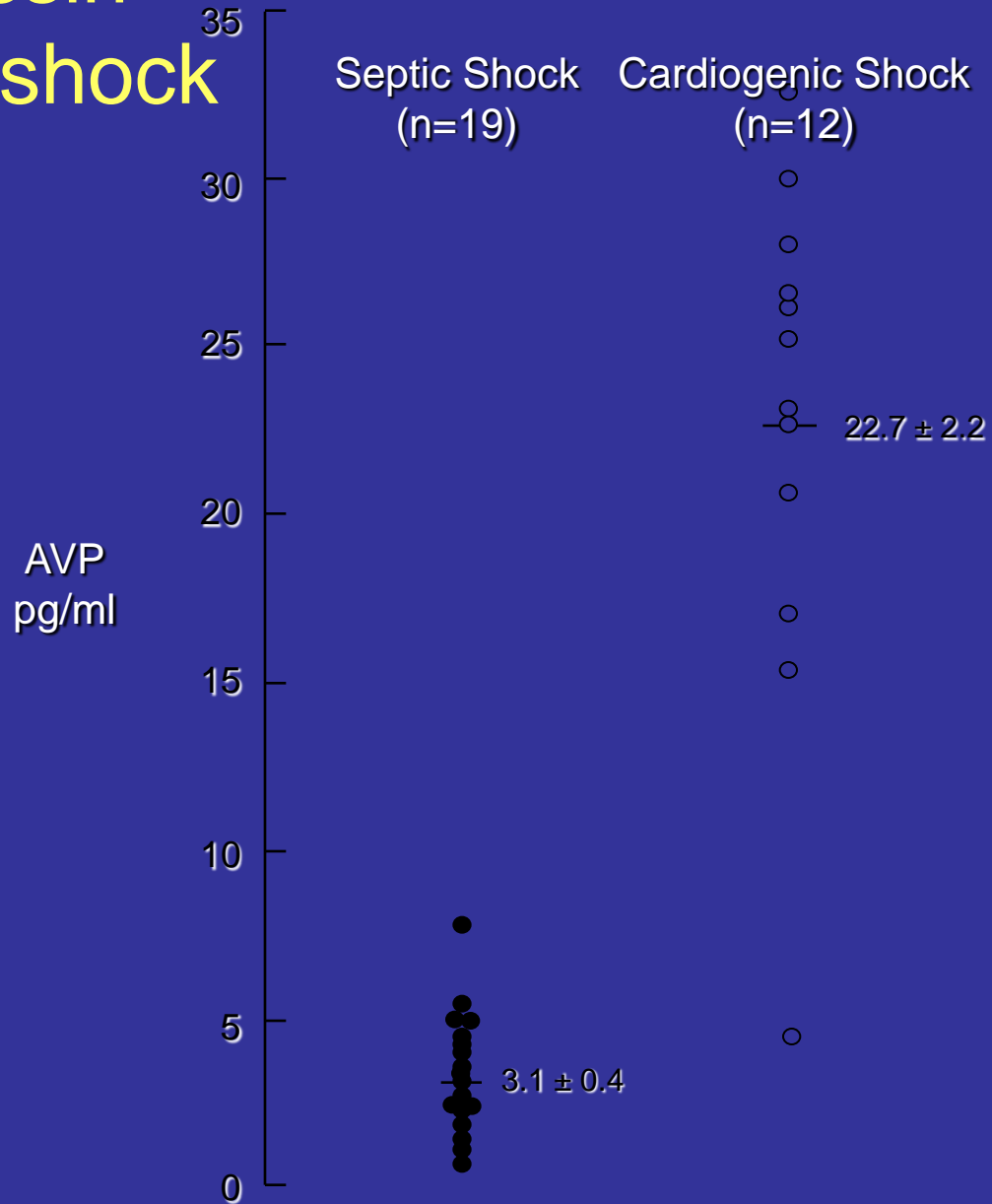
# Acute Renal Failure and Sepsis

- 51% of patients with septic shock with positive blood cultures have ARF
- Combination of ARF and sepsis is associated with 70% mortality
- Arterial vasodilation mediated by nitric oxide predisposes patients to ARF
- Metabolic acidosis and down-regulation of vasoactive hormone receptors leads to resistance to norepinephrine and angiotensin II

# Acute Renal Failure and Sepsis: Role of Vasopressin

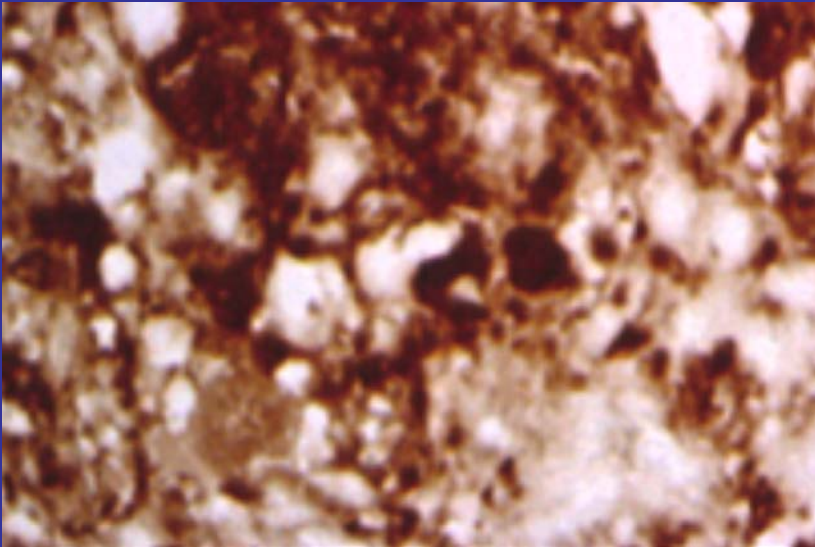
- Activates V1a receptors in vascular smooth muscle
- Modulates ATP-Sensitive K channels
- Attenuates the effect of nitric oxide
- Potentiates other adrenergic and vasoconstrictor agents
- Constricts the efferent but not the afferent arteriole, thus **preserving renal perfusion**
- Levels high for the 1<sup>st</sup> hr of vasodilatory shock, but then pituitary stores are depleted

# Vasopressin levels in shock

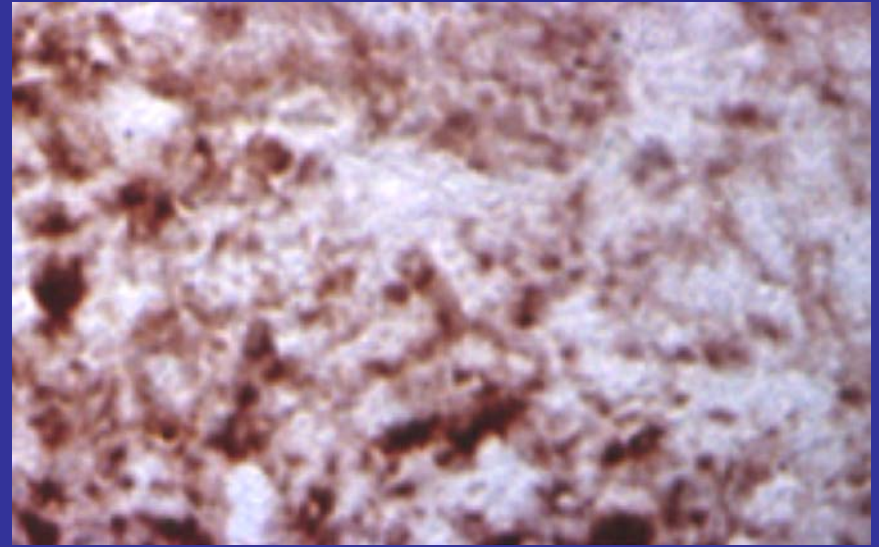


# Vasopressin Immunoreactivity in Pituitary of Dog

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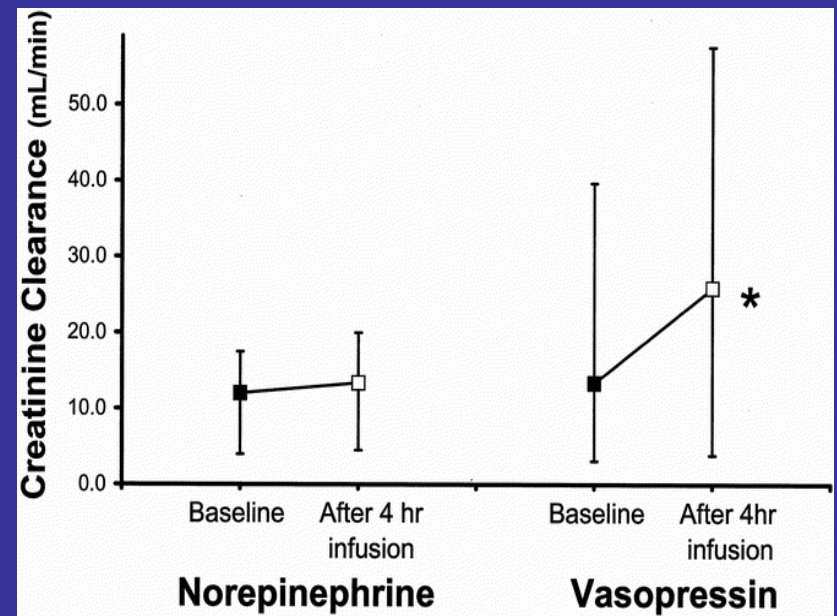
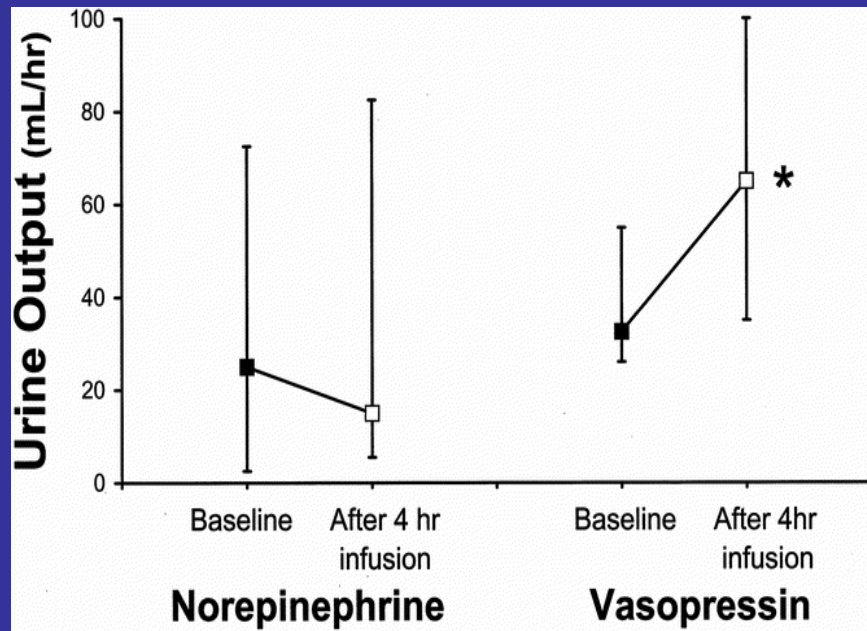


Control



Vasodilatory Shock

# Vasopressin in hormone replacement doses improves renal function in septic shock



# Intrinsic Renal Azotemia

- ATN
- Acute Interstitial Nephritis
- Acute Glomerulonephritis

# Acute Interstitial Nephritis

- Acute renal failure due to lymphocytic infiltration of the interstitium
- Classic triad of
  - fever
  - rash
  - eosinophilia

# Acute Interstitial Nephritis: Clinical Presentation

- History
  - preceding illness or drug exposure
- Physical examination
  - fever
  - rash
- Serum Findings
  - Eosinophilia
- Urine findings
  - non-nephrotic range proteinuria
  - possibly hematuria
  - **sterile pyuria** (WBC's without infection)
  - WBC casts
  - eosinophiluria



# Acute Interstitial Nephritis: causes

- Drug-induced
  - penicillins
  - cephalosporins
  - sulfonamides
  - rifampin
  - phenytoin
  - furosemide
  - NSAIDs
- Malignancy
- Idiopathic
- Infection-related
  - bacterial
  - viral
  - rickettsial
  - tuberculosis
- Systemic diseases
  - SLE
  - sarcoidosis
  - Sjögren's syndrome
  - tubulointerstitial nephritis and uveitis

# Acute Interstitial Nephritis: Treatment

- Discontinue offending drug
- Treat underlying infection
- Treat systemic illness
- Glucocorticoid therapy may be used in patients who fail to respond to more conservative therapy

# Rapidly Progressive Glomerulonephritis

- Clinical manifestations:
  - Macrohematuria
  - Oliguria
  - Edema
  - or insidious onset: fatigue and edema
  - With anti-GBM disease or pauci-immune glomerulonephritis (Granulomatosis with polyangiitis), may have pulmonary symptoms

# Rapidly Progressive Glomerulonephritis: classifications

- Type I: anti GBM disease
- Type II: Immune complex
  - IgA
  - Post-infectious GN
  - Lupus nephritis
  - Cryoglobulinemia
- Type III: pauci-immune
  - Usually ANCA positive, but can be negative

# Post-Renal Failure:obstruction

- Risk factors
  - BPH
  - Abdominal cancer
  - Nephrolithiasis with baseline chronic kidney disease
  - Abdominal compartment syndrome (maybe)
- Diagnosis
  - Check bladder scan for post-void residual
  - Renal ultrasound

CASES

# Case 1

An 87-year old female nursing home resident has been admitted for altered mental status. Records from the nursing home state that she has been more withdrawn lately, not eating, but with no specific complaints.

PMH: HTN, arthritis, dementia, osteoarthritis occasional UTIs.

Meds: HCTZ, lisinopril, naprosyn prn

In ER: pt is awake and moaning, but otherwise noncommunicative.

# Case 1...

## PE:

VS afeb, 80/40, 120, 18, O2 sat  
95% on room air

Dry mucus membranes

No JVD

CTA B

Tachy S1,S2

Abd soft, nontender, normal  
bowel sounds

No peripheral edema

UOP 5cc/hr

## LABS

Sodium 148, K 4.4, Cl 104, CO2  
18, BUN 40, Creatinine 1.5  
(baseline 0.8)

LFTs normal

WBC 10, HCT 38, Plts 200

UA: sp grav 1.020, pH 6.0, tr  
protein, lg LE, + nitrites, 1-5  
rbc, 20-30 wbc

- Urine Sodium 40, creatinine 150
- Fractional Excretion of Sodium (FENa) =  $(UNa \times PCr) / (PNa \times UCr) \times 100$   
= 0.3%
- Urine eosinophils negative



# Which of the following is the most likely diagnosis?

1. Prerenal acute renal failure
2. Ischemic acute tubular necrosis
3. Interstitial nephritis
4. ANCA-associated pauciimmune glomerulonephritis
5. Thrombotic microangiopathy

## How would you treat?

1. IV fluids
2. Hold bp meds and start vasopressors
3. Hold bp meds only
4. Diuretics

# Case 1 continued...

Hospital course: she is admitted to the ICU, given aggressive hydration and antibiotics for UTI. Over the next 2 days, her weight increases from 66kg to 72kg. BP 120/80, hr 88. She is still lethargic.

Sodium 143, BUN 35, Creatinine 2.6. UOP 0.

Urine Sodium 80, Urine creatinine 60

Fractional Excretion of Sodium (FENa) =  $(\text{UNa} \times \text{PCr}) / (\text{PNa} \times \text{UCr}) \times 100$   
= 2.4%

Urine eosinophils negative

Urine Culture >100,000 E. Coli

## Now which of the following is the most likely diagnosis?

1. Prerenal acute renal failure
2. Ischemic acute tubular necrosis
3. Interstitial nephritis

## How would you treat?

1. Continue IV fluids
2. Start vasopressors
3. Diuretics
4. Dialysis
5. Stop the Zosyn that was started for her UTI.

## Case 2:

- 38-year-old woman is evaluated in the emergency department for generalized itching, an erythematous skin rash, and joint pain.
- She initially tried diphenhydramine but her itching and rash did not improve.
- She was diagnosed with a sinus infection 2 weeks ago that was treated with a course of amoxicillin. Her sinus drainage and cough have improved. However, her joint pain remains and her temperature has been between 37.5 °C and 37.8 °C. She states that she has otherwise been healthy and takes no additional medications.
- Physical exam: T 37.3, BP 122/68, HR 88; lungs clear, heart regular, abdomen benign, skin exam with diffuse erythematous macular papular skin rash involving her trunk, arms, and upper thighs.

# Laboratory Studies

- Hemoglobin 12.5
- WBC 9.8
- Platelets 325
- Blood urea nitrogen 36
- Creatinine 2.6
- Sodium 138 meq/L
- Potassium 4.4 meq/L
- Bicarbonate 26 meq/L
  
- Urinalysis pH 5, specific gravity 1.020, 2+ blood, trace protein, 4+ leukocyte esterase, 20–25 leukocytes and several leukocyte casts/hpf, 3–5 intact erythrocytes/hpf, Hansel stain shows eosinophils
- Urine culture is negative

## Which of the following is the most likely diagnosis in this patient?

1. Thrombotic thrombocytopenic purpura
2. Antineutrophil cytoplasmic autoantibody–associated vasculitis
3. Acute tubular necrosis
4. Acute interstitial nephritis
5. Membranous glomerulopathy



# Which of the following conditions can present with eosinophiluria?

1. Atheroembolic disease
2. Postinfectious glomerulonephritis
3. Rapidly progressive glomerulonephritis
4. Pyelonephritis
5. All of the above

# Why not ANCA-associated vasculitis?

- Antineutrophil cytoplasmic autoantibody– associated small-vessel vasculitis also should be considered in patients with kidney failure and concomitant arthralgias, skin rash, and fever.
- Lack of dysmorphic erythrocytes or erythrocyte casts makes this diagnosis unlikely.

# Why not TTP?

- Thrombotic thrombocytopenic purpura should be considered in patients with fever, skin rash, and kidney failure.
- Absence of concomitant anemia, mental status changes, and thrombocytopenia makes this diagnosis less likely.

## Case 3

- 33-year-old woman with advanced cirrhosis secondary to hepatitis C is hospitalized for tense ascites and leg edema.
- She undergoes therapeutic paracentesis with removal of 5 L of ascitic fluid and begins treatment with intravenous furosemide and oral spironolactone.
- Over the next 3 days, she has a net diuresis of 4 kg during which the creatinine level increases from a baseline level of 0.8 to 1.6 mg/dL. Her urine output decreases to 280 mL/24 h.
- On physical examination, blood pressure is 88/40 mm Hg. There is scleral icterus. Pulmonary examination reveals decreased breath sounds at lung bases. She has modest ascites and no edema.

## Case 3...

Labs:

INR 2.7

Blood urea nitrogen 21 mg/dL

Creatinine 1.6 mg/dL

Sodium 118 meq/L

Potassium 3.4 meq/L

Chloride 83 meq/L

Bicarbonate 26 meq/L

Total bilirubin 25 mg/dL

Albumin 2.1 g/dL (23 g/L)

Urinalysis Several granular and epithelial casts/hpf

Urine sodium 12 meq/L

Fractional Excretion of Sodium 0.8%

# Case 3...

Hospital course: Patient was given a fluid challenge with IV albumin. She remains oliguric with urine sodium 16, and FENa 0.9%.

What is the most likely diagnosis?

- A. Prerenal azotemia
- B. Hepatorenal syndrome
- C. Acute Tubular Necrosis
- D. Membranoproliferative glomerulonephritis
- E. Post infectious glomerulonephritis

# Large volume paracentesis

- >5L volume removal carries greater risk of hemodynamic compromise and renal ischemia
- Albumin solution 6-8g/L of fluid removed is recommended

# Hepatorenal syndrome: criteria

- Presence of liver disease
- AKI (creat increase 0.3 or more within 48hrs)
- Absence of other cause of renal failure
- Bland urine sediment
  - Urine RBCs <50/hpf
  - Urine Protein <500mg/day
- Lack of improvement after volume expansion with IV albumin (1g/kg of body weight per day – up to 100g/day) for 2 days



# CASE 4

A 56 year old man is admitted to the hospital with shortness of breath and lower extremity edema.

PMH: HTN, coronary artery disease s/p stents, diabetes mellitus, benign prostatic hypertrophy

PE: afebrile, BP 75/45, HR 100, RR 28, Bibasilar rales on lung exam, S1, S2, and S3 gallop, point of maximal impulse laterally displaced, jugular venous pressure is 10cm H<sub>2</sub>O, abdomen is normal, 2+ lower extremity edema.

LABS: sodium 125, potassium 3.8, chloride 89, bicarbonate 25, blood urea nitrogen 46, creatinine 2.4, albumin 3.0, urinalysis 1.020/5.0/1+ protein/no blood, urine protein to creatinine ratio 1.1g/g. Urine sodium 14, FENa 0.6%.

CXR: bilateral infiltrates, cardiomegaly

## Case 4...

What is the most likely diagnosis for his acute renal failure?

- A. Prerenal azotemia
- B. Acute Tubular Necrosis
- C. Acute Interstitial Nephritis
- D. ANCA-associated pauci immune glomerulonephritis

# Summary:take-home points

- Careful history
  - Look for factors increasing renal susceptibility to ischemia
- Physical exam cues
  - Careful investigation of blood pressure trends over the days leading up to the insult.
  - Consider causes of normotensive ischemic renal failure
- Lab data:
  - BUN:Cr ratio
  - Urine sodium & creatinine (FENa)
  - Urinalysis
  - Urine eosinophils

# Summary:take-home points (cont.)

- Pre-renal does not always mean volume depleted, hemodynamic compromise is a frequent culprit (CHF, too many bp meds, sepsis)
- Consider causes of normotensive ischemic renal failure
- If no response to volume/bp correction, check renal ultrasound for obstruction.
- If there is an active urine sediment, may need biopsy. Low-threshold for expedient biopsy if renal function deteriorating.

# Summary:take-home points (cont.)

- In septic shock:
  - Early aggressive intervention
  - Consider adding vasopressin early on to improve renal perfusion and to reduce norepinephrine resistance