

Acute Kidney Injury (Acute Renal Failure)

Pedram Fatehi, MD
Division of Nephrology

September 2015

Objectives

- Recognize the three main categories of acute kidney injury:
 - pre-renal
 - intrinsic renal
 - post-renal
- Understand the diagnostic approach of acute kidney injury
- Describe the management of acute kidney injury

Key Words / Definitions

- AKI: Acute Kidney Injury
- ARF: Acute Renal Failure
- ATN: Acute Tubular Necrosis

- Acute: hours to days
- 'Sub-acute': days to weeks
- Chronic: months (>3 mo)



AKIN / KDIGO

Stages

1

Risk

Inc creat by ≥ 0.3 mg/dL or
Increased creatinine $\times 1.5$ or
GFR decrease $> 25\%$
within 48hrs / 7days

Urine output criteria

UO < 0.5 ml kg^{-1} h^{-1}
 $\times 6$ h

High sensitivity

2

Injury

Increased creatinine $\times 2$ or
GFR decrease $> 50\%$

UO < 0.5 ml kg^{-1} h^{-1}
 $\times 12$ h

3

Failure

Increased creatinine $\times 3$ or
GFR decrease $> 75\%$ or
creatinine ≥ 4 mg per
100 ml (acute rise of
 ≥ 0.5 mg per 100 ml dl)

UO < 0.3 ml kg^{-1} h^{-1}
 $\times 24$ h or
anuria $\times 12$ h

Oliguria

High specificity

Loss

Persistent ARF = complete loss of
renal function > 4 weeks

ESRD

End-stage renal disease

Key Words / Definitions

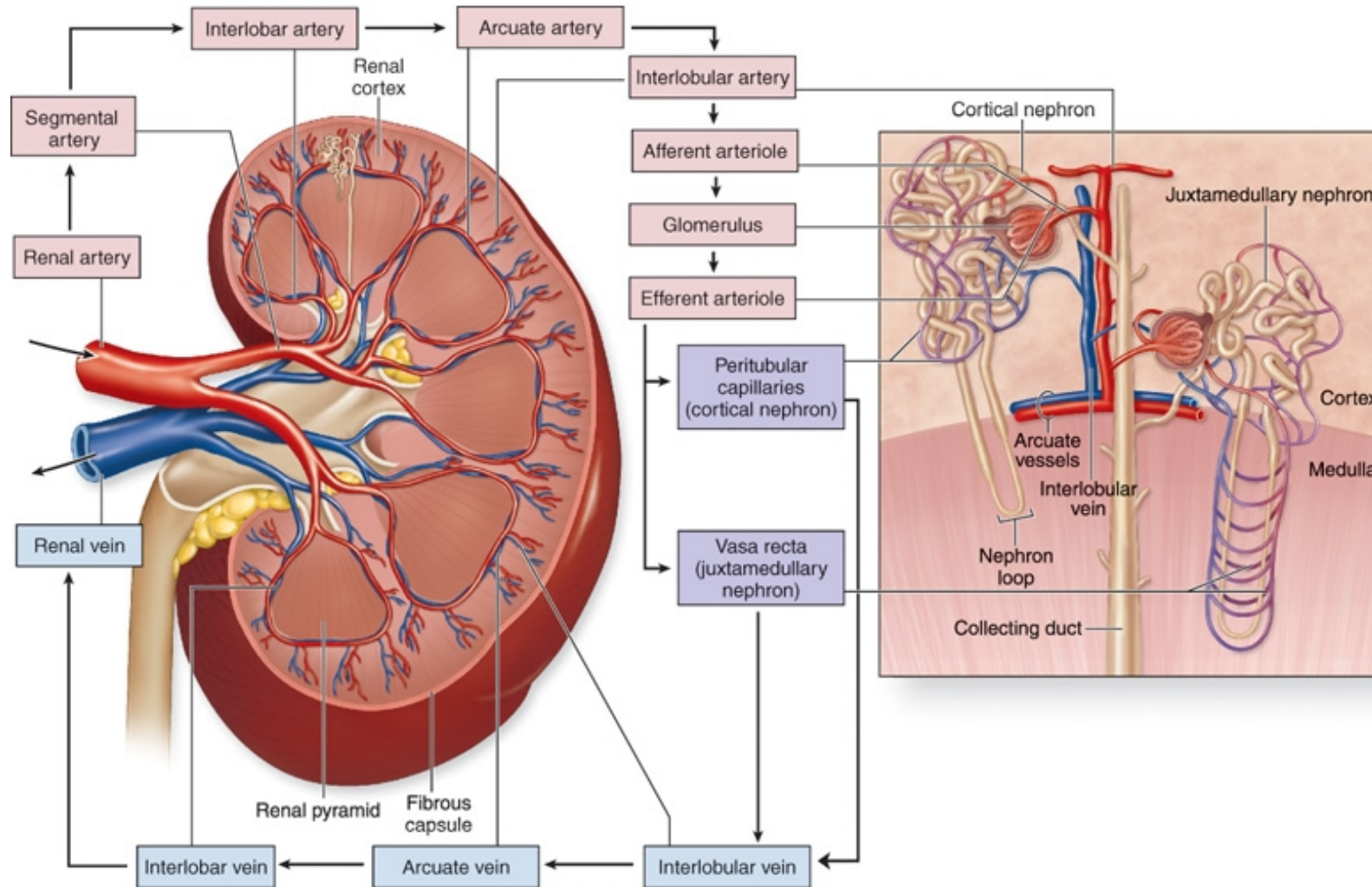
- Oliguria: low urine output
 - $< 0.5 \text{ mL/kg/hr}$
 - eg. $< 35 \text{ mL/hr}$ for a 70kg patient
 - $< 500 \text{ mL/day}$
- Anuria: $< 50 \text{ mL/day}$
- Non-oliguric (normal UOP 1-2 L/day)

Typical Case

A 72 year old male presents with fever, two weeks of cough, and infiltrates on chest x-ray. The diagnosis of pneumonia is made and the patient is started on antibiotics. The hospitalization is complicated by low blood pressure and on the 6th day there is a decrease in urine output and the serum creatinine begins to rise:

	<u>Admission</u>	<u>6th</u>	<u>7th</u>	<u>8th</u>	<u>9th</u>
Creatinine	1.0 mg/dl	1.1	1.7	2.7	3.7

Form and Function



Acute Renal Failure

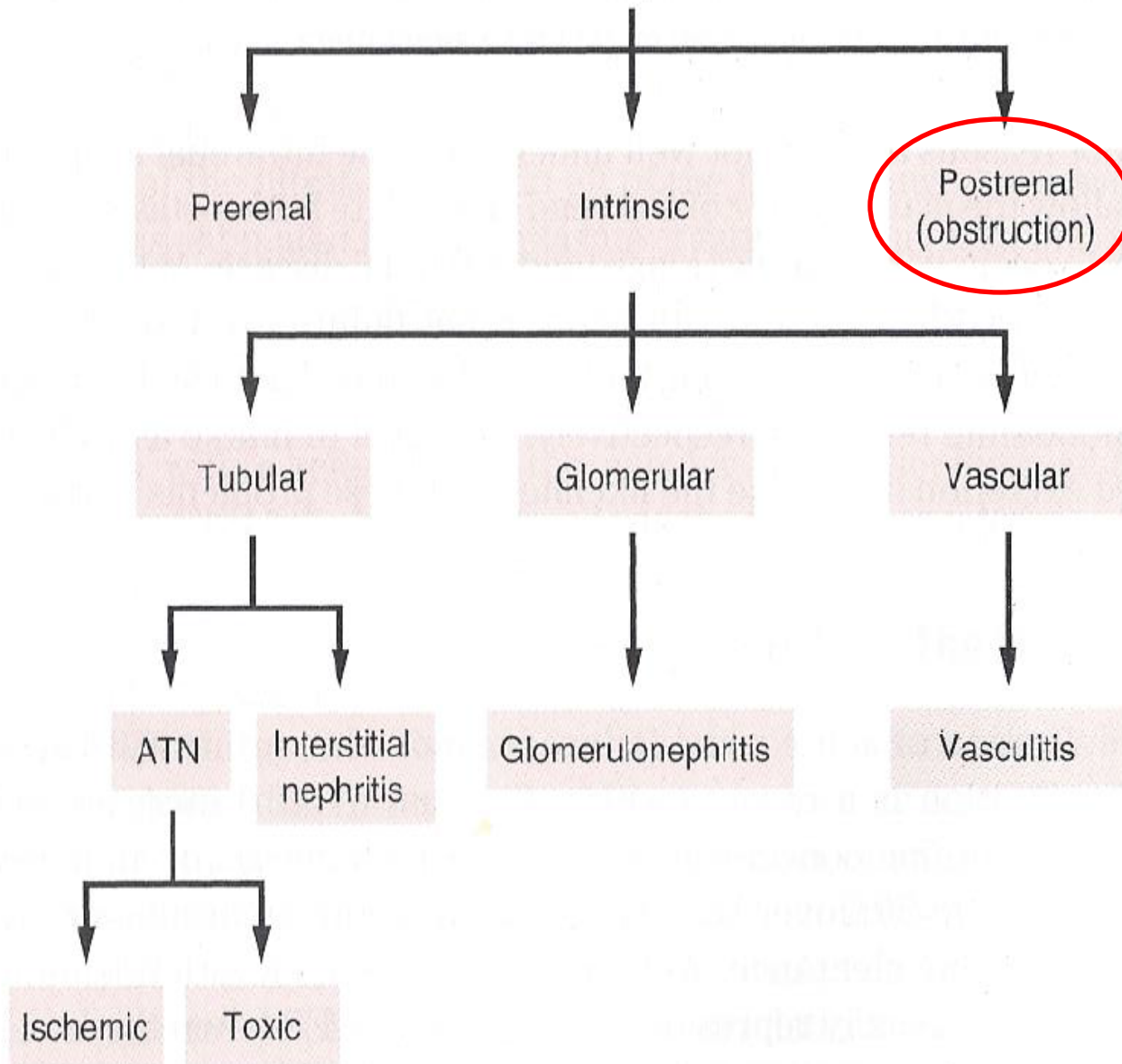
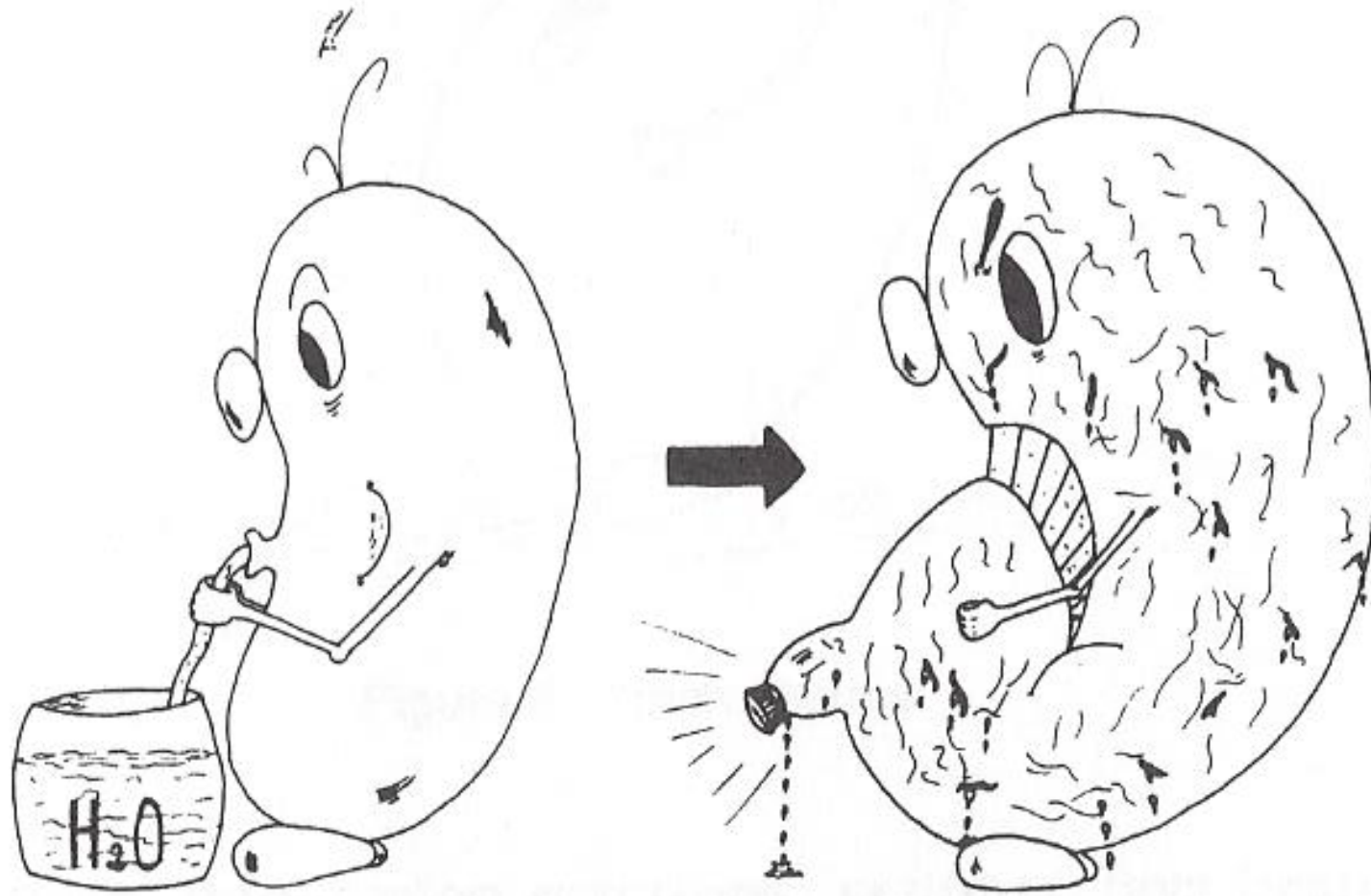
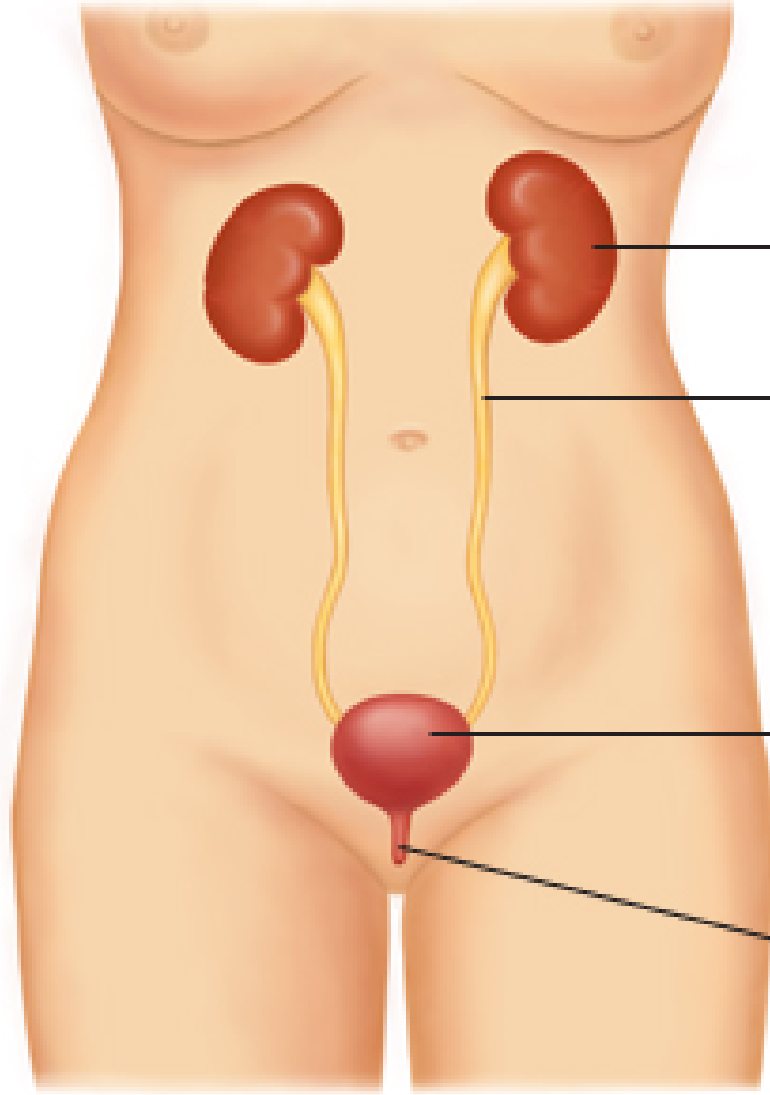


FIGURE 11.1. Main categories of acute renal failure. Postrenal (obstructive etiologies) should be diagnosed early since the etiology and treatment are usually anatomic. About 40% to 50% of patients with acute renal failure in the outpatient setting have prerenal etiologies. Once intrinsic renal disease is established, about 75% to 80% are the result of acute tubular necrosis (ATN), approximately 10% interstitial, and only about 5% to 10% the result of acute glomerulonephritis or vasculitis.

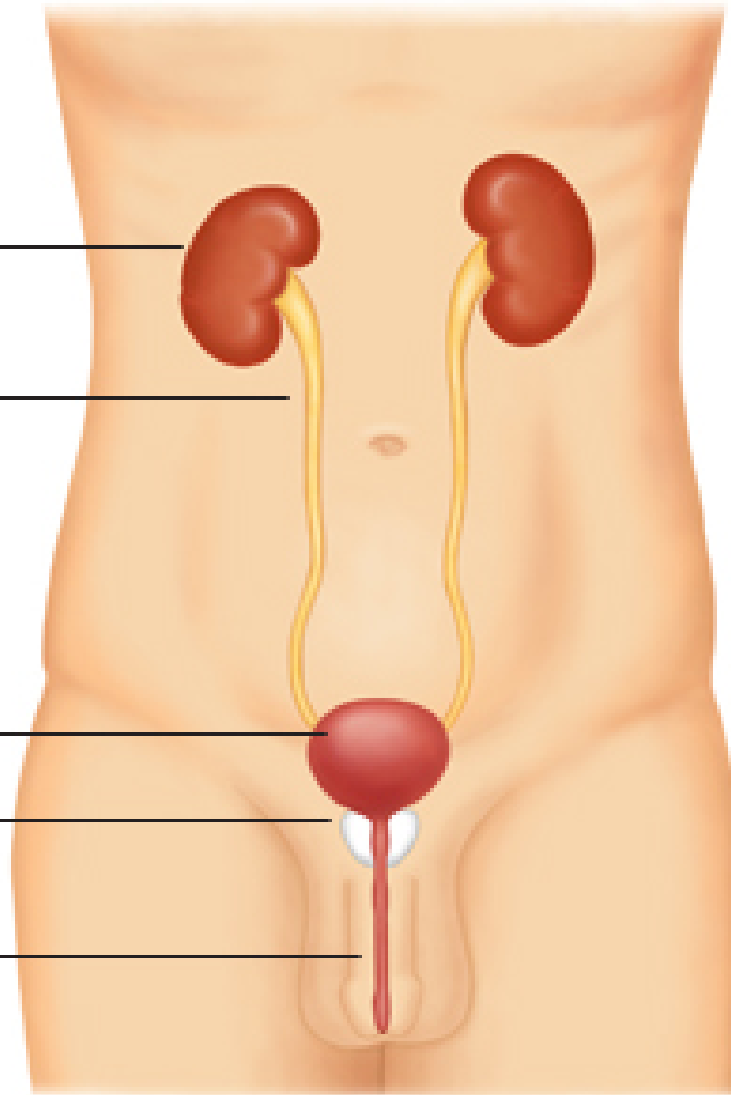


Post-renal (obstructive) injury

Female



Male



Kidney

Ureter

Bladder

Prostate

Urethra

- BPH
- Pelvic malignancy
- Bladder stone
- Urethral stricture

Typical Case

A 72 year old male presents with fever, two weeks of cough, and infiltrates on chest x-ray. The diagnosis of pneumonia is made and the patient is started on antibiotics. The hospitalization is complicated by low blood pressure and on the 6th day there is a decrease in urine output and the serum creatinine begins to rise:

	<u>Admission</u>	<u>6th</u>	<u>7th</u>	<u>8th</u>	<u>9th</u>
Creatinine	1.0 mg/dl	1.1	1.7	2.7	3.7

Case

On hospital day 6, the nurse pages you to report less than 30cc of urine output for each of the prior several hours. If you want to rule out obstruction, you order a/an

and scan the result for evidence of

_____.

Case

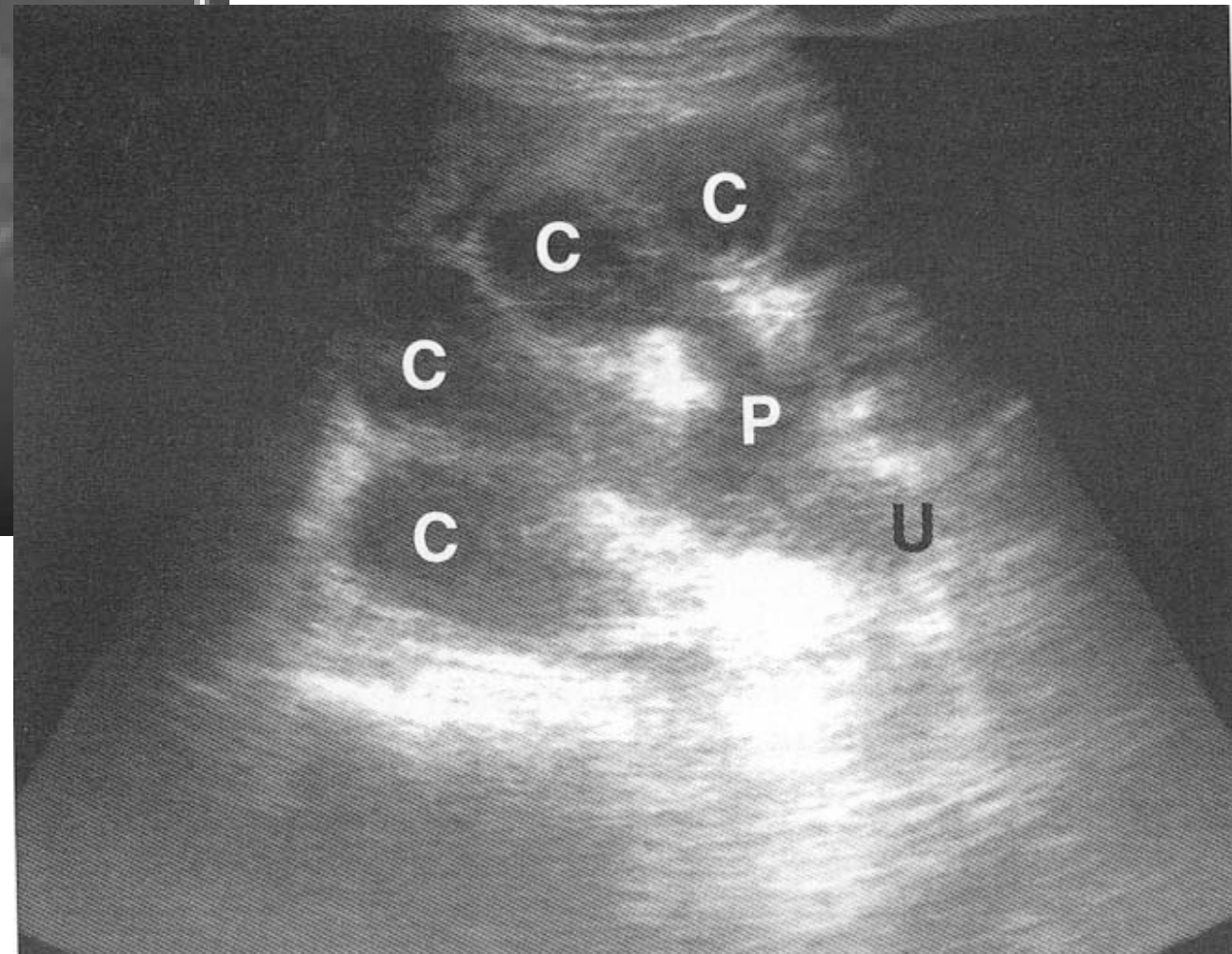
On hospital day 6, the nurse pages you to report less than 30cc of urine output for each of the prior several hours. If you want to rule out obstruction, you order a/an ultrasound or bladder scan and scan the result for evidence of hydronephrosis or increased post-void residual.

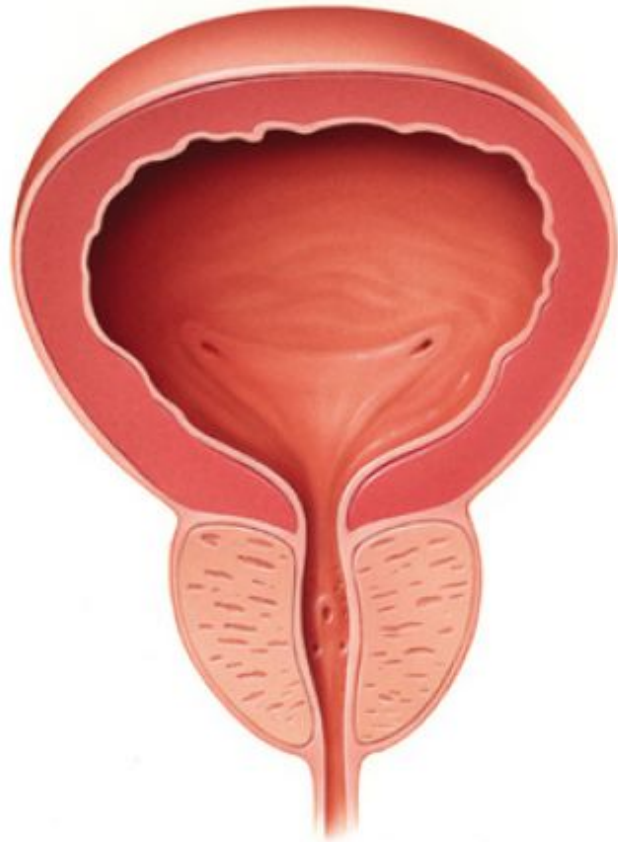
RIGHT LONG
FLANK

POST VOID

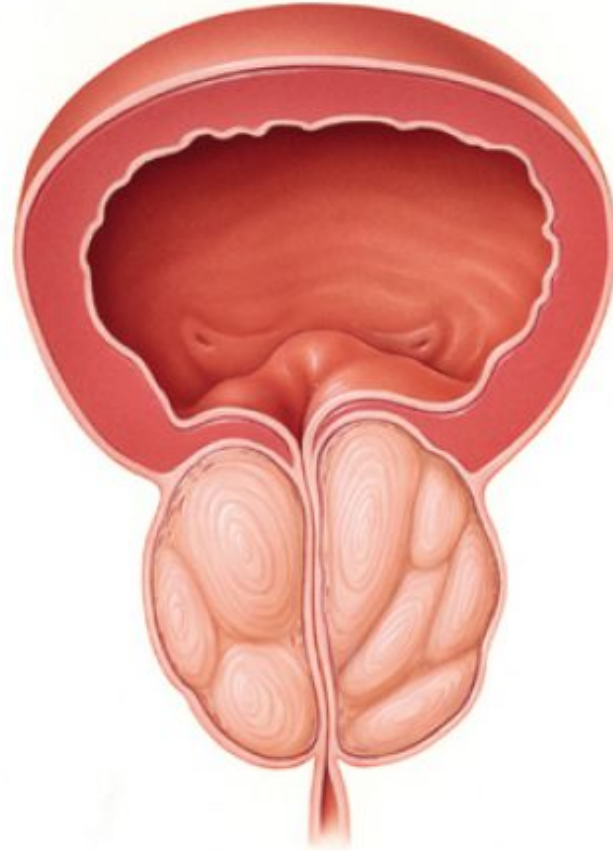
DEPTH
GEN/AB

PWR =
50dB 0
GAIN =





Normal Prostate



Enlarged Prostate

Bladder Capacity

- Normal desire to void: 150 - 350 mL
- Strong sensation to void: 250 -500 mL
- Max capacity: 400 – 600 mL

Placement of a foley catheter, esp in older man, can be diagnostic and therapeutic

Acute Renal Failure

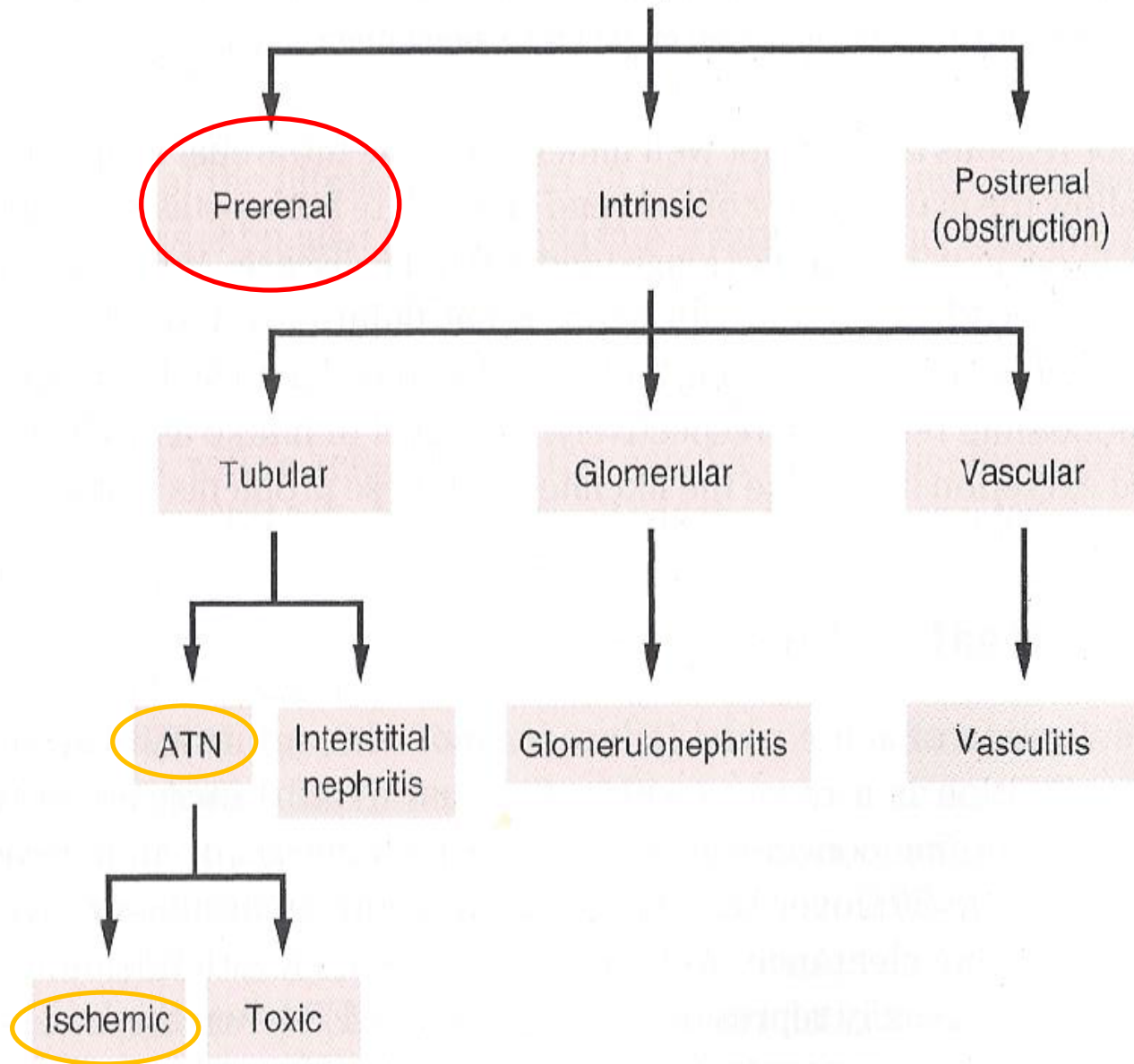
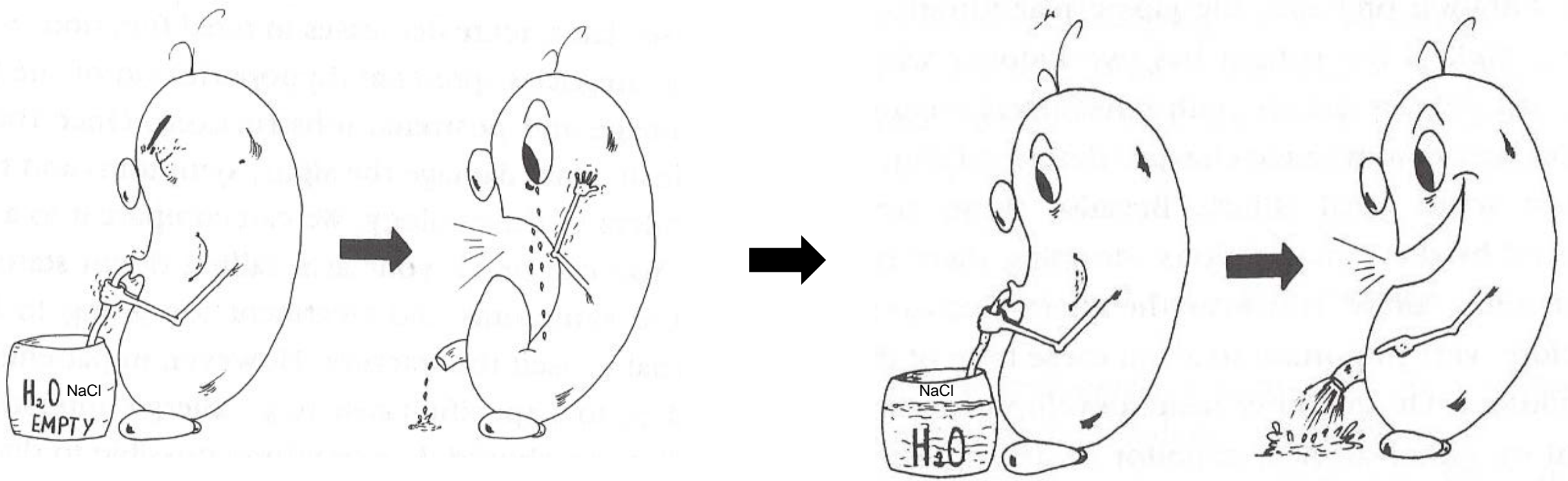


FIGURE 11.1. Main categories of acute renal failure. Postrenal (obstructive etiologies) should be diagnosed early since the etiology and treatment are usually anatomic. About 40% to 50% of patients with acute renal failure in the outpatient setting have prerenal etiologies. Once intrinsic renal disease is established, about 75% to 80% are the result of acute tubular necrosis (ATN), approximately 10% interstitial, and only about 5% to 10% the result of acute glomerulonephritis or vasculitis.

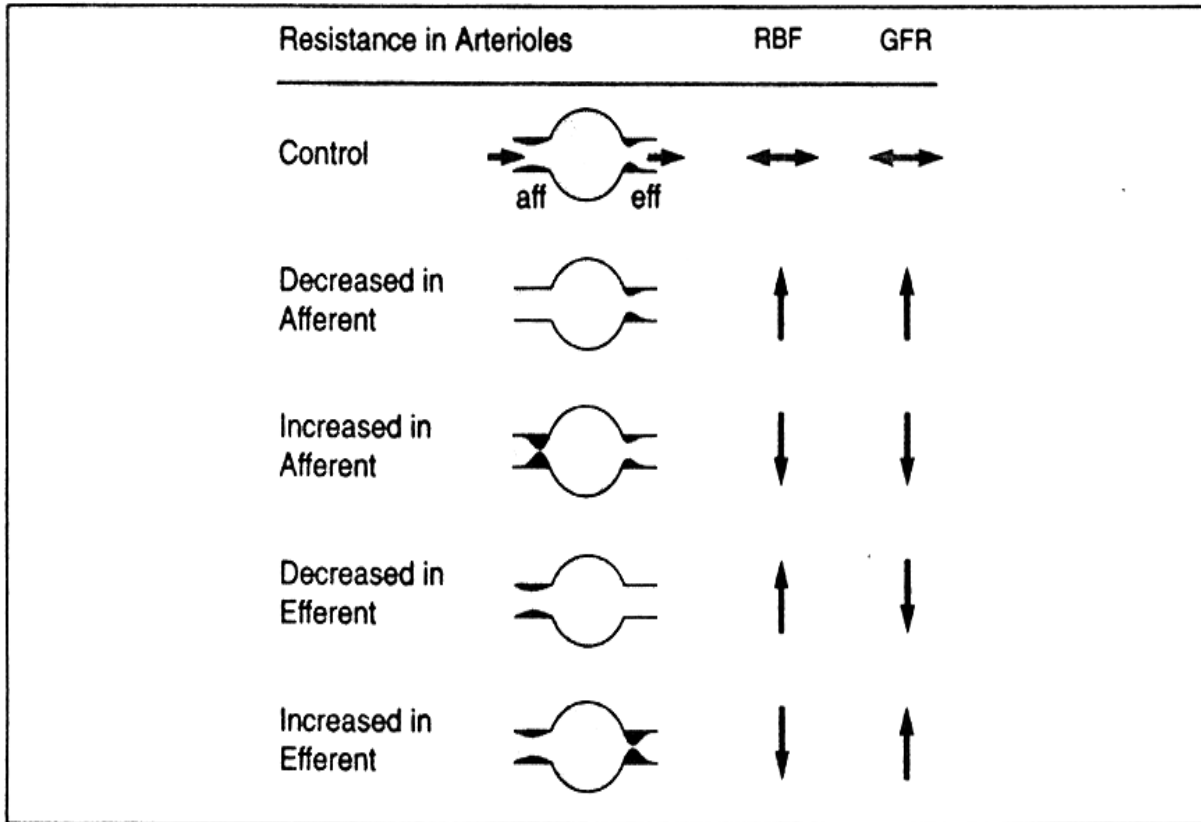


Pre-renal Azotemia

Including states of low effective circulating volume (eg. cirrhosis, CHF)

Biopsy would show no change from normal

Figure 6-3. Changes in renal blood flow (RBF) and glomerular filtration rate (GFR) that occur when resistance is altered in either the afferent or efferent arterioles, provided that the renal perfusion pressure does not change. The changes in RBF and GFR are not usually in exact proportion to one another, as might be implied by arrows of equal length. For details and for exceptions to this schema, see text.



What are the effects of NSAIDs and ACEi/ARBs ?

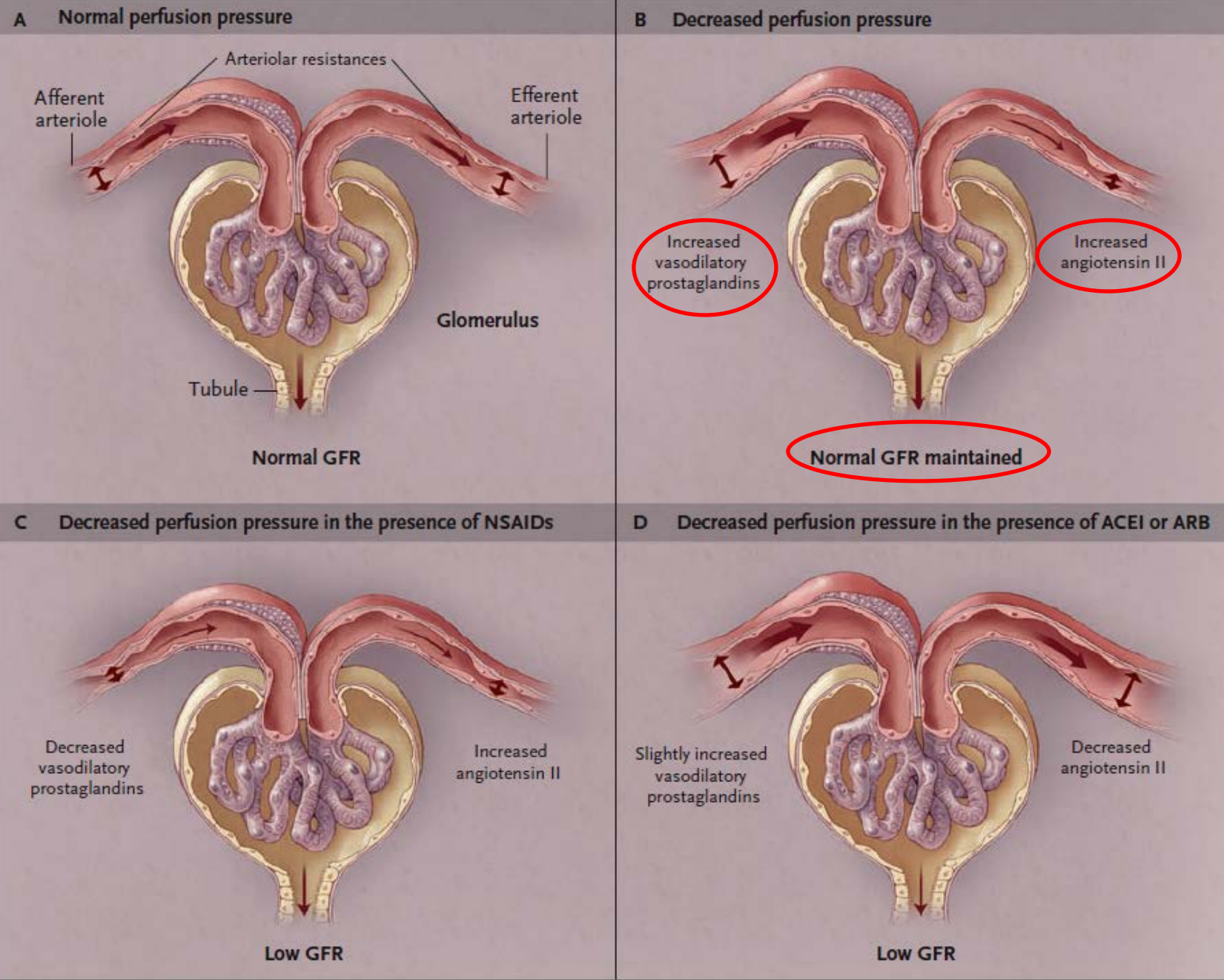
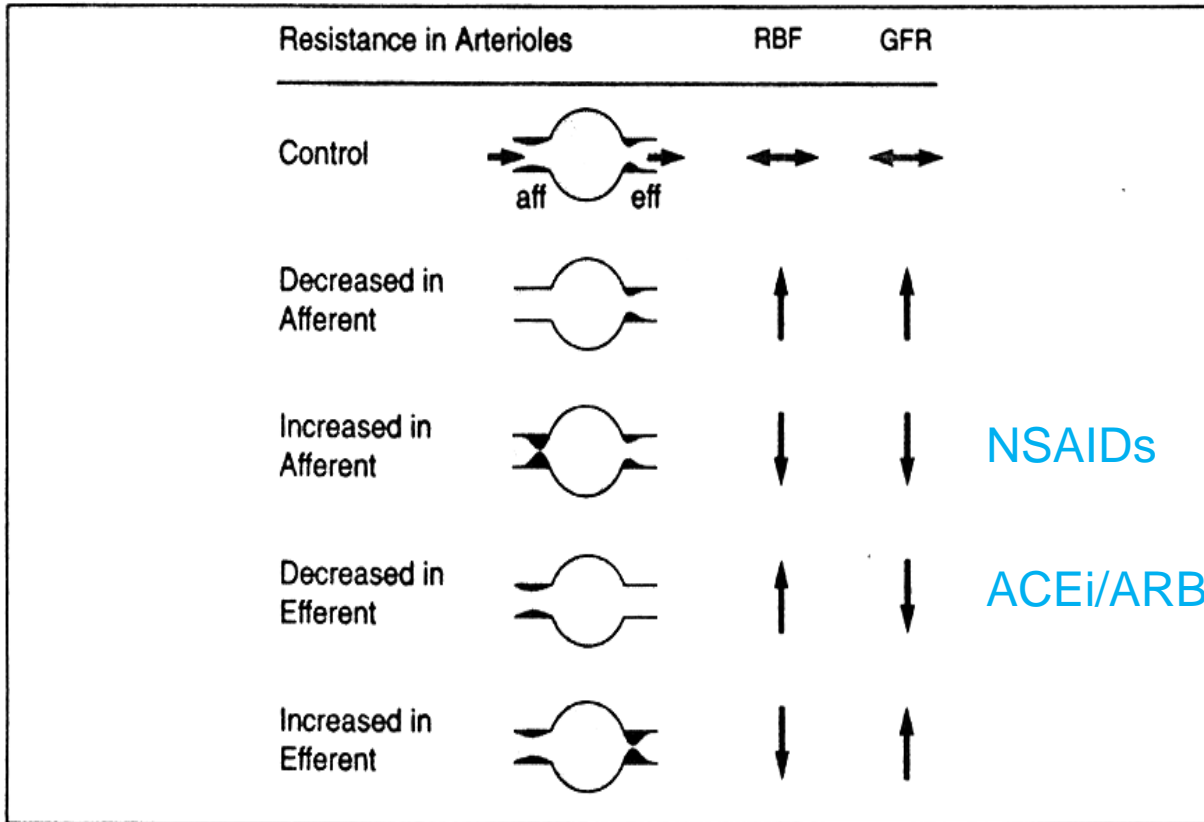


Figure 2. Intrarenal Mechanisms for Autoregulation of the Glomerular Filtration Rate under Decreased Perfusion Pressure and Reduction of the Glomerular Filtration Rate by Drugs.

Panel A shows normal conditions and a normal glomerular filtration rate (GFR). Panel B shows reduced perfusion pressure within the autoregulatory range. Normal glomerular capillary pressure is maintained by afferent vasodilatation and efferent vasoconstriction. Panel C shows reduced perfusion pressure with a nonsteroidal antiinflammatory drug (NSAID). Loss of vasodilatory prostaglandins increases afferent resistance; this causes the glomerular capillary pressure to drop below normal values and the GFR to decrease. Panel D shows reduced perfusion pressure with an angiotensin-converting-enzyme inhibitor (ACEI) or an angiotensin-receptor blocker (ARB). Loss of angiotensin II action reduces efferent resistance; this causes the glomerular capillary pressure to drop below normal values and the GFR to decrease.

Figure 6-3. Changes in renal blood flow (RBF) and glomerular filtration rate (GFR) that occur when resistance is altered in either the afferent or efferent arterioles, provided that the renal perfusion pressure does not change. The changes in RBF and GFR are not usually in exact proportion to one another, as might be implied by arrows of equal length. For details and for exceptions to this schema, see text.



What are the effects of NSAIDs and ACEi/ARBs ?

Laboratory Findings in Prerenal Disease and ATN

Test	Favors Prerenal Disease	Favors ATN
BUN-to-PCr ratio	>20:1	10–15:1
Urinalysis	Normal or near normal with few cells or casts; hyaline casts may be seen but are not abnormal	Many granular casts with renal tubular epithelial cells and epithelial cell casts
Urine sodium	<25 mEq/L	>40 mEq/L
FENa	<1%	>2%
Urine osmolality	>500 mOsm/kg	300–350 mOsm/kg

What mechanisms contribute to these findings?

ATN = acute tubular necrosis; BUN = blood urea nitrogen; PCr = plasma creatinine.

Laboratory Findings in Prerenal Disease and ATN

Test	Favors Prerenal Disease	Favors ATN
BUN-to-PCr ratio	>20:1	10–15:1
Urinalysis	Normal or near normal with few cells or casts; hyaline casts may be seen but are not abnormal	Many granular casts with renal tubular epithelial cells and epithelial cell casts
Urine sodium	<25 mEq/L	>40 mEq/L
FENa	<1%	>2%
Urine osmolality	>500 mOsm/kg	300–350 mOsm/kg

What mechanisms contribute to these findings?

RAAS

ADH/AVP

ATN = acute tubular necrosis; BUN = blood urea nitrogen; PCr = plasma creatinine.

Acute Renal Failure

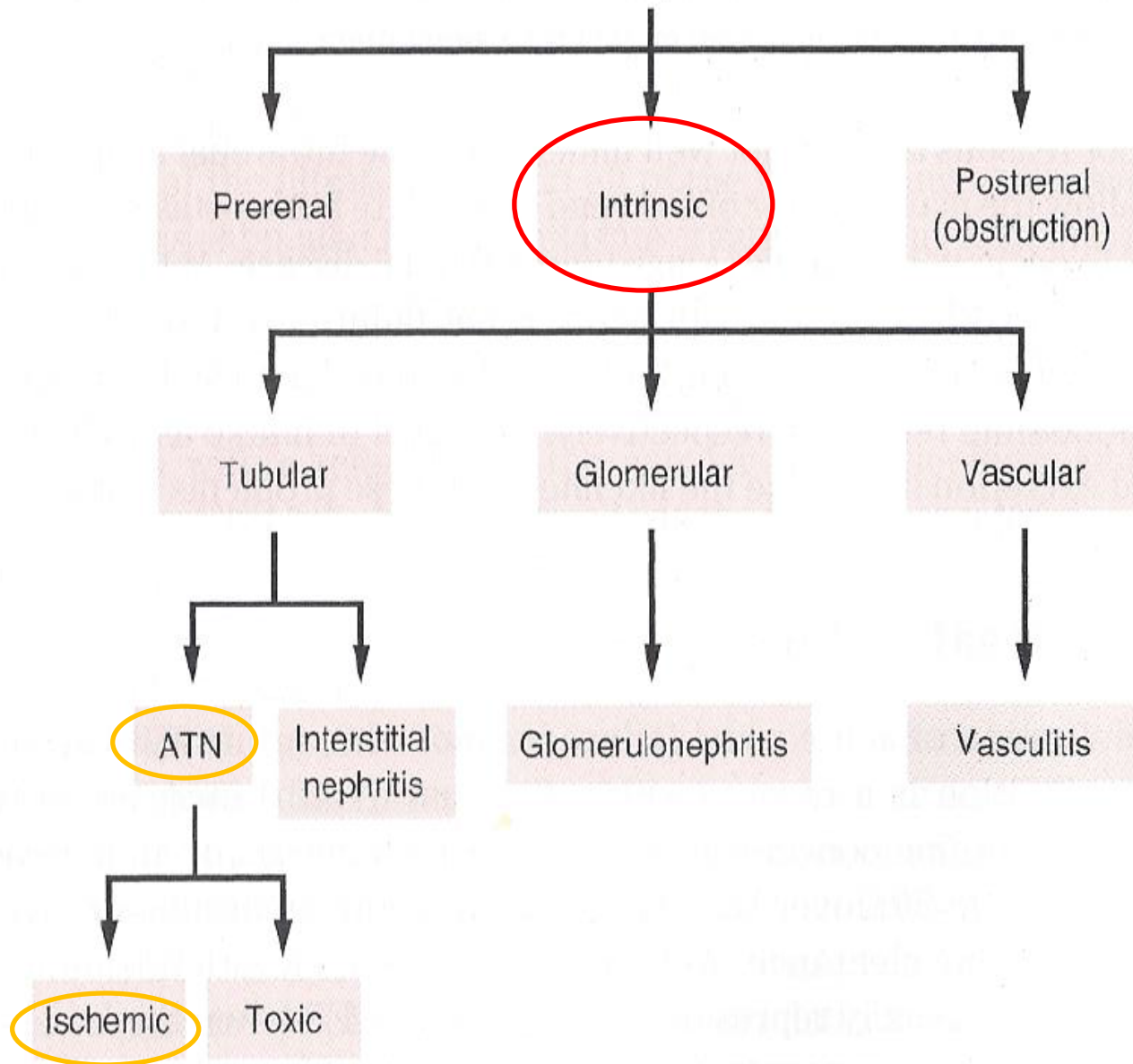
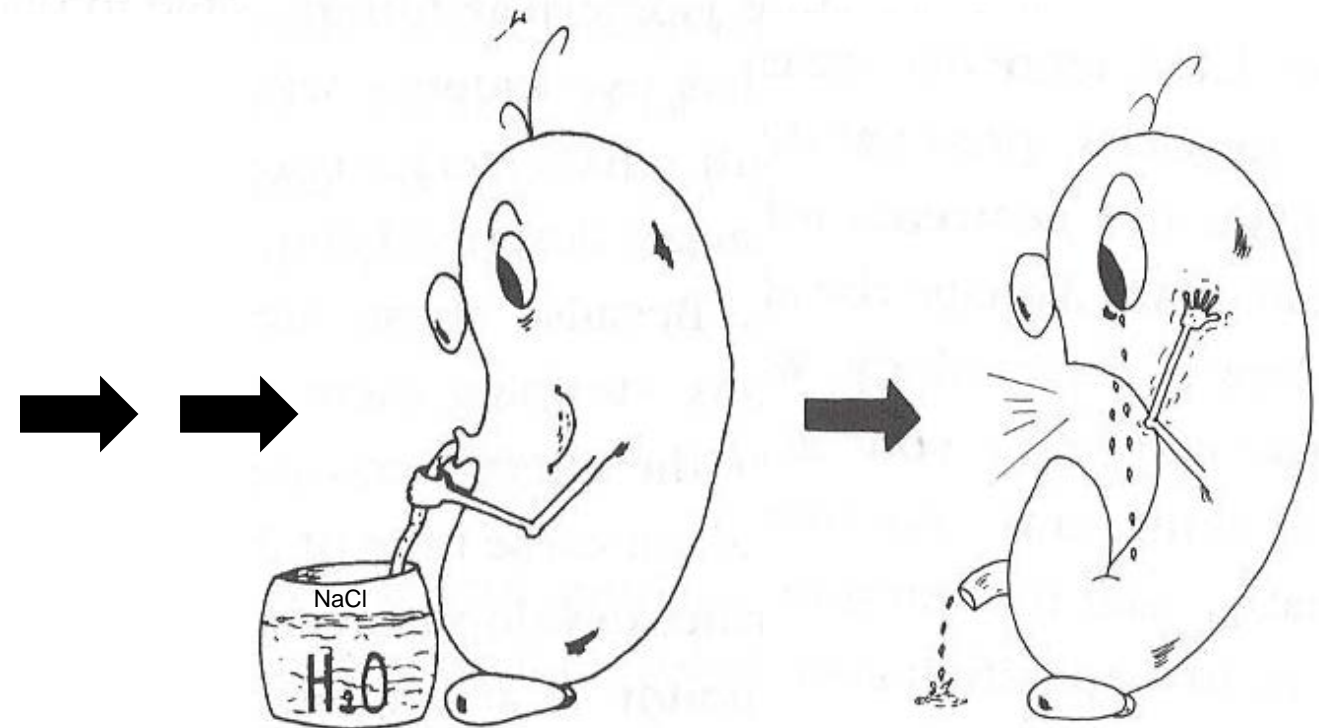
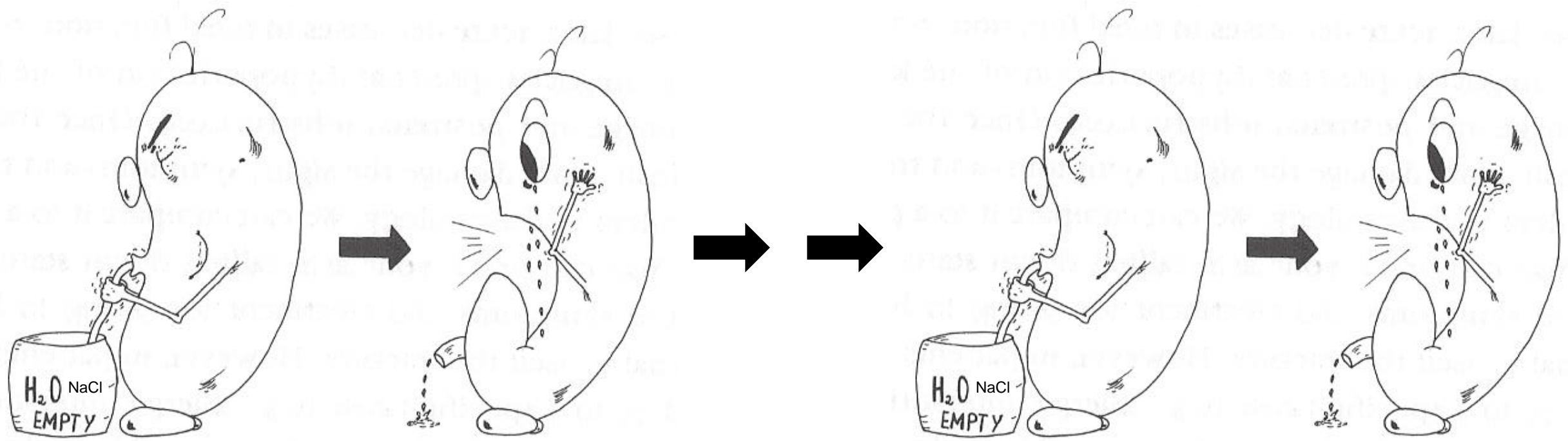
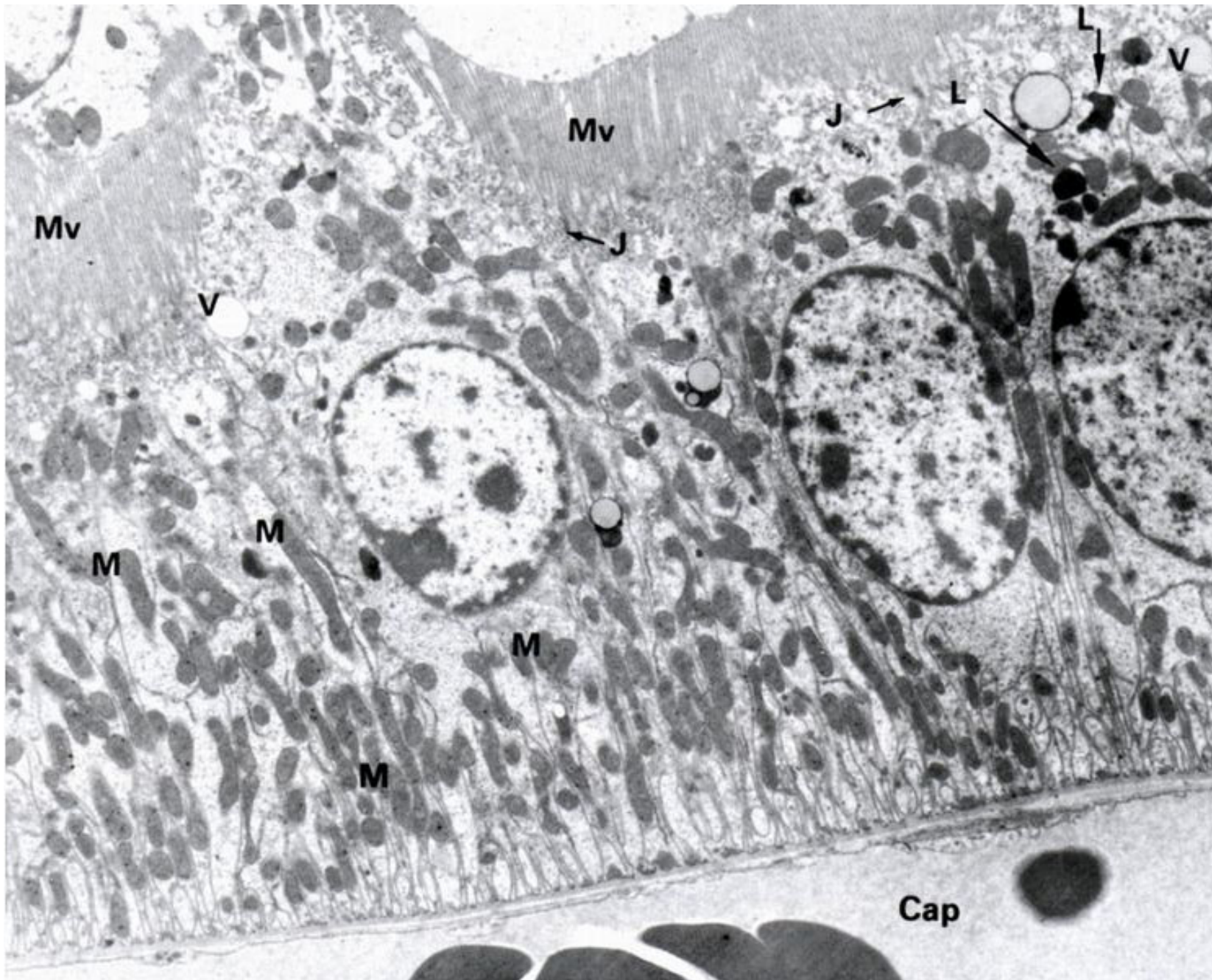


FIGURE 11.1. Main categories of acute renal failure. Postrenal (obstructive etiologies) should be diagnosed early since the etiology and treatment are usually anatomic. About 40% to 50% of patients with acute renal failure in the outpatient setting have prerenal etiologies. Once intrinsic renal disease is established, about 75% to 80% are the result of acute tubular necrosis (ATN), approximately 10% interstitial, and only about 5% to 10% the result of acute glomerulonephritis or vasculitis.

Spectrum of injury from
Pre-renal to
Ischemic ATN

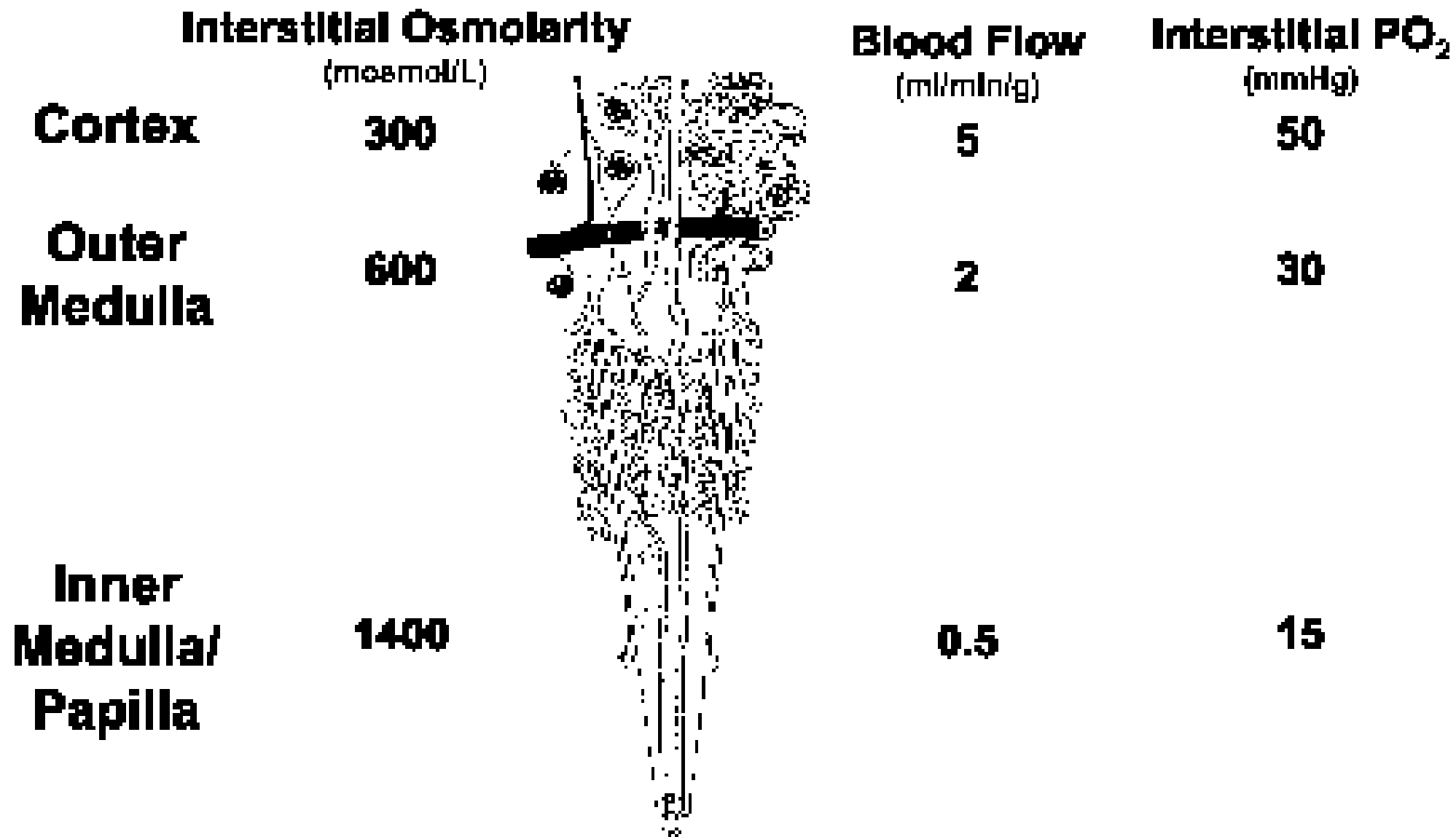


Ischemic Acute Tubular Necrosis
(Intrinsic AKI)



Proximal Tubular Cells

This is an EM section of the proximal convoluted tubule. Note the microvilli (**Mv**) forming the brush border on the apical surface and the mitochondria (**M**) alongside the basolateral regions of the plasma membrane.



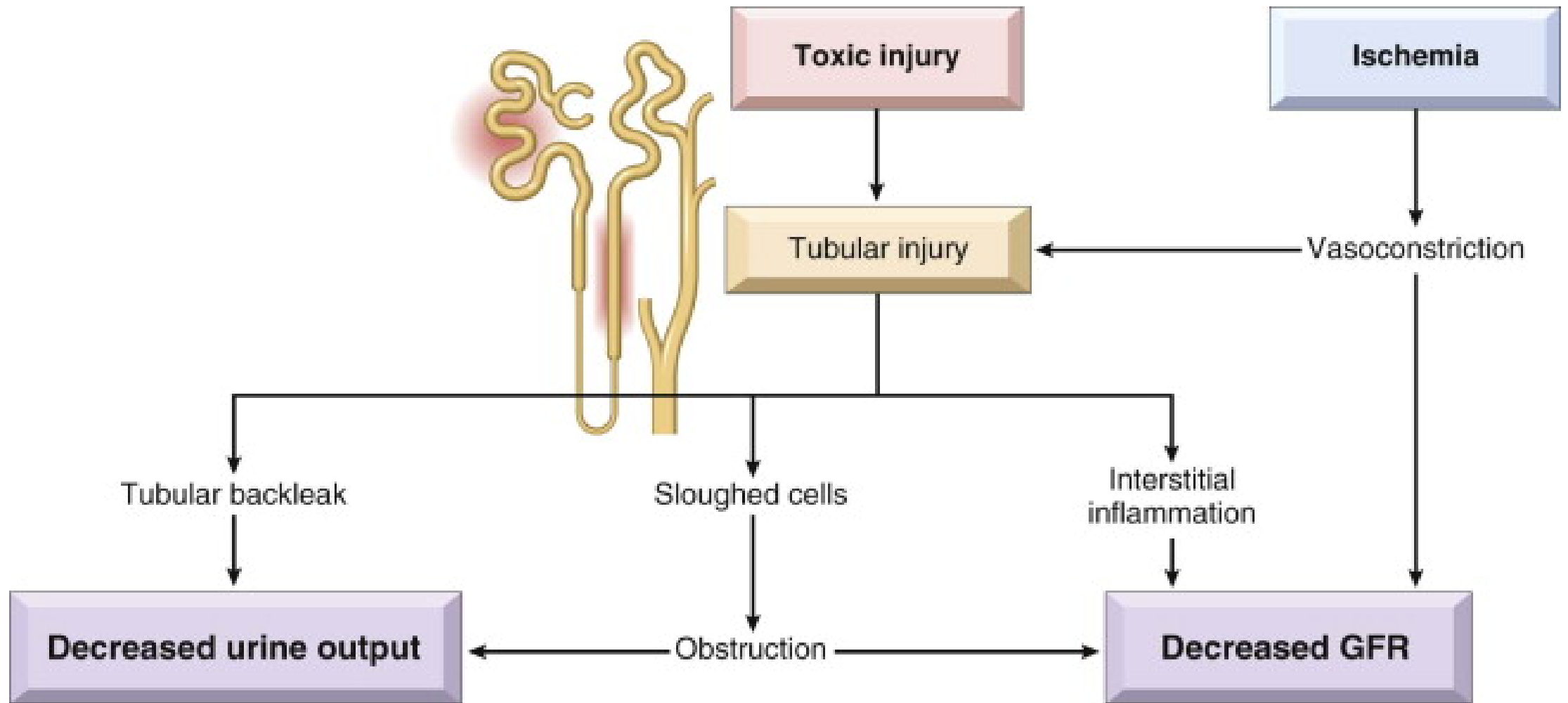


Figure 20-22

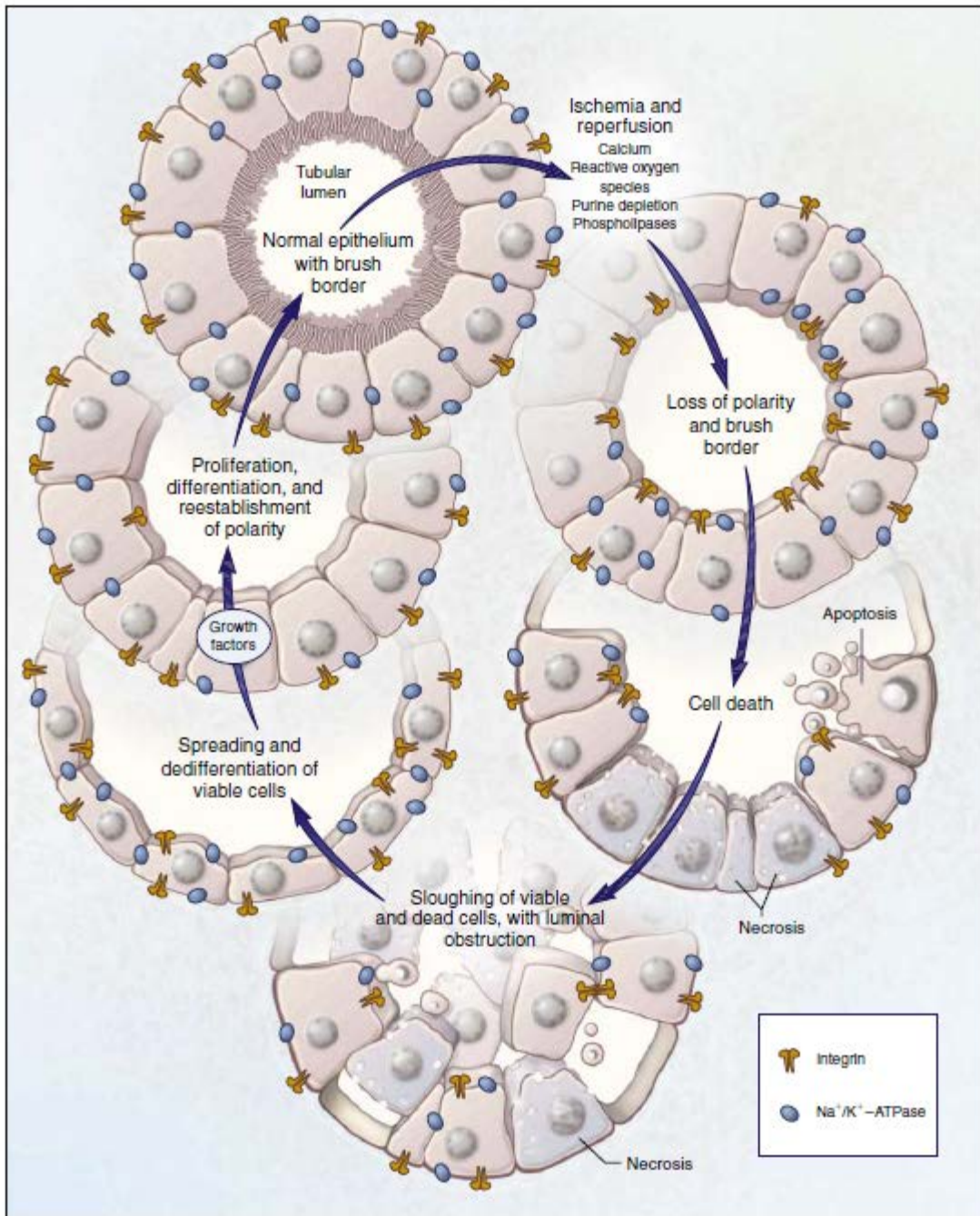


Figure 3. Tubular-Cell Injury and Repair in Ischemic Acute Renal Failure.

After ischemia and reperfusion, morphologic changes occur in the proximal tubules, including loss of the brush border, loss of polarity, and redistribution of integrins and Na/K-ATPase to the apical surface. Calcium, reactive oxygen species, purine depletion, and phospholipases probably have a role in these changes in morphology and polarity as well as in the subsequent cell death that occurs as a result of necrosis and apoptosis. There is a sloughing of viable and nonviable cells into the tubular lumen, resulting in the formation of casts and luminal obstruction and contributing to the reduction in the glomerular filtration rate. The severely damaged kidney can completely restore its structure and function. Spreading and dedifferentiation of viable cells occur during recovery from ischemic acute renal failure, which duplicates aspects of normal renal development. A variety of growth factors probably contribute to the restoration of a normal tubular epithelium.

Laboratory Findings in Prerenal Disease and ATN

Test	Favors Prerenal Disease	Favors ATN
BUN-to-PCr ratio	>20:1	10–15:1
Urinalysis	Normal or near normal with few cells or casts; hyaline casts may be seen but are not abnormal	Many granular casts with renal tubular epithelial cells and epithelial cell casts
Urine sodium	<25 mEq/L	>40 mEq/L
FENa	<1%	>2%
Urine osmolality	>500 mOsm/kg	300–350 mOsm/kg

What mechanisms contribute to these findings?

ATN = acute tubular necrosis; BUN = blood urea nitrogen; PCr = plasma creatinine.

Laboratory Findings in Prerenal Disease and ATN

Test	Favors Prerenal Disease	Favors ATN
BUN-to-PCr ratio	>20:1	10–15:1
Urinalysis	Normal or near normal with few cells or casts; hyaline casts may be seen but are not abnormal	Many granular casts with renal tubular epithelial cells and epithelial cell casts
Urine sodium	<25 mEq/L	>40 mEq/L
FENa	<1%	>2%
Urine osmolality	>500 mOsm/kg	300–350 mOsm/kg

What mechanisms contribute to these findings?

Tubular backleak and tubular obstruction from cellular debris

ATN = acute tubular necrosis; BUN = blood urea nitrogen; PCr = plasma creatinine.

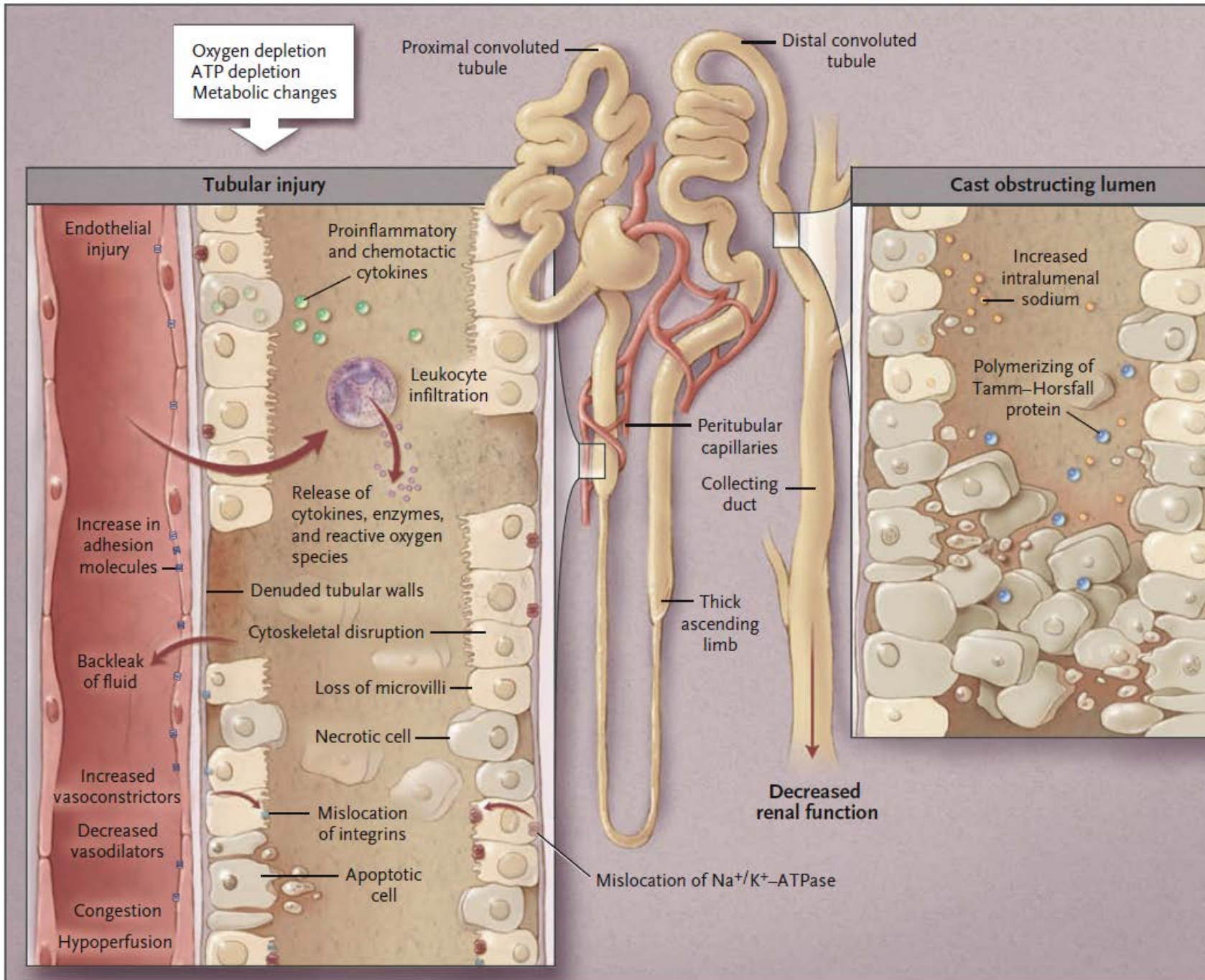


Figure 3. Pathophysiological Mechanisms of Ischemic Acute Tubular Necrosis.

Tubular injury is a direct consequence of metabolic pathways activated by ischemia but is potentiated by inflammation and microvascular compromise. The inset shows shedding of epithelial cells and denudation of the basement membrane in the proximal tubule, with back-leak of filtrate (inset, left) and obstruction by sloughed cells in the distal tubule (inset, right).

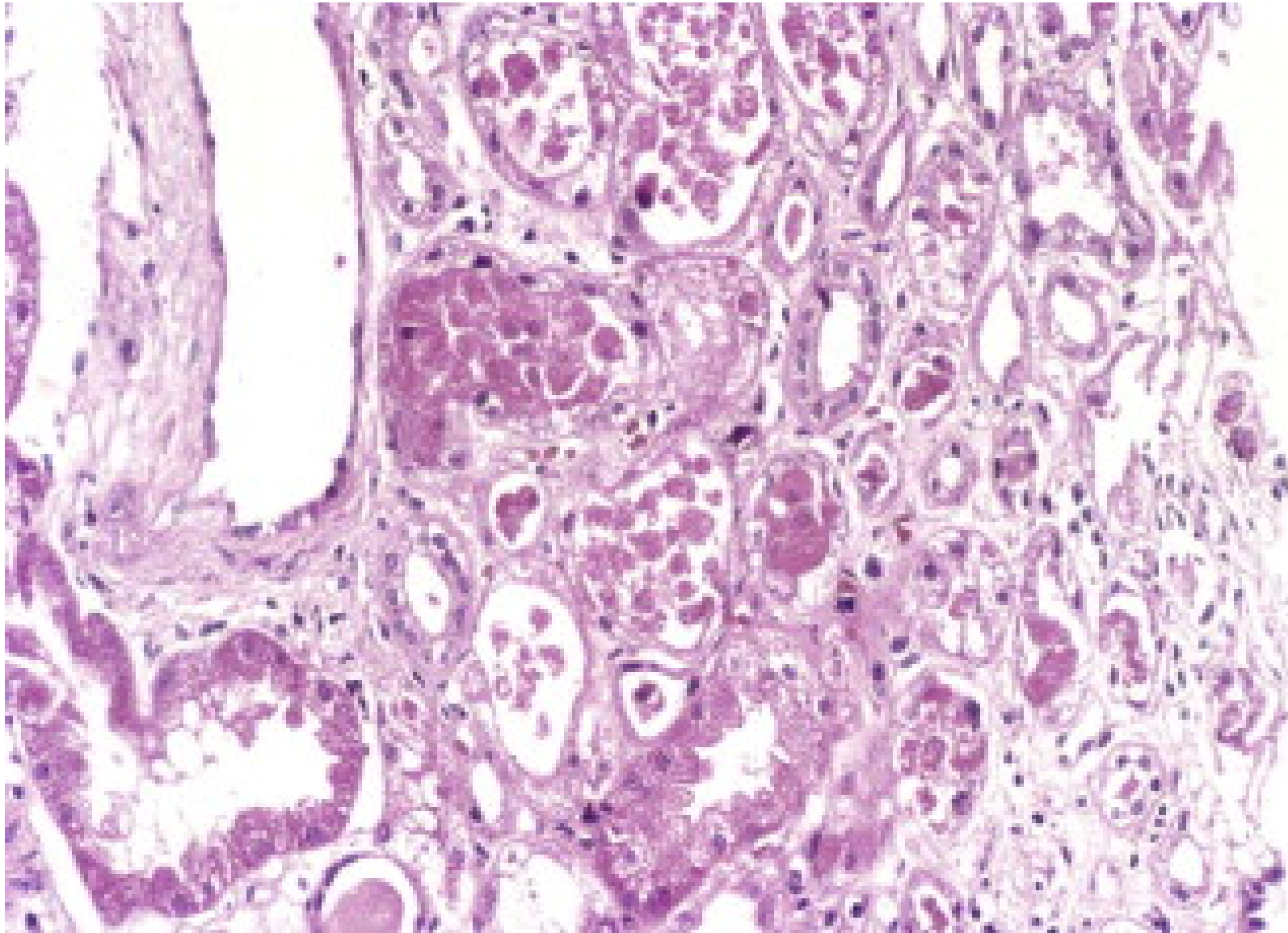
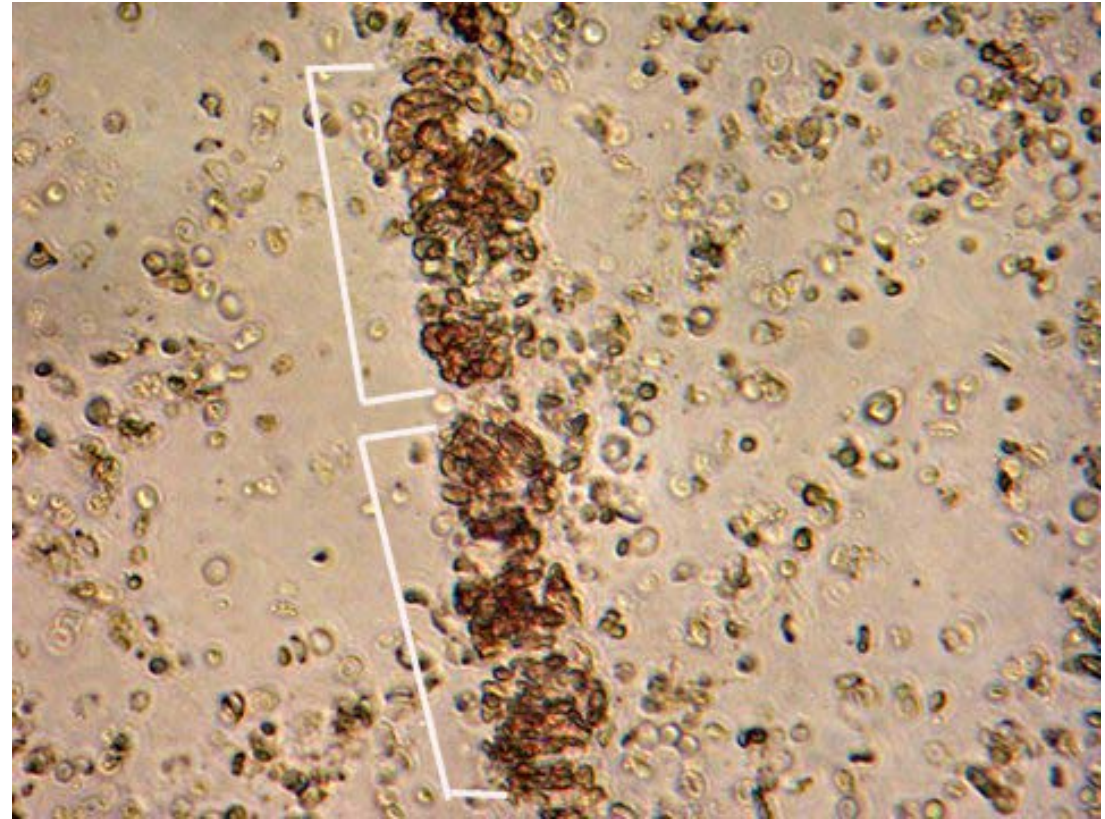
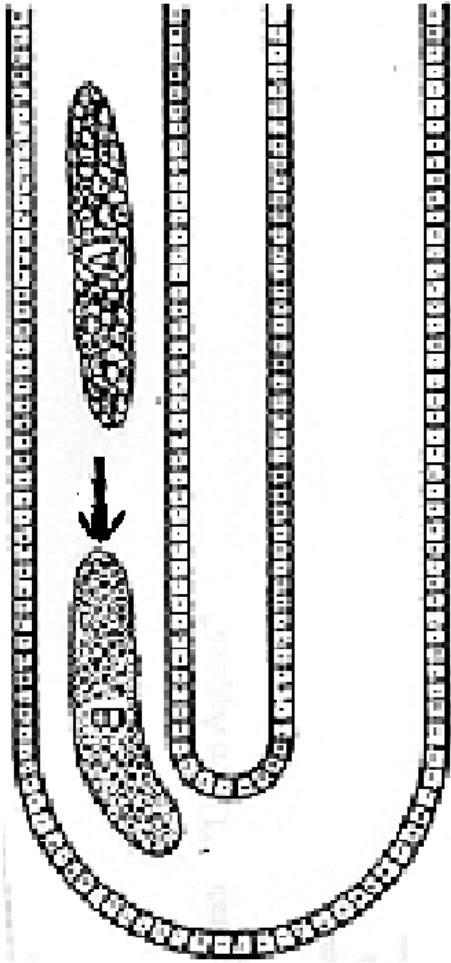


Figure 20-24
Acute tubular injury. Some of the tubular epithelial cells in the tubules are necrotic, and many have become detached (from their basement membranes) and been sloughed into the tubular lumens, whereas others are swollen, vacuolated, and regenerating



Granular cast with renal tubular epithelial cells ("muddy brown")

Typical Case

A 72 year old male presents with fever, two weeks of cough, and infiltrates on chest x-ray. The diagnosis of pneumonia is made and the patient is started on antibiotics. The hospitalization is complicated by low blood pressure and on the 6th day there is a decrease in urine output and the serum creatinine begins to rise:

	<u>Admission</u>	<u>6th</u>	<u>7th</u>	<u>8th</u>	<u>9th</u>
Creatinine	1.0 mg/dl	1.1	1.7	2.7	3.7

Case

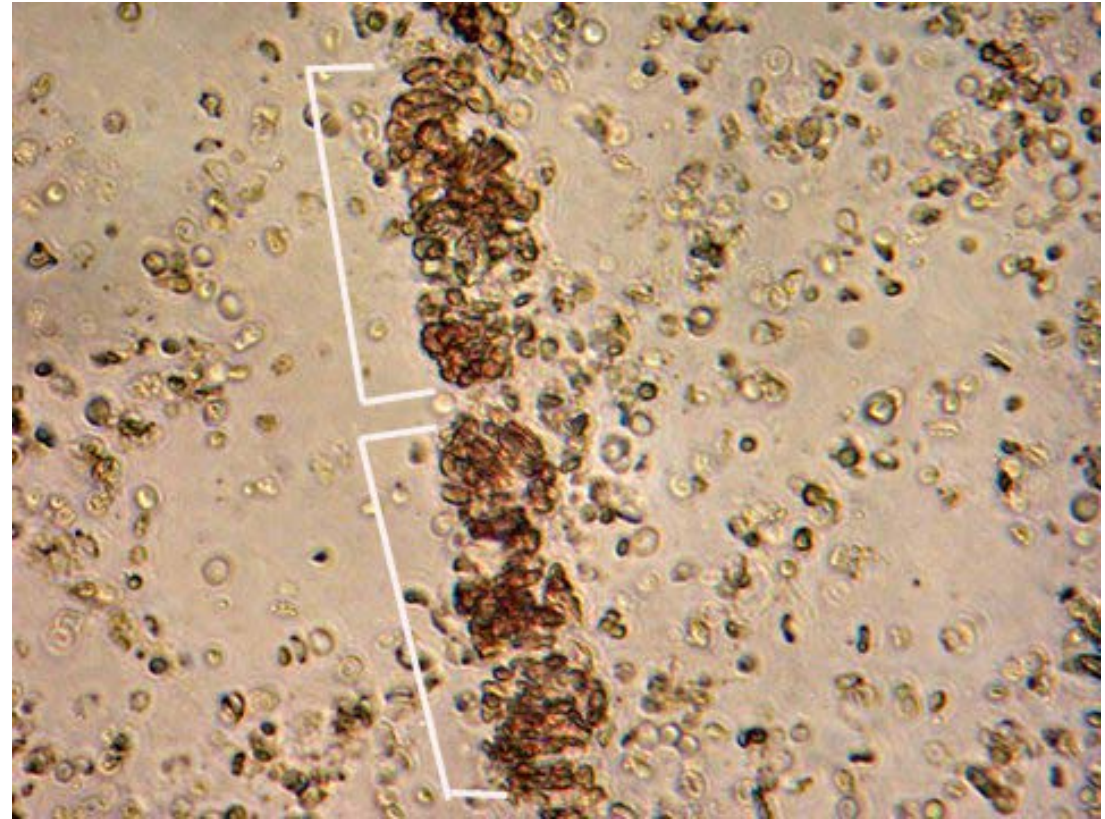
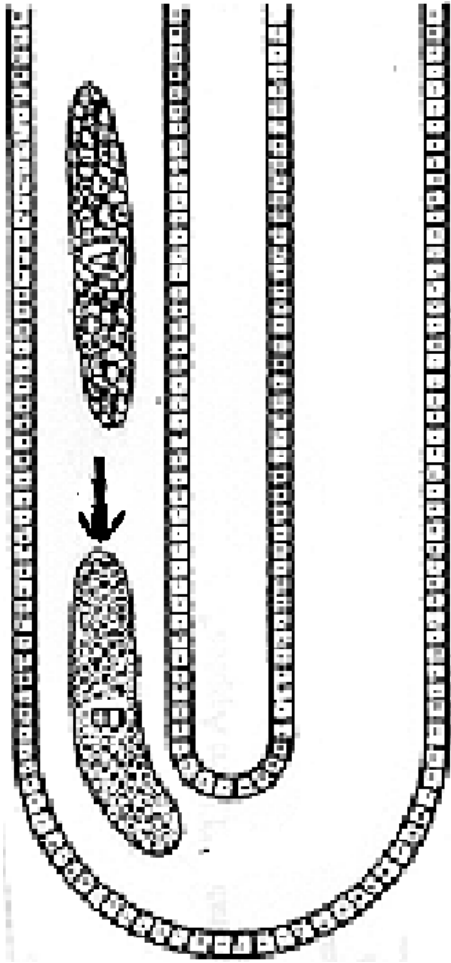
You collect a fresh urine specimen, carry it to the lab, test with urine dipstick, centrifuge a small sample, and review the urine microscopy. What would each finding suggest?

- a. Muddy brown casts
- b. Red blood cell casts
- c. White blood cell casts
- d. Dysmorphic red cells
- e. Acyclovir crystals

Case

You collect a fresh urine specimen, carry it to the lab, test with urine dipstick, centrifuge a small sample, and review the urine microscopy. What would each finding suggest?

- a. Muddy brown casts **ATN* (most likely)**
- b. Red blood cell casts **Glomerulonephritis (GN)**
- c. White blood cell casts **Interstitial Nephritis (AIN)**
- d. Dysmorphic red cells **GN**
- e. Crystals **Drug toxicity, kidney stones**



Oliguric vs Non-oliguric ATN

Acute Renal Failure

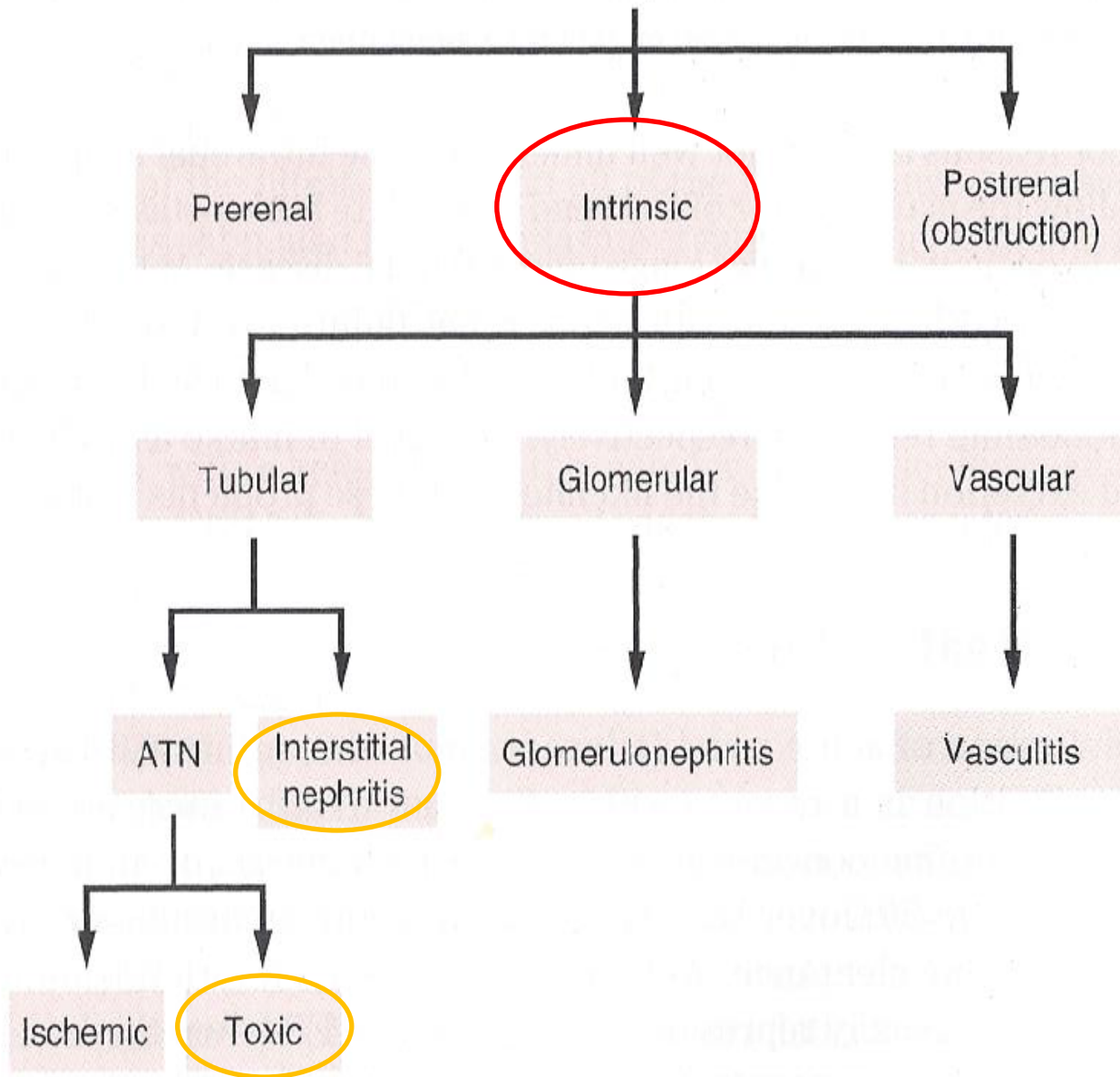


FIGURE 11.1. Main categories of acute renal failure. Postrenal (obstructive etiologies) should be diagnosed early since the etiology and treatment are usually anatomic. About 40% to 50% of patients with acute renal failure in the outpatient setting have prerenal etiologies. Once intrinsic renal disease is established, about 75% to 80% are the result of acute tubular necrosis (ATN), approximately 10% interstitial, and only about 5% to 10% the result of acute glomerulonephritis or vasculitis.

Review of medications is crucial with dose adjustment or discontinuation of renal toxins (if possible).

Indications for urgent dialysis

A E I O U

- Acidosis
- Electrolyte abnormality (hyperK, hyperCa)
- Intoxication / Ingestion (AG, OG)
- Overload of volume (pulmonary edema)
- Uremia (clinical, not any specific creat or BUN level)

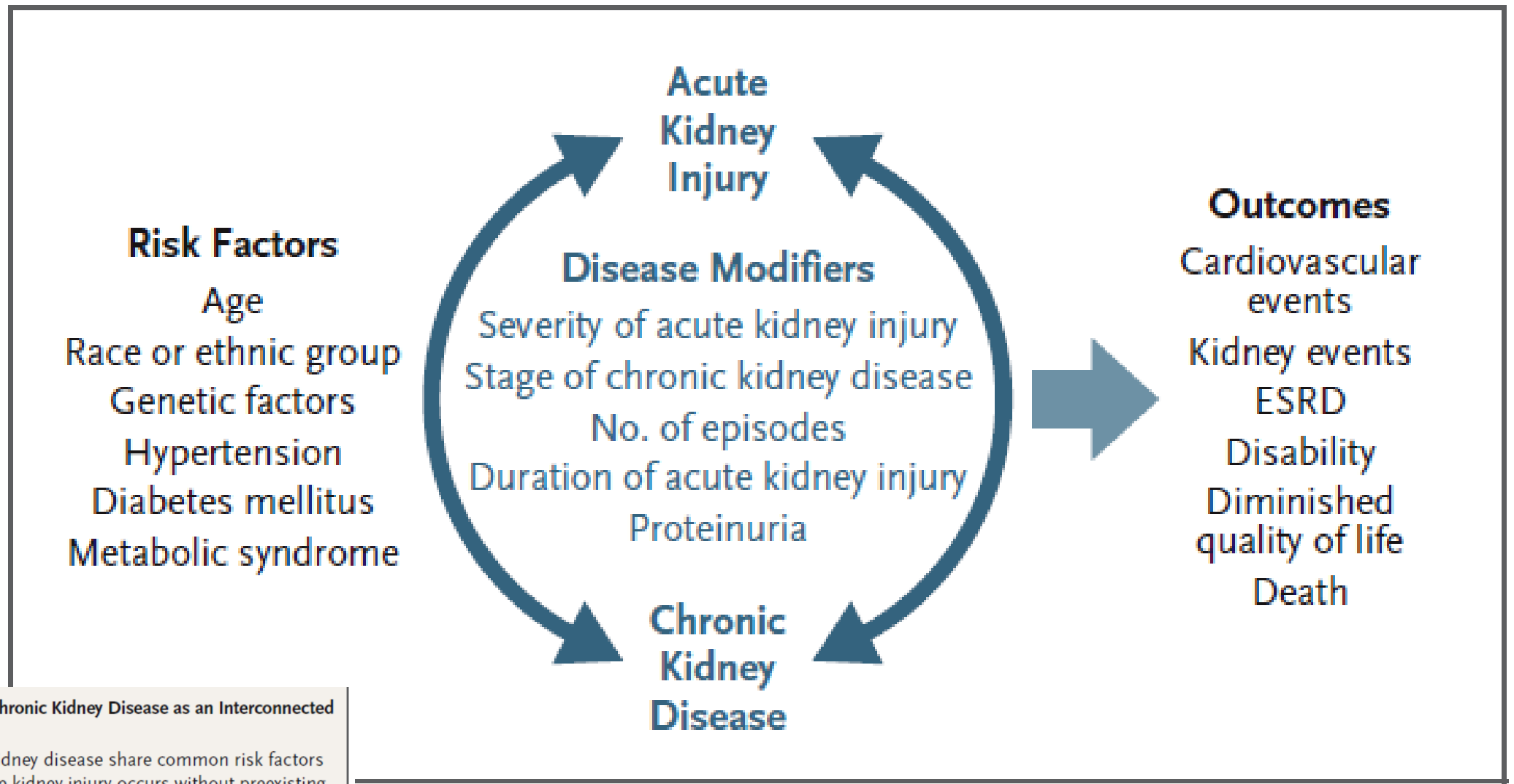


Figure 1. Acute Kidney Injury and Chronic Kidney Disease as an Interconnected Syndrome.

Acute kidney injury and chronic kidney disease share common risk factors and disease modifiers. When acute kidney injury occurs without preexisting kidney disease, chronic kidney disease still may develop. Conversely, the presence of chronic kidney disease is an important risk factor for the development of acute kidney injury. Either acute kidney injury or chronic kidney disease (and presumably their combination) is associated with an increased risk of death and may result in complications such as cardiovascular disease, progressive decreases in kidney function, diminished quality of life, and the development and progression of disability. ESRD denotes end-stage renal disease.

Objectives

- Recognize the three main categories of acute kidney injury:
 - pre-renal
 - intrinsic renal
 - post-renal
- Understand the diagnostic approach of acute kidney injury
- Describe the management of acute kidney injury

Questions

fatehi@stanford.edu

Appenix

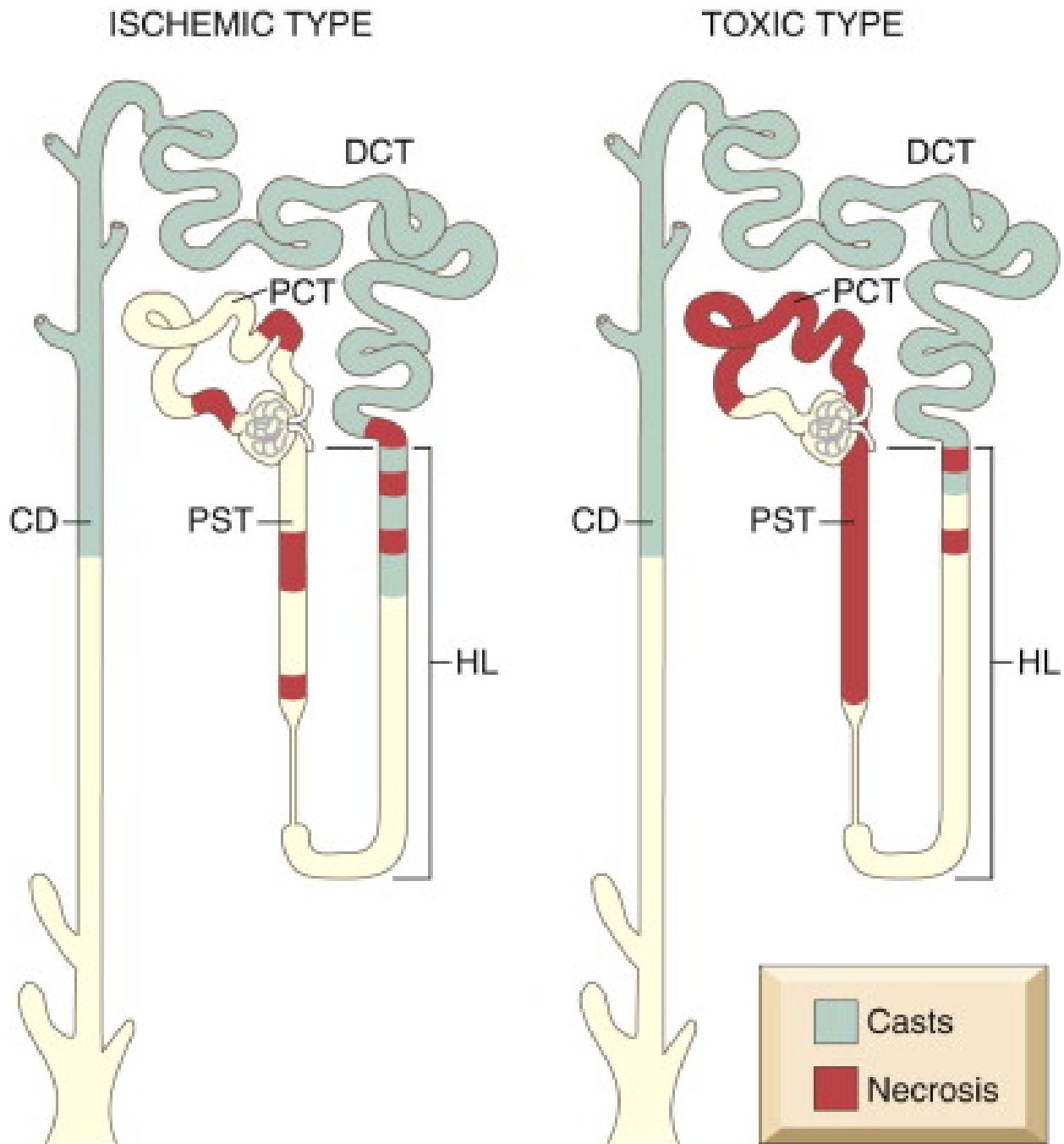


Figure 20-23

Patterns of tubular damage in ischemic and toxic acute tubular injury. In the ischemic type, tubular necrosis is patchy, relatively short lengths of tubules are affected, and straight segments of proximal tubules (PST) and ascending limbs of Henle's loop (HL) are most vulnerable. In toxic acute tubular injury, extensive necrosis is present along the proximal convoluted tubule segments (PCT) with many toxins (e.g., mercury), but necrosis of the distal tubule, particularly ascending HL, also occurs. In both types, lumens of the distal convoluted tubules (DCT) and collecting ducts (CD) contain casts.

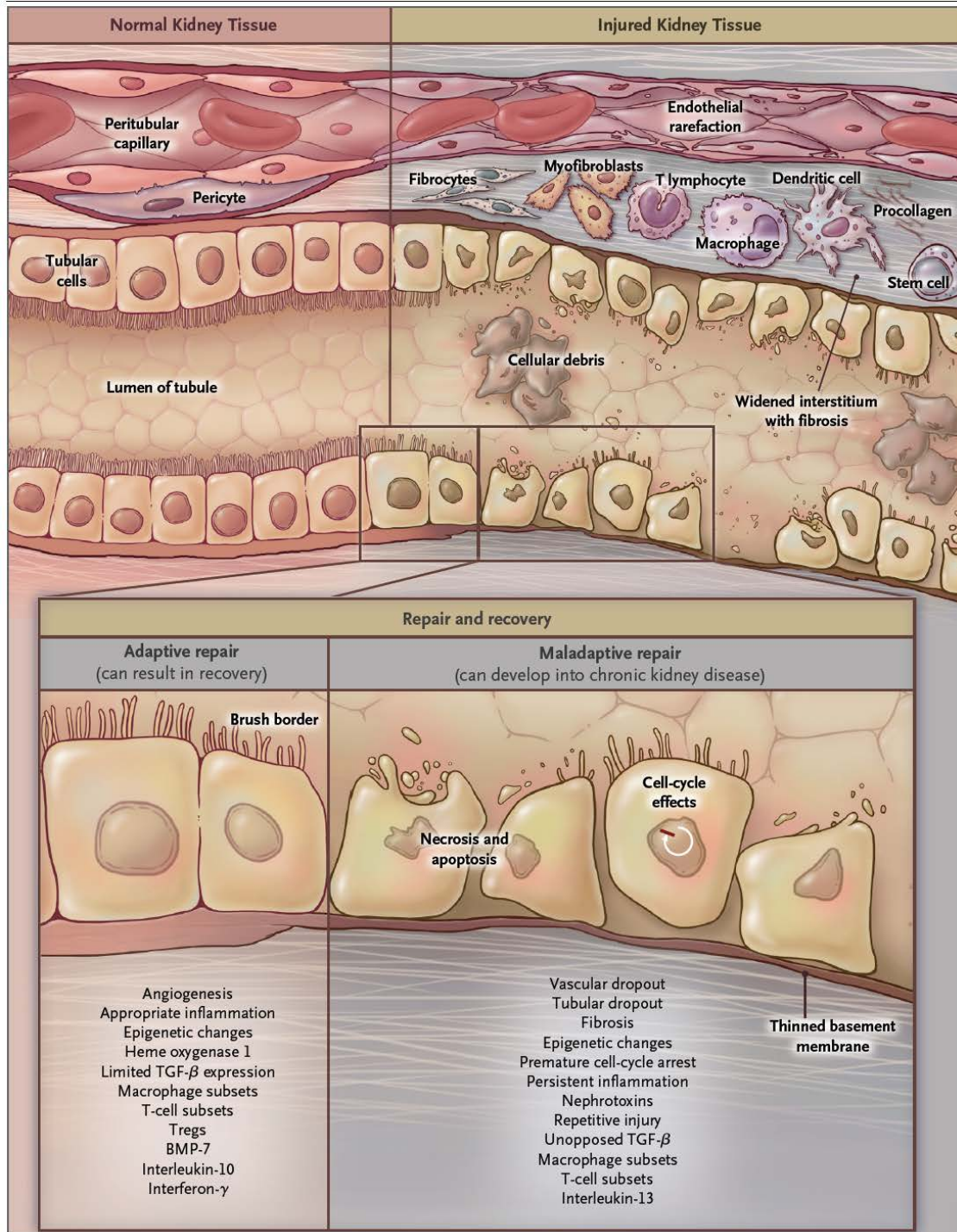


Figure 2 (facing page). Pathophysiological Features of Acute Kidney Injury Leading to Chronic Kidney Disease.

The architecture of normal kidney tissue is compared with that of injured tissue after an episode of acute kidney injury. Injured tissue shows alteration of tissue architecture and cell structure, including changes in the brush border. A variety of pathologic processes are initiated in injured and regenerating cells, including premature cell-cycle arrest, activation of myofibroblasts and fibrocytes, recruitment of various infiltrating immune and bone marrow cells to the site of injury, vascular dropout, and fibrosis. The change in tissue architecture leads to altered anatomical relationships between structures and a tissue microenvironment that promotes additional fibrosis and vascular dropout. Specific subpopulations of cells such as macrophages and T cells, differentially recruited into injured kidney tissues, may determine whether organ responses are ameliorative or maladaptive. The factors mediating recruitment, the populations of cells in human tissues that will have different responses leading to different long-term outcomes, and the interaction of recruited cells to determine outcomes are still incompletely understood. The inset shows renal tubular epithelial cells after an episode of acute kidney injury. Representative examples from various experimental studies in animals are listed in the inset. The fate of the cell, as well as the microenvironment and organ, depends on the balance between the results of repair and regenerative pathways, including apoptosis, dedifferentiation, and proinflammatory and antiinflammatory, epigenetic, and profibrotic changes. These processes may occur differentially in heterogeneous cell sets in the kidney microenvironment. Specific macrophage and T-cell subsets, as well as certain cytokines and immunoreactants, may be associated with either injury or repair. The chronic dysregulation of these factors over time and their net interactions are likely to determine the extent of fibrotic responses and organ function. BMP-7 denotes bone morphogenetic protein 7, TGF- β transforming growth factor β , and Tregs regulatory T cells.

Criteria for acute kidney injury

	Serum creatinine criteria			Urine output criteria
	RIFLE	AKIN	KDIGO	
Definition	Increase in serum creatinine of >50 percent developing over <7 days	Increase in serum creatinine of 0.3 mg/dL or >50 percent developing over <48 hours	Increase in serum creatinine of 0.3 mg/dL developing over 48 hours or >50 percent developing over 7 days	Urine output of <0.5 mL/kg/hr for >6 hours
Staging				
RIFLE-Risk AKIN/KDIGO stage 1	Increase in serum creatinine of >50 percent	Increase in serum creatinine of 0.3 mg/dL or >50 percent	Increase in serum creatinine of 0.3 mg/dL or >50 percent	Urine output of <0.5 mL/kg/hr for >6 hours
RIFLE-Injury AKIN/KDIGO stage 2	Increase in serum creatinine of >100 percent	Increase in serum creatinine of >100 percent	Increase in serum creatinine of >100 percent	Urine output of <0.5 mL/kg/hr for >12 hours
RIFLE-Failure AKIN/KDIGO stage 3	Increase in serum creatinine of >200 percent	Increase in serum creatinine of >200 percent	Increase in serum creatinine of >200 percent	Urine output of <0.3 mL/kg/hr for >12 hours or anuria for >12 hours
RIFLE-Loss	Need for renal replacement therapy for >4 weeks			
RIFLE-End-stage	Need for renal replacement therapy for >3 months			

AKIN: Acute Kidney Injury Network; KDIGO: Kidney Disease/Improving Global Outcomes.

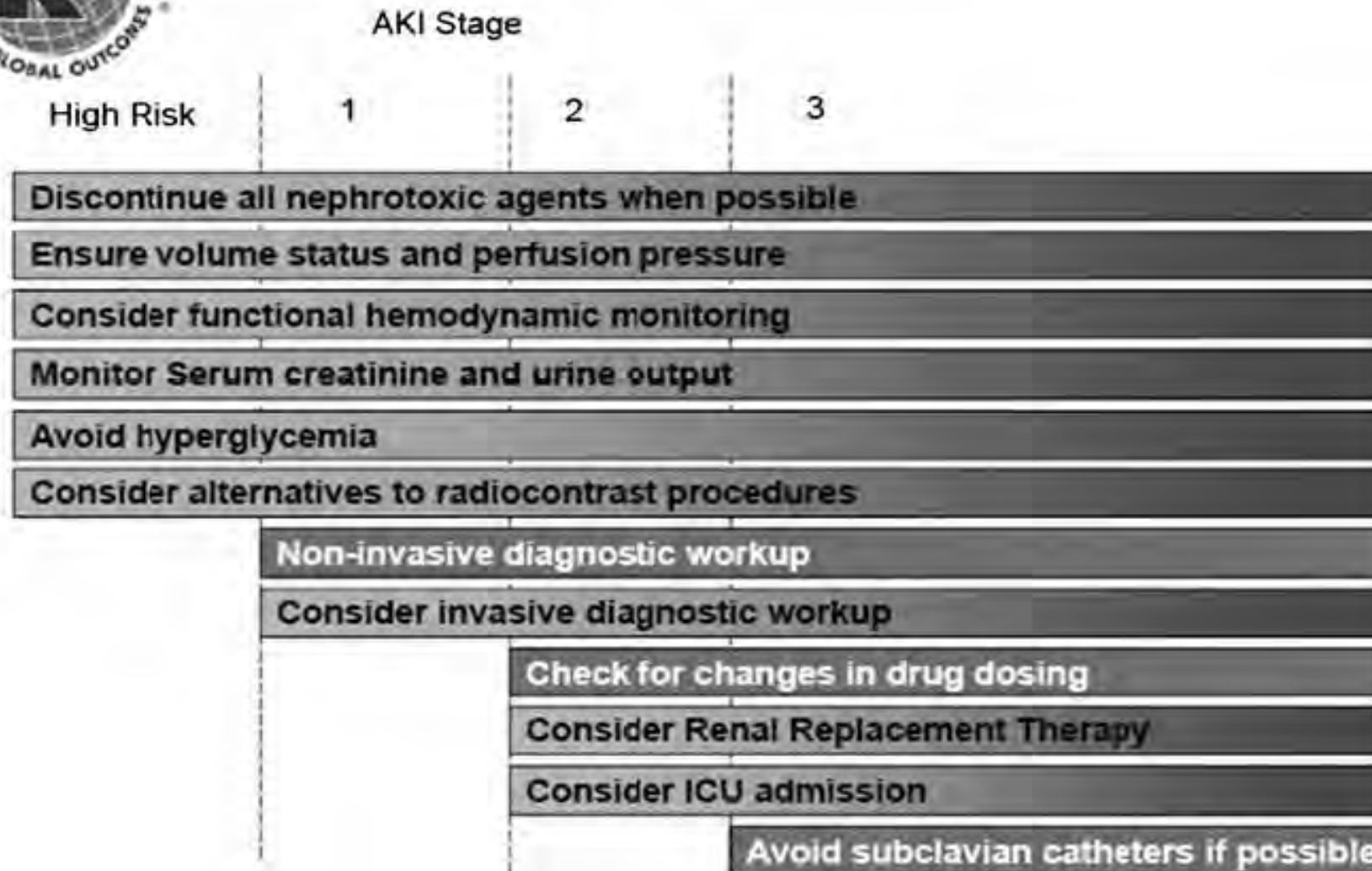


Figure 4 | Stage-based management of AKI. Shading of boxes indicates priority of action—solid shading indicates actions that are equally appropriate at all stages whereas graded shading indicates increasing priority as intensity increases. AKI, acute kidney injury; ICU, intensive care unit.