Basic Nephrology for Residents

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Outline

- **Urinalysis**
- **Urine biochemistry**
- **Quiz**

Urinalysis

- **Specimen collection**
- **Components**
  - **Appearance**
  - **Dipstick**
  - **Microscopic examination**
- **Application**
  - **Diagnosis**
  - **Prognosis**

Automated urinalysis sensitivity and specificity for detection of pathologic casts vary from 39-45% and 98-93%, respectively.

Cavanaugh C, Perazella MA. Am J Kidney Dis. 2019;73(2):258-272.

Specimen collection

- **Cleaned genitalia and midstream specimen**
- **Directly from a catheter tube in case of an indwelling catheter**
- **Preferred morning & first void**
- **Examined within 2 hr (if refrigerated within 8 hr 2-8°C)**
- **Centrifuged 10 ml of urine for 5 mins with 1,500 rpm.**
- **Low (x10) and high (x40) power, at least 10 fields/power**

Cavanaugh C, Perazella MA. Am J Kidney Dis. 2019;73(2):258-272.
UpToDate.

Components of urinalysis

- Appearance
  - Color: A faint yellow tinge (darker when concentrated)
  - Turbidity: Transparent (turbid in the presence of concentrated particle – RBC/WBC/Crystal)
  - Odor: Strong odor in UTI due to production of ammonia by bacteria and fruity odor due to ketonuria

Cavanaugh C, Perazella MA. Am J Kidney Dis. 2019;73(2):258-272.
Fogazzi GB, Verdesca S, Garigali G. Am J Kidney Dis. 2008;51(6):1052-1067.

Red/Dark urine

Table 2. Causes and Macroscopic Features of Red and Brown Urine.

Cause	Results of Test for Blood in Fresh Urine* ★	Sediment†‡	Supernatant‡
Hematuria	+ to ++++	Red	Yellow
Myoglobinuria	+ to ++++	Normal	Red to brown
Hemoglobinuria	+ to ++++	Normal	Red to brown
Porphyria	Negative	Normal	Red
Bile pigments	Negative	Normal	Brown
Food and drugs§	Negative	Normal	Red to brown

★ Erythrocyte positive on dipstick

Bosch X, Poch E, Grau JM. N Engl J Med. 2009;361(1):62-72.

Red/Dark urine

- Steps
  1) Centrifuge of urine, if red sediment only = hematuria
  2) Red supernatant -> test for heme
  3) If heme positive supernatant = hemoglobinuria or myoglobinuria
  4) If supernatant heme negative + normal sediment
     - Drugs: rifampicin, phenytoin or hydroxycobalamin (B12)
     - Food dyes
     - Beets/senna
     - Acute intermittent porphyria

Bosch X, Poch E, Grau JM. N Engl J Med. 2009;361(1):62-72.
UpToDate.

Hemoglobinuria vs Myoglobinuria

	Hemoglobinuria	Myoglobinuria
Causes	**Intravascular** hemolysis	Rhabdomyolysis
Clinical features	Pale +/- mild jaundice	History of **muscle injury**
Laboratory investigation	**Anemia**, abnormal PBS, ↓ haptoglobin, ↑reticulocyte count, ↑LDH, ↑AST, ↑indirect hyperbilirubinemia, ↑ urobilinogen > bilirubin	**↑CPK**, ↑AST, ↑Cr (out of proportion)
Plasma	**Pink** (large size + binding to haptoglobin)	**Normal** (smaller molecule + not protein bound = **rapidly filtered**)

Bosch X, Poch E, Grau JM. N Engl J Med. 2009;361(1):62-72.
UpToDate.

Color Change	Substances
White	Chyle, pus, calcium phosphate crystals, triple phosphate (struvite) crystals, propofol
Pink/red/brown	Erythrocytes, hemoglobin, myoglobin, porphyrins, beets, blackberries, senna, cascara, levodopa, methyldopa, deferoxamine, phenolphthalein and congeners, food colorings, metronidazole, phenacetin, anthraquinones, doxorubicin, phenothiazines, propofol, triple phosphate (struvite) crystals (salmon colored)
Yellow/orange/brown	Bilirubin, urobilin, phenazopyridine urinary analgesics, senna, cascara, mepacrine, iron compounds, nitrofurantoin, riboflavin, rhubarb, sulfasalazine, rifampin, fluorescein, phenytoin, metronidazole
Brown/black	Methemoglobin, homogentisic acid (alcaptonuria), melanin (melanoma), levodopa, methyldopa
Blue or green, green/brown	Biliverdin, *Pseudomonas* infection, dyes (methylene blue and indigo carmine), triamterene, vitamin B complex, methocarbamol, indican, phenol, chlorophyll, propofol, amitriptyline, triamterene
Purple staining of indwelling plastic urine collection devices	Infection with *Escherichia coli, Pseudomonas, Enterococcus,* others

Odor	Substance or Condition
Sweet or fruity	Ketones
Ammoniac	Urea-splitting bacterial infection
Fetid, pungent	Asparagus (sulfurous breakdown products)
Maple syrup	Maple syrup urine disease
Musty or mousy	Phenylketonuria
“Sweaty feet”	Isovaleric or glutaric acidemia, or excess butyric or hexanoic acid
Rancid	Hypermethioninemia, tyrosinemia

National Kidney Foundation Primer on Kidney Diseases, 8th edition

Specific gravity

- Specific gravity = weight of solution/equal volume of water
  - Determined by the number and size of particles in urine
  - Proportional to the osmolality (0.001 for 35-40 mOsmol/kg)
  - Affected by protein, mannitol, dextran, and contrast media (false high)

- Urine osmolality = the number of osmoles of solute/kg of solvents
  - Gold standard (not affected by size/temperature)
  - Urine osmolality 280 mOsmol/Kg = Isosthenuria

Brenner and Rector's The Kidney, 11th edition.
UpToDate.

Urine dipstick

- Urine pH
  - Reflects **free** hydrogen ion concentration
  - Marker of **“final”** renal acid secretion **≠ net acid secretion**
  - Physiologic ranges from 4.5 – 8 depending **on acid-base balance** (> 6.5-7 = bicarbonaturia)
  - **Falsely high in “urease” producing pathogens** (*P. mirabilis*)
  - Falsely low if delay in handling of the specimen (bacterial metabolism of glucose)/low distal Na delivery

Brenner and Rector's The Kidney, 11th edition.
Kraut JA, Madias NE. Clin J Am Soc Nephrol. 2012;7(4):671-679.
UpToDate.

Urine dipstick

- Urine Heme (erythrocyte)
  - Contained peroxide which interacted with "pseudoperoxidase action of Heme"
  - False positive in hemoglobinuria, myoglobinuria, semen, povidone-iodine, hypochlorite, and bacteria with pseudoperoxidase activity (*Enterobacteriaceae*)
  - False negative in urinary ascorbic acid (interfere peroxidase reaction)
  - Sensitivity 95-100% and specificity 65-93%

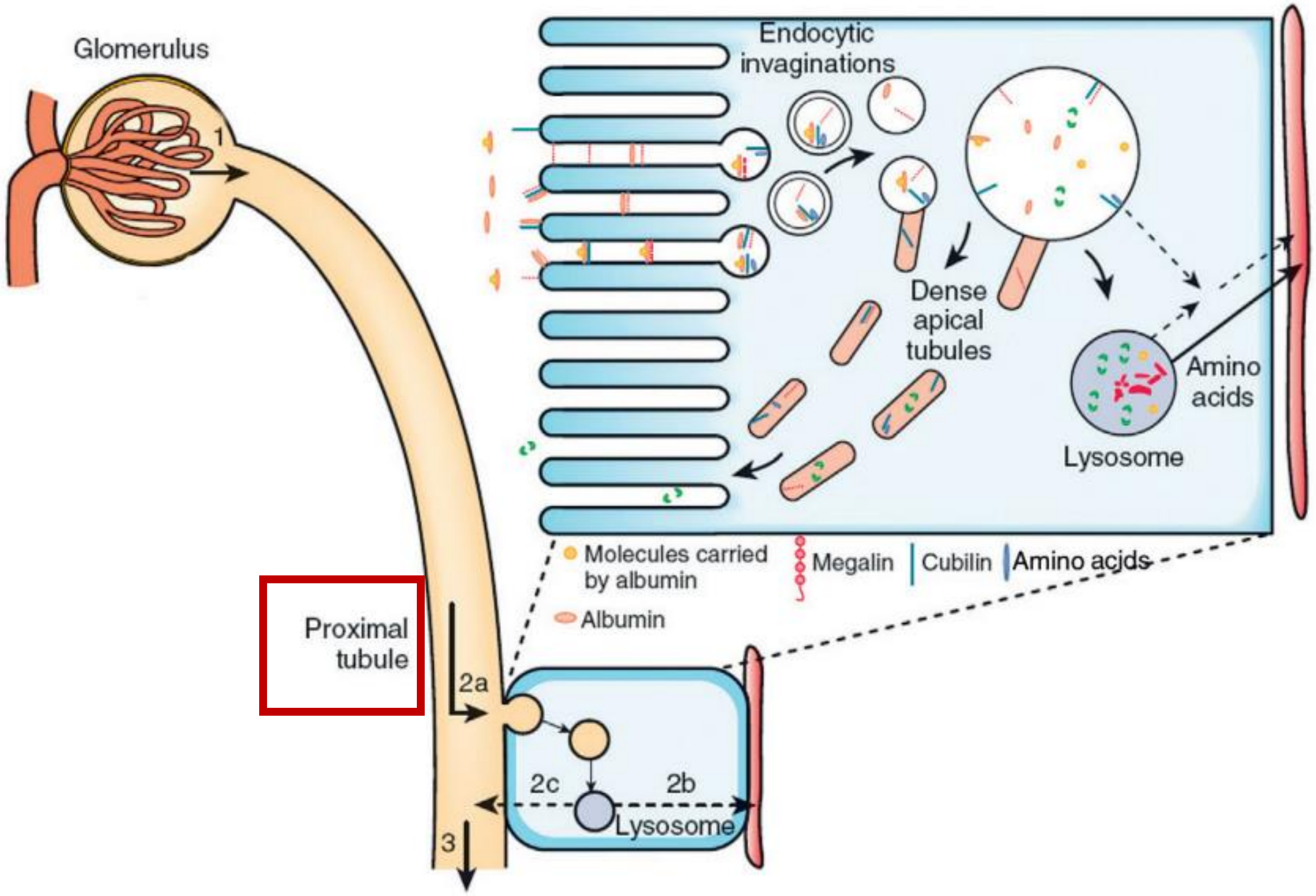
Brenner and Rector's The Kidney, 11th edition.
UpToDate.
Fogazzi GB, Verdesca S, Garigali G. Am J Kidney Dis. 2008;51(6):1052-1067.

Urine dipstick

- **Leukocyte esterase**
  - **Released from lysed PMN and macrophages, a marker of WBCs**
  - **Positive if WBC > 5-15/HPF**
  - **Falsely high (↑ lysis): Delayed collection, low pH, low sp.gr.**
  - **Falsely low: High glucose, albumin, Vit C, tetracycline and high oxalate**
- **Nitrite**
  - **Detect nitrite (converted from nitrate by most bacteria)**
  - **False low: Enterococcus and Pseudomonas, Vit C, low intake**

Brenner and Rector's The Kidney, 11th edition.
UpToDate.
Cavanaugh C, Perazella MA. Am J Kidney Dis. 2019;73(2):258-272.

Urine Protein



Physiology

- In GFR 100 ml/min, 180 L/d of primary urine was produced by plasma which contains 10 kg of protein
- Only 1 g of protein passes to filtrate which is then reabsorbed at the **proximal tubule**
- Most proteins left in normal urine are **secreted** from **tubules** such as **Tamm-Horsfall protein** (50%), IgA, and urokinase. (total of **< 150 mg/d**)
- Albumin accounts for 20% of total protein in normal urine (**< 30 mg/d** mean ≈ 10 mg/d)

Brenner and Rector's The Kidney, 11th edition.

Urine Protein

	Normal to Mildly Increased (KDIGO A1)	Moderately Increased (KDIGO A2)	Severely Increased (KDIGO A3)
AER (mg/24 h)	<30	30–300	>300
PER (mg/24 h)	<150	150–500	>500
ACR:			
mg/mmol	<3	3–30	>30
mg/g	<30	30–300	>300
PCR:			
mg/mmol	<15	15–50	>50
mg/g	<150	150–500	>500
Protein reagent strip	Negative to trace	Trace to +	+ or greater

The protein dipstick determines "**protein concentration**"

Trace	5-20 mg/dL
1+	30 mg/dL
2+	100 mg/dL
3+	300 mg/dL
4+	> 2,000 mg/dL

*** Poor sensitivity for detecting AER < 300 mg/d**

- **pH, urine concentration-dependent**, and sensitive to albumin
- **Falsely high**: high pH, **concentrated urine**, high dose penicillin, sulfonamide, and contrast
- **Falsely low**: **non-albumin protein (e.g. light chain)**

Brenner and Rector's The Kidney, 11th edition.
National Kidney Foundation Primer on Kidney Diseases, 8th edition

Urine Protein

- ถ้าตรวจพบมีโปรตีนรั่วทางปัสสาวะตั้งแต่ระดับ **1+ ขึ้นไป** และไม่มีสาเหตุอื่นที่สามารถทำให้เกิดผลบวกลวง ถือได้ว่ามีความผิดปกติ (2, C)
- ข้อแนะนำในกรณีผู้ป่วย**เบาหวานและ/หรือความดันโลหิตสูง**ที่ตรวจไม่พบโปรตีนรั่วทางปัสสาวะด้วยแถบสีจุ่ม ควรพิจารณาตรวจเพิ่มด้วยวิธีใดวิธีหนึ่งดังนี้ (2, B), **ACR or microalbumin strip** (cutoff 20 mg/L)
- ควรได้รับการ**ตรวจซ้ำอีกครั้งในระยะเวลา 3 เดือน** หากยืนยันความผิดปกติสามารถให้การวินิจฉัยว่าผู้ป่วยเป็นโรคไตเรื้อรัง หากผลการตรวจซ้ำไม่ยืนยันความผิดปกติ ให้ทำการตรวจคัดกรองผู้ป่วยในปีถัดไป (2, D)

Practice Point 1.3.1.1: Use the following measurements for initial testing of albuminuria (in descending order of preference). In all cases, a first void in the morning midstream sample is preferred in adults and children.

(i) urine ACR, or
(ii) reagent strip urinalysis for albumin and ACR with automated reading.

If measuring urine protein, use the following measurements:

(i) urine protein-to-creatinine ratio (PCR),
(ii) reagent strip urinalysis for total protein with automated reading, or
(iii) reagent strip urinalysis for total protein with manual reading.

NST CKD guideline 2022
KDIGO CKD guideline 2024

Urine Protein

Table 16 | Factors causing biological variation in urine albumin or urine protein

Factor	Falsely elevated ACR or PCR	False decrease in ACR or PCR
Variability in urine albumin or protein		
Hematuria	Increases albumin and protein in the urine	
Menstruation	Increases albumin and protein in the urine	
Exercise[259]	Increases albumin and protein in the urine	
Infection[260,261]	Symptomatic urinary infection can cause production of protein from the organism	
Nonalbumin proteins		Other proteins may be missed by albumin reagent strips
Variability in urinary creatinine concentration		
Biological sex	Females have lower urinary creatinine excretion, therefore higher ACR and PCR	Males have higher urinary creatinine excretion, therefore lower ACR and PCR
Weight[73,160]	Low urinary creatinine excretion consistent with low weight can cause high ACR or PCR relative to timed excretion	High urinary creatinine excretion consistent with high weight can cause low ACR or PCR relative to timed excretion
Changes in creatinine excretion	Lower urinary creatinine excretion with AKI or low-protein intake	High urinary creatinine excretion with high-protein intake or exercise

Urine Protein

	Urine protein	Urine albumin
Overall prognosis in CKD (CKD progression, RRT, CV, mortality, etc.)	✓	✓✓✓ **(more sensitive and specific) esp. DKD**
Diagnosis of glomerular disease (e.g. Nephrotic syndrome)	✓✓ (24h 3.5 g/d, UPCR 3 g/g)	✓
Response/target of treatment in glomerular disease (IgAN, FSGS, LN, MN, etc.)	✓✓✓	✓
Pregnancy-related disease/preeclampsia	✓✓	↔

24 hours vs spot protein/albumin

- 24-hour urine collection is considered the **gold standard**
- Considered before **treatment decision** (e.g. immunosuppression in glomerular disease)
- Preferred in patients with **altered creatinine secretion (AKI)**

24-hour urine creatinine to determine adequacy

Men 20-50 years: 18.5-25 MKD (15.7-20.2 MKD if age >50)

Women 20-50 years: 16.5-22.4 MKD (11.8-16.1 MKD if age > 50)

Generally: Female 15-20 MKD, male 20-25 MKD or 1 g/d

Brenner and Rector's The Kidney, 11th edition.
KDIGO CKD guideline 2024

Urine dipstick

- **Urine glucose**
  - The reagent strip detects glucose concentrations of 0.5 to 20 g/L (blood glucose > 180 mg/dL), positive in high blood glucose or proximal tubule dysfunction
  - Falsely positive in exposure to hydrochloric acid and very low urine pH
  - Falsely negative in large ketone, Vit C, and bacteriuria
- **Urine Ketone**
  - Nitroprusside reaction detecting only "acetoacetate and acetone" not β-hydroxybutyrate (80% of serum ketone)
  - Falsely positive patients taking levodopa/captopril/mesna
  - Falsely negative in early DKA/alcoholic ketosis

Brenner and Rector's The Kidney, 11th edition.
National Kidney Foundation Primer on Kidney Diseases, 8th edition.

TABLE 4.2 Urine Reagent Strip Testing

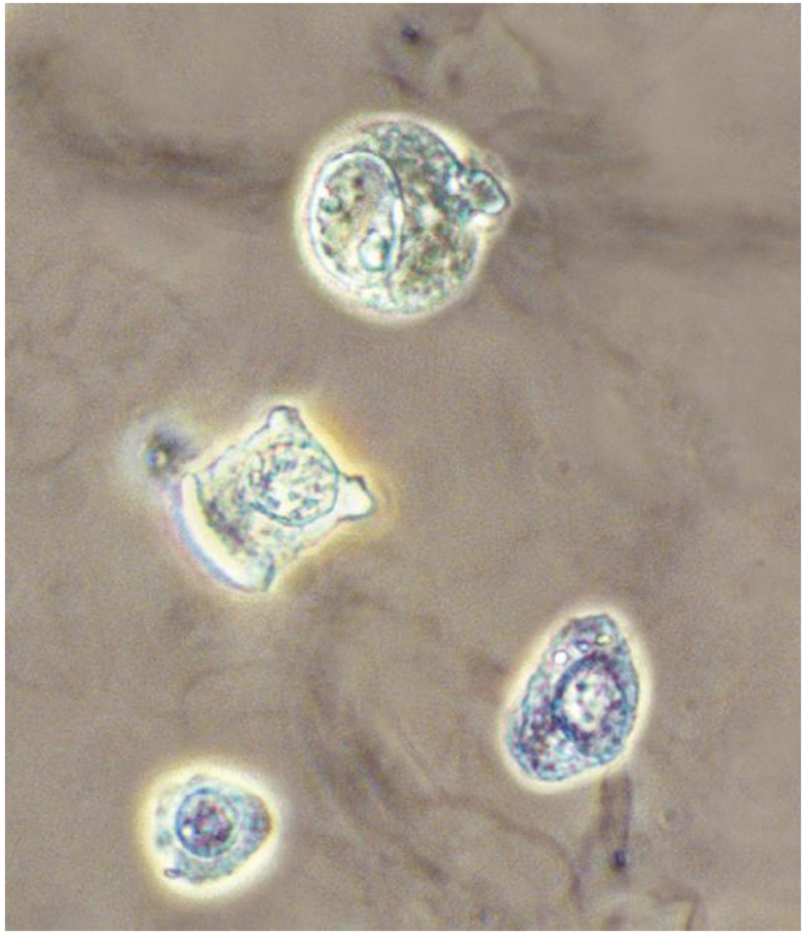
Constituent	False-Negative Results	False-Positive Results
Specific gravity (SG)	Urine pH > 6.5	Urine protein > 7.0 g/L
pH	Reduced values in presence of formaldehyde	—
Hemoglobin	High urine specific gravity Ascorbic acid Formaldehyde (0.5 g/L) used to preserve samples	Myoglobin Microbial peroxidases
Glucose	Ascorbic acid Bacteria	Very acidic urine pH Oxidizing detergents
Albumin	Low urine specific gravity Albumin < 0.25–0.30 g/L Low urine Tubular proteins Monoclonal heavy/light chains	Urine SG ≥ 1.030 Urine pH > 8.0 Quaternary ammonium detergents Chlorhexidine Polyvinylpyrrolidone
Leukocyte esterase	High urine specific gravity Ascorbic acid Glucose ≥ 20 g/L Protein >5.0 g/L Cephalothin (strong inhibition) Tetracycline (strong inhibition) Cephalexin (moderate inhibition) Tobramycin (mild inhibition)	Formaldehyde (0.4 g/L) Imipenem Meropenem Clavulanate Abnormally colored urine
Nitrites	Bacteria that do not reduce nitrates to nitrites Lack of vegetables in diet Short bladder incubation time	Abnormally colored urine
Ketones	Improper storage	Free sulfhydryl groups (e.g., captopril) Levodopa Abnormally colored urine

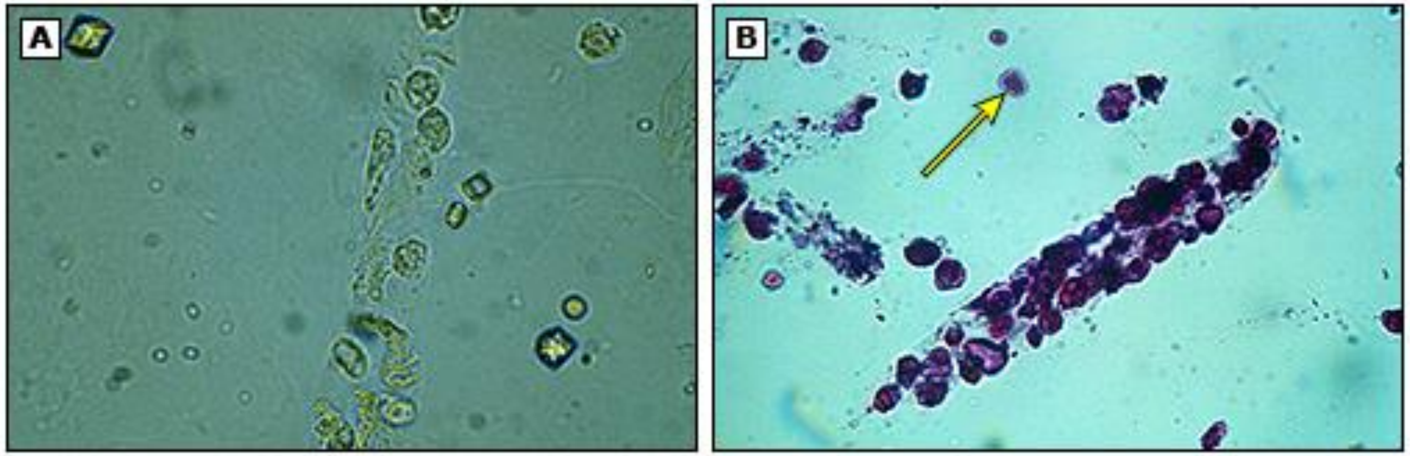
Comprehensive Clinical Nephrology, 7th edition.

Microscopic examination

- Cells (RTEC, WBC, RBC, oval fat body)
- Casts (Hyaline, broad-waxy, granular, RBC cast, WBC cast, oval fat cast)
- Crystals (oxalate, triple phosphate, uric, cholesterol, cystine, and drugs crystal)

Renal tubular epithelial cell

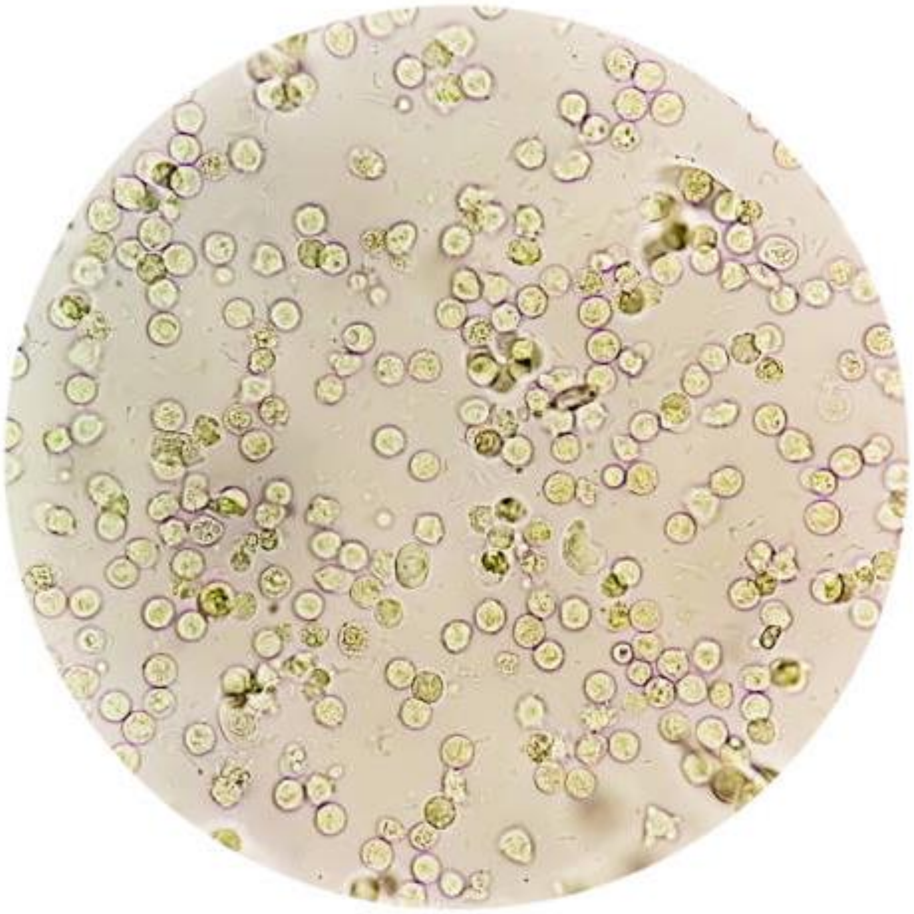




- Diameter ~14 µm
- Roundish to rectangular or columnar, with a **central** or peripheral **large nucleus**
- **Not found in healthy** individuals
- Found when there is acute tubular damage (**ATN, AIN** +/- nephritis)
- Determined **prognosis of ATN**

Comprehensive Clinical Nephrology, 7th edition.
Brenner and Rector's The Kidney, 11th edition.
UpToDate.

Pyuria

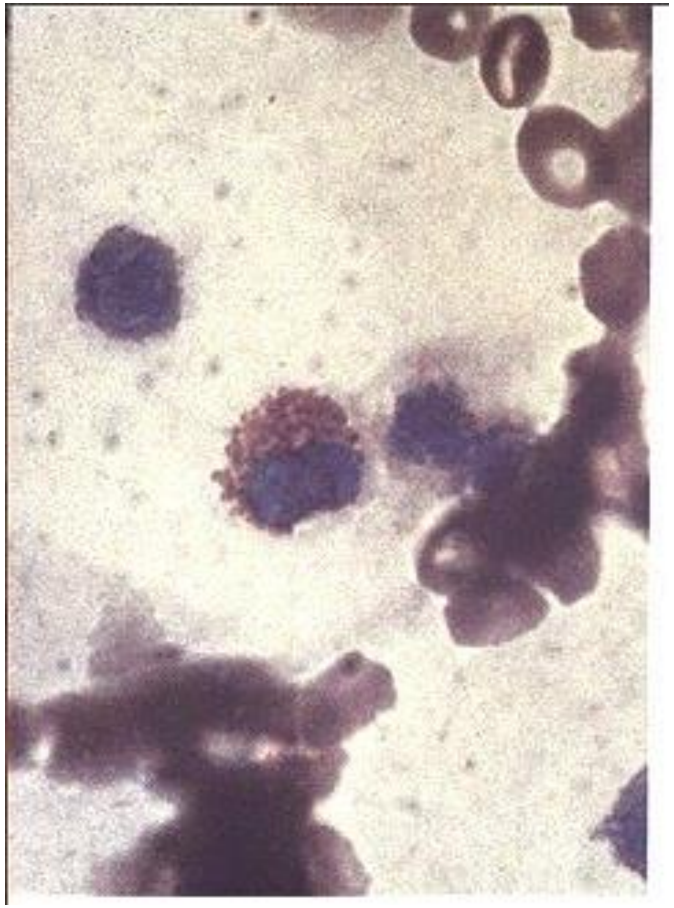


- **Definition**
  - **≥ 10 WBCs/mm³**
  - **≥ 3 WBCs/HPF in unspun urine**
  - **≥ 5-10 WBCs/HPF in spun urine**

- **Mostly PMN (+/- if ↑monocyte/eosinophil may suggest AIN)**
- **≠ UTI!!!**
- **Can be both infectious (bacterial/TB/fungus/viral) or sterile (AIN, papillary necrosis, rejection, stones, cancer)**
- **Can be both renal/non-renal causes (Appendicitis)**

Wise GJ, Schlegel PN. N Engl J Med. 2015;372(11):1048-1054.
Comprehensive Clinical Nephrology, 7th edition.
TTC 2016.

Eosinophiluria



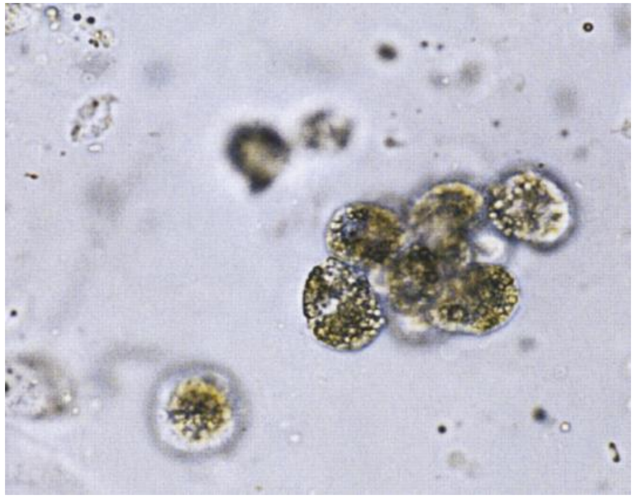
Bilobed nucleus, with eosinophilic granules
Wright stain > 5%, Hansel stain > 1%
Low sensitivity (30-50%) and **specificity** (70-80%) for AIN/drug-induced AIN

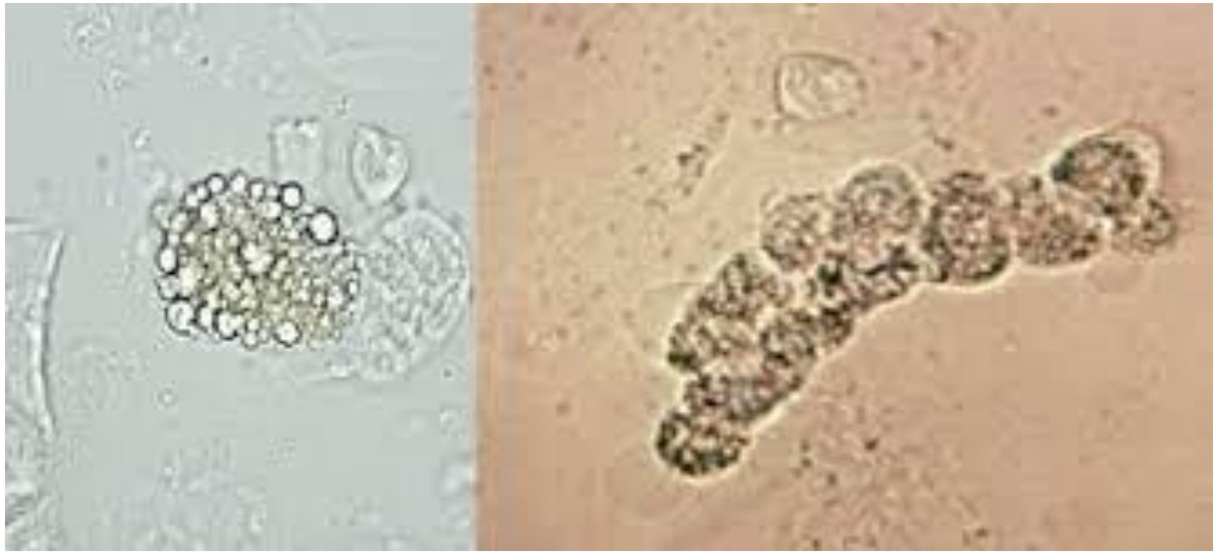
Eosinophiluria Positive

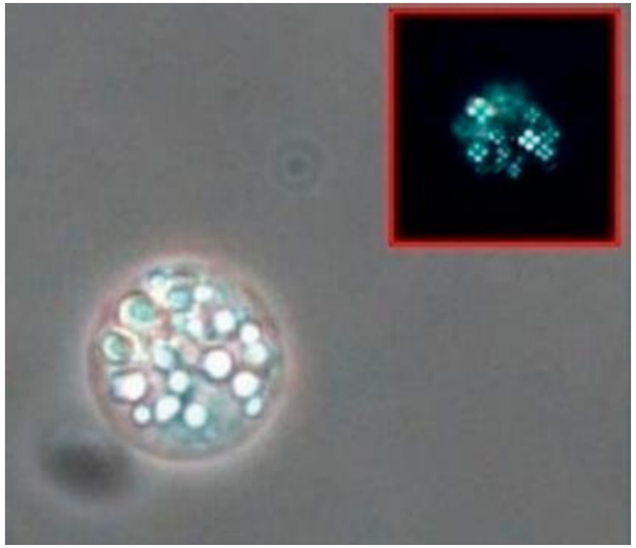
- **AIN** (drug or other causes)
- ATN
- UTI (pyelonephritis/prostatitis/cystitis), Bacterial, **schistosomal infection**
- **Cholesterol emboli**
- Glomerulonephritis/RPGN

Brenner and Rector's The Kidney, 11th edition.
Muriithi AK, Nasr SH, Leung N. Clin J Am Soc Nephrol. 2013;8(11):1857-1862.

Oval fat body (lipiduria)



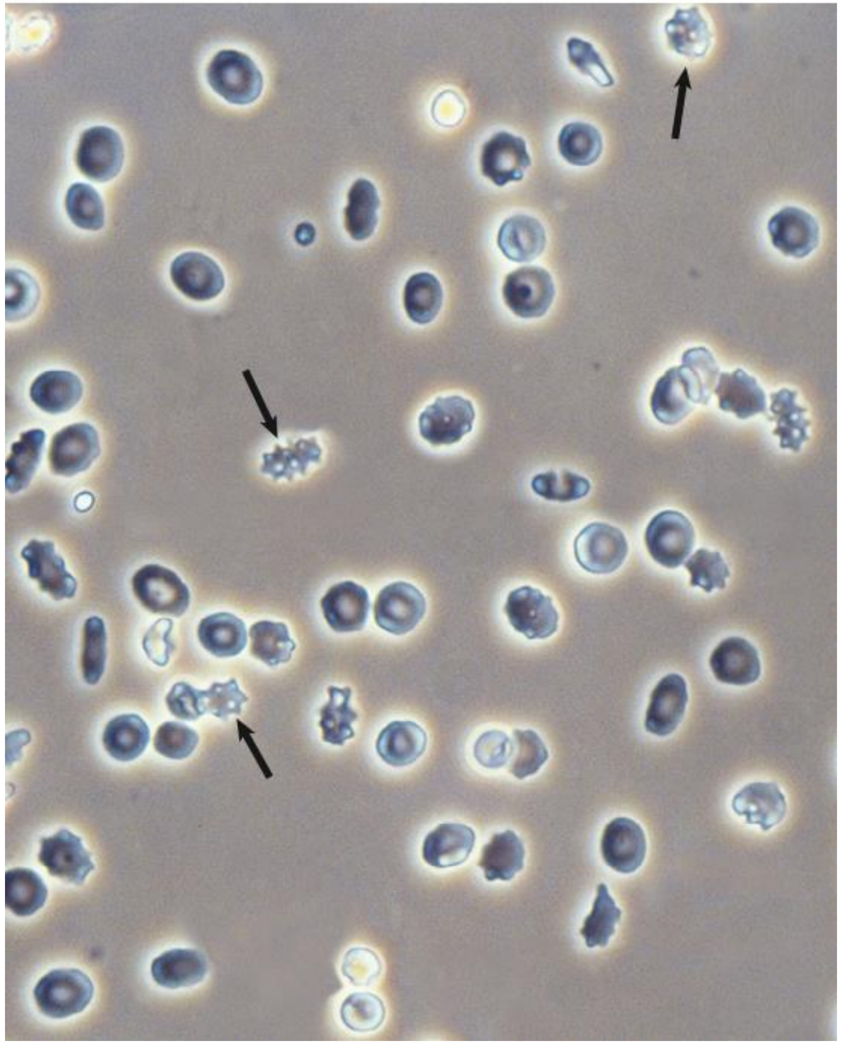




- Cholesterol engulfed by desquamated tubular cell
- Variable size, dark outline, and the "Maltese cross" appearance under polarized light
- May form oval fat body cast
- Found in Nephrotic syndrome +/- in ADPKD

Comprehensive Clinical Nephrology, 7th edition.
UpToDate.

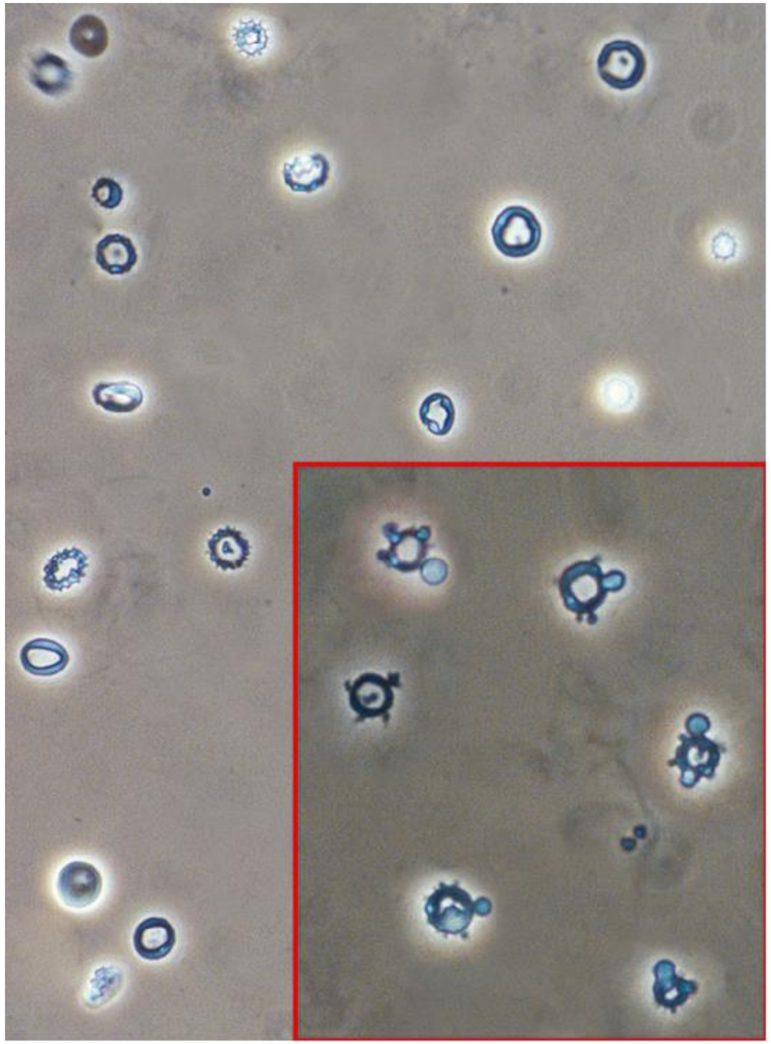
Hematuria



- **Gross (macroscopic) vs microscopic hematuria**
- **Small, anucleated cells shaped as biconcave discs**
- **Definition: ≥ 3 RBCs/HPF in spun urine (persistent > 2-3 occasions)**
- **Isomorphic RBC: MCV > 80 fL (7-8 microns) or same as RBCs in blood**

Ingelfinger JR. N Engl J Med. 2021;385(2):153-163.
Brenner and Rector's The Kidney, 11th edition.
Offringa M, Benbassat J. Postgrad Med J. 1992;68(802):648-654.

Dysmorphic RBCs/glomerular hematuria



- Dysmorphic RBC: small and irregular appearance RBC from the glomerular capillary
- Consequence of damage due to pH and osmolality changes as the cells travel through the tubule
- Glomerular hematuria: 10-80% of dysmorphic RBCs or > 5% of acanthocytes or a presence of RBC cast
- Acanthocyte: a subtype of dysmorphic erythrocytes with a distinguishing appearance by the presence of blebs of different sizes and shapes protruding from a ring-shaped body

Brenner and Rector's The Kidney, 11th edition.
Comprehensive Clinical Nephrology, 7th edition.

	Glomerular hematuria	Non-glomerular hematuria
LUTS	-	+++
Flank pain	- (+/-IgAN with gross hematuria)	+++
Color	Red to **dark/cola**	Red
Clot/contents	No clots	+++/stones
Dysmorphic RBCs	**+++ (esp. RBC cast)**	-
Proteinuria	**> 1-2 g/d** (esp. nephrotic range)	< 1 g/d
Extra-renal	**Systematic disease** with glomerular involvement (**SLE**, vasculitis, IE), **edema**	**UTI, history of stones**, malignancy, **trauma**, infarction/thrombosis, systemic bleeding

Harrison's Principles of Internal Medicine, 21th edition
Ingelfinger JR. N Engl J Med. 2021;385(2):153-163.
Brenner and Rector's The Kidney, 11th edition.

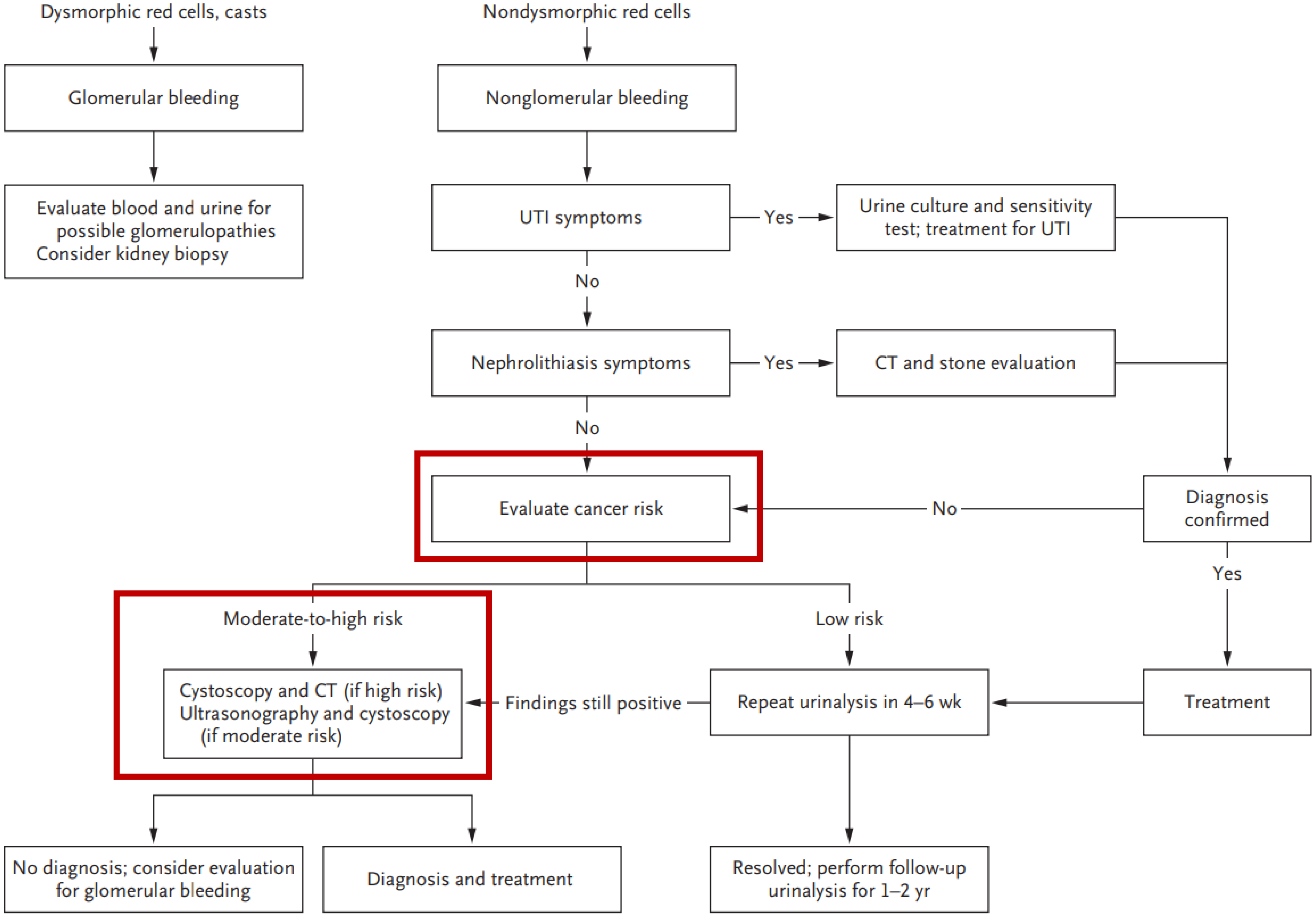


Table 2. Risk Stratification for Bladder Cancer.

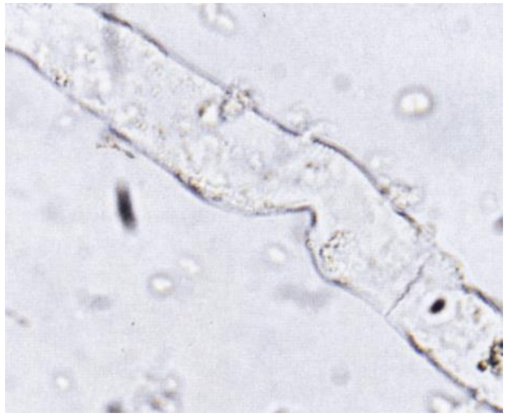
Low risk (all criteria must be met)
<40 Yr of age for men, <50 yr of age for women
Never smoked or <10 pack-yr of smoking
3–10 Red cells per high-power field on one urinalysis
No risk factors for urothelial cancer
Intermediate risk (one criterion raises the risk to intermediate)
40–59 Yr of age for men and women
10–30 Pack-yr of smoking
11–25 Red cells per high-power field on repeat urinalysis
Additional risk factors for urothelial cancer
High risk (one criterion raises the risk to high)
≥60 Yr of age for men and women
>30 Pack-yr of smoking
>25 Red cells per high-power field on single urinalysis
History of gross hematuria
Additional risk factors for urothelial cancer
Irritative lower urinary tract symptoms
Previous pelvic radiation therapy
Previous chemotherapy with cyclophosphamide or ifosfamide
Family history of urothelial cancer or Lynch syndrome
Occupational exposure to benzene or aromatic amines
Chronic indwelling foreign body in the urinary tract

Analgesic/aristolochic

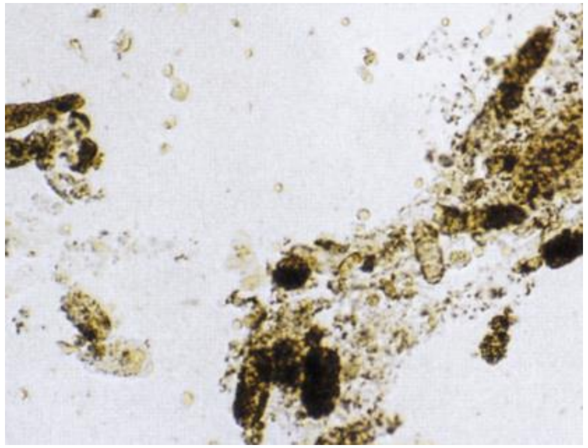
Ingelfinger JR. N Engl J Med. 2021;385(2):153-163.

Casts

- A matrix of Tamm-Horsfall urinary glycoprotein (uromodulin) +/- cells

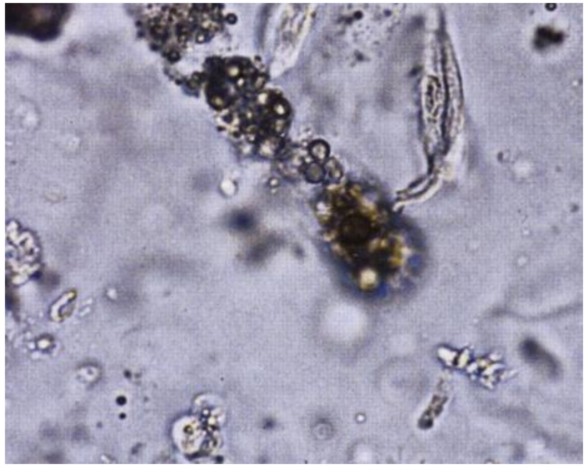


Hyaline cast
Normal/pre-renal AKI



Muddy brown cast
ATN

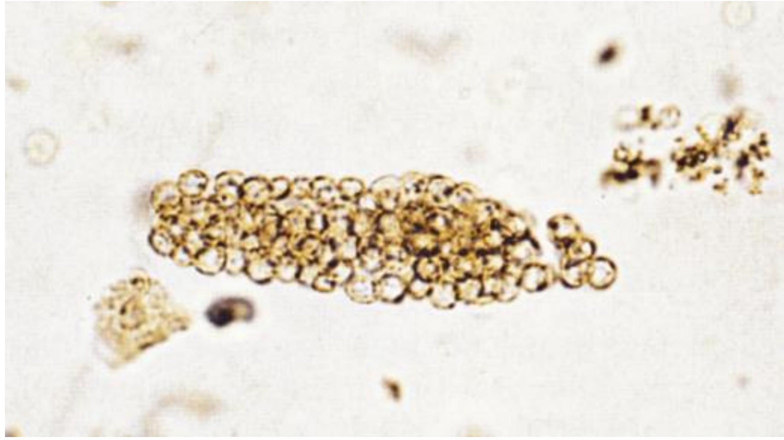
Broad waxy cast
CKD (advanced)



Oval fat body cast
Nephrotic syndrome

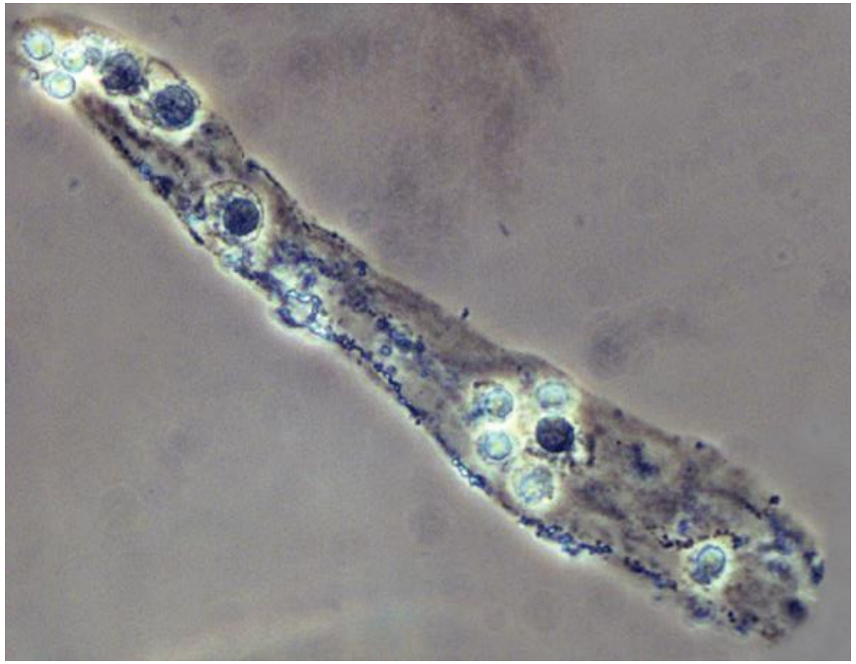
Brenner and Rector's The Kidney, 11th edition.
National Kidney Foundation Primer on Kidney Diseases, 8th edition.

Casts



RBC cast
Glomerulonephritis

WBC cast
AIN, pyelonephritis



Renal tubular epithelial cast
ATN

Brenner and Rector's The Kidney, 11th edition.
National Kidney Foundation Primer on Kidney Diseases, 8th edition.

Utility of urine microscopy

Table 1. Urine Sediment Examination in Diagnosis of Prerenal AKI and ATN Using Likelihood Ratios

	Diagnosis[a]		Likelihood Ratio	
Urine Findings	**ATN**	**Prerenal AKI**	**ATN**	**Prerenal AKI**
Urine sediment score				
1	21	82	0.28	4.5
2	64	21	3.57	0.32
3	40	3	23.25	0.07
Granular casts/LPF				
0	23	84	0.23	4.35
1-5	73	21	2.97	0.34
>6	31	2	15.60	0.06

Note: Urine sediment score: 1 for 0 casts/LPF and 0 RTECs/HPF; 2 for 1 to 5 casts/LPF or 1 to 5 RTECs/HPF; 3 for 1 to 5 casts/LPF and 1 to 5 RTECs/HPF or >6 casts/LPF or >6 RTECs/HPF.

Highly specific for the diagnosis of ATN

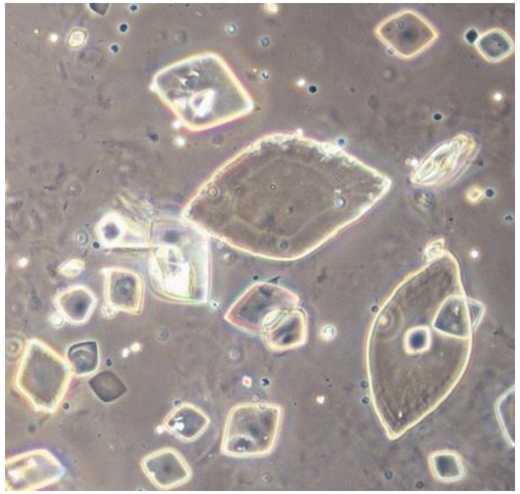
Table 3. Studies evaluating urine microscopy and prognosis of AKI

Study Year (Reference)	Population	Patients (n)	Scoring System	Outcomes	Findings
Chawla *et al.*, 2008 (16)	AKI on renal consult service	18	Grade 1–4[a]	Renal nonrecovery	AUC, 0.79
Perazella *et al.*, 2010 (17)	AKI on renal consult service	197	Score 0 to ≥3[b]	Worsened AKI (increase in AKIN stage, RRT, or death)	AUC, 0.75 Score 1: RR, 3.4 Score 2: RR, 6.6 Score ≥3: RR, 7.3
Bagshaw *et al.*, 2011 (23)	ICU patients with AKI	83	Score 0 to ≥3[c]	A) Worsened AKI B) RRT/death	AUC, 0.85 Score 1–2: OR, 5.6 Score ≥3: OR, 8.0
Hall *et al.*, 2011 (24)	AKI ≥ stage 1	249	Score 0 to ≥3[b]	Worsened AKI (increase in AKIN stage, RRT, or death)	AUC, 0.66; NRI, 24% Score 1: RR, 1.6 Score 2: RR, 2.3 Score ≥3: RR, 3.5

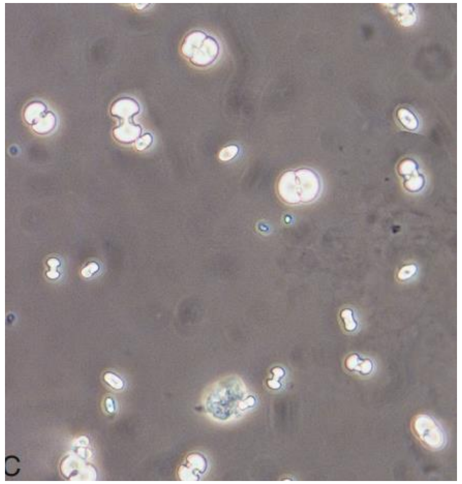
Useful for severity assessment

Perazella MA. *Am J Kidney Dis*. 2015;66(5):748-755.
Perazella MA, Coca SG. *Clin J Am Soc Nephrol*. 2012;7(1):167-174.

Crystals



Uric crystal
- **Rhomboid**/needle
- **Acidic urine** (5-5.8)
- TLS, metabolic syndrome



Ca Oxalate monohydrate
- **Dumbbell/**ovoid shape
- Gastric bypass, ethylene glycol, primary oxalosis, high Vit C, starfruit

Ca Oxalate dihydrate
- **Envelope (bipyramidal)**
- Gastric bypass, ethylene glycol, primary oxalosis, high Vit C, starfruit

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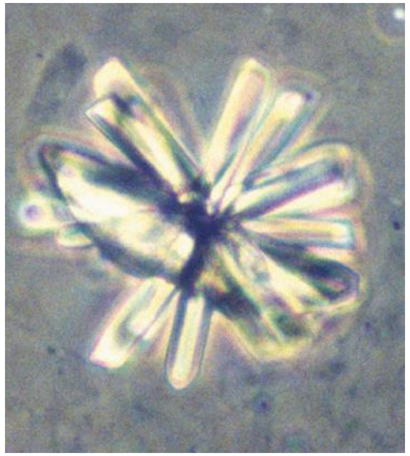
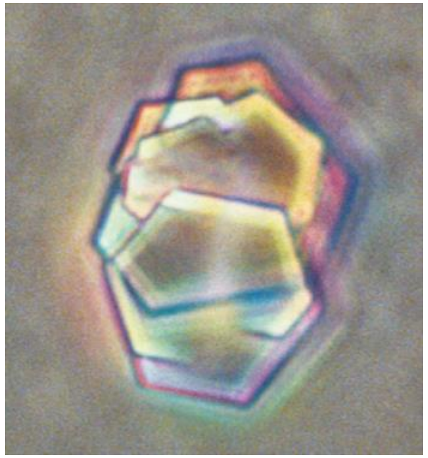
National Kidney Foundation Primer on Kidney Diseases, 8th edition.

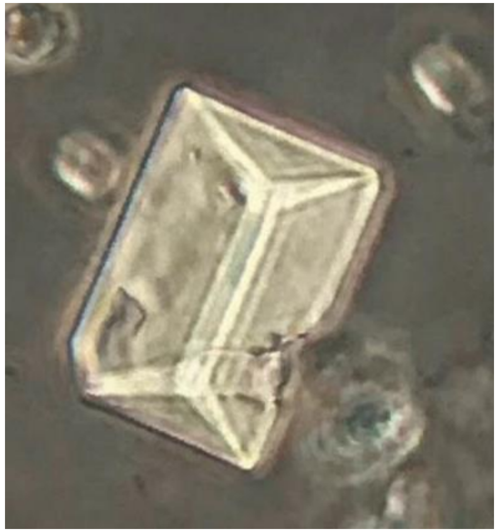
Crystals



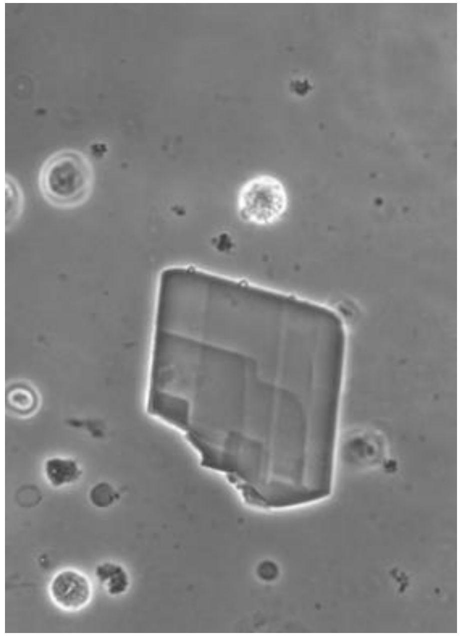
Ca Phosphate crystal (brushite)
- Pleomorphic shape
- **Alkaline urine** (> 7)
- **dRTA**, PHPTH



Cystine crystal
- **Hexagonal**
- Acidic urine
- Cystinuria



Magnesium ammonium phosphate (Triple phosphate/struvite)
- Coffin lid shape
- **Alkaline urine** (> 7)
- **Infection (Proteus, Klebsiella)**



Cholesterol crystal
- thin, transparent plates
- Any pH
- **Normal** or nephrotic syndrome (**lipiduria**)

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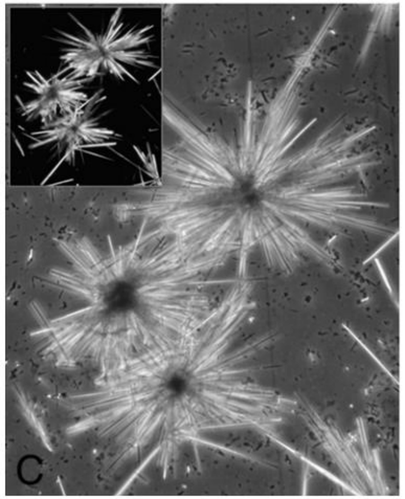
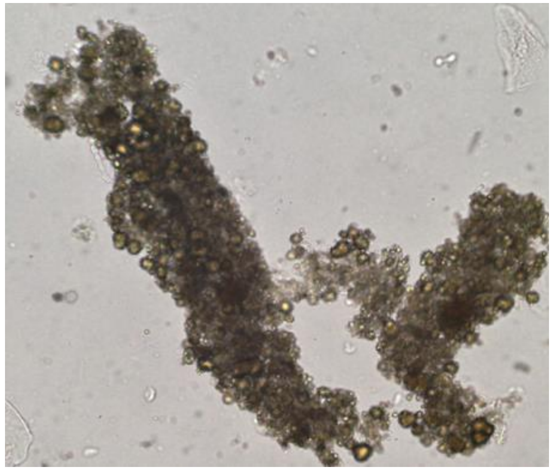
National Kidney Foundation Primer on Kidney Diseases, 8th edition.
Cavanaugh C, Perazella MA. Am J Kidney Dis. 2019;73(2):258-272.

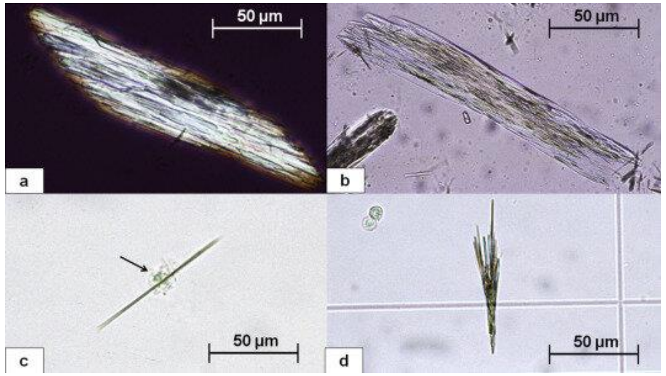
Crystals (drug-crystals)



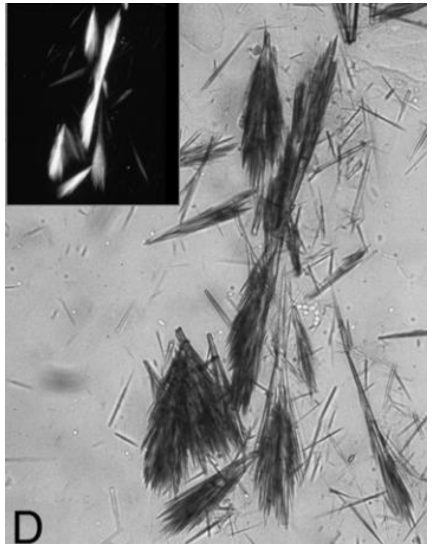
Ciprofloxacin
pleomorphic



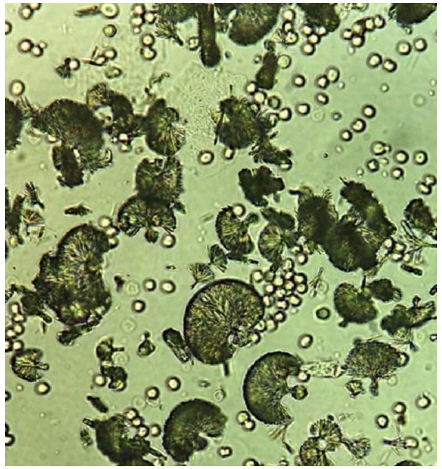
Methotrexate
Golden brown clumps



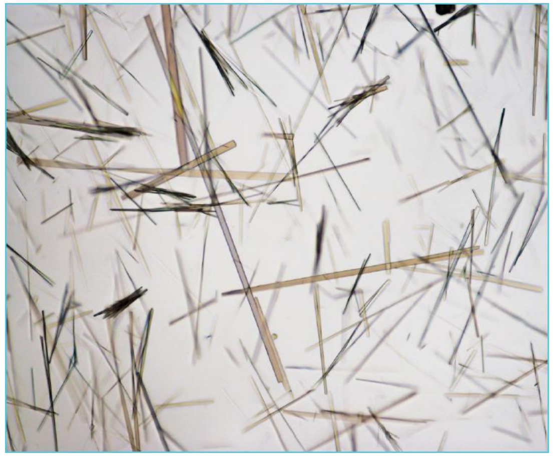
Atazanavir
Needle-like



Amoxycillin
Straw floor broom



Sulfadiazine
Shock of weaves



Acyclovir
Needle with a blunt end

Brenner and Rector's The Kidney, 11th edition.
National Kidney Foundation Primer on Kidney Diseases, 8th edition.
Cavanaugh C, Perazella MA. Am J Kidney Dis. 2019;73(2):258-272.

	Morphology	pH Range	Birefringence
Endogenous			
Calcium oxalate	Monohydrated: colorless ovoid, dumbbells, rods Dihydrated: colorless bipyramidal	5.4-6.7 5.4-6.7	Strong (mono) Weak (di)
Calcium phosphate	Prisms, sticks, needles, stars, rosettes in isolation or in aggregates	6.7-7.0	Strong
Triple phosphate	Trapezoids, prisms, feather-like, "coffin lids"	6.2-7.0	Strong
Uric acid	Amber with variety of shapes: rhomboids, barrels, rosettes, needles, 6-sided plates	5.4-5.8	Strong polychromatic
Cystine	Colorless hexagonal plates with irregular sides	5.5	Weak
Leucine	Yellow-brown spheres with concentric striations	5.5-6.5	Maltese cross
2,8-Dihydroxyadenine	Reddish-brown round with central spicules and dark outline	5.5-7.0	Maltese cross
Tyrosine	Colorless to yellow thin needles in bundles or rosettes	5.5-6.5	Strong
Cholesterol	Thin plates with well-defined edges	5.5	Negative
Ammonium biurate	Yellow-brown spheres with spicules, thorn apples	5.5-7.0	Strong
Calcium carbonate	Dumbbells, thick rods, 4-leaf clover	7.0	Strong
Bilirubin crystals	Yellow needle-like crystals, attach to cell surfaces	5.5	Weak
Drug-Related			
Sulfadiazine	Amber as shocks or sheaves of wheat, shells	5.5	Strong
Acyclovir	Thin needles with sharp or blunt ends	5.5-7.0	Strong
Atazanavir	Thin needles in isolation or as aggregates	6.0-7.0	Strong
Methotrexate	Yellow-brown	5.4-6.0	Strong
Vitamin C (calcium oxalate)	Same as for monohydrated calcium oxalate	5.4-6.7	Strong
Triamterene	Brown and other colors (green/orange/red); spheres	5.5	Maltese cross
Ciprofloxacin	Colorless needles, stars, fans, sheaves	>7.0	Strong
Amoxicillin	Colorless thin needles, broom/brush-like	5.5-6.5	Strong

Alkaline urine crystal
- Ca phosphate
- Triple phosphate
- Atazanavir
- Ciprofloxacin

Pathologic crystal
- Triple phosphate
- Cystine

Cavanaugh C, Perazella MA. Am J Kidney Dis. 2019;73(2):258-272.

Application of urinalysis

Kidney Lesion/Syndrome	Urine Sediment	Urine Dipstick
Prerenal azotemia	Bland, hyaline casts, few finely granular casts, occasional RTECs	−/+ protein
Acute tubular injury	RTECs, RTEC casts, course granular casts, "muddy brown" casts	−/+ protein **Maybe bland**
Acute interstitial nephritis	WBCs, WBC casts, RTECs, RTEC casts, RBCs, occasional RBC casts	−/+ protein, +/++ LE, +/++ blood
Nephritic syndrome	Dysmorphic RBCs (acanthocytes), isomorphic RBCs, WBCs, RBC casts, WBC casts	+/++ protein, ++/+++ blood
Nephrotic syndrome	Lipid droplets, oval fat bodies, birefringent Maltese cross, lipid laden casts, cholesterol crystals	+++/++++ protein
Crystalline nephropathy	Various endogenous or drug-related crystals, RTECs, RBCs, WBCs, some WBCs engulfing crystals	−/+ blood, −/+ LE
Osmotic nephropathy	Swollen RTECs with cytoplasmic vacuoles, RTEC/granular casts	−/+ protein

RPGN: telescopic urine sediment (Dysmorphic RBCs, WBCs, oval fat and broad cast)

Cavanaugh C, Perazella MA. Am J Kidney Dis. 2019;73(2):258-272.

Urine biochemistry

- Urine protein and albumin
- Urine electrolytes and creatinine
- Urine osmolality

Urine biochemistry for AKI

- Urine Na
  - Indirect measure of volume status (effective circulatory volume) and reflects the integrity of the kidney to regulate that status
  - Low urine Na in volume depletion state due to sympathetic and RAAS
  - High urine Na in adequate/volume expanded status due to natriuretic peptide
- FE Na
  - Ratio of Na excretion to filtered Na
  - Na excretion = urine Na x urine flow rate
  - Na filtered = plasma Na x GFR
  - FE Na accounted for Na handling independent of urine concentration

$$
\begin{aligned}
FE_{Na} &= 100 \times \frac{[Na]_{urinary} \times UFR}{[Na]_{plasma} \times GFR} \\
&= 100 \times \frac{[Na]_{urinary} \times UFR}{[Na]_{plasma} \times \left(\frac{[creatinine]_{urinary} \times UFR}{[creatinine]_{plasma}} \right)} \\
&= 100 \times \frac{[Na]_{urinary} \times [creatinine]_{plasma}}{[Na]_{plasma} \times [creatinine]_{urinary}}
\end{aligned}
$$

Brenner and Rector's The Kidney, 11th edition.
Palmer BF, Clegg DJ. Clin J Am Soc Nephrol. 2019;14(2):306-316.

Urine biochemistry

Table 29.5 Urine Indices Used in the Differential Diagnosis of Prerenal Acute Kidney Injury and Acute Tubular Necrosis

Diagnostic Index	Prerenal AKI	ATN
Fractional excretion of sodium (%)	<1[a]	>2[a]
Urine sodium concentration (mmol/L)	<20	>40
Urine creatinine-to-plasma creatinine ratio	>40	<20
Urine urea nitrogen-to-plasma urea nitrogen ratio	>8	<3
Urine specific gravity	>1.018	~1.010
Urine osmolality (mOsm/kg H_2O)	>500	~300
Plasma BUN-to-creatinine ratio	>20	<10-15
Renal failure index, $U_{Na}/(U_{Cr}/P_{Cr})$	<1	>1
Urine sediment	Hyaline casts	Muddy brown granular casts

[a]FE_{Na} may be >1% in prerenal AKI associated with diuretic use and/or the setting of bicarbonaturia or chronic kidney disease; FE_{Na} often <1% in acute tubular necrosis caused by radiocontrast or rhabdomyolysis.

AKI, Acute kidney injury; *ATN*, acute tubular necrosis; *BUN*, blood urea nitrogen; P_{Cr}, plasma creatinine; U_{Cr}, urine creatinine; U_{Na}, urine sodium.

***More accurate in oliguric AKI** ****FE Urea or FE uric in baseline diuretics usage**

Brenner and Rector's The Kidney, 11th edition.

Urine biochemistry ★

Table 1. Limitations of fractional excretion of sodium

Scenarios with FeNa $<$ 1%	Scenarios with FeNa $>$ 2%
normal kidney function with low or moderate salt intake	normal kidney function with high salt intake or IV saline
acute GN	late urinary obstruction
early AIN	late AIN
acute urinary obstruction	glucosuria
transplant rejection	bicarbonaturia
FeNa $<$ 1% despite ATN	**FeNa $>$ 2% despite prerenal AKI**
AKI with liver failure or CHF	use of diuretics
sepsis-associated AKI	CKD
radiocontrast nephropathy	FeNa after IVF therapy
nonoliguric ATN	glucosuria
myoglobinuric ATN	bicarbonaturia
hemoglobinuric ATN	salt-wasting disorders
Causes with renal vasoconstriction (ACEIs/NSAIDs/CNIs/hyperCa/SRC)	**(pre-existing tubulopathy)**
	1° Adrenal insufficiency

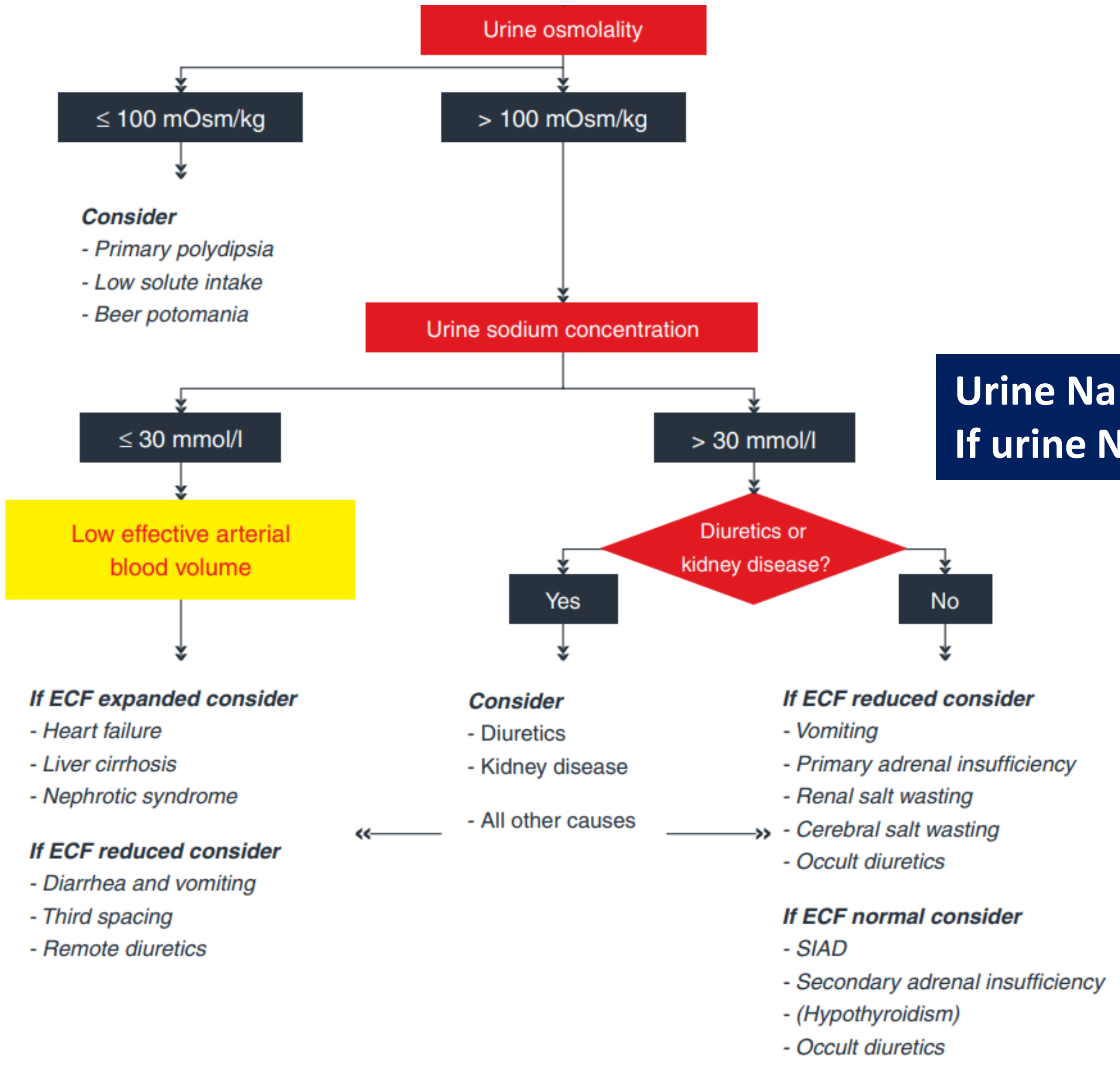
Perazella MA, Coca SG. *Clin J Am Soc Nephrol*. 2012;7(1):167-174.

Urine biochemistry for AKI

- FE urea
  - Urea is mostly reabsorbed at the proximal tubule and diuretics such as furosemide/thiazide affect the more distal part
  - FE urea < 35% suggests low effective circulatory volume
  - Limitation: proximal tubule involvement in
    - Acetazolamide
    - Osmotic diuresis due to administration of mannitol
    - Glycosuria as in uncontrolled diabetes
    - Increased urea excretion resulting from high protein intake or catabolism
    - Elderly patients (down-regulation of urea transport)
    - Sepsis (endotoxin affects urea transport)

Brenner and Rector's The Kidney, 11th edition.
Palmer BF, Clegg DJ. Clin J Am Soc Nephrol. 2019;14(2):306-316.

Urine biochemistry for Hyponatremia



Urine osmolality represents ADH activity
> 100 mOsm/kg = presence of ADH

Urine Na represents an effective arterial blood volume (EABV)
If urine Na < 30 mmol/L = low EABV

EABV ≠ ECF (determined by physical exam)

Spasovski G, Vanholder R, Allolio B, et al. *Eur J Endocrinol*. 2014;170(3):G1-G47.

Urine biochemistry for metabolic acidosis

- Determination of net acid excretion by kidneys
  - Mostly in the form of NH_4^+ > 200 mEq/d (75 mEq/L) in 3-5 days is not available in routine lab
- Indirect measurement of NH_4^+ "net acid excretion"
  - $Cl^- + HCO_3^- + UA = Na^+ + K^+ + UC$ (electroneutrality of urine)
  - $UA - UC = Na^+ + K^+ - Cl^- = UAG$ (assumes HCO_3^- is very low)
  - Urine anion gap is inverted to NH_4^+ (one of the UC)
  - Normal response to acidosis is -20 and abnormal is +20

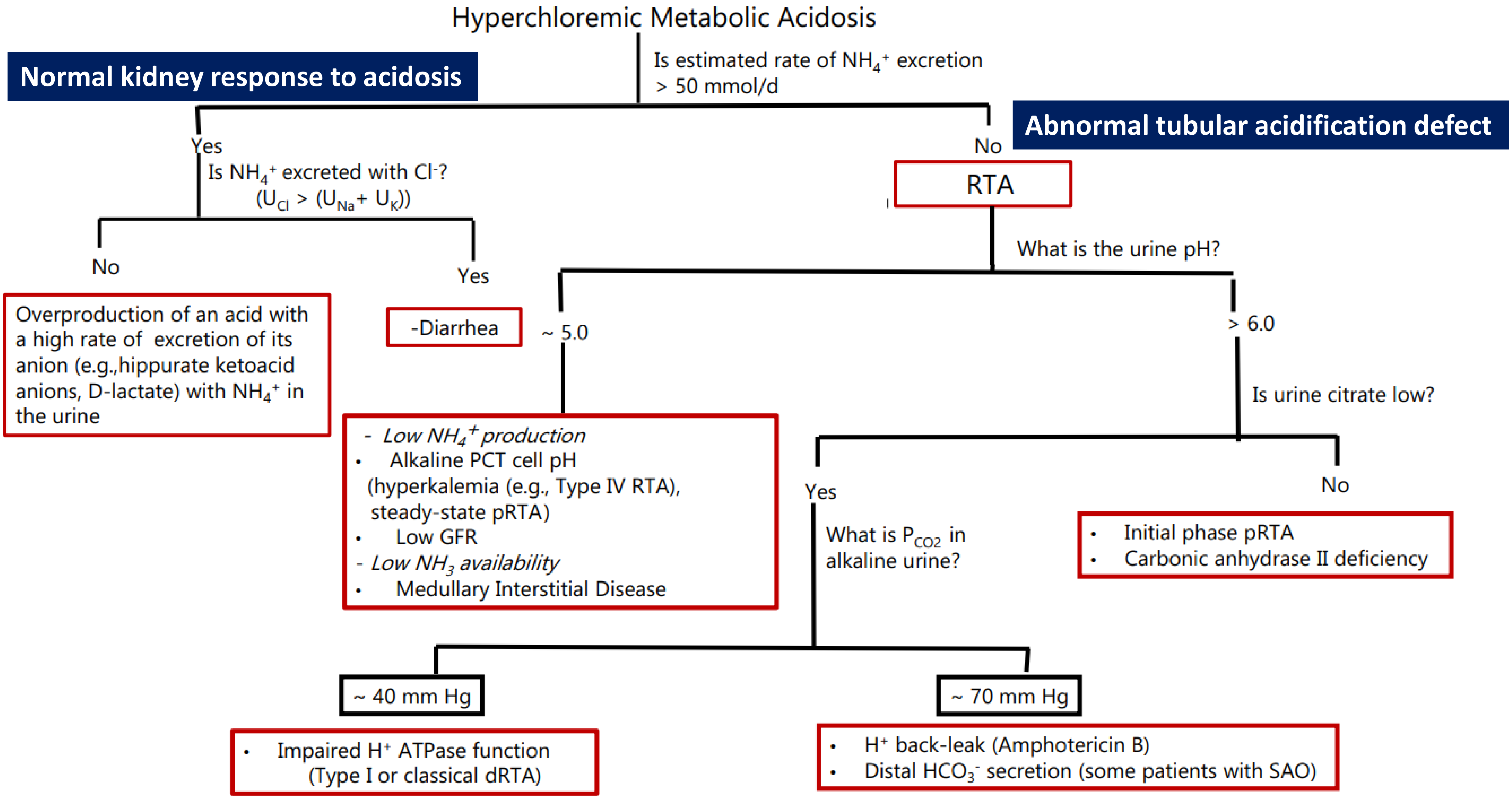
UA: unmeasured anion, UC: unmeasured cation, UAG: urine anion gap

Brenner and Rector's The Kidney, 11th edition.
Palmer BF, Clegg DJ. Clin J Am Soc Nephrol. 2019;14(2):306-316.
Kraut JA, Madias NE. Clin J Am Soc Nephrol. 2012;7(4):671-679.

Urine biochemistry for metabolic acidosis

- Urine anion gap limitations
  - Alteration of UC or UA (Bicarbonaturia/d-Lactate/Hippurate)
  - Low Na flow (< 25 mEq/L)
  - Renal impairment
- Urine osmolal gap (UOG)
  - Assumption of NH_4^+ and its accompanied anion as UOG
  - NH4+ can be calculated from UOG/2, UOG < 150 in acidosis = dRTA
  - Limitations: Unusual compounds (alcohols), high urine Ca/Mg
  - UOG = Measured osmol – 2 (Na+K) – Glucose/18 – Urea/2.8

Brenner and Rector's The Kidney, 11th edition.
Palmer BF, Clegg DJ. Clin J Am Soc Nephrol. 2019;14(2):306-316.
Kraut JA, Madias NE. Clin J Am Soc Nephrol. 2012;7(4):671-679.



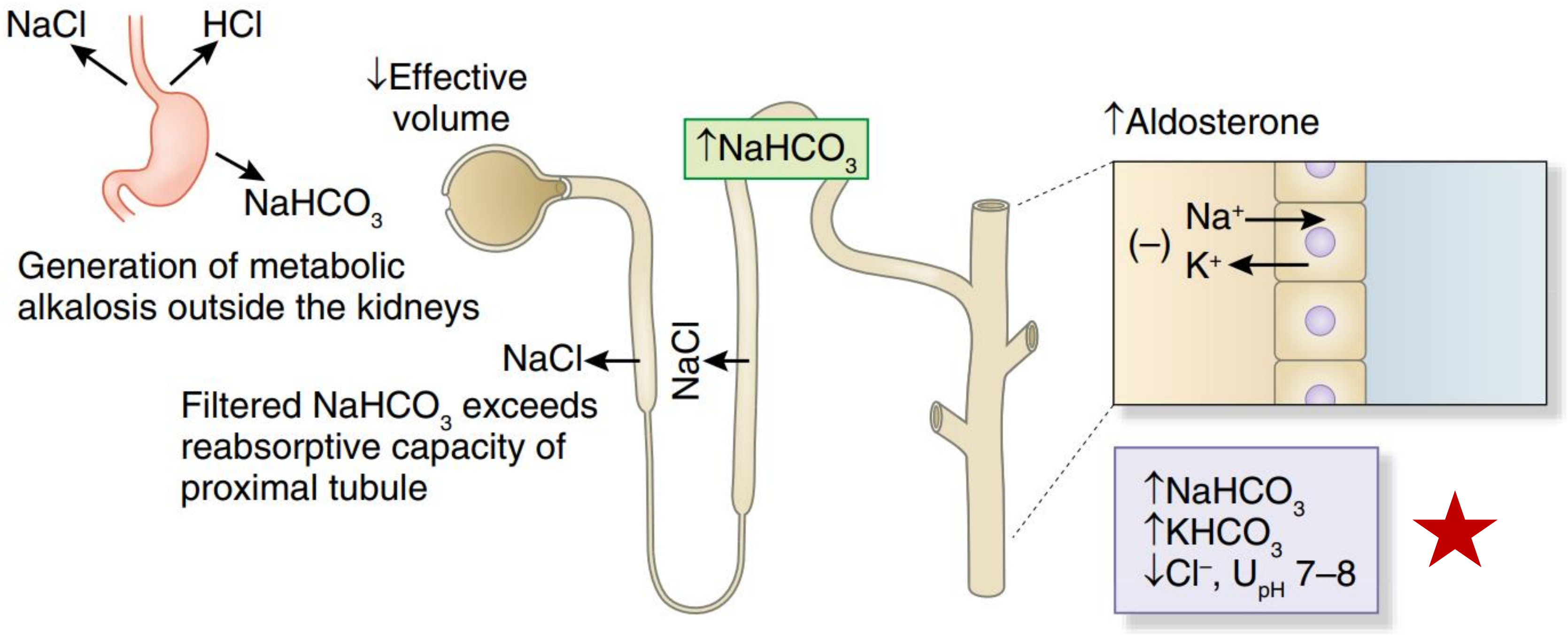
Kamel KS, Halperin ML. *Kidney Int Rep*. 2021;6(5):1211-1224.

Urine biochemistry for metabolic alkalosis

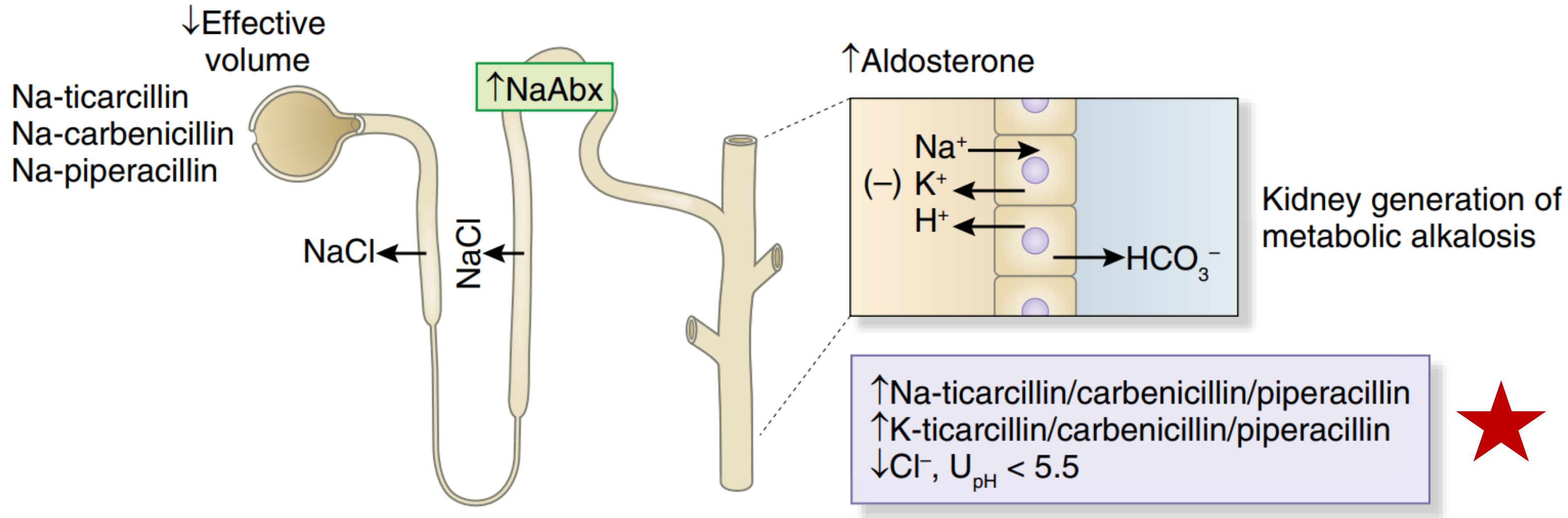
- Urine Cl
  - Urinary excretion of chloride mirrors sodium excretion in response to dietary intake
  - Indirect markers of effective circulatory volume
  - Loss of correlation to urine Na in the presence of increased urine anion or cation
  - Increased urine anion (bicarbonaturia/other unabsorbed anion): Na/Cl ratio > 1.6
  - Increased urine cation (ammonium in diarrhea): Na/Cl ratio < 0.76

Brenner and Rector's The Kidney, 11th edition.
Palmer BF, Clegg DJ. Clin J Am Soc Nephrol. 2019;14(2):306-316.

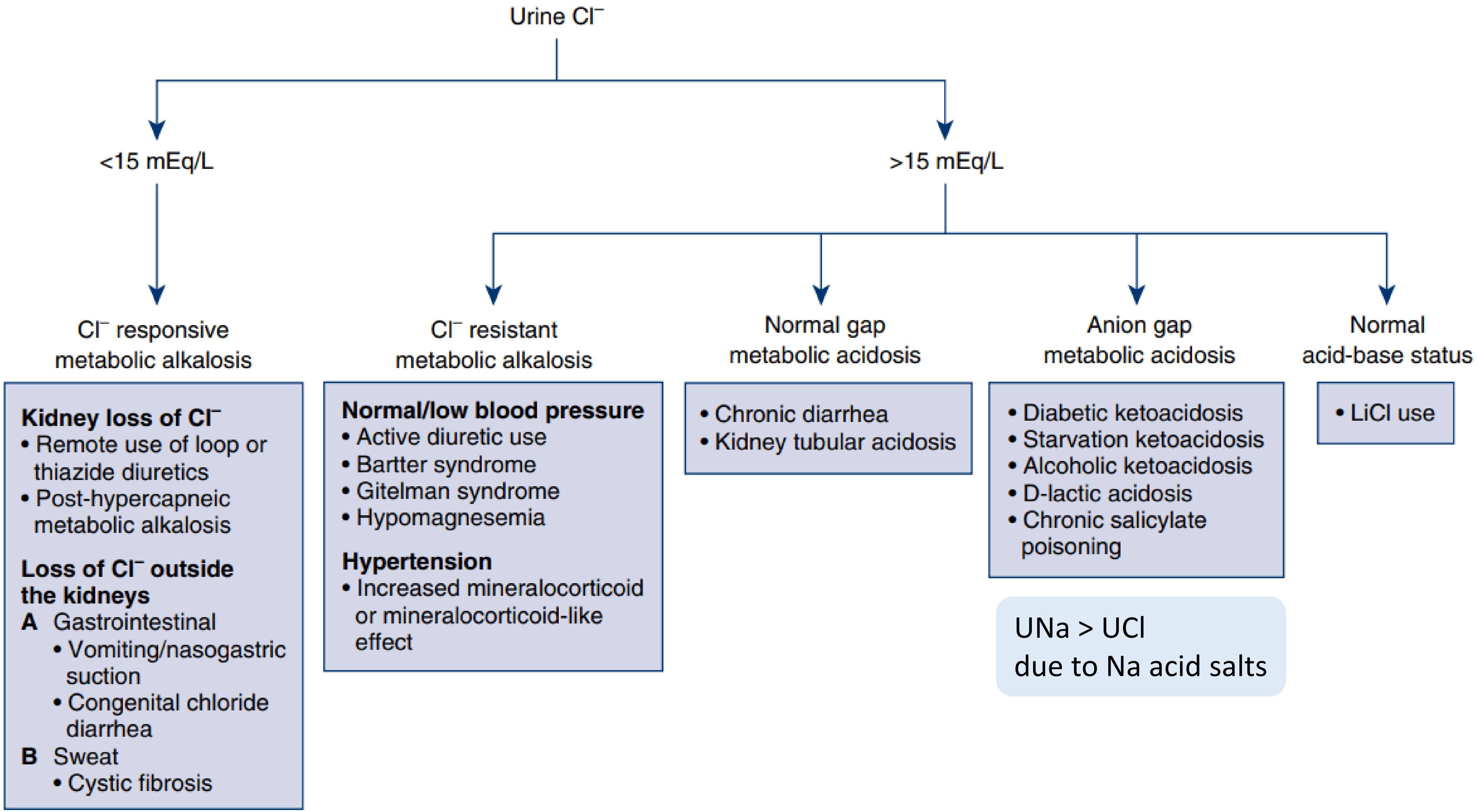
Active vomiting



Non-absorbable anion



Palmer BF, Clegg DJ. Clin J Am Soc Nephrol. 2019;14(2):306-316.



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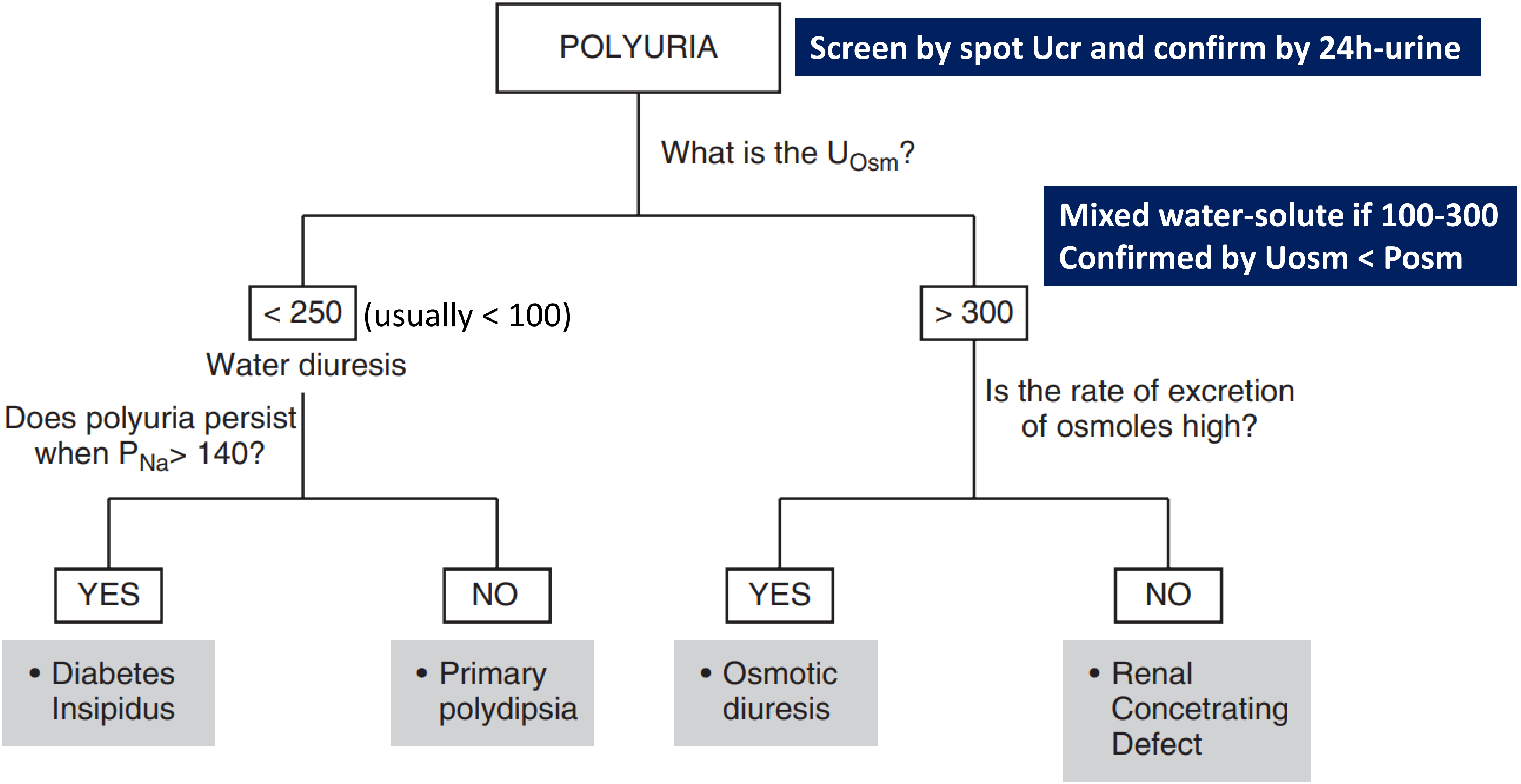
Palmer BF, Clegg DJ. Clin J Am Soc Nephrol. 2019;14(2):306-316.

Urine biochemistry for polyuria

- Urine creatinine for estimation of total urine volume
  - Assumption of total urine creatinine excretion = 1 g/d
  - Urine output (L) = 100/spot urine creatinine (mg/dL)
- Urine Osmolality
  - Differentiates types of diuresis (water <100, mixed 100-300, and solute > 300 mOsm/kg)
  - Normal daily solute intake ≈ 600 – 900 mOsm/kg/d
  - Solute diuresis means daily urine solute excretion > normal daily solute intake (UOP (L) x Urine Osmol) (> 1,000 mOsm/kg/d)

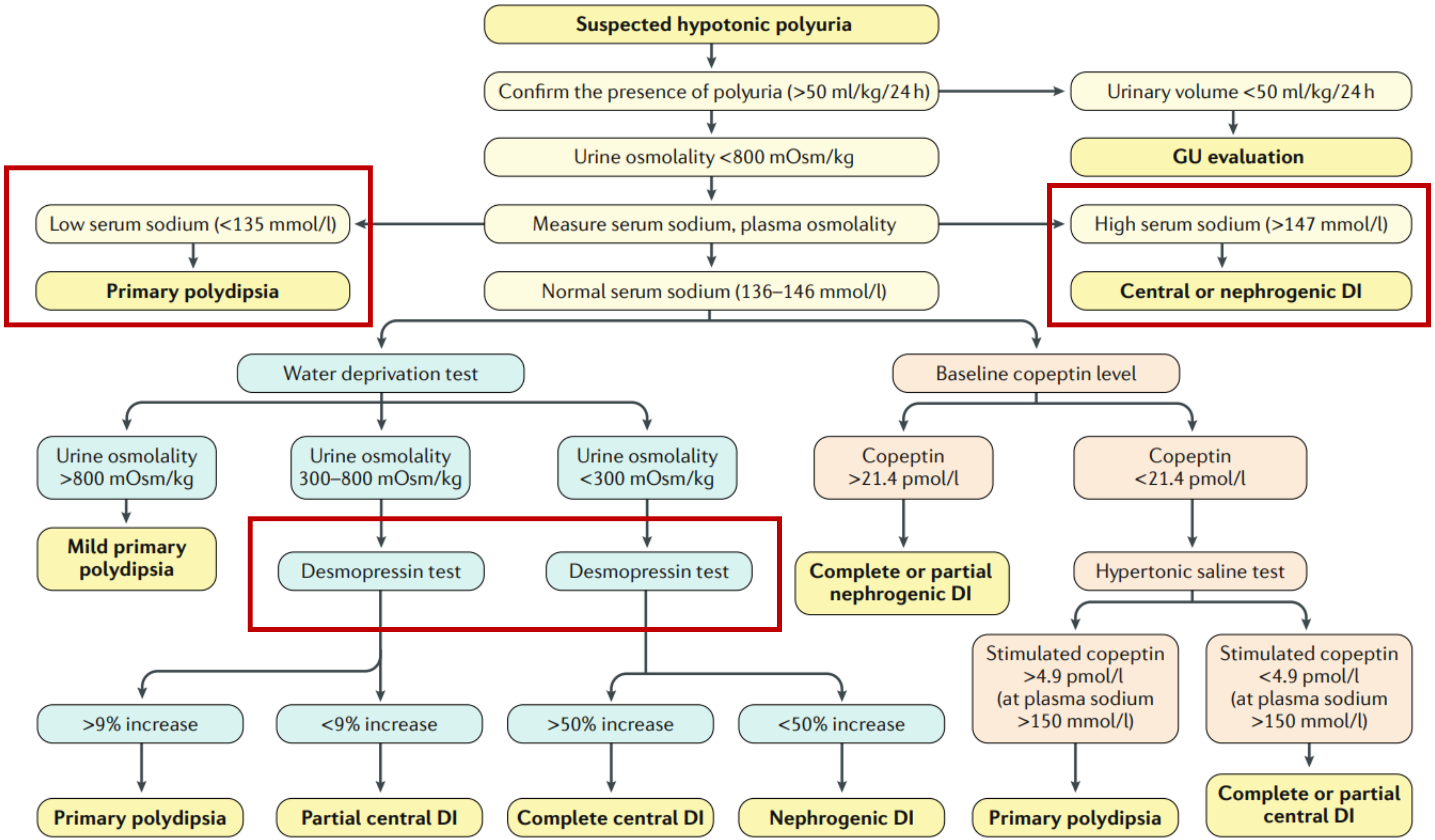
Brenner and Rector's The Kidney, 11th edition.
Palmer BF, Clegg DJ. Clin J Am Soc Nephrol. 2019;14(2):306-316.

Urine biochemistry for polyuria



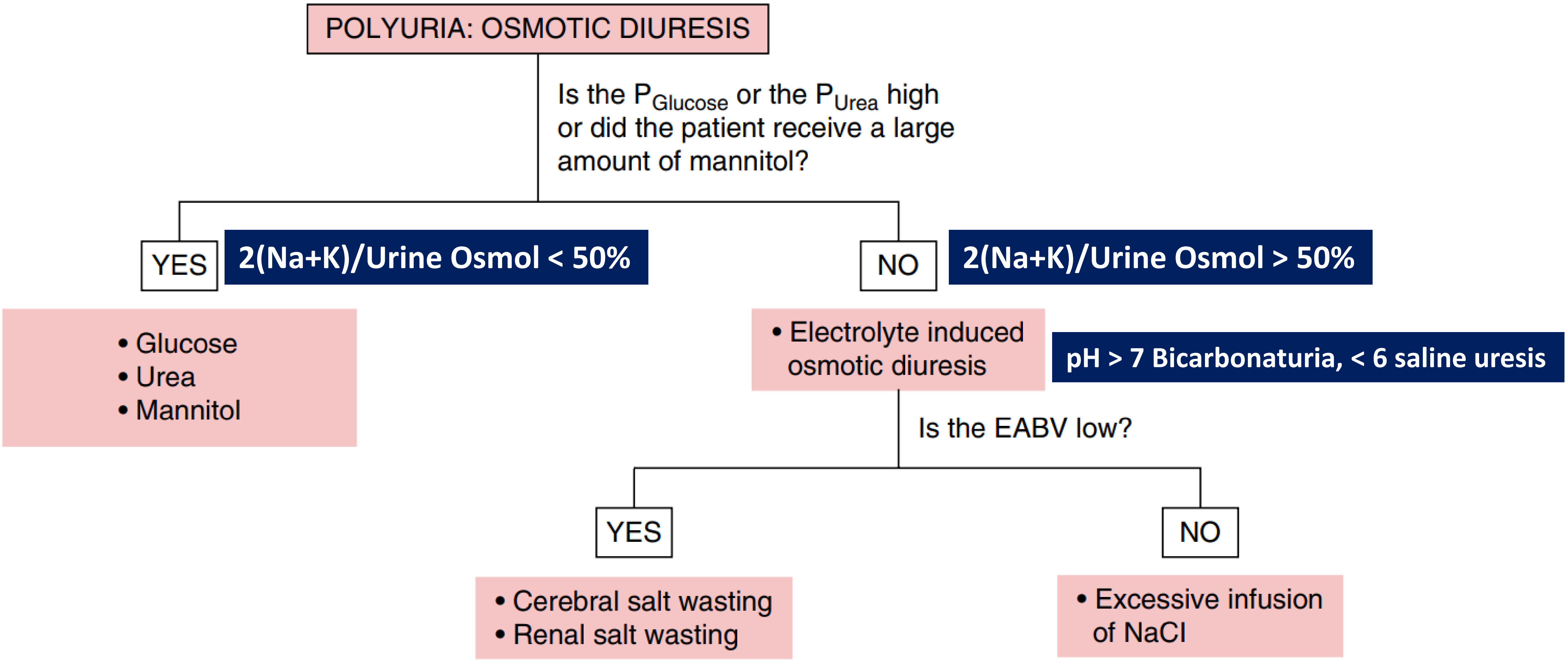
Brenner and Rector's The Kidney, 11th edition.
Fluid, Electrolyte and Acid-Base Physiology, 5th edition.

Urine biochemistry for DI



Brenner and Rector's The Kidney, 11th edition.
Christ-Crain M, Bichet DG, Fenske WK, et al. Nat Rev Dis Primers. 2019;5(1):54.
Palmer BF, Clegg DJ. Clin J Am Soc Nephrol. 2019;14(2):306-316.

Urine biochemistry for solute diuresis



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Fluid, Electrolyte and Acid-Base Physiology, 5th edition.
Palmer BF, Clegg DJ. Clin J Am Soc Nephrol. 2019;14(2):306-316.

TABLE 12-1 DIFFERENTIAL DIAGNOSIS OF POLYURIA

BASIS	KEY FEATURE	DIAGNOSTIC TOOLS
Water Diuresis		
• Primary polydipsia	• $P_{Na} < 136$ mmol/L	• ↑U_{Osm} and ↓urine flow rate if water intake is stopped
• Central DI	• Central nervous system pathology	• ↑U_{Osm} and ↓urine flow rate after dDAVP is given
• Vasopressinase	• Necrotic tissue **(pregnancy)**	• Responds to dDAVP but not to "low-dose" vasopressin
• Nephrogenic DI	• Often caused by lithium **(most common: CKD)**	• No response to dDAVP
Osmotic Diuresis		
• Organic compounds (e.g., urea, glucose) or electrolytes ($Na^+ + Cl^-$ ions)	• $U_{Osm} > 300$ mosmol/L and osmole excretion >1000 mosmol/day	• Calculate osmole excretion rate • Establish nature of the urine osmoles
Renal Concentrating Defect		
• Low osmolality in the renal medulla	• Maximum U_{Osm} is <600 mosmol/kg H_2O • Osmole excretion rate is <1000 mosmol/day	• Diseases or drugs that affect the renal medulla

Fluid, Electrolyte and Acid-Base Physiology, 5th edition.

Thank you for your attention