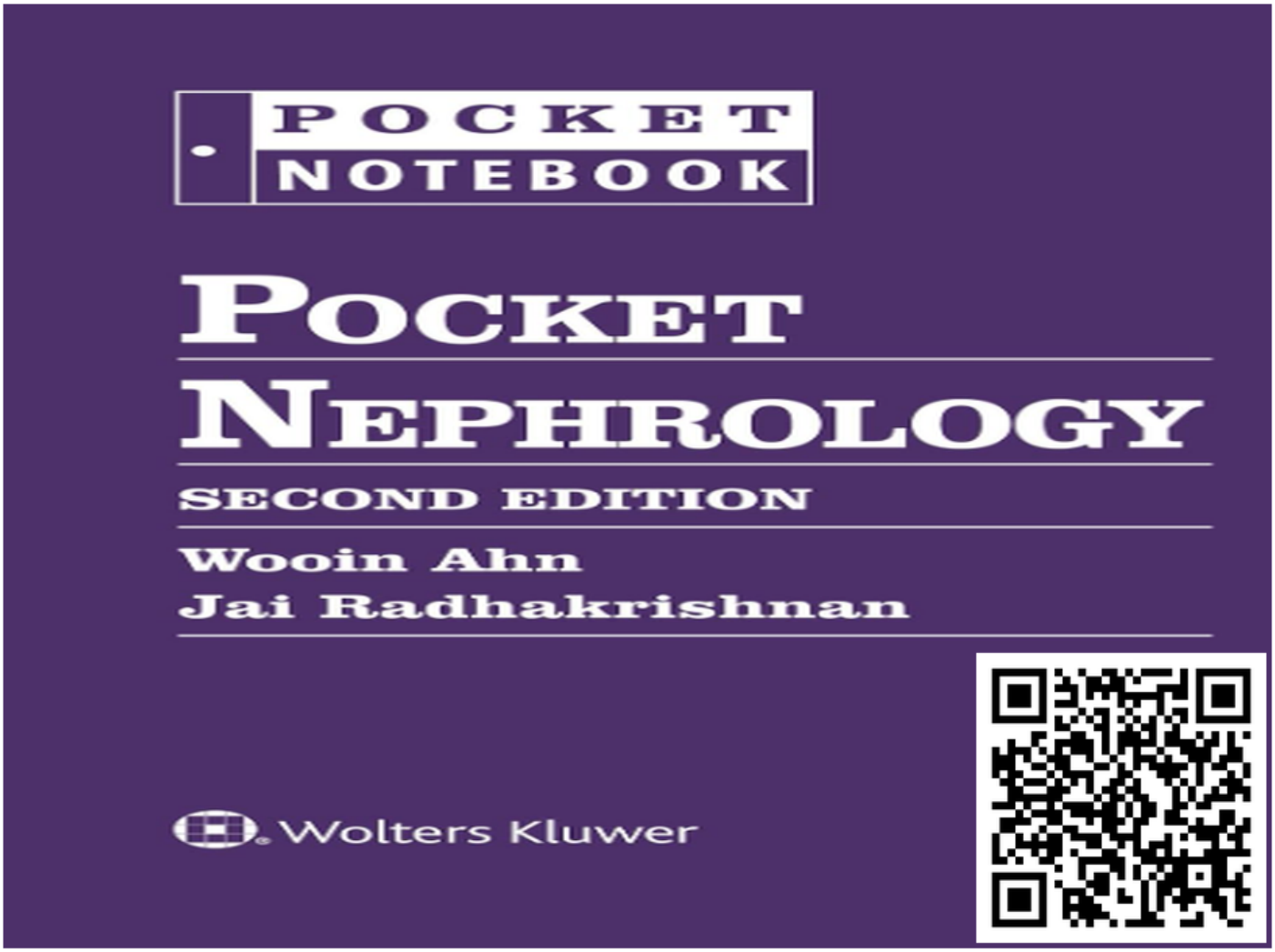

POCKET NOTEBOOK

POCKET NEPHROLOGY

SECOND EDITION

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Edited by

WOOIN AHN

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CONTRIBUTING AUTHORS

Syeda Behjat Ahmad, MD
Clinical Associate Professor, University of Washington

Wooin Ahn, MD, PhD
Associate Professor of Medicine, Oregon Health & Science University

Gerald B. Appel, MD
Professor of Medicine, Columbia University

Farid Arman, MD
Nephrology Fellow, Columbia University Irving Medical Center

Rupali S. Avasare, MD
Associate Professor of Medicine, Oregon Health & Science University

Qais Al-Awqati, MD
Robert Loeb Professor of Medicine, Professor of Physiology and Cellular Biophysics, Columbia University

Andrew S. Bomback, MD, MPH
Associate Professor of Medicine, Columbia University

Pietro Canetta, MD, MSc
Associate Professor of Medicine, Columbia University

Mariana Chang, MD
Nephrology Fellow, Columbia University Irving Medical Center

Jae Hyung Chang, MD
Associate Professor of Medicine, Columbia University

Totini Sagorika Chatterjee, MD
Nephrology Fellow, Baylor College of Medicine

Russell J. Crew, MD
Associate Professor of Medicine, Columbia University

Yelena Drexler, MD
Assistant Professor, University of Miami

Sami Droubi, MD
Nephrology Fellow, Columbia University Irving Medical Center

Geoffrey K. Dube, MD
Associate Professor of Medicine, Columbia University

Josh Earl, MD
Internal Medical Resident, Columbia University Irving Medical Center

Hilda Elena Fernandez, MD, MSCE
Assistant Professor of Medicine, Columbia University

Abdallah S. Geara, MD
Associate Professor of Clinical Medicine, University of Pennsylvania

Heedeok Han, MD
Assistant Professor of Medicine, Columbia University

S. Ali Husain, MD, MPH
Assistant Professor of Medicine, Columbia University

Anushya Jeyabalan, MD
Instructor in Medicine, Harvard University

Sean D. Kalloo, MD, MBA
Associate Professor of Medicine (in Radiology), Columbia University

Pascale Khairallah, MD

Assistant Professor of Medicine, University of California San Francisco

Minesh Khatri, MD
Clinical Associate Professor, NYU Grossman Long Island School of Medicine

Krzysztof Kiryluk, MD, MS
Professor of Medicine, Columbia University

Anna Krieger, MD
Nephrology Fellow, Columbia University Irving Medical Center

Satoru Kudose, MD
Assistant Professor of Pathology and Cell Biology, Columbia University

Pedro Mogrovejo, MD
Nephrology Fellow, Columbia University Irving Medical Center

Sumit Mohan, MD, MPH
Professor of Medicine and Epidemiology, Columbia University

Andrew A. Moses, MD
Assistant Professor of Medicine, Zucker School of Medicine at Hofstra/Northwell

Jordan Gabriela Nestor, MD
Assistant Professor of Medicine, Columbia University

Yonatan Peleg, MD
Assistant Professor of Medicine, Northwestern University

Sindhuri Prakash-Polet, MD
Assistant Professor of Medicine, Columbia University

Jai Radhakrishnan, MD, MS
Professor of Medicine, Columbia University

Soumya Rajendren, MD
Nephrology Fellow, Columbia University Irving Medical Center

Maya K. Rao, MD
Associate Professor of Medicine, Columbia University

Dominick Santoriello, MD
Associate Professor of Pathology and Cell Biology, Columbia University

Shayan Shirazian, MD
Associate Professor of Medicine, Columbia University

Meghan E. Sise, MD, MS
Associate Professor of Medicine, Harvard University

Jacob Stevens, MD
Assistant Professor of Medicine, Columbia University

Mariela Navarro-Torres, MD
Assistant Professor of Medicine, Columbia University

Anthony M. Valeri, MD
Professor of Medicine, Columbia University

Hector Alvarado Verduzco, MD
Instructor in Medicine, Columbia University

Benjamin Wooden, MD
Assistant Professor of Medicine, Columbia University

Teena Zachariah, MD
Assistant Professor, Nephrology, Columbia University

PREFACE

Pocket Nephrology is designed to serve as a concise, yet comprehensive reference for clinicians, trainees, and health care providers involved in the care of patients with kidney diseases. This portable guide distills complex nephrologic concepts into accessible, evidence-based information. Whether in the clinic, hospital, or at the bedside, *Pocket Nephrology* offers a quick reference to essential topics, including diagnostics, therapeutics, and management strategies, making it an indispensable resource for nephrologists and all health care professionals engaged in nephrology care.

WOOIN AHN AND JAI RADHAKRISHNAN

CONTENTS

PROTEINURIA

Albuminuria and Proteinuria (mg/d or mg/g Cr) Categories (KDIGO *KI* 2020;97:1117)		
Category	**Albuminuria**	**Proteinuria**
Normal (nl)	<10	<50
A1: nl to mildly increased	<30	<150
A2: moderately increased	30–300	150–500
A3: severely increased	>300	>500
Nephrotic range	>2,200	>3,500

- ↑ End-stage kidney disease (ESKD) risk w/ UACR 20–200 mg/g in men and 30–300 mg/g in women × 13.0; UACR >200 mg/g in men and >300 mg/g in women × 47.2 (*JASN* 2009;20:1069)

Urinary Proteins		
Protein	**Nl Value/Size**	**Remarks**
Tamm–Horsfall protein (THP; uromodulin)	9–35 mg/d 85 kD	Predominant urinary protein in nl condition Synthesized and secreted in TAL Defense against UTI; inhibit Ca crystallization Present in matrix of casts, including LC cast Gene mutation causes ADTKD
Albumin (alb)	<10 mg/d 69 kD	Predominant serum protein Small proportion is filtered & reabsorbed in PT
Retinol-binding protein (RBP)	<163 µg/d 21 kD	Urine level is ↑ in early stage of graft failure (*AJT* 2013;13:676)
α_1-microglobulin	<19 mg/d 27 kD	Heme-binding protein w/ antioxidant activity Radical scavenger w/ reductase properties
β_2-microglobulin	<100 µg/d 12 kD	Synthesized in all nuclear cells Component of class I MHC ↑ serum level in renal dysfunction, MM, lymphoma Precursor of Aβ2M (dialysis related) amyloid
Other minor proteins (kD): myoglobulin (18), hemoglobin (64), Cystatin C (13), κ (22.5) and λ (45) light chain, vitamin D–binding protein (58), polypeptides		

Low-Molecular-Weight Proteins (<20 kDa)

- Proteins of a size smaller than alb; RBP, α_1, β_2-microglobulin and Ig light chain
- Freely filtered; megalin–cubilin–amnionless complex in PT reabsorbs LMW proteins & alb; urine level ↑ in proximal tubule dysfunction: tubular proteinuria

Workup

Evaluation of Proteinuria		
Test	**Pros**	**Cons**
Dipstick: reaction w/ tetra-bromophenol blue	Sensitive to alb Rapid, cheap Possible home monitoring	Insensitive to LMW proteins; Semiquantitative: affected by urine concentration False ⊕: pH >9 w/ urea splitting organisms
Protein to creatinine ratio (UPCR)	Convenient Correlates w/ 24-h (*NEJM* 1983;309:1543)	Affected by diurnal variation AKI (*KIR* 2025;McCoyl) Less accurate if U_{cr} <39 or >62 (*PLoS One* 2015;10:e0137460)
Albumin to creatinine ratio (UACR)	Sensitive in detecting glomerular lesion	Affected by diurnal variation Will miss non-alb proteinuria
24-h urine protein	Gold standard Can ✓ CrCl together	Cumbersome Over- or undercollection: ✓ w/ creatinine

- Initial proteinuria w/u: ✓ both UPCR and UACR
- Spot urine alb to protein ratio: tubulointerstitial <0.4 (*NDT* 2012;27:1534), <0.54 (*AJKD* 2024;83:557); <0.25: light chain cast nephropathy in monoclonal gammopathy (*CJASN* 2012;7:1964); spot urine protein to alb gap may suggest MM (*AJKD* 2023;81:732)
- Sulfosalicylic acid (SSA): semiquantitatively detects all proteins including LC; add 3% SSA to urine & ✓ turbidity; false ⊕: iodinated contrast, PCN, & ceph.; false ⊖: high pH

Assay Sensitivity of Various Proteins and Substances					
Assay	**Alb**	**LMW Proteins**	**Light Chain**	**Lysozyme**	**Iodinated Contrast**
Dipstick	+	+/–	+/–	+	+
SSA	+	+	+	+	+
Total protein	+	+	+	+	+
Alb	+	–	–	–	–

- Transient proteinuria: by fever, extreme cold, seizure, and exercise; resolves w/o Tx
- Orthostatic proteinuria: common in child and adolescents; benign condition

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Glomerular Proteinuria

- Alb dominant; loss of glomerular filtration barrier and/or endothelial damage
- Albuminuria ↑ ESKD, all-cause and CV mortality (*Circulation* 2002;106:1777; *Lancet* 2010;375:2073)
- Tool to monitor glomerular ds: ↓ proteinuria w/ stable kidney function = remission

General Management

- Low sodium diet: more effective than dual RAASi (*BMJ* 2011;343:d4366)
- ACEi or ARB; non-DHP CCB (*KI* 2004;65:1991)
- BP goal: 125/75 in 24-h UPCR >0.22 a/w ↓ CKD progression (HR 0.73) (*AASK NEJM* 2010;363:918); in ≥1 g/d proteinuria a/w ↓ ESKD after 14 y (HR 0.59) (*JASN* 2017;28:671)

Tubular Proteinuria

- Proximal tubular damage → inability of absorption of filtered LMW protein

- Can be missed w/ dipstick (discordance between UPCR and dipstick)

Acquired Causes
- ATN, tubulointerstitial ds, lead, cadmium, mercury, copper, ifosfamide, tenofovir
- Light-chain proximal tubulopathy: m/c cause of acquired Fanconi synd

Cystinosis
- AR mutations of *CTNS* gene–encoding lysosomal protein **cystinosin**; cystine accumulation in proximal tubular cells (cystinosis); m/c cause of inherited Fanconi synd

Dent Disease
- Type 1: x-linked defect in *CLCN5* gene–encoding Cl^-/H^+ exchanger, **CLC-5**, expressed in the PT and CD intercalated cells → ↓ cubilin and megalin expression → LMW proteinuria
- Type 2: x-linked defect in *OCRL* gene–encoding 4,5-bisphophate 5-phosphatase
- PT damage (unclear mechanism): aminoaciduria, glycosuria, phosphaturia, and hypercalciuria; CaOx/CaP nephrolithiasis/nephrocalcinosis; FGGS (*CJASN* 2013;8:1979)
- Bx: FGGS (83%), mild segmental FPE (57%), focal interstitial fibrosis (60%), interstitial lymphocytic infiltrate (53%), tubular damage (70%) (*CJASN* 2016;11:2168)

Rare Genetic Causes of Tubular Proteinuria
- Donnai–Barrow/facio-oculo-acoustico-renal synds: AR mutation of LDL receptor protein 2 (**megalin**). Hypertelorism, myopia, hearing loss, and proteinuria
- Gräsbeck–Imerslund ds: AR defect in either **cubilin** or **amnionless**. Megaloblastic anemia; B_{12} absorption is mediated by cubilin amnionless complex
- Wilson ds: AR mutation of *ATP7B* gene–encoding copper-transporter, ATPase 2. Accumulation of copper in liver and kidney that can present as renal tubular dysfunction

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Overflow Proteinuria

- The amount of filtered protein exceeding reabsorption capacity
- Causes: light chain cast nephropathy, rhabdomyolysis (myoglobulin, β on UPEP), hemolysis (hemoglobulin), lysozyme-induced nephropathy

Lysozyme-Induced Nephropathy (*AJKD* 2009;54:159)
- Lysozyme (muramidase): small (15-kD) cationic protein produced by monocytes and macrophages; filtered by glomeruli and reabsorbed in the PT, causing injury
- CMML: neoplasm producing mature monocytes; chronic monocytic leukemia, multiple myeloma, sarcoidosis (*AJKD* 2012;59:xxxiii)
- ↑ γ region in SPEP w/ ⊖ SIEP; ⊕ urine dipstick protein; ↑ serum, urine lysozyme
- Overflow proteinuria exceeding PT cell capacity → AKI, hypokalemia AKI, hypokalemia
- LM: eosinophilic protein granules in PT; EM: large prominent lysosomes in PT

Proteinuria After Kidney Transplantation

- Albuminuria (>proteinuria) predicts renal outcome after txp (*AJKD* 2011;57:733)
- Proteinuria is a/w cardiovascular morbidity and mortality (*Transplantation* 2002;73:1345)
- Proteinuria from native kidney rapidly declines after txp (*AJT* 2006;6:1660)
- Causes: transplant glomerulopathy, *de novo* or recurrent glomerular ds, acute rejection
- Bx if unexplained proteinuria

HEMATURIA

- **Hematuria:** ≥3 RBC/HPF on a properly collected specimen (avoid during menstruation)
- Dipstick ⊕, sediment ⊖ for RBC: not hematuria; consider myo- or hemoglobinuria, semen
- **Hemoglobinuria:** caused by intravascular hemolysis (eg, MAHA, transfusion reaction, & PNH) w/ **hemosiderinuria** (Prussian blue ⊕ tubular cells), ↓ hapto, ↑ LDH; May cause Prussian blue ⊕ hemosiderin deposit in PT & tubular injury (*AJKD* 2010;56:780)
- Prevalence of hematuria: 2.4–31.1% in healthy individuals (*J Urol* 2020;204:778)
- Glomerular hematuria may serve as marker of activity in IgAN (*JASN* 2017;28:3089) & ANCA (*CJASN* 2018;13:251); a/w worse kidney outcomes in MCD, FSGS, & MN (*CJASN* 2023;19:56)

- Persistent microscopic hematuria: ↑ CKD (×3.9–8.3) (*AJKD* 2020;76;90; *AJKD* 2023;81:425) & ESKD (×18.5) (*JAMA* 2011;306:729)

Causes of Hematuria	
Origin	**Selected Causes**
Glomerular	IgAN/IgAV, thin basement membrane ds, Alport synd Warfarin-related nephropathy, Loin pain hematuria synd, TMA Any glomerular ds including DN (41%) (*Nephron Clin Pract* 2008;109:c119) and MCD (29%) (*CJASN* 2007;2:445)
Non-glomerular renal	Interstitial nephritis, papillary necrosis, pyelonephritis, BKV infection Cystic ds (PKD, acquired cystic kidney ds), Benign mass Malignancy: RCC, lymphoma, metastasis; hypercalciuria, hyperuricosuria
Nonrenal urinary tract	Nephro/urolithiasis, trauma (catheterization, instrumentation) Prostatitis, BPH, endometriosis, malignancy (TCC, SCC, prostate) Cystitis (infection, chemical, eg, CYC), urethritis
Vascular	Renal artery thromboembolism, renal vein thrombosis, renal AVM, AVF

Clinical Manifestation

Relevant History for Hematuria Evaluation	
Hx and Manifestation	**Potential Causes**
AKI	RPGN, intratubular RBC casts (eg, IgAN)
CKD	Acquired cystic kidney ds
Blood clot	Nonglomerular origin
Recent upper respiratory infection	Postinfectious GN, IgA nephropathy
Sensorineural hearing loss, retinopathy, lenticonus	Alport synd
Heavy exercise	Exercise-induced hematuria/hemolysis
Kidney procedure or injury	Arteriovenous fistula, pseudoaneurysm
Unilateral flank pain	Stone, renal infarction, pyelonephritis
Irritative voiding sxs (frequency, urgency, dysuria), suprapubic pain	Bladder cancer, cystitis
Increased sexual activity, perineal pain, dysuria, terminal hematuria	Prostatitis
Cyclic hematuria a/w menstruation	Endometriosis of urinary tract
Blunt trauma a/w lower rib fractures	Traumatic renal injuries
Excessive anticoagulation	Anticoagulant-related nephropathy
Travel/residence in Africa, the Middle East	Schistosoma hematobium cystitis
Sickle cell ds	Renal infarction, papillary necrosis
Sickle cell trait	Renal medullary carcinoma

- Anticoagulation ↑ hematuria-related complications, bladder ca dx (*JAMA* 2017;318:1260); should continue hematuria w/u for underlying causes (*Arch IM* 1994;154:649)

Gross Hematuria Timing Pattern and Potential Sites	
Timing	**Potential Site of Bleeding**
At the beginning of urination	Urethra
At the end of urination	Prostate gland or the trigonal area of the bladder
Throughout urination	Bladder, ureter, or kidney

Possible Causes of AKI in Hematuria

- Gross and glomerular: intratubular RBC cast and ATN; common in IgAN
- Microscopic and glomerular: crescentic GN, vascular lesion (vasculitis, TMA)
- Gross and nonglomerular: blood clot causing urinary tract obstruction

Workup

- Urine dipstick: detects peroxidase activity of Hb & myoglobin; false ⊖: ascorbic acid
- Supernatant should be clear in hematuria; extreme pH (<5 or >8) can cause RBC lysis
- Squamous epithelial cells ≤2/HPF is properly collected in ♀ (*J Urol* 2022;207:385)
- Urine sediment: RBC casts, >25% dysmorphic RBC: glomerular; >10 RBC/HPF + 2 g/d proteinuria, 93% glomerular, 83% GN (*NDT* 2018;33:1397)
- Proteinuria >0.5 g/d: glomerular; hematuria itself doesn't cause significant proteinuria
- Urine albumin/protein >0.59, w/ urine protein ≥5: glomerular (*AJKD* 2008;52:235)
- Urocrit (Hct test of urine) >1%: urologic; if culture ⊕, re-evaluate 6 wk after tx
- Renal U/S: blood clot can cause hydronephrosis; Doppler study detects AVM and AVF
- Stone protocol (low radiation) CT w/o contrast only if stone is likely cause

Risk of Urothelial Cancer & Recommended Workup of Hematuria (*J Urol* 2020;204:778)		
Low: should meet all criteria	♀ <50 y/o; ♂ <40 y/o; Never smoker or <10 py 3–10 RBC/HPF on a single U/A No additional RFs for urothelial cancer	U/A w/i 6 mo or cystoscopy & renal U/S
Intermediate: any criterion	♀ 50–59 y/o; ♂ 40–59 y/o; 10–30 py smoking 11–25 RBC/HPF on a single U/A Low-risk pt w/ no prior evaluation and 3–10 RBC/HPF on repeat U/A Additional RFs: irritative lower urinary tract sxs, prior pelvic radiation, CYC, ifosfamide, FHx of urothelial cancer or Lynch Sd, occupational exposures to benzene or aromatic amines (eg, rubber, petrochemicals, dyes), chronic indwelling foreign body in the urinary tract	Cystoscopy & renal U/S
High: any criterion	≥60 y/o; >30 py smoking; >25 RBC/HPF on a single U/A; hx of gross hematuria	Cystoscopy & CT urography

- Cytology: very low sensitivity; not recommended for initial w/u (*Ann IM* 2016;164:488)
- 24-hour urine study: detect hypercalciuria, hyperuricosuria

Treatment

- Glomerular hematuria: RASi, kidney bx
- Nonglomerular origin gross hematuria: generous fluid intake to prevent blood clot obstruction of the ureter or bladder; bladder irrigation if refractory
- If urologic w/u is negative, ✓ annual U/A. After 2 negative annual U/A, no further U/A are necessary (*J Urol* 2012;188:2473)

Exercise-Induced Hematuria

- Direct trauma to the kidneys +/– bladder in contact sports; renal ischemia d/t ↑ blood flow to muscles and nutcracker synd in noncontact sports
- Gross or microscopic hematuria after strenuous exercise; resolves w/i 1 wk w/ rest
- Tx: observation; if persists after 1 wk of rest r/o other causes
- ≠ Exercise-induced hemolysis, aka march hemoglobinuria or runner's hemolysis: presents w/ intravascular hemolysis, hemoglobinuria (dipstick ⊕, sediment ⊖)

Hemosiderinuria (Prussian blue ⊕ tubular cells), urine iron loss → IDA

Nutcracker Syndrome (*Mayo Clin Proc* 2010;85:552)

- Clinical manifestations of gross or microscopic hematuria ± left flank pain due to nutcracker phenomenon; common in children and Asians
- Nutcracker phenomenon: LRV entrapment between SMA and aorta → LRV HTN → rupture of thin vein into collecting system; not always cause nutcracker synd
- L Gonadal vein congestion: pain synd/pelvic congestion, varicocele; rarely left RVT
- Dx: Doppler U/S, MRA of LRV
- Tx: stent; transposition of the SMA or LRV, autotransplantation of left kidney

Loin Pain Hematuria Syndrome

- Glomerular hypertension or GBM instability, causing capillary rupture into renal tubules and tubular obstruction (*AJKD* 2006;47:419)
- Recurrent uni- or bilateral flank pain, microscopic or gross, w/ nl renal function
- Urine sediment: dysmorphic RBCs. Kidney bx: RBCs or RBC casts in the tubules
- Tx: RASi; analgesics, celiac plexus block, kidney autotransplantation, renal denervation (*AJKD* 2017;69:156). Unilateral nephrectomy not recommended d/t frequent relapses in the contralateral kidney

URINE OUTPUT CHANGES

Determinants of Urine Output (UOP)

- **Renal function** (glomerular filtration): UOP can be preserved in advanced kidney impairment such as in nonoliguric AKI or stage V CKD
- **Tubular water reabsorption:** directed by ADH-mediated water reabsorption
  - U_{osm}: 60–1,200 mOsmol/kg; correlate w/ ADH activity
- **Urine solute** (mOsmol/d): affected by diet and protein catabolism. 600–900 w/ usual diet
  - If U_{osm} is fixed at 150 (eg, nephrogenic DI), solute should be decreased

    Solute load 600: UOP 600/150 = 4 L
    Solute load 900: UOP 900/150 = 6 L: may lose more water, increasing [Na]
  - If U_{osm} is fixed at 300 (eg, SIADH), solute intake should be increased

    Solute load 600: UOP 600/300 = 2 L: may retain water, decreasing [Na]
    Solute load 900: UOP 900/300 = 3 L

Reduced Urine Output

Oliguria

- Used to define and stage AKI along w/ creatinine elevation

Definitions of Oliguria and UOP Criteria in AKI	
Conventional	<400 or 500 mL/d. If solute load is 600 mOsmol/d and kidney can maximally concentrate urine (1,200 mOsmol/kg), UOP will be 500 mL
RIFLE (*Critical Care* 2004;8:R204)	Risk: <0.5 mL/kg/h for 6 h Injury: <0.5 mL/kg/h for ≥12 h Failure: <0.3 mL/kg/h for ≥24 h or anuria for ≥12 h
AKIN (*Crit Care* 2007;11:R31, KDIGO AKI 2012)	Stage 1: <0.5 mL/kg/h for 6–12 h Stage 2: <0.5 mL/kg/h for ≥12 h Stage 3: <0.3 mL/kg/h for ≥24 h or anuria for ≥12 h

- Consecutive oliguria for a shorter (3–5 h) period may predict AKI risk (*CJASN* 2014;9:1168)
- Oliguria is a/w ↑ mortality (*KI* 2011;80:760), ↑ dialysis requirement, >90 d dialysis and hospital mortality c/t nonoliguric AKI (*Nephron Clin Prac* 2010;115:c59)
- Diuretic use for conversion from oliguria to nonoliguric AKI is a/w worse outcome (*JAMA* 2002;288:2547). Diuretics to be used only in AKI w/ volume overload
- In AKI requiring KRT, urine output w/ cessation of CKRT w/o diuretics is the best predictor of renal recovery (*Crit Care Med* 2009;37:2576)

Can ✓ CrCl when UOP >30 mL/h (720 mL/d) (*NEJM* 2008;359:7)

Anuria

- UOP <100 mL/d; severe AKI, eg, shock, RPGN, renal infarct, bilateral urinary obstruction

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Polyuria

- UOP >3 L/d; frequently present w/ nocturia and polydipsia
- CDI: AVP def; NDI: AVP resistance (*JCEM* 2022;108:1)

Initial Workup and Causes

- ✓ serum Na, Osm, urine Na, K, Osm, volume
- Hyponatremia: 1° polydipsia (U_{osm} <100) or solute diuresis from glc or mannitol (↑ S_{osm})
- Normonatremia: most pts w/ normal cognition and thirst reflex
  U_{osm} >600: solute diuresis; U_{osm} <300: water diuresis
  U_{osm} 300–600: ✓ daily osmolar output: U_{osm} × 24-h UOP
  <900 osm/d: water diuresis, >1,000 osm/d: osmotic diuresis
- Hypernatremia: impaired cognition or thirst reflex, w/ any cause except 1° polydipsia
  U_{osm} >600: correct hypernatremia w/ hypotonic fluid and re✓ U_{osm}
  If remains >600: solute diuresis; 300–600: solute + DI; <300: DI
  U_{osm} <300: DI; proceed to desmopressin test
  U_{osm} 300–600: DI (<900 osm/d) or solute diuresis (>1,000 osm/d)

Causes of Polyuria	
Solute (osmotic) Diuresis	
Sodium	IV fluid: 2 × (U_{Na} + U_K) ≈ U_{Osm}; if << U_{osm}, one of other etiologies: below
Glucose	Uncontrolled DM, SGLT2 inhibitor (SGLT2i)
Urea	Improving AKI, high-protein diet, tissue catabolism, parenteral nutrition
Mannitol	Used to lower ICP
Water Diuresis	
1° polydipsia	High free water intake d/t psychiatric illness, hypothalamic lesions (thirst center); usually present w/ hyponatremia
CDI	Idiopathic, trauma, pituitary surgery, ischemic, familial
NDI	Lithium (chronic), cidofovir, foscarnet, vasopressin antagonists, ifosfamide, demeclocycline Hypercalcemia, hypokalemia Sickle cell ds/trait, Sjögren's, bilateral obstructive uropathy Hereditary: Bartter's, cystinosis, mutations of *AVPR2* (X-linked), aquaporin-2 (AD or AR)
Gestational DI	Release of vasopressinase from the placenta during pregnancy

Water Restriction Test: Workup for Water Diuresis, 1° Polydipsia vs DI

- Indication: normonatremic polyuria to ✓ ADH activity after inducing serum hypertonicity
- Restrict water intake to achieve S_{Na} >145, S_{osm} >295

  U_{osm} <100: ✓ UOP and U_{osm} q1h and S_{Na} and S_{osm} q2h to avoid severe hypernatremia

  U_{osm} 100–600: may perform overnight water restriction
- Required time (hour) = weight (kg) × 30/urine rate (mL/h) (*Endocr Pract* 2018;24:963)
- If the goal is not achieved w/ water restriction, 3% NaCl 0.1 mL/kg/min checking U_{osm}, S_{Na} and S_{osm} q1h
- Interpretation: intact ADH activity, 1° polydipsia if U_{osm} >700; otherwise DI, give desmopressin

Desmopressin Test: Workup for DI, CDI vs NDI

- Indication: U_{osm} <700 after water restriction and hypernatremic polyuria w/ U_{osm} <300
- Give desmopressin 10 mcg IN or 2–4 mcg SC or IV or aqueous vasopressin 5 units SC
- Desmopressin should be given when S_{Na} >145 S_{osm} >295; ✓ Uosm q30min × 2 h

Interpretation of Desmopressin Response		
U_{osm} Elevation	**U_{osm}**	**Interpretation**
<15%	<300	Complete NDI
<15%	>300	Nondiagnostic: 1° polydipsia or partial CDI
15–45%	<300	Partial NDI
15–100%	>300	Partial CDI
>100%		Complete CDI

Copeptin (C-terminal segment of vasopressin prohormone) Assay (pmol/L)	
Intervention	**Interpretation**
Basal	>21.4: NDI (*JCEM* 2015;100:2268)
3% NaCl 250 mL then 0.15 mL/kg/min until S_{Na} ≥150	≤4.9: CDI; >4.9: 1° polydipsia (*NEJM* 2018;379:428; *NEJM* 2023;389:1877)
Arginine 0.5 g/kg over 30 min	≤3.8: CDI; >3.8: 1° polydipsia (*Pituitary* 2022;25:636)

Central Diabetes Insipidus (CDI, AVP Deficiency)

Pathogenesis

- ↓ release of ADH (or AVP) from the hypothalamus
- Idiopathic or autoimmune (30–50%)
- Hypothalamic lesions: tumor, infiltrative ds (eg, Langerhans cell histiocytosis, sarcoidosis, GPA, and autoimmune lymphocytic hypophysitis), trauma, surgery
- Autoimmune ds: IgG4-related ds, GPA
- Familial: AR or AD mutations in ADH gene
  Wolfram synd (DIDMOAD): AR mutation of *WFS1* encoding wolframin, endoplasmic reticulum protein.
  Manifestations: DI, DM, optic atrophy, and deafness; hydronephrosis
- Congenital hypopituitarism, septo-optic dysplasia
- Post-SVT: transient (↑ left atrial and systemic pressure → ↓ secretion of ADH)

Clinical Manifestations

- Polyuria, polydipsia, nocturia, preference for iced water; abrupt onset
- Na high normal range (>142), concurrent stimulation of thirst minimizes water losses
- U_{osm}: <700 after water restriction; ↑ >100% or ↑ 15–100% w/ >300 after desmopressin
- Low bone mineral density: not corrected by desmopressin therapy
- During pregnancy, asymptomatic pts w/ partial CDI start to have sxs d/t vasopressinases released from the placenta
- Surgical or traumatic damage of the hypothalamus has triphasic response: initial polyuric phase (1–5 d ↓ ADH release), antidiuretic phase (6–11 d; release of ADH by degenerating posterior pituitary) followed by permanent CDI or resolution (most cases are not permanent)

Treatment

- Desmopressin: 0.1- or 0.2-mg PO tablet, 60 mcg sublingual, or 5–10 mcg nasal spray preferably at bedtime (to decrease the nocturia), titrate up depending on the nocturia
- Response to intranasal desmopressin is more predictable than PO
- Na should be measured w/in 24–48 h to check for hyponatremia (pt should be educated to decrease free water intake and recognize sxs of hyponatremia)
- Discontinuation of desmopressin can lead to overly rapid correction of hyponatremia
- Thiazide diuretics and NSAIDs (used mainly in NDI)
- Other drugs (less effective, more toxic): chlorpropamide and carbamazepine (enhances renal response to ADH) and clofibrate (↑ ADH release)
- Low-solute (mostly low-sodium, low-protein) diet: for pts w/ partial and mild DI

Nephrogenic Diabetes Insipidus (NDI, AVP Resistance)

Pathogenesis

- Hereditary NDI: V2 receptor (*AVPR2*) (X-linked) and aquaporin-2 gene (AD, AR)
- Chronic lithium toxicity: dysfunction of the aquaporin-2 in the principal cells, defect is often irreversible
- Hypercalcemia and hypokalemia: interference w/ the countercurrent mechanism; ↓ aquaporin-2 expression
- Mild NDI (elderly, AKI, CKD): interference w/ the countercurrent mechanism
- Postobstructive AKI, sickle cell ds or trait, ADPKD, renal amyloidosis, Sjogren's
- Drugs: vasopressin antagonists, cidofovir, foscarnet, amphotericin B, demeclocycline, ifosfamide, ofloxacin, orlistat, and didanosine
- Hereditary tubular synd: Bartter's, cystinosis, familial hypomagnesemia w/ hypercalciuria and nephrocalcinosis

Clinical Manifestations

- Polyuria, polydipsia, nocturia; gradual onset
- Na >142, U_{osm} <700 after water restriction; <300 after desmopressin

Treatment

- A low-solute (low-sodium <2.3 g/d, low-protein ≤1 g/kg/d) diet is sufficient in most pts w/ intact thirst response; medical therapy only if intolerant to polyuria/polydipsia
- Thiazides diuretics: (1) volume depletion → proximal sodium reabsorption → ↓ UOP; (2) inhibition of the urine concentration in the DCT
- Amiloride: added to thiazide (corrects thiazide-induced potassium wasting) or in lithium-induced NDI (blocks lithium entry through ENaC in the collecting tubule cells
- NSAIDs: inhibition of renal PG synthesis, mainly for Bartter-like synd
- Desmopressin can help in some cases of partial NDI

Gestational Diabetes Insipidus (*J Obstet Gynaecol Can* 2010;32:225)

- Polyuria can be d/t release of vasopressinase from the placenta
- Same lab pattern as central DI
- Polyuria response to desmopressin (DDAVP) since it is not inactivated by the vasopressinase (arginine vasopressin is degraded by vasopressinase)
- Transient condition; tx is by increasing access to free water +/– desmopressin

OTHER SYMPTOMS

Causes and Associated Conditions of Urine Change	
Bright red	Nonglomerular hematuria Beets, blackberries, rhubarb, food coloring, fava beans phenytoin, phenolphthalein, doxorubicin, deferoxamine, chloroquine, ibuprofen
Brown, tea, or cola color	Glomerular hematuria, myoglobinuria, hemoglobinuria, choluria (direct bilirubin), levodopa, methyldopa, metronidazole, nitrofurantoin, iron sorbitol, chloroquine, senna
Black	Disseminated melanoma (*NEJM* 2019;380:1166), alkaptonuria (homogentisic acid)
Orange	Vitamin C, carrots, rifampin, phenazopyridine
Pink	Uric acid crystal (*Intensive Care Med* 2013;39:389; *KI* 2012;81:1281)
Bright yellow	Riboflavin (vit B_2)
Green or blue	Methylene blue, amitriptyline, indomethacin, triamterene, Propofol (*Lancet* 2009;373:1462); pseudomonas
Purple	Porphyria (↑ porphobilinogen, porphyrins), purple urine bag synd: *E. coli, K. pneumoniae, Providencia rettgeri, Proteus* (*Clin Interv Aging* 2008;3:729)
Turbid, milky	WBCs, bacteria, fungi; chyluria (*KI* 2006;70:1518) Crystals: uric acid, Ca pyrophosphates and indinavir
Foamy	Alb, non-alb proteins (light chains), amino acids (Fanconi), concentrated urine, amphiphilic metabolites/bile salts (*CJASN* 2019;14:1664)

Urinary Retention

- Definition: inability to voluntarily pass urine
- Normal postvoid residual volume: <50 mL in <65 y/o, <100 mL in ≥65 y/o
- 24% of hospitalized ≥70 y/o pts have urinary retention >150 mL (*Am J Med* 2015;128:77)
- Acute: predominantly in elderly men a/w prostatic enlargement
- Chronic: postvoid residual >300 mL that persisted for >6 mo and documented on 2 or more separate occasions (AUA *J Urol* 2017;198:153)

Causes

- Bladder outlet obstruction: BPH (m/c in ♂), constipation, malignancy (prostate, bladder), urethral stricture, urolithiasis, phimosis, paraphimosis, blood clots (nonglomerular hematuria, eg, kidney bx), urethral diverticulum
  ♀: organ prolapse (eg, cystocele or rectocele), fibroids obstructing the urethra
- Underactive bladder: autonomic dysfunction (DM, Parkinson ds), spinal cord injury, stroke, medications w/ antimuscarinic property

Medications a/w Urinary Retention (*J Am Geriatr Soc* 2012;60:616; *Emerg Med Pract* 2014;16:1)	
Antimuscarinic	Darifenacin, fesoterodine, flavoxate, oxybutynin, solifenacin, tolterodine, trospium, Inhaled ipratropium, tiotropium (♂ only) (*Arch IM* 2011; 171:914)
Antihistamines	Brompheniramine, carbinoxamine, chlorpheniramine, clemastine, cyproheptadine, dimenhydrinate, diphenhydramine, doxepin, doxylamine, hydroxyzine, loratadine, meclizine
Antipsychotics	Chlorpromazine, clozapine, fluphenazine, loxapine, methotrimeprazine, perphenazine, pimozide, prochlorperazine, promethazine, thioridazine, thiothixene, trifluoperazine Atypical antipsychotics (quetiapine, risperidone, olanzapine) a/w AKI (×1.73), urinary retention (×1.98) (*Ann IM* 2014;161:242)
Antidepressant	Amitriptyline, amoxapine, clomipramine, desipramine, doxepin, imipramine, nortriptyline, paroxetine, protriptyline, trimipramine
Antiparkinson	Benztropine, trihexyphenidyl
Muscle relaxants	Carisoprodol, cyclobenzaprine, orphenadrine, tizanidine
Antispasmodics	Atropine, belladonna alkaloids, dicyclomine, homatropine, hyoscyamine products, propantheline, scopolamine
Antiemetics	Hydroxyzine, meclizine, promethazine, scopolamine
Sympathomimetics (α-agonist)	Ephedrine sulfate, phenylephrine, phenylpropanolamine, pseudoephedrine

Diagnosis and Workup

- Bladder scan: postvoid >300 cc diagnostic; 150–300 cc possible retention
- Bladder and renal U/S to r/o hydronephrosis; BMP, urinalysis, urine culture
- Urodynamic study if high-risk: CKD, recurrent UTI, & hydronephrosis (AUA *J Urol* 2017;198:153)

Treatment and Monitoring

- Urinary catheterization: sometimes also diagnostic; indwelling or intermittent
- Bladder decompression may cause transient HoTN; monitor BP, UOP, and Na
- Treat UTI: common complication

Nocturia

- Nocturia: the need to wake at night ≥1 for voiding; ≥2 a/w impaired QoL (*Eur Urol* 2010;57:488)
- Nocturnal polyuria: nocturnal UOP >33% of daily UOP in >65 y/o (>20% in younger adults) of daily UOP w/o global polyuria (>3 L/d)

Causes and Pathogenesis

- Global polyuria (>3 L/d): osmotic (DM, salt) or water diuresis (DI, primary polydipsia)
- Nocturnal polyuria:
  Edema states (CKD, NS, liver cirrhosis, CHF): supine position → mobilization of fluid from the LE to trunk → fluid shift into vascular space → ↑ natriuretic peptide
  High salt intake (*Int J Urol* 2017;24:384)
  Aging: blunted diurnal variation of vasopressin: high at night in normal
  Pelvic floor dysfunction: position change may ↓ pelvic floor musculature support
  Autonomic dysfunction (eg, Parkinson ds): ↓ sympathetic activity
  Evening dose diuretics; excessive drinking in the evening
- Low bladder capacity: postvoid residual (BPH), bladder irritation (cystitis), bladder wall fibrosis, surgery, cancer, stone and detrusor overactivity
- Sleep apnea (*Intern Med* 2016;55:901): wake up d/t sleep disorder ± ↑ atrial natriuretic peptide

Clinical Manifestations

- Low QoL, fall, fracture, death (*J Urol* 2010;184:1413; *J Urol* 2011;185:571), depression (*Urology* 2007;69:691); uncontrolled HTN (*JAHA* 2019;8:e010794)

Workup and Treatment

- Frequency volume chart: polyuria evaluation if present
- Screen for and treat underlying conditions, eg, sleep apnea (STOP-BANG), DM, CHF
- Empty bladder before going to bed, avoid fluid, caffeine, alcohol, & diuretics in the evening
- α-1 antagonist if a/w BPH
- Antimuscarinic, topical vaginal estrogen for postmenopausal ♀
- Desmopressin: refractory nocturia in <65 y/o (*CDSR* 2017;CD012059)

Lower Urinary Tract Symptoms (LUTS) (*J Urol* 2021;206:806)

Types of LUTS (*NEJM* 2012;367:248)

	Obstructive Symptoms	Storage Symptoms
Sxs	Incomplete emptying, weak stream, hesitancy, delay in initiation, intermittency, involuntary interruption, straining, terminal dribbling	Frequency, nocturia, bladder pain Overactive bladder: urgency ± urge incontinence
Causes	All causes of bladder outlet obstruction including: BPH, prostate cancer (♂) Urethral stricture	BPH, prostatitis, epididymitis (♂) Bladder: cystitis, cancer Low bladder capacity, ureterovesical reflux, urethral and meatal stricture Spinal cord injury
Symptomatic txs	**α1 antagonist** (-osin): doxaz-, teraz-, alfuz-*, tamsul-*, silod-* s/e: (orthostatic) HoTN; **α1a** selective drugs (*) may have less ↓ BP	**Antimuscarinic:** oxybutynin, tolterodine, darifenacin, solifenacin, fesoterodine, trospium s/e: urinary/gastric retention, ↑ HR, dry mouth, blurred vision, dementia, brain atrophy (*JAMA Neurol* 2016;73:721)

- β-3 agonist: mirabegron and vibegron; used w/ α-1 antagonist; s/e: HTN

Dysuria

- ♀ >> ♂; common causes include cystitis, urethritis, vaginitis, and prostatitis
- Common organisms causing urethritis (♀): *N. gonorrhoeae, Chlamydia, Mycoplasma genitalium, Trichomonas vaginalis*, HSV
- Other causes: bladder irritating foods (caffeine, spicy foods, high K), ureteral stents, recent urethral procedure, bladder calculi, endometriosis, atrophic vaginitis, urethral strictures
- Symptomatic tx: phenazopyridone (avoid in CrCl <50), antimuscarinics, α-1 antagonists
- Interstitial cystitis/bladder pain synd (IC/BPS): bladder pain, pressure, discomfort a/w LUTS of >6 wk, w/o infection or other identifiable causes (*Neurourol Urodyn* 2009;28:274)
- Tx of IC/BPS: analgesics, pelvic floor physical therapy, amitriptyline, pentosan polysulfate sodium (a/w retinal abnormalities); if refractory ✓ cystoscopy to r/o hunner lesions

Urinary Incontinence

Urinary Incontinence (ACP Guideline *Ann IM* 2014;161:429)		
	Stress Incontinence	**Urge Incontinence**
Sx	Small amount urine loss w/ exertion, sneezing, coughing or laughing Daytime/standing position only	Frequent, small volume voids Inability to make it to the bathroom in time
Causes	Weakened urethral support structures Age, obesity, pregnancy, repetitive pelvic floor stress; radical prostatectomy >TURP; vaginal delivery (*JAMA* 2018;320:2438)	Bladder irritation: infection, inflammation, stone, cancer Stroke, spinal cord injury
Workup	Pelvic examination	Urine culture, cystoscopy
Tx	Pelvic floor muscle training Weight loss/bariatric surgery if overweight (*JAMA IM* 2015;175:1378) Midurethral sling (*NEJM* 2013;369:1124)	Bladder training Antimuscarinic Mirabegron: β-3 agonist (s/e: HTN)

- Mixed incontinence: sxs of both stress and urge urinary incontinence
- Overflow incontinence: urine leakage d/t underactive bladder ± outlet obstruction
- Urodynamic testing: if dx is unclear or to investigate tx failure (*Urol Clin North Am* 2014;41:353)

Xerostomia: Dry Mouth

Causes

- Water deficit, oral infection, uremia (*AJKD* 2003;42:722); Sicca: Sjogren synd, RA
- Radiation, head and neck surgery, oral desiccants (coffee, alcohol, tobacco and cannabis)
- Burning mouth synd: burning sensation in tongue or other oral sites in absence of clinical and laboratory findings (*Am Fam Physician* 2002;65:615)
- Drugs: diuretics, anticholinergics, opioids, antihistamines, phenothiazine

Clinical Manifestations and Treatment

- Altered taste, dysphagia, caries; hyponatremia, polydipsia, ↑ IDWG in HD
- Tx: frequent oral hygiene, ice chips, sugar-free lozenges, artificial saliva

Other Symptoms

Causes of Flank (Loin) Pain	
Parenchymal renal	Pyelonephritis, abscess, complicated cyst, infarction, RVT, renal tumor, IgAN, loin pain hematuria synd, acute interstitial nephritis
Nonparenchymal renal	Nephrolithiasis, strictures, extrinsic compression, bladder outlet obstruction, papillary necrosis
Musculoskeletal	Muscle injury, rib fracture
Neurologic	Herpes zoster, radiculitis
Vascular	AAA rupture, aortic dissection, retroperitoneal hemorrahge
Pulmonary	Pulmonary embolism, basilar pneumonia
Gastrointestinal	Appendicitis, colitis, bowel obstruction, biliary ds
Gynecologic	Ectopic pregnancy, ovarian cyst/torsion

Salt Craving

- Salt wasting: diuretic, Bartter, Gitelman, primary adrenal insufficiency, cerebral salt wasting
- Volume depletion; pregnancy; iron deficiency–associated pica
- Favor pickle juice and salt sachets

Polydipsia: Chronic or Intermittent Ingestion of Large Volumes of Water	
Appropriate Polydipsia	**Primary (Inappropriate) Polydipsia**
DM, DI, chronic hypokalemia	Psychogenic polydipsia, dry mouth, dipsogenic polydipsia (hypothalamic lesions, eg, sarcoidosis), habitual polydipsia (water fasting)
↑ Na if water intake is limited	↓ Na if water intake > water clearance

EDEMA

- Edema: abnormal accumulation of fluid in interstitial space
- Pitting edema: graded by indentation time and depth; not standardized
  1+, immediate 2 mm; 2+, a few s 3–4 mm; 3+, >10–15 s 5–6 mm; 4+, >20 s 8 mm
- Nonpitting edema: caused by hypothyroidism or lymphedema

Causes and Pathogenesis

- **Primary sodium retention**
  CKD: ↓ GFR → inadequate sodium excretion
  Nephrotic syn: RAAS & ENaC activation ± ↓ oncotic pressure
  Drugs: thiazolidinediones, CNI, NSAIDs, GC, fludrocortisone, estrogens
  Insulin: insulin edema, refeeding edema; ↑ NHE3 and Na/K ATPase activity
- **Secondary renal sodium retention w/ arterial underfilling** (*JASN* 2007;18:2028)
  HF and cirrhosis: ↓ effective intravascular volume → RAAS activation
- Severe hypoalbuminemia: usually <2.0, generally a/w relative or absolute hypotension
  NS, kwashiorkor, severe chronic illness (particularly infection)
  Protein losing gastroenteropathy: excessive loss of protein into the GI tract
- **Decreased arteriolar tone** causing increased capillary pressure
  Vasodilators: minoxidil, hydralazine, dihydropyridine calcium channel blockers, clonidine, diazoxide
- **Increased capillary permeability**

Sepsis, burns, allergic reactions (eg, angioedema), preeclampsia, pancreatitis, Idiopathic systemic capillary leak synd (SCLS) aka Clarkson ds
Drugs: IL-2, IL-11, IL-12, gemcitabine, OKT-3, alemtuzumab and rituximab
Engraftment synd, GVHD following allogeneic HCT
Differentiation synd, ovarian hyperstimulation synd
Hemophagocytic lymphohistiocytosis
Viral hemorrhagic fever (hantavirus, dengue), COVID-19 (*Chest* 2020;158:e267)

- Mechanical causes
  Venous obstruction or insufficiency, DVT
  Lymphedema (lymphatic obstruction): lymph node enlargement, mastectomy
- Hypothyroid/myxedema: characterized by ↑ plasma volume, ↓ cardiac output, and ↓ GFR
- Gabapentin, pregabalin (*J Am Geriatr Soc* 2021;69:2842)

Clinical Manifestations

- Evaluate dependent area: lower extremities if ambulatory, sacral area if bed-ridden
- Localized edema at nondependent area: not volume overload/sodium retention
  Face, neck or upper extremities: r/o SVC synd; face, lips and throat: r/o angioedema
- Bilateral/symmetric edema: nonmechanical causes > mechanical causes
- Dyspnea, DOE or orthopnea: HF > CKD > cirrhosis
- Pulmonary edema, serous cavity effusions (pleural, pericardial, peritoneal): in nonmechanical causes
- HTN: CKD > cirrhosis; ↑ JVP, S3 gallop in HF
- Stasis dermatitis & lipodermatosclerosis: in mechanical causes

Workup

- History and physical: relevant new medications; evidence of heart failure, cirrhosis, NS
- NS and CKD: serum creatinine, urine protein: creatinine ratio, serum albumin
- Liver ds: coagulation studies and albumin, abdominal ultrasound
- Heart failure: B-type natriuretic peptide, cardiac ultrasound
- Myxedema: TSH, free T4
- Venous insufficiency: venous LE U/S to evaluate competence of venous valves
- Further evaluation for uncommon causes as dictated by the clinical presentation

Treatment

Treatment of Edema	
Cause	**Treatment**
Sodium retention, volume overload	Loop diuretics ± thiazide diuretics
Severe hypoalbuminemia (<2) in cirrhosis or nephrotic synd	IV albumin (to achieve serum albumin >2.0) + loop diuretics ± thiazides
Mechanical causes	Compression, leg elevation

FLUID IMBALANCE

Fluid Intake

- Water and food intake ~25–35 mL/kg/d; CHO oxidation 200–300 mL/d

Body Fluid Compartments

Estimation by Percentage of IBW			
Body Fluid Compartment	**Young Male**	**Elderly Male, Young Female**	**Elderly Female**
TBW	60	50	45
ICF: 2/3 of TBW	40	33	30
ECF:1/3 of TBW	20	16.7	15
Interstitial fluid: 3/4 of ECF	15	12.5	11.3
Intravascular fluid: 1/4 of ECF	5	4.2	3.8

- Transcellular (1–2 L): synovial, peritoneal, pericardial, intraocular, and CSF

Measurement of Body Fluid Volumes	
Volume	**Indicators**
TBW	Deuterium, tritium, antipyrine
Extracellular	^{22}Na, ^{125}I-iothalamate, thiosulfate, inulin
Intracellular	*Calculate = TBW – extracellular volume*
Plasma	^{125}I-albumin, Evans blue dye
Blood volume	^{51}Cr-labeled RBCs; *calculate = plasma volume/(1-Hct)*
Interstitial fluid	*Calculate = extracellular – plasma volume*

Fluid Loss

- Water turnover: affected by temperature, humidity, physical activity (*Science* 2022;378:909)
- Insensible: respiratory tract, skin 500–700 mL/d → ↑ extensive burns, cold weather, fever, tachypnea, open wounds, ↑ metabolism (>10-fold)
- Sweat: hypotonic, highly variable ~100 mL/d → ↑ exercise, hot climate (1–2 L/h)
- Feces/GI: ~150 mL/d; ↑ diarrhea, NGT drainage fistula
- Urine: main regulator, multiple mechanisms (0.5–20 L/d); also regulates Na, Cl, K

Minimum 0.5 L to excrete 600 mOsm w/ maximal ADH activity (1,200 mOsm/L)

Sodium and Water Imbalance

Manifestation of Salt and Water Imbalance		
	Salt	**Water**
Deficit	Volume depletion	Dehydration/Hypernatremia
Excess	Volume overload	Hyponatremia

Salt and Water Balance and Mechanisms (↓: deficit, ↑: excess)			
Volume Status	**Salt**	**Water**	**Common Mechanisms**
Hyponatremia			
Hypovolemic	↓	↑	Appropriate ADH
Euvolemic	nl	↑	Inappropriate ADH: SIADH
Hypervolemic	↑	↑↑	Heart failure, cirrhosis, CKD
Hypernatremia			
Hypovolemic	↓	↓↓	Loss of hypotonic fluids
Euvolemic	nl	↓	Loss of electrolyte free water
Hypervolemic	↑	nl or ↓	Excessive salt intake

Dehydration (Free Water Depletion)

- Effective osmoles: cannot cross cell membranes w/o transporter activity, eg, Na, K, glucose, and mannitol
- Ineffective osmoles: freely cross cell membranes, do not affect transmembrane water flow, eg, urea and alcohol
- **Osmolality:** the milliosmoles of solutes per 1 kg of water. Osmolality of ICF and ECF are same since water (via aquaporins) can freely traverse plasma membrane

  $$\text{Calculated } P_{osm} = 2 \times [Na] + [\text{glucose (mg/dL)}]/18 + [\text{BUN (mg/dL)}]/2.8$$

  Measured P_{osm} is performed in labs by freezing point depression

  Osmolar gap = Measured-calculated P_{osm}. Osm gap >10 indicates unmeasured osmoles, eg ingestion of alcohols
- **Tonicity:** the ratio of plasma effective osmoles (solutes that do not cross membrane barriers) to plasma water. It dictates the movement of water across a membrane

  $$\text{Approximately } 2 \times [Na] + (\text{glucose [mg/dL]})/18$$
- Dehydration: a loss of TBW, resulting in hypertonicity; ≠ volume depletion
- **Hypernatremia:** [Na] >145, mainly from water deficit, rarely from total body Na or K increase w/ relative TBW deficit
- High urea is hyperosmolar, but not hypertonic; hypernatremia is hyperosmolar and hypertonic

Pathophysiology

- Changes in plasma tonicity >280–289 mOsm/kg are sensed in hypothalamus
  → thirst sensation/water intake and **ADH** increase linearly
  → ADH acts on the V2 receptor on the outer and inner medullary collecting duct resulting in luminal AQP channel placement in a cAMP-dependent manner
  → ↑ water absorption → ↓ tonicity → hypothalamic stimulus is turned off
- Water deficit/hypernatremia results from decreased thirst/water intake +/– decreased renal concentrating capacity (**DI**), although the former is the more common mechanism
- Increased plasma osmolality→ water shift from the intracellular to the extracellular space → cellular shrinkage
- In hypernatremia/hypertonicity, brain cells generate osmolytes to increase intracellular osmolality and counter the increase in extracellular osmolality. **If hypernatremia correction is rapid, iatrogenic cerebral edema can occur** d/t the delayed decrease in intracellular osmolality in brain cells

Clinical Manifestations

- Thirst, oliguria, anorexia, N/V, weakness, fatigue, lethargy, irritability, confusion
- Severity of neurologic sxs related to rate of rise of [Na] than absolute value
- Signs: dry mucous membranes, longitudinal tongue furrows, seizures, coma, ICH (in infants)
- Hypernatremia, ↑ U_{osm}, ↑ Urine specific gravity, relative polycythemia

Workup

- Determine the pt's overall sodium balance (volume status)
- Hypovolemic hypernatremia (negative sodium balance): loss of hypotonic fluids
  U_{Na} >20: renal loss; diuretics, post-ATN, postobstructive, osmotic

U_{Na} <20: extrarenal loss; vomiting, diarrhea, enterocutaneous fistula, sweating, burns

- Euvolemic hypernatremia (normal sodium balance): loss of electrolyte free water
  U_{osm} <300: renal loss, complete DI
  U_{osm} 300–600: renal loss, partial DI, compensated diuresis
  U_{osm} >700–800: extrarenal (cutaneous, respiratory) losses, primary hypodipsia, limited H_2O access, post seizures, severe exercise

Causes of Diabetes Insipidus (DI)	
ADH-Dependent DI	**ADH-Independent DI**
Exogenous vasopressin ↑ U_{osm}	Exogenous vasopressin does not ↑ U_{osm}
CDI: congenital, trauma, neurosurgery, CNS tumor, infiltrative, hypoxia encephalopathy, hemorrhage, CNS infection, aneurysm Gestational DI: vasopressinase mediated	Hereditary NDI: X-linked recessive, complete or partial Acquired NDI: ↑ Ca, ↓ K, lithium, demeclocycline, amphotericin B, foscarnet, methoxyflurane, vaptans, chronic interstitial kidney ds d/t medullary cystic ds, sickle cell ds, amyloid, Sjögren's, malnutrition

Hypernatremia Not Caused by TBW Deficit

- Hypervolemic (positive sodium balance): least common; often iatrogenic after receiving hypertonic fluids, salt poisoning, rarely d/t mineralocorticoid excess
- Intracellular water shift: electroshock-induced seizures & severe exercise, transient

Treatment

- Identify and treat underlying cause and replete water deficit
- Slow correction <0.25 mEq/L/h is a/w mortality × 2.63 (*AJMS* 2011;341:356)
- Rapid correction >0.5 mEq/L/h is not a/w cerebral edema or mortality; a/w better survival rates (*CJASN* 2019;14:656; *JAMA NO* 2023;6:e2335415)
- CDI (AVP-D): desmopressin
- NDI (AVP-R):
  Thiazide: (1) mild volume depletion → ↑ reabsorption → ↓ tubular fluid and urine volume; (2) NCC-independent aquaporin 2 expression (*AJP Renal* 2014;306:F525)
  Low Na and protein diets: decreased urine output and water loss
  NSAID: PGE_2 ↓ AQP2 expression; desmopressin if partial
- Positive sodium balance: diuretics/dialysis; loop diuretics ↑ electrolyte free water loss as well as natriuresis and thus requires ongoing free water replacement

Volume Status Evaluation

Volume Status Evaluation			
	Depletion	**Overload**	**Comments**
Physical Exam	Dry mucus membranes, Prolonged refill time (>3 s), poor skin turgor, orthostatic HoTN	External jugular vein distension (>3 cm above sternal angle), peripheral edema, lung crackles	Peripheral edema present in hypoalbuminemia, lymphatic obstruction, s/e of CCBs etc.
U_{Na}	<20	Variable	Low in CHF and cirrhosis (low effective plasma volume) High in metabolic alkalosis d/t obligate bicarbonaturia: ✓ U_{Cl} High in ATN: impaired tubular function
FE_{Na}	<1%	Variable	High during diuresis, use FE_{Urea} <35%
BUN/Cr	>20	Variable	↑ urea reabsorption in proximal tubule False (+): steroid, GIB, tetracycline
Hb, albumin	↑ (Hemoconcentration)	↓ (Hemodilution)	Confounding: anemia, hypoalbuminemia
U_{osm}, U specific gravity	↑		False (+): dehydration, SIADH
Central Hemodynamics			
CVP (0–6 mmHg)	<4	>10	Poor prediction of fluid responsiveness, overestimated in mechanically ventilation, COPD, abdominal hypertension
PCWP (6–12 mmHg)	<15	>22	
Dynamic Parameters (predicts volume responsiveness) (Following passive leg raising or 250–500 mL IV fluid over 5–10 min)			
Stroke volume or pulse pressure variation	>12% predictive of fluid responsiveness		Limited to mechanically ventilated pts w/ arterial lines
Ultrasound (*POCUS J* 2022;7:65–77)			
IJ diameter	<7 mm	>12.5 mm	
IVC diameter	<1 cm, >12% respiratory variation	>2 cm, no respiratory variation	
Ventricular size	small ventricular cavities, kissing papillary muscles	Dilated cavities	
B lines		>3 lines in a lung zone	

Volume Depletion

Definitions

- **Volume depletion: a deficit in ECF volume,** caused by loss or sequestration of sodium containing fluids
- Effective arterial blood volume: required to maintain effective tissue perfusion
  In nonedematous states (eg, diarrhea and diuresis), it is proportion to ECF volume
  In edematous states (eg, CHF and cirrhosis), ECF and effective arterial blood volume are not proportionate

Pathophysiology

Control Mechanisms of Extracellular Fluid Volume		
Component	**Regulation**	**Effect**
Response to ECF Volume Deficit		
RAAS	↑ renin release at JG apparatus granular cells by: 1. ↓ perfusion pressure at afferent arteriole by baroreceptor 2. ↓ NaCl delivery to macula densa in the TALH 3. β-adrenergic receptor activation	Sodium reabsorption Vasoconstriction
SNS	Activated by ↓ perfusion pressure/stretch at carotid sinus and aorta	↑ HR, BP RAAS activation
ADH	Nonosmotic release of ADH AII ↑ release of ADH	Water retention Vasopressor effect
Response to ECF Volume Excess		
Natriuretic Peptides	Released by stretch at atria and LV	Sodium excretion ↓ renin release

Causes

- GI: vomiting, diarrhea, bleeding, external drainage (while on avg only 150 cc/d, 3–6 L/d are generated by GI tract, normally all resorbed, if GI pathology lose ability to resorb and become volume depleted)
- Renal: diuretics, osmotic diuresis, salt wasting nephropathies, hypoaldosteronism
  In healthy kidney, 120–180 L/day filtered across glomerulus w/ >98% resorbed, if there is even a mild tubulopathy w/ even a slight ↓ in resorptive capacity, this will result in volume depletion (seen in chronic interstitial ds)
- Skin: 1–2 L/h can occur in hot/dry climate; burn
- Hemorrhage; sequestration into a third space: GI catastrophes (pancreatitis, obstruction, peritonitis), crush injuries

Clinical Manifestations

- Weight loss, orthostatic dizziness, oliguria, muscle cramps, agitation, thirst, confusion
- Orthostatic hypotension, ↑ HR: progress to supine hypotension ↑ HR
- Diminished skin turgor (less reliable in the elderly), delayed capillary refill
- Organ ischemia: nonocclusive mesenteric ischemia
- Hypovolemic shock: cold, clammy extremities, cyanosis, pulsus paradoxus (↓ SBP ≥10 during inspiration; DDx: cardiac tamponade, constrictive pericarditis)

Diagnosis

- Fluid responsiveness: improvement of stroke volume/cardiac index following a fluid challenge is diagnostic of volume depletion
- Hx including weight change
- Physical examination: insensitive (*JAMA* 1999;281:1022; *J Crit Care* 2013;28:537.e1)

Static Assessments

- CVP/PAWP: did not predict fluid responsiveness (*Chest* 2008;134:172; *Crit Care Med* 2013;41:1774)

- PAC/PCWP-guided therapy in CHF (*JAMA* 2005;294:1625), ARDS (*JAMA* 2003;290:2713), and acute lung injury (*NEJM* 2006;354:2213) did not improve survival

Dynamic Assessments may be more indicative of volume responsiveness and potentially improve clinical outcome (*Crit Care Med* 2017;45:1538)

- Pulse pressure variation (PPV) (*AJRCCM* 2000;162:134; *Crit Care Med* 2009;37:2642)
- Stroke volume variation (SVV) (*Br J Anaesth* 2008;101:761; *Anesth Analg* 2009;108:513)
- Passive leg raising: semirecumbent position w/ 45° elevation of upper part of body → lower upper body and elevate leg at 45° × 1 min: brings 300–500 cc to the heart; ↑ CO and ↑ SVV and PPV predict fluid responsiveness (*Ann Intensive Care* 2011;1:1; *Crit Care Res Pract* 2012;2012:513480)
- IVC respiratory variation (*Intensive Care Med* 2004;30:1834; *Intensive Care Med* 2004;30:1740)

Treatment

- Rapid 1–2 L of isotonic fluid to restore tissue perfusion if there is evidence of shock
- Not possible to precisely predict the total fluid deficit for a given pt, clinical signs such as BP, MAP, UOP, MS, peripheral perfusion can guide adequacy of resuscitation

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Volume Overload

Background and Clinical Implication

- Volume overload: ECF sodium and ECF volume excess
- a/w longer ICU stay and mortality (*Crit Care* 2013;17:R288)
- In septic shock, a/w ↑ mortality (*VASST Crit Care Med* 2011;39:259)
- In decompensated HF, hemoconcentration (measured by ↑ protein, albumin, Hct by diuresis is a/w ↓ eGFR, but ↑ survival) (*Circulation* 2010;122:265)
- In acute lung injury, conservative management targeting CVP <4, PCWP <8 was a/w improved oxygenation index increasing ventilator-free and ICU free days c/t liberal management targeting CVP 10–14 or PCWP 14–18 (FACTT *NEJM* 2006;354:2564).
- In AKI a/w ↑ mortality × 2.07 (*KI* 2009;76:422), ↓ renal recovery (*KI* 2009;76:422; *NDT* 2012;27:956)
- In CKD a/w rapid progression (*AJKD* 2014;63:68)
- Volume overload at the RRT initiation is a/w mortality (*Crit Care* 2012;16:R197)
- Hemodilution may lead to underestimation of the severity of AKI (*Crit Care* 2010;14:R82)

Pathophysiology

- Appropriate response: ↑ stretch at cardiac receptors (atria and ventricle) → atria release ANP, ventricles release BNP → natriuresis
- **Heart failure:** ↓ cardiac output → ↓ perfusion pressure → low effective arterial blood volume → ↑ SNS and RAAS activation
- **Cirrhosis:** vasodilatation → ↓ perfusion pressure → low effective arterial blood volume → ↑ SNS and RAAS activation
- **Nephrotic synd:** ↓ oncotic pressure → ↓ tissue perfusion → low effective arterial blood volume → ↑ SNS and RAAS activation (underfill); 1° Na retention (overfill)
- Chronic kidney ds: blunted response to rapid sodium intake

Clinical Manifestations

- ↑ weight, ↑ BP, JVD, orthopnea, paroxysmal nocturnal dyspnea, nocturia
- Peripheral edema: pretibial and ankle in ambulatory; sacral in bedridden pts; periorbital edema in nephrotic synd

Consequences of Fluid Overload in Organs	
Lungs	Pulmonary edema (rales), pleural effusion
CVS	↑ filling pressure, ↓ cardiac output, conduction disturbances, vasodilation
GI	Ascites, gut edema, malabsorption
Liver	Congestive hepatopathy
Skin, soft tissue	Wound infection, poor wound healing, pressure ulcer
CNS	Cerebral edema, delirium
Kidney	Interstitial edema, ↑ renal venous congestion → ↓ renal function

- Hyponatremia: ↓ tissue perfusion in HF, cirrhosis → ↑ ADH
- Hypoalbuminemia: ↑ urinary loss in the NS, ↓ synthesis in cirrhosis, dilutional; dilutional anemia
- ↑ PCWP >22 mmHg; ↑ BNP, NT-proBNP: cleared by kidney; less reliable in CKD;
- Thoracic ultrasound: B lines (aka comet-tail images) (*Chest* 2005;127:1690)

Treatment

- Monitor volume status; ✓daily fluid balance and weight
- Address underlying cause and treat appropriately
  HF: neurohormonal blockade
  Cirrhosis: antivirals/immunosuppression depending on etiology
  NS: immunosuppression/RAAS inhibition
- Low salt diet: restrict dietary Na intake to <2 g (87 mEq) per day
- Avoid drugs a/w Na retention: NSAIDs, GC, fludrocortisone, thiazolidinediones, diazoxide
- Diuretics based on underlying conditions
- Adjust dose to achieve threshold dose: if weight loss is not achieved, can ✓24-h urine urinary Na excretion OR 1–2 h post loop diuretic FE_{Na}
  - If U_{Na} >100 mEq/d or FE_{Na} >2%: effective diuretics; ↓ salt intake
  - If U_{Na} <100 mEq/d or FE_{Na} <2%: ineffective diuretics; ↑ diuretic dose
- In severe hypoalbuminemia (eg, cirrhosis w/ ascites or nephrotic synd), albumin-assisted diuresis may be used (*JASN* 2001;12:1010; *Saudi J Kidney Dis Transpl* 2012;23:371)
- In decompensated HF, it is essential to maintain BP to ensure tubular delivery of furosemide (*NEJM* 2011;364:797). Inotrope-assisted diuresis can be considered in low output and congestive status in severe LV systolic dysfunction
- If refractory consider dialysis initiation

Fluid Imbalance in ESKD

Background

- Volume depletion: a/w loss of vascular access and residual renal function (*CJASN* 2010;5:1255); hypotension, death (*JASN* 2015;26:724)
- Volume overload: a/w LVH and death (*Circulation* 2009;119:671; *JASN* 2017;28:2491)
- Postdialysis weight >2 kg above and below target weight a/w mortality (*CJASN* 2015;10:808)

Dry Weight (DW)

- The lowest tolerated postdialysis weight at which there are minimal signs or sxs of either hypovolemia or hypervolemia (*Semin Dial* 2009;22:480)
- Normal blood pressure s/p iHD can be used to assess euvolemia, but this requires the pt to not be on any other antihypertensive which is rare in HD pts
- Needs to be re-evaluated periodically to follow muscle weight change
- Over-estimated DW: may cause pulmonary edema and HTN
- Under-estimated DW: weakness, cramps, and hypotension

DW Assessment

- Physical examination is the mainstay but BP, JVP and edema may not correlate well w/ volume status (*KI* 2020;97:861)

- Bioimpedance: applying electrodes to the skin and estimating volume status by measuring resistance encountered by an electrical current passed through the body's tissues; not FDA approved in the U.S. (*NDT* 2008;23:808, *KI* 2014;86:489)

Relative Blood (or Plasma) Volume Monitoring

- Blood volume estimation w/ continuous Hct measurement
  Volume overload: continuous transfer of fluid from interstitial to intravascular compartment during UF → stable Hct, flat curve
  Volume depletion: refill rate from the interstitium to intervascular space lags behind the UF rate → ↑ Hct
- More hospitalization and mortality than conventional care (*JASN* 2005;16:2162)
- No ↓ intradialytic hypotension (*CJASN* 2017;12:1831)

Treatment (*AJKD* 2014;64:685)

- The normalization of the ECF volume is a primary goal of dialysis ("volume first")
- In HD, fluid removal should be gradual: ↓ interdialytic weight gain, Tx duration ≥4 h, UF rate <10–13 mL/kg/h; excessive UF during routine HD a/w morbidity and mortality (DOPPS *KI* 2006;69:1222; HEMO *KI* 2011;79:250; *AJKD* 2016;68:911)
- Avoiding intradialytic sodium loading: sodium profiling ↑ mortality (*CJASN* 2019;14:385)
- Low dialysate Na a/w ↓ IDWG but ↑ intradialytic hypotension (*JASN* 2020;31:1078)
- Dietary counseling: low sodium diet; fluid restriction
- High-dose loop diuretics: if urine output >200 mL/d; ↓ interdialytic weight gain, UF amount, and intradialytic hypotension (*CJASN* 2019;14:95)

HYPOTENSION & SHOCK

Definition of Hypotension & Shock

- HoTN: absolute (SBP <90, MAP <65) or relative (drop in SBP >40 from baseline)
- Intradialytic HoTN: symptomatic ↓ SBP or a nadir intradialytic SBP <90 (*KI* 2020;97:861)
- Shock: HoTN a/w tissue hypoxia d/t inadequate oxygen delivery or impaired oxygen utilization or a combination of these

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Hypotension-Induced AKI

- NI autoregulation: HoTN, ↓ perfusion pressure → PG-mediated afferent arteriole dilation, & AII–mediated efferent arteriole constriction → maintained GFR
- PG inhibition (eg, NSAID) and RASi impair autoregulatory mechanisms
- If perfusion pressure drops below the autoregulatory range, endogenous vasoconstrictors & endothelial cell injury ↑ afferent arteriolar resistance → ↓ glomerular capillary pressure → ↓ GFR
- If autoregulation is impaired, renal perfusion is dependent on MAP (*KI* 1994;46:318)
- Systemic arterial vasodilation from distributive shock (eg, sepsis) and liver cirrhosis ↓ renal perfusion and GFR ± systemic HoTN
- Persistent renal hypoperfusion leads to tubular cell injury (ATN)

Shock

- Most commonly occurs when there is reduced tissue perfusion in setting of HoTN

Types of Shock and Physiologic Characteristics (Parameter: Normal Range)				
Types: Causes	**Preload** (PCWP: 6–12 mmHg)	**Pump Function** (CO: 4–8 L/min, CI: 2.5–4.0 L/min/m^2)	**Afterload** (SVR: 700–1,500 dynes/sec/cm^5)	**Tissue Perfusion** (S_vO_2: 70–75%)
Hypovolemic: fluid loss, hemorrhage	↓	NL or ↓	↑	NL or ↓
Distributive: septic, anaphylactic, neurogenic, adrenal insufficiency, thyroid dysfunction, burns, trauma, pancreatitis, postop vasoplegia	NL or ↓	NL or ↑	↓	↑
Cardiogenic: MI, CHF, arrhythmia, valve rupture, VSD, critical valvular stenosis, dissection, myocarditis	↑	↓	↑	↓
Obstructive: tension pneumothorax, PE, pulmonary hypertension crisis, cardiac tamponade	NL or ↓	NL or ↓	↑	NL or ↓

- Multiple types of shock often coexist

Clinical Manifestations

- HoTN, tachycardia, altered mental status, tachypnea, oliguria, cool clammy, or warm/vasodilated depending on etiology of shock
- Exam: mucous membrane, rashes, JVD, murmurs/rubs, lungs crackles/breath sounds/hyperinflation, tense or soft abdomen, LE edema, cap refill

Workup

- Lactate, cardiac enzymes, renal/liver function, CBC and differential, coagulation parameters, ABG, natriuretic peptides
- ECG, CXR, TTE, infectious cultures, bedside ultrasound, additional imaging as needed
- No benefit to the routine use of pulmonary artery catheter monitoring for shock or ARDS (*JAMA* 2003;290:2713; *NEJM* 2006;254:2213), high-risk surgical pts requiring ICU stay (*NEJM* 2003;348:5); no large studies examining use in cardiogenic shock

Treatment

- Treat underlying etiology of shock while providing resuscitation
- Fluid for hypovolemic & distributive, vasopressors for distributive, inotropes for cardiogenic

Vasopressors and Inotropes

Properties of Vasopressors and Inotropes				
Dose	**Mechanisms**	**Afterload (SVR)**	**Inotropy (CO)**	**Chronotropy (HR)**
Dopamine (mcg/kg/min)				
1–3	DA >> β1	↑ or ↓	+	+
3–10	β1 > β2, DA > α1	↑	++	++
>10	α1 > β1 >>> β2	↑↑	+++	++
Low dose does not prevent ATN; can lead to HoTN and tachycardia (*KI* 2006;69:1669)				
Epinephrine (mcg/min)				
1–20	α1, α2, β1 > β2	↑↑↑	++++	++++
Low dose may ↓ SVR; A first-line agent in anaphylactic shock				
Norepinephrine (mcg/min)				
1–40	α1, α2 >> β1	↑↑↑↑	++	+
Preferred as the first-line agent over other vasopressors in septic shock; Vasopressin then epinephrine can be added to norepinephrine to meet MAP target				
Phenylephrine (mcg/min)				
10–400	α1 >> α2	↑↑↑↑	-	-
May be considered when tachyarrhythmias preclude use of norepinephrine				
Vasopressin (U/min)				
0.04–0.06	V1/V2	↑↑	-	-
Vasopressin vs Norepinephrine: in septic shock no difference in kidney failure-free days or death, but vasopressin group had less use of KRT (VANISH *JAMA* 2016;316:509)				
Dobutamine (mcg/kg/min)				

- Vasopressors generally improve GFR (*J Physiol* 1981;321:21; *CJASN* 2008;3:546)
- Angiotensin II (Giapreza®): in vasodilatory shock, ↑ MAP (*NEJM* 2017;377:419); in AKI requiring KRT, ↓ 28-d mortality and ↑ KRT liberation (*Crit Care Med* 2018;46:949)
- Methylene blue: early initiation reduces time to vasopressor discontinuation and increases vasopressor-free days (*Crit Care* 2023;27:110)
- High-dose hydroxycobalamine: used in refractory shock; can cause false blood leak alarm in certain HD machine (*CKJ* 2017;10:357)
- Inotropes are added in pts with septic shock and cardiac dysfunction with persistent hypoperfusion despite adequate volume status and arterial blood pressure,

Kidney Replacement Therapy in Shock

CKRT

- More likely to ↓ fluid accumulation than HD (*KI* 2009;76:422)
- Timing of KRT (early initiation vs standard of care): No differences in outcome: (*NEJM* 2016;375:122; STARRT-AKI *NEJM* 2020;383:240; IDEAL-ICU *NEJM* 2018;379:1431)
- Early KRT initiation did not ↓ mortality, no differences in KRT dependence or serum Cr on discharge or in ventilator or vasopressor use (*Lancet* 2020;395:1506)

Orthostatic Hypotension (OH)

- Physiologic response to standing: the pooling of 500–1,000 mL of blood in the lower extremities and splanchnic circulation → ↓ venous return to the heart and ↓ cardiac output and BP → ↑ sympathetic outflow (baroreceptor reflex) → ↑ peripheral vascular resistance, venous return, cardiac output, and BP
- OH: postural reduction in SBP ≥20 or DBP ≥10 w/i 3 min of standing
- BP fall w/i 1 min was a/w dizziness, fracture, syncope, and death (*JAMA IM* 2017;177:1316)
- Delayed OH: OH after 3 min of standing; a/w Parkinson ds (*Neurology* 2015;85:1362)
- Postural tachycardia synd (POTS): ↑ HR ≥30 beats/min w/i 10 min of standing or head-up tilt in the absence of OH

Causes

- Volume depletion: fluid loss, overdiuresis, overdialysis; adrenal insufficiency, anemia
- Autonomic dysfunction: amyloidosis, DM, Parkinson ds, multiple system atrophy
- Drugs: all antihypertensives, α1-blockers (for BPH or HTN), trazodone, SSRI, MAOi, TCA, vasodilators (including PDE5 inhibitors)

Clinical Manifestations

- Dizziness, weakness, palpitations, blurred vision, fall, syncope, fall
- Sometimes asymptomatic d/t autoregulation of the cerebral blood flow

Treatment

- Volume repletion, d/c drugs a/w OH; avoid rapid postural change
- Compression stockings, abdominal binder
- Fludrocortisone: mineralocorticoid; useful when sx improve with volume repletion (avoid: supine HTN, hypokalemia, sodium retention)
- Sympathomimetic agents (midodrine, droxidopa) for supine norepinephrine <220 pg/mL
  - Midodrine: α1-agonist
    s/e: supine HTN, urinary retention, piloerection, scalp pruritus and paresthesia, bradycardia, bowel ischemia (*Crit Care Med* 2018;46:e628)
  - Droxidopa: norepinephrine precursor; less supine HTN than midodrine, carbidopa blocks the conversion of droxidopa to norepinephrine (*Ann Pharmacother.* 2018;52: 1182)
  - Atomoxetine: short-acting norepinephrine transporter (NET) inhibitor, effective in neurogenic OH, use if serum norepinephrine >220 pg/mL (*Hypertension.* 2007;50(1):47)

Postprandial Hypotension

- Fall of SBP ≥20 within 2 h of eating; common in elderly and DM
- Pathogenesis: defective splanchnic vasoconstriction, insulin, and gastrointestinal peptides–mediated vasodilation
- Behavioral tx: avoid large meals, ingest meals low in CHO, avoid alcohol intake, drink water w/ meals, avoid activities, or sudden standing immediately after eating
- Tx: acarbose, octreotide, caffeine, guar gum

Familial Dysautonomia (Riley–Day syndrome)

- Ashkenazi Jewish, AR, mutation of *IKBKAP*, orthostatic HoTN, supine HTN, ↑ CKD
- 19% at age 25 required dialysis (*AJKD* 2006;48:780); KT is an option (*CJASN* 2010;5:1676)

NEPHROTIC SYNDROME (NS)

Definition: Required NS Criteria

- Proteinuria: >3.5 g/d or >3 g/g cr from increased glomerular permeability
- Hypoalbuminemia: <3.5 g/dL); urinary losses + tubular metabolism > hepatic synthesis
- Edema: 1° Na retention/plasminogen-mediated ENaC activation (overfilling) ± ↓ oncotic pressure → RAAS activation (underfilling)

Other Clinical Manifestations: Not Required for NS Criteria

- Hyperlipidemia: ↓ lipoprotein lipase & HMG-CoA reductase activity → ↑ cholesterol; ↑ angiopoietin-like 4 → ↑ TG; ↑ CAD (*KI* 1993;44:638); nephrotoxicity (*NRN* 2018;14:57)
- Urine oval fat bodies; microscopic hematuria: possible in any NS eg, MCD & DN
- AKI: ATN (common w/ MCD), collapsing FSGS, MN w/ bilateral RVT, superimposed proliferative GN or interstitial nephritis (eg, NSAIDs)

- Hypercoagulability: VTE 1.5% c/t 0.9% in general (*Am J Med* 2008;121:226); more common in adults, venous (esp. renal), MN; RF: Alb <2.8, heavy proteinuria (*CJASN* 2012:7:513); ↑ hepatic fibrinogen & coagulation factors synthesis & urinary antithrombin III loss
- Pleural effusion: transudative pattern; pericardial effusion
- Ascites: serum ascites albumin gradient <1.1 as in peritonitis, peritoneal carcinomatosis
- Gut edema: N/V, abdominal discomfort
- ↑ TSH, vit D def, infection/hypogammaglobulinemia: urinary loss of thyroxine-binding globulins, vit D–binding protein and Ig, respectively

Causes and Epidemiology

- MCD, FSGS, & MN. Some cases of IgAN, MPGN
- Glomerular injury d/t systemic ds: DM (nephrotic range proteinuria > NS), amyloidosis/monoclonal gammopathy of renal significance, lupus nephritis (esp. class V)
- ≤18 y/o: MCD >> MPGN > FSGS (*KI* 1978:13:159)
- 18–60 y/o: FSGS ≈ MN > MCD > LN > DN > IgAN
- ≥60 y/o: FSGS > DN > MN > amyloid (*CJASN* 2017:12:614)
- ≥80 y/o: MCD > MN > amyloid > FSGS > IgAN > DN (*ACKD* 2012:19:61)

Conditions and Drugs Associated with Nephrotic Syndromes	
NSAIDs, penicillamine, syphilis	MCD, MN
Lithium, IFN, pamidronate, HIV	MCD, Collapsing FSGS
Rifampin, ampicillin, EBV, ehrlichiosis, mycoplasma Hodgkin lymphoma, thymoma, atopy/eczema	MCD
Strongyloides stercoralis (*KIR* 2018;3:14)	MCD, Tip FSGS
Heroin, anabolic steroids, sirolimus, HCV DAA CMV, SV40, parvovirus B19, leishmaniasis, filariasis, malaria HLH, polycythemia vera, acute monoblastic leukemia Essential thrombocythemia, primary myelofibrosis Adult-onset Still ds, MCTD, SCD, cerebral arteritis	FSGS
Gold, mercury, captopril, lipoic acid; HBV, SLE, RA Malignancy: lung, colon, breast, prostate, uterus, gastric	MN
Chronic osteomyelitis, tuberculosis, RCC, RA, IBD Familial Mediterranean fever, hidradenitis suppurativa	AA amyloidosis

Workup and Diagnosis

- Depending on clinical presentation: HBV, HCV, HIV, Strongyloides, tuberculosis, ANA, C3, C4, SIFE, free light chain, UIFE, Hb A1c, PLA2R Ab
- Kidney bx required in most cases; in DM, consider bx if rapidly progressive kidney ds, extrarenal sxs c/w systemic ds, ⊕ serologies, and short duration of DM

Treatment (KDIGO GD 2021)

- Low Na diet: <2 g/d; SBP <120 with RASi
- Edema: loop, thiazides, amiloride, or MRA diuretics; PO drug absorption may be reduced from gut edema; IV diuretics ± IV albumin if severe, refractory or $U_K/(U_{Na} + U_K)$ >0.5–0.6 in pediatric population (*Eur J Pediatr* 2018;177:79)
- Diuretic resistance: gut edema ↓ PO absorption; hypoalbuminemia ↑ volume of distribution of loop diuretic and ↑ furosemide metabolism (*BJP* 1996;119:885)
- Hypercoagulability: warfarin with INR goal 2–3 if alb <2.5 and low bleeding risk (https://www.med.unc.edu/gntools); otherwise aspirin if alb <3.2 considering Framingham risk score, eGFR, race, DM and previous arterial thromboembolism. DOAC may be considered in selected pts (*Ann Pharmacother* 2023;57:787)
- Hyperlipidemia: statins if persistent; ezetimibe and PCSK9 inhibitors if statin-refractory/intolerant (*KIR* 2021;6:101)
- Hypothyroidism: treat unless resolves with management of NS
- Vaccination: influenza, COVID-19, pneumococcus, and HBV

GLOMERULONEPHRITIS (GN)

Definition and Epidemiology (*CJASN* 2017;12:614)

- GN: inflammation of the glomeruli, caused by proliferation of indigenous cells and/or leukocyte infiltration; aka nephritic synd
- <40 y/o, LN, IgAN; 40–60 y/o, LN, IgAN, ANCA; ≥60 y/o, ANCA > IgAN
- Male: IgAN > ANCA > LN; Female: LN >> ANCA ≈ IgAN

Clinical Manifestations and Workup

Extrarenal Clinical Manifestations of GN

Manifestations	Possible Causes
Small vessel vasculitis: palpable purpura, petechia, multiple mononeuropathy	IgAV, staphylococcus-associated IgA dominant IRGN, ANCA, cryoglobulinemia
Diffuse alveolar hemorrhage	ANCA, anti-GBM, LN, IgAV, cryoglobulinemia
Upper respiratory infection	Poststreptococcal GN: hematuria 7–10 d after URI IgAN: concurrent URI, synpharyngitic hematuria
Arthritis and fever	ANCA, LN, cryoglobulinemia, endocarditis

- Hematuria: dysmorphic RBCs/acanthocytes, RBC casts on sediment
- AKI, HTN; proteinuria, usually albumin dominant and subnephrotic (<3.5 g/d)
- W/u depending on clinical presentation: C3, C4, ANCA, anti-GBM Ab, HBV, HCV, HIV, ASO, ANA, dsDNA Ab, SIFE, free light chain, cryoglobulins, RF, and blood culture
- Non-GN causes of low complement: IgG4-RD, atheroemboli, liver failure (synthetic dysfunction), acute pancreatitis, serum sickness, urticarial vasculitis, hereditary angioedema, sepsis, malnutrition

Kidney Biopsy

- LM: mesangial, membranoproliferative, endocapillary and/or extracapillary (crescents) proliferative inflammation of glomeruli
- IF: classify GN into 3 categories, pauci-immune, linear, and granular pattern
- EM: substructure evaluation dxs cryo, ITGN, and MIDD

Typical Serum Complements Level and Biopsy IF Pattern in Glomerular Diseases

C3	C4	Kidney Biopsy IF	Possible Causes
NL	NL	Pauci-immune	ANCA-associated vasculitis
		Linear, IgG	Anti-GBM ds
		Granular, IgA	IgAN/IgAV, IgA dominant IRGN
↓ or NL*	↓*	Granular, polytypic: immune complex GN	Autoimmune: SLE (LN), Sjögren's Infections: HCV, HBV, HIV IC-mediated MPGN, cryo type II & III
		Granular, monotypic	PGNMID, MIDD (esp. heavy chain) ITGN, cryo type I
↓#	NL#	Granular, C3 ≥ polytypic Ig	Infection related GN (IRGN)
		Granular, C3 > polytypic Ig	C3G: C3GN and DDD
		Negative	Complement-mediated TMA (CM-TMA)

[*] NL or ↓ C3 & ↓ C4: classical complement pathway activation.

[#] ↓ C3 & NL C4: fluid (C3G, IRGN) or solid phase (CM-TMA) alternative pathway activation.

Rapidly Progressive Glomerulonephritis (RPGN)

- Acute inflammation of glomeruli causing rapid loss of kidney function w/in d to wk
- If untreated, significant kidney injury and death may occur
- Bx: crescentic (extracapillary proliferation, typically >50%) GN d/t disruption of glomerular capillary wall; fibrinoid necrosis in ANCA & anti-GBM
- Causes of GN with crescents ≥50% (*KI* 2003;63:1164)
  All age: pauci-immune (60%) > immune complex (24%) > Anti-GBM (15%)
  1–20 y/o: pauci-immune (42%) ≈ **immune complex (45%)** > Anti-GBM (12%)
  21–60 y/o: pauci-immune (48%) > immune complex (35%) > Anti-GBM (15%)
  >60 y/o: pauci-immune (79%) > **Anti-GBM** (15%) > immune complex (6%)
- Pauci-immune: 85–90% is ANCA associated GN
- Noncrescentic GN mimicking RPGN: vascular lesion (atheroemboli, acute TMA), light chain cast nephropathy, AKI (eg, RBC casts) + chronic glomerular ds (eg, IgAN, DN)
- Empiric Tx awaiting bx: if no active infection is suspected, pulse IV methylprednisolone 500–1,000 mg/d × 3 d; will not change bx results
- PLEX: consider in DAH and severe AKI before anti-GBM ds is ruled out

THROMBOTIC MICROANGIOPATHY (TMA)

Pathogenesis

- Endothelial damage ± complement abnormalities → MAHA, platelet aggregation, & consumption → ischemic organ damage
- Complement pathway activation: typical of complement-mediated TMA (CM-TMA); other categories (eg, infection, preeclampsia, APS) are also a/w complement abnormalities

Causes (*NEJM* 2014;371:654; *JTH* 2017;15:312; *Front Pharmacol* 2023;1088031)

- Infection: Shiga toxin–producing *E. coli* (STEC, typical HUS), *Shigella dysenteriae*, *S. pneumonia*, Influenza A/H1N1, HIV, EBV, CMV, *M. pneumoniae, Bordetella pertussis*, Parvovirus B19, COVID-19, fungemia
- TTP: hereditary or acquired ADAMTS13 (VWF cleaving protease) deficiency
- Complement-mediated (CM-TMA, aka aHUS): disorders of complement regulation
- Pregnancy or postpartum: preeclampsia, eclampsia, HELLP synd
- Transplantation: solid organ or hematopoietic cell transplantation
- TA-TMA ABO incompatible, age >40 (*BMT* 2005;36:993); GVHD
- Metabolism mediated: cobalamin C (vitamin B_{12}) deficiency
- Autoimmune: SLE, APS, SRC (in systemic sclerosis type)
- Mucin-secreting adenocarcinoma (breast, stomach), Malignancies: solid tumor, metastasis, POEMS, monoclonal gammopathy (*KI* 2017;91:691)
- Severe hypertension (aka malignant hypertension), pancreatitis, Castleman ds
- Coagulation mediated: *DGKE* mutation (*Nat Genet* 2013;45:531; *CJASN* 2015;10:1011)
- Quinine, levofloxacin, leflunomide, IFN, gemcitabine, mitomycin C, oxaliplatin, bleomycin, mitomycin, CNI, borte/carfil/ixazomib (*Am J Hematol* 2017;92:E53), mTOR inhibitors, VEGFi

Clinical Manifestation (*Front Pediatr* 2014;2:97; *JTH* 2017;15:312, *KI* 2017;91:539)

- MAHA (↑ retic count, ↑ LDH, ↓ haptoglobin, ↑ indirect bilirubin, schistocytes, negative DAG test) + thrombocytopenia (<150 or >25% ↓ from baseline)
- Absence of MAHA is possible: 31% of kidney limited TMA (*Am J Hematol* 2022;97:E426)
- Renal TMA: AKI, proteinuria, glomerular hematuria, HTN; no proteinuria if vascular TMA
- Neurologic: irritability, mental status change, stroke, focal deficits, seizure, coma
- GI: N/V, bloody diarrhea, pancreatitis, liver injury
- Skin: purpura, small vessel vasculopathy, gangrene

Workup

- Peripheral blood smear, LDH, haptoglobin, PT/PTT (r/o DIC), ADAMTS13

TMA Workup Based on Suspected Cause	
Suspected Cause	**Workup**
HUS: diarrhea (D)+	Stool studies (culture, RT-PCR) for STEC EHEC
Autoimmune	ANA, anti-dsDNA, aCL Ab, β2GP-1 Ab, lupus anticoagulant RNA polymerase III Ab, anti–Scl-70 Ab, ACA, skin exam
Severe (malignant) HTN	Retinal exam, TTE, and ECG (for LVH)
Preeclampsia/HELLP	LFTs, fetal monitoring, placental ultrasound
Monoclonal gammopathy	SIFE, sFLC

- Complement studies if no clear cause: C3, C4, CH50, AH50, FH, CD46 (MCP), FI, FB, genetic study (*C3, CFH, CFI, CFB, THBD, CFHR1-5, DGKE*), anti-FH antibody
- TTP pretest probability: French (*PLOS One* 2010;5:e10208) or PLASMIC score (*Lancet Haematol* 2017;4:e157; *JTH* 2018;16:164; available at QxMD)

Kidney Biopsy

- Not generally required with typical clinical presentation (MAHA, thrombocytopenia, organ dysfunction). Only way to make the dx in renal-limited cases
- LM: fibrin thrombi (when acute), endotheliosis, mesangiolysis, intimal edema, "onion skinning" (myocyte proliferation) of vessel walls; glomeruloid body (organized thrombus, specific for APLA), capillary loop duplication (MPGN pattern); FSGS, esp collapsing form is common (*KI* 2016;90:1321)
- IF: fibrinogen + thrombi; EM: subendothelial electrolucent material (in chronic)
- Scleroderma renal crisis and severe hypertension: vascular damage predominantly
- Preeclampsia, VEGFi, Castleman ds, POEMS: typically, no thrombi

Treatment

- Stop potential offending causes; Empiric GC: if low suspicion of scleroderma
- Empiric PLEX: if high probability of TTP based on French or PLASMIC score (*JTH* 2020;18:2486)

ACUTE KIDNEY INJURY (AKI)

Background and Epidemiology

- Overall global incidence 22% in hospitalized pts (*CJASN* 2013;8:1482)
- Up to 67% of ICU pts (*Crit Care* 2006;10:R73)
- Up to 50% in septic shock; associated mortality ~70% (KDIGO AKI 2012)
- **Risk factors:** volume depletion, age, hypoalbuminemia, female, CKD, DM, ↓ EF, cardiac surgery, chronic liver ds, malignancy (KDIGO AKI 2012)

Definition

- Sudden loss of kidney function, clinically manifested as ↑ Cr +/– ↓ UOP

AKI Staging (KDIGO AKI 2012)		
	Serum Creatinine (SCr, mg/dL)	**Urine Output (UOP, mL/kg/h)**
1	↑ to × 1.5–1.9 baseline w/in 7 d or by ≥0.3 w/i 48 h	<0.5 for >6–12 h
2	↑ to × 2.0–2.9 baseline w/i 7 d	<0.5 for ≥12 h
3	↑ to × ≥3.0 baseline w/in 7 d; OR increase in Cr to ≥4.0; OR need for KRT	<0.3 for ≥24 h or anuria for ≥12 h

- More advanced stages a/w worse outcomes and mortality
- Acute kidney disease (AKD): the abnormalities in kidney structure and/or function that have existed for <3 mo; AKI is subcategory of AKD

Causes of AKI

Prerenal AKI

- ↓ effective arterial volume
- Hypovolemia, cirrhosis, early shock of any etiology before progressing to ATN, cardiorenal (CHF, AS, RV dysfunction), abdominal compartment synd, hepatorenal synd, capillary leak synd, afferent arteriole vasoconstriction by NSAIDs, IV contrast, and hypercalcemia

Intrarenal AKI

- Glomeruli: look out for RPGN
  Pauci-immune: ANCA-associated (GPA, MPA); Anti-GBM ds
  Immune complex: infection-related GN, SLE, cryoglobulinemia, IgAN, IgAV/HSP, endocarditis
  TMA: TTP/HUS, DIC, complement/drug-mediated TMA, APS, preeclampsia, malignancy
- Vasculature: TMA (malignant HTN, scleroderma renal crisis), emboli (eg, cholesterol), renal artery occlusion, renal vein thrombosis, polyarteritis nodosa
- Tubules: ATN (sepsis, ischemia, toxins), light chain cast nephropathy, IV contrast, Crystal induced: urate from tumor lysis, PO_4 (oral and enema) (*KI* 2016;90:13)
- Interstitium: acute interstitial nephritis (AIN)
  Drugs (70%) esp abx, NSAIDs, PPIs
  Infections (many bacterial incl staph, strep, syphilis, Legionella; viruses; mycobacteria)
  Autoimmune ds (SLE, Sjögren's, IgG4 vasculitis, sarcoidosis)
  Miscellaneous (TINU synd, lymphoma)

Postrenal AKI

- Stones, BPH, prostate cancer, retroperitoneal fibrosis, bladder/pelvic malignancies, TCC, fungus balls, blood clots, papillary necrosis w/ sloughed tissue causing obstruction

Workup of AKI

History and Physical Examination

- HoTN: absolute or relative vs baseline
- Drugs: NSAIDs, diuretics, ACEi/ARB, PPI, abx, herbal remedies/illicit drug
- Volume depletion: diarrhea, poor PO intake; Infection/sepsis, IV contrast
- Recent surgery/arterial catheterization: cholesterol emboli
- Markers of volume status: BP, skin turgor, mucous membranes, JVD, edema, rales
- Changes in urine output (oliguria), hematuria

Laboratory Workup

- **FE_{Na}:** distinguish prerenal from other causes; valuable if oliguric (*CJASN* 2022;17:785)
  <1% (prerenal); 1–2% (prerenal or intrarenal); >2% (intrarenal or obstruction)
  <1% cutoff for prerenal only applies for marked ↓ GFR, prerenal physiology w/ normal kidney function can have FE_{Na} <0.1%
  Caveats: nonprerenal <1% can occur w/ contrast nephropathy, rhabdomyolysis, GN, ATN in background of severe prerenal state (eg, cirrhosis, CHF); prerenal w/ >1% can occur w/ background CKD or diuretic therapy
  FE_{Na} accounts for water handling, better than urine sodium alone
- **FE_{Urea}:** likely better than FE_{Na} on diuretics (*Nephron Clin Pract* 2010;114:c145)

Laboratory Findings of Prerenal AKI and ATN		
Measurement	**Prerenal**	**ATN**
BUN/Cr ratio	>20:1	<20:1
Urine sediment	Bland or hyaline casts	Renal tubular epithelial cells, "muddy brown casts," granular casts
Urine-specific gravity	>1.020	~1.010
Urine osmolality	>500	<350
Urine sodium	<10–20	>20–40
FE_{Na}	<1%	>2%
FE_{Urea}	<35%	>35%

- **Urine sediment:** utility controversial; considerable interoperator variability; look for dysmorphic RBCs and RBC casts (GN), WBC casts (AIN), "muddy brown casts" (ATN), and polarized light to see crystals, lipid droplets in NS (maltese crosses)
- **Urinalysis**
  Specific gravity (SG) can approx urine osmolality; 1.010≈300 mOsms/kg (intrinsic ds, >1.020 w/ prerenal ds); discordance w/ large, heavy molecules (contrast, glucose) which ↑ SG more than osmolality
  (+) blood w/o RBC: myoglobin (rhabdomyolysis, ✓ CK), Hb (✓ blood smear, hemolysis)
  (+) proteinuria only detects albumin (and usually only >300 mg/g Cr, previously known as "macroalbuminuria"); if discordance between dipstick proteinuria and quantified proteinuria, then likely LMW proteins or paraproteins present; sulfosalicylic acid can be added to detect nonalbumin proteinuria
  (+) glucose w/ serum glucose <180 suggests proximal tubular defect (aminoglycosides, paraprotein ds, heavy metals, cisplatin, tenofovir) or SGLT2 inhibitor
- **Quantified proteinuria**
  Spot UPCR or UACR; approximates 24-h urine protein or albumin excretion if daily Cr excretion is ~1 g/d (can significantly underestimate or overestimate daily proteinuria in large/muscular or low muscle mass/elderly, respectively)
  Spot ratio can also be inaccurate when serum Cr is fluctuating
  Nevertheless 24-h urine collection not usually needed in AKI
  Quantify proteinuria even if dipstick protein negative to evaluate for nonalbumin proteinuria (eg, paraproteins in multiple myeloma)
  % Ualb excretion <25% may predict cast nephropathy in MG (*CJASN* 2012;7:1964)
  AKI on CKD: proteinuria may be d/t the chronic process, and not acute (eg, ATN in pt w/ preexisting diabetic nephropathy)
- **CBC w/ differential**
  Eosinophilia may suggest AIN, atheroembolic ds
  Significant anemia can suggest CKD, TMA (esp if thrombocytopenia), multiple myeloma, hemolysis (and pigment-related injury)
  Thrombocytopenia can suggest TMA (eg, TTP, HUS, DIC), SLE, antiphospholipid antibody synd, cirrhosis; ✓ smear for schistocytes if anemic, coags
  Leukocytosis can suggest sepsis, myeloproliferative disorder
- **Calcium**
  ↑: can cause AKI (prerenal, ATN); or clue for multiple myeloma, sarcoidosis, malignancy
  ↓: CKD, hyperphosphatemia; pancreatitis, tumor lysis, rhabdomyolysis
- **Serum albumin**
  If low, in nephrotic range proteinuria, suggests primary NS
  Very low levels (<2.8) in NS can increase risk of thrombosis, including renal vein thrombosis (esp w/ primary membranous nephropathy)
  Large gap between total protein and albumin level suggests paraprotein ds

Radiographic Testing

- Renal ultrasound (preferred) or noncontrast CT in most pts to r/o obstruction
  Small kidneys (<9 cm): chronicity (except w/ diabetes)
  Large kidneys (>11–12 cm): AIN, DM, amyloid, PKD, lymphoma, HIVAN, RVT
  Echogenicity not a reliable indicator of CKD (*CJASN* 2014;9:373)

- Asymmetric kidneys suggest unilateral renovascular or congenital ds

Additional Testing: Dictated by Other Clinical Findings

- **Paraprotein w/u—**✓ SPEP/IFE, serum free light chains, UPEP
  Get if > age 50 w/ unexplained AKI; or manifestations of MM, amyloidosis, etc.
- **Serum uric acid:** ↑ in any renal ds d/t decreased renal clearance; esp ↑ in tumor lysis, rhabdomyolysis, myeloproliferative disorders, acute urate nephropathy
  If ↑ out of proportion to renal failure (ie, >15) then could be cause rather than effect of kidney ds; urine uric acid:Cr ratio >1 suggestive of this
  If acute urate nephropathy suspected, tx is IV saline, rasburicase, XOI
  ↓ in renal hypouricemia w/ exercise Induced AKI (URAT1 pathogenic variant)
- **If suspecting glomerular ds:** serologic w/u can include hepatitis B/C, ANCA, ANA, dsDNA, C3, C4, cryo, anti-GBM, SPEP/IFE, serum free light chains, UPEP, HIV, blood cultures; ultimately need kidney bx to confirm

Novel Biomarkers

- Cr is a late and indirect marker of AKI
- Neutrophil gelatinase–associated lipocalin (NGAL) and kidney injury molecule-1 (KIM-1) are released from injured proximal tubular cells; potentially useful in early detection of AKI and differentiating prerenal ds from ATN
- Insulin-like growth factor–binding protein 7 (IGFBP7) and tissue inhibitor of metalloproteinases-2 (TIMP-2) expressed in epithelial cells and act to arrest cell cycle in AKI; thought to predict severe AKI (*Crit Care* 2013;17:R25)

Typical Clinical Features and Biomarker Changes Associated with AKI/AKD

Findings	Possible Diagnosis
Anuria	Severe shock, RPGN, bilateral (or single if one kidney) renal artery or urinary obstruction
Acellular urine, proteinuria <1 g/d	Prerenal and ATN most likely, AIN also possible (even w/o pyuria or proteinuria), obstruction, crystal ds (oxalate, urate, phosphate nephropathy), cast nephropathy, atheroemboli
Nephrotic range proteinuria ± microhematuria	NS w/ ATN (usually minimal change), FSGS (esp collapsing), amyloid and other paraprotein-related glomerulopathy, renal vein thrombosis (esp MN)
Pyuria w/ proteinuria <1 g/d	Infection, AIN, atheroemboli
Subnephrotic proteinuria and cellular urine	Inflammatory glomerulonephritis (immune-complex eg, LN, IRGN, IgAN, anti-GBM, ANCA), TMA, malignant HTN, PAN
Pulmonary renal synds	ATN from sepsis (pneumonia), ANCA, anti-GBM, LN, cryo, AIN from pulmonary infection (Legionella, TB, Streptococcus) or the abx used for tx, IRGN, AKI w/ volume overload and pulmonary edema, scleroderma, sarcoidosis, drugs (PTU, cocaine), IgAV (rare pulmonary hemorrhage), IgAN (hematuria following URI), C3G following URI
Dermatology renal synds	Vasculitis (ANCA, SLE, cryo, PAN, IgAV), AIN, endocarditis, infection-related (cellulitis), scleroderma, atheroemboli, hep C (porphyria), amyloidosis (purpura), HIV (Kaposi sarcoma, eosinophilic folliculitis)
Low complements	LN, infection-related, cryo, C3G, other MPGN, IgG4-related ds, endocarditis, atheroembolism

Indications for Kidney Biopsy

- Cause not apparent, unresolving AKI; RPGN; AIN for which GC is being considered

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Prevention of AKI

- General preventive measures: minimize nephrotoxins (eg, contrast, NSAIDs), volume depletion, HoTN; renally dose medications
- No single medication consistently shown to prevent septic or ischemic ATN

- Remote ischemic preconditioning w/ uncertain efficacy and safety; not recommended currently for ischemic ATN prevention (*CDSR* 2017;CD010777)
- Off pump cardiac surgery did not ↓ rates of AKI-D (*NEJM* 2013;368:1179)
- Withholding ACEi/ARB prior to surgery likely not harmful, and prevent peri-op HTN (*Eur Heart J* 2024;45:1146)
- Aminoglycosides: once-daily dosing reduces AKI w/o affecting efficacy (*Am J Health Syst Pharm* 1996;53:1141); gentamicin > tobramycin > amikacin, in decreasing toxicity
- **It is unclear if** balanced crystalloids reduce kidney events vs NS

Treatment of AKI

- Mainly supportive; control of underlying process (eg, sepsis, volume depletion, RPGN)
- Loop diuretics can be used to treat volume overload, but does not hasten renal recovery and should not be used to delay dialysis if indicated

Kidney Replacement Therapy

- Dialysis requiring AKI (AKI-D) is increasing 10% per year (*JASN* 2013;24:37)
- 1–2% of AKI requiring KRT; if req. KRT, 40–60% inpatient mortality, 80% w/ prog. to CKD, & following discharge 50% 90-day mortality if remain on KRT (*CJASN* 2015;10:1859)
- **Indications:** acidosis, hyperkalemia, volume overload refractory to medications, uremia (pericardial effusion, ΔMS), certain ingestions
- **Modalities:**
  Continuous kidney replacement therapy (CKRT), intermittent HD (iHD), slow low efficiency dialysis (SLED); no modality proven to be superior (*JAMA* 2008;299:793)
  Hemofiltration may improve clearance of middle molecules but no improvement in outcomes over hemodialysis (*Crit Care* 2012;16:R146)
  CKRT or SLED preferred over iHD if pt is hemodynamically unstable, or w/ increased intracranial pressure (less dramatic osmotic shifts than iHD)
- **Dose:** 3×/wk noninferior to 6×/wk for iHD, effluent rate of 20 cc/kg/hr noninferior to 35 cc/kg/hr for CKRT (*NEJM* 2008;359:7); aim for modestly higher effluent rate for CKRT as interruptions will limit actual delivered dose compared to prescribed dose; weekly Kt/V ≥3.9 for intermittent or extended daily dialysis (KDIGO AKI 2012)
- **Initiation:** most evidence does not suggest mortality benefit for early vs delayed initiation of KRT (STAKRT-AKI *NEJM* 2020;383:240; AKIKI *NEJM* 2016;375:122; IDEAL-ICU *NEJM* 2018;379:1431); no specific BUN or Cr threshold when to start
- **Discontinuation:** No consensus on timing, needs to be individualized; Consider once: CrCl > 15 cc/min a timed urine collection, UOP > 400 mL/d w/o diuretic or >2 L/day on diuretic (*Semin Dial* 2019;32:205)

Prognosis of AKI

Course

- Maintenance phase typically lasts between 7 and 21 days
- Depends on severity and duration of injury, presence of recurrent ischemia occurs or ongoing exposure to nephrotoxins
- Nonoliguric ATN generally w/ better prognosis, possibly d/t less severe injury and better volume status
- Furosemide “stress test”: 1–1.5 mg/kg of furosemide; increased urine output predicts more favorable outcome, but does not alter outcome (*JASN* 2015;26:2023)
- RASi use is a/w better outcome in mortality (*JASN* 2023 34:1721; *KI* 2021;99:1202)

Recovery

- Pts w/ CKD who develop AKI more likely to progress to ESKD c/w pts w/ CKD and no AKI (*CJASN* 2009;4:891)
- Non-recovery from AKI-D a/w baseline eGFR, proteinuria, old age, DM & HF (*KI* 2018;93:968)
- AKI recurrence a/w poor outcomes → 5 × mortality increase in 1 year compared to early sustained AKI recovery (*Am J Respir Crit Care Med* 2017;195:784)
- Increased risk of progressive CKD even among pts who recover from in-hospital AKI; RF: albuminuria, CKD, older age, greater severity of AKI, higher Cr at discharge, multiple comorbidities (*AJKD* 2012;60:402)
- 21% of pts w/ recovery of kidney function after kidney failure restart dialysis w/in 3 y; RFs are young age, Black or Hispanic, cystic kidney disease, DM, HF and outpatient dialysis start (*CJASN* 2022;17:1346)
- Pts who develop in-hospital AKI need evaluation w/in 3 mo for resolution or new onset or worsening of preexisting CKD (KDIGO AKI 2012)

Mortality

- AKI a/w ↑ in-hospital and long-term mortality
- RF: older age, oliguria, sepsis, respiratory or liver failure, cerebrovascular events, severity of illness
- Long-term mortality in survivors of AKI worse if renal function doesn’t normalize (46% vs 83%) (*Crit Care* 2012;16:R13)

CHRONIC KIDNEY DISEASE (CKD)

Definition (KDIGO CKD 2024)

- CKD: presence of kidney damage and/or ↓ kidney function (eGFR <60) for ≥3 mo
- Kidney damage: UACR >30 mg/g, abnormalities on urine sediment, histology or imaging, persistent hematuria, abnormalities d/t tubular disorders, KT

GFR (G) Categories and Albuminuria (A) Categories in CKD
(KDIGO CKD 2024)

	GFR (mL/min/1.73 m^2)				Albuminuria (mg/d or mg/g)
G1	≥90 + kidney damage			A1	<30
G2	60–89 + kidney damage			A2	30–300
G3a	45–59	G4	15–29	A3	>300
G3b	30–44	G5	<15		

- G3a A3, G3b A2/3, all G4 and all G5 are very high risk for complications

Epidemiology (2023 USRDS annual data report)

- Prevalence of predialysis CKD (G1–5) was 14% of the U.S. population in 2017–2020
- Stage G3 the most prevalent (5.1%)
- Females > males (56.7%); CKD ↑ w/ age (20.1% of adults ≥65)
- <10% of CKD pts aware of ds (*AJN* 2012;35:191), 57% awareness in stage G4 CKD
- CKD resulted in 35.8 million disability-adjusted life-years (*Lancet* 2020;395:709)

Causes of CKD

Category	Possible Causes	Urinalysis	Renal U/S
Prerenal	Chronic CHF Chronic cirrhosis	Minimal protein, bland sediment	
Vascular	HTN Renal vascular ds TMA	Minimal protein, bland sediment	Small kidneys excluding DM
Glomerular	Chronic glomerular ds: eg, FSGS DM (m/c cause)	(+) protein, ± RBCs	HIV, DM: large kidneys
Tubulointerstitial	Inherited: ADPKD, CAKUT Infiltrative; Chronic TIN	(+) protein <2 g/d, ± WBCs	ADPKD: large cystic kidneys DM, infiltrative: large kidneys
Postrenal	Obstructive uropathy RP fibrosis	Minimal protein	(+) hydronephrosis RP fibrosis: ± hydro

CV and All-Cause Mortality of CKD

- CKD a/w traditional CAD risk factors such as HTN, DM, smoking, HLD, older age, and the metabolic synd (*JASN* 2005;16:529)
- ↓ eGFR, ↑ UACR = **independent** risk factors for CV and all-cause mortality (*Arch IM* 2007;167:2490; *JASN* 2002;13:745)
- CKD is CAD risk equivalent → risk factor reduction is needed (*Circulation* 2003;108:2154)
- Nontraditional CAD risk factors: anemia (*Am J Cardiol* 2008;102:266), inflammation (*JASN* 2004;15:538), + calcium balance (*NDT* 2006;21:2464), CKD-MBD (*NDT* 2006;21:2464)
- Proportion of CV deaths, infections, DM complications ↑ w/ ↓ eGFR (*JASN* 2015;26:2504)

Progression to ESKD

- Injury → adaptive hyperfiltration initially ↓ Cr → eventually CKD progression
- Rate of transition 3 + 4 CKD → ESKD: 1.5%/y (*Ann IM* 2004;141: 95)
- Early change in albuminuria predicts renal outcome (*AJKD* 2019;75:84)
- Pts w/ uncontrolled HTN, DM, and CKD lose ~12 mL/min GFR/y. When treated ~4 mL/min GFR/y (*KI* 2001;59:702)
- Two *APOL1* G1 and/or G2 alleles: common in West African descent; substantially higher risk of CKD and ESKD
- Other RF: old age, male, poor socioeconomic status, LBW, HIV, HCV, nephrolithiasis, recurrent UTIs, metabolic acidosis, high aldosterone, hyperphosphatemia, smoking, obesity, hyperlipidemia
- KFRE: 2- and 5-y kidney failure risk can be predicted w/ 4 or 8 variables (*JAMA* 2011;305:1553; *JAMA* 2016;315:164, available at QxMD®)

Clinical Manifestation

- Usually asymptomatic, fatigue, loss of appetite, malnutrition, metallic taste, feeling cold
- Encephalopathy, seizure, bleeding, edema, pruritus, frost (*NEJM* 2018;379:669)
- Pleuritis, dyspnea, orthopnea, pericarditis, cardiac tamponade, hypertension
- Osteopenia, osteitis fibrosa cystica, extraskeletal (eg, vascular) calcification, fracture
- U/S: small bilaterally echogenic kidneys w/ cysts

General CKD Treatment

- Evaluate etiology and treat reversible causes: d/c potential injuries, eg, NSAIDs, urinary obstruction; adjust medications by kidney function
- Tx to slow progression and manage complications
- Avoid PICC if life expectancy ≥2 y and high KF risk (eg, KFRE >10%) (*JVA* 2023;24:329)
- Refer to nephrology when GFR <30, UACR ≥300 mg/g, glomerular hematuria, or CKD of unknown etiology
- KRT modality discussion: KT referral once eGFR <20; vascular access if HD is the preferred modality once eGFR <30, PD catheter at least 2 wk prior to PD start
- KRT indication evaluation and initiation

CKD Treatment to Slow Progression (*AJKD* 2021;77:969; *KDIGO CKD* 2024)

- Protein intake: maintain 0.8 g/kg/d & avoid >1.3 g/kg/d if at risk of progression; <0.8 g/kg/d may ↓ nondiabetic CKD G4/5 progression to ESKD (*CDSR* 2020;CD001892)
- Smoking cessation: ↓ CKD progression (*JASN* 2004;15:S58)
- $NaHCO_3$ PO if [HCO_3] <18; does not affect BP (*CJASN* 2023;18:435)
- Multifactorial therapy (diet, exercise, smoking cessation, RASi, and statins) ↓ CKD progression (*NEJM* 2003;348:383)
- BP control: SBP goal <120 (KDIGO BP 2021)
  If nonproteinuric, ↓ BP has not slowed CKD progression but ↓mortality (*JASN* 2017;28:2812)
  If proteinuric, ↓ BP (SBP 110–129) ↓ CKD progression (*Ann IM* 2003;139:244)
- RASi for CKD G1–G4, A2–A3 w/ or w/o DM (KDIGO BP 2021)
  RASi ↓ CKD progression in proteinuric CKD independent of BP (*Lancet* 1998;352:1252)
  In proteinuric CKD w/ Cr 1.5–3, RASi ↓ CKD progression (*NEJM* 2006;354:131)
  In nondiabetic CKD w/ proteinuria ≥0.5 g/d, ACEi ↓ CKD progression (*JASN* 2007;18:1959)
  In eGFR <30, d/c not a/w change in long-term decline in eGFR (*NEJM* 2022;387:2021)
  ACEi + ARB combination did not ↓ CKD progression or ↓ mortality; ↑ serious adverse events (eg, acute dialysis) (ONTARGET *Lancet* 2008;372:547)
- SGLT2 inhibitor (SGLT2i)
  - eGFR 25–75 w/ UACR 0.2–5 g/g dapagliflozin ↓ progression (9.2% vs 14.5%) (DAPA-CKD *NEJM* 2020;383:1436)
  - eGFR 20–45 **regardless of albuminuria** or eGFR 45–90 w/ UACR >0.2 g/g (EMPA-KIDNEY *NEJM* 2023;388:117; *NEJM* 2024;39453837)
  - SGLT2i + MRA had additional ↓ albuminuria w/ less ↑ K than MRA only (*JASN* 2022;33:1569)

RCT	randomized controlled trial
REMS	Risk Evaluation and Mitigation Strategies
RF	replacement fluid, risk factor or rheumatoid factor
RI	resistive index
RKF	residual kidney function
ROMK	renal outer medullary potassium channel
ROS	reactive oxygen species or review of systems
RP	retroperitoneal
RPGN	rapidly progressive glomerulonephritis
RPR	rapid plasma reagin
RR	relative risk, respiratory rate
RT	radiation therapy
RTA	renal tubular acidosis
RTE	renal tubular epithelial
RTX	rituximab
RVT	renal vein thrombosis
Rx	therapy
RYGB	roux-en-Y gastric bypass
RZV	recombinant zoster vaccine
s/e	side effect
s/p	status post
s/s	symptoms and signs
SAH	subarachnoid hemorrhage
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SBP	spontaneous bacterial peritonitis/systolic blood pressure
SC	subcutaneous
SCC	squamous cell carcinoma
SCD	sickle cell disease or sudden cardiac death
SCLC	small cell lung cancer
SCr	serum creatinine
SCT	stem cell transplantation
SD	standard deviation
Se	sensitivity
sFLC	serum free light chain
SG	specific gravity
SGA	small for gestational age
SGLT	sodium-glucose cotransporter
SGLT2i	sodium-glucose cotransporter 2 inhibitor
SIADH	syndrome of inappropriate ADH
SIEP	serum immunoelectrophoresis
SIFE	serum immunofixation electrophoresis
SIR	standardized incidence Ratio
siRNA	small interfering ribonucleic acid
SJS	Stevens–Johnson syndrome
SLE	systemic lupus erythematosus

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