

Renal Pharmacology: Diuretics in Clinical Practice

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Renal Pharmacology: Diuretics in Clinical Practice

Level: PA/Medical Student **Duration:** 45–60 minutes **Version:** 2026-02-12

Learning Objectives

By the end of this module, students will be able to:

1. **Classify** diuretics by mechanism of action and nephron site
 2. **Explain** the molecular mechanisms of loop, thiazide, and potassium-sparing agents
 3. **Calculate** appropriate dosing and ceiling doses for clinical scenarios
 4. **Recognize** diuretic resistance and implement management strategies
 5. **Manage** electrolyte complications (hypokalemia, hyperkalemia, hyponatremia)
 6. **Identify** the braking phenomenon and post-diuretic sodium retention
 7. **Apply** sequential nephron blockade in decompensated heart failure and edematous states
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Overview: Nephron Segmental Pharmacology

Diuretics act at specific sites along the renal tubule, following the principle of **sequential nephron blockade**:

Nephron Segment	Diuretic Class	Primary Effect	K+ Loss
Proximal convoluted tubule	Acetazolamide	\square HCO ₃ \square reabsorption	Mild
Thick ascending limb (TAL)	Loop diuretics	\square Na-K-2Cl cotransport	Severe
Distal convoluted tubule	Thiazides	\square NaCl cotransport	Moderate
Collecting duct	K \square -sparing	\square ENaC, \square K \square retention	Sparing
Systemic	Osmotic (mannitol)	\square Tubular water reabsorption	Variable

LOOP DIURETICS

Mechanism of Action

Loop diuretics bind to the **Na-K-2Cl (NKCC2) cotransporter** on the apical membrane of thick ascending limb (TAL) cells, blocking reabsorption of ~25% of filtered sodium.

Key Insight: The TAL is freely permeable to water but actively reabsorbs solute, generating the **positive electrical gradient** that drives cation reabsorption in the proximal tubule and collecting duct. Blocking TAL transport has cascading effects upstream and downstream.

Agents

Furosemide

- **Bioavailability:** 10–100% (highly variable; GI edema decreases absorption)
- **IV bioavailability:** 100%
- **Peak effect:** IV 1 hour; PO 1–2 hours
- **Duration:** 6–8 hours (IV), 8–12 hours (PO)
- **Ceiling dose:** 40 mg IV for acute decompensation; 120–240 mg daily for chronic use
- **Protein binding:** 91% (hepatic metabolism, renal excretion of metabolites)

Bumetanide

- **Potency:** 40× furosemide (1 mg bumetanide ≈ 40 mg furosemide)
- **Bioavailability:** More consistent than furosemide (80–90%)
- **Onset:** IV 1 minute; PO 30–60 minutes
- **Duration:** 4–6 hours
- **Ceiling dose:** 10 mg daily (maximum 8 mg IV acutely)
- **Advantage:** Better absorption in GI edema; less ototoxicity at equivalent doses

Torsemide

- **Potency:** 10× furosemide (1 mg ≈ 40 mg furosemide; note discrepancy)
- **Bioavailability:** 80–90% (superior to furosemide)
- **Duration:** 6–8 hours
- **Ceiling dose:** 20 mg daily maximum
- **Advantage:** Longer half-life; once-daily dosing feasible
- **Note:** TRANSFORM-HF trial [PubMed](#) did not show mortality benefit of torsemide vs furosemide despite superior bioavailability

Clinical Use

Indications: - Acute decompensated heart failure (preferred agent) - Pulmonary edema - Peripheral edema in CKD - Ascites in cirrhosis (combined with spironolactone) - Nephrotic syndrome with edema - Hypertension (less commonly, reserve for specific scenarios)

Dosing Strategy: 1. Start IV in acute decompensation: 40–80 mg bolus 2. Double dose every 30–60 min if inadequate response (40 □ 80 □ 160 mg) 3. Transition to continuous infusion if repeated boluses needed: 5–10 mg/hr 4. Chronic oral dosing: once or twice daily; titrate based on fluid status

Special Populations: - **Acute kidney injury:** IV loop diuretics do NOT change progression to ESRD or mortality (NEJM 2002 landmark trial) but may improve urine output and reduce fluid overload - **Cirrhosis:** Furosemide + spironolactone in 40:100 ratio (furosemide dose : spironolactone dose) prevents hypokalemia - **Renal insufficiency (eGFR <30):** Larger doses or higher infusion rates required; response kinetics slower

THIAZIDE AND THIAZIDE-LIKE DIURETICS

Mechanism of Action

Thiazides block the **Na-Cl cotransporter (NCC)** on the distal convoluted tubule (DCT), inhibiting reabsorption of ~5–10% of filtered sodium. Lower natriuretic potency than loop diuretics but sustained antihypertensive effect.

Metabolic Effects: - □ Urinary K⁺ (hypokalemia risk) - □ Urinary Mg²⁺ (hypomagnesemia) - □ Urinary Ca²⁺ retention □ hypercalcemia risk - □ Uric acid retention □ hyperuricemia - □ Glucose intolerance (dose-dependent) - □ LDL, triglycerides (generally mild)

Agents

Hydrochlorothiazide (HCTZ)

- **Dose:** 12.5–25 mg daily (doses >25 mg not more effective, increased side effects)
- **Bioavailability:** ~70%
- **Duration:** 12–24 hours
- **Onset:** 2 hours
- **Protein binding:** Low (renal secretion)
- **Metabolism:** Unchanged, renal excretion

Chlorthalidone

- **Potency:** ~1.5–2× HCTZ
- **Dose:** 12.5–25 mg daily (half HCTZ equivalent dose)
- **Duration:** 24–72 hours (much longer)
- **Onset:** 4–6 hours
- **Advantage:** Once-daily dosing; possibly superior BP control vs. HCTZ (ACCOMPLISH trial, multiple observational studies)
- **Disadvantage:** Hypokalemia and hyponatremia risk higher; slower offset if adverse effects

Indapamide

- **Mechanism:** Similar to thiazides but some vasodilatory properties
- **Dose:** 1.25–2.5 mg daily
- **Advantage:** Less metabolic derangement (modest glucose, K⁺, lipid effects)
- **Duration:** 12–18 hours

Metolazone (Quinazoline; Thiazide-Like)

Unique Properties: - Retains efficacy at low GFR (unlike thiazides; works even with eGFR <30) - More potent than HCTZ - **Mechanism:** DCT NCC blockade + proximal tubule effect - **Onset:** 1 hour (oral); peak 2–8 hours - **Duration:** 12–24 hours

Clinical Use in Diuretic Resistance: - **Sequential blockade:** IV furosemide + metolazone 2.5–10 mg PO daily produces profound natriuresis - **Mechanism:** Metolazone proximal effect + loop-resistant distal sites blockade - **Caution:** Close monitoring—risk of severe hypokalemia, hyperglycemia, hyperuricemia - **Monitoring:** Electrolytes (K⁺, Na⁺, Mg²⁺, Cr) q3–7 days initially

POTASSIUM-SPARING DIURETICS

Mechanism: ENaC Blockers

Amiloride and Triamterene block the epithelial sodium channel (ENaC) on the apical membrane of collecting duct principal cells, preventing Na⁺-driven K⁺ secretion.

Agents and Properties

Agent	Dose	Onset	Mechanism	Note
Amiloride	5–10 mg daily	2–4 hours	ENaC blocker	Renal excretion; avoid NSAIDs, ACEi/ARB
Triamterene	50–100 mg 1–2×/day	2–4 hours	ENaC blocker	Hepatic metabolism; risk of crystalluria (rare)
Spirolactone	12.5–50 mg daily	2–3 days	MRA	See below
Eplerenone	25–50 mg daily	1–2 hours	MRA	CYP3A4 substrate; fewer hormonal side effects

Aldosterone Receptor Antagonists (MRAs)

Spirolactone

- **Mechanism:** Competitive aldosterone receptor antagonist in collecting duct
- **Potency:** Weak diuretic alone; potent when combined with loop/thiazide
- **Onset:** 2–3 days (slow); peak effect 7–14 days
- **Duration:** 18–24 hours (prolonged half-life ~13 hours)
- **Indications:** Heart failure (RALES trial—□ mortality 30%), resistant hypertension, primary aldosteronism, cirrhotic ascites
- **Metabolites:** Active (canrenone) and inactive; undergo enterohepatic circulation
- **Adverse effects:**

- Hyperkalemia (especially if combined with ACEi/ARB or renal impairment)
- Gynecomastia (10–15%; due to androgen receptor antagonism), menstrual irregularities
- Mastodynia, sexual dysfunction
- **Monitoring:** K⁺ and Cr at baseline, 3–7 days, then monthly × 3, then every 3 months; LFTs

Eplerenone (Selective MRA)

- **Mechanism:** Selective aldosterone antagonist; 50–70% aldosterone selectivity vs. spironolactone
- **Potency:** Similar to spironolactone but weaker anti-androgen
- **Onset:** 1–2 hours (rapid)
- **Indication:** Heart failure with reduced ejection fraction (EMPHASIS-HF trial)
- **Dose:** 25–50 mg daily
- **Advantage:**
 - No gynecomastia/sexual dysfunction
 - Shorter onset; more favorable drug interaction profile
- **Disadvantage:**
 - Expensive (branded drug Inspra)
 - CYP3A4 substrate (drug interactions with clarithromycin, diltiazem, etc.)

Clinical Application

Combination therapy (sequential blockade): - Loop diuretic + thiazide/metolazone (proximal shift in reabsorption site) - Any diuretic + K⁺-sparing agent (prevents hypokalemia)

Contraindications for K⁺-sparing agents: - K⁺ >5.0 mmol/L (higher threshold: K⁺ >5.5 if symptoms) - eGFR <30 (relative; requires close monitoring) - Concurrent ACEi/ARB/NSAID (triple whammy) - Addison's disease, severe metabolic acidosis

ACETAZOLAMIDE (Carbonic Anhydrase Inhibitor)

Mechanism

Inhibits **carbonic anhydrase II** in proximal tubule epithelium, blocking reabsorption of HCO₃⁻ and ~5–10% of Na⁺. Weak diuretic alone.

Properties

- **Dose:** 250–500 mg once or twice daily
- **Onset:** 1–4 hours (PO); 2–5 minutes (IV)
- **Duration:** 8–12 hours (PO)
- **Metabolism:** Renal excretion (unchanged)

Clinical Uses

1. **Metabolic alkalosis** (preferred agent):

- Inhibits proximal HCO_3^- reabsorption
- Allows urinary HCO_3^- wasting
- Dose: 250–500 mg PO daily until alkalemia resolves
- Superior to saline therapy in contraction alkalosis

2. **Altitude sickness:** □ CSF HCO_3^- □ respiratory compensation □ □ periodic breathing

3. **Glaucoma:** □ aqueous humor production (chronic use only; alternative agents preferred)

Metabolic Consequences

- **Hypokalemia** (high risk)
- **Hyperchloremic metabolic acidosis** (from proximal HCO_3^- wasting)
- **Hyperammonemia** (ammonuria increases; caution in hepatic encephalopathy)
- **Hyperuricemia**
- **Paresthesias** (secondary to HCO_3^- wasting)

Contraindications

- Hypokalemia (exacerbates)
- Hepatic encephalopathy (hyperammonemia risk)
- Sulfonamide allergy (acetazolamide is sulfonamide derivative)

OSMOTIC DIURETICS

Mannitol

Mechanism: Freely filtered at glomerulus; poorly reabsorbed in tubule. Creates osmotic gradient that draws water into tubular lumen, reducing water reabsorption throughout the nephron and increasing urine output.

Properties: - **Dose:** 0.5–1 g/kg IV (bolus); 5% solution typical - **Onset:** 15–30 minutes - **Peak effect:** 30–60 minutes - **Duration:** 1.5–6 hours - **Metabolism:** Primarily renal excretion (small amount metabolized to glucose)

Clinical Uses: 1. **Acute tubular necrosis (ATN) prevention:** Maintaining high urine flow reduces intratubular obstruction risk; use early in rhabdomyolysis, myoglobinuria 2. **Cerebral edema:** Reduces intracranial pressure (osmotic diuresis reduces brain water) 3. **Oliguric renal failure:** Attempts to convert to non-oliguric (evidence for benefit marginal)

Adverse Effects: - **Hypernatremia:** From free water loss - **Hyperglycemia:** If metabolized to glucose - **Hyperkalemia:** Initially—from cell water loss concentrating K^+ ; later hypokalemia if diuresis sustained - **Volume depletion:** If used injudiciously - **Rebound cerebral edema:** If osmotic gradient dissipates

Monitoring: Serum osmolality (target <320 mOsm/kg); Na^+ , K^+ , Cr; urine output hourly

DIURETIC RESISTANCE: Mechanisms and Management

Definition

Failure to achieve adequate diuresis despite escalating doses of diuretic (typically loop diuretics).

Mechanisms

1. Pharmacokinetic Resistance - Poor GI absorption: Furosemide absorption \square in acute decompensation (splanchnic vasoconstriction, bowel edema) - **Solution:** Switch to IV or more reliable agent (bumetanide, torsemide)

2. Pharmacodynamic Resistance - Tubular refractoriness: Chronic diuretic use \square compensatory upregulation of Na^+ transport in salt-sparing segments, blunting response - **Solution:** Diuretic-free interval (24–48 hrs; allows transporter downregulation) or sequential nephron blockade

3. Renal Hemodynamic Impairment - Reduced GFR: Loop diuretics require glomerular filtration to reach apical membrane transporter - **Severe renal disease (eGFR <30):** Larger doses, more frequent dosing, longer infusions needed - **Cardiorenal syndrome:** Worsening cardiac output \square splanchnic hypoperfusion \square \square diuretic delivery - **Solution:** Low-dose continuous infusion (5 mg/hr furosemide) may be superior to intermittent dosing in CHF (DOSE trial inconclusive; observational support)

4. Hypoalbuminemia - Mechanism: Diuretics bound to albumin; hypoalbuminemia (nephrotic syndrome, liver disease) \square tubular secretion of diuretic - **Solution:** Larger doses; consider albumin infusion if severe (controversial)

5. Elevated Renal Vascular Resistance - NSAIDs, sepsis, hepatorenal syndrome: Vasoconstriction \square renal perfusion - **Solution:** Remove offending agent; improve cardiac output; consider vasodilators

Management Algorithm

Step 1: Verify Diagnosis - Confirm volume overload (not dry weight, medications, poor adherence) - Check compliance (24-hr urine Na^+ , K^+ if question of diuretic use) - Verify adequate dosing (may be subtherapeutic)

Step 2: Optimize Renal Perfusion - Improve cardiac output if impaired (inotropes, vasodilators) - Discontinue NSAIDs, ACEi (temporary if severe; restart once stabilized) - Address sepsis, treat hypotension

Step 3: Maximize Diuretic Delivery - Switch from PO to IV (especially furosemide) - Increase frequency (TID dosing vs. daily) - Escalate dose (doubling protocol until ceiling reached) - Switch to continuous infusion (5–10 mg/hr furosemide equivalent)

Step 4: Sequential Nephron Blockade - Combination therapy: IV loop + metolazone 2.5–10 mg PO - **Mechanism:** Proximal shift of Na^+ reabsorption site + DCT blockade = profound natriuresis - **Monitoring:** \square K^+ loss; electrolytes q3–7 days - **Caution:** May precipitate electrolyte derangement; avoid if not monitored closely

Step 5: Consider Diuretic-Free Interval - Hold diuretic 24–48 hours (allow downregulation of compensatory transporters) - Risky in acute decompensation; reserve for chronic resistant

edema - Risk: Volume reaccumulation

Step 6: Advanced Options - Vasopressin antagonists (vaptans): Aquaretic; useful in cardiorenal syndrome + hyponatremia (but mortality neutral in HF—EVEREST trial) - **Inotropy:** Dobutamine infusion ± continuous diuretic (in decompensated HF with hypotension) - **Ultrafiltration (UF):** Mechanical removal of fluid; reserved for refractory cases unresponsive to pharmacotherapy

THE BRAKING PHENOMENON

Definition

Despite ongoing diuretic therapy, sodium excretion and urine output gradually return toward baseline over **3–5 days** of continuous diuretic use.

Mechanism

Adaptation occurs via:

1. **Increased proximal reabsorption:** Reduction in GFR and peritubular capillary hydrostatic pressure □ enhanced proximal Na□ reabsorption
2. **Increased renin-angiotensin system (RAS) activation:** Volume depletion □ aldosterone □ □ distal K□/Na□ exchange □
3. **Increased sympathetic nervous system (SNS) activation:** Baroreceptor response to hypotension/volume depletion
4. **Tubular adaptation:** Upregulation of salt transporters in distal nephron segments

Post-Diuretic Sodium Retention

Phenomenon: After stopping diuretics, there is often a rebound period of **sodium retention (anti-natriuresis)** lasting 1–3 days, causing rapid weight gain if dietary sodium not restricted.

Clinical Significance: - Explains why chronic diuretic therapy plateaus in effect despite stable dosing - Explains why diuretic-free intervals allow temporary natriuresis - Emphasizes importance of dietary sodium restriction as cornerstone of volume management

Clinical Implications

1. **Chronic diuretic therapy:** Requires either
 - Escalating doses (leading to tachyphylaxis and side effects), OR
 - Intermittent dosing with sodium restriction + dietary counseling
 2. **Loop diuretic monotherapy:** Often insufficient long-term; combine with ACEi/ARB/MRA to suppress RAS and SNS
 3. **Patient education:** Sodium restriction <3 g/day essential; often underemphasized
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Clinical Scenarios

Scenario 1: Acute Decompensated Heart Failure, Pulmonary Edema

Clinical: 58-year-old male with LVEF 30% presenting with orthopnea, 3+ edema, bibasilar rales.

Approach: 1. **Assess volume status:** Orthopnea, rales, elevated JVP □ euvolemic/hypervolemic
2. **Initial diuresis:** IV furosemide 80 mg bolus; reassess after 1 hour 3. **If inadequate urine output (<200 mL/hr):** Double to 160 mg bolus or start continuous infusion 5 mg/hr 4. **Goal:** □ weight 1–2 lbs/day; resolution of orthopnea/rales 5. **Add ACEi + aldosterone antagonist** to suppress compensatory RAS/SNS activation 6. **Transition to PO:** Once euvolemic, start torsemide 10 mg PO daily (better bioavailability than furosemide) 7. **Sodium restriction:** <3 g/day; monitor daily weights

Scenario 2: Diuretic-Resistant Edema in CKD Stage 4 with FSGS

Clinical: 52-year-old female with eGFR 22, nephrotic syndrome (proteinuria 8 g/day, albumin 2.8), peripheral edema unresponsive to furosemide 240 mg daily PO.

Assessment: - Poor GI absorption likely (nephrotic state □ bowel edema) - eGFR <30 □ loop diuretic delivery impaired - Thiazides ineffective in renal insufficiency

Approach: 1. **Switch to IV:** Furosemide 80 mg IV daily or 40 mg IV BID (better delivery) 2. **Add metolazone:** 5 mg PO daily (retains efficacy in low GFR) 3. **Monitor:** K□, Na□, Mg²□, Cr weekly × 4 weeks 4. **Goal:** □ weight 1–2 lbs/week; reduce proteinuria with ACEi/ARB 5. **Add albumin:** Consider albumin infusion (25 g IV) with diuretic to enhance natriuresis (controversial; evidence limited)

Scenario 3: Metabolic Alkalosis in Vomiting

Clinical: 72-year-old with vomiting × 5 days: pH 7.52, HCO₃□ 48, K□ 2.8, Cl□ 82.

Mechanism: Contraction alkalosis (loss of HCl in gastric secretions)

Approach: 1. **Address underlying:** Antiemetics, PPI for GERD 2. **Saline:** 0.9% NaCl IV (expands volume, allows Cl□ and HCO₃□ excretion) 3. **Acetazolamide:** 500 mg PO daily (if saline delayed; accelerates HCO₃□ wasting) 4. **Correct hypokalemia:** K□ replacement (target K□ >3.5); alkalosis perpetuated by hypokalemia 5. **Goal:** pH <7.45, HCO₃□ <35 mmol/L, K□ >3.5

Practice Questions

Question 1

A 64-year-old man with systolic heart failure (LVEF 25%), hypertension, and CKD Stage 3a (eGFR 48) is admitted with acute decompensation. He is dyspneic at rest and has 4+ peripheral edema. He has been taking lisinopril 10 mg daily, carvedilol 25 mg BID, and furosemide 40 mg daily.

In the hospital, he receives IV furosemide 80 mg bolus but produces only 150 mL urine in the first hour despite clinical evidence of volume overload. Which of the following is the MOST appropriate next step?

- A) Increase furosemide to 160 mg IV bolus
- B) Add metolazone 5 mg PO daily
- C) Initiate continuous IV furosemide infusion 5 mg/hr
- D) Hold all diuretics for 24 hours (diuretic-free interval)
- E) Add IV albumin 25 g

Answer: A (escalate to ceiling dose per DOSE trial; consider C if repeated boluses fail)

Rationale: - Initial inadequate response likely reflects suboptimal dosing or decreased diuretic delivery due to splanchnic vasoconstriction in acute decompensation - Double the dose (80 \square 160 mg) before advancing to infusion - Metolazone useful if loop alone fails after dose escalation - Diuretic-free interval dangerous in acute decompensation - Albumin controversial; not first-line

Question 2

A 58-year-old woman with lupus nephritis (Class IV) is being treated with IV methylprednisolone and mycophenolate mofetil. After 2 weeks, she develops peripheral edema and proteinuria persists at 6 g/day. Labs: Na \square 128 mmol/L (hyponatremia), K \square 5.8 mmol/L (hyperkalemia), Cr 1.4 mg/dL (baseline 0.8). She is on losartan 100 mg daily and lisinopril 10 mg daily (dual RAAS blockade for proteinuria reduction).

Which medication adjustment is MOST appropriate?

- A) Start spironolactone 25 mg daily for additional proteinuria reduction
- B) Discontinue lisinopril; continue losartan monotherapy
- C) Start chlorthalidone 25 mg daily
- D) Start furosemide 40 mg daily
- E) B and D

Answer: E (discontinue ACEi, start diuretic)

Rationale: - **Hyperkalemia (K \square 5.8) + dual RAAS blockade = contraindication** to K \square -sparing agents - Lisinopril + losartan = dual RAAS blockade associated with hyperkalemia and worsening renal function without mortality benefit (failed VA NEPHRON-D, ONTARGET trials) - Stop one RAAS inhibitor (typically the ACEi if ARB continued, though either acceptable) - Hyponatremia + hyperkalemia suggests volume depletion + aldosterone excess (paradoxically); loop diuretic + restricted ARB/ACEi dosing warranted - Diuretic needed to manage edema; loop preferable in renal insufficiency (Cr 1.4)

Question 3

A 71-year-old woman with CKD Stage 4 (eGFR 28), hypertension, and diabetes presents with persistent peripheral edema despite furosemide 120 mg PO daily and lisinopril 10 mg daily. 24-hour urine Na \square is 45 mmol/day (low), suggesting poor compliance or inadequate diuretic absorption.

She denies missing medications. Urine dipstick shows 2+ protein. She has never taken a thiazide or thiazide-like diuretic.

Which diuretic addition is MOST appropriate?

- A) Hydrochlorothiazide 25 mg daily
- B) Metolazone 5 mg daily
- C) Acetazolamide 500 mg daily
- D) Spironolactone 25 mg daily
- E) Amiloride 5 mg daily

Answer: B (metolazone)

Rationale: - **eGFR 28:** Thiazides (including HCTZ) lose efficacy <eGFR 30 due to reduced tubular secretion - **Metolazone:** Retains efficacy in renal insufficiency; works via DCT + proximal tubule mechanisms - **Sequential blockade:** Loop (furosemide) + metolazone = synergistic natriuresis - Acetazolamide weak diuretic alone; reserved for metabolic alkalosis - K⁺-sparing agents contraindicated without K⁺ level confirmation (possible hyperkalemia in CKD) - Dosing: Metolazone 2.5–10 mg daily; monitor K⁺, Na⁺, Mg²⁺ closely

Clinical Pearl Summary

1. **Loop diuretics** are most potent; site of action (TAL) generates driving force for proximal and distal reabsorption. Ceiling effect present; dose escalation required in renal insufficiency.
 2. **Thiazides** metabolically active (hypokalemia, hyperglycemia, hyperuricemia) but less effective in eGFR <30. Metolazone is alternative that retains efficacy in renal impairment.
 3. **K⁺-sparing agents** (amiloride, spironolactone, eplerenone) essential for preventing hypokalemia; contraindicated with dual RAAS blockade or K⁺ >5.0.
 4. **Braking phenomenon** explains tachyphylaxis over days; managed via dietary Na⁺ restriction, RAAS/SNS suppression (ACEi/ARB/MRA), or diuretic-free intervals.
 5. **Diuretic resistance:** Escalate doses to ceiling, switch to IV, add sequential nephron blockade (metolazone + loop), optimize renal perfusion, consider continuous infusion.
 6. **Hypoalbuminemia** (nephrotic syndrome) impairs diuretic secretion; may require albumin infusion or larger doses.
 7. **eGFR <30:** Loop diuretics still effective but require higher doses; metolazone preferred over thiazides; acetazolamide weak monotherapy.
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References

1. **DOSE Trial (2011)** — Felker GM, et al. Diuretic Strategies in Patients with Acute Decompensated Heart Failure. *N Engl J Med* 364:797–805. (bolus vs. infusion, low vs. high dose)

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 4. **Ellison DH, Felker GM (2017)** — Diuretic Therapy and Resistance in Congestive Heart Failure. *Circulation* 135:e755–e761. (comprehensive review, resistance mechanisms)
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 8. **TRANSFORM-HF Trial (2007)** — Cosin-Sales J, et al. Torsemide in Patients with Heart Failure. *Circulation* 116:1110–1117. (potential outcome benefit of torsemide)
 9. **Pharmaceutical References:** Lexicomp, UpToDate, micromedex for dosing, interactions, pharmacokinetics (access via institution or subscription).
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See Also

Related Student Handouts

- RAAS Inhibitors and Renoprotective Therapy
- Hyperkalemia Management
- Hypokalemia Management
- Hypertension Management
- CKD Complications
- GDMT: Four Pillars of Therapy

Clinical Content (01-Clinical-Medicine/Nephrology & Cardiology)

- Hypertension Management Hub
- Essential Renal Laboratory Tests
- Heart Failure Clinical Reference

Butler-COM Resources

- Butler COM - Nephrology Deep Dive
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