Brigham and Women's Hospital
Founding Member, Mass General Brigham

Revisiting Electrolytes

Bradley M. Denker, MD.
Clinical Chief
Renal Division, Department of Medicine
Beth Israel Deaconess Medical Center and
Atrius Health
Associate Professor of Medicine
Harvard Medical School

Bradley M. Denker, MD

- State University of New York at Syracuse Medical School
- Medicine Residency at Johns Hopkins Hospital
- Nephrology Fellowship at BWH
- Associate Professor of Medicine@ HMS
- Clinical Chief Nephrology at BIDMC and Atrius Health
  - Clinical focus: General Nephrology, fluids and electrolytes

Financial disclosures

Bradley M. Denker, MD

No conflict of interest to disclose.

Outline

I. Na^+ disorders-

- Hyper- and hyponatremia

II. K^+ disorders

- Hyper- and hypokalemia

Objectives

1. Use physiologic approach to identify dysregulated physiology of:
    1. Sodium disorders
    2. Potassium disorders

2. Identify appropriate treatment for disorder based on physiology

Brief Case

A 26 yr-old otherwise healthy male presents with seizure. No other history available. Euvolemic on exam. Labs return:

Na 115, Serum Osmolality 240mOsm/kg
K 3.5, Cl 88, CO_2 23, BUN 5, Cr 0.7
Urine: Na 40 mEq/L, Osm 45 mOsm/kg

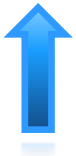
What is the most likely diagnosis:

A. SIADH
B. Hypothyroidism
C. Psychogenic polydipsia
D. Hepatic cirrhosis
E. Adrenal insufficiency

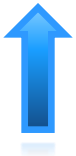
Na^+ disorders

Vast Majority are *Water* Disorders

$[Na^+]$= Amount of Na^+/Amount of H_2O



Renin/Angiotensin/Aldo (RAS) "Volume"



ADH Osmolality/tonicity

Plasma Osmolality ~ 2x $[Na^+]$

Intracellular:
$[Na^+]$=5mEq/L
$[K^+]$=145mEq/L

Extracellular (plasma/interstitial):
$[Na^+]$=145mEq/L
$[K^+]$=5mEq/L

Hyponatremia

$[Na^+]$= Amount of Na^+/Amount of H_2O

$\downarrow Na^+/H_2O$ - Volume Depletion

or

$Na^+/\uparrow H_2O$ - Water Excess; Euvolemic

or

$\downarrow Na^+/\uparrow\uparrow H_2O$ - Combined Volume Depletion + Hypotonic Fluids

RAS ADH

Hyponatremia

P_{osm}

> 290 mOsm/kg	Normal "Pseudohyponatremia"	< 275 mOsm/kg
↑Glucose* Mannitol	Lipid ↑ Protein ↑	Hypoosmolal hyponatremia*

*Correct serum Na^+ by 1.6 for every 100 mg/dL Δ in glucose

**Requires ADH+ Water Intake*

Next Slide

Hypoosmolal hyponatremia

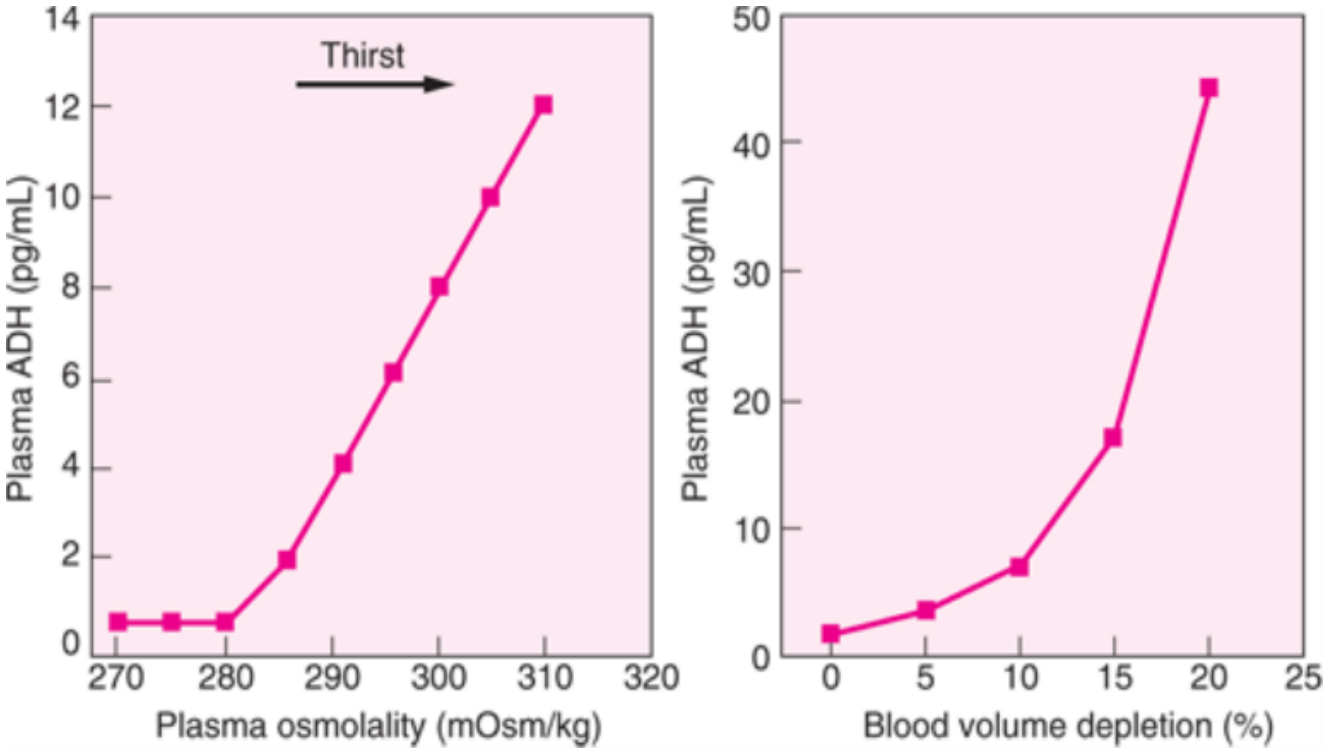
Volume status

Hypovolemic	Euvolemic	Edematous
Dehydration*	Psych. polydipsia†	CHF*
Addison's	SIADH	Liver failure*
Diuretics	Hypothyroid	

* U_{Na} < 20 = *RAS activated*; Extrarenal cause of ECV depletion

†U_{Osm} < 100 = ADH appropriately suppressed

Stimuli for ADH release (Steps 1 and 2!): *Hyperosmolality and volume depletion*



Volume depletion is a **very potent** stimulus for ADH release, whereas an increase in osmolality results in smaller increments of ADH once the threshold is reached

Rennke and Denker, Renal Pathophysiology: The Essentials

Rx of hyponatremia

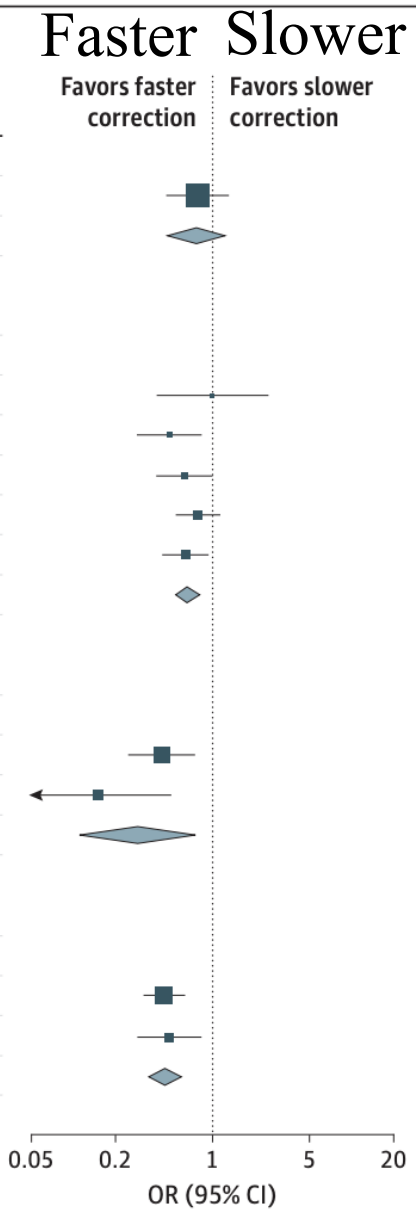
Hypovolemia	Isotonic saline
Polydipsia	Water restriction
SIADH	Water restriction Hypertonic saline / Na tablets Furosemide Aquaretics (“vaptans”)

Rate of correction of hyponatremia

- Acute (< 48 hr, usually due to hypotonic fluid intake) or severely symptomatic
  - 100 mL of 3% saline bolus to increase S_{Na} by 2-3 mEq/L
- Chronic (> 48 hr) including SIADH and asymptomatic
  - 0.5 mEq/l per hour
- Do not exceed Δ8-12 mEq/L in 1st day; more conservative in higher risk patients

Figure 2. Adjusted In-Hospital Mortality by Speed of Correction

Source	Log (OR)	SE	Total No. Faster correction	Total No. Slower correction	OR (95% CI)
Very rapid vs rapid correction					
MacMillan et al,[9] 2023	-0.2485	0.2585	595	823	0.78 (0.47-1.29)
Subtotal (95% CI)			595	823	0.78 (0.47-1.29)
Heterogeneity: NA					
Test for overall effect: $z = 0.96$; $P = .34$					
Rapid vs slow correction					
Geoghegan et al,[22] 2015	0	0.4675	114	211	1.00 (0.40-2.50)
Grim et al,[24] 2021	-0.7133	0.2676	91	197	0.49 (0.29-0.83)
Kinoshita et al,[10] 2023	-0.4711	0.2288	451	573	0.62 (0.40-0.98)
MacMillan et al,[9] 2023	-0.2390	0.1808	823	1538	0.79 (0.55-1.12)
Seethapathy et al,[11] 2023	-0.4463	0.1912	1067	952	0.64 (0.44-0.93)
Subtotal (95% CI)			2546	3471	0.67 (0.55-0.82)
Heterogeneity: $\tau^2 = 0$; $\chi^2_4 = 3.05$; $P = .55$; $I^2 = 0\%$					
Test for overall effect: $z = 3.94$; $P < .001$					
Rapid vs very slow correction					
Grim et al,[24] 2021	-0.8440	0.2767	91	118	0.43 (0.25-0.74)
Turkmen et al,[29] 2022	-1.8991	0.6155	18	145	0.15 (0.04-0.50)
Subtotal (95% CI)			109	263	0.29 (0.11-0.79)
Heterogeneity: $\tau^2 = 0.33$; $\chi^2_1 = 2.44$; $P = .12$; $I^2 = 59\%$					
Test for overall effect: $z = 2.42$; $P = .02$					
Slow vs very slow correction					
Geoghegan et al,[22] 2015	-0.7985	0.1698	114	211	0.45 (0.32-0.63)
Grim et al,[24] 2021	-0.7133	0.2676	0	0	0.49 (0.29-0.83)
Subtotal (95% CI)			114	211	0.46 (0.35-0.61)
Heterogeneity: $\tau^2 = 0$; $\chi^2_1 = 0.07$; $P = .79$; $I^2 = 0\%$					
Test for overall effect: $z = 5.40$; $P < .001$					
Test for subgroup differences: $\chi^2_3 = 7.51$; $P = .06$; $I^2 = 60\%$					



<4-6 to >8-10

Very Rapid vs Rapid

Rapid vs Slow

Rapid vs Very Slow

Slow vs Very Slow

JAMA Intern Med 2025 Vol. 185 Issue 1 Pages 38-51

Osmotic demyelination syndrome

- Central and extrapontine myelinolysis
  - Risk factors :
    - P_{Na} < 105 mmol/L
    - Hypokalemia
    - Malnutrition
    - Alcohol use disorder
    - Liver disease
- Classic CPM presents with dysphagia, quadriparesis, locked-in syndrome
- Can be permanent or fatal
  - **No cases of CPM if total <12mEq/L within 24h *and* <18 in 48h**

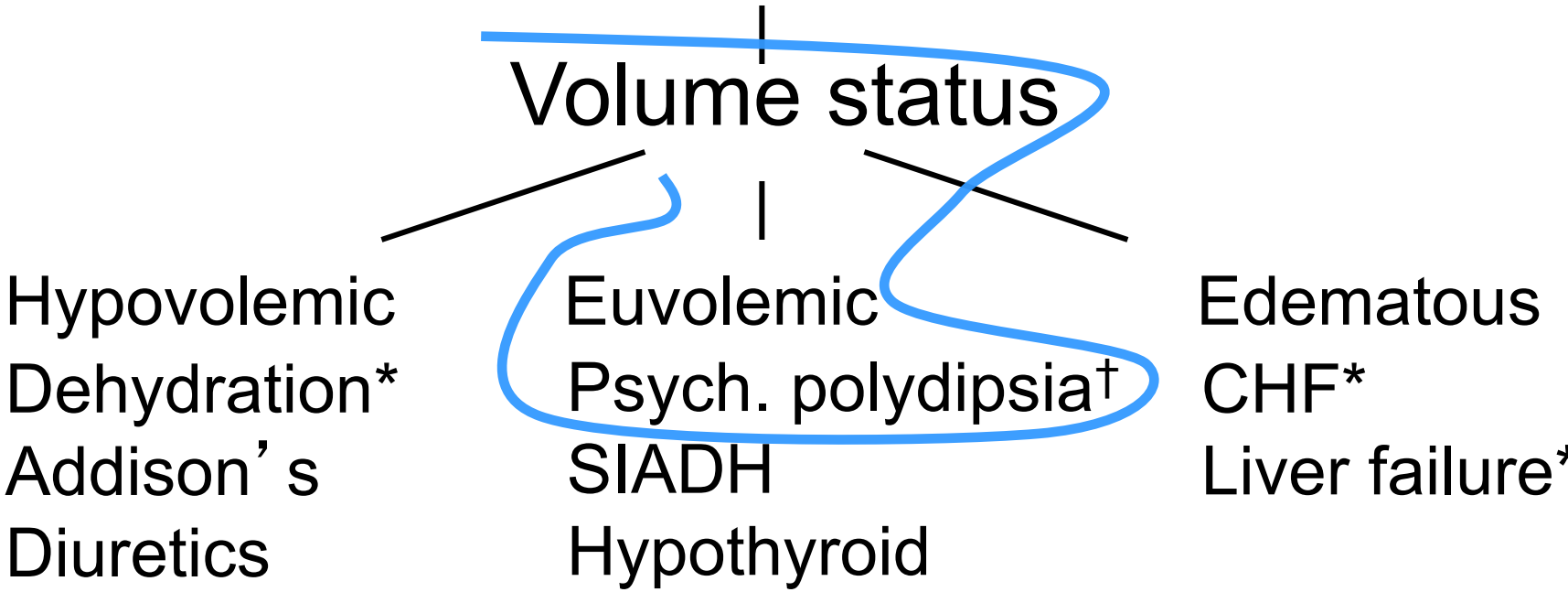
Stern, Clin J Am Soc Nephrol 13: 641–649, 2018

Back to Case:

-Confirmed Hypo-osmolar (Sosm-240)

-Euvolemic

-Ras off (Una>20)/ADH off (Uosm low)



†U_{Osm} < 100 = ADH appropriately suppressed

* U_{Na} < 20 = Extrarenal cause of ECV depletion

Hypernatremia

$[Na^+]$= Amount of Na^+/Amount of H_2O

↑Na^+/H_2O (Rare)

or

$Na^+/$↓H_2O

Water loss: renal versus other sources

Hypernatremia

Urine Osmolality [mOsm/**kg**]

Low < 300

Renal H_2O loss

Diabetes insipidus

- CDI — ADH Deficiency
- NDI — ADH Resistance

Intermediate 300-600

Osmotic diuresis

Glucose, urea, mannitol

High > 800

- **Insensible H_2O loss**
- **GI H_2O loss**

+

↓ Water intake

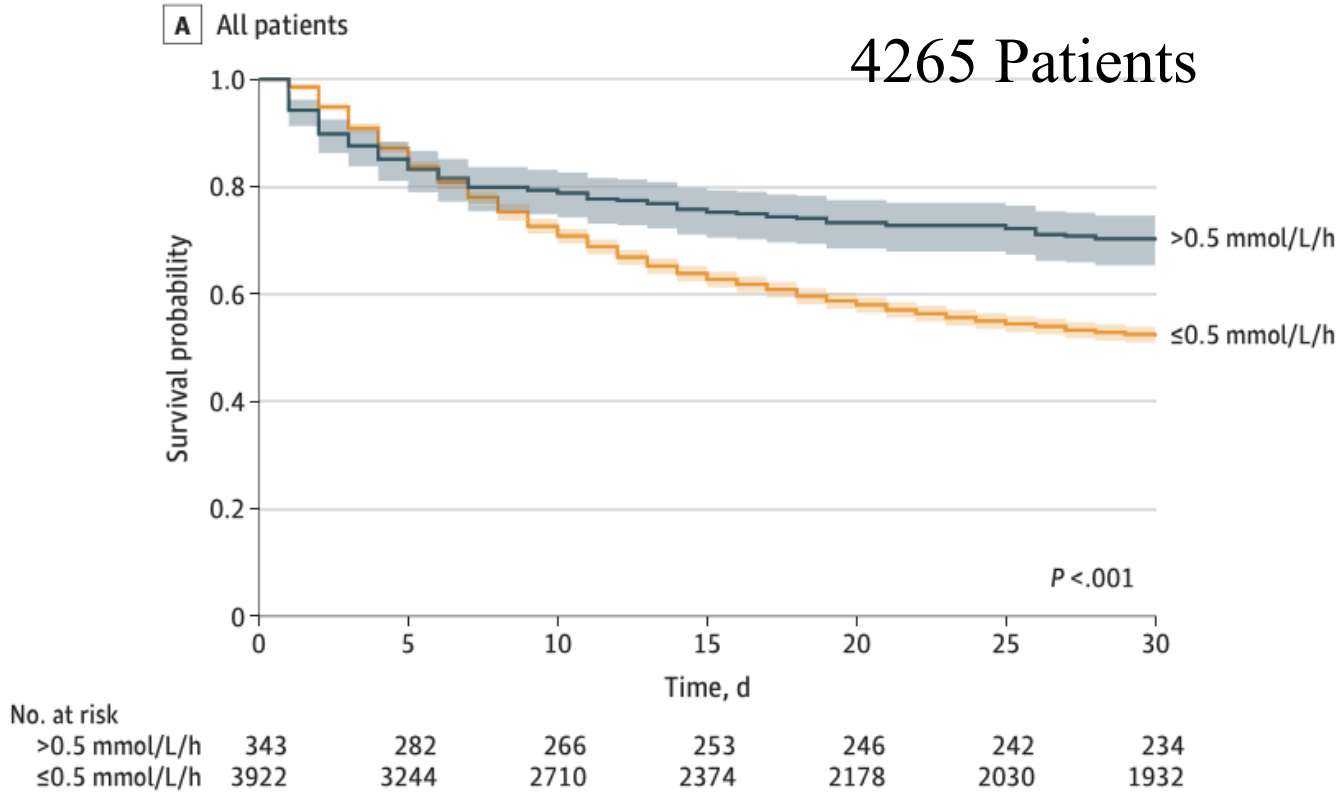
- Na^+ Intoxication

Nephrogenic diabetes insipidus

- Hypokalemia
- Hypercalcemia
- Tubulointerstitial nephropathies
  - Sickle cell disease
  - Myeloma
  - Obstructive uropathy
  - Recovery from ATN or obstruction
  - Lithium
- Chronic renal failure

Management of hypernatremia (I)

Faster (0.5mEq/h)=better outcomes



Rate of Correction and All-Cause Mortality in Patients With Severe Hypernatremia
E. Feigin, L. Feigin, M. Ingbir, O. K. Ben-Bassat and D. Shepshelovich
JAMA Netw Open 2023 Vol. 6 Issue 9 Pages e2335415

Management of hypernatremia (II)

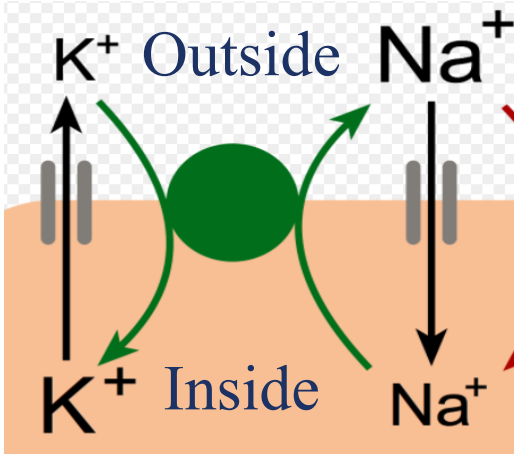
- Treat underlying cause of impaired water intake
- Central DI
  - Vasopressin
- Nephrogenic DI
  - Vasopressin may have partial activity
  - Stop Lithium if possible (but may not reverse)
  - Attempt to reduce urine volume with:
    - Solute/Na restriction
    - Thiazides

Hyperkalemia

- Exclude Pseudohyperkalemia
  - Hemolysed blood sample
  - Leukocytosis/thrombocytosis
  - Check EKG, whole blood potassium (e.g. blood gas analyzer)

K^+ Disorders

Physiology-Na/K ATPase



Extracellular (plasma/interstitial):

$[Na^+]$=145mEq/L

$[K^+]$=5mEq/L

Extracellular Volume ~ 14 Liter

Total K ~70mEq

Intracellular:

$[Na^+]$=5mEq/L

$[K^+]$=145mEq/L

Intracellular Volume ~28L

Total K~4000mEq

Brief Case

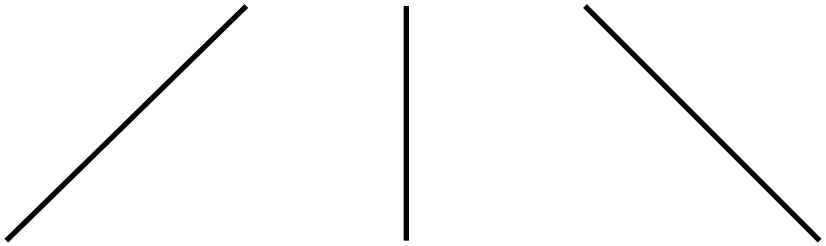
A 75 yr-old male with known coronary and peripheral vascular disease presents with worsening hypertension despite treatment with HCTZ, amlodipine and candesartan.

Na 141, K 3.0, Cl 108, CO_2 29, BUN 25, Cr 1.9

Which diagnostic test is most likely to be useful?

A. Urine diuretic screen
B. Genetic test for mutations in NKCC2
C. CT scan of the adrenal glands
D. Urine metanephrines
E. Doppler ultrasound of the renal arteries

Hypokalemia



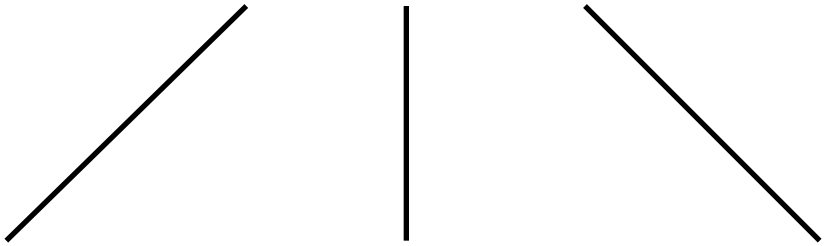
Cellular shift

Alkalemia
Insulin
β-agonist
Hypokalemic periodic paralysis

GI cause

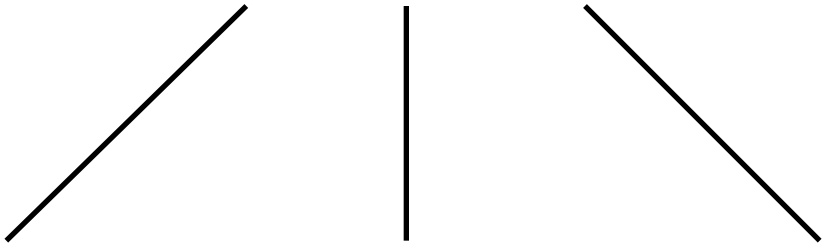
Urinary K wasting

DDX of hypokalemia



Cellular shift	GI cause	Urinary K wasting
Alkalemia	Vomiting	24 hr U_K > 25 mEq
Insulin	Diarrhea	Random U_K/Creat > 13 mEq/g
β-agonist		
Hypokalemic periodic paralysis		

DDX of hypokalemia



Cellular shift

Alkalemia
Insulin
β-agonist
Hypokalemic periodic paralysis

GI cause

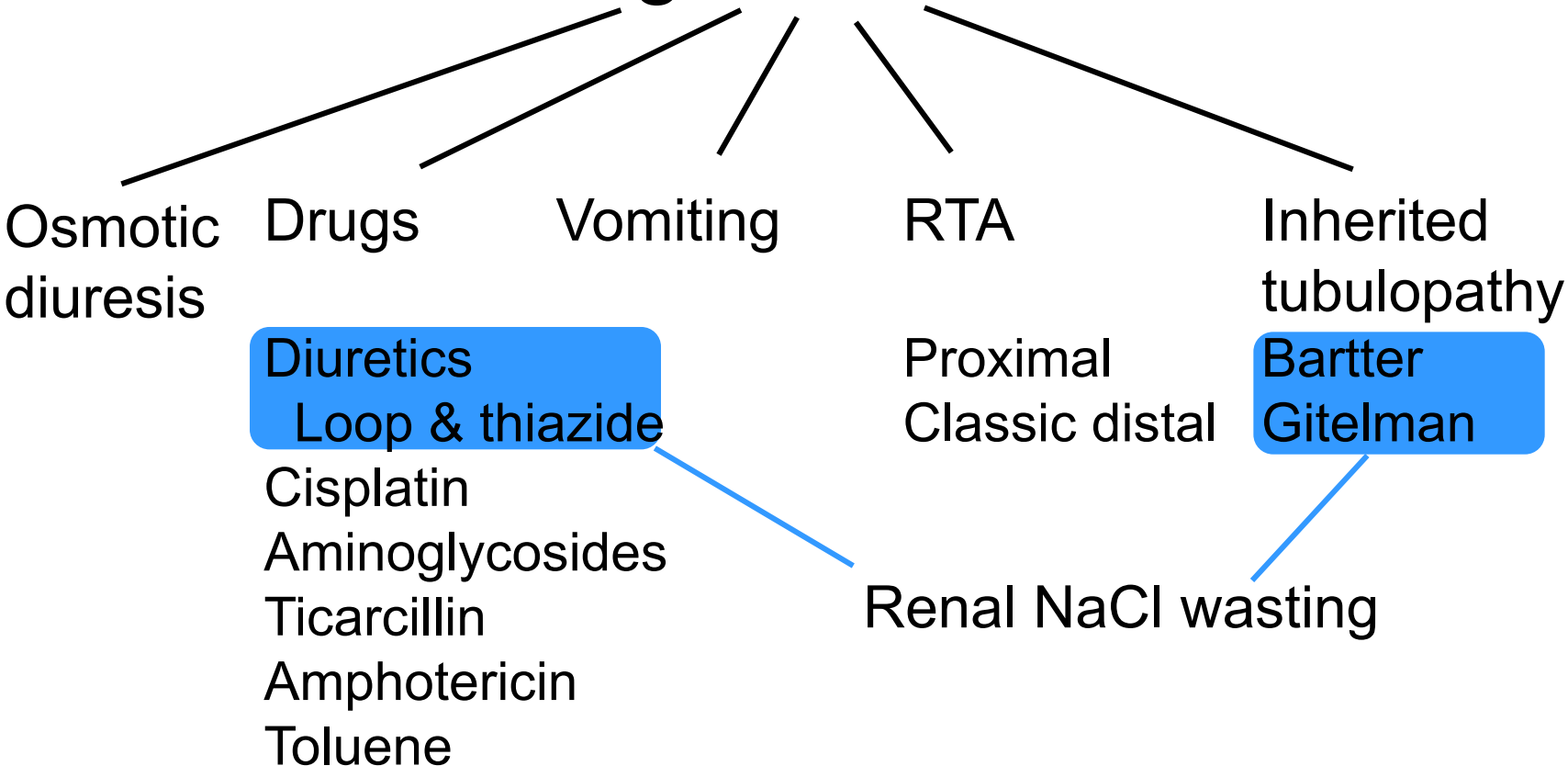
Diarrhea

Urinary K wasting

24 hr U_K > 25 mEq

→ Vomiting

Renal K wasting with normal or low BP



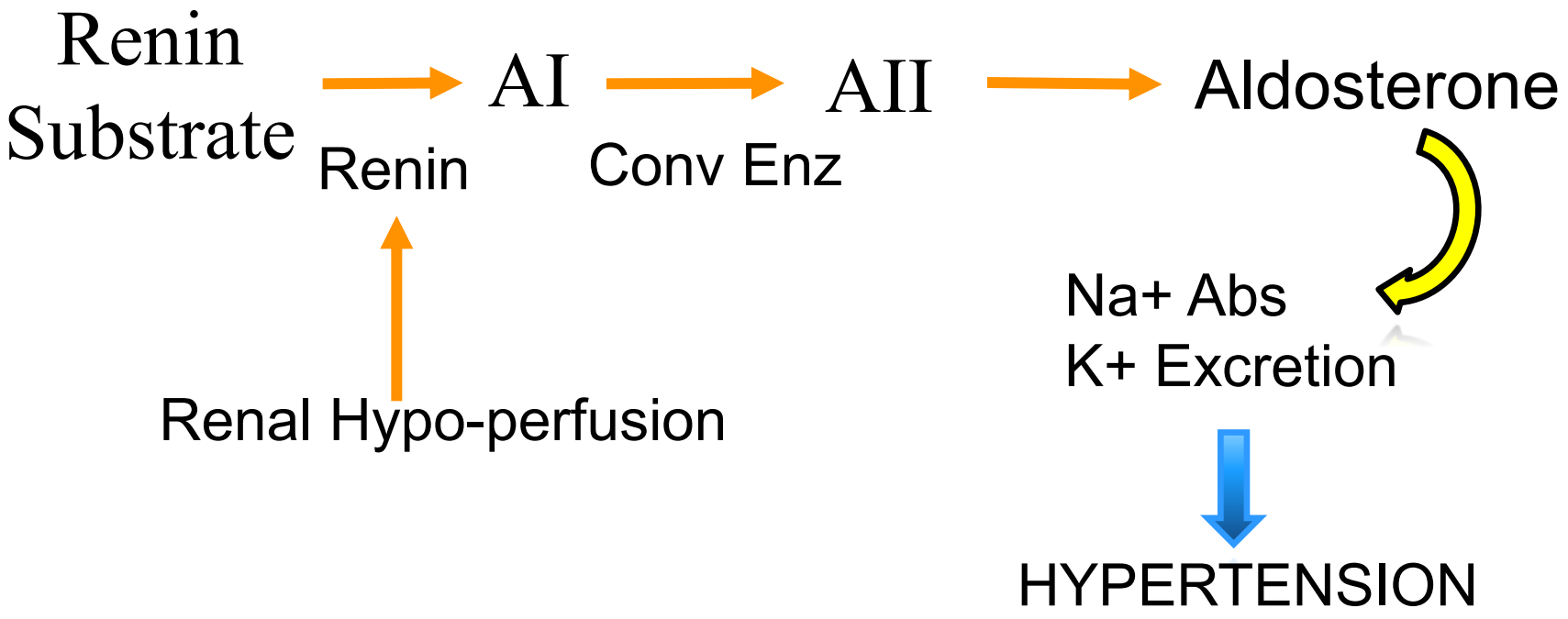
Use of the urine chloride

- In the setting of metabolic alkalosis, urine Cl^- is a more reliable marker of hypovolemia than urine Na^+
- *Low urine Cl^- indicates hypovolemia due to extrarenal (GI) cause*
- *High urine Cl^- in the setting of hypovolemia/euvolemia suggests renal salt wasting*

Cryptogenic hypokalemic metabolic alkalosis

	Volume status/BP	Urine Cl^-	Urine diuretics
Hyperaldosteronism	↑	> 40 mEq/L	-
Surreptitious vomiting	Nl or ↓	< 25 mEq/L	-
Diuretic abuse	Nl or ↓	> 40 mEq/L	+
Bartter/Gitelman syndrome	Nl or ↓	> 40 mEq/L	-

Hypokalemia/Renal K^+ wasting & hypertension



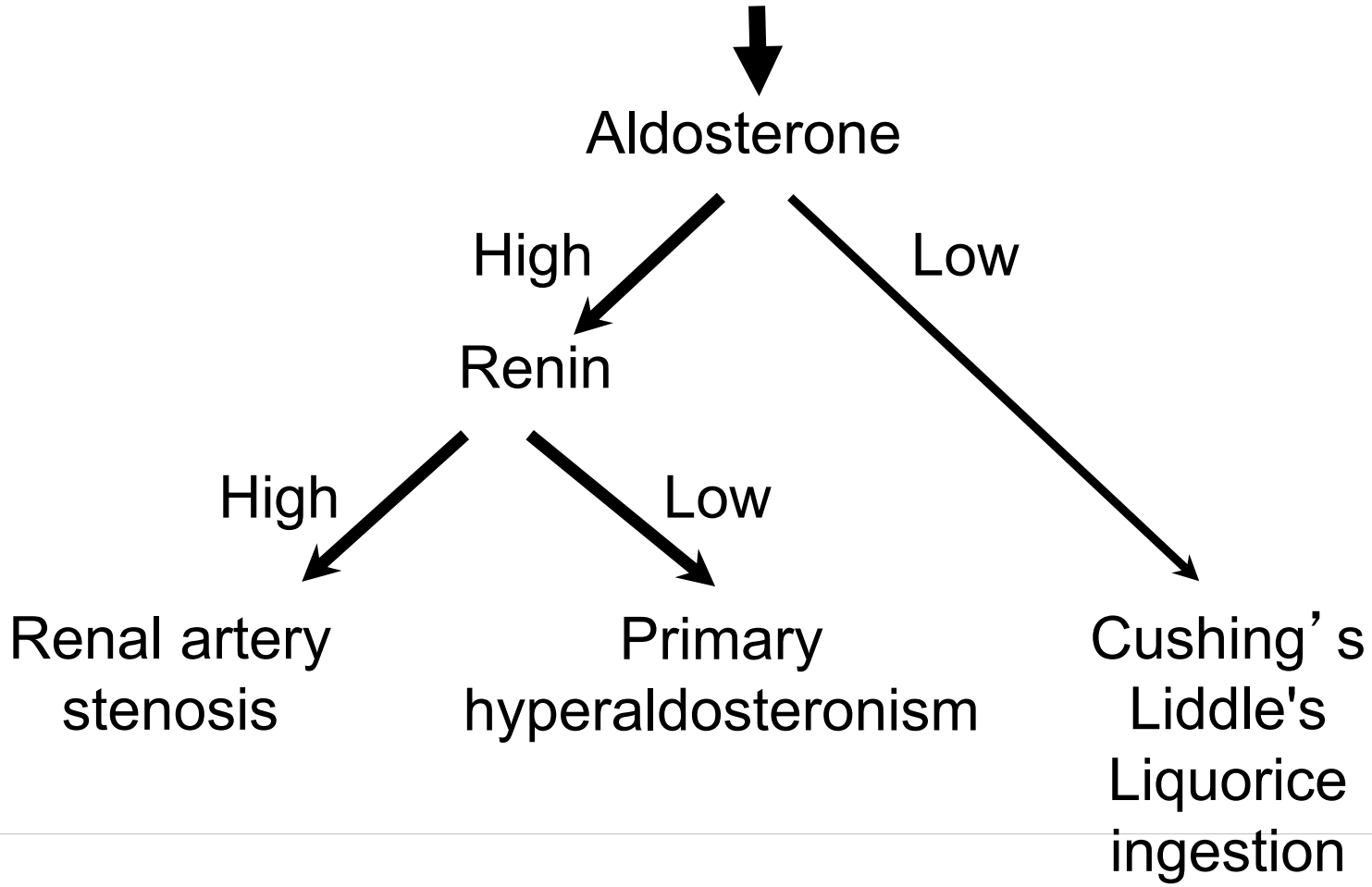
Back to our Case
Vascular disease, HTN, Hypokalemia

Na 141, K 3.0, Cl 108, CO_2 29, BUN 25, Cr 1.9

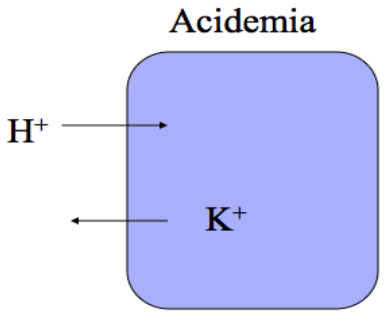
Which diagnostic test is most likely to be useful?

A. Urine diuretic screen – low bp
B. Genetic test for mutations in NKCC2- low bp
C. CT scan of the adrenal glands - Possible
D. Urine metanephrines – no K issues
E. Doppler ultrasound of the renal arteries - Possible

Hypokalemia/Renal K^+ Wasting and Hypertension: Think of Mineralocorticoid Excess Conditions



Hyperkalemia



↑ Intake

Decreased urinary
K^+ excretion
24 hr urine K^+ < 40 mEq

Next Slide

Cell shift
Metabolic acidosis
Hyperglycemia
β-blocker
Digitalis
Hyperkalemic
periodic paralysis
Cell lysis

Decreased urinary K^+ excretion

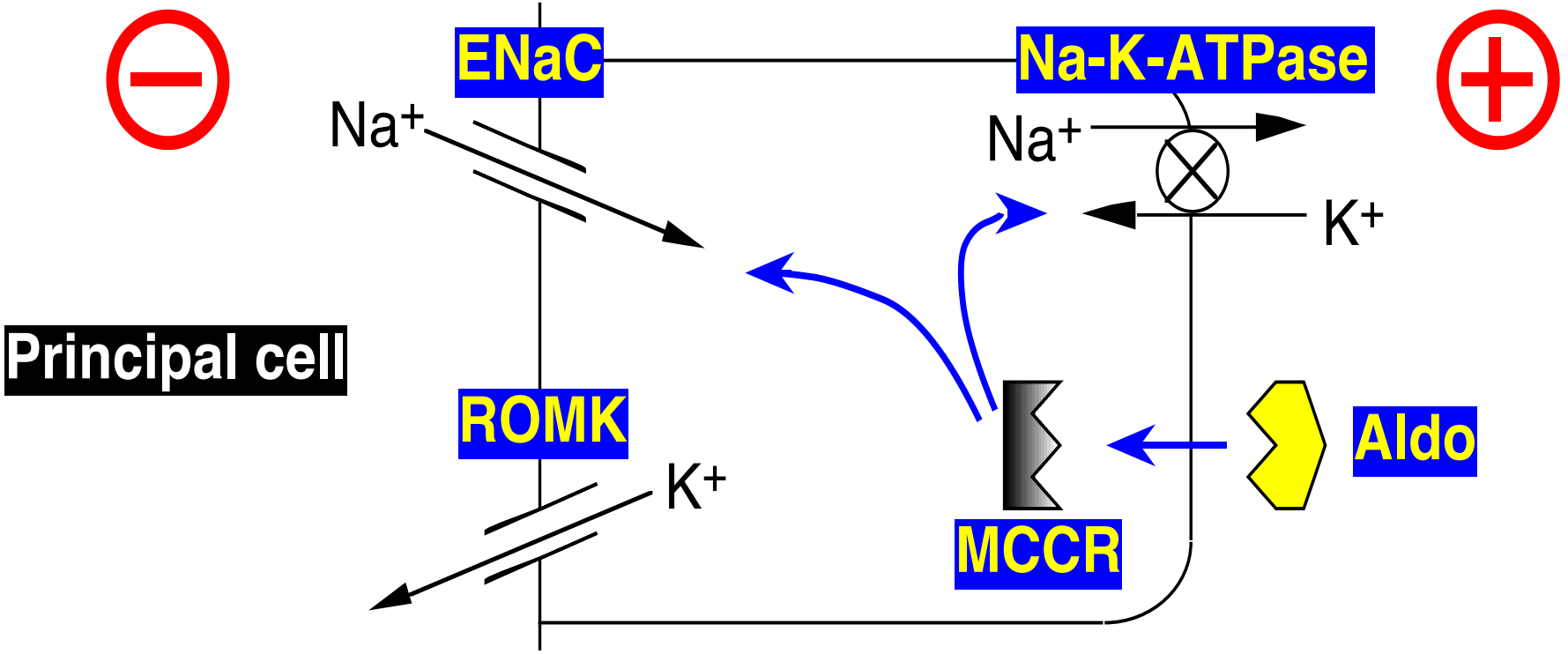
↓GFR

Renal failure

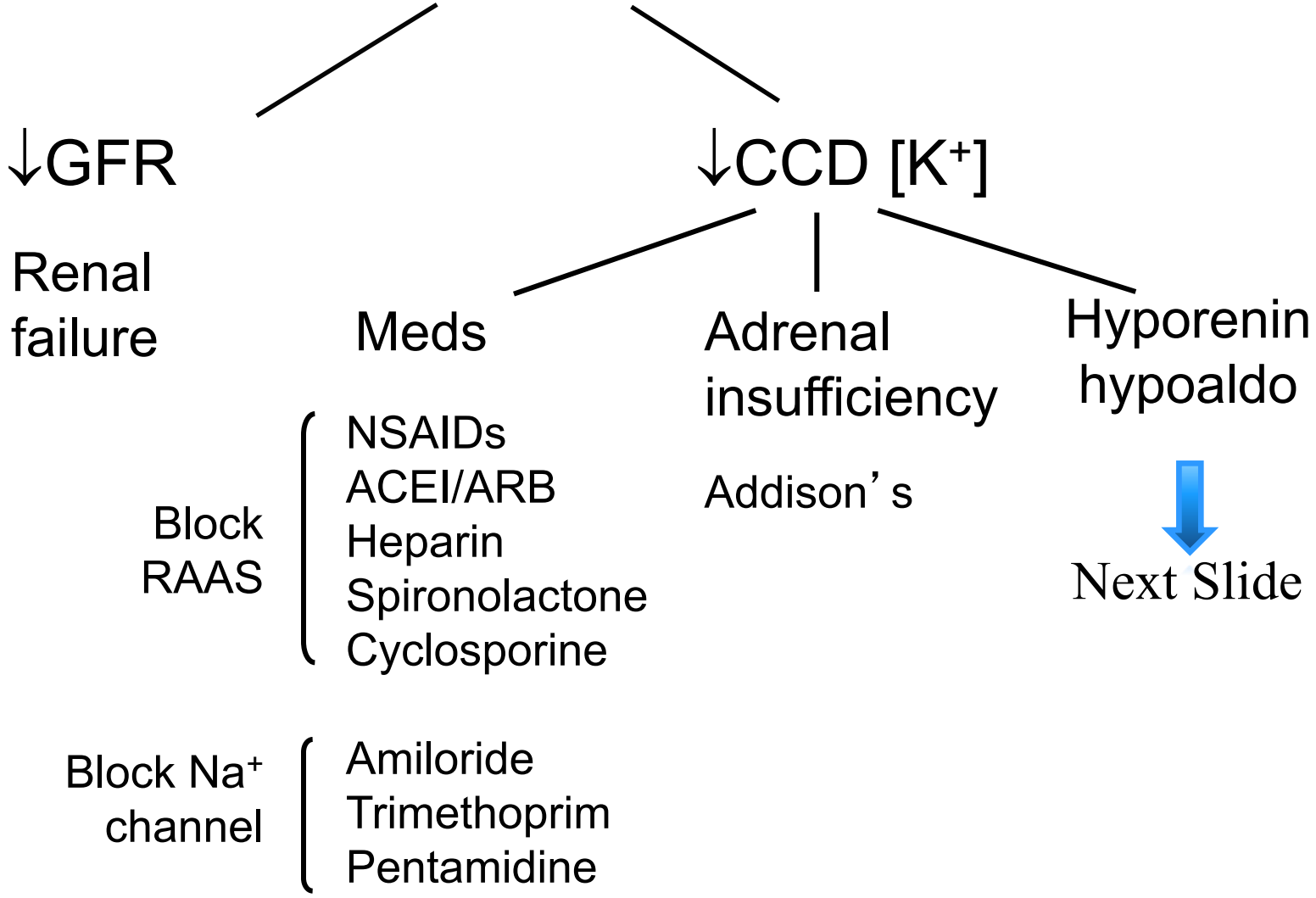
↓CCD [K^+]

Next Slide

Cortical Collecting Duct (CCD)



Decreased urinary K^+ excretion



Type IV RTA (hyporeninemic hypoaldosteronism)

- Hyperkalemia (disproportionate to level of GFR)
- Non-gap metabolic acidosis with normal urine acidifying ability
- Mild CKD
- Often underlying tubulointerstitial disease:
  - DM
  - SLE, obstruction, myeloma/amyloid, HIV etc.
  - *NSAIDs*

Treatment of Hyperkalemia

- Stabilize membrane excitability (does not lower K
  - Calcium chloride or gluconate, 1 g IV
- Increase K^+ entry into cells
  - Glucose 25 g and insulin 10 U
  - β_2-adrenergic agonist (albuterol 10-20 mg inh)
  - $NaHCO_3$
- Removal of excess K^+
  - Cation exchange resin (sodium zirconium cyclosilicate, patiromer, sodium polystyrene)
  - Diuretics
  - Dialysis
- Dietary K^+ restriction

Take Away Messages (1)

- Hypo- and Hyper-Natremia are usually *water imbalances;*
  - Volume depletion (Na loss) stimulates RAS
    - (low Urine Na)
  - Water depletion (hypersomolality) stimulates ADH
    - ADH is *also* stimulated by volume depletion
  - Urine Osmolality (ADH) and Urine Na (RAS) are essential for determining cause

Take Away Messages (2)

- Potassium Disorders
  - The vast majority of K is intracellular
  - Serum K is regulated by intake, cellular shift, and renal excretion
  - Intake alone does not cause elevated serum K
  - Renal K excretion is regulated by GFR, Aldosterone, and distal delivery of Na
  - In Hypokalemia, urine studies can determine renal vs. GI loss
    - However, vomiting results in renal loss of K

Suggested reading

- Rennke, H.G., Denker, B.M., **Renal Pathophysiology – The Essentials**, 5th Edition, Lippincott Williams & Wilkins, 2025

- Mount, D.B., **Fluid and Electrolyte Distrubances**. In Harrison's Principles of Internal Medicine, 21st Edition, Eds. Loscalzo, Joseph; Fauci, Anthony S.; Kasper, Dennis L.; Hauser, Stephen; Longo, Dan; Jameson, J. Larry. Chapter 53

- DuBose, T.D.,Jr. **Acidosis and Alkalosis**. In Harrison's Principles of Internal Medicine, 21st Edition, Eds. Loscalzo, Joseph; Fauci, Anthony S.; Kasper, Dennis L.; Hauser, Stephen; Longo, Dan; Jameson, J. Larry. Chapter 55