Renal Tubular Disorders: Pathophysiology and Clinical Management

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Learning Objectives

By completion of this handout, students will be able to:

1. Understand the pathophysiology of hereditary tubulopathies affecting renal electrolyte and acid-base handling
2. Distinguish Bartter syndrome (Types I-V) from Gitelman syndrome clinically and genetically
3. Recognize and manage renal tubular acidosis (RTA Types 1, 2, and 4)
4. Diagnose Fanconi syndrome and cystinosis; initiate cysteamine therapy
5. Understand nephrogenic diabetes insipidus and differentiate congenital from acquired forms
6. Recognize Liddle syndrome and pseudohypoaldosteronism as monogenic hypertension disorders
7. Understand nephronophthisis and ciliopathies in children
8. Recognize clinical presentation patterns and guide diagnostic workup for each disorder

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I. BARTTER AND GITELMAN SYNDROMES

A. Overview of Bartter and Gitelman Syndromes

Classification: Autosomal recessive salt-wasting tubulopathies characterized by: - **Hypokaliemia** (low serum potassium) - **Metabolic alkalosis** - **Hyperreninemia and hyperaldosteronemia** (secondary to volume depletion) - **NORMAL blood pressure** (distinguishes from pseudohyperaldosteronism) - **Normal renal function** (GFR preserved early; may decline with age)

Historical Context: - Bartter syndrome first described 1962; Gitelman 1966 - Originally called “normotensive hyperreninemic hypokalemic alkalosis” - Genetic characterization began 1990s with identification of mutations in genes encoding ion transporters and signaling molecules

B. Bartter Syndrome Types I-V

Genetic Basis and Pathophysiology:

Type	Gene	Protein	Location	Mechanism
I	SLC12A1	Na-K-2Cl cotransporter (NKCC2)	TAL thick ascending limb	☐ NaCl reabsorption
II	KCNJ1	ROMK potassium channel	TAL, distal collecting duct	☐ K+ recycling in TAL; ☐ positive potential
III	CLCNKB	ClC-Kb chloride channel	TAL, DCT	☐ Cl☐ reabsorption
IV	CASR	Calcium-sensing receptor	TAL	☐ Mg^{2}☐ reabsorption; secondary effects
V	CASR (gain of function)	Calcium-sensing receptor	TAL	Mimics hypercalcemia; ☐ PTH

Pathophysiology (All Types): 1. Defect in salt reabsorption in thick ascending limb (TAL) of loop of Henle 2. ☐ Volume depletion ☐ activation of renin-angiotensin-aldosterone system (RAAS) 3. ☐ Increased sodium reabsorption in distal tubule via epithelial sodium channel (ENaC) 4. ☐ Increased potassium and hydrogen ion secretion in collecting duct 5. ☐ Hypokalemia and metabolic alkalosis 6. ☐ Renal vasoconstriction from angiotensin II (GFR relatively preserved)

Clinical Presentation:

Prenatal/Neonatal (Type I and II particularly): - Polyhydramnios (increased fetal urine output) - Preterm delivery (50% of cases) - Neonatal presentation: Lethargy, poor feeding, muscle weakness, seizures (severe hypokalemia)

Infancy/Early Childhood (Type III typically presents here): - Failure to thrive - Polyuria, polydipsia (impaired concentrating ability; acquired nephrogenic diabetes insipidus) - Recurrent episodes of hypokalemia with muscle weakness, cramps, tetany - Developmental delay if untreated - Craving for salt (salt-wasting state)

Childhood/Adolescence: - Growth failure - Musculoskeletal manifestations: Muscle weakness, fatigue, cramping - Developmental impairment if inadequately treated - Progressive renal insufficiency (Types I-III more likely; incidence increases with age) - Nephrolithiasis risk (alkalosis, hypercalciuria in Types I and II) - Hearing loss (Type IV particularly; associated with mutations affecting chloride channel expression in cochlea)

Type I-Specific Features: - **Most severe in utero presentation** (polyhydramnios, preterm birth common) - Neonatal onset with severe symptoms - Nephrogenic diabetes insipidus (difficulty concentrating urine) - Hypercalciuria and nephrolithiasis risk

Type II-Specific Features: - Neonatal presentation - ROMK channel mutations ☐ severe hyperkalemia possible early (unlike other types) - Rapid progression to severe symptoms

Type III-Specific Features: - Later childhood onset (often age 2-6 years) - Milder symptoms early; progressive - Hearing loss not associated - Somewhat slower progression than Types I-II

Type IV-Specific Features: - CASR mutations ☐ associated hypercalcemia - **Hearing loss**

(sensorineural, progressive) - Polyuria from hypercalcemia - May present with seizures from hypokalemia

Type V-Specific Features: - Gain-of-function CASR mutation - Mimics primary hyperparathyroidism picture - Hypercalcemia, hypercalciuria - Suppressed PTH level (distinguishes from hyperparathyroidism)

Laboratory Findings (All Types):

Finding	Value
Serum potassium	<3.5 mEq/L (often <3.0)
Serum chloride	<98 mEq/L
Serum HCO_3□	>28 mEq/L
Blood pH	>7.45 (alkalemia)
Serum renin	Elevated (5-10× normal)
Plasma aldosterone	Elevated (>15 ng/dL)
Serum sodium	Low-normal to normal
Serum magnesium	Low (especially Type III)
Urinary potassium	Elevated
Urinary chloride	Elevated
Blood pressure	Normal (distinguishes from pseudohypoaldosteronism)
Serum creatinine	Normal early; may rise with age

Diagnostic Approach: 1. Confirm hypokalemic metabolic alkalosis with normal BP 2. Assess renin-aldosterone axis (elevated = consistent with diagnosis) 3. Genetic testing: NKCC2, ROMK, ClC-Kb, CASR gene sequencing 4. Exclude other causes: vomiting, diuretic abuse, hyperaldosteronism 5. **Prenatal diagnosis possible** with early genetic testing (very early onset polyhydramnios suspicious)

Management:

Potassium Replacement: - **Dose:** 1-4 mEq/kg/day (in divided doses; see target below) - **Target serum K+:** 3.5-4.5 mEq/L (higher goals—closer to 4.5—reduce hypokalemia-related symptoms) - **Forms:** Potassium chloride (preferred, replaces both K+ and Cl□), potassium acetate - **Monitoring:** Check serum K+ every 2-4 weeks initially; then every 1-3 months once stable

NSAIDs: - **Mechanism:** Inhibit prostaglandin synthesis □ reduce renal renin release □ reduce secondary aldosteronism □ reduce K+ wasting - **Drugs:** Indomethacin (first-line), ibuprofen, naproxen - **Dosing:** Indomethacin 0.5-1.0 mg/kg/day (divided, max 75 mg/day) - **Efficacy:** Raises serum K+ by 0.5-1.5 mEq/L in majority of patients - **Monitoring:** Monitor renal function, GFR; risk of chronic kidney disease with long-term NSAID use - **Relative contraindications:** Renal insufficiency, GI bleeding, platelet dysfunction - **Duration:** Often lifelong therapy needed; some reduction possible with maturity/improved dietary compliance

ACE Inhibitors/Angiotensin Receptor Blockers: - **Mechanism:** Reduce angiotensin II generation/signaling □ reduce aldosterone secretion - **Less effective alone than NSAIDs** but additive when combined - **Use:** Particularly if NSAID contraindicated or insufficient response - **Caution:** May cause hyperkalemia if renal function declines (monitor K+)

Salt Supplementation: - **Rationale:** Restore intravascular volume; reduce RAAS activation - **Approach:** Encourage dietary salt intake; may need oral salt supplementation - **Risk:** Must balance against hypertension risk if renal function declines with age

Dietary Management: - **High sodium diet** (3-4 g sodium/day) - **Adequate fluid intake** (address polyuria) - **Nutritional support** (growth failure prevention) - **Calcium intake:** Assess for nephrolithiasis risk; evaluate urinary calcium

Specific Management by Type: - **Types I-II (severe):** More aggressive K+ replacement, NSAIDs, may need ACE inhibitor added - **Type III:** Often lower initial severity; respond better to NSAIDs alone; slower progression - **Type IV:** Management of hypercalcemia (thiazide diuretics, adequate hydration)

Long-Term Complications: - Progressive renal insufficiency (30-40% reach ESRD by adulthood in Types I-II; less common in Type III) - Nephrolithiasis - Growth failure if inadequately treated - Hearing loss (Type IV) - Hypertension develops in some patients with aging (paradoxical; mechanism unclear)

Outcome: - Early diagnosis and aggressive replacement therapy improves growth and development - Neurodevelopmental outcome excellent if treated before age 2-3 years - Many patients achieve normal adult height with adequate therapy - Prognosis for renal function variable; progression to ESRD possible but not inevitable

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C. Gitelman Syndrome

Genetics: - Gene: SLC12A3 (chromosome 16q13) - Protein: Thiazide-sensitive sodium-chloride cotransporter (NCCT) in distal convoluted tubule (DCT) - Inheritance: Autosomal recessive - Incidence: 1 in 40,000 live births (more common in some populations: Japan, Turkey)

Pathophysiology: 1. Defect in NCCT ☐ impaired NaCl reabsorption in DCT 2. ☐ Volume depletion ☐ RAAS activation 3. ☐ Increased K+ and H+ secretion in collecting duct (via aldosterone effect) 4. ☐ **Hypokalemia + metabolic alkalosis** 5. Unique feature: **Hypocalciuria** (increased urinary magnesium, decreased urinary calcium)

Clinical Presentation:

Age of Onset: - Usually **age 6-16 years** (later than Bartter; varies widely) - Some present in infancy; others not until adulthood

Symptoms: - Muscle weakness, cramps, tetany (from hypokalemia) - Paresthesias - Polydipsia, polyuria (from hypokalemia-induced nephrogenic DI) - Growth retardation (if untreated) - Fatigue, decreased exercise tolerance - Periodic paralysis (rare; severe hypokalemia)

Clinical Features (Distinguishes from Bartter): - **Hypomagnesemia** (more severe and clinically significant than Bartter) - **Hypocalciuria** (low urinary calcium; distinguishes from Bartter types with hypercalciuria) - **Normal to low serum calcium** (hypokalemia-induced, mild) - **Chondrocalcinosis** (calcium pyrophosphate deposition in joints; occurs from hypomagnesemia) - **Absence of hearing loss** (unlike Bartter Type IV)

Laboratory Findings:

Finding	Value
Serum potassium	<3.5 mEq/L
Serum magnesium	<1.7 mg/dL (often <1.5)
Serum calcium	Normal to low
Serum chloride	<98 mEq/L
Serum HCO_3□	>28 mEq/L
Plasma renin	Elevated
Plasma aldosterone	Elevated
Urinary calcium	**LOW** (<100 mg/day; distinguishes from Bartter)
Urinary magnesium	Elevated
Blood pressure	Normal

Diagnostic Approach: 1. Confirm hypokalemic metabolic alkalosis with normal BP 2. Check serum magnesium (expect marked hypomagnesemia in Gitelman) 3. Check urinary calcium (low in Gitelman; normal-high in Bartter) 4. Genetic testing: SLC12A3 gene sequencing 5. Exclude secondary causes (diuretic abuse, vomiting)

Management:

Potassium Replacement: - Similar to Bartter; however, **repletion often difficult** due to magnesium depletion limiting K+ correction - **Goal:** Serum K+ 3.5-4.5 mEq/L - Forms: Potassium chloride (combined with magnesium replacement often necessary)

Magnesium Replacement: - **Critical difference from Bartter:** Magnesium depletion severe and must be corrected for K+ repletion to be effective - **Oral replacement:** Magnesium oxide, magnesium gluconate - **Dose:** 0.3-0.6 g elemental Mg daily (divided doses; often 2-4 g MgO daily) - **Target serum Mg^2□:** >1.7 mg/dL (ideally >2.0) - **GI side effect:** Diarrhea common (may limit dose); switch formulations if needed - **Monitoring:** Serum Mg^2□ every 4-8 weeks initially; monthly once stable - **Duration:** Lifelong supplementation typically required

NSAIDs: - Similar rationale and dosing as Bartter - **Caution:** NSAIDs may cause GI symptoms; magnesium-containing NSAIDs (magnesium salicylate) may provide additional benefit - Less dramatically effective in Gitelman than Bartter; often used adjunctively

Potassium-Sparing Diuretics: - **Amiloride:** 0.3-0.6 mg/kg/day - **Mechanism:** Blocks ENaC in collecting duct; reduces K+ and H+ secretion - **Efficacy:** May be very effective in Gitelman (better than Bartter response) - **Caution:** Risk of hyperkalemia; must monitor serum K+ - **Role:** Alternative or additive to NSAIDs if response inadequate

Thiazide Diuretics (Paradoxically): - **Hydrochlorothiazide** at very low doses - **Rationale:** TSHould worsen hypokalemia but paradoxically, in Gitelman, may improve symptoms - Proposed mechanism: Increases urinary sodium losses □ improved volume depletion compensation - **Use:** Reserved for severe refractory cases; not first-line

Dietary: - **High sodium diet** (similar to Bartter; 3-4 g daily) - **Adequate magnesium intake** (difficult to achieve orally; supplementation necessary) - **Adequate fluid intake** (address polyuria)

Long-Term Outcome: - **Much better prognosis than Bartter** (renal function typically preserved throughout life) - **Most patients achieve normal adult height and normal development** with adequate therapy - **ESRD very rare** in Gitelman (unlike Bartter with higher progression rate) - **Complications:** Chondrocalcinosis (calcium pyrophosphate deposition) common but often asymptomatic - Early diagnosis and treatment crucial for normal growth and development

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II. RENAL TUBULAR ACIDOSIS (RTA)

A. Overview of RTA

Definition: Metabolic acidosis resulting from dysfunction of renal tubular acid secretion or bicarbonate reabsorption, **WITHOUT significant reduction in GFR**.

Types: - **Type 1 (Distal) RTA:** Impaired acid secretion in collecting duct - **Type 2 (Proximal) RTA:** Impaired HCO_3□ reabsorption in proximal tubule - **Type 4 (Hyperkalemic) RTA:** Aldosterone deficiency or resistance in collecting duct

Note: Type 3 RTA (rare mixed proximal + distal) rarely seen in clinical practice

B. Type 1 (Distal) RTA

Genetics and Etiology:

Primary (Hereditary): - **Autosomal recessive:** Gene SLC4A1 (band 3 anion exchanger; basolateral membrane) or ATP6V0B (vacuolar H+-ATPase) - **Autosomal dominant:** Gene SLC4A1 (missense mutations) - Incidence: Rare; 1 in 10,000 children (variable by ethnicity)

Secondary (More common): - Amphotericin B - NSAIDs (chronic use) - Systemic lupus erythematosus - Sjogren syndrome - Chronic pyelonephritis - Medullary sponge kidney - Kidney transplant rejection

Pathophysiology: - **Distal collecting duct** cannot secrete H+ ions adequately - Result: **Inability to lower urine pH** below 5.5 (normal: <4.5) - □ **Hyperchloremic metabolic acidosis** (normal anion gap) - □ Increased urinary potassium and sodium losses (to maintain electroneutrality; Cl□ is reabsorbed instead) - □ Hypokalemia (often severe) - □ Hypocitraturia (citrate required for acid buffering; wasted in urine) - □ Hypercalciuria (acidosis mobilizes bone calcium; reduced citrate promotes urinary calcium precipitation)

Clinical Presentation:

Infancy/Early Childhood: - Failure to thrive - Recurrent vomiting - Polyuria, polydipsia - Muscle weakness (from hypokalemia) - Developmental delay if untreated - Bone pain (osteomalacia from chronic acidosis)

Childhood/Adolescence: - Growth failure - Bone disease (rickets) - Recurrent nephrolithiasis (calcium phosphate stones despite low urine pH) - Chronic diarrhea (from loss of bicarbonate)

Laboratory Findings:

Finding	Value
Serum HCO3□	<15 mEq/L (may be 10-20)
Serum pH	<7.35 (acidemia)
Anion gap	Normal (<12 mEq/L)
Serum potassium	Often <3.5 mEq/L (hypokalemia)
Serum chloride	High (98-110 mEq/L; hyperchloremia)
Urine pH	>5.5 (inability to acidify)
Urinary potassium	Elevated
Urinary calcium	Elevated (hypercalciuria)
Urinary citrate	Low
GFR	Normal

Diagnostic Confirmation: 1. **Fludrocortisone stimulation test:** Acute acid load (ammonium chloride 0.1 g/kg) □ normal kidneys lower urine pH to <5.5; RTA Type 1 cannot 2. **OR:** Furosemide + fludrocortisone test (alternative)

Management:

Alkali Replacement: - **Goal:** Normalize serum HCO3□ (>20 mEq/L); achieve urine pH <5.5 if possible - **Agents:** Sodium bicarbonate, potassium citrate (preferred; replaces both HCO3□ and K+) - **Dose:** 1-3 mEq/kg/day (divided in 2-4 doses) - **Target:** Serum HCO3□ 20-24 mEq/L - **Titration:** Adjust based on serum HCO3□ checks every 4-8 weeks

Potassium Supplementation: - Often necessary despite bicarbonate therapy - Potassium citrate preferred (addresses both K+ and HCO3□ deficiency) - Avoid potassium chloride (increases Cl□ load, worsening metabolic acidosis)

Prevention of Nephrolithiasis: - Aggressive alkali therapy (maintains higher urine pH, reducing calcium phosphate precipitation) - **Thiazide diuretics:** Hydrochlorothiazide 0.5-1 mg/kg/day (reduces urinary calcium excretion) - **Citrate supplementation:** Potassium citrate (increases urinary citrate, inhibitor of stone formation) - Adequate hydration

Bone Management: - Vitamin D supplementation (1,25-dihydroxyvitamin D3, calcitriol, 0.02-0.08 mcg/kg/day) - Calcium supplementation if deficient - Address acidosis (improves bone metabolism)

Long-Term Outcome: - With adequate alkali and K+ replacement, growth and development normal - Adult height usually normal with early diagnosis and therapy - **Renal function preserved** (GFR normal throughout life unless nephrolithiasis causes obstruction) - **Hearing loss possible** with mutations in vacuolar H+-ATPase genes (genetic hearing loss syndromic association)

C. Type 2 (Proximal) RTA

Genetics: - Autosomal recessive: Gene SLC4A4 (sodium-bicarbonate cotransporter in proximal tubule) - Rare in isolation; often part of syndromic presentation (Fanconi syndrome)

Pathophysiology: - **Proximal tubule** cannot reabsorb filtered HCO3□ adequately - Result: **Bicarbonate wasting in urine** - Serum HCO3□ drops until levels low enough to be filtered

below reabsorption capacity - ☐ **"Equilibrium point"** reached (serum HCO_3☐ usually 15-18 mEq/L) - ☐ Urine pH appropriately low (<5.5); kidneys can acidify normally (distinguishes from Type 1)

Clinical Presentation: - Similar to Type 1: growth failure, bone disease, weakness - Often associated with **Fanconi syndrome** (additional proximal tubular dysfunction: phosphate, glucose, amino acid, urate wasting)

Laboratory Findings:

Finding	Value
Serum HCO_3☐	15-20 mEq/L (less severe than Type 1)
Anion gap	Normal
Urine pH	<5.5 (normal acidification)
Urine HCO_3☐	Elevated
Serum potassium	Variable (hypokalemia possible but often less severe)
GFR	Normal to mildly reduced

Diagnostic Distinction from Type 1: - **Type 1:** Cannot lower urine pH (<5.5 normal); hyperchloremia + hypokalemia prominent - **Type 2:** CAN lower urine pH (<5.5 normally); serum HCO_3☐ less dramatically low

Management: - Alkali replacement: sodium bicarbonate or potassium citrate (similar doses as Type 1) - Large doses often required (may need 5-10 mEq/kg/day) due to continued wasting - Thiazide diuretics: Paradoxically effective in Type 2 (reduce glomerular filtration ☐ reduce HCO_3☐ wasting) - If associated with Fanconi syndrome: additional management required (see Fanconi/Cystinosis section)

D. Type 4 (Hyperkalemic) RTA

Classification:

Type 4A: Hyporenin-Hypoaldosteronism (HHA) - Genetics: Gene mutations in renin, angiotensinogen, or aldosterone synthase - Pathophysiology: Reduced renin-aldosterone response to acid/K+ load - Etiology: Congenital (rare); acquired (diabetes, chronic kidney disease, NSAIDs, ACE inhibitors/ARBs)

Type 4B: Aldosterone Resistance (Pseudohypoaldosteronism) - Genetics: Gene ENaC (epithelial sodium channel); autosomal recessive - Pathophysiology: Receptor or post-receptor defect in collecting duct response to aldosterone - Clinical: Salt-wasting, hyperkalemia, metabolic acidosis despite normal/high aldosterone levels

Pathophysiology (Both Types): - **Impaired potassium secretion in collecting duct** (due to aldosterone deficiency or resistance) - ☐ **Hyperkalemia** (serum K+ >5.5 mEq/L) - ☐ Reduced ammoniagenesis (K+ accumulation suppresses ammonia production) - ☐ **Metabolic acidosis** (reduced renal acid excretion)

Clinical Presentation: - **Hyperkalemia** (primary finding) - Metabolic acidosis (mild-to-moderate) - Cardiac arrhythmias (from hyperkalemia) - Type 4B (pseudohypoaldosteronism): **Salt-wasting, hyperkalemia, hypokalemic features** (muscle weakness despite high K+ due to transcellular shift) - Growth failure if untreated

Laboratory Findings:

Finding	Value
Serum potassium	>5.5 mEq/L
Serum HCO_3□	15-22 mEq/L
Serum pH	<7.35
Anion gap	Normal
Urine pH	Usually >5.5 (cannot fully acidify)

Type 4A-Specific: - Plasma renin: Low (differentiates from Type 4B) - Aldosterone: Low

Type 4B-Specific: - Plasma renin: Elevated (high K+ should stimulate) - Aldosterone: Elevated (resistance to hormone effect)

Management:

Type 4A (Hypoaldosteronism): - **Fludrocortisone:** 0.05-0.2 mg daily (synthetic aldosterone; expands volume, increases K+ excretion) - **Sodium supplementation:** Enhance volume expansion effect - **Diuretics:** Furosemide (promotes K+ wasting; careful with volume status) - Avoid NSAIDs, ACE inhibitors/ARBs (reduce aldosterone)

Type 4B (Aldosterone Resistance): - **Fludrocortisone:** Often **ineffective** (resistance to aldosterone) - **Diuretics:** Loop and thiazide diuretics (promote K+ wasting independent of aldosterone) - **Dietary potassium restriction:** <2 g/day - **Potassium binders:** Sodium polystyrene sulfonate, patiromer (newer agent), sodium zirconium cyclosilicate - **Alkali:** Sodium bicarbonate or potassium citrate (carefully; K+ content)

Long-Term Management: - Regular monitoring of serum K+ and HCO_3□ - Dietary compliance (sodium/potassium balance) - EKG if K+ persistently >6.5 mEq/L (assess for arrhythmia risk)

III. FANCONI SYNDROME AND CYSTINOSIS

A. Fanconi Syndrome

Definition: Generalized dysfunction of renal proximal tubule characterized by **wasting of multiple solutes:** - Phosphate - Glucose - Amino acids - Urate - Carnitine - Bicarbonate (Type 2 RTA features)

Etiology:

Primary (Idiopathic): - Rare; genetic basis incompletely characterized

Secondary (More common): - **Cystinosis** (most common genetic cause) - Tyrosinemia Type 1 - Lowe syndrome (oculocerebrorenal) - Wilson disease - Mitochondrial diseases - Dent disease

- Heavy metals (mercury, lead, cadmium) - Drugs: Aminoglycosides, amphotericin B, ifosfamide, tenofovir, adefovir

Pathophysiology: - Mitochondrial dysfunction; impaired cellular energy production - Loss of intact proximal tubule cells (epithelial cell damage) - Impaired active reabsorption mechanisms for small solutes and proteins

Clinical Presentation:

Infantile Onset (Cystinosis): - Failure to thrive (first year of life) - Recurrent vomiting, anorexia - Polyuria, polydipsia - Rickets (phosphate wasting ☐ hypophosphatemia) - Photophobia, eye pain (cystine crystal accumulation in cornea) - Growth failure

Delayed Presentations (Other etiologies): - Variable age of onset - Growth failure - Bone disease (rickets) - Renal insufficiency (progressive in some types)

Laboratory Findings:

Solute	Finding
Glucose	Glycosuria (glucose <400 mg/dL)
Amino acids	Aminoaciduria (generalized, low/high-molecular-weight)
Phosphate	Hypophosphatemia; increased urinary phosphate
Urate	Hypouricemia; increased urinary urate
Carnitine	Low serum carnitine
Bicarbonate	Often HCO_3☐ wasting (Type 2 RTA features)
Protein	Low-molecular-weight proteinuria
Potassium	Hypokalemia
Renal function	Normal initially; may decline with progression

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B. Cystinosis

Genetics: - Gene: CTNS (cystine transporter 1; chromosome 17p13) - Inheritance: Autosomal recessive - Incidence: 1 in 100,000-200,000 live births

Pathophysiology: - **Defect in cystine efflux transporter** in lysosomal membrane - ☐ **Cystine accumulation in lysosomes** (cystine cannot exit; accumulates in crystals) - ☐ Cellular toxicity; apoptosis of renal tubular cells - ☐ Proximal tubule dysfunction (Fanconi syndrome) - ☐ Progressive accumulation in other organs (eye, bone, thyroid, pancreas, CNS)

Clinical Presentation:

Infantile-Onset Nephropathic Cystinosis (Most common, 95% of cases):

Infancy (0-1 year): - Presentation age 3-6 months typically - Failure to thrive, poor growth - Polyuria (2-4 liters/day; up to 10 in severe cases) - Recurrent vomiting, anorexia - Severe dehydration risk (large urinary losses) - Rickets (develops within first year)

Early Childhood (1-5 years): - Growth failure becomes apparent (significant growth deficit if untreated) - Photophobia and eye pain (cystine crystalline deposits in cornea; "cystine crys-

tals") - Ocular findings: Crystal deposits in cornea (anterior and posterior surface), conjunctiva, retina; can lead to reduced visual acuity - Fanconi syndrome fully apparent: phosphate wasting, aminoaciduria, glycosuria

Progression to ESRD: - Progressive renal insufficiency; most reach ESRD by age 10 years if untreated - **With cysteamine therapy:** ESRD delayed to age 20-30s (dramatic improvement in prognosis) - Without therapy: Renal failure by age 6-10 years

Ocular Manifestations (Distinctive): - Photophobia, eye pain (due to crystalline deposits) - Corneal crystals (bilateral, anterior and posterior) - Visual impairment (progressive) - Retinal crystals (uncommon but possible) - **Cystine crystal deposition in eye is PATHOGNOMONIC** for cystinosis

Other Organ Involvement (Late manifestations without treatment): - Pancreatic insufficiency (diabetes mellitus; pancreatic enzyme deficiency) - Thyroid dysfunction (hypothyroidism) - Neurodegeneration (tremor, myopathy, CNS involvement) without therapy - Bone disease (rickets from phosphate wasting, vitamin D deficiency)

Adolescent/Adult-Onset Cystinosis (Rare, <5% of cases): - Slower progression - May not reach ESRD until adulthood or remain stable - Ocular symptoms may be mild

Laboratory Findings: - **Elevated urinary cystine** (hallmark finding; >300 mg/day normal <100) - **Elevated leukocyte cystine content** (diagnostic; >2 nmol half-cystine per mg protein normal <0.2) - Fanconi syndrome features: Glycosuria, amino aciduria, hypophosphatemia, hyperparathyroidism - Progressive renal insufficiency (serum creatinine rises; GFR declines) - Elevated PTH, FGF23

Diagnosis: 1. Clinical suspicion: Fanconi syndrome + photophobia + ocular crystals (pathognomonic) 2. Elevated 24-hour urinary cystine (>300 mg/day) 3. **Leukocyte cystine content** (definitive; >2 nmol/mg protein diagnostic) 4. Genetic testing: CTNS gene sequencing (confirms; allows for family counseling) 5. Slit-lamp examination: Shows crystalline deposits in cornea/conjunctiva

Management:

Cysteamine Therapy (Cystine-Depleting Agent): - **Mechanism:** Converts cystine to cysteine (plus cysteine-cysteamine disulfide) via mixed disulfide formation; products can exit lysosome - **Drug:** Cysteamine hydrochloride (Cystagon) or cysteamine bitartrate (Procysbi, delayed-release) - **Dosing:** - **Standard cysteamine:** 1.3 g/m²/day (divided into 4 doses every 6 hours; OR can divide into 2 doses of delayed-release) - **Delayed-release (Procysbi):** 0.65 g/m²/dose twice daily (more convenient; lower GI side effect profile) - **Target:** Leukocyte cystine content <1 nmol/mg protein (goal is <0.5) - **Dosing adjustment:** May require 1.3-1.9 g/m²/day depending on response

Efficacy: - **Renal function:** Delays progression to ESRD by 10+ years; some patients never reach ESRD with early therapy - **Growth:** Normalizes with adequate cysteamine (if started <age 2 years) - **Ocular protection:** Reduces cystine crystal deposition; slows/prevents corneal damage - **Pancreatic:** May slow development of diabetes (unclear if preventive)

Side Effects: - GI: Nausea, vomiting, abdominal pain (particularly early; improved over time or with delayed-release formulation) - Odor: Characteristic rotten egg smell (due to cysteamine metabolism) - Rash (rare; discontinue if severe) - Neuropsychiatric: Depression (reported; monitor mood)

Monitoring: - Leukocyte cystine content every 3-6 months; adjust dose to maintain <1 nmol/mg protein - Serum creatinine and eGFR: Every 3-6 months - Urinalysis, serum phosphate, potassium, calcium every 3-6 months - Ophthalmology: Slit-lamp exam annually; assess visual acuity

Additional Management:

1. **Renal Replacement Therapy:**
   - **Target GFR:** Initiate dialysis/transplantation when GFR <15 mL/min/1.73 m^2
   - **Transplantation:** Often recommended; cysteamine continued post-transplant
   - **Recurrence:** Cystinosis recurs in transplanted kidney (cystine accumulation begins again); cysteamine continues to work
2. **Bone Management:**
   - Phosphate binders: Calcium carbonate, sevelamer
   - Vitamin D supplementation: Calcitriol 0.02-0.08 mcg/kg/day (adjust for serum calcium)
   - Calcium supplementation
3. **Metabolic Acidosis:**
   - Sodium bicarbonate or potassium citrate (if RTA features present)
4. **Growth Support:**
   - Ensure adequate caloric and protein intake
   - Growth hormone therapy if marked growth failure despite medical management
5. **Pancreatic Monitoring:**
   - Screen for diabetes starting age 5-10 years (HbA1c, glucose tolerance test)
   - Pancreatic enzyme replacement if insufficiency develops
6. **Ocular Care:**
   - Protective sunglasses
   - Corneal lubricant eye drops
   - Ophthalmology follow-up
7. **Neurological Monitoring:**
   - Assess for tremor, weakness, encephalopathy (late manifestations of systemic cystinosis)

Long-Term Outcome with Early Cysteamine Therapy: - **Renal:** ESRD typically delayed to age 20-30s (vs. 6-10 years without therapy) - **Growth:** Normal height achievable with early therapy initiation (<age 2 years) - **Visual:** Slowed progression of ocular crystals; visual function better preserved - **Neurological:** Risk of late neurodegenerative complications reduced but not eliminated - **Quality of life:** Significantly improved with early diagnosis and cysteamine initiation

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IV. NEPHROGENIC DIABETES INSIPIDUS (NDI)

A. Overview

Definition: Inability of kidney collecting duct to respond to antidiuretic hormone (ADH/vasopressin) ☐ **inability to concentrate urine** ☐ massive polyuria.

Classification: 1. **Congenital:** Genetic mutations 2. **Acquired:** Medications, metabolic abnormalities, chronic kidney disease

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B. Congenital Nephrogenic Diabetes Insipidus

Genetics:

X-Linked NDI (Most common, 90% of familial cases): - Gene: AVPR2 (vasopressin receptor 2 V2R; X chromosome) - Hemizygous males: Severe phenotype - Heterozygous females: Variable severity (X-inactivation affects manifestation)

Autosomal Recessive NDI (Less common): - Gene: AQP2 (aquaporin-2 water channel on chromosome 12) - Both sexes equally affected

Pathophysiology: - **V2R mutation:** Collecting duct principal cells cannot respond to ADH signaling ☐ no aquaporin-2 insertion into apical membrane - **AQP2 mutation:** Water channel absent or non-functional; cannot transport water across cell membrane - Result: **Unable to reabsorb water from collecting duct ☐ massive urine output (5-15 liters/day)**

Clinical Presentation:

Neonatal Period: - **Hypernatremia** (often severe; Na+ >150 mEq/L) - High osmolality (>300 mOsm/kg) - Polyuria (large output despite dehydration) - Failure to pass meconium (some cases; severe dehydration) - Fever, lethargy, seizures (from severe hypernatremia) - Diagnosis may be made emergently in NICU for hypernatremia

Infancy/Early Childhood: - Persistent polyuria (5-15 liters/day in untreated cases) - Severe polydipsia (if access to water; comatose if denied water) - Growth failure - Developmental delay (if recurrent hypernatremic episodes) - Nephrogenic polyuria refractory to desmopressin (DDAVP)

Later Childhood: - Chronic thirst; large fluid intake required - Massive polyuria (unresponsive to desmopressin) - Growth can be normal if water access adequate - Behavioral/emotional impact (frequent urination, bed-wetting)

Laboratory Findings:

Finding	Value
Serum sodium	>145 mEq/L (hypernatremia; often severe)
Serum osmolality	>300 mOsm/kg
Urine output	5-15 liters/day (polyuria)
Urine osmolality	<300 mOsm/kg (dilute; inability to concentrate)
Urine specific gravity	<1.005 (very dilute)
ADH (vasopressin)	Elevated (appropriate for osmolality; fails to produce renal response)
Renal function	Normal GFR initially
Serum potassium	Variable; may be elevated with dehydration

Diagnostic Confirmation: 1. **Desmopressin (DDAVP) trial:** - Central DI responds with ☐ polyuria, ☐ urine osmolality - NDI shows **no response** to desmopressin (hallmark finding) 2. Genetic testing: AVPR2 or AQP2 gene sequencing

Management:

Hydration: - **Free access to water at all times** (critical; risk of severe dehydration/hypernatremia if access restricted) - Large, frequent water intake required (5-15 liters/day) - In infants: Breast/bottle feeding with water offered frequently between feeds - Education: Family must understand critical importance of unlimited water access

Thiazide Diuretics: - **Hydrochlorothiazide:** 1-2 mg/kg/day (divided) - **Mechanism:** Produces mild volume depletion ☐ increased proximal tubule sodium + water reabsorption ☐ ☐ urine output to collecting duct - **Efficacy:** Reduces polyuria by 30-50% (additive with NSAIDs) - **Monitor:** Electrolytes, renal function, volume status

NSAIDs: - **Indomethacin:** 0.5-1 mg/kg/day - **Mechanism:** Inhibits prostaglandin synthesis; reduces cAMP in collecting duct; ?direct effect on aquaporins - **Efficacy:** Modest reduction in polyuria (20-30%) - **Caution:** Monitor renal function; risk of chronic kidney disease with long-term use

Amiloride (Potassium-Sparing Diuretic): - **Dose:** 0.3-0.6 mg/kg/day - **Mechanism:** Blocks ENaC in collecting duct; reduces intracellular Na+, enhancing aquaporin-2 expression - **Particularly useful if X-linked NDI** (may be more effective than other agents) - **Monitor:** Serum potassium (risk of hyperkalemia)

Combined Therapy: - Often more effective: Thiazide + NSAID + amiloride - Goal: Reduce polyuria to 3-5 liters/day (more manageable)

Renal Complications: - **Medullary nephrolithiasis** (calcium phosphate stones from chronic dehydration) - **Hydronephrosis** (from recurrent dehydration episodes) - **Chronic kidney disease** (from repeated osmotic injury; progressive in some cases)

Long-Term Outcome: - Life-threatening complications if water access restricted - Normal growth possible with adequate management - Neurodevelopmental outcome depends on frequency/severity of hypernatremic episodes - Renal function usually preserved but at risk for late CKD - Social impact: Frequent urination, school disruption, psychological burden

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C. Acquired Nephrogenic Diabetes Insipidus

Common Causes:

Category	Examples
Medications	Lithium (common), amphotericin B, cisplatin, demeclocycline, NSAIDs
Metabolic	Hypercalcemia, hypokalemia
Renal disease	Chronic pyelonephritis, medullary sponge kidney, polycystic kidney disease
Systemic	Sickle cell, amyloidosis, sarcodosis

Management: - Address underlying cause (discontinue offending drug if possible) - Hydration, thiazide + NSAID therapy - More responsive to desmopressin than congenital NDI (partial response common)

V. LIDDLE SYNDROME

Genetics: - Gene: SCNN1B or SCNN1G (epithelial sodium channel, ENaC, beta or gamma subunit) - Inheritance: Autosomal dominant - Mutations: Gain-of-function (increased channel activity or stability)

Pathophysiology: - **Overactive ENaC in collecting duct** ☐ enhanced sodium reabsorption - ☐ Increased potassium secretion (electroneutrality) - ☐ **Severe hypokalemia** - ☐ Increased hydrogen ion secretion - ☐ **Metabolic alkalosis** - ☐ Sodium retention ☐ **hypertension** - Suppressed renin and aldosterone (due to volume expansion)

Clinical Presentation: - **Early-onset hypertension** (childhood or adolescence; sometimes neonatal hypertension) - **Severe hypokalemia** (serum K+ 2.5-3.5 mEq/L) - **Metabolic alkalosis** - Muscle weakness, cramps, tetany (from hypokalemia) - Normal renal function

Laboratory Findings:

Finding	Value
Blood pressure	Elevated (>95th percentile for age/height)
Serum potassium	<3.5 mEq/L (often <3.0)
Serum sodium	High-normal to high
Serum chloride	Low
Serum HCO_3 ☐	>28 mEq/L (alkalosis)
Plasma renin	**LOW** (distinguishes from primary hyperaldosteronism)
Aldosterone	**LOW** (distinguishes from hyperaldosteronism)
GFR	Normal

Key Distinguishing Features: - **Hypertension + hypokalemia + metabolic alkalosis + LOW renin + LOW aldosterone** = Liddle syndrome - Contrast: Primary hyperaldosteronism also has hypertension + hypokalemia + alkalosis, but renin/aldosterone elevated

Management: - **Potassium-sparing diuretics:** Amiloride (0.3-0.6 mg/kg/day) or triamterene - Blocks overactive ENaC directly; very effective in Liddle - Raises serum K+ dramatically - **Avoid:** Potassium supplementation alone (ineffective; ENaC still causes excessive K+ wasting); NSAIDs; ACE inhibitors/ARBs (don't address primary ENaC problem) - **Blood pressure control:** Amiloride usually sufficient; may need additional antihypertensive if BP not controlled - **Genetic counseling:** Autosomal dominant; 50% risk to offspring

Outcome: - Excellent with amiloride therapy - Normal growth and development - Normal renal function - Blood pressure control achieved

VI. PSEUDOHYPOALDOSTERONISM (PHA)

Classification:

Type 1 (PHA1) - Autosomal Recessive Form (Systemic):

Genetics: - Gene: SCNN1B, SCNN1G (ENaC subunits; same genes as Liddle but recessive loss-of-function mutations) - Inheritance: Autosomal recessive

Pathophysiology: - **Loss-of-function ENaC mutations** ☐ collecting duct cannot reabsorb sodium adequately - ☐ Salt-wasting (sodium cannot be reabsorbed; wasted in urine) - ☐ **Hyperkalemia** (reduced positive charge gradient; K+ cannot be secreted) - ☐ **Metabolic acidosis** (H+ cannot be secreted; K+ competes for secretion) - ☐ **Elevated renin and aldosterone** (volume depletion stimulates RAAS; kidneys fail to respond despite high aldosterone)

Clinical Presentation: - **Severe salt-wasting** (neonatal; failure to thrive) - Hyperkalemia (serum K+ 6-8 mEq/L) - Metabolic acidosis - Elevated BP in some cases (paradoxically; mechanism unclear; perhaps from renin-angiotensin effects) - Recurrent hyperkalemic episodes if sodium restricted

Laboratory Findings:

Finding	Value
Serum sodium	Low to normal; hyponatremia possible
Serum potassium	**HIGH** (6-8 mEq/L)
Serum HCO_3☐	<20 mEq/L (metabolic acidosis)
Plasma renin	**Elevated** (appropriate for salt-wasting)
Aldosterone	**Elevated** (appropriate for hyperkalemia/acidosis)
Urinary sodium	Elevated (sodium-wasting)
Urinary potassium	Low (inability to excrete K+)
GFR	Normal

Key Distinguishing Features from Other Hyperkalemic States: - **Aldosterone ELEVATED** (not suppressed as in Liddle syndrome) - Salt-wasting phenotype (not hypertension as in Liddle) - **Resistant to aldosterone:** High aldosterone but kidneys cannot respond (ENaC non-functional)

Management: - **High sodium diet** (3-4 g sodium/day); may need parenteral sodium in severe neonatal cases - **Fluid resuscitation:** Address volume depletion - **Potassium restriction:** <2 g/day - **Diuretics:** Loop diuretics (furosemide) for K+ wasting; **avoid potassium-sparing agents** (contraindicated) - **Potassium-lowering agents:** Sodium polystyrene sulfonate, patiromer (in acute severe hyperkalemia) - **Alkali:** Sodium bicarbonate (addresses acidosis; also Na+ supplementation) - **Avoid medications:** ACE inhibitors, ARBs, NSAIDs (increase hyperkalemia risk)

Prognosis: - Excellent if salt intake maintained - Growth normal with adequate sodium - Renal function preserved (assuming no obstruction from hyperkalemia-induced effects)

VII. NEPHRONOPHTHISIS AND CILIOPATHIES

A. Nephronophthisis

Definition: Progressive, bilaterally symmetric tubulointerstitial nephritis leading to renal insufficiency; most common genetic cause of ESRD in children (4-10% of pediatric ESRD).

Genetics: - **Autosomal recessive inheritance** (most common) - Gene: NPHP genes (NPHP1-13; mutations encode proteins involved in ciliary structure/function) - Most common: NPHP1 (del chromosome 2q13, homozygous in 85% of Northern European cases)

Pathophysiology: - **Defect in primary cilium** structure or function in renal tubular epithelial cells - Primary cilium: Sensory organelle; involved in fluid flow sensing, cell-cell signaling - Loss of ciliary function ☐ abnormal cell signaling ☐ tubulointerstitial inflammation - Characteristic histology: Corticomedullary cysts (medullary or inner cortical cysts); chronic tubule-interstitial fibrosis; glomeruli initially spared

Clinical Presentation:

Early Childhood (Age 1-10 years, typically): - Polyuria, polydipsia (earliest symptom; from distal tubule dysfunction) - Nocturnal enuresis (common) - Anemia (mild; from CKD) - Growth failure - Progressive renal insufficiency; serum creatinine rising

Progression: - Progressive loss of renal function; GFR declining - Median age at ESRD: 13 years (range 5-20+; depends on genotype) - NPHP1 deletions: Earlier ESRD (median age 13); NPHP mutations: Slower progression (median age 20+)

Extrarenal Manifestations (Syndromic Forms): - **NPHP1:** Pure nephronophthisis (no extrarenal features) — most common - **NPHP4 (Senior-Loken syndrome):** Nephronophthisis + ocular dystrophy (retinitis pigmentosa; progressive vision loss) - **NPHP8-10 (Joubert syndrome - related):** Nephronophthisis + cerebellar hypoplasia, developmental delay - **NPHP13:** Nephronophthisis + short-rib thoracic dysplasia - **Other ciliopathy associations:** Situs inversus totalis, heterotaxy, bronchiectasis, liver disease (congenital hepatic fibrosis)

Diagnosis:

Clinical Suspicion: - Polyuria + progressive renal insufficiency in child - Family history of ESRD in cousins/siblings (autosomal recessive)

Imaging: - **Renal ultrasound:** Small, echogenic kidneys; characteristic cysts at corticomedullary junction (may not be obvious early) - **CT:** Corticomedullary cysts; helps confirm diagnosis - **MRI:** Excellent visualization of cysts; shows interstitial fibrosis

Histology: - Kidney biopsy (if diagnosis uncertain): Tubulointerstitial fibrosis; corticomedullary cysts; relatively spared glomeruli - Electron microscopy: May show ciliary abnormalities (short, irregular cilia or complete absence)

Genetic Testing: - NPHP1 homozygous deletion testing (covers 85% of cases) - Full NPHP gene panel (NPHP1-13) if deletion testing negative - **Ciliary function testing:** Immunohistochemistry for ciliary marker proteins

Management: - **Supportive care:** ACEI/ARB (slow renal function decline; reduce proteinuria) - **CKD management:** Blood pressure control, anemia management, renal osteodystrophy

prevention - **Renal replacement therapy:** Dialysis/transplantation when ESRD reached - **Genetic counseling:** Autosomal recessive; 25% risk to siblings - **Screening relatives:** Ultrasound for asymptomatic family members - **Syndromic assessment:** Ophthalmology (if Senior-Loken), neurology (if Joubert-related), cardiology (if situs anomalies)

Prognosis: - Inevitable progression to ESRD (median 13-20 years depending on genotype) - Transplantation: Good outcomes; disease does not recur in transplanted kidney

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B. Ciliopathies Overview

Spectrum of Ciliary Disorders: Ciliopathies involve dysfunction of primary cilium (found on most cell types, including renal tubular epithelium).

Renal Manifestations: 1. **Nephronophthisis** (tubulointerstitial disease; progressive) 2. **Cystic kidney disease** (polycystic kidney, cystic dysplasia; linked to ciliary dysfunction in PKD genes) 3. **Glomerulonephritis** (rare; inverted architecture secondary to ciliary dysfunction)

Syndromic Ciliopathies with Renal Involvement:

Syndrome	Key Features	Renal Manifestation
Bardet-Biedl (BBS)	Retinitis pigmentosa, polydactyly, obesity, cognitive delay	Cystic kidneys, CKD (30-40% develop ESRD)
Joubert Syndrome	Cerebellar hypoplasia, developmental delay	Nephronophthisis if ciliopathy-related
Senior-Loken	Nephronophthisis + retinitis pigmentosa	Progressive renal failure
Kearns-Sayre	Mitochondrial disease; retinitis pigmentosa, cardiomyopathy	Variable renal involvement
Oral-Facial-Digital	Cleft lip, digital abnormalities, developmental delay	Cystic kidneys (variable severity)

Common Theme: Ciliary dysfunction ☐ abnormal epithelial signaling ☐ abnormal tubule development, inflammation, and cyst formation

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VIII. CLINICAL PEARLS

1. **Bartter vs. Gitelman Key Differences:** Both present with hypokalemic metabolic alkalosis and normal BP, but Gitelman has **marked hypomagnesemia and LOW urinary calcium** (hypocalciuria), while Bartter types with hypercalciuria.
2. **NSAID Paradox:** NSAIDs worsen renal function overall but paradoxically improve Bartter/Gitelman by reducing renin-angiotensin-aldosterone activation; use with caution and monitor renal function.

3. **Type 1 RTA Nephrolithiasis Risk:** Contrary to expectations of "acidic urine prevents stones," Type 1 RTA patients form **calcium phosphate stones** due to alkaluria (high urine pH) + hypercalciuria + hypocitraturia; aggressive alkali therapy critical.
4. **Cystinosis Diagnosis:** Photophobia + ocular cystine crystals (visible on slit-lamp) = **pathognomonic** for cystinosis; don't miss by not asking about light sensitivity.
5. **Cysteamine Timing:** Earlier initiation (<age 2 years) dramatically improves long-term renal and growth outcomes in cystinosis; delayed diagnosis results in poor prognosis despite late therapy initiation.
6. **NDI Hypernatremia Crisis:** Congenital NDI infants at severe risk for **hypernatremic dehydration** if water access restricted; educate families that water access is lifesaving, not a behavioral indulgence.
7. **Liddle Hypertension:** Low-renin hypertension in a child = think Liddle or secondary forms; amiloride is **first-line** (ENaC blocker), not calcium channel blocker.
8. **PHA1 Salt-Wasting:** High aldosterone DESPITE salt-wasting and hyperkalemia = key finding distinguishing PHA1 from Liddle; aldosterone level is diagnostic clue.
9. **Nephronophthisis Polyuria:** Polyuria may precede renal insufficiency by years in nephronophthisis; ask children about nocturia/enuresis when evaluating for CKD.
10. **Ciliary Connection:** Many "unrelated" disorders (nephronophthisis, PKD, Bardet-Biedl, Senior-Loken) are ciliopathies; think cilia dysfunction when confronted with syndromic presentation + kidney disease.

IX. PRACTICE QUESTIONS

Question 1: A 5-year-old girl with a history of "salt-craving" behavior presents with muscle cramps and weakness. Lab work shows K+ 2.8 mEq/L, Cl□ 96 mEq/L, HCO3□ 31 mEq/L, plasma renin 8.5 ng/mL/hr (elevated), and plasma aldosterone 42 ng/dL (elevated). Urine calcium is 40 mg/day (LOW). Blood pressure is 105/68 mmHg (normal for age). What is the most likely diagnosis?

A) Bartter syndrome Type I
B) Gitelman syndrome
C) Primary hyperaldosteronism
D) Liddle syndrome

Answer: B. Gitelman syndrome is most consistent with: **hypokalemia, metabolic alkalosis, normal BP, elevated renin/aldosterone** (RAAS activation from volume depletion), AND **low urinary calcium** (hypocalciuria). Gitelman presents with marked hypomagnesemia (not listed but typical); Bartter types with normal-high urinary calcium. Liddle would have LOW renin/aldosterone (not elevated). Primary hyperaldosteronism is rare in children and presents without hypomagnesemia.

Question 2: An 18-month-old boy presents with failure to thrive, polyuria (8 liters/day), and photophobia with eye pain. Slit-lamp exam reveals bilateral corneal crystalline deposits. Urinalysis

shows glycosuria, amino aciduria, and markedly elevated urinary cystine (450 mg/day). Leukocyte cystine content is 3.2 nmol half-cystine/mg protein. What is the immediate next step in management?

A) Start cysteamine therapy; initiate referrals for dialysis planning
B) Start cysteamine therapy; initiate nephrology, ophthalmology, and nutritional support; arrange follow-up leukocyte cystine testing in 4-6 weeks
C) Continue observation without medication; renal function is currently normal; initiate therapy only after GFR declines
D) Treat with high-dose vitamin D supplementation and phosphate restriction; defer cysteamine until ESRD

Answer: B. This patient has **infantile nephropathic cystinosis** (confirmed by elevated urinary cystine, elevated leukocyte cystine content, and pathognomonic corneal crystals). Early cysteamine therapy (started <age 2) dramatically improves long-term renal and growth outcomes. Immediate management includes: (1) start cysteamine, (2) coordinate multidisciplinary care (nephrology, ophthalmology, dietitian), (3) supportive care, (4) monitor response via leukocyte cystine content. With early therapy, ESRD can be delayed to age 20-30s.

Question 3: A 3-year-old with polyuria (3.5 L/day) and chronic polydipsia has serum Na+ 152 mEq/L, osmolality 315 mOsm/kg, and urine osmolality 180 mOsm/kg. Desmopressin (DDAVP) trial: no change in polyuria or urine osmolality (remains dilute). What is the most appropriate next management?

A) Increase DDAVP dose; continue trial for 2 weeks
B) Prescribe hydrochlorothiazide 1-2 mg/kg/day and indomethacin 0.5 mg/kg/day; ensure unrestricted water access at all times
C) Initiate hypertonic (3%) saline infusion to correct hypernatremia
D) Restrict water intake to 1-2 liters/day; place Foley catheter for output monitoring

Answer: B. This child has **congenital nephrogenic diabetes insipidus** (confirmed by: polyuria, inability to concentrate urine despite elevated osmolality/hypernatremia, and **no response to DDAVP**—hallmark of NDI). Management: (1) **thiazide + NSAID** (reduce collecting duct fluid load, modest reduction in polyuria), (2) **unrestricted water access** (critical; risk of severe dehydration/hypernatremia if restricted), (3) genetic testing (AVPR2 or AQP2). Water restriction (option D) is dangerous and contraindicated. Hypertonic saline would worsen hypernatremia.

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