Metabolic Acidosis and Renal Tubular Acidosis in the Hospital Setting

Definition and Epidemiology

Metabolic acidosis is a systemic disorder characterized by a decrease in blood pH (<7.35) due to reduced serum bicarbonate (HCO3- <22 mEq/L), resulting from acid accumulation (high anion gap) or bicarbonate loss (normal anion gap). Renal tubular acidosis (RTA) encompasses Type 1 (distal), Type 2 (proximal), and Type 4 (hyperkalemic) disorders caused by impaired renal acid-base regulation, leading to normal anion gap acidosis.

- Prevalence
  - Metabolic acidosis affects ~15-20% of hospitalized patients, with high anion gap causes (e.g., lactic acidosis, ketoacidosis) in 60% and normal anion gap (e.g., RTA, diarrhea) in 40%. RTA is rare, with Type 1 and Type 2 affecting <0.1% of the population; Type 4 is more common in diabetics with CKD (1-2%).
- Risk Factors
  - Sepsis, diabetic ketoacidosis (DKA), renal failure, diarrhea, medications (e.g., metformin), diabetes (Type 4 RTA).
- Rare Demographics
  - Pediatric genetic RTAs, drug-induced RTAs (e.g., ifosfamide), autoimmune RTAs (e.g., lupus).

Pathophysiology

Mechanisms

- Metabolic acidosis arises from increased acid production or intake (e.g., lactate, ketones, toxins) or loss of HCO3- (e.g., diarrhea, RTA). Type 1 RTA results from defective H+ secretion in the distal tubule, impairing ammonia buffering. Type 2 RTA involves impaired proximal HCO3- reabsorption, causing bicarbonate wasting. Type 4 RTA stems from hypoaldosteronism or aldosterone resistance, reducing H+ and K+ excretion.

- **Effects**
  - Acidemia triggers compensatory hyperventilation (Kussmaul respirations), shifts K+ extracellularly (hyperkalemia), and depresses myocardial contractility. RTAs lead to chronic acidosis, nephrolithiasis (Type 1), osteomalacia (Type 2), or hyperkalemia (Type 4).
- **Molecular Pathways**
  - **Lactic acidosis:** Hypoxia upregulates LDH, producing lactate. DKA: Insulin deficiency activates HMG-CoA, forming ketones. Type 1 RTA: ENaC/H+-ATPase mutations impair proton secretion. Type 2: SLC4A4 mutations reduce HCO3- transport. Type 4: Low aldosterone increases ANG II, reducing NH4+ excretion.
- **Key Pathway**
  - **Acid accumulation or HCO3- loss → Decreased pH/HCO3- → Compensatory hyperventilation → Systemic effects (cardiac, renal, bone).**

Causes

Category	Common Causes	Additional Causes	Notes
High Anion Gap	Lactic acidosis (sepsis, shock), DKA, alcoholic ketoacidosis	Propylene glycol (IV lorazepam), pyroglutamic acidosis (acetaminophen), toluene (inhalant abuse), paraldehyde, starvation ketoacidosis	AG >12 mEq/L; use MUDPILES mnemonic (Methanol, Uremia, DKA, Propylene glycol, Isoniazid/ Iron, Lactic acidosis, Ethylene glycol, Salicylates)
Normal Anion Gap	Diarrhea, RTA, TPN (chloride-rich)	Pancreatic fistula, cholestyramine, laxative abuse, ammonium chloride, post-hypocapnia, hypoalbuminemia	AG 8-12 mEq/L; urine AG differentiates renal vs. GI loss
Type 1 RTA (Distal)	Sjögren's, amphotericin B, lithium	SLE, rheumatoid arthritis, primary hyperparathyroidism, vitamin D deficiency, medullary sponge kidney, sickle cell nephropathy, obstructive uropathy, chronic lithium, toluene exposure	Hypokalemia, urine pH >5.5, nephrolithiasis
Type 2 RTA (Proximal)	Fanconi syndrome, topiramate, acetazolamide	Multiple myeloma, Wilson's disease, Lowe syndrome, galactosemia, hereditary fructose intolerance, tenofovir, ifosfamide, outdated tetracycline, heavy metal poisoning (lead, cadmium)	HCO3- wasting, hypokalemia, osteomalacia
Type 4 RTA	Diabetic nephropathy, ACEi, NSAIDs	Hyporeninemic hypoaldosteronism, Addison's disease, Gordon's syndrome, spironolactone, trimethoprim, heparin, sickle cell disease, urinary tract obstruction, tubulointerstitial disease	Hyperkalemia, no nephrolithiasis

Clinical Presentation

- Symptoms
  - Fatigue, weakness, confusion
  - Dyspnea, Kussmaul respirations (pH <7.2)
  - Nausea, vomiting (DKA, uremia)
  - Rare Bone pain (Type 2 RTA), flank pain (Type 1 RTA stones), seizures (severe acidemia)
- Exam
  - Tachypnea, tachycardia
  - Dehydration (diarrhea, DKA)
  - Muscle weakness (hypokalemia, Types 1/2 RTA)
  - Rare Tetany (hypocalcemia, Type 2), rickets (Type 2, pediatric)
- Red Flags
  - pH <7.1, HCO_3^- <10 mEq/L, K^+ >6 mEq/L (Type 4), lactate >10 mmol/L

Labs and Studies

- Labs
  - ABG pH <7.35, HCO_3^- <22 mEq/L, $PaCO_2$ <35 mmHg (compensation)
  - Anion Gap (AG) $Na^+ - (Cl^- + HCO_3^-)$; >12 high, 8-12 normal
  - Lactate >2 mmol/L (lactic acidosis), ketones (DKA), salicylates (toxins)
  - CMP K^+ (hyperkalemia Type 4, hypokalemia Types 1/2), Cr (renal failure)
  - Advanced: Urine pH (>5.5 Type 1, <5.5 Type 2), urine AG (negative in RTA), aldosterone (low in Type 4), 5-oxoproline (pyroglutamic acidosis)
- Imaging
  - Renal Ultrasound Nephrolithiasis (Type 1 RTA), hydronephrosis
  - CT Abdomen Stones, structural anomalies (medullary sponge kidney)
  - X-ray Osteomalacia, rickets (Type 2 RTA, pediatric)
  - Advanced Bone densitometry (Type 2, osteoporosis), renal biopsy (Fanconi)
- Other
  - Winter's Formula Expected $PaCO_2 = 1.5(HCO_3^-) + 8 \pm 2$; confirms compensation
  - Urine Studies Urine citrate (low in Type 1), ammonium (low in Type 1/4)
- Advanced: Genetic testing (SLC4A1 for Type 1, SLC4A4 for Type 2), metabolomics (acid profiles)

Diagnosis

- Criteria
  - **Metabolic acidosis:** pH <7.35, HCO3- <22 mEq/L. High AG (>12): Lactic acidosis, DKA, toxins. Normal AG (8-12): Diarrhea, RTA (Type 1: urine pH >5.5, hypokalemia; Type 2: HCO3- wasting, osteomalacia; Type 4: hyperkalemia, low aldosterone).
- Differential
  - Respiratory acidosis, mixed acid-base disorders, hyperchloremic acidosis (TPN), alkalosis (vomiting mimic).
- Flowsheet
  - Step 1: ABG/CMP Confirm pH <7.35, HCO3- <22, calculate AG
  - Step 2: History/Exam Sepsis, DKA, diarrhea, meds; check K+, urine pH
  - Step 3: Labs Lactate, ketones, tox screen (salicylates, methanol); urine AG, ammonium
  - Step 4: Imaging Ultrasound (stones), X-ray (bone, Type 2)
  - Step 5: Classify High AG (lactate, ketones, toxins), normal AG (RTA, diarrhea)

Treatment

- General Principles
  - Correct acidemia, treat underlying cause, and prevent complications (arrhythmias, bone disease).
- Supportive Care
  - IV Fluids NS 1-2 L bolus (DKA, lactic acidosis), avoid LR (HCO3- precursor)
  - Electrolyte Replacement K+ (Types 1/2, 20-40 mEq IV), PO4- (20 mmol IV, refeeding)
  - Ventilation BiPAP/intubation if pH <7.1, respiratory fatigue
- Specific Therapies
  - High Anion Gap
    - **Lactic Acidosis Treat cause (sepsis:** antibiotics; shock: NE 5-20 mcg/min)
    - DKA Insulin 0.1 units/kg/h IV, NS 1 L/h, K+ replacement
    - Toxins Ethanol (methanol), fomepizole 15 mg/kg IV (ethylene glycol), dialysis
    - Pyroglutamic Acidosis Stop acetaminophen, NaHCO3 1 mEq/kg IV
  - Normal Anion Gap
    - Diarrhea NaHCO3 1-2 mEq/kg IV if HCO3- <15, oral rehydration
    - Type 1 RTA NaHCO3 1-3 mEq/kg/day PO, potassium citrate (stones)

        - Type 2 RTA NaHCO3 5-15 mEq/kg/day PO, thiazide (↑HCO3- reabsorption)
        - Type 4 RTA Fludrocortisone 0.1 mg PO daily, furosemide 40 mg PO (hyperkalemia)
    - Advanced Dialysis (pH <7.1, toxins), carnitine (Type 2, Fanconi), anti-TNF (Sjögren's RTA)
    - Rare Causes Amphotericin cessation (Type 1), cysteamine (cystinosis, Type 2), stop trimethoprim (Type 4)
- Monitoring
    - ABG/CMP q4-6h (severe acidosis), q12h (RTA)
    - Daily urine pH, K+, HCO3- (RTA response)
- Renal ultrasound q6 months (Type 1, stones)

Complications

- Acute
    - Arrhythmias Hyperkalemia (Type 4), hypokalemia (Types 1/2, 5-10%)
    - Cerebral Edema Rapid HCO3- correction (<1%, pH <7.1)
    - Hypotension Lactic acidosis, sepsis (20-30% mortality)
- Long-Term
    - Nephrolithiasis Type 1 RTA, 30-50% develop stones
    - Osteomalacia Type 2 RTA, 20% in adults
    - CKD Type 4 RTA, 10-20% progress to ESRD
    - Rare Growth stunting (pediatric RTA), amyloidosis (Sjögren's)

Clinical Scenarios

Case 1 Lactic Acidosis from Sepsis

- **Presentation** 60 y/o M with sepsis presents with dyspnea, confusion. Vitals BP 90/60, HR 120, SpO2 92%, RR 28. Exam Kussmaul respirations, dehydration.
- **Labs/Studies** ABG pH 7.15, HCO3- 10 mEq/L, PaCO2 25 mmHg, AG 20. Lactate 8 mmol/L.
- **Interpretation** High AG metabolic acidosis, lactic acidosis.
- **Management** NS 2 L bolus, NE 10 mcg/min, ceftriaxone 2 g IV. NaHCO3 100 mEq IV (pH <7.2). Lactate clears by 12h, pH 7.35 by day 2.

Case 2 Type 1 RTA

- **Presentation** 35 y/o F with Sjögren's, flank pain, weakness. Vitals BP 110/70, HR 80, SpO2 98%, RR 16. Exam Dry mucous membranes, no edema.

- **Labs/Studies** ABG pH 7.30, HCO3- 18 mEq/L, AG 10. Urine pH 6.0, K+ 3.0 mEq/L. Ultrasound Renal stones.
- **Interpretation** Normal AG acidosis, Type 1 RTA.
- **Management** NaHCO3 650 mg PO TID, potassium citrate 15 mEq PO BID. Rheumatology consult. pH 7.38, stones stable by month 3.

Case 3 Type 4 RTA (Rare)

- **Presentation** 70 y/o M with DM, CKD, fatigue, weakness. Vitals BP 130/80, HR 90, SpO2 96%, RR 14. Exam No Kussmaul, mild edema.
- **Labs/Studies** ABG pH 7.32, HCO3- 20 mEq/L, AG 9. K+ 6.2 mEq/L, aldosterone low. ECG Peaked T-waves.
- **Interpretation** Type 4 RTA, hyperkalemic acidosis.
- **Management** Furosemide 40 mg PO daily, fludrocortisone 0.1 mg PO daily, insulin 10 units IV (K+). K+ 4.5 mEq/L, pH 7.40 by day 3.

Expert Tips

- Calculate AG immediately; high AG prompts lactate, ketones, tox screen (add propylene glycol, 5-oxoproline)
- Use Winter's formula to confirm respiratory compensation; mismatch suggests mixed disorder
- Check urine pH in normal AG acidosis; >5.5 confirms Type 1 RTA, <5.5 Type 2
- Avoid rapid NaHCO3 in lactic acidosis; worsens intracellular acidosis, CO2 production
- Suspect Type 4 RTA in CKD with hyperkalemia; low aldosterone or renin key
- Pitfall Missing pyroglutamic acidosis; chronic acetaminophen use in malnourished
- Advanced Metabolomics for toxin identification, next-gen sequencing (SLC4A1, Type 1 RTA)

Key Pearls

- **Metabolic acidosis:** pH <7.35, HCO3- <22; AG >12 (lactic, DKA, toxins), 8-12 (RTA, diarrhea)
- **Type 1 RTA:** Hypokalemia, stones; Type 2: HCO3- wasting; Type 4: Hyperkalemia
- Treat cause (sepsis, DKA); NaHCO3 only if pH <7.2 or HCO3- <15
- Monitor K+, PO4- q4-6h in severe acidosis; ECG for arrhythmias
- Rare RTAs (cystinosis, Wilson's) need specialized therapy (cysteamine, penicillamine)

References

UpToDate "Metabolic Acidosis: Diagnosis and Management" (2025)

NEJM "Renal Tubular Acidosis: A Review" (2024)

Lancet "Lactic Acidosis in Critical Care" (2023)

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