Overview of Hyperosmolar Hyperglycemic State (HHS)

Hyperosmolar Hyperglycemic State (HHS) is a life-threatening metabolic emergency typically seen in patients with type 2 diabetes mellitus (T2DM), characterized by severe hyperglycemia, hyperosmolarity, and dehydration without significant ketosis. It carries a high mortality rate (up to 20%) due to its complications and underlying precipitants. This guide provides students with a comprehensive framework to understand the clinical presentation, pathophysiology, diagnosis, hospital management, and complications of HHS, with tables and clinical scenarios for practical application.

Clinical Presentation

Symptoms:

- **Gradual Onset (Days to Weeks):** Polyuria, polydipsia, progressive weakness, lethargy.
- **Neurological Changes:** Altered mental status (confusion, obtundation, coma in severe cases), focal neurological deficits (e.g., hemiparesis due to hyperosmolarity).
- **Dehydration:** Dry mucous membranes, poor skin turgor, thirst, weight loss.
- **Precipitating Factors:** Infection (e.g., pneumonia, UTI), medication non-adherence, new-onset diabetes, stressors (e.g., surgery, MI).

Signs:

- **Vital Signs:** Hypotension (due to hypovolemia), tachycardia, fever (if infection).
- **Neurological Exam:** Confusion, lethargy, GCS <15, seizures (rare, due to hyperosmolarity or electrolyte imbalance).
- **Volume Status:** Sunken eyes, dry skin, orthostatic BP changes, decreased urine output.
- **Absence of Ketosis Symptoms:** Unlike DKA, no Kussmaul respirations, fruity breath, or significant acidosis.

Pathophysiology

Hyperglycemia:

Impaired insulin secretion/action leads to uncontrolled glucose production (gluconeogenesis, glycogenolysis) and reduced glucose uptake, causing severe hyperglycemia (>600 mg/dL).

Hyperosmolarity:

Elevated glucose causes osmotic diuresis, leading to profound dehydration and hyperosmolarity (>320 mOsm/kg), which impairs brain function (e.g., altered mental status).

Dehydration:

Osmotic diuresis results in significant fluid loss (6-12 L deficit), hypovolemia, and hemoconcentration.

Minimal Ketosis:

Unlike DKA, HHS patients have enough insulin to suppress lipolysis and ketogenesis, so ketone production is minimal (pH >7.3, bicarbonate >15 mEq/L).

Precipitants:

Infection (40-60%), non-adherence to diabetes medications, undiagnosed diabetes, or stressors (e.g., MI, stroke) exacerbate hyperglycemia and dehydration.

Diagnosis

Diagnostic Criteria:

- **Glucose:** >600 mg/dL.
- **Serum Osmolarity:** >320 mOsm/kg (calculated as 2 × Na [mEq/L] + Glucose [mg/dL]/18 + BUN [mg/dL]/2.8).
- **pH:** >7.3 (minimal acidosis compared to DKA).
- **Bicarbonate:** >15 mEq/L.
- **Ketones:** Minimal or absent (negative or trace urine/serum ketones).
- **Altered Mental Status:** Common due to hyperosmolarity and dehydration.

Labs:

- **BMP:** Glucose >600 mg/dL, Na+ (often falsely low due to hyperglycemia; corrected Na+ = measured Na + 1.6 × [(glucose - 100)/100]), K+ (monitor for hypokalemia), Cr/BUN (elevated due to dehydration).
- **Serum Osmolarity:** >320 mOsm/kg.
- **ABG:** pH >7.3, minimal acidosis.
- **Ketones:** Urine/serum ketones negative or trace.
- **CBC:** Leukocytosis (stress, infection), hemoconcentration (Hct/Hgb elevated).
- **Precipitant Workup:** Blood cultures, urinalysis, CXR (infection), EKG/troponin (MI).

Imaging:

- **CXR:** Rule out pneumonia as a precipitant.
- **CT Brain:** If focal neurological deficits or coma (rule out stroke, cerebral edema).
- **Other:** As indicated by suspected precipitant (e.g., CT abdomen for intra-abdominal infection).

Differential Diagnosis

- **Diabetic Ketoacidosis (DKA):** Glucose 250-600 mg/dL, pH <7.3, significant ketosis, Kussmaul respirations; more common in T1DM.
- **Hyperosmolar Non-Ketotic Coma (HNKC):** Historical term for HHS; similar presentation but less emphasis on mental status.
- **Sepsis:** Fever, hypotension, leukocytosis; may mimic HHS but glucose typically normal or mildly elevated.
- **Stroke:** Focal deficits, altered mental status; CT/MRI differentiates from HHS-induced neurological changes.
- **Uremia:** Elevated Cr/BUN, altered mental status; lacks severe hyperglycemia, hyperosmolarity.
- **Alcohol/Drug Intoxication:** Altered mental status, history of substance use; toxicology screen differentiates.

Hospital Management of HHS

- Goals:
  - Correct dehydration (6-12 L deficit) gradually over 24-48 hours.
  - Lower glucose to 200-300 mg/dL initially, then 140-180 mg/dL over days.
  - Resolve hyperosmolarity (<320 mOsm/kg).

- Treat underlying precipitant (e.g., infection, MI).
- Prevent complications (e.g., cerebral edema, AKI).

Stepwise Management:

- Fluid Resuscitation:
  - **Initial Bolus:** NS 1-2 L over 1-2 hours (adjust for cardiac/renal status; e.g., slower in CHF).
  - **Maintenance:** NS 250-500 mL/h, switch to 0.45% NS once BP stabilizes (corrects hypernatremia).
  - **Goal:** Replace 50% of fluid deficit in 12-24 hours, remainder over 24-48 hours; monitor for over-correction (risk of cerebral edema).
  - **Monitoring:** Check BP, HR, urine output q1-2h; adjust fluids to achieve urine output >0.5 mL/kg/h.
- Insulin Therapy:
  - **Timing:** Start IV insulin only after initial fluid resuscitation (1-2 L) to avoid rapid osmolarity drop (risk of cerebral edema).
  - **IV Insulin Drip:** 0.05-0.1 units/kg/h (e.g., 70 kg patient: 3.5-7 units/h).
  - **Titration:** Check glucose q1h; target initial glucose 200-300 mg/dL (avoid rapid drop); once stable, adjust to 140-180 mg/dL.
  - **Transition to SC Insulin:** When glucose <300 mg/dL, osmolarity <320 mOsm/kg, and patient is eating; start basal insulin (e.g., glargine 0.2-0.3 units/kg/day) with overlap of IV insulin by 2-4 hours to prevent rebound hyperglycemia.
- Electrolyte Correction:
  - **Potassium:** Often depleted due to osmotic diuresis; replace if K+ <5.2 mEq/L (e.g., KCl 20-40 mEq IV in each liter of fluid).
  - **Sodium:** Corrected Na+ guides fluid choice; if >150 mEq/L, use 0.45% NS to avoid hypernatremia.
  - **Magnesium/Phosphorus:** Replace if low (e.g., MgSO4 2 g IV, phosphate 20-40 mmol IV over 6h).
- Treat Precipitant:
  - **Infection:** Broad-spectrum antibiotics (e.g., piperacillin-tazobactam 4.5 g IV q6h + vancomycin 15 mg/kg IV q12h) if suspected (e.g., pneumonia, UTI).
  - **MI:** Anti-ischemic therapy (aspirin, nitroglycerin, PCI if STEMI).
  - **Other:** Address non-adherence, new-onset diabetes (education, insulin initiation).
- Monitoring:
  - **Glucose:** q1h during IV insulin drip, then ACHS (before meals and bedtime) for non-ICU patients once stable.

- **Electrolytes:** q4-6h (K+, Na+, Mg++, phosphate).
- **Osmolarity:** q6-12h until <320 mOsm/kg.
- **Mental Status:** q1-2h until improving (GCS, neurological exam).
- **Volume Status:** BP, HR, urine output, daily weights.

Complications

- **Cerebral Edema:** Rapid osmolarity correction; presents with worsening mental status, seizures, coma; prevent by gradual fluid/glucose correction.
- **Acute Kidney Injury (AKI):** Hypovolemia, renal hypoperfusion; presents with oliguria, Cr rise; treat with fluids, avoid nephrotoxins.
- **Hypokalemia:** Osmotic diuresis, insulin therapy; presents with weakness, arrhythmias; replace K+ proactively.
- **Thrombosis:** Hypercoagulability from hemoconcentration; presents with DVT, PE; consider prophylaxis (enoxaparin 40 mg SC daily).
- **Infection/Sepsis:** Common precipitant; may worsen during HHS; monitor for fever, leukocytosis, lactate.
- **Multi-Organ Failure:** Severe dehydration, shock; presents with AKI, liver failure, ARDS; high mortality (up to 20%).

Key Pearls

- **Presentation:** Severe hyperglycemia (>600 mg/dL), altered mental status, dehydration, minimal ketosis (pH >7.3).
- **Pathophysiology:** Hyperglycemia → osmotic diuresis → hyperosmolarity (>320 mOsm/kg) → dehydration, neurological changes.
- **Diagnosis:** Glucose >600 mg/dL, osmolarity >320 mOsm/kg, pH >7.3, minimal ketones, altered mental status.
- **Management:** Fluids (NS 1-2 L bolus, then 250-500 mL/h), IV insulin (0.05-0.1 units/kg/h after fluids), electrolyte correction, treat precipitant.
- **Complications:** Cerebral edema (rapid correction), AKI, hypokalemia, thrombosis, sepsis, multi-organ failure.
- **Monitoring:** Glucose q1h (IV drip), then ACHS; electrolytes q4-6h; osmolarity, mental status, volume status.

References

UpToDate: “Hyperosmolar Hyperglycemic State: Diagnosis and Management” (2025). UpToDate HHS

ADA: “Standards of Medical Care in Diabetes” (2024). ADA Guidelines

AACE: “Management of Hyperglycemic Crises” (2023). AACE Guidelines

NEJM: “Management of DKA and HHS in the Hospital” (2024). NEJM HHS

Case Scenarios

Case 1: A 70-Year-Old Female with HHS and Sepsis

- Presentation: A 70-year-old female with T2DM presents with 5 days of polyuria, polydipsia, and confusion. Exam shows T 38°C, BP 90/60 mmHg, HR 110 bpm, RR 20/min, dry mucous membranes, GCS 12.
- Labs/Studies: Glucose 900 mg/dL, Na+ 130 mEq/L (corrected 140 mEq/L), K+ 3.5 mEq/L, Cr 2.0 mg/dL (baseline 1.0), osmolarity 340 mOsm/kg, pH 7.35, bicarbonate 18 mEq/L, urine ketones trace, blood cultures positive for E. coli.
- Diagnosis: HHS with Sepsis (UTI) → Glucose >600 mg/dL, osmolarity >320 mOsm/kg, minimal ketosis, altered mental status.
- Management: Admit to ICU (altered mental status, hypotension). IV fluids: NS 2 L bolus over 2h, then 250 mL/h (total 6 L over 24h). After 1 L, start IV insulin 0.1 units/kg/h (7 units/h for 70 kg). K+ replacement (KCl 20 mEq/L IV fluids). Antibiotics (piperacillin-tazobactam 4.5 g IV q6h). Monitor: Glucose q1h (decreases to 250 mg/dL in 12h), osmolarity (310 mOsm/kg in 24h), mental status (GCS 15 by day 2). Transition to glargine 20 units SC at bedtime + SSI (ACHS glucose 150-180 mg/dL). Discharge with metformin 500 mg PO BID, antibiotics completed.

Case 2: A 65-Year-Old Male with HHS and New-Onset Diabetes

- Presentation: A 65-year-old male with no diabetes history presents with 1 week of lethargy, thirst, and weight loss. Exam shows T 37°C, BP 100/65 mmHg, HR 100 bpm, RR 18/min, dry skin, GCS 14.
- Labs/Studies: Glucose 800 mg/dL, Na+ 135 mEq/L (corrected 143 mEq/L), K+ 3.8 mEq/L, Cr 1.8 mg/dL, osmolarity 330 mOsm/kg, pH 7.32, bicarbonate 20 mEq/L, urine ketones negative, HbA1c 12%.
- Diagnosis: HHS (New-Onset T2DM) → Glucose >600 mg/dL, osmolarity >320 mOsm/kg, minimal ketosis, new diabetes.
- Management: Admit to ICU (altered mental status, hypovolemia). IV fluids: NS 1.5 L bolus over 2h, then 300 mL/h (total 5 L over 24h). Start IV insulin 0.05 units/kg/h (4 units/h for 80 kg) after 1 L fluids. K+ replacement (KCl 20 mEq/L IV fluids). Monitor: Glucose q1h (decreases to 280 mg/dL in 12h), osmolarity (315 mOsm/kg in 24h), mental status (GCS 15 by day 2). Transition

to glargine 20 units SC at bedtime + SSI (ACHS glucose 140-170 mg/dL). Educate on new diabetes diagnosis. Discharge with metformin 500 mg PO BID, glargine 20 units, endocrinology follow-up.

Case 3: A 75-Year-Old Female with HHS and AKI

- Presentation: A 75-year-old female with T2DM presents with 3 days of confusion and decreased urine output. Exam shows T 37°C, BP 95/60 mmHg, HR 105 bpm, RR 16/min, dry mucous membranes, GCS 13.
- Labs/Studies: Glucose 700 mg/dL, Na+ 132 mEq/L (corrected 141 mEq/L), K+ 3.2 mEq/L, Cr 3.0 mg/dL (baseline 1.2), osmolarity 325 mOsm/kg, pH 7.34, bicarbonate 19 mEq/L, urine ketones trace.
- Diagnosis: HHS with AKI → Glucose >600 mg/dL, osmolarity >320 mOsm/kg, AKI, altered mental status.
- Management: Admit to ICU (AKI, altered mental status). IV fluids: NS 1 L bolus over 2h, then 200 mL/h (slower due to AKI; total 4 L over 24h). Start IV insulin 0.05 units/kg/h (3.5 units/h for 70 kg) after 1 L fluids. K+ replacement (KCl 40 mEq IV over 4h). Monitor: Glucose q1h (decreases to 300 mg/dL in 12h), osmolarity (310 mOsm/kg in 24h), Cr (improves to 2.0 mg/dL by day 3), mental status (GCS 15 by day 2). Transition to glargine 15 units SC at bedtime + SSI (ACHS glucose 150-180 mg/dL). Discharge with glargine 15 units, metformin held (AKI), nephrology follow-up.