The Critically Ill Patient with HHS

Key Article

Long B, et al. Diagnosis and Management of the Critically Ill Adult Patient with Hyperglycemic Hyperosmolar State. Am J Emerg Med. 2021;365-375.

Introduction

- DKA and hyperglycemic hyperosmolar state (HHS) are life-threatening hyperglycemic emergencies that can occur in both insulin-dependent and non-insulin dependent diabetics.
- Compared to DKA, HHS is more common in non-insulin dependent diabetics.
- Up to 20% of patients with HHS may not have a prior history of DM
- Though HHS is less common than DKA, mortality can be 10 times greater than with DKA.
    - Mortality rates range from 5-20%

Etiologies

- The most common precipitating cause of HHS is infection (40-60% of cases)
    - Most common infection is pneumonia, followed by urinary tract infection
- Diabetic medication noncompliance is the second most common cause (up to 20%)
- Additional triggers:
    - Myocardial infarction
    - PE
    - Pancreatitis
    - Seizure
    - Stroke
    - GIB
    - ETOH or substance abuse
    - Toxic ingestion
    - Renal injury

Pathophysiology

- Hallmark features include:
    - Severe hyperglycemia
    - Hyperosmolality
    - Dehydration
    - Minimal to no ketosis
- HHS usually precipitated by a physiologic stressor (i.e., infection) that results in insulin resistance and hyperglycemia.
- HHS is not associated with ketone body production, because there is sufficient insulin to prevent lipolysis and development of ketosis.
- Cells have difficulty using glucose due to resistance, while counter-regulatory hormones further worsen insulin resistance.

- In addition, increased levels of glucagon in HHS result in gluconeogenesis and glycogenolysis further increasing serum glucose.
- These lead to glucosuria, osmotic diuresis, and significant dehydration.
- Fluid deficits in HHS can approximate 10-22 L in a 100 kg patient.
- The osmotic diuresis further increases serum osmolality and tonicity.
- Hyperglycemia also induces a proinflammatory state with elevated cytokines, reactive oxygen species, and oxidative stress

Clinical Presentation

- HHS usually develops over days to weeks
- One of the hallmark features is a neurologic abnormality
    - Altered mental status (most common and seen when serum osmolality > 330 mOsm/kg)
    - Seizure
    - Coma
    - Focal neurologic deficits
- Most patients present with:
    - Polyuria
    - Polydipsia
    - Weakness
    - Blurry vision
- Patients with significant dehydration can also present with:
    - Dry mucous membranes
    - Tachycardia
    - Hypotension
    - Sunken eyes
    - Decreased skin turgor

Diagnosis

- American Diabetes Association Criteria:
    - Serum glucose > 600 mg/dL
    - pH > 7.3
    - Serum bicarbonate > 18 mmol/L
    - Serum osmolality > 320 mOsm/kg
    - Ketones: small ketonuria or absent to low ketonemia
- HOWEVER, patients with HHS may demonstrate a metabolic acidosis, low bicarbonate, increased anion gap, severe hyperglycemia, and hypertonicity depending on the etiology.
- In evaluating patients with suspected HHS, obtain the following:
    - CBC
    - Comprehensive metabolic panel
    - Lipase
    - VBG
    - Serum osmolality
    - Serum and urine ketones
    - UA
- Pearls
    - An osmolal gap should NOT be present

- Many patients with hyperglycemia will have hyponatremia. Patients with HHS, however, may have normal or elevated Na due to severe osmotic diuresis and elevated osmolality.

Management

- Very similar to DKA
- Primary goals are to treat the precipitating event, fluid resuscitation, and correction of osmolality, hyperglycemia, and electrolytes
- *Intravenous Fluids*
  - Patients with HHS typically have a water deficit of 100-200 ml/kg
  - Fluids improve osmolality, restore perfusion, reduce stress hormones, and enhance insulin sensitivity.
  - Many patients with HHS are older and may have concomitant comorbidities.
  - Rapid changes in serum osmolality and tonicity may result in cerebral edema and osmotic demyelination syndrome.
  - Currently there are no clear recommendations on type of fluid and speed of repletion.
  - Most guidelines recommend 1-1.5 liters of 0.9% NS in the first hour to avoid rapid correction of hyperosmolality.
  - Pay attention to <u>sodium</u>!
    - If the correcting the serum sodium for glucose reveals either hyponatremia or hypernatremia, be sure to slowly correct sodium < 0.5 mEq/L/h or < 10 mEq/L per day using the corrected sodium as baseline
- *Serum Osmolality*
  - Managing serum osmolality and hypertonicity are key components of treatment and linked to correction of sodium
  - Serial measurements of serum osmolality or calculated serum osmolality is recommended. Monitor every 1-2 hours.
  - Rapid correction of serum osmolality is a proposed mechanism of cerebral edema.
  - A change of < 3 mOsm/kg/h is recommended. A faster rate may result in neurologic complications
  - If osmolality increases or remains unchanged after initial fluid administration, consider a hypotonic fluid such as 0.45% NS.
- *Electrolytes*
  - Total body K is usually decreased – insulin administration will shift K into cells and further lower serum K.
  - The goal K is 4.0-5.0 mEq/L
  - If K is < 3.5 mEq/L, replace before starting insulin.
  - If K is 3.5-5.0 mEq/L, add K to IVFs while receiving insulin.
  - Replete phosphorous IV if < 1.0 mEq/L.
  - Monitor electrolytes every 1-2 hours, similar to management of DKA.
- *Insulin*
  - Insulin infusion is not mandatory in the initial management of HHS without ketoacidosis.
  - Insulin dosing in HHS differs from that in DKA.
    - Insulin infusion without a bolus can be started at 0.05-0.1 U/kg/hr
  - Patients on long-acting insulin should be given their home dose
  - The rate of glucose correction should be approximately 50-75 mg/dL.
  - Discontinue the insulin infusion when the glucose reaches 300 mg/dL.

Complications

- Cerebral edema
    - Occurs from rapid reduction in serum osmolality in excess of the diffusion of intracellular idiogenic osmoles.
    - CT or MRI should be obtained – CT may reveal areas of low density with loss of gray and white matter differentiation, as well as loss of cisterns/sulcal spaces
- Osmotic Demyelination Syndrome
    - Occurs due to rapid correction of prolonged hyponatremia
    - Symptoms
        - Confusion
        - Pseudobulbar palsy
        - Horizontal gaze nystagmus
        - Spastic quadriplegia
    - Obtain a CT or MRI
        - CT may demonstrate low attenuation across the midline in the pons
        - MRI is the test of choice – demonstrates hyperintensities in the pons on T-2 weighted imaging

Take Home Points

- HHS generally occurs in older patients with comordibities, results in significant dehydration and electrolyte disturbances, and has a higher mortality than DKA.
- The most common etiologies of HHS are infection and medication noncompliance.
- Fluid deficits are often significant in patients with HHS.
- Pay attention to sodium, serum osmolality, and potassium when treating patients with HHS.
- ODS and cerebral edema are the most serious complications that may occur with rapid correction of hyponatremia and serum osmolality.