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Clinical Pathways

Evidence-Based Practice Collaborative

12-2022

Hyperglycemic Hyperosmolar Syndrome (HHS)

Children's Mercy Kansas City

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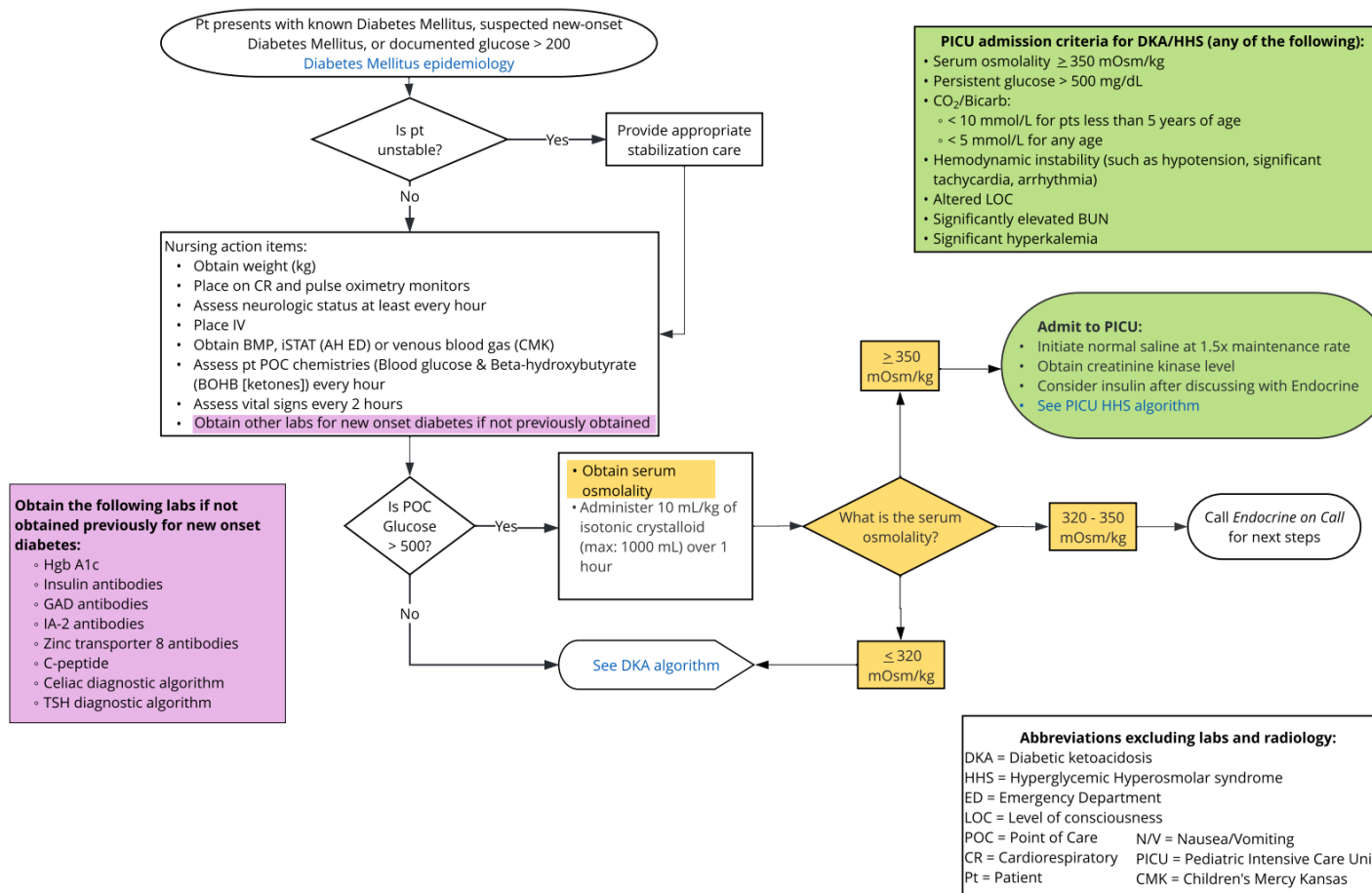
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Hyperglycemic Hyperosmolar Syndrome (HHS) Clinical Pathway Synopsis

Diabetic Ketoacidosis (DKA) vs. HHS Algorithm



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PICU HHS Algorithm

Inclusion Criteria for Hyperosmolarity

- Serum BG greater than or equal to 500 mg/dL **AND**
- Effective Serum Osmolality greater than or equal to 350 mOsm/kg

Pt with hyperglycemia AND hyperosmolarity admitted to PICU

Fluid bolus (≥ 20 mL/kg): 0.9% NS (Repeat bolus based on clinical status to restore peripheral perfusion)

Differentiating between HHS and Hyperosmolar DKA

HHS

- Serum bicarbonate ≥ 16 mmol/L
- Urine ketones small/moderate
- POC Serum ketones small (0 - 0.5 mmol/L) / moderate (0.6 - 1.5 mmol/L)

Hyperosmolar DKA

- Serum bicarbonate < 16 mmol/L[^]
- Urine ketones large
- POC Serum ketones large (≥ 1.5 mmol/L)

Continue Monitoring:

Q1hr: BG, vital signs and hydration
Q2hr: BMP (corrected Na), serum Osm, and UOP
Q4hr: CK, phosphate, magnesium

If CK increasing:

- Concern for rhabdomyolysis: High BUN/Cr, consult Nephrology
- Fever: Evaluate for infection, consider dantrolene

If low Mg:

- 25 to 50 mg/kg/dose q 4-6h (3-4 doses)

Consider the following labs based on pt severity:

Q4hr: ABG, VBG, Lactic acid, ICA
Q12hr: Troponin
Q24hr: Nt-ProBNP, LFTs, Coagulation studies

Is the pt experiencing HHS or Hyperosmolar DKA?

Hyperosmolar DKA → See DKA algorithm

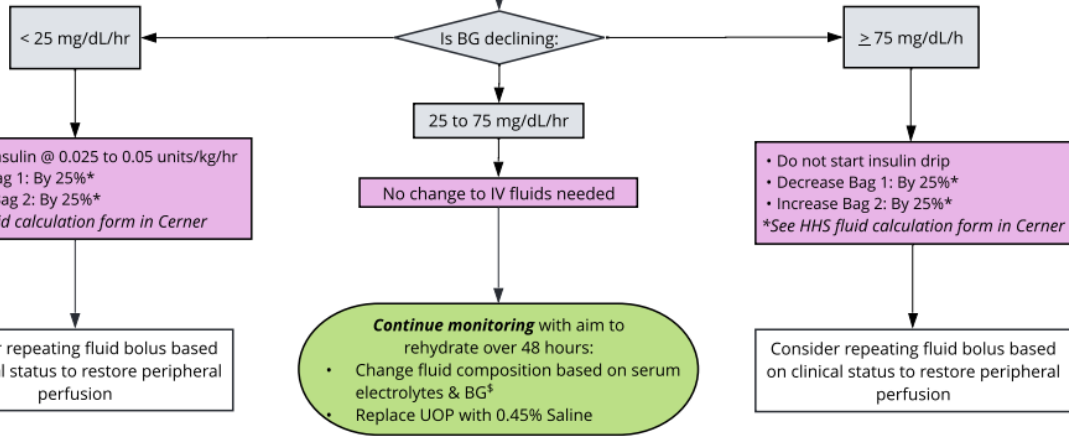
HHS

- Fluid: 1.5 maintenance over 24 to 48 hr[‡]
- Replace UOP (Bag 3: 0.45% Saline)
- Do not start insulin drip
- **Continue monitoring**

Rate Adjustment Based on BG Rate of Change
(See HHS fluid calculation form in Cerner)

	BAG 1	BAG 2
Rate of BG change (mg/dL/hr)	NS w/ additives	D₁₀NS w/ additives
≥ 75	Decrease 25%	Increase 25%
25-75	No change	No change
< 25	Increase 25%	Decrease 25%

Goal for BG decline per hour: 75 to 100 mg/dL/hr



Superscript meanings:

[‡] = Fluid based on: serum electrolytes (Corrected Na), blood glucose, urine output and clinical hydration status. Consider using additive free selection if K⁺>4

[^] = Serum bicarbonate: 12 to 15 mmol/L; Review insulin and fluids plan with consideration for complications from hyperosmolarity

Abbreviations (laboratory & radiology excluded):

Pt = Patient
NS = Normal saline
BG = Blood glucose
HHS = Hyperglycemic Hyperosmolar Syndrome
DKA = Diabetic Ketoacidosis
UOP = Urine output
PICU = Pediatric Intensive Care Unit

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Objective of Clinical Pathway

To provide care standards for the patient diagnosed with hyperglycemic hyperosmolar syndrome.

Background

Hyperglycemic hyperosmolar syndrome (HHS) is an acute diabetic emergency that exists in a continuum with Diabetic Ketoacidosis (DKA). In general, HHS is associated with type 2 diabetes and thus is relatively rare in pediatrics with most of the literature focused on individual case reports or case series. However, it is notably becoming more common as the prevalence of type 2 diabetes in the pediatric population increases. One case series identified HHS in 3.7% of newly diagnosed type 2 diabetes pediatric patients (Fournier et al., 2005). HHS has been diagnosed in patients with antibody negative diabetes as young as age 5. Diagnosis of antibody negative diabetes in younger patients may be delayed, which increases risk for development of complications such as HHS (Al Hassani & Kaplan, 2019). However, it has also been reported in rare cases in patients with type 1 diabetes (Hernandez Moreno et al., 2016). Approximately 25-30% of cases of patients with hyperglycemic crises present with combined features of DKA and HHS (Pasquel et al., 2020). Treatment for HHS is distinct from DKA, though, and there have been case reports of poorer outcomes in those managed on a standard DKA protocol (Nambam et al., 2017). HHS often has a delayed diagnosis compared to DKA due to the rare occurrence of HHS in children and non-specific presenting symptoms (headache and abdominal pain). Delay in diagnosis can lead to significant morbidity in patients with severe dehydration, electrolyte imbalances and altered level of consciousness (Price et al., 2016; Venkatraman & Singhi, 2006). This HHS Clinical Pathway serves to bridge the gap between diagnosis and care of the patient with HHS while recognizing the difference between HHS and DKA.

Target Users

- Emergency Medicine Providers
- Pediatric Hospitalists
- Endocrinologists
- Fellows
- Resident Physicians
- Pediatric Nursing Practitioners
- Staff nurses within Emergency Medicine, Pediatric Critical Care, and Inpatient Services

Target Population

Inclusion Criteria

- Severe hyperglycemia (greater than 500 mg/dL)
- Effective Serum Osmolality greater than or equal to 350 mOsm/kg
- Serum bicarbonate greater than or equal to 16 mmol/L

Practice Recommendations

Definitions

The exact definition of HHS varies in the literature. Historically called hyperglycemic hyperosmolar non-ketotic coma, obtundation was one of the required features of the disorder. Now it is characterized by significant hyperglycemia (≥ 600 mg/dL) and dehydration with hyperosmolality (typically > 320 mOsm/kg), without evidence of ketoacidosis (classically a $\text{CO}_2 > 15$ and negative to small urine ketones). Though altered mental status is a common finding in these patients, it is not necessary for significant alterations to be present to make a diagnosis of HHS (Pasquel & Umpierrez, 2014).

The osmolality cut-off value is the most variable criteria in the literature. Not only does the cut-off value vary from 300 mOsm/kg to 350 mOsm/kg, (Nambam et al., 2017; Wolfsdorf et al., 2018) but the technique for determining osmolality also varies. Some authors use measured serum osmolality, some using calculated osmolality, and some use effective osmolality (which removes urea from consideration of the calculated value, as it moves freely across the cell membrane) (Bhowmick et al., 2005).

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Based on discussions with the HHS Clinical Pathway Committee and review of our own cases of DKA and HHS, we classify diagnosis of HHS based on cut-off values of blood glucose ≥ 500 mg/dL and a calculated or measured serum osmolality ≥ 350 mOsm/kg. These cut-off values were chosen based on the observation of patients who seem to have additional complications, such as altered mental status or acute kidney injury. The formula used by our lab to calculate osmolality is: $1.89 \times \text{Na} + 1.38 \times \text{K} + 1.08 \times (\text{Glu} \times 0.0555) + 1.03 \times \text{BUN} + 7.45$. This formula was derived using analysis of measured osmolality and BMPs obtained in our laboratory and differs from the standard calculations used in online osmolality calculators (which often underestimate the measured osmolality, especially for patients experiencing DKA (Davidson, 1992)

As the prevalence of mixed DKA/HHS is significant at our hospital, based on currently available internal data, we will not use ketone measurements or serum bicarbonate to exclude patients from the diagnosis of HHS. However, we recognize that management may need to be individualized based on the degree of ketoacidosis, that is, those with lower bicarbonate levels and higher ketone levels may need to be treated more like classic DKA with monitoring for additional complications common to HHS. Additionally, even those with serum osmolality greater than 350 mOsm/kg may not behave classically like HHS, and some patients with an osmolality between 320 and 350 mOsm/kg may behave more like HHS, particularly in those with serum glucoses >1000 mg/dL or elevated creatinine. Therefore, evaluation of the entire clinical picture is important when evaluating and managing these patients.

Additional Questions Posed by the Clinical Pathway Committee

No new clinical questions were posed for this review.

Children's Mercy Practice Recommendations and Reasoning

There is minimal guidance in the literature particularly for the management of HHS in the pediatric patient. Here, we provide a summary of case reports and case series with recommendations for management.

Initial ED Management

The goal of the initial management is to recognize HHS early during treatment. If new onset diabetes or DKA/HHS is suspected, initial labs should include a point of care (POC) glucose and ketones, BMP with osmolality, and lactate level (as elevated lactate can also cause a high anion gap metabolic acidosis) (Venkatraman & Singhi, 2006). If no previous history of diabetes and POC glucose suggests diagnosis, new onset labs should also be obtained. If febrile, blood cultures and other infectious workup should be obtained as clinically indicated.

New onset diabetes with hyperosmolality should be suspected in patients who are hypertensive with signs of dehydration (Bhowmick et al., 2005), those with dehydration and continued brisk urine output (Venkatraman & Singhi, 2006), or in those with dehydration and altered mental status.

If POC glucose is greater than 500 mg/dL (or reads 'H', the patient should receive an initial fluid bolus of 10 mL/kg (max 1000 mL) over 1 hour. If there is evidence of hemodynamic instability (such as hypotension), this bolus should be administered faster, and boluses continued until the patient is normotensive. Additional blood pressure support may be needed to achieve this goal.

Patients with HHS should not receive Lantus (or other long-acting insulins) initially so that the fall in blood glucose levels can be managed more closely.

If initial BMP confirms the diagnosis of HHS and the blood glucose levels remains above 500 mg/dL, hourly plasma/serum glucose checks will need to be performed, along with BMP with Osm every 2 hours to monitor changes in electrolyte concentrations.

Admission to the ICU

PICU admission or transfer should be considered in any patient with:

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1. Serum osmolality greater than or equal to 350 mOsm/kg
2. Persistent glucose greater than 500 mg/dL (unable to read on POC glucose monitor)
3. Bicarbonate level less than 5 mmol/L at any age or less than or equal to 10 mmol/L if under 5 years of age
4. Hemodynamic instability (hypotension, significant tachycardia, arrhythmia, etc.)
5. Altered level of consciousness (LOC)
6. Significantly elevated BUN
7. Significant hyperkalemia

Fluid Management

The degree of dehydration in patients with HHS is often masked due to hypertonicity. Initially, there is often poor renal perfusion resulting in a low urine output. As renal perfusion improves with fluid therapy, a profound osmotic diuresis occurs as the kidneys work to excrete excess glucose. This diuresis, combined with a decrease in serum osmolality, results in movement of water out of the intravascular spaces (either into the urine or into intracellular spaces during rehydration), resulting in hypovolemic shock (Wolfsdorf et al., 2018).

There are no prospective data to guide management of children and adolescents with HHS. These guidelines are derived from recommendations for management of HHS in adults with the recognition that children may be at a higher or lower risk of complications (cerebral edema, etc.) based on additional factors.

1. The goal of initial fluid therapy is to expand intra- and extra- vascular volume and restore normal renal perfusion.
2. Initial bolus should be 20 mL/kg of isotonic saline up to 1000 mL. Additional boluses may be necessary to restore perfusion and maintain normal blood pressure.
3. Fluid deficit should be assumed to be 12-15% of body weight and replaced over 24-48 hours
4. Fluids should be adjusted to ensure sodium level declines slowly (0.5 mmol/L/hr)
5. Dextrose should be added to fluids earlier than in DKA. To maintain glucose, drop 75-100 mg/dL/hr and stabilize at 250-300 mg/dL until rehydration occurs (i.e. serum sodium level normalizes).
6. Consider replacing urine output 1:1 with ½ NS to reduce ongoing fluid losses. One study suggested starting urine replacement once UOP exceeded 40 mL/m²/hr, which approximates 1.5 ml/kg/hr (Bhowmick et al., 2005).

Caution should be used in those with mixed DKA/HHS, as fluid administration more than 4 L/m²/day has been associated with the development of cerebral edema.

Cardiovascular Status

As above, there is often a period of refractory hypovolemic shock following initial rehydration. Early initiation of vasopressor support (epinephrine, norepinephrine, dopamine) should be considered. An echocardiogram should be obtained if inotropes are needed.

Electrolyte abnormalities are not uncommon (see Electrolytes section) and can result in arrhythmias. Therefore, cardiac lead monitoring is recommended in any patient with HHS during the initial phases of treatment.

Insulin

Insulin is generally not recommended in the initial management of HHS. Rather, recommendations are to continue aggressive fluid management and start an insulin drip once the drop in blood glucose levels falls below 50 mg/dL/hr.

However, in cases of mixed DKA and HHS, insulin may be needed to stop ketosis. In these cases, starting an insulin drip at 0.02 to 0.05 u/kg/hr may be reasonable, along with titration of the insulin drip and fluid rate to achieve a decline in blood glucose no more than 75-100 mg/dL/hr (Wolfsdorf et al., 2018). The Children's Mercy endocrinology team then recommends

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increasing the insulin drip up to the standard 0.1 u/kg/hr once serum osmolality is less than 320 mOsm/kg if necessary for treatment of DKA.

Lantus (or other long-acting insulin analogs) should not be administered until blood glucose levels are <400 mg/dL to reduce the risk of a rapid drop in glucose levels.

Electrolytes

HHS is associated with risk of multiple electrolyte abnormalities, particularly with potassium. Frequent monitoring of potassium and phosphorus (recommendation for BMP every 2-3 hours and phosphate every 3-4 hours) should be included in management, with replacement as needed.

Hypokalemia is the most worrisome of the electrolyte abnormalities, as these patients tend to have very high potassium losses (more significant than in DKA). There are reports of pediatric patients having cardiac rhythm abnormalities, including ventricular tachycardia (Sorcher et al., 2019), because of hypokalemia. Therefore, it is recommended to start replacement of potassium at 40 mEq/L once levels are in the normal range and adequate renal function has been established. Higher rates of potassium may be needed once insulin therapy is initiated (Wolfsdorf et al., 2018). Bicarbonate **should not** be administered, as it increases the risk of hypokalemia

Hyperkalemia may also be present initially. In these cases, insulin may need to be started sooner to manage potassium levels but should be administered with dextrose to prevent a rapid decline in glucose levels.

Hypophosphatemia has been associated with HHS (Morales & Rosenbloom, 2004; Zubkiewicz-Kucharska et al., 2019). Severe hypophosphatemia may lead to rhabdomyolysis (see Rhabdomyolysis section). Therefore, phosphate should be administered in a 50:50 mixture of potassium phosphate and another potassium salt (such as potassium chloride or potassium acetate) to reduce the risk of severe hypophosphatemia or hypocalcemia from phosphate replacement (Wolfsdorf et al., 2018).

Hyper- or hypocalcemia may also occur, requiring frequent monitoring of ionized calcium. In cases of hemodynamic instability calcium acts as an inotrope. The goal should be to maintain ionized calcium in the normal range. In addition, calcium levels can be very low in the oliguric phase of rhabdomyolysis and acute renal injury, requiring frequent replacement. Levels can also be high in the diuretic phase of recovery from acute renal injury (Akmal et al., 1986).

There is no guidance on whether magnesium replacement is beneficial in the treatment of HHS. However, it should be repleted in the setting of hypocalcemia to allow improvement in calcium levels (Wolfsdorf et al., 2018).

Kidney Injury

The significant dehydration that defined HHS results in acute kidney injury. There is often significant elevation in the BUN and creatinine with initial labs, which often improves with rehydration. However, other features of HHS (especially rhabdomyolysis, detailed in the following section) may result in additional injury after the initial hypoperfusion is corrected. Therefore, consideration for CRRT or hemodialysis, should be ongoing based on the clinical status of the patient, particularly if urine output decreases during treatment.

Rhabdomyolysis

Rhabdomyolysis is a frequently cited complication of HHS and is occasionally seen in DKA (Akmal et al., 1986). It may be induced by hypophosphatemia (Nambam et al., 2017). It has also been associated with a malignant hyperthermia-like syndrome (see Fever/Hyperthermia section) (Hollander et al., 2003).

It is recommended to trend creatine kinase (CK) levels every 2-3 hours for early detection (Wolfsdorf et al., 2018). If previously normal, but a rise in creatinine is noted, CK levels should be repeated.

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Fever/Hyperthermia

In adults, infection is often a trigger for the development of HHS, and thus fevers are relatively common. However, infection has not been identified as a common cause of HHS in pediatrics (Fourtner et al., 2005). There has been an association of a malignant hyperthermia-like syndrome that occurs with HHS (Hollander et al., 2003). It has been proposed to be a reaction to a preservative in IV insulin (Wappler et al., 1996), but not all cases have been associated with insulin initiation (Hollander et al., 2003).

It is recommended that in instances of fever or hyperthermia, an infectious workup should be completed, and any underlying infection treated. If no infectious etiology is found, dantrolene may be considered for treatment of hyperthermia.

Hematology

Thrombosis has been identified as a complication of HHS (Fourtner et al., 2005). This is thought to be due to the dehydration and hemoconcentration that results, though elevated vasopressin levels may also promote clotting tendencies (Nambam et al., 2017). Current recommendations are to reserve anticoagulant therapy for those who have central lines or are expected to be immobile for longer than 24-48 hours (Wolfsdorf et al., 2018).

DKA (Alsaied et al., 2016; Khan et al., 2013; Patra & Scott, 2011) and HHS have also been associated with thrombocytopenia-associated multi-organ failure (Tufan-Pekkucuksen et al., 2018). This condition is defined by new onset thrombocytopenia (<100K) or drop of 50% from baseline over less than 30 hours, and overt disseminated intravascular coagulopathy (DIC). If suspected, an lactate dehydrogenase (LDH) level can be drawn and is typically high in this condition. Those with multi-organ dysfunction may benefit from plasma exchange (Fortenberry et al., 2019).

Mental Status and Cerebral Edema

It is not uncommon to have altered mental status associated with HHS. In general, mental status improves during treatment. A complication not infrequently seen in DKA is cerebral edema. There have been few reported cases of cerebral edema in the setting of HHS (Fourtner et al., 2005; Morales & Rosenbloom, 2004), indicating that the incidence is significantly less than DKA. However, if there is a deterioration of mental status during treatment, this should be promptly investigated and treatment of cerebral edema should be considered (Wolfsdorf et al., 2018). Of note, less is known about the incidence of cerebral edema in cases of mixed DKA/HHS, so particular care should be taken in this population.

Deteriorating mental status should also raise concern for cerebral thrombosis, as cerebral thromboses have been noted in patients with HHS (Misra et al., 2017; Nwosu et al., 2012). Anecdotally, there have been instances of CNS venous thrombosis in patients with severe dehydration secondary to HHS, though this is not widely reported in the literature. In these cases, a head CT should be obtained urgently.

Measures

- Rate of accurate diagnosis of HHS in hospitalized patients
- Use of HHS Power Plans
- Length of hospital stay
- Timing of insulin initiation
- Complication rates of patients with HHS (including cerebral edema, shock, acute kidney injury, rhabdomyolysis, thrombosis, arrhythmias, malignant hyperthermia, and intubation)

Potential Cost Implications

The following potential improvements may reduce costs and resource utilization for healthcare facilities and reduce healthcare costs and non-monetary costs (e.g., missed school/work, loss of wages, stress) for patients and families.

- Appropriate triage to intensive care vs inpatient care
- Decreased intensive care length of stay

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- Decreased unwarranted variation in care
- Decreased risk of acute kidney injury

Potential Organizational Barriers and Facilitators

Potential Barriers

- Lack of national standards to care for patients experiencing HHS
- Difficulty distinguishing HHS and DKA
- Low index of suspicion for new onset diabetes in those without classic features of HHS/DKA

Potential Facilitators

- Collaborative engagement among critical care, endocrinology, and other stakeholders during clinical pathway development
- Standardized order set for Pediatric Intensive Care

Power Plans

- EDP Diabetes: DKA, Bicarb < 16 Pathway
- PICU Hyperglycemic Hyperosmolar Syndrome

Associated Policies

- There are not any policies associated with this clinical pathway

Clinical Pathway Preparation

This clinical pathway was prepared by the Evidence Based Practice Department (EBP) in collaboration with content experts at Children's Mercy Kansas City. Development of this clinical pathway supports the Division of Quality Excellence and Safety's initiative to promote care standardization that is evidenced by measured outcomes. If a conflict of interest is identified the conflict will be disclosed next to the committee member's name.

Hyperglycemia Hyperosmolar Syndrome Clinical Pathway Committee Members and Representation

- M. Knoll, MD, MHPE | Endocrinology | Committee chair
- R. McDonough, DO | Endocrinology | Committee member
- A. Stoner, MS, DO | Critical Care Medicine | Committee member
- S. Fagan, RN, BSN, CCRN-K | Pediatric Intensive Care Unit | Committee member

MIT Committee Members

- Tammy Frank, RPh, CPHIMS | Medical Informatics - Pharmacy

EBP Committee Members

- Jacqueline (Jackie) Bartlett, PhD, RN | Evidence Based Practice
- Kathleen Berg, MD, FAAP | Hospitalist, Evidence Based Practice
- Megan Gripka, MT (ASCP) SM | Evidence Based Practice
- Kelli Ott, OTD, OTR/L | Evidence Based Practice

Additional Review & Feedback

- The clinical pathway was presented to each division or department represented on the clinical pathway committee as well as other appropriate stakeholders. Feedback was incorporated into the final product.

Implementation & Follow-Up

- Order sets consistent with clinical pathway recommendations were created
- Education was provided to all stakeholders:
 - Nursing units: Emergency Department, Pediatric ICU
 - Providers from Emergency Medicine, Endocrinology, Critical Care
 - Resident physicians
- Additional institution-wide announcements were made via email, hospital website, and relevant huddles.

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- Metrics will be assessed on an ongoing basis and shared with appropriate care teams to determine if changes need to occur.

Development Funding

The development of this clinical pathway was underwritten by the following departments/divisions: Evidence Based Practice, Emergency Medicine, Critical Care Medicine, and Endocrinology

Approval Process

This CLINICAL PATHWAY was reviewed and approved by the HHS Clinical Pathway Committee, Content Expert Departments/Divisions, and the EBP Department. Clinical Pathways are reviewed and updated as necessary every 3 years within the EBP Department at CMKC. Content expert teams are involved with every review and update.

Approval Obtained

Department/Unit	Date Approved
Emergency Medicine	June 2022
Endocrinology	October 2022
Critical Care Medicine	October 2022

Version History

Date	Comments
July 2021	Version one (clinical pathway developed and consensus obtained)
May 2022	Version two (clinical hyperosmolality data reviewed and hyperosmolality criteria refined)
October 2022	Version three (PICU algorithm added to clinical pathway)

Date for Next Review

- December 2025

Disclaimer

When evidence is lacking or inconclusive, options in care are provided in the supporting documents and the power plan(s) that accompany the clinical pathway.

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