TEXAS CHILDREN'S HOSPITAL
EVIDENCE-BASED OUTCOMES CENTER
Hyperglycemic Hyperosmolar State [with or without DKA]
Evidence-Based Guideline

Definition: Hyperglycemic Hyperosmolar Syndrome (HHS) is defined as hyperosmolality due to elevated serum glucose without significant ketosis. Mild to moderate acidosis may be due to severe dehydration and associated hypoperfusion and lactic acidosis.

Fluid losses in HHS are estimated to be two times more than those in diabetic ketoacidosis (DKA). Aggressive fluid resuscitation is needed to prevent intravascular collapse.

Patients may have both HHS and DKA (mixed type). In these cases, the significant serum glucose elevation and hyperosmolality are accompanied by ketosis and acidosis (pH <7.3 with anion gap that is elevated due to moderate or higher ketones). The degree of hyperglycemia and dehydration in these patients is often greater than that of DKA, with fluid and electrolyte therapy often exceeding that of DKA alone.

Pathophysiology/Etiology: HHS is a critical condition most often seen in patients with type-2 diabetes, but can also be seen in those with type-1 diabetes and infants with diabetes. Onset of HHS is often insidious, with gradually increasing polyuria and polydipsia due to hyperglycemia resulting in severe dehydration and electrolyte losses at the time of presentation. Recent literature reports that HHS is present in 2% of youth with type-2 diabetes at the time of presentation. While incidence of HHS is lower than that of DKA, mortality is estimated to range from 10-60%, significantly higher than that of DKA. Beyond new diagnosis of diabetes, other precipitating factors include infections, non-adherence to medical therapy for diabetes, and substance abuse.

HHS occurs due to insulin resistance causing net ineffective action of insulin and elevated counter regulatory hormones that stimulate hepatic glucose production. This results in increased hepatic glucose production and impaired glucose utilization in peripheral tissue leading to significant hyperglycemia, intracellular water depletion and osmotic diuresis. Severe dehydration leading to hypoperfusion and resultant lactic acidosis can cause mild to moderate acidosis. However, given some degree of preserved insulin production, lipolysis and ketogenesis are suppressed leading to minimal ketoacidosis except in those with mixed type.

The glucosuria in HHS causes greater water loss compared to sodium, resulting in hyperosmolality and dehydration. Decrease in intravascular volume decreases the glomerular filtration rate (GFR), decreasing glucose clearance and further increasing serum glucose levels. Despite severe dehydration and electrolyte losses, hypertonicity can preserve intravascular volume despite substantial total body dehydration, and signs of dehydration may be less evident. Concurrent obesity can make clinical assessment of dehydration challenging.

Mixed type (both HHS and DKA) presents with the severe hyperglycemia and dehydration seen in HHS with ketosis. In these patients, decreased insulin secretion results in the inability to suppress lipolysis and ketogenesis. This can be seen in type-2 diabetes patients with severe glucotoxicity causing beta cell impairment. It can also be seen in type-1 diabetes where insulin deficiency resulting in DKA is exacerbated by severe dehydration (inability to compensate urinary losses with fluid intake) or use of sugar containing beverages to manage increased thirst.

Inclusion Criteria
- Patients 10 years of age and older
- Weight 50 kg or greater

HHS without DKA
- Plasma glucose concentration >600 mg/dL
- Serum bicarbonate >15 mmol/L
- Beta-hydroxybutyrate <4 mmol/L
- pH >7.2
- Effective serum osmolality >320 mOsm/kg

Mixed HHS with DKA
- Plasma glucose concentration >600 mg/dL
- Beta-hydroxybutyrate >4 mmol/L
- pH <7.2, without other causes of low pH (i.e. lactic acidosis)
- Effective serum osmolality >320 mOsm/kg

Exclusion Criteria
- Total parenteral nutrition (TPN) induced hyperglycemia
- Pregnancy
- Drug induced altered mental status

Differential Diagnosis
- DKA
- Inborn errors of metabolism

Diagnostic Evaluation
History: Assess for
- Previous diagnosis of diabetes
- Altered mental status
- Polydipsia
- Polyuria/Nocturia
- Weight loss

Physical Examination
- Altered mental status
- Vital signs
- Skin turgor

Laboratory Tests
- Chem 7
- Serum osmolality*
- *Calculated serum osmolality [(1)] = 2(Na) + glucose/18 + BUN/1.8
  The calculated serum osmolality can be calculated based on the above formula while awaiting the measured serum osmolality
- Point of care glucose
- Beta-hydroxybutyrate
- Hemoglobin A1C
- pH
- Venous blood gas
- Diabetes panel

Critical Points of Evidence*

Recommendations adopted/adapted from the International Society for Pediatric and Adolescent Diabetes (ISPAD) Clinical Practice Consensus Guidelines 2018: Diabetic ketoacidosis and the hyperglycemic hyperosmolar state

Fluid Therapy

- The initial bolus should be 20 mL/kg (max 1 L) of isotonic saline (Normal Saline [NS]), a fluid deficit of approximately 12% to 15% of body weight should be assumed. After the initial bolus, the patient should be clinically reassessed (heart rate, perfusion, blood pressure) before giving additional fluid boluses. No more than a maximum of 4 L total should be given. [(2)] - This recommendation was adapted.
- Start isotonic saline (NS) as continuous fluid replacement, administered at a rate of 250 mL/hour. Assess the patient's vital signs and titrate the fluid rate as needed. If the patient's heart rate or corrected serum sodium or osmolality is not decreasing within 2 hours of the start of continuous fluids, increase the rate by 100 mL/hour and continue to titrate up (max rate 500 mL/hour) until appropriate decrease in heart rate, serum sodium or serum osmolality is seen. After two hours at 500 mL/hour, consider switching to ½ NS or ¾ NS if serum sodium and osmolality is not decreasing appropriately. [(2)] - This recommendation was adapted.
  Remarks: Appropriate decrease in serum sodium is considered to be a corrected serum sodium drop between 0.5 to 1 mEq/L/h (12-24 mEq/L/day). Appropriate decrease in calculated/measured serum osmolality is considered to be between 0.5 to 1 mOsm/kg H20 per hour (12-24 mOsm day).
- "Because isotonic fluids are more effective in maintaining circulatory volume, isotonic saline should be restarted if perfusion and hemodynamic status appear inadequate as serum osmolality declines" [(2)] -This recommendation was adopted.
- "Serum sodium concentrations should be measured frequently and the sodium concentration in fluids adjusted to promote a gradual decline in corrected serum sodium concentration."-This recommendation was adopted.
  Remarks: Corrected serum sodium concentration= measured Na + [(glucose level - 100) x 0.016]
- Obtain electrolyte panel every 2 hours x 3, then obtain Chem10 alternating with electrolyte panel every 3 hours for the first 24 hours. Obtain serum osmolality every 2 hours x 3, then every 3 hours for the first 24 hours. If patient is not improving, consider more frequent laboratory monitoring. -This is a consensus recommendation.
- Obtain a point of care (POC) glucose check hourly until the patient is downgraded from ICU status. -This is a consensus recommendation.
- Although there are no data to indicate an optimal rate of decline in serum sodium concentration, 0.5 mmol/L/h (0.5 mEq/L/h) has been recommended for hypernatremic dehydration. With adequate rehydration alone (ie, before commencing insulin therapy), serum glucose concentrations should decrease by 75-100 mg/dL (4.1 to 5.5 mmol/L) per hour. [(2)] -This recommendation was adapted.
- "A more rapid rate of decline in serum glucose concentration is typical during the first several hours of treatment when an expanded vascular volume leads to improved renal perfusion." [(2)] -This recommendation was adopted.
- If there is a continued rapid fall in serum glucose (greater than 100 mg/dL/h) after the first few hours, consider adding 5% glucose to the rehydration fluid or consider the use of D10W if the plasma glucose concentration decreases too quickly despite D5W. [(2)] -This recommendation was adapted.
- "Failure of the expected decrease of plasma glucose concentration should prompt reassessment and evaluation of renal function." [(2)] -This recommendation was adopted.
- For the first 24 hours, the patient should have a Foley catheter in place. Replace urinary losses 1:1 with 0.45% normal saline (NS) every 2 hours. [(2)] -This recommendation was adapted.

Insulin Therapy

- Insulin administration should be initiated when serum glucose concentration is no longer declining at a rate of at least ~50 mg/dL per hour with fluid administration alone. [(2)] -This recommendation was adapted.
- If the patient is getting 500 mL/hour of non-dextrose containing fluids for 2 hours and their glucose is decreasing at a rate of less than 50 mg/dL/hour and their serum glucose is persistently above 300 mg/dL, consider IV insulin at a rate of 0.025 units/kg/h (max rate of 2.5 units/hour). Transition the patient to subcutaneous insulin administration as soon as appropriate and possible. -This recommendation was adapted.
- "Insulin boluses are not recommended." [(2)] -This recommendation was adopted.
- Ensure the patient is not hypokalemic before starting insulin therapy. Treat hypokalemia first, if present. -This is a consensus recommendation.

Electrolytes

- Potassium replacement (40 mmol/L of replacement fluid) should begin as soon as serum potassium concentration is within the normal range and adequate urine output has been established. [(2)] -This recommendation was adapted.
- "Higher rates of potassium administration may be necessary after starting an insulin infusion." [(2)] -This recommendation was adopted.
- Serum potassium concentrations should be monitored every 2 hours X2, and then every 4 hours until the patient is downgraded from ICU. [(2)] -This recommendation was adapted.
- Patients should be on continuous ECG telemetry monitoring. [(2)] -This recommendation was adapted.
- "Hourly potassium measurements may be necessary if the patient has hypokalemia." [(2)] -This recommendation was adopted.
- "Bicarbonate therapy is contraindicated; it increases the risk of hypokalemia and may adversely affect tissue oxygen delivery." [(2)] -This recommendation was adopted.
- "Severe hypophosphatemia may lead to rhabdomyolysis, hemolytic uremia, muscle weakness and paralysis. Although administration of phosphate is associated with a risk of hypocalcemia, an IV solution that contains a 50:50 mixture of potassium

phosphate and another suitable potassium salt (potassium chloride or potassium acetate), generally permits adequate phosphate replacement while avoiding clinically significant hypocalcemia." [2] -This recommendation was adopted.
- "Serum phosphate concentrations should be measured every 3 to 4 hours." [2] -This recommendation was adopted.
- Obtain electrolyte panel every 2 hours x 3, then obtain Chem10 alternating with electrolyte panel every 3 hours for the first 24 hours. Obtain serum osmolality every 2 hours x 3, then every 3 hours for the first 24 hours. If patient is not improving, consider more frequent laboratory monitoring. -This is a consensus recommendation.
- "Replacement of magnesium should be considered in the occasional patient who experiences severe hypomagnesemia and hypocalcemia during therapy. The recommended dose is 25 to 50 mg/kg per dose for 3 to 4 doses given every 4 to 6 hours with a maximum infusion rate of 150 mg/min and 2 g/h." Use ideal body weight of 75-100 kg with a max dose of 2 g. [2] -This recommendation was adapted.

Complications
- "Venous thrombosis associated with use of central venous catheters is a common hazard in HHS. Prophylactic use of low-dose heparin has been suggested in adults but there are no data to indicate benefit from this practice. Heparin treatment should be reserved for children who require central venous catheters for physiologic monitoring or venous access and are immobile for more than 24 to 48 hours." [2] -This recommendation was adopted.
- Consider DVT prophylaxis per ICU protocol. -This is a consensus recommendation.
- Monitor creatine kinase concentrations for early detection of rhabdomyolysis on admission and then every 6 hours until 24-48 hours based on severity of illness. [2] -This recommendation was adapted.
- Remain vigilant for malignant hyperthermia. If indicated, consult anesthesia and coordinate treatment plan. [2] -This recommendation was adapted.
- "A decline in mental status after hyperosmolality has improved with treatment is unusual and should be promptly investigated." Follow neuro VS hourly. [2] -This recommendation was adapted.

Mixed HHS and DKA (moderate-severe DKA): Beta-hydroxybutyrate >4 mmol/L and pH <7.2
- After adequate fluid resuscitation and one hour of continuous fluid therapy, begin insulin drip administration at 0.05 units/kg/hour. For patients over 100 kg, discuss insulin drip rate with endocrine. -This is a consensus recommendation.

*NOTE: The references cited represent the entire body of evidence reviewed to make each recommendation.

Condition-Specific Elements of Clinical Management

General: In children and adolescents with HHS or mixed HHS with DKA picture, presenting signs and symptoms are related to severe hyperglycemia, severe dehydration and hyperosmolality. Aggressive fluid therapy to expand intra- and extravascular volume, restore renal perfusion, and promote gradual decline in serum sodium and osmolality are essential. Given acuity of required care and high morbidity associated with HHS, intensive monitoring in the pediatric intensive care unit is recommended.

Treatment Recommendations:

Fluid Therapy: Establish 2 peripheral IVs upon admission. It is essential to initiate aggressive fluid therapy early. An initial normal saline (NS) bolus of 20 mL/kg is recommended. This can be repeated as clinically indicated (max bolus 4 L total).

For subsequent fluids in patients over 50 kg, NS should be started at 250 mL/hour. Fluid rate should be titrated hourly based clinical and laboratory parameters (max 500 mL/hour).

Urinary losses should be replaced 1:1 with 0.45% NS.

Insulin Therapy: In HHS alone, insulin therapy should be initiated at low dose when serum glucose is no longer declining at a rate of 50 mg/dL per hour with fluid therapy alone, and glucose remains higher than 300 mg/dL. Insulin infusion of 0.025 unit/kg/hour (max 2.5 units/hour) is recommended. For patients over 100 kg, discuss insulin drip rate with endocrine.

For patients with mixed HHS and DKA, insulin therapy should be started earlier to manage the DKA component. Insulin infusion at 0.05 units/kg/hour is recommended after adequate fluid resuscitation and at least 1 hour on continuous fluids. For patients over 100 kg, discuss insulin drip rate with endocrine.

Electrolytes: Potassium replacement via replacement IV fluids is recommended when serum potassium is in normal range and renal function has been established.

Phosphate: Severe hypophosphatemia should be treated with an IV solution that contains a 50:50 mixture of potassium phosphate and another suitable potassium salt (potassium chloride or potassium acetate).

Bicarbonate: Administration of bicarbonate is NOT recommended.

Magnesium: Replacement should be considered in patients with severe hypomagnesemia and hypocalcemia.

Deep Vein Thrombosis (DVT) Prophylaxis: DVT prophylaxis with heparin is recommended in patients requiring central venous catheters.

Admission Criteria:
Patients meeting all of the below criteria should be admitted.

HHS without DKA
- Plasma glucose concentration >600 mg/dL
- Serum bicarbonate >15 mmol/L
- Beta-hydroxybutyrate <4 mmol/L
- pH >7.2
- Effective serum osmolality >320 mOsm/kg

Mixed HHS with DKA
- Plasma glucose concentration >600 mg/dL
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- pH <7.2, without other causes of low pH (i.e. lactic acidosis)

- Effective serum osmolality >320 mOsm/kg

Discharge Criteria

- Normalization of biochemical abnormalities
- Diabetes education
- Stable on subcutaneous insulin
- Acquisition of adequate at home supplies
- Social work consult
- School packet (if in school)

Consults/Referrals

- Consult Endocrine team upon admission to EC
- Social work
- Registered Dietician
- Diabetes Educator (Clinical Diabetes Care and Education Specialist [CDCES])
- Renal (as needed)

Measures

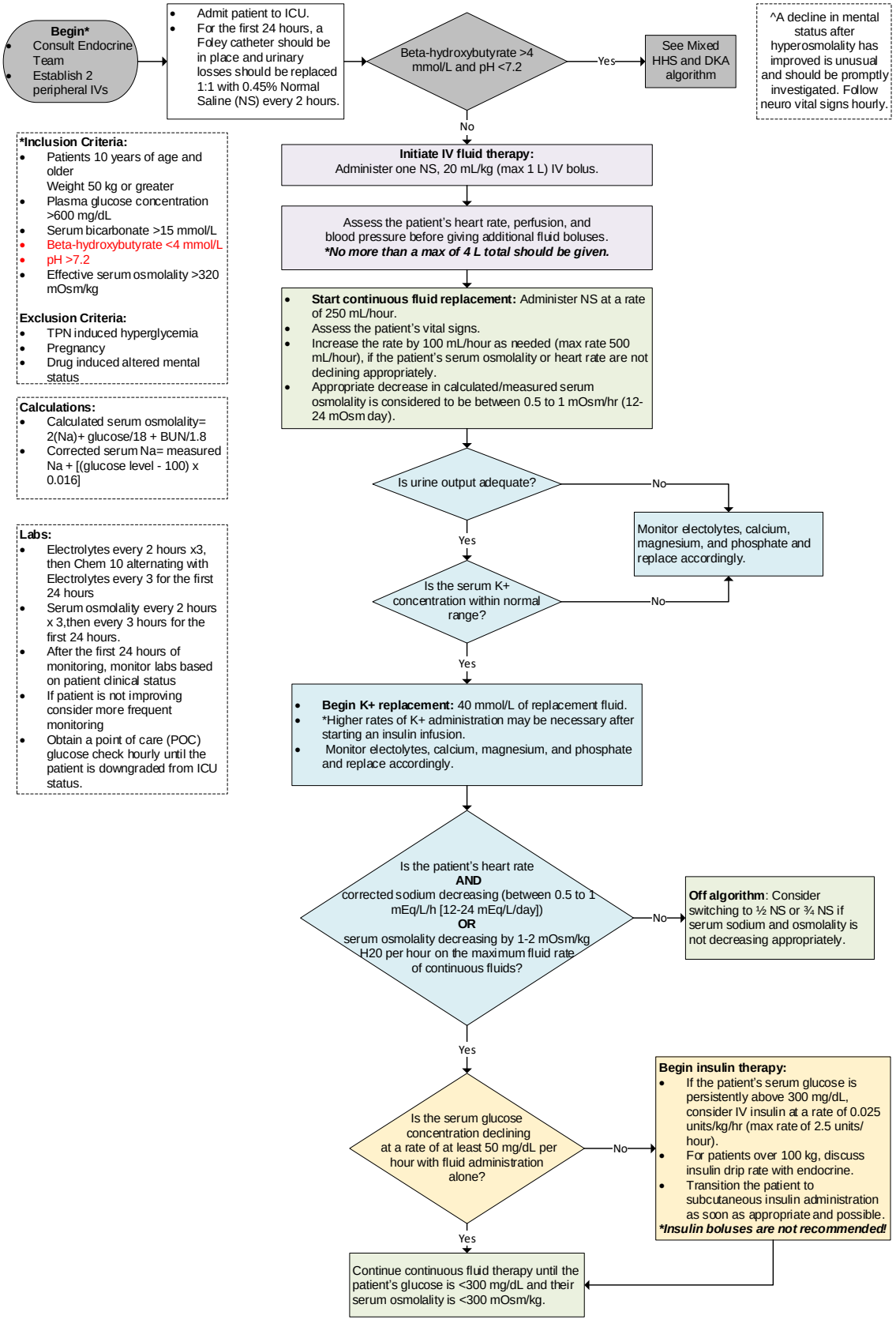
Process

- Standardized order set utilization

Outcome

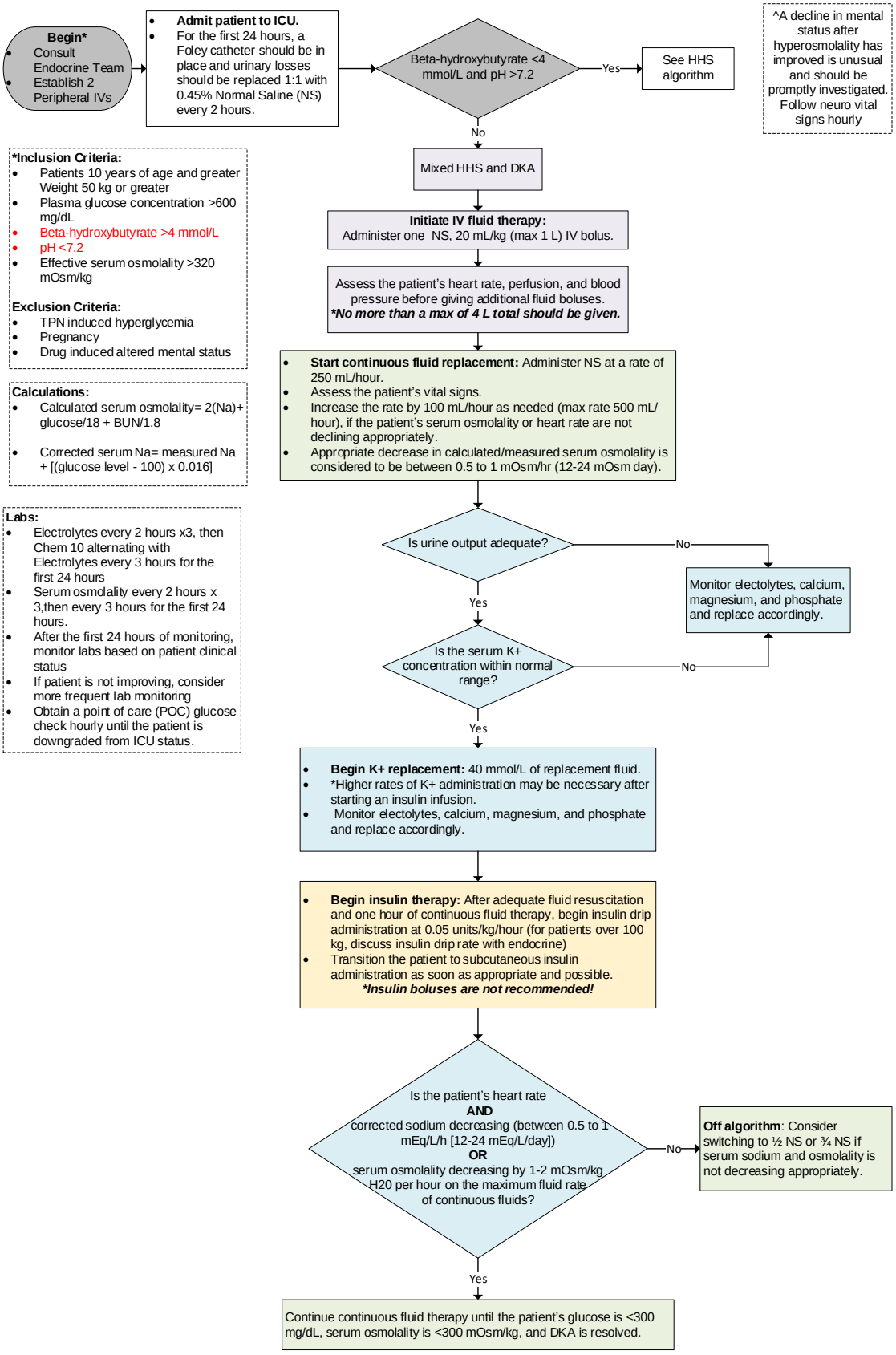
- Length of stay (ICU)
- Time to initiation of continuous fluids at recommended rate
- Time to normalization of creatinine to baseline
- POPC and PCPC score normalization

TCH Evidence-Based Outcomes Center
Clinical Algorithm for Hyperglycemic Hyperosmolar State (HHS)



Clinical standards are developed for 80% of the patient population with a particular disease. Each practitioner must use his/her clinical judgment in the management of any specific patient.

TCH Evidence-Based Outcomes Center
Clinical Algorithm for MIXED Hyperglycemic Hyperosmolar State (HHS) & Diabetic Ketoacidosis (DKA)



Clinical standards are developed for 80% of the patient population with a particular disease. Each practitioner must use his/her clinical judgment in the management of any specific patient.

References

1. Najem O, Shah MM, De Jesus O. Serum Osmolality. [Updated 2022 Jan 24]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK567764/
2. Wolfsdorf, J. I., Glaser, N., Agus, M., Fritsch, M., Hanas, R., Rewers, A., Sperling, M. A., & Codner, E. (2018). ISPAD Clinical Practice Consensus Guidelines 2018: Diabetic ketoacidosis and the hyperglycemic hyperosmolar state. *Pediatric diabetes*, *19 Suppl 27*, 155–177. https://doi.org/10.1111/pedi.12701

Clinical Standards Preparation

This clinical standard was prepared by the Evidence-Based Outcomes Center (EBOC) team in collaboration with content experts at Texas Children's Hospital. Development of this clinical standard supports the TCH Quality and Patient Safety Program initiative to promote clinical standards and outcomes that build a culture of quality and safety within the organization.

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No relevant financial or intellectual conflicts to report.

Development Process

This clinical standard was developed using the process outlined in the EBOC Manual. The literature appraisal documents the following steps:

1. Review Preparation
2. Review of Existing External Guidelines
   -International Society for Pediatric and Adolescent Diabetes (ISPAD) Clinical Practice Consensus Guidelines 2018: Diabetic ketoacidosis and the hyperglycemic hyperosmolar state
3. Critically Analyze the Evidence
4. Summarize the Evidence
   - Materials used in the development of the clinical standard, literature appraisal, and any order sets are maintained in a Hyperglycemic Hyperosmolar evidence-based review manual within EBOC.

Evaluating the Quality of the Evidence

Published clinical guidelines were evaluated for this review using the **AGREE II** criteria. The summary of these guidelines are included in the literature appraisal. AGREE II criteria evaluate Guideline Scope and Purpose, Stakeholder Involvement, Rigor of Development, Clarity and Presentation, Applicability, and Editorial Independence using a 4-point Likert scale. The higher the score, the more comprehensive the guideline.

Recommendations

Practice recommendations were directed by the existing evidence and consensus amongst the content experts. Patient and family preferences were included when possible. The Content Expert Team and EBOC team remain aware of the controversies in the diagnosis/management of Hyperglycemic Hyperosmolar State in children. When evidence is lacking, options in care are provided in the clinical standard and the accompanying order sets (if applicable).

Approval Process

Clinical standards are reviewed and approved by hospital committees as deemed appropriate for its intended use. Clinical standards are reviewed as necessary within EBOC at Texas Children's Hospital. Content Expert Teams are involved with every review and update.

Disclaimer

Practice recommendations are based upon the evidence available at the time the clinical standard was developed. Clinical standards (guidelines, summaries, or pathways) do not set out the standard of care and are not intended to be used to dictate a course of care. Each physician/practitioner must use his or her independent judgment in the management of any specific patient and is responsible, in consultation with the patient and/or the patient's family, to make the ultimate judgment regarding care.

Version History

Date	Comments
Oct 2022	Originally completed