TEXAS CHILDREN'S HOSPITAL
EVIDENCE-BASED OUTCOMES CENTER
DIABETIC KETOACIDOSIS (DKA) CLINICAL GUIDELINE
Evidence-Based Guideline

Definition: Diabetic ketoacidosis (DKA) is a decrease in effective circulating insulin associated with increases in counter regulatory hormones (e.g., glucagon, catecholamines, cortisol, and growth hormone). Hyperglycemia and acidosis result in osmotic diuresis, dehydration, and obligate loss of electrolytes. (1)

Biochemical Criteria: blood glucose >200 mg/dL; venous pH <7.25 (arterial pH <7.3) and/or bicarbonate <15 mmol/L with ketones in blood or urine. (1)

Pathophysiology: (11) Insulin deficiency is the initial primary event in progressive β-cell failure, its exogenous omission in a patient with established disease, or its relative ineffectiveness when insulin action is provoked by physiological stress (e.g., sepsis) and in the context of counterregulatory hormone excess. These hormonal changes augment glucose production from glycogenolysis and gluconeogenesis while limiting glucose utilization. This process results in hyperglycemia (>11 mmol/L, approximately 200 mg/dL), osmotic diuresis, electrolyte loss, dehydration, decreased glomerular filtration, and hyperosmolarity. Simultaneously, lipolysis provides increased free fatty acids. The oxidation of free fatty acids facilitates gluconeogenesis and generates acetoacetic and β-hydroxybutyric acids (ketones) that overwhelm buffering capacity, resulting in metabolic acidosis (pH 7.3). This is compounded by lactic acidosis from poor tissue perfusion. Progressive dehydration, hyperosmolarity, acidosis, and electrolyte disturbances exaggerate stress hormone secretion and establish a self-perpetuating cycle of progressive metabolic decompensation.

Epidemiology: DKA occurs in 26% of children with new onset type 1 diabetes (T1DM). (2) DKA is the leading cause of morbidity and mortality in children with diabetes. (3,4) Mortality rates are less than 1% with the majority (62-87%) of these caused by cerebral edema.

Risk Factors for Cerebral Edema (CE): (5-10)
- Age <5 years
- New onset diabetes
- High initial serum urea
- Low initial partial pressure of **arterial** carbon dioxide
- Rapid administration of hypotonic fluids
- Failure of corrected serum sodium to rise during treatment
- Treatment with bicarbonate (HCO_3)

Inclusion Criteria
Neonates to 18 years
Clinical findings of DKA

Exclusion Criteria
Hyperglycemia without acidosis

Differential Diagnosis
Sepsis
Stress-induced or steroid-related hyperglycemia
Inborn errors of metabolism
Hyperosmolar coma

Diagnostic Evaluation
History: Assess for
- Diabetes
- Polyuria, polydipsia, polyphagia
- Estimated weight loss
- Abdominal pain, vomiting
- Concurrent illness or infections
- Kussmaul respiration (rapid and/or deep sighing)
- Inadequate insulin therapy (e.g., non-adherence, inappropriate dosing)
- Altered sensorium˜, headache
- Steroid use

˜ The recording of conscious level is a vital assessment in the management of children with DKA as CE is rare but potentially devastating. (1)

Physical Examination
Degree of acidosis (mild, moderate, severe) is an important marker for determining the severity of DKA and is a risk factor for CE. Clinical assessment of dehydration can be imprecise. It's important to treat children with DKA based on a moderate level of dehydration.
- Airway, breathing, circulation
- Weight (actual), height, m^2
- Age <5 years
- Blood pressure, heart rate, respiratory rate, temperature
- Fruity breath
- Kussmaul respiration (rapid and/or deep sighing)
- Neurological status† (e.g., level of consciousness, fundal exam, pupils, Babinski reflex)

Degree of Acidosis: (11)
- Mild/Moderate- venous pH 7.0-7.30
- Severe- venous pH <7.0

Modified Glasgow Coma Score (GCS) for Infants , Children, and Adults

	Adult	Child	Infant	Score
Eye opening	Spontaneous	Spontaneous	Spontaneous	4
	To speech	To speech	To speech	3
	To pain	To pain	To pain	2
	None	None	None	1
Best verbal response	Oriented	Oriented, appropriate	Coos and babbles	5
	Confused	Confused	Irritable cries	4
	Inappropriate words	Inappropriate words	Cries to pain	3
	Incomprehensible sounds	Incomprehensible sounds	Moans to pain	2
	None	None	None	1
Best motor response	Obeys	Obeys commands	Moves spontaneously and purposefully	6
	Localizes	Localizes painful stimulus	Withdraws to touch	5
	Withdraws	Withdraws in response to pain	Withdraws in response to pain	4
	Abnormal flexion	Flexion in response to pain	Abnormal flexion posture to pain	3
	Extensor response	Extension in response to pain	Abnormal extension posture to pain	2
	None	None	None	1

Laboratory Tests (12)
Obtain immediately by bedside meter:
- Blood glucose
- β-hydroxybutyrate

Additional tests:
- K, HCO_3, Cl, glucose
- BUN, Cr
- β-hydroxybutyrate
- Blood gas

For new onset diabetes:
- Diabetes panel
- Celiac panel
- Thyroglobulin antibodies panel

Critical Points of Evidence*

Evidence Supports

- The use of potassium values from the venous blood gas to guide decisions regarding potassium supplementation. [12] – Strong recommendation, moderate quality evidence
- The use of 0.9% sodium chloride solution (normal saline) for rehydration in children age five years or older. Give one 20 mL/kg normal saline bolus, assess need for a second 20 mL/kg bolus, and subsequent fluid management should amount to 2500 mL per meter squared per day (subtract boluses; do not subtract boluses if rate dips below maintenance). If concerned for hyperchloremic acidosis (Cl level >110 mEq/L), consider changing fluid to LR. [13-21] – Strong recommendation, moderate quality evidence
  Remarks: In the studies reviewed, there appeared to be no clinically significant differences between types of fluids nor rate.
- The use of intravenous insulin to correct diabetic ketoacidosis when the patient has a pH <7.3. [22-25] – Strong recommendation, very low quality evidence
  Remarks: In light of the equivocal evidence, the team decided to standardize and use IV insulin as the preferred approach. In circumstances where continuous IV administration is not possible for patients with uncomplicated DKA, serial subcutaneous insulin administration every 3 hours are safe and may be as effective as IV regular insulin infusion, but ideally should not be used in patients whose peripheral circulation is impaired.
- The administration of mannitol or hypertonic saline (3%) in pediatric patients with diabetic ketoacidosis and cerebral edema. [26] – Strong recommendation, very low quality evidence
- The use of clinical judgment to determine if treatment is needed for cerebral edema. [27] – Strong recommendation, very low quality evidence
  Remarks: Do NOT delay hyperosmolar treatment for CT in a patient with suspected cerebral edema. Consider CT in patients with altered mental status who have been given hyperosmolar treatment, or in whom the neurological exam has not improved with hyperosmolar therapy, or in patients with suspected alternative etiology. If hyperosmolar therapy is not initiated, do not perform a CT; continue to monitor neurological status for changes, including need for hyperosmolar therapy and CT.
- The use of standard preparation of tubing for insulin infusions in patients with DKA. [28-31] – Strong recommendation, low quality evidence
  Remarks: With equivocal evidence, the team felt that any additional time used to prepare could potentially delay treatment.
- The administration of lower-dose insulin infusions to children with DKA under the age of 5 and higher-dose insulin infusions to children aged 5 and older. [32-34] – Strong recommendation, low quality evidence
  Remarks: Though there is evidence that a lower-dose concentration of insulin is safe and effective, there is no evidence to suggest that the higher-dose concentration is harmful.

Evidence Lacking/Inconclusive

- Use of bicarbonate reported from the venous blood gas to guide the decision to start intravenous insulin therapy in patients whose bicarbonate values are <13 mmol/L; in patients whose bicarbonate levels are ≥13 mmol/L, wait for the laboratory values to confirm before initiating treatment. – Consensus recommendation
- To treat patients with diabetic ketoacidosis and hypokalemia with IV potassium. Consider oral supplementation after continuous intravenous insulin is discontinued and patient is able to tolerate oral medications. – Consensus recommendation
- To NOT decrease the insulin infusion if the blood glucose concentration decreases too quickly (greater than 100 mg/dL/hr) or falls too low (below 150 mg/dL) before DKA has resolved; rather, increase the amount of dextrose administered unless maximum already reached. Increase the amount of dextrose if patient is on less than 100% D10. – Consensus recommendation

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

Condition-Specific Elements of Clinical Management

General: Children with DKA present with signs and symptoms that are related to the degree of hyperosmolality, volume depletion and acidosis. The severity of DKA should determine the appropriate clinical setting in which to treat the child.

Treatment Recommendations: For children being transferred from an outside hospital (OSH), please see Clinical Algorithm for Transport of Children with DKA on page 6.

Fluid and Electrolyte Therapy
Initiate fluid replacement therapy **BEFORE** insulin therapy. Normal saline should be administered at 20 mL/kg and if clinically indicated, repeat once. For subsequent fluids, administer 2.5 L/m^2/DAY and never exceed 4 L/m^2/DAY (including the initial bolus), unless discussed with Attending Physician.

Insulin Therapy
For all children who have a pH <7.3 an insulin infusion should be administered. The decision to administer subcutaneous insulin should be made in consideration of the child's hydration status.
Insulin Infusion- Administer continuous low dose IV infusions. Mix regular insulin, 100 units in 100 mL of Normal Saline (1 mL/h = 1 unit/h). Dose at 0.1 units/kg/h. Maintain glucose between 100-200 mg/dL by titrating Bag A and Bag B. See Table 1.
Subcutaneous Insulin- Administer insulin as determined by Diabetes Service.

Phosphate
Administration of phosphate bolus is not routinely recommended.

Bicarbonate
Administration of bicarbonate is not recommended**.**

Potassium (K^+)
Potassium replacement is required if K^+ is ≤5.5. See Table I.

Table I. 2 Bag System

‡2 bag system		
If K^+ ≤5.5 mEq/L: (Adjust IVF rates based on finger stick glucoses)		
• Bag A: NS + KCl 1.5 mEq/100 mL+ KPO_4 2 mmol/100 mL		
• Bag B: D10NS + KCl 1.5 mEq/100 mL+ KPO_4 2 mmol/100 mL		
If K^+ >5.5 mEq/L: (Adjust IVF rates based on fingerstick glucoses)		
• Bag A: **NS**		
• Bag B: **D10NS**		
Total IVF mL/h = Bag A mL/h + Bag B mL/h		
Blood Glucose	**A**	**B**
>300 mg/dL	___ mL/h (100%)	0 mL/h
251-300 mg/dL	___ mL/h (75%)	___ mL/h (25%)
201-250 mg/dL	___ mL/h (50%)	___ mL/h (50%)
151-200 mg/dL	___ mL/h (25%)	___ mL/h (75%)
≤150 mg/dL	0 mL/h	___ mL/h (100%)
If <100 mg/dL	Notify practitioner while on IV therapy	

NOTE: The goal is to obtain a blood glucose of 150 mg/dL. However, if rate of drop is ≥100 mg/dL or if the patient becomes hypoglycemic, please consult Diabetes Team for reconsideration of fluid rate or type.

Special Care Monitoring

Blood glucose every 1 h
Chem 10 every 12 h
Electrolytes every 2 h x 3, then every 6 h with improving anion gap (Normal anion gap <15)
Strict I&O
β-hydroxybutyrate every 6 h

Cerebral Edema

Consider administering mannitol at 0.5 grams/kg or hypertonic saline (3%), and restricting fluids. If mannitol given and patient stable, consider computed tomography (CT) scan.

Diabetes Care Unit/Progressive Care Unit Admission Criteria

Children who have mild or moderate DKA (pH 7.0 - 7.30).

Intensive Care Unit Admission Criteria

All children with one or more of the indicators below:

- Severe DKA (pH <7.0)
- Aged <5 years in DKA
- Altered mental status (AMS)
- >40 mL/kg of volume resuscitation
- Treatment with HCO_3
- Associated with sepsis/systemic inflammatory response syndrome (SIRS)

Admission Criteria

- Admission criteria to DCU/TCU
  - DCU: pH 7.0 to 7.3
  - TCU: Overflow
- Admission criteria to Critical Care
  - Severe DKA with pH <7
  - Age <5 years
  - Altered mental status
  - DKA and received >40 mL/kg of fluid
  - Sepsis/SIRS
  - $NaHCO_3$ treatment
- West Campus/Woodlands admission criteria to critical care
  - Confirmed DKA

Consults/Referrals/Follow-up Care

Consultation and follow up with a Diabetes specialist is appropriate for all children with diabetes.
Consultation with Psychology, Registered Dietician, Social Work, and Child Life for children with new onset or as determined by Endocrine.

Measures

Process

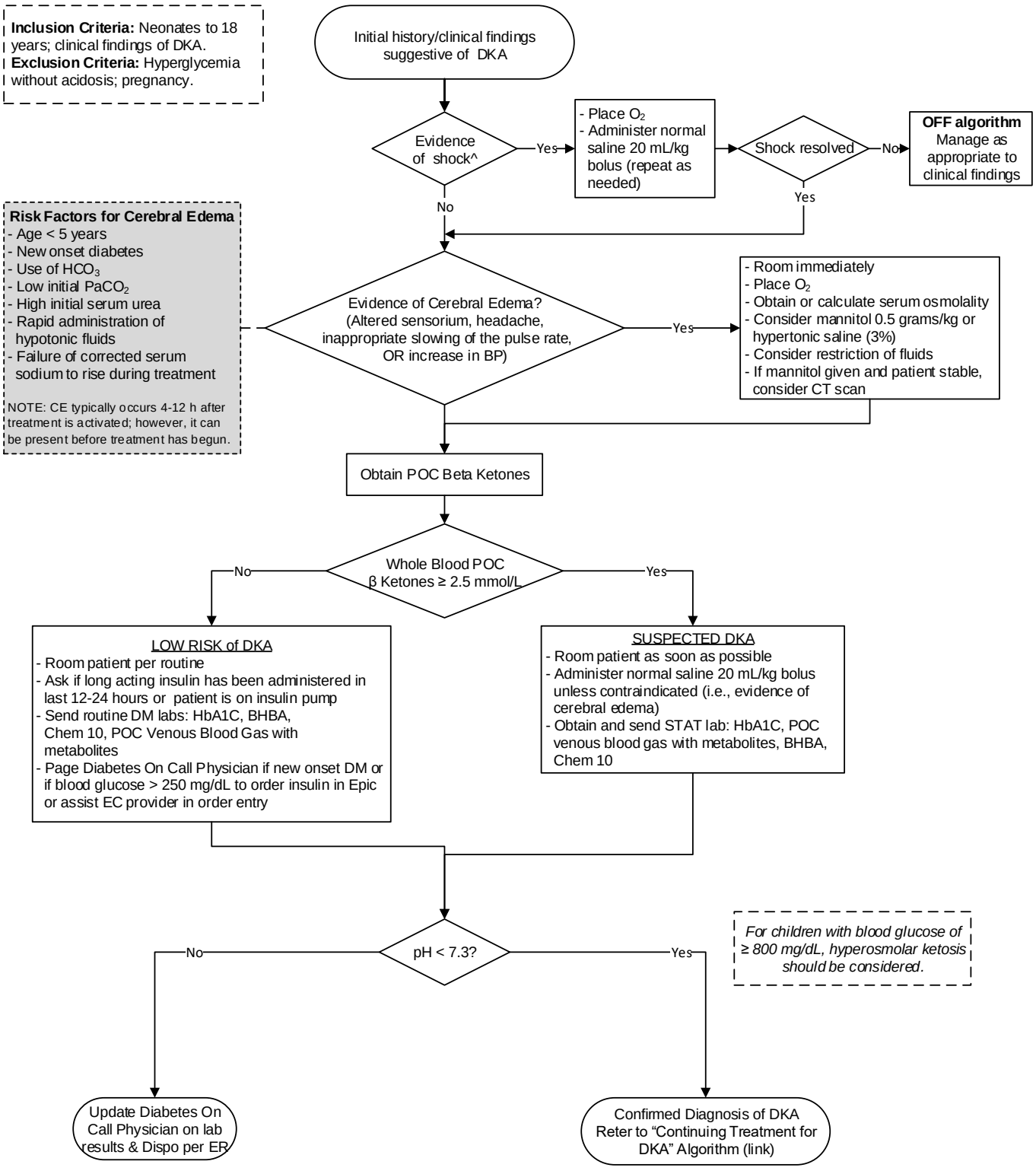
- Medical length of stay in Critical Care
- Medical length of stay in Diabetes Care Unit or Transitional Care Unit
- Total hospital medical length of stay
- # readmissions within one week of discharge

Outcome

- Time to administer subcutaneous insulin
- Incidence of cerebral edema after beginning therapy
- Time to correction of acidosis (e.g., normal anion gap <15; β-hydroxybutyrate <2; HCO_3 >15)
- pH level on arrival
- Glucose on arrival
- GCS on arrival
- # deaths with DKA diagnosis

Texas Children's Hospital Evidence-Based Outcomes Center
Clinical Algorithm for Initial Assessment of Diabetic Ketoacidosis (DKA)

For patients being transferred from outside hospital (OSH), see Clinical Algorithm for Transport of Children with DKA.



May 23, 2019

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

Texas Children's Hospital Evidence-Based Outcomes Center
Clinical Algorithm for Continuing Treatment of Diabetic Ketoacidosis

Inclusion Criteria: Neonates to 18 years; clinical findings of DKA.
Exclusion Criteria: Hyperglycemia without acidosis; pregnancy.

DKA confirmed

Contact Diabetes On Call Physician
Determine appropriate level of care

MAIN CAMPUS

Admission Criteria to DCU
DCU – pH 7.0–7.3

Admission Criteria to Intensive Care
Severe DKA with pH < 7.0
Age < 5y
Altered mental status
DKA and received more than 40mL/kg of fluid
Sepsis / SIRS
$NaHCO_3$ treatment

WEST CAMPUS/WOODLANDS

Admission Criteria to Intensive Care
Bicarb <15 mmol/L

***Risk Factors for Cerebral Edema (CE)**
- Age < 5 years
- New onset diabetes
- High initial serum urea
- Low initial pCO_2
- Rapid administration of hypotonic fluids
- Failure of corrected serum sodium to rise during treatment
- Use of bicarbonate

Clinical Signs of CE
- Altered sensorium, headache
- Inappropriate slowing of the pulse rate
- Increase in BP

NOTE: CE typically occurs 4-12 h after treatment is activated; however, it can be present before treatment has begun.

Treatment
- Initiate 2 bag system‡
- Administer insulin infusion (0.1 units/kg/h if ≥ 5 years old, 0.05 units/kg/hr if < 5 years)

Monitoring
- Continuous pulse oximetry and cardiac monitoring
- Neurological vital signs per unit policy
- POC Glucose q 1 h
- Chem 10 every 12 h
- Electrolytes every 2 h x 3, then every 6 h with improving anion gap (Normal anion gap < 15 mEq/L)
- ß-hydroxybutyrate every 6 h
- Strict I&O

Worsening labs; changes in mental status; **AND/OR** concerning vital signs

No

- Continue to manage as appropriate to clinical findings
- Contact Diabetes On Call Physician with changes in patient's status **AND/OR** patient's readiness to transition to subcutaneous insulin

Yes

- Consider transferring to higher level of care if in DCU
- Update Diabetes On Call Physician with changes in patient's status

‡2 bag system

If K^+ ≤ 5.5 mEq/L: (Adjust IVF rates based on finger stick glucoses)
- Bag A: NS + KCl 1.5 mEq/100 mL+ KPO_4 2 mmol/100 mL
- Bag B: D10NS + KCl 1.5 mEq/100 mL+ KPO_4 2 mmol/100 mL

If K^+ > 5.5 mEq/L : (Adjust IVF rates based on fingerstick glucoses)
- Bag A: **NS**
- Bag B: **D10NS**

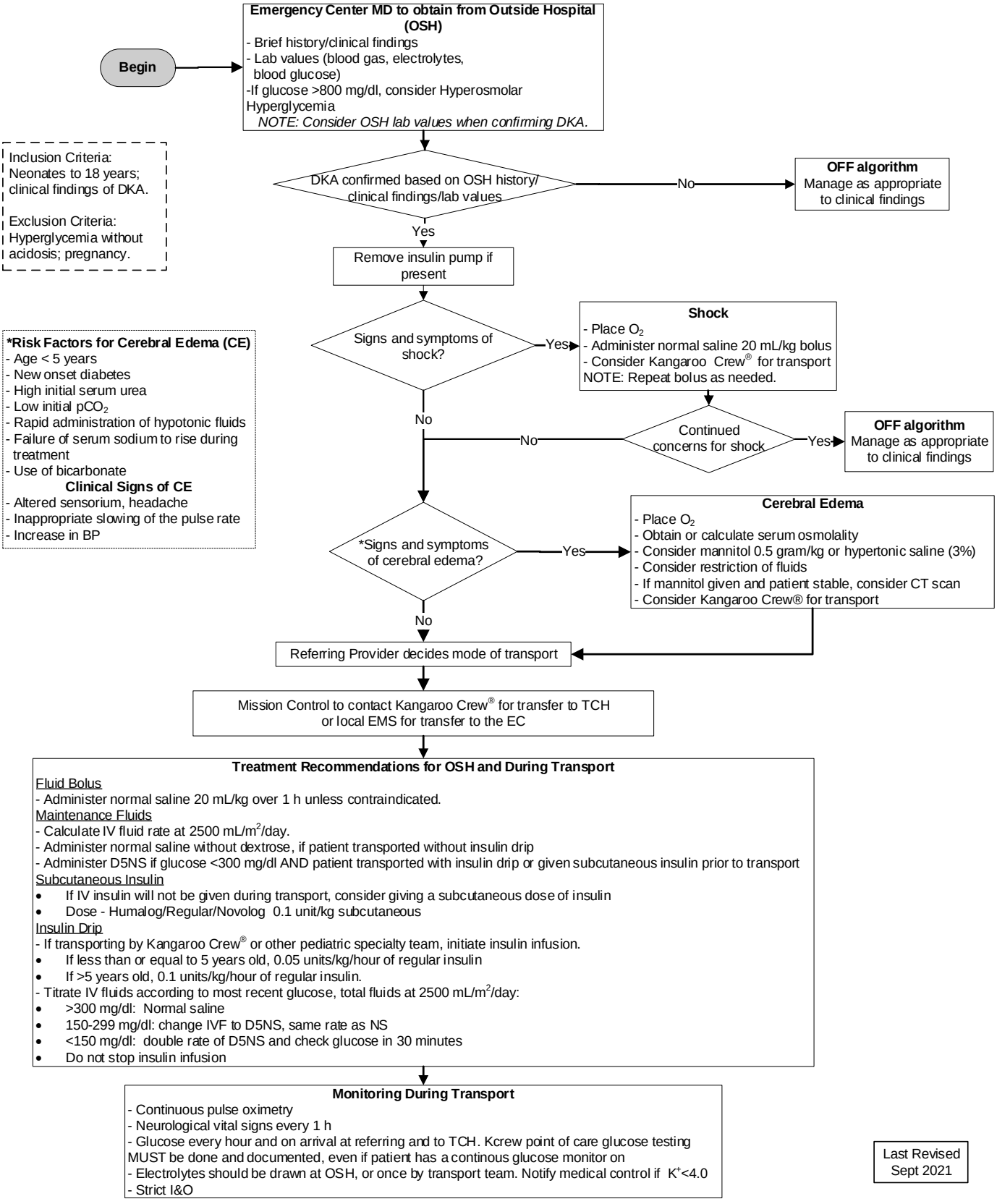
Total IVF mL/h = Bag A mL/h + Bag B mL/h

blood glucose	**A**	**B**
> 300 mg/dL	___ mL/h (100%)	0 mL/h
251-300 mg/dL	___ mL/h (75%)	___ mL/h (25%)
201-250 mg/dL	___ mL/h (50%)	___ mL/h (50%)
151-200 mg/dL	___ mL/h (25%)	___ mL/h (75%)
≤ 150 mg/dL	0 mL/h	___ mL/h (100%)
If < 100 mg/dL	Notify practitioner while on IV therapy	

May 23, 2019

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

Texas Children's Hospital Evidence-Based Outcomes Center
Clinical Algorithm for Transport of Children with DKA



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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.

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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
   - PICO questions established
   - Evidence search confirmed with content experts

2. Review of Existing External Guidelines
   - American Diabetes Association "Standards of Medical Care in Diabetes"
   - National Institute of Clinical Excellence "Diabetes (type 1 and type 2) in children and young people: diagnosis and management'
   - Ministry of Health, Social Services and Equality (Spain) "Clinical Practice Guideline for Diabetes Mellitus Type 1"

3. Literature Review of Relevant Evidence
   - Searched: Cochrane, PubMed,

4. Critically Analyze the Evidence
   - Eight randomized controlled trials, and thirteen nonrandomized studies

5. Summarize the Evidence
   - Materials used in the development of the clinical standard, literature appraisal, and any order sets are maintained in a Diabetic Ketoacidosis 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.
This clinical standard specifically summarizes the evidence *in support of* or *against* specific interventions and identifies where evidence is *lacking/inconclusive*. The following categories describe how research findings provide support for treatment interventions.
"Evidence Supports" provides evidence to support an intervention
"Evidence Against" provides evidence against an intervention.
"Evidence Lacking/Inconclusive" indicates there is insufficient evidence to support or refute an intervention and no conclusion can be drawn *from the evidence.*
The **GRADE** criteria were utilized to evaluate the body of evidence used to make practice recommendations. The table below defines how the quality of the evidence is rated and how a strong versus weak recommendation is established. The literature appraisal reflects the critical points of evidence.

Recommendation	
STRONG	Desirable effects clearly outweigh undesirable effects or vice versa
WEAK	Desirable effects closely balanced with undesirable effects
Quality	**Type of Evidence**
High	Consistent evidence from well-performed RCTs or exceptionally strong evidence from unbiased observational studies
Moderate	Evidence from RCTs with important limitations (e.g., inconsistent results, methodological flaws, indirect evidence, or imprecise results) or unusually strong evidence from unbiased observational studies
Low	Evidence for at least 1 critical outcome from observational studies, RCTs with serious flaws or indirect evidence
Very Low	Evidence for at least 1 critical outcome from unsystematic clinical observations or very indirect evidence

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 diabetic ketoacidosis 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
Nov 2009	Originally completed
Oct 2014	Algorithm modifications
Jan 2015	Algorithm modifications
Mar 2015	Algorithm modifications
Jun 2015	Algorithm modifications
May 2019	Updated
May 2020	Changed the recommendation for hyperchloremic acidosis
June 2020	Changed the recommendation for cerebral edema. Algorithm updates to reflect the change.
Sept 2021	Revision to Transport Algorithm