Diabetic Emergencies

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Review of Evidence for Adult Diabetic Ketoacidosis Management Protocols

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- A total of 85 eligible articles published between 1973 and 2016 were reviewed. The salient findings were:
- (i) Crystalloids are favored over colloids though evidence is lacking. The preferred crystalloid and hydration rates remain contentious.
- (ii) IV infusion of regular human insulin is preferred over the subcutaneous route or rapid acting insulin analogues. Administering an initial IV insulin bolus before low-dose insulin infusions obviates the need for supplemental insulin. Consensus-statements recommend fixed weight-based over “sliding scale” insulin infusions although evidence is weak.
- (iii) Potassium replacement is imperative although no trials compare replacement rates.
- (iv) Bicarbonate replacement offers no benefit in DKA with pH $>$ 6.9. In severe metabolic acidosis with pH $<$ 6.9, there is lack of both data and consensus regarding bicarbonate administration.
- (v) There is no evidence that phosphate replacement offers outcome benefits. Guidelines consider replacement appropriate in patients with cardiac dysfunction, anemia, respiratory depression, or phosphate levels $<$0.32 mmol/L.
- (vi) Upon resolution of DKA, subcutaneous insulin is recommended with IV insulin infusions ceased with an overlap of 1–2 h.
- (vii) DKA resolution rates are often used as end points in studies, despite a lack of evidence that rapid resolution improves outcome.
- (viii) Implementation of DKA protocols lacks strong evidence for adherence but may lead to improved clinical outcomes.

Diabetic Ketoacidosis (DKA)

- Life-threatening condition in which severe insulin deficiency leads to hyperglycemia, excessive lipolysis, and unrestrained fatty acid oxidation
- Produces ketone bodies (acetone, β-hydroxybutyrate, acetoacetate)
- Results in metabolic acidosis, dehydration, and deficits in fluids/electrolytes
- Excess secretion of glucagon, catecholamines, glucocorticoids, growth hormone → stimulates glycogenolysis and gluconeogenesis and impairs glucose disposal→ Hyperglycemia
- More characteristic of type 1 DM than type 2 DM
    - Usually under conditions of stress (infections, trauma, cardiovascular, or other emergencies)

DKA: Epidemiology

- DKA responsible for $>$ 500,000 hospital days per year
- Estimated annual direct medical expense and indirect cost of 2.4 billion USD
- Hospitalizations for DKA in the US are increasing
  - From 1996-2006, there was 35% increase in number of cases (136,510 cases with dx DKA)
  - Rate is more rapid than overall diagnosis of diabetes

DKA: Epidemiology

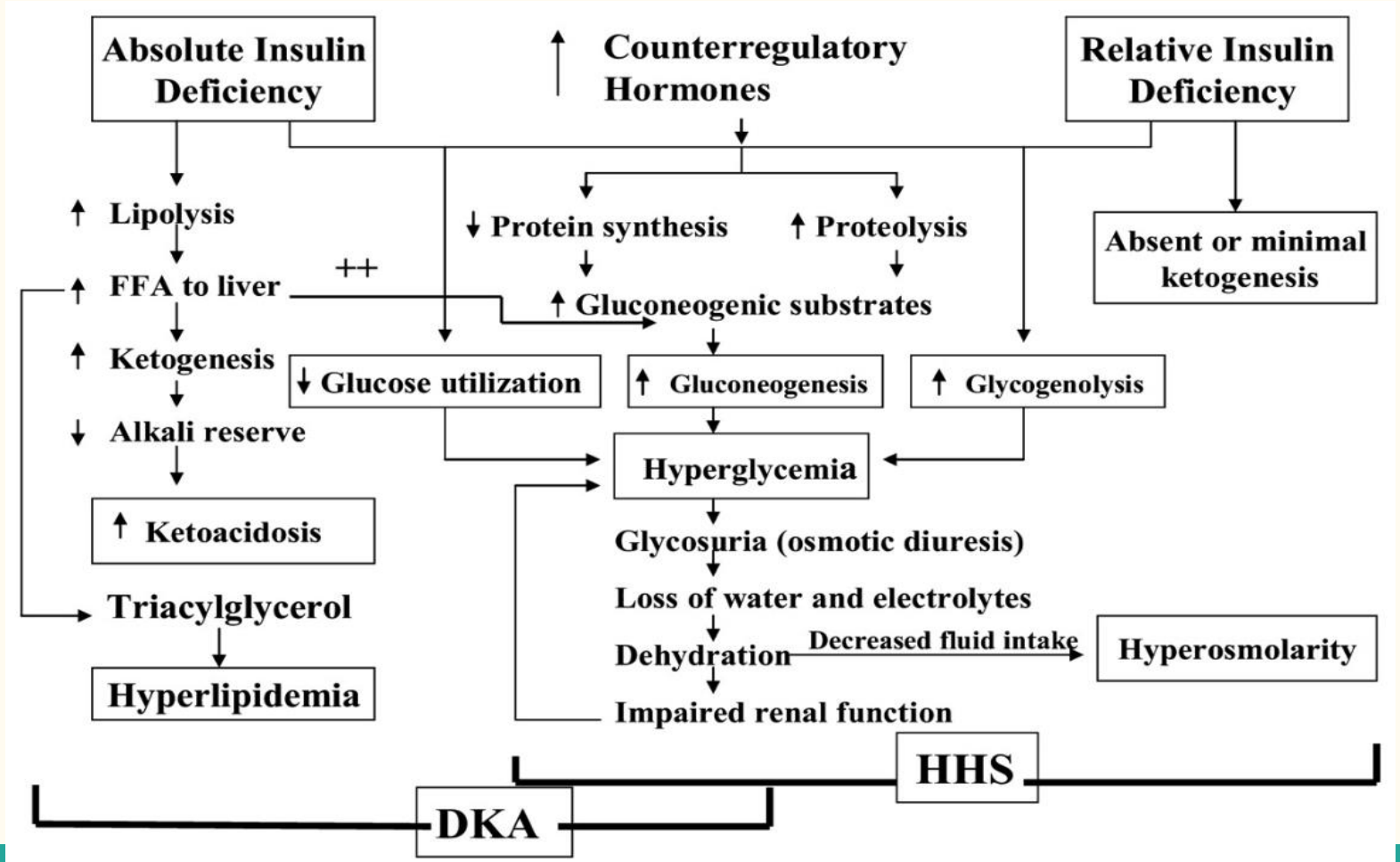
- Most patients with DKA were between ages 18-44 years (56%)
  - Ages 45-65 years (24%)
  - Age < 20 (18%)
- ⅔ of DKA patients were type 1 diabetics
- 50% female
- 45% nonwhite
- DKA is MCC death in children and adolescents with t1DM
- In adult patients, overall mortality is $< 1\%$
  - Mortality rate $> 5\%$ in elderly and patients with concomitant life-threatening illnesses

DKA: Type 2 Diabetics

- Increasing number of DKA cases without precipitating cause have been reported in type 2 diabetics (children, adolescents, adults)
  - Over half of newly diagnosed adult African Americans and Hispanics with unprovoked DKA have type 2 diabetes
  - Features: High rate of obesity, strong family history of t2DM, measurable pancreatic insulin reserve, low prevalence of autoimmune markers of B-cell destruction, ability to discontinue insulin therapy during follow up
  - Transient-insulin requiring profile after DKA recognized in mainly blacks/Hispanics, but also in Native Americans, Asians, and white populations
  - Referred to as idiopathic type 1 diabetes, atypical diabetes, “Flatbush” diabetes, type 1.5 diabetes, and more recently, **ketosis-prone type 2 diabetes**

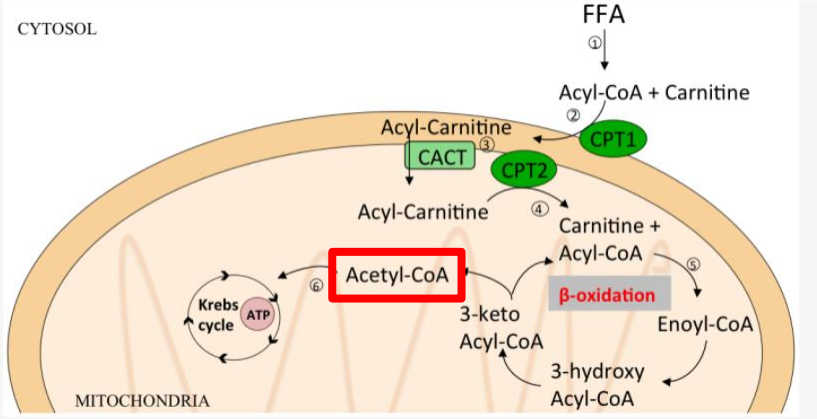
DKA: Pathogenesis

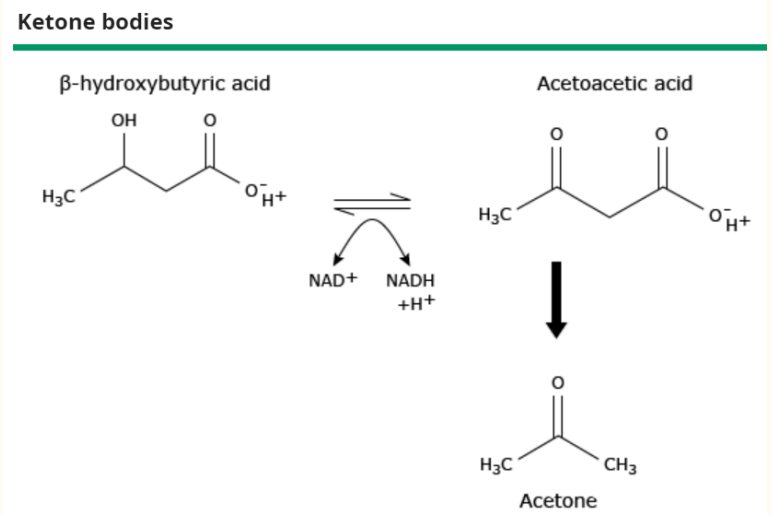
Catecholamines,
cortisol, glucagon



Ketones

- 3 major ketone bodies
- Water-soluble, fat-derived **fuels** used by many tissues for energy when glucose is limited
- Formed by the liver
- Low insulin/high glucagon levels
- FFAs enter hepatocyte mitochondria
- Excess Acetyl-CoA → oxidative capacity of Krebs cycle is exceeded → Acetyl-CoA shunted into the ketogenic pathway
- B-OH butyrate is the main ketone in DKA
- Acetone is not acidic; responsible for the "fruity breath" smell
- Ketostix measure acetoacetate only – can be "normal" in early, severe DKA

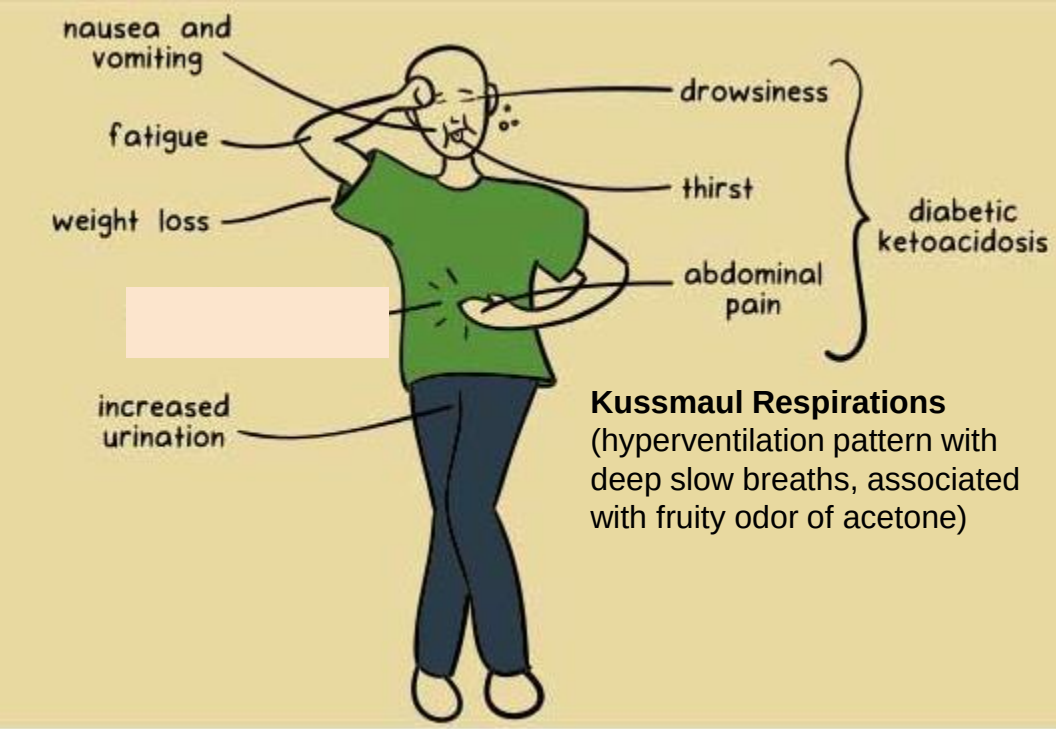




DKA: Precipitating Factors

- Most common precipitating factor: Infection
- Discontinuation of or inadequate insulin therapy (Noncompliance or out of meds)
  - New onset type 1 diabetes
  - Young patients
    - Fear of weight gain with improved metabolic control
    - Fear of hypoglycemia
    - Rebellion against authority
    - Stress of chronic disease
- Pancreatitis, MI, CVA
- Drugs that affect carb metabolism:
  - Corticosteroids, thiazides, sympathomimetic agents, pentamidine
  - A number of case reports of traditional and atypical antipsychotic drugs that cause hyperglycemia

DKA: Clinical Presentation



DKA: Clinical Presentation

- Vitals: Usually normotensive, tachycardic, and tachypneic
- Physical exam: Signs of mild to moderate volume depletion
- Severe cases: Stupor, profound dehydration, and focal neurologic deficits (Babinski reflexes, asymmetric reflexes, cranial nerve findings, paresis, fasciculations, and aphasia)
- If abdominal pain-- caution because symptoms could be from DKA or an indication of a precipitating cause of DKA
- Leukocytosis is common

DKA: Diagnosis

- Hallmarks:
  - Metabolic Acidosis with anion gap (> 14, most with AG > 20)
    - Some can have hyperchloremic metabolic acidosis without significant AG
    - Arterial pH is usually < 7.3 (and can be as low as 6.5)
    - Partial respiratory compensation with hypocarbia
    - Mildly hyperosmolar (osm > 330 mOsm/kg is unusual without mental status changes)
  - Ketones (β-hydroxybutyrate, acetoacetate, acetone)
    - Urine ketones (acetoacetate)
    - Serum β-hydroxybutyrate (predominant ketone)
    - urine “ketone” test is mainly for presence of acetoacetate, which may be at low levels during early DKA (ie false negative)
  - Serum glucose usually elevated
    - Euglycemic DKA (SGLT2 inhibitor use, decreased oral intake, pregnancy)

DKA: Differential Diagnosis

- Not all patients with hyperglycemia and AGMA have DKA-- must consider other causes of metabolic acidosis (especially if serum or urine ketones are not elevated)
  - Lactic acidosis
  - Starvation Ketosis
  - Alcoholic Ketoacidosis
  - Uremic acidosis
  - Toxic ingestions (salicylates, ethylene glycol)

DKA: Diagnosis

- Misdiagnosed DKA cases are usually patients with new-onset diabetes
- Laboratory tests are key:
  - CBC
  - BMP (glucose, Na, K, Cl, phos, BUN, creatinine)
  - Serum and urine ketones
  - Infectious workup – blood cultures, urine culture, etc
- Serum Osmolarity (mOsm/L)
  - Serum Osm $= 2(Na^+) + (Glucose/18) + (BUN/2.8)$
  - In DKA, serum osm is mildly elevated, but usually < 350 mOsm/L
  - In HHS, serum osm is usually > 350 (can exceed 400 mOsm/L)

Electrolyte deficits

- Osmotic diuresis results in significant urinary electrolyte losses
- Plasma potassium concentrations can be “normal” or even “high” despite total body potassium deficit

Table 1: Typical water and serum electrolyte deficits at presentation of diabetic ketoacidosis (DKA) and the hyperglycemic hyperosmolar state (HHS)

Parameter	DKA*	HHS*
Water, mL/kg	100 (7 L)	100–200 (10.5 L)
Sodium, mmol/kg	7–10 (490–700)	5–13 (350–910)
Potassium, mmol/kg	3–5 (210–300)	5–15 (350–1050)
Chloride, mmol/kg	3–5 (210–350)	3–7 (210–490)
Phosphate, mmol/kg	1–1.5 (70–105)	1–2 (70–140)
Magnesium, mmol/kg	1–2 (70–140)	1–2 (70–140)
Calcium, mmol/kg	1–2 (70–140)	1–2 (70–140)

*Values in parentheses (in mmol, unless stated otherwise) refer to the total body deficit for a 70-kg patient.

A 15-year-old is brought to the emergency department in a confused state. He is very thirsty and consumes a large amount of water. An alert attendant notes that the patient's breath smells like acetone. Which of the following will most likely be found on his laboratory values?

- A. A normal potassium
- B. An elevated sodium
- C. An elevated pH
- D. An elevated bicarbonate
- E. A normal white blood cell count

Correct Answer: A. A normal potassium

This patient has diabetic ketoacidosis (DKA), as suggested by the polyuria and the characteristic breath odor. Metabolic acidosis causes a shift of potassium from the intracellular compartment to the extracellular fluid resulting in a normal or elevated potassium level (this is misleading, as the DKA patient generally has a potassium deficit that averages 300 to 600 mEq). Polyuria from hyperglycemia causes increased urinary potassium excretion and progressive depletion of potassium. Despite the total body potassium deficit, hypokalemia is seen in very few (approximately only 5%) patients presenting in DKA.

Incorrect Answers:

B. Most patients with DKA are mildly hyponatremic.

C. Diabetic ketoacidosis is characterized by a pH <7.3.

D. The bicarbonate concentration in DKA is usually moderately to markedly reduced.

E. The majority of patients with hyperglycemic emergencies have at least a mild leukocytosis.

Management

- Fluids
  - Expand extracellular space (intravascular/extravascular), restore renal perfusion
  - Isotonic saline 0.9% 15-20mL/Kg/hr x 1 hour
  - NS or ½ NS thereafter, depending on corrected sodium level (250-500cc/hr)
  - Caution with ESRD, HF patients
  - Change to dextrose-containing fluids when glucose $<$ 250 in DKA, $<$ 300 in HHS

- Potassium
  - $<$ 3.3 mg/dL, hold insulin infusion
  - 3.3 – 5.2 mg/dL, replace K (put 20-40mEq in each L of fluid, may require more). Target K level is 4.0 – 5.0 mg/dL
  - $>$ 5.2 mg/dL, hold K and monitor
- Insulin
  - Bolus (0.1u/kg) vs no bolus
  - Continuous rate 0.1u/kg/hr (or 0.14u/kg/hr if no bolus is used)

Bicarbonate therapy

- Controversial
- Few prospective, randomized studies of the use of bicarbonate for DKA
- Nonetheless, recommended for pH $<$ 7.0; continue until pH $>$ 7.0
- Risks:
    - Heightened risk of hypokalemia
    - Induction of paradoxical central nervous system acidosis
    - Worsening of intracellular acidosis owing to increased carbon dioxide production
    - Prolongation of ketoanion metabolism

Phosphate therapy

- Beneficial effect of phosphate therapy is purely theoretical
- Respiratory depression, skeletal muscle weakness, hemolytic anemia, cardiac dysfunction
- Can restore 2,3-diphosphoglycerate level, shifting the oxygen dissociation curve to the right and enhancing oxygen delivery to the tissues
- Downsides: excessive phosphate can lead to hypocalcemia, tetanus, and soft-tissue calcification
- RCTs have been unable to demonstrate any clinical benefit of routine phosphate therapy
- Consider if phos level $<$ 1.0 mmol/L

A 41-year-old patient with type 1 diabetes mellitus presents with intractable vomiting, increased thirst, and increased urination. Vital signs are significant for a heart rate of 109/min. Initial laboratory values are shown below. The patient is diagnosed with diabetic ketoacidosis. Which of the following is the best order of treatments for this condition?

Sodium	133 mEq/L (normal: 136 - 146 mEq/L)
Potassium	3.1 mEq/L (normal: 3.5 - 5.0 mEq/L)
Bicarbonate	12 mEq/L (normal: 23 - 29 mEq/L)
Chloride	102 mEq/L (normal: 98 - 106 mEq/L)
pH (arterial)	7.2 (normal: 7.35 - 7.45)
Serum glucose	518 mg/dL (normal: 70 - 105 mg/dL)

- A. Intravenous isotonic fluids, insulin infusion, intravenous potassium replacement
- B. Intravenous potassium replacement, intravenous isotonic fluids, insulin infusion
- C. Intravenous isotonic fluids, oral potassium replacement, insulin infusion
- D. Oral potassium replacement, intravenous isotonic fluids, insulin infusion
- E. Intravenous isotonic fluids, intravenous potassium replacement, insulin infusion

Correct Answer: E.	**Intravenous isotonic fluids, intravenous potassium replacement, insulin infusion**

This patient has diabetic ketoacidosis (DKA) with associated significant hypokalemia. When serum potassium is <3.3 mEq/L, it should be replaced. This is ideally accomplished after providing adequate intravascular volume replenishment with isotonic saline. Because insulin administration may cause potassium levels to fall, potassium should be replaced before insulin is started. Once potassium levels are >3.3 mEq/L, insulin can be initiated (or resumed, if it was held due to hypokalemia). Potassium replacement can continue as needed to keep serum potassium levels in the normal range.

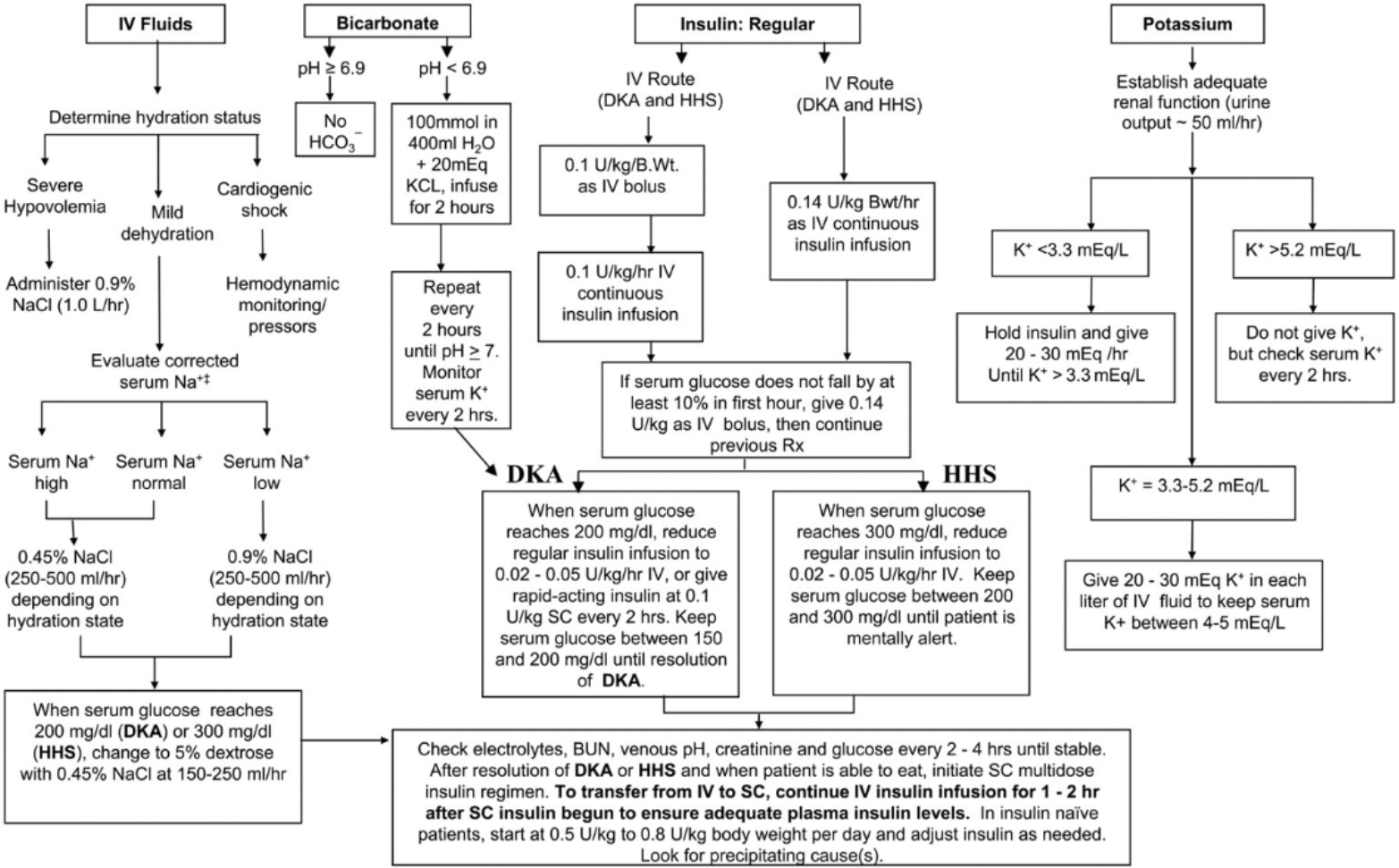
Incorrect Answers:

A. IV potassium replacement should be accomplished prior to insulin therapy.

B. Intravenous fluid therapy is the most critical first step in managing DKA, particularly when there is clinical evidence of volume depletion. This patient's tachycardia suggests volume depletion.

C. Use of oral potassium replacement is not appropriate, especially since the patient has intractable vomiting.

D. Oral potassium replacement is not appropriate. Fluid resuscitation is the first step.


Complete initial evaluation. Check capillary glucose and serum/urine ketones to confirm hyperglycemia and ketonemia/ketonuria. Obtain blood for metabolic profile. Start IV fluids: 1.0 L of 0.9% NaCl per hour.†
IV Fluids
Determine hydration status
Severe Hypovolemia
Mild dehydration
Cardiogenic shock
Administer 0.9% NaCl (1.0 L/hr)
Hemodynamic monitoring/ pressors
Evaluate corrected serum Na+‡
Serum Na+ high
Serum Na+ normal
Serum Na+ low
0.45% NaCl (250-500 ml/hr) depending on hydration state
0.9% NaCl (250-500 ml/hr) depending on hydration state
When serum glucose reaches 200 mg/dl (DKA) or 300 mg/dl (HHS), change to 5% dextrose with 0.45% NaCl at 150-250 ml/hr
Bicarbonate
pH ≥ 6.9
No HCO3−
pH < 6.9
100mmol in 400ml H2O + 20mEq KCL, infuse for 2 hours
Repeat every 2 hours until pH ≥ 7. Monitor serum K+ every 2 hrs.
Insulin: Regular
IV Route (DKA and HHS)
0.1 U/kg/B.Wt. as IV bolus
0.1 U/kg/hr IV continuous insulin infusion
IV Route (DKA and HHS)
0.14 U/kg Bwt/hr as IV continuous insulin infusion
If serum glucose does not fall by at least 10% in first hour, give 0.14 U/kg as IV bolus, then continue previous Rx
DKA
When serum glucose reaches 200 mg/dl, reduce regular insulin infusion to 0.02 - 0.05 U/kg/hr IV, or give rapid-acting insulin at 0.1 U/kg SC every 2 hrs. Keep serum glucose between 150 and 200 mg/dl until resolution of DKA.
HHS
When serum glucose reaches 300 mg/dl, reduce regular insulin infusion to 0.02 - 0.05 U/kg/hr IV. Keep serum glucose between 200 and 300 mg/dl until patient is mentally alert.
Potassium
Establish adequate renal function (urine output ~ 50 ml/hr)
K+ <3.3 mEq/L
Hold insulin and give 20 - 30 mEq /hr Until K+ > 3.3 mEq/L
K+ >5.2 mEq/L
Do not give K+, but check serum K+ every 2 hrs.
K+ = 3.3-5.2 mEq/L
Give 20 - 30 mEq K+ in each liter of IV fluid to keep serum K+ between 4-5 mEq/L
Check electrolytes, BUN, venous pH, creatinine and glucose every 2 - 4 hrs until stable. After resolution of DKA or HHS and when patient is able to eat, initiate SC multidose insulin regimen. To transfer from IV to SC, continue IV insulin infusion for 1 - 2 hr after SC insulin begun to ensure adequate plasma insulin levels. In insulin naïve patients, start at 0.5 U/kg to 0.8 U/kg body weight per day and adjust insulin as needed. Look for precipitating cause(s).

A 50-year-old male is brought to the ED by his wife with progressive stupor and confusion. The patient has a 35-year history of type 1 diabetes and a recent diagnosis of left lower lobe pneumonia. Over the past few days, he has developed excessive thirst and frequent urination. Today, he has become more somnolent. He has taken insulin since the age of 15, and his blood sugar levels have usually been well-controlled. The patient has no other comorbid conditions. Vital signs are a blood pressure of 85/54 mmHg, a heart rate of 112/min, a respiratory rate of 30/min, and an oxygen saturation of 91% in room air. He is taking deep and rapid breaths. The patient is minimally arousable. Crackles are heard over the left lung field. Abdominal examination is unremarkable. Mucous membranes are dry, and there is poor skin turgor. Laboratory findings are as follows: WBC 12,400/mm^3, Hematocrit 48%, Platelets 462,000/mm^3, sodium 142 mEq/L, potassium 5.0 mEq/L, chloride 110 mEq/L, bicarbonate 12 mEq/L, urea nitrogen 23 mg/dL, creatinine 1.0 mg/dL, and glucose 529 mg/dL. A urinalysis is positive for ketones. He is given 10 units of intravenous insulin, 1L of normal saline, and an insulin drip is started. Which factor should guide this patient's conversion from intravenous to subcutaneous insulin?

- A. Anion gap
- B. Level of consciousness
- C. Serum glucose level
- D. Serum ketones as measured by the nitroprusside method
- E. Urine ketone level

Correct Answer: A. Anion gap

This patient has diabetic ketoacidosis, likely triggered by his pneumonia. The combination of low insulin levels and high stress-hormone levels leads to hyperglycemia and ketosis. Profound dehydration results from osmotic diuresis. Patients present with nausea, vomiting, abdominal pain, and stupor or coma. Rapid, deep breathing is secondary to the anion gap metabolic acidosis caused by ketoacid production. Treatment is aimed at volume resuscitation and narrowing the anion gap. Once the anion gap indicates that the ketoacidosis has largely resolved, and if the patient is able to eat, subcutaneous insulin can be started. If the patient is not eating, then IV insulin should be continued.

Of note, a significant subset of patients will close their anion gap before their serum bicarb reaches the desired level (generally around 19 mEq/L or better) and the anion gap of such patients may become elevated again. So, most experts contend that a true measure of switch from ketosis to glucose metabolism is serum bicarb and not anion gap.

Transition to subcutaneous insulin

- Clinically stable (not on pressors, no severe ongoing illness)
- Blood glucose levels are controlled, on stable IV drip rates ($<$ 2u/hr)
- Anion gap has closed ($<$ 12)
- Serum bicarb $>$ 15
- Serum bicarb level is often $<$ 15 even when gap is closed – look for hyperchloremic acidosis

Transition to subcutaneous insulin

- Indications that it is not safe to transition:
  - High variability of drip rates
  - High variability of glucose levels
  - Drip rates still too high (> 2u/hr)
  - Fewer than 6h of IV drip administration (may not provide enough data to accurately assess the patient's current insulin requirements)

- Predictors of poor transition:
  - Advanced age
  - Wide variation in BG leading up to transition
  - Uncontrolled DM
  - Complex surgical procedure
  - ICU status
  - Receiving corticosteroids

Transition to subcutaneous insulin

- Basal insulin should be given 1-2 hours prior to discontinuation of gtt
- ? Early administration of basal insulin on admission
- Estimating the basal requirement -- no universal consensus on the “best” method

1. Home basal dose if well-controlled

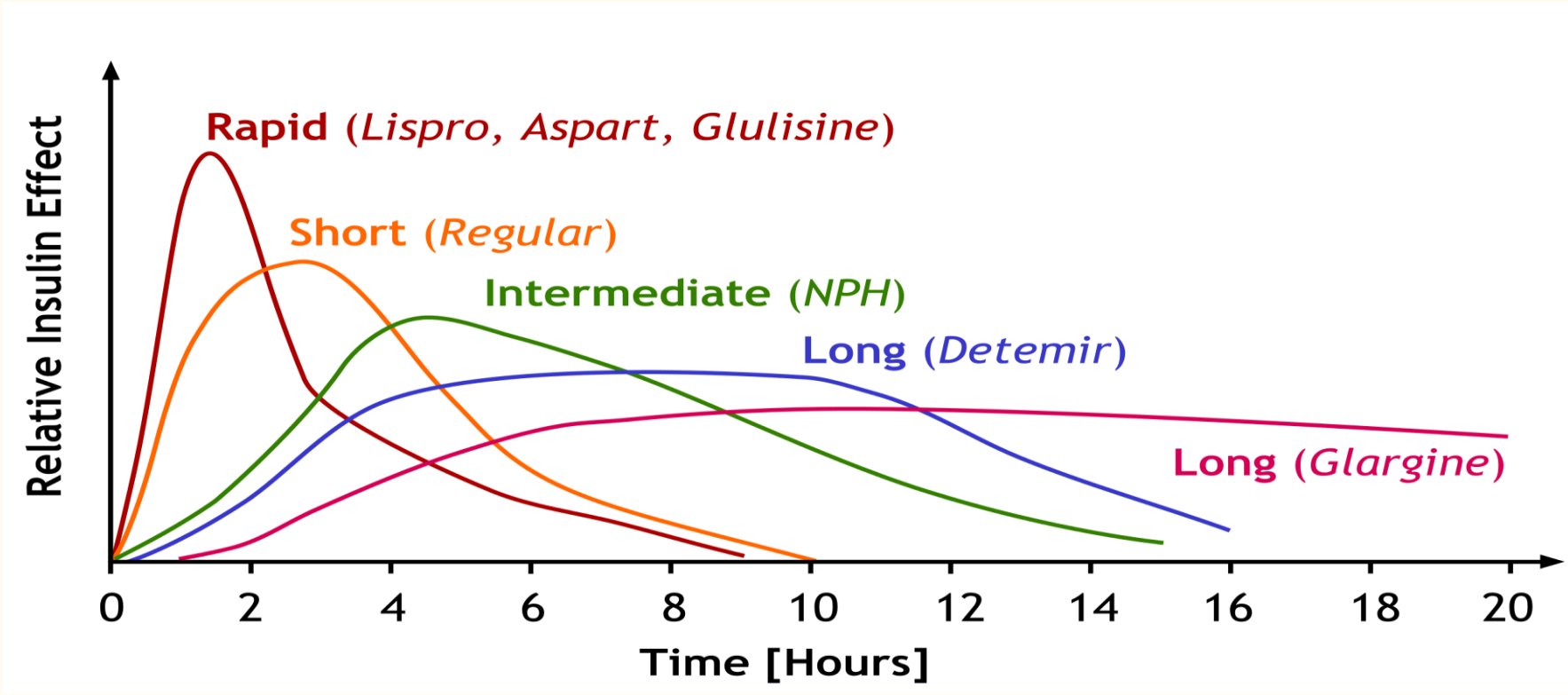
2. “24 hour utilization” cannot always be assumed to reflect the actual 24-h daily SQ insulin requirement
   Look for a period of stable infusion rates (6-8h) and then extrapolate to 24h
   then dose at 80% of that extrapolation. This TDD should then be split as 50-80% basal(higher % if patient is fasting) and 20-50% meal time bolus

3. Wt based basal requirement -- 0.25 - 0.5u/kg

Insulin products

RAPID	Humalog or Lispro	< 15 min	60-90 min	3-5 hrs	• Inject 10-15 min before mealtime • Typically used in conjunction with longer-acting insulin.
	Novolog or Aspart	< 15 min	60-120 min	3-5 hrs	
	Apidra or Glulisine	< 15 min	60-90 min	1-2.5 hrs	
SHORT	Regular (R) Humulin, Actrapid or Novolin	30-60 min	2-5 hrs	6-8 hrs	• Inject at least 20-30 minutes before mealtime
	Velosulin	30-60 min	2-3 hrs	2-3 hrs	
INTERMEDIATE	NPH (N)	1-2 hrs	4-12 hrs	18-24 hrs	• Commonly used twice daily • Often combined with rapid- or short-acting insulin
	Lente (L)	1-2.5 hrs	3-10 hrs	18-24 hrs	
LONG	Ultralente (U)	30 min- 3 hrs	10-20 hrs	20-36 hrs	• Covers insulin needs for 24 hrs • If needed, often combined with rapid- or short-acting insulin
	Lantus or Glargine	1-1.5 hrs	No Peak	20-24 hrs	
	Levemir or Detemir	1-2 hrs	6-8 hrs	Up to 24 hrs	
PRE-MIXED	Humulin 70/30	30 min	2-4 hrs	14-24 hrs	• Combination of intermediate- and short-acting insulin • Commonly used twice daily before mealtime
	Novolin 70/30	30 min	2-12 hrs	Up to 24 hrs	
	Novolog 70/30	10-20 min	1-4 hrs	Up to 24 hrs	
	Humulin 50/50	30 min	2-5 hrs	18-24 hrs	
	Humalog 75/25	15 min	30 min-2.5 hrs	16-20 hrs	

Insulin onset of action:



Inpatient Glycemic Targets

- BG 140-180 or 110-140 without hypoglycemia
- In pregnant patient,
  Fasting BG <95
  1 hr postprandial <140
  2hrs postprandial <120

Common causes of transition failure

- Stopping insulin gtt once glucose level is “normal”
- Not overlapping basal insulin with gtt
- Basal order defaults to QHS (or other time)
- Transitioning off insulin gtt too early
- Underdosing of basal insulin
- Starting diet without prandial coverage

Subcutaneous administration of glargine to diabetic patients receiving insulin infusion prevents rebound hyperglycemia

Elisa Hsia [1], Stacey Seggelke, Joanna Gibbs, R Matthew Hawkins, Elizabeth Cohlmia, Neda Rasouli, Cecilia Wang, Igal Kam, Boris Draznin

Affiliations + expand

PMID: 22685233 DOI: 10.1210/jc.2012-1244

- RCT, 61 patients, type 1 or 2
- Primary outcome – rates of rebound hyperglycemia up to 12h after transition
- **Results:** Overall, 29 subjects in the control group (93.5%) had at least one glucose value above 180 mg/dl during the 12-h follow-up period. This was significantly greater than the rate of rebound hyperglycemia in the intervention group (10 subjects or 33.3%, $P < 0.001$). The effect of the intervention was apparent in subjects who presented with diabetic ketoacidosis, after solid organ transplantation, and in patients with other surgical and medical diagnoses. There were three hypoglycemic measurements in two control subjects (68, 62, and 58 mg/dl) and none in the intervention group.

DKA and restarting diet

- NPO while on insulin gtt
- Typically keep NPO until transition off insulin gtt
- May consider feeding on rare occasions where gap is slow to improve, but clinically pt is doing well and desires to eat
- In this case, IV insulin can be used to cover basal requirement, and subQ mealtime insulin should be used to cover the meal

DKA: Complications of Treatment

- Hypoglycemia
- Hypokalemia → cardiac arrythmia
- Cerebral edema
  - Potentially fatal
  - 1.0% of pediatric cases; rare in adults (usually < 20 yo)
  - Etiology: not know with certainty; osmotically driven movement of water into the central nervous system when plasma osmolality declines too rapidly during treatment ? Increased cerebral perfusion? Activation of Na+/H+ exchangers leading to increased Na+/water influx ? Ketone bodies may also play a role – they affect vascular integrity and permeability, leading to edema formation
  - Has been reported with HHS
  - Headache, lethargy, decreased arousal, seizure, neurologic decompensation that develops during treatment
  - Brainstem herniation
  - High mortality rate
  - Mannitol, hypertonic saline, mechanical ventilation
  - Avoidance of overenthusiastic hydration and rapid reduction of plasma osmolality

Hyperchloremic acidosis

- Not uncommon during resolution of DKA
- Few clinical consequences
- Elevated serum chloride levels
- Serum bicarbonate levels < 15
- Due to:
    - 1) large amount of ketoanion loss
    - 2) large amount of chloride administration during fluid resuscitation

ESRD DKA Management

- Minimal or no signs of volume depletion (any may have volume overload)
- Often do NOT require IV fluid resuscitation in the absence of vomiting/diarrhea
- If intravascular volume is present, judicious fluids may be appropriate
- Routine potassium replacement not indicated unless < 3.3
- IV insulin – consider using lower doses to avoid too rapid of a correction
- Involve nephrology
- No systematic studies comparing HD vs non-HD treatment

SGLT2 inhibitor-associated DKA

- FDA issued a Drug Safety Communication based on 20 clinical cases of euDKA (or mildly hyperglycemic DKA) associated with SGLT2i in 2013-2014
- CANVAS – 12 cases of DKA, 17,596 participants
    - 6/12 had evidence of LADA, most were on insulin
- DECLARE – $<$ 0.1% of more than 18,000 participants
- EMPA-REG – $<$ 0.1% of ~7,000 participants
- Decreased plasma glucose → decreased insulin production → ketogenesis
- Risk factors: longstanding DMt2 with marked B-cell insufficiency or LADA, low caloric intake, low fluid intake, intercurrent illness, and etoh use

Euglycemic Diabetic Ketoacidosis: A Predictable, Detectable, and Preventable Safety Concern With SGLT2 Inhibitors
Julio Rosenstock, Ele Ferrannini
Diabetes Care Sep 2015, 38 (9) 1638-1642; **DOI:** 10.2337/dc15-1380

Hyperosmolar Hyperglycemic State (HHS)

- Characterized by severe hyperglycemia, hyperosmolality, and dehydration in the absence of significant ketoacidosis

HHS: Epidemiology

- Mortality is considerably higher than that attributed to DKA
  - Recent mortality rates of 5-20%
- Prognosis worse at extremes of age
  - Especially worse in presence of coma, hypotension, and severe comorbidities

HHS: Pathogenesis

- Not as well understood as that of DKA
- Greater degree of dehydration (due to osmotic diuresis) and differences in insulin availability distinguish it from DKA
- Relative insulin deficiency is clearly present in HHS, however endogenous insulin secretion is greater than in DKA (reflected by C-peptide levels)
- Insulin levels in HHS are inadequate to facilitate glucose utilization by insulin-sensitive tissues, but adequate to prevent lipolysis and subsequent ketogenesis

HHS: Precipitating Factors

- Underlying medical illness that provokes release of counterregulatory hormones or compromises access to water→ Leads to severe dehydration and HHS
- Restricted water intake
  - Elderly-- bedridden, altered thirst response
- 20% of these patients have no history of diabetes, so there is delayed recognition of hyperglycemic symptoms, which leads to severe dehydration
- Drugs that affect carb metabolism:
  - Corticosteroids, thiazides, sympathomimetic agents, pentamidine
  - A number of case reports of traditional and atypical antipsychotic drugs that cause hyperglycemia

HHS: Clinical Presentation

- Unlike DKA which evolves over short period of time, HHS evolves over several days to weeks
- Similar clinical picture as DKA:
  - Polyuria, polydipsia, weight loss, vomiting, dehydration, weakness, mental status changes
  - Physical findings: Poor skin turgor, tachycardia, hypotension (no Kussmaul breathing)
  - Mental status can vary from full alertness to profound lethargy or coma
  - Focal neurologic signs (hemianopia, hemiparesis) and seizures (focal or generalized) may be features of HHS
  - UNCOMMON: Nausea, vomiting, diffuse abdominal pain

A 54-year-old patient presents to the hospital with a 3-day history of worsening and intractable vomiting, increased thirst, and frequent urination. On physical examination, the patient appears to be confused and does not answer questions appropriately. Laboratory findings are shown below. Which of the following is most suggestive of a diagnosis of hyperosmolar hyperglycemic state and not diabetic ketoacidosis?

Plasma glucose:	792 mg/dL (normal: 70 - 105 mg/dL)
Arterial pH:	7.36 (normal: 7.35 - 7.45)
Serum bicarbonate:	24 mEq/L (normal: 23 - 29 mEq/L)
Serum ketones:	Small (normal: variable)
Serum osmolality:	330 mOsm/kg (normal: variable)
Anion gap:	12 (normal: ≤ 12)

- A. Increased serum osmolality
- B. Presence of serum ketones
- C. Normal arterial pH
- D. Increased anion gap
- E. Abnormal mental status

Correct Answer: C. Normal arterial pH

Hyperosmolar hyperglycemic state (HHS) is a condition in which significant hyperglycemia, hyperosmolarity, and dehydration are encountered. There is no significant ketoacidosis in HHS. Thus, the pH is typically >7.3.

Incorrect Answers:

A and E. The increased serum osmolality that is characteristic of HHS can also be encountered in diabetic ketoacidosis (DKA). Similarly, an abnormal mental status can develop with severe DKA.

B. A small amount of serum ketones is nonspecific and is not solely suggestive of either DKA or HHS.

D. While the anion gap can be variable in both conditions, it would be elevated in the setting of moderate to severe DKA.

References:

Hirsch, I. B., & Emmett, M. (2020). Diabetic ketoacidosis and hyperosmolar hyperglycemic state in adults: Clinical features, evaluation, and diagnosis. UpToDate. Retrieved from https://www.uptodate.com/contents/diabetic-ketoacidosis-and-hyperosmolar-hyperglycemic-state-in-adults-clinical-features-evaluation-and-diagnosis

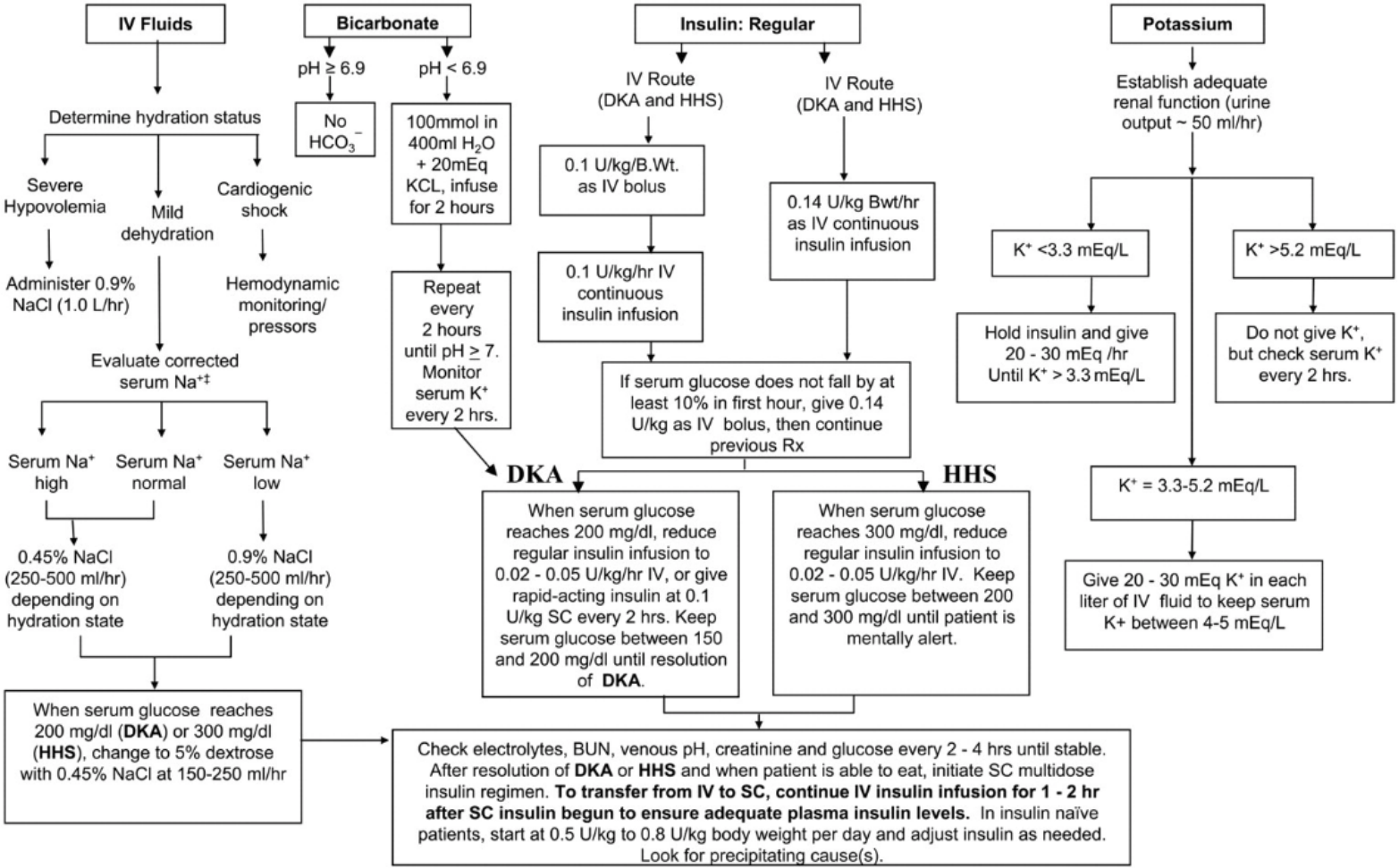
Hirsch, I. B., & Emmett, M. (2022). Diabetic ketoacidosis and hyperosmolar hyperglycemic state in adults: Treatment. UpToDate. Retrieved from https://www.uptodate.com/contents/diabetic-ketoacidosis-and-hyperosmolar-hyperglycemic-state-in-adults-treatment

Table 1

Diagnostic criteria for DKA and HHS

	DKA			HHS
	Mild (plasma glucose >250 mg/dl)	**Moderate (plasma glucose >250 mg/dl)**	**Severe (plasma glucose >250 mg/dl)**	**Plasma glucose >600 mg/dl**
Arterial pH	7.25–7.30	7.00 to <7.24	<7.00	>7.30
Serum bicarbonate (mEq/l)	15–18	10 to <15	<10	>18
Urine ketone*	Positive	Positive	Positive	Small
Serum ketone*	Positive	Positive	Positive	Small
Effective serum osmolality†	Variable	Variable	Variable	>320 mOsm/kg
Anion gap‡	>10	>12	>12	Variable
Mental status	Alert	Alert/drowsy	Stupor/coma	Stupor/coma

- *Nitroprusside reaction method.
- †Effective serum osmolality: 2[measured Na^+ (mEq/l)] + glucose (mg/dl)/18.
- ‡Anion gap: $(Na^+) - [(Cl^- + HCO_3^-$ (mEq/l)]. (Data adapted from ref. 13.)


Complete initial evaluation. Check capillary glucose and serum/urine ketones to confirm hyperglycemia and ketonemia/ketonuria. Obtain blood for metabolic profile. Start IV fluids: 1.0 L of 0.9% NaCl per hour.†
IV Fluids
Determine hydration status
Severe Hypovolemia
Mild dehydration
Cardiogenic shock
Administer 0.9% NaCl (1.0 L/hr)
Hemodynamic monitoring/ pressors
Evaluate corrected serum Na+‡
Serum Na+ high
Serum Na+ normal
Serum Na+ low
0.45% NaCl (250-500 ml/hr) depending on hydration state
0.9% NaCl (250-500 ml/hr) depending on hydration state
When serum glucose reaches 200 mg/dl (DKA) or 300 mg/dl (HHS), change to 5% dextrose with 0.45% NaCl at 150-250 ml/hr
Bicarbonate
pH ≥ 6.9
No HCO3−
pH < 6.9
100mmol in 400ml H2O + 20mEq KCL, infuse for 2 hours
Repeat every 2 hours until pH ≥ 7. Monitor serum K+ every 2 hrs.
Insulin: Regular
IV Route (DKA and HHS)
0.1 U/kg/B.Wt. as IV bolus
0.1 U/kg/hr IV continuous insulin infusion
IV Route (DKA and HHS)
0.14 U/kg Bwt/hr as IV continuous insulin infusion
If serum glucose does not fall by at least 10% in first hour, give 0.14 U/kg as IV bolus, then continue previous Rx
DKA
When serum glucose reaches 200 mg/dl, reduce regular insulin infusion to 0.02 - 0.05 U/kg/hr IV, or give rapid-acting insulin at 0.1 U/kg SC every 2 hrs. Keep serum glucose between 150 and 200 mg/dl until resolution of DKA.
HHS
When serum glucose reaches 300 mg/dl, reduce regular insulin infusion to 0.02 - 0.05 U/kg/hr IV. Keep serum glucose between 200 and 300 mg/dl until patient is mentally alert.
Potassium
Establish adequate renal function (urine output ~ 50 ml/hr)
K+ <3.3 mEq/L
Hold insulin and give 20 - 30 mEq /hr Until K+ > 3.3 mEq/L
K+ >5.2 mEq/L
Do not give K+, but check serum K+ every 2 hrs.
K+ = 3.3-5.2 mEq/L
Give 20 - 30 mEq K+ in each liter of IV fluid to keep serum K+ between 4-5 mEq/L
Check electrolytes, BUN, venous pH, creatinine and glucose every 2 - 4 hrs until stable. After resolution of DKA or HHS and when patient is able to eat, initiate SC multidose insulin regimen. To transfer from IV to SC, continue IV insulin infusion for 1 - 2 hr after SC insulin begun to ensure adequate plasma insulin levels. In insulin naïve patients, start at 0.5 U/kg to 0.8 U/kg body weight per day and adjust insulin as needed. Look for precipitating cause(s).

End

- Questions?