Diabetic Ketoacidosis and Hyperglycemic Hyperosmolar Syndrome

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Definition

	DKA	HHS
Glucose	>300	>600
pH	<7.3	>7.3
Bicarbonate	<18	>15
Serum Osm	<320	>320
Ketones	Mod-large	None-small
Dehydration	Mild-severe	Severe

DKA: Definition

- Biochemical Triad
- Hyperglycemia
- Ketonemia
- Metabolic acidosis
- Euglycemic DKA is possible
- Can occur in patients with T2DM

Precipitating Causes

- Infection
- New onset common in young children, occasionally see it in older adults misdiagnosed with T2DM
- Alcohol/drugs
- Omission of insulin – teenagers, weight control
- Drugs – steroids, antipsychotic drugs
- Pancreatitis
- Stroke
- Myocardial infarction

Ketosis Prone Type 2 Diabetes

- Obese patients with a family history of type 2
- No autoimmunity
- Upon diagnosis exhibit profound impairment in insulin action and secretion
- Recover insulin beta cell function and insulin sensitivity after resolution of DKA
- Majority do not need insulin

DKA - Presentation

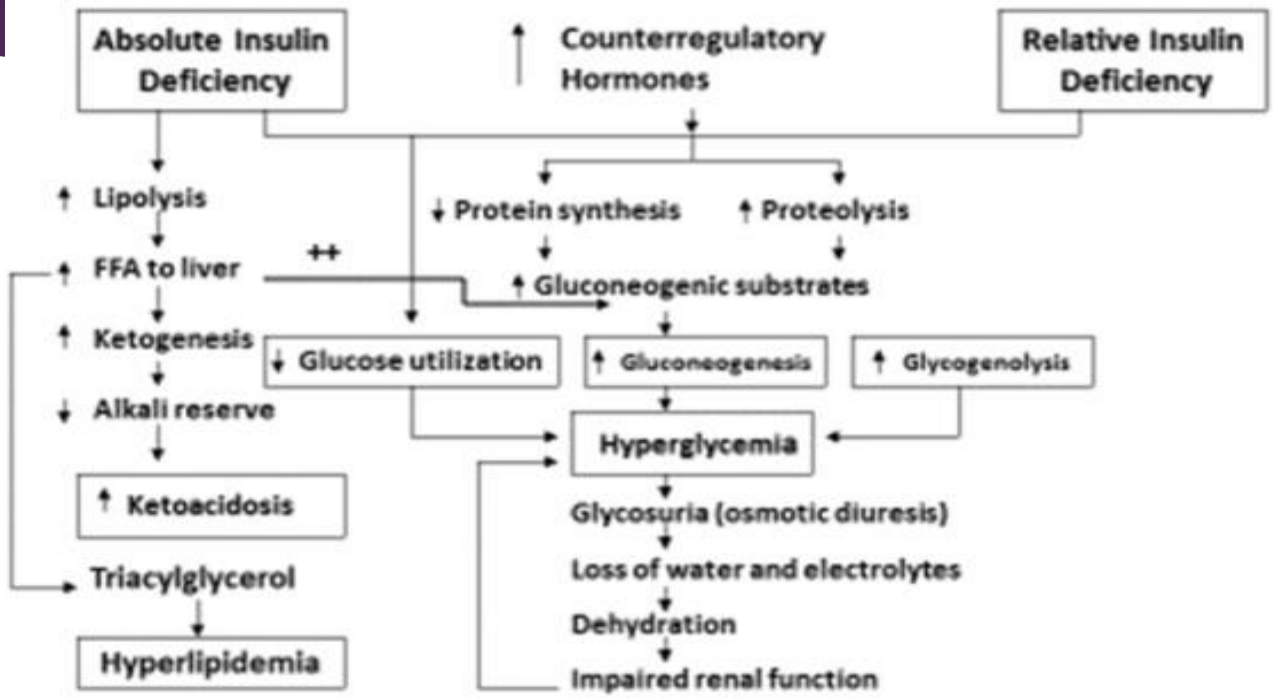
- Vomiting with no diarrhea (very commonly missed by PMD)
- Precipitating illness
- Dehydration with excessive urine output
- Respiratory distress
- Mental status changes

DKA - Pathophysiology

- Insulin deficiency
- Insulin resistance – especially in setting of illness
- Unregulated counterregulatory hormones (glucagon, cortisol, GH, catecholamines) which are normally suppressed by insulin
- Hyperglycemia results from increased glucose production (driven by CR hormones) and decreased peripheral utilization (which is driven by insulin)

Pathogenesis of DKA

Stress, Infection and/or Insufficient Insulin



Adapted from Ref 87.

Kitabchi, Metabolism, 2016

DKA - Diagnosis

- DKA generally evolves over a short period of time.
- Can occur as rapidly as 4-12 hours in persons on CSII
- High glucose levels lead to an osmotic diuresis and dehydration, with eventual hypotension.
- High ketones cause the acidosis and also contribute to the osmotic diuresis (renal threshold for ketones is low)
- The anionic charge on ketones leads to excretion of positively charged ions (Na, K, Ca, Mg) to maintain electrical neutrality

DKA - Diagnosis

- Insulin promotes reabsorption of H2O and Na from the renal tubules, so insulin deficiency promotes further loss of water and electrolytes
- Hyperglycemia causes a further shift of fluid out of cells and leads to intracellular dehydration
- The acidosis also leads to intracellular loss of K and phosphate

DKA - Diagnosis

- Nausea and vomiting, malaise, dehydration, weight loss
- Abdominal pain (ketosis vs acute surgical abdomen)
- Fever may or may not be present – however if not present do not assume no infection - patients are generally vasodilated
- Hypothermia poor prognostic sign
- Kussmaul breathing
- Decreased turgor 5% dehydration
- Orthostatic change in pulse 10%
- Change in pulse and BP 15-20%
- Supine hypotension most severe (assume sepsis)
- Mental status changes (may be associated with worsening acidosis)

DKA - Diagnosis

- Younger age consistently associated with increased risk of DKA at diagnosis
- Under 2 years of age often severe presentation
- PMDs lower incidence of suspicion
- Decompensation develops more quickly and Beta cell destruction more aggressive
- C-peptide levels often lower in children under 2 years of age at diagnosis

Physical Exam

- Perfusion
- Vital signs
- Hydration
- Mental status
- Insulin resistance
- Weight

Physical Exam

- Obtain a Glascow Coma Scale score
- Repeat hourly

Response	Score
Eye opening	
Opens eyes spontaneously	4
Opens eyes in response to speech	3
Open eyes in response to painful stimulation (eg, endotracheal suctioning)	2
Does not open eyes in response to any stimulation	1
Motor response	
Follows commands	6
Makes localized movement in response to painful stimulation	5
Makes nonpurposeful movement in response to noxious stimulation	4
Flexes upper extremities/extends lower extremities in response to pain	3
Extends all extremities in response to pain	2
Makes no response to noxious stimuli	1
Verbal response	
Is oriented to person, place, and time	5
Converses, may be confused	4
Replies with inappropriate words	3
Makes incomprehensible sounds	2
Makes no response	1

What are the signs and symptoms of neurological compromise that indicate progression to severe clinical cerebral edema (Muir et al 2004)

Bedside evaluation of neurological state of children with DKA

Diagnostic criteria
Abnormal motor or verbal response to pain
Decorticate or decerebrate posture
Cranial nerve palsy (especially III, IV, and VI)
Abnormal neurogenic respiratory pattern (e.g., grunting, tachypnea, Cheyne-Stokes respiration, apneusis)

Major criteria
Altered mentation/fluctuating level of consciousness
Sustained heart rate deceleration (decline more than 20 bpm) not attributable to improved intravascular volume or sleep state
Age-inappropriate incontinence

Minor criteria
Vomiting
Headache
Lethargy or being not easily aroused from sleep
Diastolic blood pressure > 90 mmHg
Age < 5 years

Signs that occur before treatment should not be considered in the diagnosis of cerebral edema

One diagnostic criteria, 2 major, or 1 major and 2 minor predicted cerebral edema with 92% sensitivity and 96% specificity.

Laboratory evaluation

- Glucose
- Venous blood gas
- Electrolytes
- Serum osmolality
- Phosphorous
- Hemoglobin A1c
- Ketones
- New onset labs if indicated
- Infection work-up if indicated

DKA - Treatment

- Start a flowsheet
- VS, fluids, insulin, Is/Os, labs
- Neuro checks q 1 hour
- Admit to ICU
- Occasionally mild DKA, euglycemic DKA (generally occurs rapidly in persons on insulin) can be managed in ED with fluids and SQ insulin

DKA – initial evaluation

- Hypernatremia with hyperglycemia indicates profound dehydration
- Low potassium on arrival have severe total body potassium deficiency
- Require cardiac monitoring and vigorous potassium replacement, as treatment with insulin will drop the potassium
- Hyperosmolar with severe acidosis may be at highest risk of altered mentation
- Check amylase and lipase

DKA – initial treatment

- Hydration – start with 10cc/kg NS bolus (1 liter in adults)
- Avoid more than 20cc/kg as bolus
- Restoration of intravascular volume lowers BS, decreases CR hormones and improves insulin sensitivity
- Goal is to replace deficit over 48 hours (1.5 times maintenance usual rule of thumb)
- Continual re-evaluation
- Add dextrose when BS < 300 mg/dL or if rate of drop too rapid (more than 100 mg/dl per hour)
- Generally change fluids to 0.45% saline when adding dextrose
- Aim to maintain glucose at 140-180 mg/dl

DKA – initial treatment

- Serum osmolality over 320 mOsm/kg indicates severe dehydration – requires more aggressive fluid replacement
- Hypotension should be treated with aggressive fluid replacement
- NO INSULIN without fluid replacement – especially in patients who are hypotensive

DKA - treatment

- Insulin bolus NOT indicated
- IV insulin drip at 0.05-0.1 units/kg/hr, **wait at least 1 hour prior to starting**
- Decreasing insulin drip will prolong treatment – INSULIN NECESSARY TO CLEAR ACIDOSIS
- Add dextrose to the IVFs once blood sugar below about 250 mg/dl
- Check BS q 1 hour, VBG q 2 hours in ICU cases

DKA - treatment

- Key Points:

  -wait at least 1 hour after IVFs start to begin insulin drip

  -watch Na very carefully: dropping Na is ominous sign

  -start with 4-6 hours of normal saline, then can switch to ½ normal

DKA - treatment

- Potassium

generally total body depleted

begin treatment when K < 5.5 and urine output

K 4.5 to 5.5 20 meq/L

K < 4.5 40 meq/L

Can use Kphos or Kacetate

- Bicarbonate

  Not indicated. Generally insulin will suppress the lipolysis and reverse ketogenesis. May cause paradoxical CNS acidosis

DKA - treatment

- Phosphate – generally depleted in DKA.
- During treatment with insulin phos taken up intracellularly with resultant hypophosphatemia
- Low phos may worsen CO, CNS depression, hemolysis, seizures, coma, ARF
- Phos therapy increases 2,3 DPG and improves tissue oxygenagtion

Pancreatitis in DKA

- Common in adults, rare in children
- Serum levels of amylase and lipase are often elevated, amylase is salivary in origin
- Lipase associated with degree of acidosis
- Acute pancreatitis must be considered with abdominal pain that does not resolve with correction of acidosis

Cerebral Edema

- Clinically apparent CE rare
- CE occurs in 1% of DKA episodes
- Mortality is 40 to 90%
- CE accounts for 50-60% diabetes related deaths in children
- Incidence has not changed in the last 15-20 yrs
- CE/DKA may cause deficits in neurocognitive function
- Pathophysiologic mechanism underlying CE is controversial

Cerebral Edema

- Cause of cerebral edema and best treatment to prevent it remain elusive
- No significant association with: rate of change in glucose; rate of insulin infusion; IVFs rate; type of fluid used
- Higher BUN (indicating more profound dehydration) and hypocapnia have been a/w higher risk (Glaser, NEJM, 2001)

Cerebral Edema

- CE which is asymptomatic may occur in **most** children with DKA
- Has been noted before treatment has been initiated
- There may be a spectrum of disease presentation or **different processes**
- Because it has been noted that CE can occur before treatment, it may not be caused by therapeutic interventions (although may be aggravated by them)

Cerebral Edema

- Hypothesized that CE is related to **brain ischemia**
- Both **hypocapnia**, causing cerebral vasoconstriction, and **extreme dehydration** can decrease perfusion of the brain
- **Hyperglycemia** superimposed on ischemic insult increases extent of damage
- BBB dysfunction and vasogenic edema may occur hrs after an ischemic insult due to release of vasoactive substances and mediators of inflammation
- Children at particular risk b/c they have higher oxygen requirements than adults

Cause of Cerebral Edema?

- Acidosis, hypocapnia, vasoconstriction, dehydration and hyperglycemia result in decreased cerebral blood flow
- Cerebral injury and cytotoxic edema result
- Ketones and acidosis appear to initiate the proinflammatory cytokine cascade
- **Ketones** are pro-inflammatory agents that affect endothelial cells of BBB
- Rehydration and reperfusion occur with treatment
- Reperfusion injury and vasogenic edema result
- Symptoms of cerebral edema

Cerebral Edema

- Typically occurs 4 to 12 hours after treatment is initiated, but can be present before (see chart for symptoms)
- Headache
- Gradual decrease or deterioration in level of consciousness
- Slowed pulse
- Hypertension
- May or may not see evidence radiologically

CE- Treatment

- Mannitol 1 gram/kg IV over 30 min
- Works by lowering blood viscosity and improving cerebral blood flow
- DO NOT need CT/MRI to initiate treatment, CE is a **CLINICAL** not a radiological diagnosis
- Elevate head of bed
- May need to intubate, do not aggressively hyperventilate
- Hypertonic saline 5-10mL/kg 3% saline can be used if not responding to mannitol

DKA – still no definitive treatment regimen

- DKA treatment remains controversial
- No consensus on: rate of fluids, type of fluid, insulin dose
- Bolus 10cc/kg NS
- IVFs ~ 1.5xM with NS, add dextrose when < 300 mg/dL
- Insulin at 0.05-0.10 u/kg/hr after first 1-2 hours of fluid rehydration
- Reassess mental status hourly

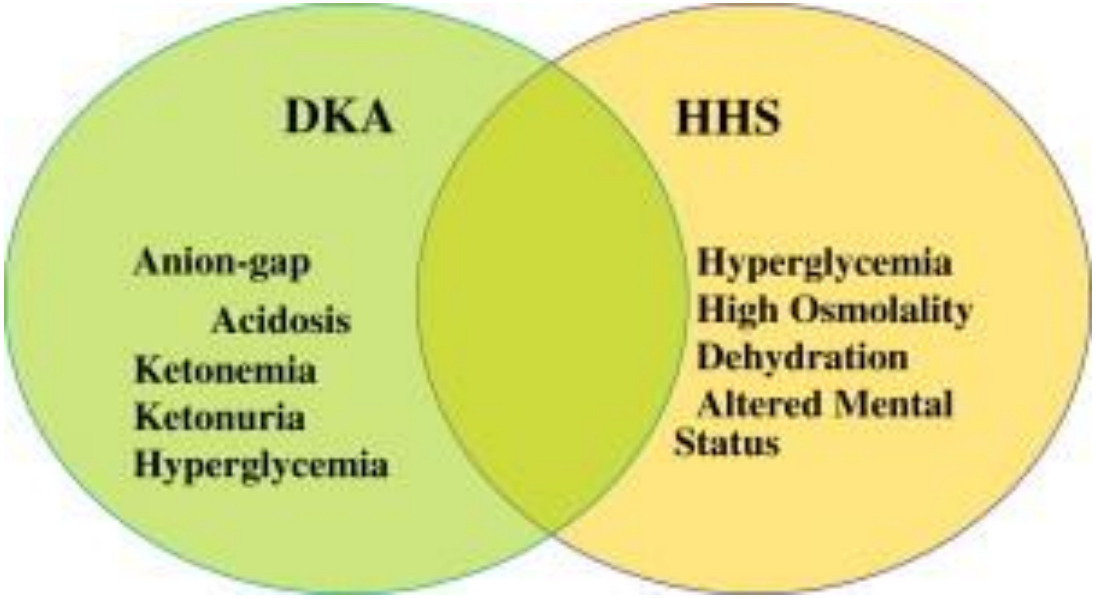
DKA – Transition off IV insulin

- pH> 7.3, HCO3 15-18
- Tolerate POs
- Give lantus, wait 1 hour, turn off IV insulin
- New patient estimate 0.5-1.0 units/kg/day

Hyperglycemic Hyperosmolar State

- Diagnostic criteria include:
  - Severe hyperglycemia > 600 mg/dl
  - Hyperosmolality > 320 mOsm/kg
  - Minimal ketosis
  - Mild metabolic acidosis
  - **PROFOUND DEHYDRATION**
- Relative insulin deficiency but enough insulin to avoid the ketosis
- Seen in pediatrics now with obesity/T2DM
- 12% fatality

DKA vs HHS


DKA
HHS
Anion-gap
Acidosis
Ketonemia
Ketonuria
Hyperglycemia
Hyperglycemia
High Osmolality
Dehydration
Altered Mental
Status

HHS

- Hyperglycemia leads to glucosuria and diuresis, dehydration
- Fluid shift from intracellular to extracellular space
- Initial loss of water with Na and potassium so hyponatremic
- Water losses greater than Na so hypernatremia ensues
- Generally process over a few days

HHS

- Intravascular volume decreases
- Renal perfusion decreases
- Less glucose excreted by kidney
- Worsening hyperglycemia
- Elevated BUN/Cr
- CR hormones increase in setting of volume depletion – more hyperglycemia
- Severe metabolic lactic acidosis can develop secondary to dehydration

HHS - Treatment

- Vigorous fluid replacement
- Initial bolus 20cc/kg isotonic saline
- Deficits of 12-15% body weight should be assumed
- Addnl boluses as necessary
- Do not want Na to drop rapidly. If rises, change to 0.45% saline
- 1 L/hr first 2-5 hours

HHS - Treatment

- DO NOT START INSULIN THERAPY FOR FIRST FEW HOURS AT A MINIMUM
- Wait until glucose no longer declining with fluids
- Too rapid decline in glucose can lead to circulatory compromise and thrombosis, insulin can also lead to hypokalemia
- Begin insulin at 0.025 to 0.05 u/kg/hr, goal is decline of 50 to 75 per hour

HHS - Treatment

- Potassium generally severely depleted – with adequate renal fxn begin at 40 mEq/L of replacement fluid
- Phosphorous should also be monitored and be in replacement fluids

HHS - Complications

- Thrombosis
- Rhabdomyolysis (measure CK q 2 to 3 hours)
- Malignant hyperthermia
- Cerebral edema and altered mental status
- Mixed HHS and DKA - servere hypertonicity with ketosis and acidosis - generally use more aggressive fluids than with DKA and proceed slower with insulin

References

- Diabetic ketoacidosis in children and adolescents with diabetes (Wolfsdorf et al, Pediatric Diabetes 2009)
- The management of diabetic ketoacidosis in children (Rosenbloom, Diabetes Ther, 2010)
- The ISPAD guidelines for management of diabetic ketoacidosis: do the guidelines need to be modified? (Wolfsdorf, Pediatric Diabetes, 2014)
- Hyperglycemic Hyperosmolar Syndrome in Children:Pathophysiological Considerations and Suggested Guidelines for Treatment (Zeitler et al, J Pediatr, 2011)
- Diabetic ketoacidosis and hyperglycemic hyperolsmolar state (Drexler et al, Endocrinol Metab Clin N Am, 2013)
- The evolution of diabetic ketoacidosis: An update of its etiology, pathogenesis and management (Kitabchi et al, Metabolism, 2016)

Grand Canyon