

# Glucose Control in ICU

# Outline

- DKA
- HONKA
- Medical patients
- Surgical patients

- What is DKA and HONKA?

# DKA pathophysiology

- DKA and HONKA are clinical syndromes that result from cellular energy starvation.
- This occurs due to a loss of intracellular glucose transfer.
- Which occurs due to absolute or relative lack of insulin.
- Insulin is produced in pancreatic beta cells. An absolute lack of insulin occurs in DM type 1.
- Insulin is utilized in peripheral tissues. A relative lack of insulin occurs due to cellular insulin resistance, or cellular loss/inactivity of glucose receptors, often seen in DM type 2.
- When cells are not able to take up glucose for energy, the body compensates by creating a hyperglycemic state.
- Unfortunately, increased amount of glucose, does not improve cells ability to utilize the glucose.

# DKA pathophysiology

- DKA/HONKA are the result of the body's compensation of depleted cellular energy state. The body compensates in this manner:
- 1) body makes available more glucose. 2) body use alternative energy sources.
- More glucose:
  - Production of glucose via liver dramatically increases increasing intravascular glucose levels. (Mechanism that creates the greatest amount of glucose in the body).
  - Less utilization of glucose by peripheral muscles also increases intravascular glucose levels.
- Use of alternative energy sources:
  - Body begins to breakdown fat into triglycerides and then FFAs (free fatty acids).
  - FFA are released into blood stream, taken up by liver, esterified within the cell to a form that can enter mitochondria, and within the mitochondria, they enter the citric acid cycle to produce energy.
  - Due to the preponderance of liberalized FFAs -> the citric acid cycle becomes overwhelmed and excessive FFA not processed by the citric acid cycle are converted into ketones-- acetoacetic acid and b-hydroxybutyric acid (b-hydroxybutyrate is the predominant ketone).
  - These ketones are released into systemic circulation with a multitude of their own effects.

# Effects of body's compensation

- Effect of ketonemia:
  - Acidosis:
    - Ketones are weak acids that disassociate at physiologic pH. As ketones are released into bloodstream, they overwhelm body's natural buffering system. This leads to metabolic acidosis.
  - Total body potassium depletion:
    - Intravascular acidosis leads to intracellular shift of H<sup>+</sup> ions with concomitant extracellular shift of K<sup>+</sup> ions (to maintain electrical neutrality). This first step in total body depletion of potassium.
- Effect of hyperglycemia:
  - Dilutional hyponatremia:
    - Shifting of free water from interstitial space to intravascular space to maintain similar osmolarities.
  - Volume and electrolyte depletion:
    - Kidneys normally reabsorb glucose until levels exceed 240 mg/dL. At this point, glucose spills into urine. Additionally, ketoacids are non-resorbable and are excreted in urine. Due to increased osmolarity in urine, kidney is not able to effectively concentrate urine and large volume of fluid and electrolytes are lost (osmotic diuresis).
    - This is the 2<sup>nd</sup> step in total body depletion of potassium. It, along with most other electrolytes, are depleted.
- Effects of prostaglandins:
  - Abdominal symptoms:
    - Generated in adipose tissue as cholesterol metabolized to FFAs. Leads to peripheral vasodilation, s/e from excessive prostaglandins including n/v, abdominal pain often experienced by patients with DKA.

- What is classic presentation of DKA?

# Presentation- symptoms

- Patients may have pre-existing diagnosis of DM (or this may be their initial presentation)
- Polyuria, polydipsia, weight loss
- Diminished activity
- Anorexia/vomiting/ abdominal pain



# Presentation- signs

Dehydration (hypovolemia by dry mucus membranes, decreased skin turgor, or by hypotension)

- Ketone breath (fruity odor)(acetoacidic acid -> converted to acetone -> removed via lungs)
- Kussamaul breathing (deep regular sigh respirations)

# Presentation- labs

- Azotemia
- Elevated transaminases (usually occur setting of dehydration -> leads to hepatic damage)
- Elevated glucose
- Elevated cholestrol levels (alterations in lipid metabolism)
- Elevated triglycerides (alterations in lipid metabolism)
- Hyponatremia
- Hypochloridemia
- Hypokalemia
- Hypocalcemia
- Hypomagnesiumia
- Hypophosphatemia
- Ketonuria
- Plasma ketones
- Metabolic acidosis
- Lactic acidosis (occurs if dehydration is significant enough)

- DKA is suspected, how do you approach patient?

# Approach

- 1) Confirm diagnosis.
  - Usually blood glucose  $>250-300$ . Beware of euglycemic DKA. Occurs in those with impaired gluconeogenesis (liver failure patients).
  - $\text{pH} < 7.3$  (met acidosis w an anion gap)
  - Elevation in serum ketones  $> 3$ .
- 2) Initiate treatment in a 3 pronged manner.
  - Insulin deficient- supply insulin.
  - Fluid depleted- supply fluids.
  - Electrolyte derangements- correct.

- What rate do you start insulin?
- How fast should serum glucose fall?
- Is it possible for serum glucose to fall too rapidly?
- When can you stop IV insulin?

# Insulin

- Insulin:
  - Prime tubing with 50 cc of insulin. Otherwise tubing will absorb insulin and may find patient with escalating doses of insulin without clear explanation.
  - Can give a bolus of 10 U of regular insulin.
  - Begin IV regular insulin infusion at rate 0.1 U/kg/hr.
  - IV regular insulin has a half life of 7-8 minutes. No interruptions should occur in drip (including transfer from ED to ICU) due to short half life.
  - Goal serum glucose fall 50-70 mg/dL in 1<sup>st</sup> hr.
  - Double insulin infusion rate until glucose is falling this much hourly.
  - If rate of glucose decline > 100 mg/dL/hr, decrease rate of insulin administration to avoid cerebral edema.
  - Continue infusion until serum ketosis (not ketouria) resolves. If glucose, bicarbonate, anion gap have resolved but serum ketosis remains, pt will remain highly resistant to insulin, should consider continuing protocol until ketosis resolves.
  - Glucose levels should be monitored hourly.
  - Target serum glucose ultimately 100-175 mg/dL.
  - Insulin replacement alone-
    - Cells are able to utilize available glucose in bloodstream.
    - Gluconeogenesis and ketone production in the liver are halted.
    - Lipolysis of adipose tissue is halted.
  - Consider holding insulin replacement for:
    - Severely hypotensive patients. As insulin administration can lead to dramatic intravascular shift which can precipitate vascular collapse.
    - Severely hypokalemic patients. As insulin administration can lead to dramatic intravascular shift, and cardiac arrhythmias can occur with significant hypokalemia.

- What rate do you start IVFs and what kind?
- When do you transition IVFs and what kind?
- How much IVF does the average DKA patient require?

# IVFs

- Fluids:
  - Average DKA patient is 5-8L depleted upon presentation.
  - Give 1-2L NS bolus in 1<sup>st</sup> hour (usually done in ER but double check them!)
  - Goal is to replace ½ fluid deficit within first 8 hrs.
  - Generally over hours 2-4, infuse NS at rate of 500 cc/hr
  - Technically when bp is stable and UOP is adequate, rate can be reduced to 250 cc/hr.
  - Type of fluid is changed to 1/2NS usually when bp and UOP are stable, or when Na > 155
  - Add 5% D5 to fluid when glucose < 250. This allows continuous replacement of insulin even though glucose levels are beginning to normalize (hormonal axis leading to hyperglycemia has not normalized and patient will experience worsening DKA without continued insulin).
  - Continue glucose administration until ketosis (not ketouria) clears and patient is able to tolerate po.
  - If glucose < 100 and pt is still ketotic, can change fluids to D10% or D20%.
  - Fluid replacement alone:
    - Expands intravascular compartment as well as interstitial compartment (improves perfusion),
    - Leads to reduction in serum glucose levels alone (by as much as 25%)
    - Leads to less circulating hormones producing hyperglycemia



- Which electrolytes might merit replacement before administering insulin?

# Electrolytes

- Electrolytes:
  - Check labs q4h.
    - Potassium:
      - $K > 5$ , no replacement
      - $K 4-5$ , 20 mEq in replacement fluid
      - $K 3-4$ , 30-40 mEq in replacement fluid
      - $K < 3$ , 40-60 mEq in replacement fluid
      - Note if the patients potassium is normal, replacement should be initiated!
      - If  $K < 3$ , consider repleting K before administering insulin.
    - Bicarbonate:
      - Generally does not need replacement.
      - Can consider if  $pH < 7$  or bicarb  $< 5$ . Can replete by adding it to fluid 1-2 amps of bicarbonate in fluid. When pH reaches 7.0, stop, to avoid late alkalosis.
    - Phosphorus:
      - Repletion not normally required.
      - If phosphate  $< 1$  or symptomatic, give 30-60 mM over 24 hrs.
      - Watch for hypocalcemia, hypomagnesium while repleting phosphate.
      - Symptoms of hypophosphatemia include: lethargy, depression, diarrhea, hemolytic anemia from lack of 2,3-diphosphoglycerate

- How do you determine insulin dose when transitioning from iv insulin to sc?

# Transitioning insulin to sc

- Overlap IV administration and subcutaneous administration is necessary due to short half life of IV insulin and delay in start of subcutaneous insulin.
- Time of overlap depends on insulin being used:
  - Regular insulin begins working subcutaneously 30-45 min.
  - Intermediate acting insulin (NPH) begins working subcutaneously 2-3 hrs.
  - Long acting insulin (lantus) begins working subcutaneously 2-3 hrs.
- To transition:
  - 1) Calculate total daily dose (TDD).
    - When insulin rate is stable for 4-6 hrs. Then take hourly rate of insulin drip x 24 x 0.666 (the 0.666 is a multiplier that takes into account differences in bioavailability between IV and sc insulin)
  - 2) Weight based formula.
    - 0.6U insulin/kg of body weight.
  - 3) Compromise. Usually need between the higher and lower level of calculation- so do both and compromise!

# Transitioning IV insulin to SC

- Once the daily dose is determined must further divide dose.
- There are multiple strategies:
  - If pt is eating:
    - 2/3 insulin in am (with further subdivided into 1/3 regular and 2/3 NPH), and 1/3 insulin pm (which is further subdivided into 1/3 regular and 2/3 NPH).
  - If the patient is not eating:
    - Daily dose/ 4. Administer this as regular insulin q6h.
    - Daily dose/ 2. Administer NPH/intermediate insulin q12h.

# Complications

- Cerebral edema:
  - With excessively rapid correction of Na and osmolarity, cerebral edema can occur. Exact etiology not known.
  - More common in pediatric patients, but can occur in adults.
  - Presents as headache, deterioration in consciousness or LOC, seizures.
  - Treat with mannitol (1-2 gm/kg to load), steroids, loop diuretics.
  - These patients tend not to survive.
- ARDS
- Embolism
  - DKA is hypercoaguable state.
- Acute gastric dilation (from excess prostaglandins)
  - Treat with reglan.

- How do DKA and HONKA differ?

# DKA vs HONKA

- DKA definition is hyperglycemia, ketosis, acidosis. Insulin can be administered such that cells begin to uptake glucose and state of cellular starvation is reversed.
- The definition of HONKA is hyperglycemia, hyperosmolarity, dehydration. Ketoacidosis is not a prominent feature (but is usually present to mild degree), as there is enough endogenous insulin to reduce ketoacid/FFA liberation/suppress some or hormonal activation seen in DKA. Fluid and electrolyte repletion are used to reverse state.
- HONKA patients tend to be older. Average age is 62 whereas in DKA average age is low 30s.
- HONKA glucose tends to be higher, > 600 rather than > 300
- HONKA dehydration tends to be 10-12 L rather than 5-8L
- HONKA acidosis tends to be mild, pH > 7.3.
- HONKA tends to be precipitated by: infection (50%), noncompliance (25%), initial presentation (20%) vs DKA tends to be 33% infection, 33% noncompliance, 33% initial presentation. Thus, for HONKA, exhaustively search for infection!
- HONKA tends to occur over weeks rather than days.
- HONKA tends to present more dramatically with hypotension and alterations in consciousness. GI symptoms tend to be less.
- HONKA has greater mortality with range 4-50% while DKA has mortality 2-17%.



- Is HONKA treated differently than DKA? If so, how?

# HONKA Treatment

- Generally fluid administration is greater:
  - If patient is hypotensive, give 2L fluid in first hour, rather than 1L.
  - Serum osm < 320, give 2-3L bolus of NS in 1<sup>st</sup> hr. (rather than 1-2L)
  - If serum osm > 320, some suggest:
    - Give 1.5L hypotonic saline for 1<sup>st</sup> hr.
    - 1 L of hypotonic saline for 2<sup>nd</sup> and 3<sup>rd</sup> hrs.
    - 500-750 cc of hypotonic saline for 4<sup>th</sup> hr.
    - Thus after 4 hrs = 4.5 L or more of hypotonic saline.
    - Continue hypotonic saline administration until serum osm < 320.
    - However, this strategy is controversial as in these patients even normal saline tends to be hypotonic.
- Insulin is less important than fluid administration:
  - Patients tend to be quite sensitive to insulin. Can start insulin at 0.05 U/kg rather than 0.1 U/kg.
  - In severe hypotension, do not start insulin. This will exacerbate hypotension and will not have effective delivery of insulin until circulating volume is improved.
  - Fall of glucose not tracked as closely. Goal is to have decrease over 2-4 hrs. If this does not occur, double insulin infusion rate. (rather than decrease by 50-70 every hour)
  - When glucose falls < 250, can add D5 to IVFs or can ½ rate of insulin administration. (in DKA must add D5 cannot stop insulin infusion!)
  - Generally protocol/incremental change based on hyperglycemia/hypoglycemia is less aggressive in HONKA than in DKA. (change in increments of 1 rather than increments of 2-3)
- Complications:
  - Thrombosis more common. MUST have heparin prophylaxis.
  - Also DIC, rhabdomyolysis more common than DKA.

# Other Formulas

- Anion gap =  $(\text{Na} + \text{K}) - (\text{bicarb} + \text{chloride})$ . Abnormal  $> 12$ .
- Osmolar gap. Measured osmoles – calculated osmoles.
- Calculated osmoles =  $2(\text{Na}) + \text{k} + (\text{bun}/2.8) + (\text{glu}/18)$
- Corrected Na =  $\text{Measured Na} + \{1.6 \times [\text{glu} - 100]/100\}$ .  
If corrected Na is normal range, then low measured Na is due to osmotic shifting. If corrected Na is below normal range, then Na is truly low due to osmotic diuresis. If measure Na is in the normal range without correction in the setting of significant hyperglycemia, this is likely due to loss free H<sub>2</sub>O.

- What are current recommendations for glucose targets in non-DKA patients?
- Are they different among surgical and medical patients, if so- how do they differ?

# Non-DKA glucose control

- Surgical patients: tight glucose control (81-108).
  - Van der Berghe (NEJM 2001) study compared 1500 patients tight control vs conventional control, all post operative, the majority post cabg.
  - Experimental arm/ tight control had reduced mortality than conventional (4.6 vs 8%). Had improvement in 2ndary endpoints as well including: less wound infections, less episodes of sepsis, decreased blood stream infections, decreased length of stay, decreased blood transfusions.
  - Various other studies have attempted to reproduce this data, but not have been able to show such overwhelming impact. Most demonstrate reduced sternal wound infections at the least (none are negative with intense control, none show increased mortality in surgical patients).
  - Based on meta-analysis, it is believed that tight glucose control particularly benefits post op cardiac patients (rather than all surgical patients).
  - For cardiac patients, glucose control of <180 is associated with less mech ventilation, less organ failure, less infection, and shorter length of stay.
  - Currently goal glucose is 140 mg/dL.
  - Overall, this needs more study.
- Medical patients: <180.
  - NICE sugar study (NEJM 2009).
    - 6,000 patients in > 40 hospitals (medical and surgical patients).
    - Patients were randomly assigned to receive tight glucose control vs conventional.
    - Tight glucose control group led to increased absolute risk of death by 2.6% (NNT 38).
    - It is postulated this was due to increased hypoglycemic events in experimental group (glucose <40 in 7% of experimental group vs 0.5 of conventional group).

# Questions?

- Works Cited:
  - Magee MF. Bhatt BA. Management of Decompensated Diabetes. Endocrine and Metabolism Dysfunction in the Critically Ill. 0749-0704/01.
  - Breithaupt T. Post op glycemic control in cardiac surgery patients. Baylor University Medical Center Proceedings. 2010 January; 23(1): 79-82.



- Some acetoacetic acid will be converted to acetone which can be eliminated via lungs (leading to ketone breath).
- Due to overwhelming amount of ketone acids, buffering systems become overwhelmed and pH becomes deranged.
- Ultimately ketoacids must be renally excreted and further lead to osmotic diuresis/ electrolyte wasting.
- Hormones that promote these above changes include glucagon, epinephrine, cortisol, and growth hormone.



# Potassium

- K is largely an intracellular ion.
- Metabolic acidosis creates an acidotic intravascular space. This leads to shift of H intracellularly. For electrical neutrality, K is moved extracellularly.
- Often on initial presentation, DKA patients have intravascular hyperkalemia due to this.
- However, from extracellular space, K is lost via vomiting as well as through renal losses/osmotic diuresis. This actually leads to total body depletion of k.
- As acidosis improves, K moves intracellularly again.
- This leads to rapid decrease in vascular levels of k with initiation of treatment.
- K should be treated aggressively.

# Phosphorous

- Major intracellular anion. It is critical for energy production and maintenance of intracellular membrane.
- If dehydration is severe, pts may initially present with hyperphosphatemia.
- Otherwise, general presentation is hypophosphatemia.
- With insulin administration -> glucose and phosphorus shift intracellularly
- Often see rapid development of hypophosphatemia with treatment.
- Most patients become symptomatic when phosphorous < 1 mg/dl ( ).

# Mortality

- Certain cells have an absolute requirement for glucose (cannot derive energy from FFAs). These are: brain, germinal epithelium of gonadal cells, retina.
- Of note, brain cells are unusual as they can uptake glucose without mediation of insulin.

# Hormonal changes that lead to DKA

- Glucagon:
- Pancreatic alpha cells produce glucagon.
- Glucagon increases glucose in three ways:
- 1) It promotes the liver to create glucose (gluconeogenesis) and 2) it promotes the liver to breakdown glycogen (glycogenolysis) which ultimately lead to more glucose 3) It leads to ketogenesis an alternative energy source.
- A small amount of glucagon leads to a large amount of glucose production. This occurs via amplification through secondary messenger system. Glucagon -> activation of cAMP within the cell -> activates other mechanisms within the cell -> ultimately changes nuclear transcription -> creates glucose. At each step in the pathway, amplification occurs.
- Glucagon will lead to liver to produce glucose even when hepatic stores are depleted.

# DKA vs HONKA

- Etiology: 1/3 new onset DM, 1/3 noncompliance, 1/3 infection.
- Consider other causes including: stroke, MI, pancreatitis, medication effect (steroids), pregnancy, etc.
- Mortality:
  - 2-14% in DKA
  - 4-50% HONKA