Diabetic Ketoacidosis
a few pearls

Mayo School of Continuous Professional Development

2nd Annual Inpatient Medicine for NPs & Pas:
Hospital Care from Admission to Discharge

Wednesday-Saturday, October 19-22, 2016
Sawgrass Marriott Hotel • Ponte Vedra Beach, Florida
Objectives

• Understand the pathogenesis of diabetic ketoacidosis

• Understand the differences between the pathophysiology and presentation of DKA and HHS

• Review the broad principles of insulin treatment for resolution of DKA

• Review other aspects of the management of DKA
And on the Fifth day, God created insulin, and commanded thus, “Thou shalt perform many tasks, foremost being…."

- Decrease hepatic glucose output
- Increase peripheral glucose uptake
- Suppress lipolysis in adipose tissue
- Stimulate lipogenesis in adipose tissue
- Stimulate protein synthesis in skeletal muscle
Primary insulin action

A. Decrease hepatic glucose output
B. Increase peripheral glucose uptake
C. Suppress lipolysis in adipose tissue
D. Stimulate lipogenesis in adipose tissue
E. Stimulate protein synthesis in skeletal muscle
• The primary function of insulin is suppression of lipolysis (breakdown of triglycerides to FFA) by inhibiting action of hormone sensitive lipase in the adipocytes

• Absence of insulin leads to unregulated lipolysis and subsequent ketogenesis
Ketone Bodies
Regulation of Fatty acid oxidation

CYTOSOL

Fatty acyl-CoA
Carnitine
CoASH
Glycerol-3-phosphate
Phospholipids, Triglycerides, etc.

MITOCHONDRIUM

Fatty acyl-CoA
CAT I
CAT II
Carnitine
CoASH
β-oxidation

Acetyl-CoA
Krebs cycle
HMG-CoA cycle
CO₂
Ketone bodies
Ketone body utilization in peripheral tissue
# Metabolism of Ketone bodies

<table>
<thead>
<tr>
<th>Liver</th>
<th>Blood</th>
<th>Extrahepatic tissues</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acyl-CoA</td>
<td>FFA</td>
<td>Glucose → Acyl-CoA → Acetyl-CoA → Ketone bodies</td>
</tr>
<tr>
<td>Glucose</td>
<td></td>
<td>Urine → Acetyl-CoA</td>
</tr>
<tr>
<td>Acetyl-CoA</td>
<td></td>
<td>Lungs</td>
</tr>
<tr>
<td>Ketone bodies</td>
<td></td>
<td>Ketone bodies → 2CO₂</td>
</tr>
<tr>
<td>Citric acid cycle</td>
<td></td>
<td>Citric acid cycle</td>
</tr>
<tr>
<td>2CO₂</td>
<td></td>
<td>2CO₂</td>
</tr>
</tbody>
</table>
Ketogenesis during insulin deficiency

**Insulin**

1. Lipolysis
2. Esterification
3. Citric acid cycle

**Glucagon**

- Cortisol
- Catecholamines

**Triacylglycerol**
- Adipose tissue
- Blood
- Liver

**FFA**
- Acyl-CoA
- Acylglycerols
- Acetyl-CoA

**Ketone bodies**
- CO₂
Non Ketotic Hyperosmolar Hyperglycemic State

- Inadequate insulin for glucose control, *but adequate for suppression of lipolysis and ketogenesis*

- Severe hyperglycemia

- Osmotic diuresis

- Inadequate fluid repletion

- Severe hyperosmolality
<table>
<thead>
<tr>
<th></th>
<th>HHS</th>
<th>DKA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type of DM</td>
<td>Type 2 DM, type 1 DM</td>
<td>Type 1 DM, type 2 DM</td>
</tr>
<tr>
<td>Age</td>
<td>Older patients</td>
<td>Younger patients</td>
</tr>
<tr>
<td>Mortality</td>
<td>Mortality up to 5-20%</td>
<td>Mortality &lt;1-5%</td>
</tr>
<tr>
<td>CV and Renal</td>
<td>Skipping insulin doses; infections</td>
<td></td>
</tr>
<tr>
<td>Insulin Deficiency</td>
<td>Relative insulin deficiency</td>
<td>Absolute insulin deficiency</td>
</tr>
<tr>
<td>Dehydration</td>
<td>Dehydration ++++</td>
<td>Dehydration ++</td>
</tr>
</tbody>
</table>
## Hyperglycemic emergencies: Diagnostic criteria and classification

<table>
<thead>
<tr>
<th></th>
<th>DKA</th>
<th>HHS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mild</td>
<td>Moderate</td>
</tr>
<tr>
<td><strong>Plasma glucose (mg/dl)</strong></td>
<td>&gt;250</td>
<td>&gt;250</td>
</tr>
<tr>
<td><strong>Arterial pH</strong></td>
<td>7.25–7.30</td>
<td>7.00–&lt;7.24</td>
</tr>
<tr>
<td><strong>Serum bicarbonate (mEq/L)</strong></td>
<td>15–18</td>
<td>10–&lt;15</td>
</tr>
<tr>
<td><strong>Urine ketone</strong>*</td>
<td>Positive</td>
<td>Positive</td>
</tr>
<tr>
<td><strong>Serum ketone</strong>*</td>
<td>Positive</td>
<td>Positive</td>
</tr>
<tr>
<td><strong>Effective serum osmolality</strong>*</td>
<td>Variable</td>
<td>Variable</td>
</tr>
<tr>
<td><strong>Anion gap</strong>*</td>
<td>&gt;10</td>
<td>&gt;12</td>
</tr>
<tr>
<td><strong>Alteration in sensorium or mental obtundation</strong></td>
<td>A</td>
<td>A/D</td>
</tr>
</tbody>
</table>

**Betahydroxy butyrate > 3.8 mmol/L**

Kitabchi et al, ADA consensus statement, Diab Care 2009
Diabetic Ketoacidosis: Differential Diagnosis

Other hyperglycemias
- Uncontrolled DM
- HHS
- Stress hyperglycemia

Hyperglycemia

Ketosis
- Ketotic hypoglycemia
- Alcoholic ketosis
- Starvation ketosis
- Isopropyl alcohol
- Hyperemesis

Acidosis
- Lactic acidosis
- Hyperchloremic acidosis
- Salicylism
- Uremic acidosis

Anion gap acidoses
- Methanol
- Uremia
- Propylene glycol
- Infection, Iron, Isoniazid
- Lactic acidosis
- Ethylene glycol
- Salicylates
- Formaldehyde
- Toluene
A 46 year old man with diabetes for 5 years presents to the ED with weakness, nausea, vomiting and shortness of breath.

Medications: Lantus insulin, Glipizide, Metformin, Canagliflozin and Lisinopril.

Blood tests: Glucose 164 mg/dL, Anion Gap 18, Bicarb 16 meq/L, B(OH)B 4.1, Lactate 2.6, Creatinine 1.8.

He likely has:

A. Diabetic Ketoacidosis
B. Alcoholic Ketoacidosis
C. Lactic acidosis due to Metformin
D. Lactic acidosis due to pneumonia
Diagnosis……….

A. Diabetic Ketoacidosis
B. Alcoholic Ketoacidosis
C. Lactic acidosis due to Metformin
D. Lactic acidosis due to pneumonia
• DKA can occur in the absence of significant hyperglycemia

• SGLT2 inhibitors have been associated with DKA without significant hyperglycemia
SGLT2 inhibitors and pathogenesis of DKA

Taylor et al JCEM 2015
FDA warns that SGLT2 inhibitors for diabetes may result in a serious condition of too much acid in the blood

Safety Announcement

[5-15-2015] The U.S. Food and Drug Administration (FDA) is warning that the type 2 diabetes medicines canagliflozin, dapagliflozin, and empagliflozin may lead to ketoacidosis, a serious condition where the body produces high levels of blood acids.

Review of diabetes medicines called SGLT2 inhibitors started
Risk of diabetic ketoacidosis to be examined

12 June 2015
EMA/390062/2015
Rosenstock & Ferrannini Diab Care 2015
A 46 year old man with diabetes for 5 years presents with DKA, and is treated with IV insulin after adequate fluid resuscitation. After 6 hours, he is on 7 units/h of insulin infusion and 250 cc/h of D5 with ½ NS. Blood tests: Glucose 114 mg/dL, Anion Gap 14, Bicarb 17 meq/L, B(OH)B 2.1.

At this time, it would be appropriate to:

A. Continue current rate of Insulin/D5
B. Decrease Insulin infusion rate to 3 Units/h
C. Hold insulin till blood glucose > 150, and then start insulin infusion at 3 Units/h
D. Change D5 to D10
E. Transition to subcutaneous insulin
Next step……

A. Continue current rate of Insulin/D5

B. Decrease Insulin infusion rate to 3 Units/h

C. Hold insulin till blood glucose > 150, and then start insulin infusion at 3 Units/h

D. Change D5 to D10

E. Transition to subcutaneous insulin
• Insulin infusion rate can be titrated down during treatment of DKA

• Avoid holding insulin infusion during treatment of DKA
PROTOCOL FOR MANAGEMENT OF ADULT PATIENTS WITH DKA

**Initial evaluation:** After history and physical examination, obtain arterial blood gases, complete blood count with differential, urinalysis, plasma glucose, BUN, electrolytes, chemistry profile, and creatinine levels STAT as well as an ECG. Chest X-ray and cultures as needed. Start IV fluid, 1.0 L of 0.9% NaCl per hour initially (15-20 ml/kg/hour).

**Diagnostic criteria:** DKA: blood glucose >250 mg/dl, arterial pH <7.3, bicarbonate <15 mEq/l, moderate ketonuria or ketonemia.

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### IV Fluids
- **Hypovolemic shock**
  - Administer 0.9% NaCl (1.0 L/hr) and/or plasma expander
- **Mild hypotension**
  - Hemodynamic monitoring
- **Cardiogenic shock**
  - Cardiogenic shock

**Evaluate corrected serum Na**
- **Serum Na high**
  - 0.45% NaCl (4-14 ml/kg/h) depending on hydration state
- **Serum Na normal**
  - 0.9% NaCl (4-14 ml/kg/h) depending on hydration state
- **Serum Na low**
  - When serum glucose reaches 250 mg/dl

**Change to 5% dextrose with 0.45% NaCl at 150-250 ml/hr with adequate insulin (0.05 - 0.1 U/kg/hour IV infusion or 5-10 U SC every 2 hours)** to keep the serum glucose between 150 and 200 mg/dl until metabolic control is achieved.

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### Insulin
- **Intravenous Route**
  - Insulin: Regular
  - 0.15 U/kg B. Wt. as IV bolus
  - 0.1 U/kg/hr IV Insulin Infusion

- **SC/IM Route**
  - Insulin: Regular
  - 0.4 U/kg B. Wt., ½ IV bolus, ½ IM or SC
  - 0.1 U/kg/hr Regular Insulin SC or IM

**If serum glucose does not fall by 50-70 mg/dl in first hour**
- Double insulin infusion hourly until glucose falls by 50-70 mg/dl in first hour
- Give hourly IV insulin bolus (10U) until glucose falls by 50-70 mg/dl

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### Potassium**
- If serum K⁺ is <3.3 mEq/L, hold insulin and give 40 mEq K/hr ($\frac{2}{3}$ KCl and $\frac{1}{3}$ KPO₄) until K ≥ 3.3 mEq/L
- If serum K ≥ 5.0 mEq/L, do not give K but check K every 2 hr.
- If serum K ≥ 3.3 but < 5.0 mEq/L, give 20-30 mEq K in each liter of IV fluid ($\frac{2}{3}$ as KCl and $\frac{1}{3}$ as KPO₄) to keep serum K at 4 - 5 mEq/L

**Assess need for Bicarbonate**
- **pH < 6.9**
  - No HCO₃⁻
- **pH > 7.0**
  - NaHCO₃ (100 mmol) Dilute in 400 ml H₂O. Infuse at 200 ml/h.
- **pH 6.9-7.0**
  - NaHCO₃ (50 mmol) Dilute in 200 ml H₂O. Infuse at 200 ml/h.

**Repeat HCO₃ administration q 2 h until pH > 7.0. Monitor serum K.**

Check electrolytes, BUN, creatinine and glucose every 2 - 4 h until stable. After resolution of DKA, if the patient is NPO, continue IV insulin and supplement with SC regular insulin as needed. When the patient can eat, initiate a multidose insulin regimen and adjust as needed. Continue IV insulin infusion for 1 - 2 hr after SC insulin is begun to ensure adequate plasma insulin levels. Continue to look for precipitating cause(s).
Check capillary blood glucose every hour, and adjust insulin and glucose infusion rates as follows:

<table>
<thead>
<tr>
<th>CBG (mg/dL)</th>
<th>Insulin (Units/h)</th>
<th>5% Dextrose (ml/h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;250</td>
<td>0.1 U/h =</td>
<td>0</td>
</tr>
<tr>
<td>200-250</td>
<td>0.05 U/h =</td>
<td>150</td>
</tr>
<tr>
<td>150-199</td>
<td>0.04 U/h =</td>
<td>175</td>
</tr>
<tr>
<td>100-149</td>
<td>0.03 U/h =</td>
<td>200</td>
</tr>
<tr>
<td>&lt;100*</td>
<td>0.02 U/h =</td>
<td>250</td>
</tr>
</tbody>
</table>
DKA: Intravenous fluids

0.9% Saline:
• 1-2 L 1\textsuperscript{st} hour

0.45/ 0.9% Saline:
• \~1-2L 2\textsuperscript{nd} and 3\textsuperscript{rd} hours

D5 – 0.45% Saline: (when glucose \~250)
• \~3L over the next 3-6 hours
DKA: IV Insulin *Regular*

- **Bolus:**
  - 0.15 units/kg IV x 1 dose (?)

- **Continuous:**
  - 0.1 units/kg/hour

- If K< 3.3 mEq/L, simultaneous potassium

**Caution:**
- If glucose not decreased by 100 after 2 hrs, - double the insulin infusion rate *temporarily.*

**Goal:**
- Blood glucose 150 – 250 mg/dL
Patient 1

- 28 year old Hispanic gentleman presents with difficulty breathing since this morning. He has had abdominal pain and nausea since yesterday, threw up coffee ground vomitus thrice during the night. Also reports to be not feeling well since the end of summer – always thirst despite drinking lot of fluids and has lost 15 lb. Not on any medications, has never seen a doctor except for occasional colds.

- Vitals: Temp 99 F, P 120/min, BP 90/60 mm Hg, RR 28/min, Spo2 98 % on 2 L, CBG > 600

- O/E: Alert and oriented, chest clear, abdomen soft, no skin infections

- Labs: Glu 695, Na 126, K 3.1, Chloride 90, Bicarb 9

- ABG: pH 7.0, Po2 86, PCo2 28, HCO3 8, Spo2 99
Patient 1

You give him 2 L of normal saline bolus, and then write orders for:

A. 10 units IV insulin bolus followed by insulin drip at 10 u/h
B. 50 units IV insulin bolus followed by insulin drip at 10 u/h
C. No bolus, start drip at 10 u/h
D. No insulin, first start bicarb drip at 100 mmol/h for 2 h
E. None of the above
(Normo)hypokalemia + acidosis

IV insulin
### DKA: Potassium Replacement

#### Non-telemetry units

<table>
<thead>
<tr>
<th>Potassium Level</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 3.3 mEq/L</td>
<td>Transfer to telemetry unit</td>
</tr>
<tr>
<td>3.3-5.0 mEq/L</td>
<td>20 mEq KCL IV over 2 hrs</td>
</tr>
<tr>
<td>&gt; 5.0 mEq/L</td>
<td>Check K⁺ every 2 hrs &amp; replace as needed</td>
</tr>
</tbody>
</table>

#### Telemetry units

<table>
<thead>
<tr>
<th>Potassium Level</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 2.8 mEq/L</td>
<td>60 mEq KCL IV over 3 hrs</td>
</tr>
<tr>
<td>2.8-3.2 mEq/L</td>
<td>40 mEq KCL IV over 2 hrs</td>
</tr>
<tr>
<td>3.3-5.0 mEq/L</td>
<td>20 mEq KCL IV over 1 hr</td>
</tr>
<tr>
<td>&gt;5.0 mEq/L</td>
<td>Check K⁺ every 2 hrs and replace as needed</td>
</tr>
</tbody>
</table>

**Renal failure requires special consideration**
Recommendations for Alkali Therapy for DKA

• it is recommended that adult patients with a pH<6.9 should receive bicarbonate
  • 100 mmol sodium bicarb in 400 ml water with 20 mEq KCl @ 200 ml/h for 2 h
  • until the venous pH is >7.0
  • if not: repeat dosing 2 h till pH >7.0

Complications of bicarb therapy:
• hypokalemia
• decreased tissue oxygen uptake
• cerebral edema
• paradoxical CNS acidosis
Phosphate Therapy for DKA

- careful PO₄ replacement may sometimes be indicated … if <1.0 mg/dL, anemia, cardiac dysfunction, respiratory depression
- 20–30 mEq/L potassium phosphate
  - max rate 4.5 mmol/h
  - stop if ≥2.0 mg/dL

Complications of phosphate therapy
- severe hypocalcemia
- hypomagnesemia
- hypotension
A 46 year old man with diabetes for 5 years presents with DKA, and is treated with IV insulin. He is doing well, and wants to eat next morning. Currently on 1 units/h of insulin infusion and 200 cc/h of D5 with ½ NS. Blood tests: Glucose 134 mg/dL, Anion Gap 10, Bicarb 17 meq/L, B(OH)B 0.2.

At this time, it would be appropriate to:

A. Continue current rate of Insulin/D5
B. Increase insulin infusion rate to 2 units/h
C. Change ½ NS to Ringers Lactate
D. Transition to subcutaneous insulin
Next step……..

A. Continue current rate of Insulin/D5
B. Increase insulin infusion rate to 2 units/h
C. Change ½ NS to Ringers Lactate
D. Transition to subcutaneous insulin
• Non gap acidosis during treatment of DKA is common, and does not necessarily require continued IV insulin infusion

• It is not clear if excess sodium chloride administration is the sole cause for non gap acidosis during treatment of DKA
DKA: Summary

- Diabetic ketoacidosis results from unregulated lipolysis and ketogenesis due to insulin deficiency.
- It can be seen in the absence of significant hyperglycemia, especially when on SGLT2 inhibitors.
- Fluid repletion, IV insulin/dextrose infusion and electrolyte monitoring are the essential steps in management of patients with DKA.
- It is also essential to address the cause for metabolic decompensation.
Questions & Discussion