Diabetic Ketoacidosis:
Sugar, sugar, please pass the salt!

The Dutch Method of Resuscitation

The "Fumigator"
Maatschappij tot Redding van Drenklingen, 1767
(the Society for the Rescue of Drowned Persons)

Diabetes Mellitus Classification

- “Sweet urine”
- Type I, insulin-dependent: treatable since insulin became available in 1921
  - “Insula” = islands, related to the islets of Langerhans, the pancreas that make it
- Type II, insulin-resistant: associated with obesity (>50%), age, family hx, rising incidence in US youth, can progress to type I
- Gestational: 5% of pregnancies

Diabetes Mellitus

- IDDM is the most common endocrine-metabolic disorder of childhood and adolescence
- It creates disturbed energy homeostasis caused by a deficiency of insulin or of its action
- It results in abnormal metabolism of carbohydrate, protein, and fat

Diabetes Mellitus

Long term morbidity and mortality stem from metabolic derangements that affect small and large vessels and result in retinopathy, nephropathy, neuropathy, ischemic heart disease, and arterial obstruction with gangrene of the extremities
**Case: History**

- 5 year-old male presents with 3-day history of nausea, vomiting, and abdominal pain
- Family members with N/V/D last week
- Good appetite and fluid intake prior to 3 days ago
- Nocturnal enuresis (bed-wetting) for 3-4 weeks
- 3 kg weight loss in the same period

**Case: Physical Exam**

- T 37.8, HR 145, RR 24, BP 80/40, SaO\textsubscript{2} 98%
- Lethargic but responds to voice
- HEENT: dry MM, sunken eyes, TM's normal
- Resp: CTA, deep regular breathing, tachypnea, fruity breath
- CV: Tachycardic, nl S\textsubscript{1} and S\textsubscript{2}, no murmur
- Abd: Voluntary guarding, decreased BS, no HSM
- Ext: weak distal pulses, cool extremities
- Skin: mottled hands and feet, CRT = 5 seconds, poor skin turgor
- How do you diagnose DKA?

**Diagnosis of DKA**

- Diagnosis of DKA is dependent on the demonstration of:
  - Hyperglycemia: usually > 300 mg/dl (glycosuria)
  - Ketosis: serum ketones > 3 mmol/L (ketonuria)
  - Acidosis: pH < 7.3 or bicarbonate < 15 mEq/L
- DKA must be differentiated from other anion gap acidosis and coma due to other causes (MUDPILES)

**Case: Laboratory**

- Bedside Glucose > 500
- Urine dipstick positive for glucose and ketones

<table>
<thead>
<tr>
<th>Glucose</th>
<th>Ketones</th>
<th>pH</th>
<th>Bicarbonate</th>
<th>Ca</th>
<th>Mg</th>
<th>PO\textsubscript{4}</th>
</tr>
</thead>
<tbody>
<tr>
<td>23</td>
<td>13.5</td>
<td>41</td>
<td>254</td>
<td>136</td>
<td>108</td>
<td>48</td>
</tr>
<tr>
<td>865/10L</td>
<td>2M/2E</td>
<td></td>
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ABG: 7.04/22/95/81-19

**DKA: Clinical Manifestations**

- DKA is responsible for the initial presentation of up to 25% of children with IDDM
- 36% < 5 yrs old
- 48% 5 - 14 yrs old
- 16% > 14 yrs old
- Mantra: children are not "little adults"
  - Higher basal metabolic rate
  - Greater BSA relative to mass
  - Less maturity of autoregulatory systems
- Mortality 0.15 - 0.3%

**DKA: Clinical Manifestations**

- Immature autoregulatory systems = poor compensatory mechanisms
- Protean presentation, a great mimicker
  - early manifestations are mild and include nausea, vomiting, polyuria, and dehydration
  - more severe cases include Kussmaul respirations, odor of acetone on the breath
  - abdominal pain or rigidity may be present and mimic acute appendicitis or pancreatitis
  - cerebral obtundation and coma ultimately ensue
Type I Diabetes Mellitus: Pathophysiology

• Progressive destruction of β-cells leads to a deficiency of insulin
• As IDDM evolves, it becomes a permanent low-insulin catabolic state, which feeding does not reverse
• Secondary changes involving stress hormones compound the problems and accelerate the metabolic decompensation

<table>
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<tr>
<th>High Plasma Insulin</th>
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<tr>
<td>Glucose uptake</td>
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<td>Glycogen synthesis</td>
<td>Glycogenolysis</td>
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<td>Ketogenesis</td>
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Type I Diabetes Mellitus: Pathophysiology

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DKA: A Hyperosmolar State

• Hyperosmolality as a result of progressive hyperglycemia contributes to cerebral obtundation in DKA
• Calculated osmolality = \( \left[ (Na^+ + K^+) \times 2 \right] + \frac{glucose + BUN}{18} + \frac{“anols”}{3} \times x \)
• Normal measured serum – calculated osmolar gap = 0-10 mOsm/L

Altered Lipid Metabolism

DKA results in altered lipid metabolism
• Increased concentrations of total lipids, cholesterol, triglycerides, and free fatty acids
• Free fatty acids are shunted into ketone body formation due to lack of insulin; the rate of formation exceeds the capacity for their peripheral utilization and renal excretion leading to accumulation of ketoacids, and therefore metabolic acidosis

Ketoacidosis in DKA

\[ \text{Fatty acids} \rightarrow \text{Acetyl-CoA} \rightarrow \text{Citric Acid Cycle} \]

\[ \text{Acetoacetic Acid} \]

\[ \beta\text{-Hydroxybutyric Acid} \]

\[ \text{Acetone} \text{ (Fruity breath)} \]
Acidosis in DKA: Ketones and Lactate

- Acidosis can be compounded by poor oxygen delivery (hypovolemia, decreased 2,3-DPG) and anaerobic glycolysis → lactic acidosis
- With progressive dehydration, acidosis, hyperosmolality, and diminished cerebral oxygen utilization, consciousness becomes impaired, and the patient ultimately becomes comatose

DKA: Fluid and Electrolytes

<table>
<thead>
<tr>
<th>Acidosis leads to shift</th>
<th>H(^+)</th>
<th>K(^+)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Organic compound breakdown in catabolic state</td>
<td>Na(^+)</td>
<td>PO(_4)(^-)</td>
</tr>
</tbody>
</table>

Inhibited by no insulin

Insulin

Case: Laboratory

Bedside Glucose > 500
Urine dipstick positive for glucose and ketones

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<td>41</td>
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</tr>
<tr>
<td>865/10/L/2/M/2/E</td>
<td>4.2</td>
<td>&lt;5</td>
</tr>
<tr>
<td>1.1</td>
<td>687</td>
<td></td>
</tr>
</tbody>
</table>
Ca 5.01
Mg 1.8
PO\(_4\) 2.4

ABG: 7.04/22/95/8/19

What is your immediate therapy in the patient with DKA?

A. Establish IV access; give 20 mL/kg of LR if signs of poor perfusion; and 1 mEq/kg NaHCO\(_3\)
B. Call the Peds Endocrinologists (via the Access Center), at any time, day or night
C. Establish IV access; give 20 mL/kg of NS for signs of poor perfusion
D. Establish IV access; give 20 mL/kg of NS to all DKA patients, regardless of perfusion

Goals of DKA Therapy

1. The ABCs: restore cardiovascular stability (intravascular volume expansion)
2. Correction of fluid deficit, electrolyte abnormalities, and acid-base status
3. Reversal of the catabolic state (initiation of insulin therapy)
4. Early recognition and avoidance of the complications associated with DKA and therapy

The Pediatric Assessment Triangle

- Appearance
- Breathing
- Circulation/Skin Color
Capillary Refill

Prolonged capillary refill (10 seconds) in a 3-month-old with cardiogenic shock

Dehydration Assessment

<table>
<thead>
<tr>
<th>3-5%</th>
<th>6-10%</th>
<th>10-15%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pulses</td>
<td>Full</td>
<td>Full to ↓</td>
</tr>
<tr>
<td>Cap refill</td>
<td>&lt; 2 sec</td>
<td>≤ 2 sec</td>
</tr>
<tr>
<td>Skin temp</td>
<td>Normal</td>
<td>NI to cool</td>
</tr>
<tr>
<td>Heart rate</td>
<td>NI to ↑</td>
<td>↑↑</td>
</tr>
<tr>
<td>BP</td>
<td>Normal</td>
<td>NI to ↑</td>
</tr>
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</table>

Fluid Resuscitation

- Not all patients in DKA require a fluid bolus
  - Over-aggressive fluid resuscitation → ↑ risk of cerebral edema
- Patients with signs/symptoms of poor tissue perfusion (10-20% dehydrated)
  - Isotonic fluid should always be used (NS, LR)
  - 10-20 mL/kg bolus until cardiovascular stability
  - This will often lower the blood glucose
  - Never use hypotonic or dextrose-containing fluids for resuscitation

Ongoing Fluid Therapy

- Calculate fluid deficit (based on clinical exam)
  - Subtract resuscitation fluids
  - Replace remaining fluid deficit over 48 hours
  - Add in maintenance fluids
  - Several good rules to follow
    - Don't exceed fluid rate of 2X hourly maintenance
    - Don't exceed 4 L/m²/day of fluid

Fluid Therapy in DKA

Two bag system for IV fluids:
- Bag A → NS with K (Cl, Phos, acetate)
- Bag B → D10 NS with K (Cl, Phos, acetate)

<table>
<thead>
<tr>
<th>Blood Glucose Level</th>
<th>Bag “A” no dextrose</th>
<th>Bag “B” dextrose bag</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 350</td>
<td>100%</td>
<td>Zero</td>
</tr>
<tr>
<td>301–350</td>
<td>75%</td>
<td>25%</td>
</tr>
<tr>
<td>251–300</td>
<td>50%</td>
<td>50%</td>
</tr>
<tr>
<td>201–250</td>
<td>25%</td>
<td>75%</td>
</tr>
<tr>
<td>&lt; 200</td>
<td>Zero</td>
<td>100%</td>
</tr>
<tr>
<td>&lt; 80</td>
<td>Zero</td>
<td>100%, ↓ or hold insulin</td>
</tr>
</tbody>
</table>

Goinberg, J Pediatr 1999

Electrolytes in DKA Therapy

- K⁺ is started early due to risk of hypokalemia as acidosis is reversed, volume restored, insulin started, and renal function improves.
- Total body phosphate is depleted: using KPO₄ helps avoid hyperchloremic acidosis.
- Acetate is used by some, unproven benefit.
- “Pseudohyponatremia” is often present
  - Corrected Na⁺ = Na⁺ + ((glucose - 100) x 0.016)
  - Na⁺ level should rise during therapy
  - If Na⁺ does not rise, true hyponatremia may be present (increasing cerebral edema risk) and should be treated (consider 3% saline)
When is bicarbonate use indicated for a child in DKA?

A. All patients with severe acidosis (pH < 7.1)
B. All DKA patients with acidosis (pH < 7.3)
C. Patients with dysrhythmias
D. Patients with myocardial dysfunction manifested by severe shock

If given, NaHCO₃ should be given slowly to avoid complications of therapy.

Bicarbonate Therapy

Why treatment of acidosis with bicarbonate is discouraged:

\[ H^+ + HCO_3^- \leftrightarrow H_2CO_3 \leftrightarrow CO_2 + H_2O \]

- HCO₃⁻ does not cross the blood-brain barrier
- CO₂ crosses the blood-brain barrier
- Correction of acidosis → hypokalemia
- Left shift of O₂ curve → tissue hypoxia
- Increased cerebral blood flow, ↑ICP

What is an acceptable way to initiate insulin therapy in DKA?

A. Subcutaneous insulin 0.1 - 0.4 u/kg
B. Continuous IV insulin infusion at 0.05 - 0.1 u/kg/hr
C. Intranasal insulin 1 u/kg
D. IV insulin bolus of 0.1 u/kg followed by a continuous infusion at 0.05 - 0.1 u/kg/hr

Treatment: Insulin

- Continuous infusion of low-dose insulin IV (~ 0.1 u/kg/hr) is effective, simple, and physiologically sound
- Goal is to slowly decrease serum glucose (≤ 100 mg/dL/hr)
- Do not:
  - Give insulin bolus
  - Give subcutaneous insulin in DKA
  - Withhold insulin

Insulin Therapy

- Insulin is used to reverse the catabolic state and correct acidosis and hyperglycemia
  - insulin should never be stopped if ongoing acidosis persists
- When the acidosis is corrected, the continuous insulin infusion may be discontinued and subcutaneous insulin initiated
- With the regimen, DKA is usually fully corrected in 36 to 48 hours

Monitoring the Patient in DKA

- Cardiovascular monitoring
- Frequent (q 1 hour) neurologic assessment
- Frequent monitoring of labs
  - Glucose q 1 hour (Accu-Chek)
  - Electrolytes & osmolality q 1-2 hours
  - Blood gas q 2-4 hours (venous is fine)
  - Urine ketones and glucose
- Fluid balance
Preparing for PICU Discharge & Subcutaneous Insulin

- Endocrinology involvement
- Consider subcutaneous insulin when:
  - Acidosis resolved (pH > 7.30 or HCO₃⁻ > 20)
  - Patient able to drink/eat (no N/V)
- Food is available
- Give SQ insulin, 30 minutes later discontinue continuous IV insulin and IV fluids
- IV fluids are usually not required once patient is taking PO fluids

Recovery: Fluid and Electrolytes

What are the complications of DKA therapy?

- Cerebral edema
- Cardiac dysrhythmias
  - Hypokalemia
  - Hypophosphatemia
  - Hypocalcemia
- Hypoglycemia

DKA and Cerebral Edema

All children with DKA have some cerebral edema on presentation (Krane et al, NEJM 1985)

In general, the development of clinically relevant cerebral edema is related to the severity of the DKA at presentation and the rapidity of correcting the fluid and electrolyte abnormalities

A good rule is to think of a nice wine and “keep them a little sweet and a little dry.” It took the patient a while to develop DKA, take time to correct it.

Cerebral Edema

- Cerebral edema is the major life-threatening complication seen in the treatment of children with DKA
  - manifestations include headache, alteration in level of consciousness, bradycardia, emesis, diminished responsiveness to painful stimuli, and unequal or fixed, dilated pupils
  - 20-25% mortality
  - 10-25% significant morbidity
- Accounts for 60-90% of DKA related deaths

Timing of Cerebral Edema

Glaser et al, NEJM 2001
Risk Factors for Cerebral Edema

- Demographic factors
  - Younger age
  - New onset of diabetes
- Factors affecting osmolality (idiogenic osmols)
  - Rapid decrease in serum glucose? Equivocal
  - Decrease in serum Na with therapy? Very likely
  - High BUN (> 40) on presentation
- Factors affecting cerebral vascular tone and acidosis
  - Low PaCO₂ (< 20) on presentation
  - Treatment with bicarbonate
- Fluid administration > 4 L/m²/day or > 50 mL/kg in the first 4 hours of therapy

Diagnosis of Cerebral Edema

- Major criteria
  - Altered mentation
  - Sustained HR decels
  - Incontinence
- Minor criteria
  - Vomiting
  - Headache
  - Not easily aroused from sleep
  - Diastolic BP > 90
  - Age < 5 years

- Diagnostic criteria
  - Abnl motor/verbal response to pain
  - Posturing
  - Cranial nerve palsy
  - Abnl respiratory pattern

- Dx with 92% sensitivity and 96% specificity:
  - One diagnostic
  - Two major
  - One major and two minor

Muir AB, et al. Diabetes Care 2004

What is your treatment of clinical cerebral edema?

A. Hypertonic (3%) saline 1 mL/kg/hr
B. Dexamethasone 0.5 mg/kg IV
C. Mannitol 0.5-1 gram/kg IV
D. RSI, 100% oxygen and hyperventilation
E. Surgical craniectomy

Cardiac Dysrhythmias

- Typically caused by poor oxygen delivery, acidosis, electrolyte abnormalities
- Therapy is directed at correcting the underlying etiology
- Is one time in DKA that bicarbonate therapy is indicated to correct acidosis … but slowly

Hypoglycemic Reactions (Insulin Shock)

- Symptoms and signs include pallor, sweating, apprehension, trembling, tachycardia, hunger, drowsiness, mental confusion, seizures and coma
- Management
  - Administration (if conscious) of carbohydrate-containing snack or drink
  - Glucagon 0.5 mg IV/IM is administered to an unconscious or vomiting child
  - PICU therapy may include increasing dextrose infusion and decreasing/holding insulin infusion

Other Complications

- Sepsis, infections, aspiration pneumonia, pulmonary edema, ARDS, pneumomediastinum, K⁺ disturbances, rhabdomyolysis
- CNS hematoma
- CNS thrombosis
  - 20% localized basilar edema, hemorrhage, thromboses, infection
  - Multiple case reports 1974-2006
  - Retrospective studies show increased incidence of DVTs in children with DKA and CVCs
Etiology of Thrombosis in DKA

- Hypercoagulability?
  - Increased plasminogen
  - Decreased fibrinolysis
  - DIC
  - Increased thrombin-antithrombin complex
  - Increased carotid artery intima-media thickness

- Hyperviscosity?
  - Dehydration
  - Hypersimilarity
  - Hyperlipidemia
  - Increased platelet aggregation

- Others?
  - Tissue hypoxia
  - pH reduction
  - Lactic acidosis
  - Vasogenic edema
  - Vasospasm
  - Hyperventilation-associated arterial constriction

- Multifactorial
  - All of the above

The New Diabetic Patient

With a DKA presentation in a new diagnosis IDDM child, education and training starts in the ED & PICU and can be the most powerful and effective time to discuss close management and prevention of complications.

References


Furhman, ed. Pediatric Critical Care, 1999


Rosenbloom et al, Diabetes Care 1990


Rogers, ed. Pediatric Intensive Care, 1996