Management of Hyperglycemic Crises

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## Dr. Guillermo Umpierrez, Personal/Professional Financial Relationships with Industry
January 2017

<table>
<thead>
<tr>
<th>External Industry Relationships *</th>
<th>Company Name(s)</th>
<th>Role</th>
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<tr>
<td>Equity, stock, or options in biomedical industry companies or publishers</td>
<td>BMJ Open Diabetes Research &amp; Care, American Association Clinical Endocrinologists, Endocrine Society</td>
<td>Editor-in-Chief, Board of Director, Council At Large</td>
</tr>
<tr>
<td>Industry funds to Emory University for my research</td>
<td>Merck, Sanofi, Novo Nordisk, Boehringer Ingelheim, Astra Zeneca</td>
<td>Investigator-Initiated Research Projects</td>
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<tr>
<td>Industry Advisory/Consultant activities</td>
<td>Sanofi</td>
<td>Consultant/Advisory Boards</td>
</tr>
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Hyperglycemic Crises in Adult Patients with Diabetes: DKA and HHS

- Epidemiology
- Pathogenesis
- Precipitating factors
- Diagnosis
- Treatment
- Prevention
Hyperglycemic Crises

DKA

HHS

Hyperglycemia

DKA

HHS
Hyperglycemic Crises

- **DKA**
  - Most common hyperglycemic emergency in patients with type 1 and type 2 diabetes
  - DKA accounts for 4 - 9% of all hospital discharge summaries among patients with diabetes
  - Annual average of > 135,000 hospitalizations for DKA in the United States
  - Mortality rate <5%

- **HHS**
  - Hospitalization rate lower than DKA, ~ less than 1% of all primary diabetic admissions
  - Mortality rates ~15%
DKA Incidence from NHDS

Growth in incidence since 1980 (primary diagnosis)

Year
Number (in Thousands)

2006 Incidence: 134,663 episodes

Type 1 Diabetes Accounts for the Majority of Primary DKA Episodes

- 34% of episodes are Type 2, \( \Rightarrow \) \( \approx \)46,000 cases
- Longer Hospital Stays, \( \Rightarrow \)4.2 vs average of 3.5
- Very few have CV issues or serious infections, \( \Rightarrow \) Less than 15%

T2D accounts for 34% of primary DKA cases and more than 50% of secondary causes

Primary DKA Episodes

T1D - Children
18%

T1D - Adults
48%

T2D
34%

National Hospital Discharge Survey (NHDS); 2006.
DKA-related Mortality Rates Have Been in Decline Since the 90s

Overall 2006 mortality rate for DKA: 0.41%

Death Rates for Hyperglycemic Crises as Underlying Cause, By Age, United States, 2009

Hospitalization cost of DKA has risen significantly since the 90’s

Key Statistics (Source: HCUP) - 2006
- Number of DKA episodes: 136,510
- Mean Length of Stay: 3.5 days
- Mean charges per episode: $17,559
- Total DKA-related Hospitalisation Cost: $2.4 billion

Source: Center for Disease Control
Pathogenesis of Hyperglycemic Crises

- **Insulin Deficiency**
  - Increased glucose production
  - Decreased glucose uptake
  - Electrolyte abnormalities

- **Counterregulatory Hormones**
  - Hyperglycemia osmotic diuresis
  - Dehydration
  - Lipolysis-Increased FFA
  - Increased ketogenesis
  - Metabolic acidosis
  - Hypertonicity

DKA HHS

Pathogenesis of Hyperglycemia in DKA

Relative or absolute insulin deficiency

Liver

Muscle

↑ glucose output

↑ glycogenolysis

↓ glucose uptake
Increased Glucose Production in DKA

Gluconeogenesis

Glucose

Activity of gluconeogenic enzymes (PEPCK, PC, PFK)

Glycerol

Amino acids
Lactate

TG

Lipolysis

Protein breakdown

Glucotoxicity
Increased Production of Ketones in DKA

- Lipolysis
- FFA
- Glycerol
- Ketogenesis
  - B-OH-B
  - Acetoacetate
  - TG
  - Lipolysis

- Insulin
- Glucagon
  - reduction of malonyl-CoA
  - Inhibition of CPT-I
Pathogenesis of DKA

Liver

- Increased glucose production

Peripheral tissue

- Decreased glucose uptake

Adipose tissue

- Increased release FFA

Liver

- Increased ketogenesis

HYPERGLYCEMIA

- Osmotic diuresis

- Volume depletion

KETOACIDOSIS

- Decreased alkali reserve

- Metabolic acidosis

### Diagnostic Criteria for DKA and HHS

<table>
<thead>
<tr>
<th></th>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
<th>HHS</th>
</tr>
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<tbody>
<tr>
<td><strong>Plasma glucose (mg/dl)</strong></td>
<td>&gt;250</td>
<td>&gt;250</td>
<td>&gt;250</td>
<td>&gt;600</td>
</tr>
<tr>
<td><strong>pH</strong></td>
<td>7.25-7.3</td>
<td>7.0-&lt;7.24</td>
<td>&lt;7.0</td>
<td>&gt;7.30</td>
</tr>
<tr>
<td><strong>Bicarbonate (mEq/l)</strong></td>
<td>15-18</td>
<td>10-&lt;15</td>
<td>&lt;10</td>
<td>&gt;15</td>
</tr>
<tr>
<td><strong>Urine ketones</strong>*</td>
<td>positive</td>
<td>positive</td>
<td>positive</td>
<td>small</td>
</tr>
<tr>
<td><strong>Serum ketones</strong>*</td>
<td>positive</td>
<td>positive</td>
<td>positive</td>
<td>small</td>
</tr>
<tr>
<td><strong>Effective serum Osmol (mOsm/kg)</strong>*</td>
<td>variable</td>
<td>variable</td>
<td>variable</td>
<td>&gt;320</td>
</tr>
<tr>
<td><strong>Alteration in sensoria or mental obtundation</strong></td>
<td>alert</td>
<td>alert/</td>
<td>stupor/</td>
<td>stupor/</td>
</tr>
<tr>
<td></td>
<td></td>
<td>drowsy</td>
<td>coma</td>
<td>coma</td>
</tr>
</tbody>
</table>

* Nitroprusside reaction method
† Calculation: 2[measured Na (mEq/l)] + glucose (mg/dl)/18

<table>
<thead>
<tr>
<th>Reason</th>
<th>Cases</th>
<th>Percent</th>
<th>Other Cases</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>New diabetes</td>
<td>25</td>
<td>(17)</td>
<td>4</td>
<td>(17)</td>
</tr>
<tr>
<td>Failure to take insulin</td>
<td>59</td>
<td>(41)</td>
<td>8</td>
<td>(35)</td>
</tr>
<tr>
<td>Infection</td>
<td>40</td>
<td>(28)</td>
<td>8</td>
<td>(35)</td>
</tr>
<tr>
<td>Medical illness</td>
<td>14</td>
<td>(10)</td>
<td>3</td>
<td>(13)</td>
</tr>
<tr>
<td>Unknown</td>
<td>6</td>
<td>(4)</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

## Precipitating causes of DKA

<table>
<thead>
<tr>
<th></th>
<th>Australia</th>
<th>Brazil</th>
<th>China</th>
<th>Korea</th>
<th>Spain</th>
<th>Syria</th>
<th>Nigeria</th>
<th>USA</th>
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</thead>
<tbody>
<tr>
<td>New Dx</td>
<td>5.7</td>
<td>12.2</td>
<td>NR</td>
<td>NR</td>
<td>12.8</td>
<td>NR</td>
<td>NR</td>
<td>17–23.8</td>
</tr>
<tr>
<td>Infection</td>
<td>28.6</td>
<td>25.0</td>
<td>39.2</td>
<td>25.3</td>
<td>33.2</td>
<td>47.8</td>
<td>32.5</td>
<td>14–16.0</td>
</tr>
<tr>
<td>Poor Compliance</td>
<td>40.0</td>
<td>39.0</td>
<td>24.0</td>
<td>32.7</td>
<td>30.7</td>
<td>23.5</td>
<td>27.5</td>
<td>41–59.6</td>
</tr>
<tr>
<td>Other</td>
<td>25.7</td>
<td>15.0</td>
<td>10.9</td>
<td>11.2</td>
<td>23.3</td>
<td>7.8</td>
<td>4.8</td>
<td>9.7–18</td>
</tr>
<tr>
<td>Unknown</td>
<td>--</td>
<td>8.8</td>
<td>25.9</td>
<td>30.8</td>
<td>--</td>
<td>20.9</td>
<td>34.6</td>
<td>3.0-4.2</td>
</tr>
</tbody>
</table>

Diabetic Ketoacidosis (DKA) In Urban African Americans

Precipitating Cause

First episode of DKA

Recurrence of DKA

Randall et al. Diabetes Care 34:1–6, 2011
Euglycemic Diabetic Ketoacidosis: A Potential Complication of Treatment With Sodium-Glucose Cotransporter 2 Inhibition

DOI: 10.2337/dc15-0843

Anne L. Peters,¹ Elizabeth O. Buschur,² John B. Buse,³ Pejman Cohan,⁴ Jamie C. Diner,³ and Irl B. Hirsch⁵
SGLT2-I Associated DKA in T1D

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>CANA 100 mg</th>
<th>CANA 300 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any ketone-related AEs, n (%)*</td>
<td>0</td>
<td>6 (5.1)</td>
<td>11 (9.4)</td>
</tr>
<tr>
<td>Serious DKA AEs, n (%)**</td>
<td>0</td>
<td>5 (4.3)</td>
<td>7 (6.0)</td>
</tr>
<tr>
<td>Non-Serious AEs, n (%)***</td>
<td>0</td>
<td>1 (0.9)</td>
<td>5 (4.3)</td>
</tr>
</tbody>
</table>

* DKA, ketoacidosis, urine ketones  
** Requiring hospitalization  
*** Increased urine ketones, mild –moderate DKA or acidosis

Henry et al. Diabetes Care 2015; 38:2258-2265
Pathogenesis of SGLT2-Induced DKA

Clinical Presentation of DKA

Symptoms
- Polydipsia
- Polyuria
- Weakness
- Weight loss
- Nausea
- Vomiting
- Abdominal pain

Signs
- Hypothermia
- Tachycardia
- Tachypnea
- Kussmaul breathing
- Ileus
- Acetone breath
- Altered sensorium

The onset of DKA is usually relative short, ranging from hours to a day or two.
Mental Status at Presentation in DKA

Level of Consciousness
- Coma: 13%
- Lethargy: 39%
- Alert: 48%

Mental Status and Osmolality

Serum Osmolality (mOsm/L)
- n = 71
- n = 55
- n = 18

Correlation Between Admission Mental Status and Serum Osmolality in 144 Patients with DKA

## DKA and Abdominal Pain

<table>
<thead>
<tr>
<th></th>
<th>DKA with abdominal pain</th>
<th>DKA without abdominal pain</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>86</td>
<td>103</td>
</tr>
<tr>
<td>Age (years)</td>
<td>37 ± 1†</td>
<td>41 ± 2</td>
</tr>
<tr>
<td>Gender (M/F)</td>
<td>47/43</td>
<td>64/39</td>
</tr>
<tr>
<td>History of alcohol use</td>
<td>44 (51) *</td>
<td>25 (24)</td>
</tr>
<tr>
<td>History of cocaine use</td>
<td>11(13) ‡</td>
<td>2 (2)</td>
</tr>
<tr>
<td>Blood glucose (mg/dl)</td>
<td>596 ± 24</td>
<td>586 ± 24</td>
</tr>
<tr>
<td>Bicarbonate (mmol/L)</td>
<td>9 ± 1 *</td>
<td>15 ± 1</td>
</tr>
<tr>
<td>PH</td>
<td>7.12 ± .02 *</td>
<td>7.24 ± .09</td>
</tr>
<tr>
<td>Sodium (mmol/L)</td>
<td>133 ± 1</td>
<td>133 ± 1</td>
</tr>
<tr>
<td>Serum osmolality (mmol/L)</td>
<td>307 ± 2</td>
<td>307 ± 2</td>
</tr>
</tbody>
</table>

Data are means ± SEM or n (%)

† p < 0.05
‡ p < 0.01
* p < 0.0001

### Admission Clinical characteristics – Abdominal Pain

<table>
<thead>
<tr>
<th></th>
<th>Total # DKA cases</th>
<th># cases (%) with abdominal pain</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Bicarbonate (mmol/L)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 5</td>
<td>29</td>
<td>25 (86)</td>
</tr>
<tr>
<td>5 - &lt;10</td>
<td>47</td>
<td>31 (66)</td>
</tr>
<tr>
<td>10 - &lt;15</td>
<td>66</td>
<td>24 (36)</td>
</tr>
<tr>
<td>15 – 18</td>
<td>47</td>
<td>6 (13)</td>
</tr>
<tr>
<td><strong>Glucose (mg/dL)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 400</td>
<td>55</td>
<td>20 (36)</td>
</tr>
<tr>
<td>400 – 600</td>
<td>60</td>
<td>29 (48)</td>
</tr>
<tr>
<td>&gt;600</td>
<td>74</td>
<td>37 (50)</td>
</tr>
<tr>
<td><strong>Serum Osmolality (mmol/kg)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;300</td>
<td>63</td>
<td>30 (48)</td>
</tr>
<tr>
<td>300 – 320</td>
<td>89</td>
<td>36 (40)</td>
</tr>
<tr>
<td>&gt;320</td>
<td>37</td>
<td>20 (54)</td>
</tr>
</tbody>
</table>

Initial Laboratory Studies

- Immediate determination of blood glucose by finger stick, and serum ketones (3-BH) by finger stick or urinary ketones.

- Laboratory studies:
  - ABG’s
  - CBC with differential
  - CMP (glucose, electrolytes, bicarbonate, PO4, Mg, BUN, creatinine)
  - Serum ketones
  - Urinalysis
  - Bacterial cultures*
  - Cardiac enzymes*

* If clinically indicated
Useful Formulas for the Evaluation of DKA and HHS

1. Calculation of anion gap (AG):
   \[ AG = [Na^+] - [Cl^- + HCO_3^-] \]

2. Total and effective serum osmolality:
   \[
   \text{Total} = 2[Na^+] + \frac{\text{glucose (mg/dl)}}{18} + \frac{\text{BUN (mg/dl)}}{2.8}
   \]
   \[
   \text{Effective} = 2[Na^+] + \frac{\text{glucose (mg/dl)}}{18}
   \]

Hyponatremia is common in patients with DKA

**Corrction of Serum sodium:**

\[ \text{Corrected } Na^+ = [Na^+] = 1.6 \times \text{glucose (mg/dl)} - 100 \]

Serum Potassium

- Admission serum potassium is frequently elevated (due to a shift of K⁻ from the intracellular to the extracellular space)

Serum Phosphorus

- Admission serum phosphorus is frequently elevated (due to a shift of K⁻ from the intracellular to the extracellular space)

Can Serum $\beta$-Hydroxybutyrate Be Used to Diagnose Diabetic Ketoacidosis?

A HCO3 level of 18 mEq/l corresponded with BOHB levels of 3.0 and 3.8 mmol/l in children and adults, respectively.

Clinical Utility of $\beta$-Hydroxybutyrate Determined by Reflectance Meter in the Management of DKA

- **Serum/urinary ketones**
  - Key diagnostic feature of DKA
  - Nitroprusside reaction (semiquantitative estimation of acetoacetate and acetone, but fails to measure B-OH-B)
  - Direct measurement of B-OH-B is preferable
    - Ketosite test
    - Precision Xtra

Umpierrez et al, Diabetes Care 18:137, 1995
Blood $\beta$-OHB Levels in DKA

• $\beta$-OHB concentrations $>0.5$ mmol/L are considered “abnormal”

• Patients presenting with DKA can range between 3-12 mmol/L $\beta$-OHB
  
  – $\beta$-OHB $\leq 1.0$ mmol/L — treat blood glucose level appropriately

  – $\beta$-OHB 1.1 to 3.0 mmol/L — insulin and fluids; retest in 1 hr and, if no improvement, contact physician

  – $\beta$-OHB $>3.0$ mmol/L — insulin, fluids, urgent medical attention

Management of DKA and HHS

- Replacement of fluids losses
- Correction of hyperglycemia/metabolic acidosis
- Replacement of electrolytes losses
- Detection and treatment of precipitating causes
- Conversion to a maintenance diabetes regimen (prevention of recurrence)
Management of Adult Patients with DKA

**IV Fluids**
- Determine hydration status
  - Hypovolemic shock
  - Mild hypotension
  - Cardiogenic shock
  - Administer 0.9% NaCl (1.0 L/h) and/or plasma expander
- Hemodynamic monitoring
- 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
    - 0.45% NaCl (4-14 ml/kg/h) depending on hydration state
- When serum glucose reaches 250 mg/dl
  - Change to 5% dextrose with 0.45% NaCl at 150-250 ml/h with adequate insulin (0.05-0.1 U/kg/h IV infusion or 5-10 U SC every 2h) to keep the serum glucose between 150 and 200 mg/dl until metabolic control is achieved.

**Insulin**
- IV Route
  - Insulin: Regular 0.15 U/kg as IV bolus
- SC/IM Route
  - Insulin: Regular 0.4 U/kg IM bolus, ½ IM or SC
- 0.1 U/kg/h IV insulin infusion
- 0.1 U/kg/h Regular insulin SC or IM
- If serum glucose does not fall by 50-70 mg/dl in first h
  - Double insulin infusion hourly until glucose falls by 50-70 mg/dl
- When serum glucose reaches 250 mg/dl
  - Change to 5% dextrose with 0.45% NaCl at 150-250 ml/h with adequate insulin (0.05-0.1 U/kg/h IV infusion or 5-10 U SC every 2h) to keep the serum glucose between 150 and 200 mg/dl until metabolic control is achieved.

**Potassium**
- If serum K⁺ is < 3.3 mEq/L, hold insulin and give 40 mEq K⁺ per h (2/3 KCl and 1/3 KPO₄) until K ≥ 3.3 mEq/L
- If serum K⁺ ≥ 5.5 mEq/L
  - Do not give K⁺ but check K⁺ every 2 h
- If serum K⁺ ≥ 3.3 but < 5.5 mEq/L, give 20-30 mEq K⁺ in each liter of IV fluid (2/3 as KCl and 1/3 as KPO₄) to keep serum K⁺ at 4-5 mEq/L

**Bicarbonate**
- Dilute NaHCO₃ (110 mmol) in 400 ml H₂O. Infuse at 200 ml/h.
- Dilute NaHCO₃ (50 mmol) in 200 ml H₂O. Infuse at 200 ml/h.
- If pH < 6.9, repeat HCO₃ admin. every 2 h until pH > 7.0, Monitor serum K⁺.

Fluid Therapy in DKA

Normal saline, 1-2 L over 1-2 h

Calculate corrected serum sodium

High or normal serum sodium:
½ NS at 250-500 mL/h

Low serum sodium:
NS at 250-500 mL/h

Glucose < 250 mg/dl:
Change to D5% NS or 1/2NS

ADA. Diabetes Care 26:S109-S117, 2009
### Suggested Initial Rate of Fluid Replacement*

<table>
<thead>
<tr>
<th>Hours</th>
<th>Volume</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st hour</td>
<td>1,000 – 2,000 mL</td>
</tr>
<tr>
<td>2nd hour</td>
<td>1,000 mL</td>
</tr>
<tr>
<td>3rd-5th hours</td>
<td>500 – 1,000 mL/hour</td>
</tr>
<tr>
<td>6th-12th hours</td>
<td>250 – 500 mL/hour</td>
</tr>
</tbody>
</table>

*average replacement after initial hemodynamic resuscitation with normal saline when indicated

Intravenous Insulin Therapy in DKA

I.V. Bolus: 0.1 U/kg body Wgt

I.V. drip: 0.1 U/kg/h body Wgt

Glucose < 250 mg/dl

I.V. drip: 0.05 – 0.1 U/kg/h
Until resolution of ketoacidosis
Is a Priming Dose of Insulin Necessary in a Low-Dose Insulin Protocol for the Treatment of Diabetic Ketoacidosis?

Adapted from Kitabchi et al, 31:2081-2085, 2008
Intravenous Insulin Therapy in DKA

- Bolus: 0.1 U/kg, + drip at 0.1 U/kg/h Normal saline
- Decrease drip at 0.05 U/kg/h
- Change to D5%1/2 NS
Potassium Replacement

\[ K^+ = > 5.5 \text{ mEq/l}; \text{ no supplemental is required} \]

\[ K^+ = 4 - 5 \text{ mEq/l}; 20 \text{ mEq/L of replacement fluid} \]

\[ K^+ = 3 - 4 \text{ mEq/l}; 40 \text{ mEq/L of replacement fluid} \]

If admission \( K^+ = <3 \text{ mEq/l} \) give 10-20 mEq/h until \( K^+ >3 \text{ mEq/l} \), then add 40 mEq/L to replacement fluid
Bicarbonate Administration

\[ \text{pH} \geq 7.0 \rightarrow \text{no bicarbonate} \]

\[ \text{pH} < 7.0 \text{ and bicarbonate} < 5 \text{ mEq/l} \rightarrow 44.6 \text{ mEq} \]
\[ \text{in 500 ml 0.45\% saline over 1 h until pH} \geq 7.0 \]

ADA. Diabetes Care 26:S109-S117, 2009
Phosphorus Administration

Not routinely recommended.

If serum phosphorus $< 1 \text{ mg/dl} \rightarrow 30\text{-}40 \text{ mmol K-Phos over 24 h.}$

Monitor serum calcium level.

ADA. Diabetes Care 26:S109-S117, 2009
Efficacy of Subcutaneous Insulin Lispro versus Continuous Intravenous Regular Insulin for the Treatment of Patients with Diabetic Ketoacidosis

**IV - Regular Insulin**
- Bolus: 0.1 u/kg, i.v. infusion
- 0.1 u/kg/hr until BG <250 mg
- Then, decrease insulin rate to 0.05 u/kg/h until resolution

**SQ - Lispro Insulin**
- Bolus: 0.2 u/kg/SQ, then
- 0.1 u/kg/hr until BG <250 mg
- Then, decrease s.q. insulin to 0.05 u/kg/h until resolution

Changes in Metabolic and Acid-Base Parameters During Treatment of DKA

Treatment of Diabetic Ketoacidosis With Subcutaneous Insulin Aspart

Guillermo E. Umpierrez, MD, FACP, FACE
Ruben Cuervo, MD
Ana Karabell, MD

Kashif Latif, MD
Amado X. Freire, MD, MFH
Abbas E. Kitabchi, PhD, MD

Umpierrez et al. Diabetes Care 27:1873-1878, 2004

Treatment of DKA with SQ aspart insulin every 1 and 2 hours versus IV regular insulin

Aspart SC-1hr (n=15):
Initial dose SC: 0.3 u/kg, then 0.1 U/kg/hr until BG<250 mg/dl
Thereafter, 0.05 U/kg SC-1hr until resolution of DKA

Aspart SC-2hr (n=15):
Initial dose SC: 0.3 U/kg, then 0.2 U/kg 1 hr later and Q 2 hr until BG<250 mg/dl. Then, 0.01 U/kg SC-2hr until resolution of DKA

IV Regular (n=15):
Initial dose IV: 0.1 unit/kg, then 0.1 U/kg/hr until BG<250 mg/dl.
Thereafter, 0.05 U/kg/il resolution of DKA
Changes in Metabolic Profile in Patients Treated with Aspart SC-1hr and SC-2hr, or with IV Regular Insulin

Umpierrez et al. Diabetes Care 27:1873-1878, 2004
# Response To Medical Treatment and Cost of Hospitalization

<table>
<thead>
<tr>
<th></th>
<th>Aspart SC-1hr</th>
<th>Aspart SC-2hr</th>
<th>Regular Intravenous</th>
</tr>
</thead>
<tbody>
<tr>
<td>L.O.S. (days)</td>
<td>3.4 ± 0.8</td>
<td>3.9 ± 1.3</td>
<td>4.5 ± 0.8</td>
</tr>
<tr>
<td>Duration of therapy until BG&lt;250 mg/dl (hr)</td>
<td>6.9 ± 1.1</td>
<td>6.1 ± 1</td>
<td>7.1 ± 1</td>
</tr>
<tr>
<td>Duration of therapy until Resolution of DKA (hr)</td>
<td>9.9 ± 0.7</td>
<td>10.7 ± 0.8</td>
<td>11 ± 0.7</td>
</tr>
<tr>
<td>Amount of insulin until BG&lt;250 mg/dl (units)</td>
<td>67 ± 4</td>
<td>65 ± 7</td>
<td>62 ± 8</td>
</tr>
<tr>
<td>Amount of insulin until resolution of DKA (units)</td>
<td>85 ± 4</td>
<td>94 ± 8</td>
<td>82 ± 9</td>
</tr>
<tr>
<td>Episodes of hypoglycemia</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Hospitalization Cost ($)</td>
<td>10,733 ± 2,017</td>
<td>10,173 ± 1,738</td>
<td>16,828 ± 2,563*</td>
</tr>
</tbody>
</table>

Data are means ± SE

* P < 0.01
Summary of studies comparing SC injections of insulin lispro vs continuous infusion of regular insulin in DKA patients

<table>
<thead>
<tr>
<th>Insulin arm</th>
<th>Studies in adult patients</th>
<th>Ersöz et al., 2006 [11] (Turkey)</th>
<th>Karoli et al., 2011 [12] (India)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Umpierrez et al., 2004 [9] (USA)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Lispro</td>
<td>Regular</td>
<td>Lispro</td>
</tr>
<tr>
<td>n</td>
<td>20</td>
<td>20</td>
<td>10</td>
</tr>
<tr>
<td>Age and diabetes duration, mean years (SD)</td>
<td>37 (12)</td>
<td>39 (14)</td>
<td>39 (20)</td>
</tr>
<tr>
<td>Time to resolution of DKA, mean (SD)</td>
<td>10 (3) h (P=0.87 vs regular)</td>
<td>11 (4) h</td>
<td>14.8 (7.0) h (NS vs regular)</td>
</tr>
<tr>
<td>Total insulin required, mean (SD)</td>
<td>84 (32) IU (P=0.22 vs regular)</td>
<td>98 (26) IU</td>
<td>61.7 (10.9) IU</td>
</tr>
<tr>
<td>Hospital days, mean (SD)</td>
<td>4 (2) (P=0.14 vs regular)</td>
<td>4 (1)</td>
<td>n.r.</td>
</tr>
<tr>
<td>Hypoglycaemia episodes [n (severity)]</td>
<td>1 (mild)</td>
<td>1 (mild)</td>
<td>0</td>
</tr>
<tr>
<td>Other safety data</td>
<td>No death</td>
<td>No deaths; no serious side-effects associated with treatment protocols in both groups</td>
<td>No deaths; no complications</td>
</tr>
</tbody>
</table>

Criteria for Resolution of Hyperglycemic Crises

- **Ketoacidosis**
  - Blood glucose <200 mg/dl
  - Two of the following criteria:
    - A serum bicarbonate level ≥15 mEq/l
    - A venous pH >7.3
    - A calculated anion gap of ≤12 mEq/l

- **HHS**
  - Normal osmolality
  - Normal mental status

Transition to Subcutaneous Insulin after Resolution of DKA

After Initial IV or SQ therapy
(pH>7.3, HCO3 >18, AG < 14)

Give SQ basal insulin 2 – 4 hours before stopping IV insulin

Start multi-dose insulin (basal bolus) regimen
• Insulin analogs are preferred over human insulin
  • Basal: glargine / detemir
  • Rapid-acting insulin analogs (lispro, aspart, glulisine)
• Analogs results in similar BG control, but less hypoglycemia than human insulin (15% vs. 41%)

Use ‘early’ glargine insulin during treatment of DKA may prevent rebound hyperglycemia during insulin infusion

Insulin Analogs versus Human Insulin in the Treatment of Patients with Diabetic Ketoacidosis

68 subjects with DKA

Open-labeled randomization

Insulin Analogs (n= 34)

IV Glulisine insulin therapy until resolution of DKA

Transition to SC glargine once daily and glulisine before meals

Human Insulin (n= 34)

IV regular insulin therapy until resolution of DKA

Transition to SC NPH and regular insulin twice daily

Umpierrez et al, Diabetes Care 32:1164–1169, 2009
<table>
<thead>
<tr>
<th>Blood Glucose (mg/dL)</th>
<th>0</th>
<th>200</th>
<th>400</th>
<th>600</th>
<th>800</th>
</tr>
</thead>
<tbody>
<tr>
<td>Admit</td>
<td>100</td>
<td>200</td>
<td>300</td>
<td>400</td>
<td>500</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>pH</th>
<th>7.10</th>
<th>7.15</th>
<th>7.20</th>
<th>7.25</th>
<th>7.30</th>
<th>7.35</th>
<th>7.40</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bicarbonate (mEq/L)</td>
<td>12</td>
<td>14</td>
<td>16</td>
<td>18</td>
<td>20</td>
<td>22</td>
<td></td>
</tr>
</tbody>
</table>

| Anion Gap (mEq/L)   | 12   | 14   | 16   | 18   | 20   | 22   |

**Glucose pH**

**Bicarbonate Anion Gap**

**Insulin Glulisine vs Regular Insulin**

Umpierrez et al, Diabetes Care 32:1164–1169, 2009
Mean Daily Glucose and Hypoglycemia During Transition to SC Insulin

<table>
<thead>
<tr>
<th></th>
<th>NPH/Regular</th>
<th>Glargine/Glulisine</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 1</td>
<td>188 ± 61</td>
<td>213 ± 76</td>
<td>0.234</td>
</tr>
<tr>
<td>Day 2</td>
<td>206 ± 71</td>
<td>220 ± 61</td>
<td>0.370</td>
</tr>
<tr>
<td>Day 3</td>
<td>207 ± 86</td>
<td>180 ± 80</td>
<td>0.417</td>
</tr>
<tr>
<td>Day 4</td>
<td>211 ± 63</td>
<td>158 ± 44</td>
<td>0.068</td>
</tr>
<tr>
<td>Day 5</td>
<td>190 ± 45</td>
<td>124 ± 41</td>
<td>0.068</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Hypoglycemia</th>
<th>NPH/Regular</th>
<th>Glargine/Glulisine</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with BG &lt;70 mg/dl, n (%)</td>
<td>14 (41)</td>
<td>5 (15)</td>
<td>0.03</td>
</tr>
<tr>
<td>Episodes of BG &lt;70 mg/dl, n</td>
<td>26</td>
<td>8</td>
<td>0.019</td>
</tr>
<tr>
<td>Patients with BG &lt;40 mg/dl, n (%)</td>
<td>2 (6)</td>
<td>1 (3)</td>
<td>NS</td>
</tr>
<tr>
<td>Episodes of BG &lt;40 mg/dl, n</td>
<td>2</td>
<td>1</td>
<td>NS</td>
</tr>
</tbody>
</table>

Data for glucose levels are means ± SD.
Summary

- DKA and HHS are common, serious and expensive complications in patients with type 1 and type 2 diabetes.

- Prevention of metabolic decompensation through patient education, strict surveillance of glucose homeostasis and aggressive diabetes management might reduce the high morbidity and mortality associated with DKA and HHS.

- Recent treatment protocols have improved clinical outcome in patients with DKA and HHS.
Thank you!

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