NON-COMPLICATED DIABETIC KETOACIDOSIS: SAFETY, COST AND EFFECTIVENESS OF ALTERNATIVE TREATMENT STRATEGIES TO INTENSIVE CARE UNIT MANAGEMENT

Brandi Addison, D.O.
Mentor: L. Maria Belalcazar, M.D.
Endocrinology Grand Rounds
Funding provided by Endocrine Fellows Foundation
BACKGROUND

- Diabetic Ketoacidosis (DKA) is a costly, acute and life threatening complication of diabetes

- Hospital admissions for DKA are increasing

- Adults account for over 80% of DKA hospital admissions

Mortality in adults with DKA is low after excluding individuals at the extremes of age or those who present with coma, hypotension or severe comorbidities.

The severity of illness of the average DKA patient admitted to the ICU is usually lower than that of other patients receiving ICU care.

DKA hospital admission are often the result of a new diagnosis of diabetes or due to discontinuation of insulin therapy in the absence of other underlying precipitating factors.
BACKGROUND

- DKA accounts for at least $1 of every $2 spent on medical care for patients with Type 1 diabetes who experience multiple episodes of DKA

- National cost burden from avoidable DKA hospitalizations, including those related to cases that could have been managed in the emergency department (ED), was estimated to reach $1,821 million in 2004

STANDARD TREATMENT

• Administration of insulin as a continuous intravenous infusion is generally preferred

• Patients with severe DKA should be managed with insulin infusion in the ICU setting.
Data from prospective cohort studies in the ICU and randomized trials comparing regular insulin infusion with subcutaneous insulin analogs for treatment of DKA suggest that a number of patients who present with DKA may be managed without insulin infusion and/or out of the ICU setting.
# INSULIN INFUSION VS. SC INSULIN IN NON-COMPLICATED PATIENTS WITH DKA

## Table 3—Response to medical treatment

<table>
<thead>
<tr>
<th></th>
<th>SC-1h</th>
<th>SC-2h</th>
<th>Regular IV insulin</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>n</strong></td>
<td>15</td>
<td>15</td>
<td>15</td>
</tr>
<tr>
<td><strong>Length of hospital stay (days)</strong></td>
<td><strong>3.4 ± 3</strong></td>
<td><strong>3.9 ± 5</strong></td>
<td><strong>4.5 ± 3</strong></td>
</tr>
<tr>
<td><strong>Duration of therapy until glucose &lt;13.8 mmol/l (h)</strong></td>
<td><strong>6.9 ± 4</strong></td>
<td><strong>6.1 ± 4</strong></td>
<td><strong>7.1 ± 5</strong></td>
</tr>
<tr>
<td><strong>Duration of therapy until resolution of DKA (h)</strong></td>
<td><strong>10 ± 3</strong></td>
<td><strong>10.7 ± 3</strong></td>
<td><strong>11 ± 3</strong></td>
</tr>
<tr>
<td><strong>Amount of insulin until glucose &lt;13.8 mmol/l (units)</strong></td>
<td><strong>67 ± 37</strong></td>
<td><strong>65 ± 26</strong></td>
<td><strong>62 ± 28</strong></td>
</tr>
<tr>
<td><strong>Amount of insulin until resolution of DKA (units)</strong></td>
<td><strong>85 ± 33</strong></td>
<td><strong>94 ± 32</strong></td>
<td><strong>82 ± 28</strong></td>
</tr>
<tr>
<td><strong>Episodes of hypoglycemia</strong></td>
<td><strong>1</strong></td>
<td><strong>1</strong></td>
<td><strong>1</strong></td>
</tr>
</tbody>
</table>

Data are means ± SD.
CLASSIFICATION OF DKA

- **Non-complicated DKA**: No underlying precipitating factor other than insulin treatment cessation or new onset of diabetes in a patient without major co-morbidities.

- **Complicated DKA**: Precipitating factor or severe co-morbidities present, or pregnancy or extremes of age (<18 and >65).
### Classification of DKA

#### Severity of DKA

<table>
<thead>
<tr>
<th>DKA</th>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma glucose (mg/dl)</td>
<td>&gt;250</td>
<td>&gt;250</td>
<td>&gt;250</td>
</tr>
<tr>
<td>Arterial pH</td>
<td>7.25–7.30</td>
<td>7.00–&lt;7.24</td>
<td>&lt;7.00</td>
</tr>
<tr>
<td>Serum bicarbonate (mEq/l)</td>
<td>15–18</td>
<td>10–&lt;15</td>
<td>&lt;10</td>
</tr>
<tr>
<td>Urine ketones*</td>
<td>Positive</td>
<td>Positive</td>
<td>Positive</td>
</tr>
<tr>
<td>Serum ketones*</td>
<td>Positive</td>
<td>Positive</td>
<td>Positive</td>
</tr>
<tr>
<td>Effective serum osmolality</td>
<td>Variable</td>
<td>Variable</td>
<td>Variable</td>
</tr>
<tr>
<td>(mOsm/kg)*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anion gap†</td>
<td>&gt;10</td>
<td>&gt;12</td>
<td>&gt;12</td>
</tr>
<tr>
<td>Alteration in sensoria</td>
<td>Alert</td>
<td>Alert/drowsy</td>
<td>Stupor/coma</td>
</tr>
<tr>
<td>or mental obtundation</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Nitroprusside reaction method; †calculation: 2[measured Na (mEq/l)] + glucose (mg/dl)/18; ‡calculation: \((Na^+) - (Cl^-) - \text{HCO}_3^-\) (mEq/l). See text for details.

Kitabchi et al, Diabetes Care 2009.
PRELIMINARY DATA:
RETROSPECTIVE STUDY

• 214 adult cases of DKA admitted to John Sealy Hospital from October 2010 to February 2014 were reviewed

• Patients who received insulin infusion in the ED and were deemed to have non-complicated DKA were analyzed (n = 48)
### Preliminary Data: Sample Eligibility

<table>
<thead>
<tr>
<th>Inclusion</th>
<th>Exclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ages 18-65 y/o</td>
<td>Hypotension (&lt;90/60 mmg/Hg)</td>
</tr>
<tr>
<td>Etiology include: non-complicated/omission of insulin therapy or new onset of diabetes</td>
<td>Stupor or Coma</td>
</tr>
<tr>
<td></td>
<td>Sepsis, pregnancy, history of CHF, CKD</td>
</tr>
<tr>
<td></td>
<td>Stage 3 or more</td>
</tr>
<tr>
<td></td>
<td>Cirrhosis</td>
</tr>
<tr>
<td></td>
<td>Organ transplantation on immunosuppressive therapy</td>
</tr>
<tr>
<td></td>
<td>Transfer from outside hospital or discharged against medical advice</td>
</tr>
</tbody>
</table>
Characteristics of Admission and Outcomes of Interest for Non-Complicated DKA Cases Treated with Initial Insulin Infusion and Admitted to the ICU or to the General Medicine Floor

<table>
<thead>
<tr>
<th>Characteristics on Admission</th>
<th>Admitted to ICU, n=39</th>
<th>Admitted to General Floor, n=9</th>
<th>p-value §</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>38.6 (12.6)</td>
<td>28.1 (11.4)</td>
<td>0.095</td>
</tr>
<tr>
<td>Charlson Co-morbidity Index</td>
<td>1.64 (0.99)</td>
<td>1.22 (0.44)</td>
<td>0.31</td>
</tr>
<tr>
<td>Glucose (mg/dL)</td>
<td>593.3 (188.6)</td>
<td>696.8 (277.3)</td>
<td>0.13</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Outcomes of Interest</th>
<th>Admitted to ICU, n=39</th>
<th>Admitted to General Floor, n=9</th>
<th>p-value §</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time for Anion Gap Closure (hours)*</td>
<td>10.54 (6.37)</td>
<td>5.93 (2.51)</td>
<td>0.015</td>
</tr>
<tr>
<td>Cases with Reopening of Gap, %</td>
<td>13.6</td>
<td>11.1</td>
<td>1.0 §§</td>
</tr>
<tr>
<td>Cases with Hypoglycemia (FSBG &lt;50 mg/dL), %</td>
<td>7.8</td>
<td>11.1</td>
<td>1.0 §§</td>
</tr>
<tr>
<td>Length of Stay Observed (Days)†</td>
<td>2.66 (1.08)</td>
<td>1.78 (1.09)</td>
<td>0.025</td>
</tr>
<tr>
<td>Total Direct Costs Corrected to 2014 U.S. Dollars‡</td>
<td>$6,434.35</td>
<td>$3,688.58</td>
<td>0.001</td>
</tr>
</tbody>
</table>

* Calculated from initial electrolyte panel on admission to time of first electrolyte panel showing gap closure.
† Determined by United Health Consortium definition (number of days with midnight bed occupancy).
‡ Corrected to 2014 U.S. dollars using the CPI inflation calculator from the U.S. Bureau of Labor Statistics
§ Estimated by the Mann-Whitney test with correction for ties (2-tailed)
§§ Fisher’s exact test statistic, significant at p <0.05.
HYPOTHESIS

Adult patients with non-complicated DKA of mild to moderate severity may be safely and effectively treated in the ED or in the inpatient general medicine wards with similar clinical outcomes as those treated in the ICU, with the additional benefit of a reduction in direct costs.
AIMS

1. To compare the efficacy and safety of two non-ICU approaches for the care of DKA with that of usual ICU care

2. To compare direct cost related to the management of non-complicated DKA of mild to moderate severity resulting from each of three approaches:
   a. General ward protocol with every 2 hour SC insulin aspart
   b) An ED/RDU-only approach with continuous regular insulin infusion
   c) An usual ICU care algorithm with continuous intravenous regular insulin infusion
METHODS

• Non-blinded randomized clinical trial with three treatment arms for the management of uncomplicated adult DKA

• Efficacy, safety and cost outcomes analyzed across treatment arms
  Efficacy: Time to clearance of gap (anion gap <12)
  Safety: Absence of recurrent DKA and severe hypoglycemia
  Cost: Direct costs using hospital’s financial database (EPSI software)
## ELIGIBILITY CRITERIA

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<td>Stupor or Coma</td>
</tr>
<tr>
<td>Presenting Glucose ≤ 600 mg/dL</td>
<td>Sepsis, pregnancy, history of CHF, CKD ≥ Stage 3</td>
</tr>
<tr>
<td></td>
<td>Cirrhosis</td>
</tr>
<tr>
<td></td>
<td>Organ transplantation on immunosuppressive therapy</td>
</tr>
<tr>
<td></td>
<td>Transfer</td>
</tr>
</tbody>
</table>
Patient presents with DKA to ER

Initial Evaluation

Start IVF, insulin infusion and replacement of electrolytes

Complicated/High Risk

- Age < 18 or > 65 yrs.
- Respiratory distress
- CKD ≥ Stage 3
- Liver dx.
- Infection
- MI/Stroke
- H/o CHF Stage III/IV
- Shock
- Organ transplantation
- Pregnancy
- Pancreatitis
- Stupor/Coma

ICU

Excluded

Reassessment

- CO2 < 10
- And/or
- Glucose reduction < 20%
- And/or
- Glucose > 600

Non-Complicated Low-to-Moderate Risk DKA

Randomized

Floor Admission

Subcutaneous Insulin Aspart Protocol until resolution of DKA

Emergency Room

Regular Insulin Intravenous Infusion until Resolution of DKA

ICU

Regular Insulin Intravenous Infusion until Resolution of DKA
Patient Received to Floor from ER

FSBG upon patient’s arrival to the floor

Glucose ≤ 200 mg/dL
- Change IV fluid to D5 1/2NS
- SC aspart 0.1 unit/kg every 2 hours with goal glucose of 150-200 mg/dL until DKA resolved
- BMP & FSBG every 2 hours

Glucose >200 mg/DL
- SC Aspart 0.2 units/kg every 2 hours until glucose < 200 mg/dL
- Glucose ≤ 200 mg/dL

Notify House Office (NHO)
- If potassium is < 4 mEq/L
- If potassium is ≥ 5.3 mEq/L
- Anion gap ≥ 12

DKA resolution defined:
1. Anion Gap closed (≤12)
2. HCO₃ ≥ 15
3. Glucose ≤ 200 mg/dL

H.O.: Hold insulin if K⁺ < 3.3
Main outcomes for the study include:

- Time to resolution of DKA (hours)
- Direct costs (U.S. dollars)
- Length of stay (hours)
- Frequency of hypoglycemia (%)
- DKA relapse (% of cases with gap reopening)
Comparisons between groups will be made via One-way Analysis of Variance with Tukey’s test to identify where specific differences lie, non-parametric variables will be subject to Kruskal-Wallis testing or Chi-square testing, as appropriate. Statistical significance will be defined by $p < 0.05$. 
**Power estimates:**

- Estimation of sample size was based on preliminary data

- We estimated the following sample size per group to detect at least a 20% difference between each non-ICU treatment arm and the ICU arm with an alpha level of ≤0.05 and a power of 80% for the following outcomes:
  
  a) Direct costs: 12 subjects per group
  
  b) Time to clearance of anion gap: 20 subjects per group
  
  c) Length of stay: 32 subjects per group.

- A review of the number of John Sealy Hospital ED visits with any diagnosis of DKA revealed significant growth in the number of ED visits with a diagnosis of DKA.
STUDY IMPLEMENTATION

- May 2015: ED/RDU Physicians and RDU/9D Nurses Educated
- 7/2015: IM Residents Educated on Floor Protocol
- 9/2015: Study Enrollment Started
- 1/2016: Meeting with heads of nursing, RDU and ED
- 2-3/2016: Study Inclusion modified, Update meeting with ED nurses and physicians
- 4/2016: Data analyzed, QI project
- Ongoing
INTERIM ANALYSIS JANUARY 2016

13 Patients Met diagnoses of Non-complicated DKA

- 2 Patients included in Study as of 1/2016

11 Patients Excluded from Study

- 2 Patients Met criteria but not included by ED
- 3 Patients Excluded Due to 2-hr Post-infusion CO2 <10 with insulin infusion administration errors
- 2 Patients with Low Risk DKA but excluded from protocol due to glucose on arrival >500 mg/dL
- 4 Patients with low risk DKA excluded due to transfer status
PROTOCOL MODIFICATIONS BASED ON JANUARY 2016 FINDINGS

13 Patients Met diagnoses of Non-complicated DKA

2 Patients Included in Study as of 1/2016

11 Patients Excluded from Study

2 Patients Met criteria but not included by ED

5 Patients Excluded due to 2-hr Post-infusion CO2 <10 with insulin infusion administration errors

2 Patients with Low Risk DKA but excluded from protocol due to glucose on arrival >600 mg/dL

4 Patients with low risk DKA excluded due to transfer status

Education

Adjustments made to insulin initiation in DKA order set

Exclusion criteria changed to <700 mg/dL
FREQUENCY OF ERRORS IN PROCESSES OF CARE AND DECISION-MAKING DURING MANAGEMENT OF DKA
CHANGES TO DKA ORDER SET

- Removal of required insulin bolus to avoid duplicate doses

- Insulin initiation rate on electronic DKA protocol was changed to default directly to 1 unit of insulin /kg/hour

- Rate of fluid with dextrose was corrected to default to rates ≥150 cc/hr
## Preliminary Baseline Characteristic

<table>
<thead>
<tr>
<th></th>
<th>MICU</th>
<th>RDU</th>
<th>Floor</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>n</strong></td>
<td>1</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td><strong>Age (years)</strong></td>
<td>21</td>
<td>34.6</td>
<td>38</td>
</tr>
<tr>
<td><strong>Females (n)</strong></td>
<td>1</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td><strong>BMI (kg/m²)</strong></td>
<td>22.9</td>
<td>23.42</td>
<td>24.5</td>
</tr>
<tr>
<td><strong>HbA1C (%)</strong></td>
<td>12.9</td>
<td>10.7</td>
<td>9.3*</td>
</tr>
<tr>
<td><strong>Admission glucose (mg/dL)</strong></td>
<td>298</td>
<td>418</td>
<td>504</td>
</tr>
<tr>
<td><strong>Admission CO²</strong></td>
<td>12</td>
<td>15.3</td>
<td>11.5</td>
</tr>
<tr>
<td><strong>Admission anion gap</strong></td>
<td>24</td>
<td>22.6</td>
<td>31.5</td>
</tr>
</tbody>
</table>

Data shown as mean ± standard deviation. *n=1
## PRELIMINARY RESULTS

<table>
<thead>
<tr>
<th></th>
<th>MICU</th>
<th>RDU</th>
<th>Floor</th>
</tr>
</thead>
<tbody>
<tr>
<td>( n )</td>
<td>1</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>*Time to closure of anion gap (minutes)</td>
<td>461</td>
<td>276</td>
<td>1089</td>
</tr>
<tr>
<td>Recurrence of DKA (n)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>( ^{\circ} ) Hypoglycemia (n)</td>
<td>1</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Length of Stay (days)</td>
<td>3</td>
<td>2.6</td>
<td>2</td>
</tr>
</tbody>
</table>

*Time from initiation of insulin to bmp
\( ^{\circ} \) Occurrence within primary therapy group
Environment
- Imbalance between efficiency and quality
- Disintegration of care
- Social stigma of diabetes

Support Tools
- EMR
- Protocols

Physicians
- Gaps in knowledge
- Decrease familiarity with complex protocol
- Competing priorities
- Communication fragmentation within team
- Deficiency in initial management of DKA

Patient
- Decrease participation in care while hospitalized

Pharmacy
- Lack of insulin availability in ED

Nursing
- Deficiencies in knowledge
- Decrease familiarity with protocol
- Communication gaps
- Multiple priorities
The frequency of appropriate initiation of insulin therapy increased from 28% to 100% by Q4.
IMPROVEMENT IN TIME TO INITIATION OF INSULIN

Time from ED admission to start of insulin infusion decreased from 370 minutes to 127 minutes by Q4
The randomized prospective study for non-complicated DKA is ongoing. Current sample is too small to draw any conclusions in relation to outcomes.

Interventions to improve DKA management are effective in improving outcomes when combining an electronic health record order set with educational strategies that incorporate team feedback and process flow analysis.
FUTURE DIRECTION

• To increase inclusion of eligible subjects by encouraging participation of ED providers
  • Periodic protocol progress reports and discussion sessions with ED team
  • Involvement of rotating ED medicine intern/residents
  • On-going educational efforts for nurses and providers

• To consider eliminating the floor location and limit the study to ED/RDU and ICU, maintaining a randomized sc and iv component for patients admitted to the ED/RDU
THANK YOU
SPECIAL THANKS

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- ED Nursing and Physicians
- RDU Nursing and Physicians