Algorithm:

1. **Patient presents with known Diabetes Mellitus, suspected new-onset Diabetes Mellitus, or documented glucose > 200**
   - **Is patient exhibiting critical organ instability (shock, respiratory failure, cerebral edema, renal failure, etc.)?**
     - **Yes**
       - Patient receives appropriate stabilization care
     - **No**
       - **Nursing action items:**
         - Obtain weight (in kg)
         - Place on CR and O₂ monitors
         - Obtain and document POC chemistries
           - Glucose
           - Beta-hydroxybutyrate (BOHB) (Ketones)
         - Assess vital signs every 2 hours
         - Assess neurologic status at least every 1 hr
         - Measure I & O

2. **Is patient exhibiting critical organ instability?**
   - **Yes**
     - Patient receives appropriate stabilization care
   - **No**
     - **Is POC BOHB (ketones) ≥ 3.3 mmol/L?**
       - **Yes**
         - Initiate DKA CPG PowerPlan Subphase for BOHB < 3.3 mmol/L and call Endocrine on Call for disposition
       - **No**
         - **Is patient a new or known diabetic?**
           - **Known**
             - **Is patient currently using an insulin pump?**
               - **Yes**
                 - Patients who have insulin pumps should be disconnected from the pump and infusion site removed until a Diabetes Team member is available to assess the equipment.
               - **No**
                 - Initiate DKA CPG Powerplan Subphase for BOHB ≥ 3.3 mmol/L
               - **New**
                 - **Initiate DKA CPG Powerplan Subphase for BOHB ≥ 3.3 mmol/L**

3. **Call Endocrine on Call**
4. **Admit Patient**

**Notes:**
- Patients who have insulin pumps should be disconnected from the pump and infusion site removed until a Diabetes Team member is available to assess the equipment.
**Insulin Drip Guidelines**

Patients who have insulin pumps should be disconnected from the pump and infusion site removed until a Diabetes Team member is available to assess the equipment.

**Initiate Insulin Drip**
- 100 Units of Regular insulin in 100 mL Normal Saline
- Administer Regular insulin 0.1 Units/kg/hr

**Administer Maintenance IV Fluids**
- IV Rate is 1.5 maintenance fluids
- Dextrose concentration is determined by patient’s glucose level using the DKA Titration Schedule
- Text page physician to inform of titration schedule changes and associated blood glucose
- Dextrose concentration is developed from:
  - D10 NS with 20 mEq K Acetate/L and 20 mEq K Phosphate/L
  - Normal saline with 20 mEq K Acetate/L and 20 mEq K Phosphate/L
  - Use caution in replacing potassium in patients with hyperkalemia or renal failure by making sure these patients are able to void prior to initiation of therapy

**Monitor BMP every 4 hours**
- Obtain the following labs if not obtained previously:
  - HgA1c
  - Insulin Antibodies
  - GAD Antibodies
  - Islet Cell AB-512
  - C Peptide
  - Znc Transporter 8 Auto Ab
  - Celiac Diagnostic Algorithm
  - TSH Algorithm

**Epidemiology:**

In most western countries, type 1 diabetes accounts for over 90% of childhood and adolescent diabetes, although less than half of individuals with type 1 diabetes are diagnosed before the age of 15 years. Type 2 diabetes is becoming more common in adolescents, particularly in the peri-pubertal period, and accounts for a significant proportion of youth onset diabetes in certain at risk populations (International Diabetes Federation, 2010).

Type 1 diabetes incidence varies greatly between different countries, within countries, and between different ethnic populations. Annual incidence rate for childhood type 1 diabetes in the United States is 19 per 100,000. There has been a well-documented rise in the incidence within the United States, with a disproportionately greater increase in those under the age of 5 years. A seasonal variation in the presentation of new cases is well described, with the peak being in the winter months (International Diabetes Federation, 2010).

Susceptibility to autoimmune type 1 diabetes is associated with multiple genetic loci. HLA genes having the strongest known association and account for approximately 40% of familial clustering of type 1 diabetes.
Initial April 29, 2013; Revisions: 4/13; 1/14; 9/14; 12/14; 12/15, 12/16

Linkage to specific combinations of alleles at the DRB1, DQA1 and DQB1 loci, with both susceptible or protective haplotypes (International Diabetes Federation, 2010).

The environmental triggers (chemical and/or viral) which initiate pancreatic beta cell destruction remain largely unknown, but the process usually begins months to years before the manifestation of clinical symptoms. Enterovirus infection has been associated with development of diabetes associated autoantibodies in some populations and enteroviruses have been detected in the islets of individuals with diabetes (International Diabetes Federation, 2010).

Despite familial aggregation, which accounts for approximately 10% of cases of type 1 diabetes, there is no recognizable pattern of inheritance. The risk of diabetes to an identical twin of a patient with type 1 diabetes is about 36%; for a sibling the risk is approximately 4% by age 20 years and 9.6% by age 60 years; compared with 0.5% for the general population. Type 1 diabetes is 2-3 times more common in the offspring of diabetic men (3.6–8.5%) compared with diabetic women (1.3–3.6%) (International Diabetes Federation, 2010).

**Objective of Guideline:** The objective of this guideline, besides standardizing care and the benefits associated with care standardization, is to correct dehydration and acidosis, reverse ketosis, restore blood glucose to near normal, avoid complications of therapy (including cerebral edema), and identify and treat any precipitating event(s) to prevent future DKA.

**Target Users:** Physicians, nurse practitioners and staff nurses caring for children, with DKA, in Emergency Departments, outpatient settings and inpatient settings. (Note: Endocrine Service is available for consultation.)

**Guideline Inclusion Criteria:** Patient is a known or presumed diabetic with a point of care (POC) β-hydroxybutyrate of ≥ 3.3 mmol/L.

**Guideline Exclusion Criteria:** Hyperglycemia without acidosis.

**Clinical Questions Answered by Guideline:**
1. In the pediatric patient presenting with DKA which route (intravenous or subcutaneous) of insulin therapy is most efficacious in resolving DKA?
2. In the pediatric patient presenting with DKA is serum ketone point of care testing as accurate as a serum ketone testing?

**Differential Diagnosis:** Three key features of diabetic acidosis are hyperglycemia, ketosis, and dehydration. The conditions that cause these metabolic abnormalities overlap. The primary differential diagnosis for hyperglycemia is hyperosmolar hyperglycemic state. Abdominal pain may be a symptom of ketoacidosis or part of the inciting cause of DKA, such as appendicitis or cholecystitis. If surgery is necessary, the timing needs to be individualized for each patient with input from a surgical consultant (Trachtenbarg, 2005). No patient with hyperglycemia should go to the OR prior to Endocrine consultation.
Practice Recommendations: are based on the degree of acidosis defined as:

- **Severe:** bicarbonate < 5mmol/L, venous pH < 7.1
- **Moderate:** bicarbonate 5-10mmol/L, venous pH < 7.2
- **Mild:** bicarbonate 11-15mmol/L, venous pH < 7.3

**Diagnostic evaluation:**

1. **History:**
   - Family history of diabetes
   - Polyuria, polydipsia, polyphagia
   - Weight loss
   - Abdominal pain, nausea, vomiting
   - Mental status
   - Concurrent illness or infections
   - Inadequate insulin therapy in a known diabetic such as non-adherence or inappropriate dosing or interruption of insulin delivery from insulin pump
   - Steroid use
   - Age 3 years or less (increased risk for cerebral edema)

2. **Physical Exam (PE)/Monitoring:** The degree of acidosis (mild, moderate, severe) is an important marker for determining the severity of DKA and is a risk factor for cerebral edema. PE/monitoring include:
   - Assess dehydration - in DKA patients clinical assessment of dehydration can be imprecise. May assume 5-10% dehydration in moderate to severe DKA.
   - Assess level of consciousness
   - Assess for Kussmaul respirations – deep labored breathing

**Mild DKA**

- Heart rate, respiratory rate, and blood pressure every 4 hours until resolution of DKA (normalization of bicarbonate or venous pH), then per routine
- Input and output should be accurately measured

**Moderate/Severe DKA**

- Hourly heart rate, respiratory rate, and blood pressure (CR/sat monitors)
- Hourly fluid input and output measured
- Hourly neurologic assessment for warning signs of cerebral edema (headache, inappropriate slowing of heart rate, recurrent vomiting, change in neurologic status, rising blood pressure, decreased oxygen saturation).

**Diagnostics:**

**DKA**

- Obtain blood β-hydroxybutyrate immediately by POC meter. Based on the correlation study accomplished at Children’s Mercy (Ferguson et al., 2015) the ROC and the subsequent bootstrap analysis validated that a POC β-hydroxybutyrate of ≥ 3.3 indicates that the patient is in DKA.
- Hourly capillary blood glucose for patients on insulin drips and those receiving every 2 hour correction doses of subcutaneous insulin.
- BMP initially will assist emergency department clinicians in determining patient placement, subsequent BMP should be obtained every 4 hours.
Criteria for Floor and PICU admission stratified by age:

For Children ≤ 5 years of age

Criteria for 6 Henson Admission:
- Bicarbonate level > 10

Criteria for PICU Admission:
- Patients at significant risk for cerebral edema (see risk factors under complications: cerebral edema section of the synopsis) or
- Neurologic signs that might indicate cerebral edema or
- Bicarbonate level ≤ 10 mmol/L or
- BUN level significantly elevated.

For Children > 5 years of age

Criteria for 6 Henson Admission:
- Bicarbonate level > 5

Criteria for PICU Admission:
- Patients at significant risk for cerebral edema (see risk factors under complications: cerebral edema section of the synopsis) or
- Neurologic signs that might indicate cerebral edema or
- Bicarbonate level < 5 mmol/L

Treatment:

Moderate/Severe DKA

1. If patient is exhibiting critical organ failure (such as shock, respiratory failure, cerebral edema, etc.) follow PALS resuscitation guideline until stable.

2. Fluid and electrolyte replacement
   - Administer 10 ml/kg IV bolus of isotonic crystalloid over 1 hour (maximum bolus 1 liter). In severe dehydration a second fluid bolus of 10 ml/kg over 1 hour may be necessary. After the fluid bolus is administered begin 1.5 maintenance IV fluid (IVF) of normal saline.
   - Patients in DKA are inherently potassium and phosphorus depleted and will require replacement therapy regardless of current levels of electrolytes on lab. If hypokalemic at presentation, begin potassium therapy at time of initial volume expansion. Use caution in replacing potassium in patients with hyperkalemia or renal failure. Verify these patients are able to void prior to initiation of therapy. Contact the Endocrinologist on Call.
   - 1.5 maintenance fluids should be changed to Normal Saline (NS) with 20 mEq/L K acetate and 20 mEq/L K Phosphate as soon as available.
     - NS with 20 mEq K Acetate/L and 20 mEq of K Phosphate/L will be replaced with NS with 40 mEq of KCl/L
   - An additional IVF bag of D10 NS , 20 mEq/L K Acetate and 20 mEq/L K Phosphate should be ordered to the bedside for use as indicated below under “continuous IV insulin infusion” and/or “rapid acting subcutaneous insulin”.
     - D10 NS with 20 mEq K Acetate/L and 20 mEq of K Phosphate/L will be replaced with D10 NS with 40 mEq KCl/L
   - NPO.
3. Insulin initiation
   a. Basal subcutaneous insulin: Basal insulin should be given as soon as possible and may be administered while a patient is on continuous IV insulin infusion.
      - New diabetic – administer subcutaneous insulin glargine:
        - 0-4 years = 0.2 units/kg
        - 5-7 years = 0.3 units/kg
        - 8-10 years = 0.4 units/kg
        - 11 and up = 0.5 units/kg
      - Known diabetic – if patient is connected to an insulin pump disconnect the pump and administer glargine insulin based on above “new diabetic” recommendations. If patient is on injections administer home dose of glargine or use above “new diabetic” recommendations if home dose is unknown.
   b. Continuous IV insulin infusion:
      - 0.1 units/kg/hour of IV regular insulin
      - Monitor capillary blood glucose hourly. Follow the titration table below and adjust NS with additives and D₁₀ NS with additives fluids based on blood glucose.

<table>
<thead>
<tr>
<th>Plasma Glucose</th>
<th>NS w/ additives</th>
<th>D₁₀ NS w/ additives</th>
<th>Final Dextrose Concentration</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 250</td>
<td>100%</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>200-249</td>
<td>50%</td>
<td>50%</td>
<td>5%</td>
</tr>
<tr>
<td>150-199</td>
<td>25%</td>
<td>75%</td>
<td>7.5%</td>
</tr>
<tr>
<td>&lt; 150</td>
<td>0%</td>
<td>100%</td>
<td>10%</td>
</tr>
</tbody>
</table>

- If blood glucose drops between 80 to 99 mg/dL decrease IV insulin to 0.05 units/kg/hour and contact the Supervising Physician.
- If blood glucose drops < 80 mg/dL stop IV insulin, follow hypoglycemia protocol located under supportive documents, and contact Supervising Physician.
- Continue IV insulin infusion until bicarbonate level is >17 mmol/L, anion gap is normalized, or blood ketones are <0.6 mmol/L. Revision added 1/27/14: Upon discontinuing IV insulin, discontinue D₁₀NS with additives if patient’s blood glucose is stable.
c. Rapid acting subcutaneous insulin:

- Rapid acting insulin (lispro, aspart, glulisine) may be administered in moderate to severe DKA if unable to administer continuous IV insulin.
- Rapid acting insulin should be administered 0.2 units/kg subcutaneously every 2 hours.
- Monitor capillary blood glucose hourly. Follow the titration table below and adjust NS with additives and D₁₀ NS with additives fluids based on blood glucose.

<table>
<thead>
<tr>
<th>Plasma Glucose</th>
<th>NS w/ additives</th>
<th>D₁₀ NS w/ additives</th>
<th>Final Dextrose Concentration</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 250</td>
<td>100%</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>200-249</td>
<td>50%</td>
<td>50%</td>
<td>5%</td>
</tr>
<tr>
<td>150-199</td>
<td>25%</td>
<td>75%</td>
<td>7.5%</td>
</tr>
<tr>
<td>&lt; 150</td>
<td>0%</td>
<td>100%</td>
<td>10%</td>
</tr>
</tbody>
</table>

- If blood glucose drops between 80 to 99 mg/dL DO NOT administer subcutaneous insulin without contacting the Supervising Physician.
- If blood glucose drops < 80 mg/dL follow hypoglycemic protocol located under supportive documents and contact Supervising Physician. Do not administer additional subcutaneous rapid acting insulin until speaking with the Supervising Physician.
- Continue every 2 hour subcutaneous rapid acting insulin until bicarbonate level is > 17mmol/L, anion gap is normalized, or blood ketones <0.6mmol/L. **Revision added 1/27/14:** Upon discontinuing IV insulin, discontinue D₁₀NS with additives if patient’s blood glucose is stable.
Mild DKA

1. Fluid and electrolyte replacement
   - Administer 10 ml/kg IV bolus of isotonic crystalloid over 1 hour (maximum bolus 1 liter) followed by 1.5 maintenance fluids of normal saline (International Diabetes Federation, 2010 & Wolfsdorf, Glaser, & Sperling, 2006).
   - Patients in DKA are inherently potassium and phosphorus depleted and will require replacement therapy regardless of current levels of electrolytes on lab. If hypokalemic at presentation, begin potassium therapy at time of initial volume expansion. Use caution in replacing potassium in patients with hyperkalemia or renal failure. Verify these patients are able to void prior to initiation of therapy, and contact the Endocrinologist on Call.
   - 1.5 maintenance fluids should be changed to NS with 20 mEq/L K Acetate and 20 mEq/L K Phosphate as soon as available.
     - NS with 20 mEq K Acetate/L and 20 mEq of K Phosphate/L will be replaced with NS with 40 mEq of KCl/L
   - An additional IVF bag of D10 NS, 20 mEq/L K Acetate and 20 mEq/L K Phosphate should be ordered to the bedside for use as indicated below under “continuous IV insulin infusion” and/or “rapid acting subcutaneous insulin”.
     - D10 NS with 20 mEq K Acetate/L and 20 mEq of K Phosphate/L will be replaced with D10 NS with 40 mEq KCl/L
   - NPO with ice chips initially. If patient clinically appears well and would like to eat, contact endocrinologist on call for insulin to carbohydrate ratio.

2. Insulin initiation
   a. Basal subcutaneous insulin:
      - New diabetic – administer subcutaneous insulin glargine:
        o 0-4 years = 0.2 units/kg
        o 5-7 years = 0.3 units/kg
        o 8-10 years = 0.4 units/kg
        o 11 and up = 0.5 units/kg
      - Known diabetic – if patient is connected to an insulin pump disconnect the pump and administer glargine insulin based on above “new diabetic” recommendations. If patient is on injections administer home dose of glargine or use “new diabetic” recommendations if home dose is unknown.
b. Continuous IV insulin infusion:
- Preferred treatment for mild DKA is IV regular insulin. IV insulin may be utilized on the medical/surgical floors for mild DKA. However, staffing and bed availability may make this option unavailable in which case rapid acting subcutaneous insulin is an effective alternative.
- 0.1 units/kg/hour of IV regular insulin
- Monitor capillary blood glucose hourly. Follow the titration table below and adjust NS with additives and D₁₀ NS with additives fluids based on blood glucose.

### DKA Titration Schedule

<table>
<thead>
<tr>
<th>Plasma Glucose</th>
<th>BAG 1</th>
<th>BAG 2</th>
<th>Final Dextrose Concentration</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 250</td>
<td>100%</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>200-249</td>
<td>50%</td>
<td>50%</td>
<td>5%</td>
</tr>
<tr>
<td>150-199</td>
<td>25%</td>
<td>75%</td>
<td>7.5%</td>
</tr>
<tr>
<td>&lt;150</td>
<td>0%</td>
<td>100%</td>
<td>10%</td>
</tr>
</tbody>
</table>

- If blood glucose drops between 80 to 99 mg/dL, decrease IV insulin to 0.05 units/kg/hour, and contact Supervising Physician.
- If blood glucose drops < 80 mg/dL, stop IV insulin, follow hypoglycemia protocol located under supportive documents, and contact Supervising Physician.
- Continue IV insulin infusion until bicarbonate level is >17mmol/L, anion gap is normalized, or blood ketones <0.6mmol/L. Revision added 1/27/14: Upon discontinuing IV insulin, discontinue D10NS with additives if patient’s blood glucose is stable.

### Rapid acting subcutaneous insulin:

- Rapid acting insulin (lispro, aspart, glulisine) should be administered 0.2 units/kg subcutaneously every 2 hours
- Monitor capillary blood glucose hourly. Follow the titration table below and adjust NS with additives and D₁₀ NS with additives fluids based on blood glucose.

### DKA Titration Schedule

<table>
<thead>
<tr>
<th>Plasma Glucose</th>
<th>BAG 1</th>
<th>BAG 2</th>
<th>Final Dextrose Concentration</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 250</td>
<td>100%</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>200-249</td>
<td>50%</td>
<td>50%</td>
<td>5%</td>
</tr>
<tr>
<td>150-199</td>
<td>25%</td>
<td>75%</td>
<td>7.5%</td>
</tr>
<tr>
<td>&lt;150</td>
<td>0%</td>
<td>100%</td>
<td>10%</td>
</tr>
</tbody>
</table>

- If blood glucose drops < 80 mg/dL follow hypoglycemic protocol located under supportive documents and contact Supervising Physician. Do not administer additional subcutaneous insulin until speaking with the Supervising Physician.
- Continue every 2 hour subcutaneous rapid acting insulin until bicarbonate level is > 17mmol/L, anion gap is normalized, or blood ketones < 0.6mmol/L.
Complications of DKA

1. Cerebral edema
   - Those at increased risk include younger age, new onset diabetes, and longer duration of symptoms.
   - Additional risk factors at diagnosis or during treatment include – more severe acidosis or very elevated BUN at presentation, use of bicarbonate for treatment of acidosis, volumes of fluid over 40 mL/kg given in the first 4 hours of treatment, administration of insulin in the first hour of fluid treatment (International Diabetes Federation, 2010 & Wolfsdorf, Glaser, & Sperling, 2006).
   - Signs and symptoms – headache, slowing or irregular heart rate, change in neurologic status (restlessness, irritability, increased drowsiness, and /or incontinence), cranial nerve palsies or other specific neurologic signs, increasing blood pressure, decreased oxygen saturation.
   - One diagnostic criterion, 2 major criteria, or one major and 2 minor criteria have a sensitivity of 92% and a false positive rate of only 4% for detecting cerebral edema (Muir, Quisling, Yang, & Rosenbloom, 2004).
     - Diagnostic criteria – abnormal motor or verbal response to pain, decorticate or decerebrate posture, cranial nerve palsy, abnormal neurogenic respiratory pattern (grunting, tachypnea)
     - Major criteria – altered mental status, fluctuating level of consciousness, sustained heart rate deceleration (decrease more than 20 beats per minute) not attributable to improved hydration or sleep, age-inappropriate incontinence
     - Minor criteria – vomiting, headache, lethargy, diastolic BP >90 mm Hg, age <5 years.
   - Medical/Surgical Treatment:
     - Contact and begin immediate transfer to critical care unit:
       - Elevate head of bed
       - Reduce fluid rate by 1/3
       - Give mannitol 0.5-1 g/kg IV over 20 minutes
       - Hypertonic saline (3%), 5-10 mL/kg over 30 minutes may be used as an alternative to mannitol
       - Obtain CT head after treatment has been started to rule out other possible intracerebral causes of neurologic deterioration (thrombosis or hemorrhage).

2. Hypokalemia – may precipitate cardiac arrhythmia, cardiac monitoring is recommended
3. Hypoglycemia – increase dextrose in IVF to treat, additionally see hospital guidelines for treatment of hypoglycemia in diabetics under supporting documents
4. Hypophosphatemia
5. Pancreatitis

Discharge Criteria for DKA:
- Resolution of DKA: bicarbonate >17mmol/L, venous pH >7.3, normal anion gap, or blood ketones <0.6mmol/L.
Outcome Measures:
Time duration to resolution of DKA based on severity
Number of PICU admissions
Frequency of hypoglycemia
Potential cost savings with decreased PICU admissions and lab utilization

Potential Cost Implications:
Potential cost savings with decreased PICU admissions and lab utilization

Potential Organizational Barriers:
Acquisition of ketone meters
Training staff on use of new protocol and new equipment

Clinical Questions Answered:
Question 1: In the pediatric patient presenting with DKA which route of insulin therapy, intravenous or subcutaneous, is most efficacious in resolving DKA as evidenced by a:
- normalized pH,
- bicarbonate,
- B-hydroxybutyrate,
- negative urine ketones,
- length of hospitalization,
- duration of treatment until resolution of DKA (hrs),
- duration of therapy until hyperglycemia < 200 - 250 mg/dL, and
- amount of insulin (units) until resolution of DKA.

DKA Team Recommendations:
The DKA Team STRONGLY RECOMMENDS based on moderate-quality evidence the administration of insulin, via the intravenous route, to children. We value improving DKA symptoms in children safely and effectively while reducing the amount of painful procedures to this population at the same time. Data from Ersoz (2006), Fisher et al. (1977), Umpierrez, Cuervo, et al. (2004), and Umpierrez, Latif, et al. (2004) demonstrate that insulin drip therapy is as effective as subcutaneous insulin therapy. Fisher et al. (1977) reports a significant increase observed in the rate of plasma glucose and total ketone bodies with intravenous insulin versus subcutaneous within the first two hours of insulin administration; however, data was presented in a figure leaving the EBP Scholars unable to table this outcome.

Literature (see Appendix A) supporting this recommendation:
Literature was searched. Fourteen citations were found from the search with five citations appearing to answer the question; however, only four (Ersoz, et al., 2006; Fisher, et al., 1977; Umpierrez, Cuervo, et al., 2004; Umpierrez, Latif, et al., 2004) articles address the specific question.
Question 2: In the pediatric patient presenting with DKA does point of care ketone analysis correlate with serum ketone analysis?

DKA Team Recommendations:
The DKA Team STRONGLY RECOMMENDS based on low quality evidence the use of point of care ketone meters to manage children with DKA. We placed a high value on equitable and patient-centered care through the use of ketonemia monitoring which would enable providers to deliver safe, effective, timely and efficient care through prompt resolution of symptoms and reduction in cost of treatment. Rewers, McFann and Chase (2006) and Voulgari and Tentolouris (2010) provides highly correlated data between the POC monitor and the laboratory testing. However, the data was not presented to validate this information. This recommendation may be applied to all DKA patients. Further research (if performed) is likely to have an important effect on our confidence and may change this recommendation.

Literature (see Appendix B) supporting this recommendation:
Sixty one citations were identified in the medical literature search, six from a related citations search in PubMed and Google Scholar search with two citations (Rewers, McFann, & Chase, 2006; Voulgari & Tentolouris, 2010) found to answer the question.

Supporting tools
Care Cards:
1. Ketone Management Injection Care Card
2. Ketone Management Pump Care Card
3. Ketone Management Calculator Care Card

Informational Tools:
1. Types of Insulin

Procedures:
1. Hypoglycemia
2. New Onset Diabetes
3. Known Diabetic with Diabetic Ketoacidosis
4. Known Diabetic at Risk for Diabetic Ketoacidosis

Types of Insulin

<table>
<thead>
<tr>
<th>Type of Insulin</th>
<th>Onset of Action</th>
<th>Peak of Action</th>
<th>Total Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rapid acting</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aspart, lispro, glulisine</td>
<td>10-15 minutes</td>
<td>30-90 minutes</td>
<td>2-3 hours</td>
</tr>
<tr>
<td>Short acting</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Regular</td>
<td>30-60 minutes</td>
<td>2-4 hours</td>
<td>6-9 hours</td>
</tr>
<tr>
<td>Intermediate acting</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NPH</td>
<td>1-2 hours</td>
<td>3-8 hours</td>
<td>12-15 hours</td>
</tr>
<tr>
<td>Long Acting</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glargine</td>
<td>1-2 hours</td>
<td>No peak</td>
<td>24 hours</td>
</tr>
<tr>
<td>Detemir</td>
<td>1-2 hours</td>
<td>No peak</td>
<td>16-24 hours</td>
</tr>
<tr>
<td>Premixed</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>70/30 NPH/regular</td>
<td>30-60 minutes</td>
<td>3-8 hours</td>
<td>12-15 hours</td>
</tr>
<tr>
<td>75/25 NPH/lispro</td>
<td>10-15 minutes</td>
<td>30min-8hours</td>
<td>12-15 hours</td>
</tr>
</tbody>
</table>
Hypoglycemia

1. Patients currently in DKA on IV insulin drip:
   a. Blood glucose < 80 mg/dL
      i. Stop insulin drip. Maximize D\textsubscript{10} NS with additives IV fluids if not already at 100%.
         Recheck glucose in 15 minutes. If > 80 mg/dL continue current management and
         contact Supervising Physician. If blood glucose remains < 80 mg/dL treat with:
            1. If patient is alert and oriented without nausea/vomiting treat the patient with 15
               grams of simple carbohydrate to eat/drink: 4 ounces of fruit juice, 5-6 ounces
               of non-caffeinated regular soda, 6-7 saltine crackers, or 1 package of snack
               size crackers. Recheck blood glucose in 15 minutes. If blood glucose is < 80
               mg/dL repeat treatment and contact Supervising Physician.
            2. If patient is not able to cooperate and swallow safely and has IV access
               administer either D\textsubscript{10}W 5 ml/kg bolus IV through peripheral IV, if central line
               present may administer D\textsubscript{25}W 1 ml/kg bolus IV.

2. Patients on subcutaneous insulin:
   a. Blood glucose <80 mg/dL
      i. Mild hypoglycemia:
         1. Signs/symptoms (shaky, weak, tired, hungry, irritable, or difficulty focusing),
            but alert enough to safely take oral fluids/solids.
         2. Administer 15 grams of simple carbohydrate to eat/drink: 4 ounces of fruit
            juice, 5-6 ounces of non-caffeinated regular soda, 6-7 saltine crackers, or 1
            package of snack size crackers. Recheck blood glucose in 15 minutes and
            repeat above steps if still hypoglycemic. If blood glucose does not increase to
            > 80 mg/dL within 30 minutes contact Supervising Physician.
      ii. Moderate to severe hypoglycemia:
         1. Signs/symptoms (pale, sweaty, confused, distant, poor coordination, slurred
            speech, difficulty cooperating, altered mental status, semi-conscious, unconscious,
            or seizing).
         2. If patient is able to cooperate, follow directions, and swallow safely administer
            15 grams of simple carbohydrate to eat/drink: 4 ounces of fruit juice, 5-6
            ounces of non-caffeinated regular soda, 6-7 saltine crackers, or 1 package of
            snack size crackers. Recheck blood glucose in 15 minutes and repeat above
            steps if patient remains hypoglycemic. If blood glucose does not increase to
            > 80 mg/dL within 30 minutes contact Supervising Physician.
         3. If patient is not able to cooperate and swallow safely and has IV access
            administer either D\textsubscript{10}W 5 ml/kg bolus IV through peripheral IV, if central line
            present may administer D\textsubscript{25}W 1 ml/kg bolus IV.
         4. If patient does not have IV access give glucagon IM injection.
            a. 0.5 mg IM for <6 y/o.
            b. 1 mg IM for 6 y/o and older.
**New Onset Diabetes**

1. Begin management of DKA as per clinical practice guidelines if patient meets DKA criteria.
2. Obtain the following labs: Antibodies (ICA-512, GAD-65, zinc transporter, insulin), c-peptide, TSH, Free T4, transglutaminase algorithm for diagnosis of celiac disease.
3. If patient is not in DKA or upon resolution of DKA the following guidelines should be used:
   a. **Insulin**
      i. Administer long acting insulin (insulin glargine) subcutaneously if not already done. Bedtime administration is preferred if patient is not currently in DKA.
         1. < 5 yoa: 0.2 units/kg every 24 hours
         2. 5 to < 7 yoa: 0.3 units/kg every 24 hours
         3. 7 to 10 yoa: 0.4 units per kg every 24 hours
         4. > 10 yoa: 0.5 units/kg every 24 hours
      ii. Initiate subcutaneous rapid acting insulin (lispro, aspart, glulisine) based on insulin to carbohydrate ratio for meals and snacks.
         1. Patients < 5 y/o administer 1 unit for every 30 grams of carbohydrate (consider dosing after the meal/snack)
         2. Patients 5 y/o or older administer 1 unit for every 15 grams of carbohydrate (pre meal dosing is preferred).
      iii. Correction doses
         1. If blood glucose is > 300 mg/dL prior to a meal administer a correction dose of subcutaneous rapid acting (lispro, aspart, glulisine) insulin based on insulin sensitivity factor (ISF).
            \[
            ISF = \frac{1800}{Lantus \ dose \times 2}
            \]
         2. If patient is < 5 yoa contact Endocrinologist on Call prior to administering correction doses.
   b. **Glucose monitoring**
      i. Finger stick capillary glucoses should be obtained before meals, 2 hours after meals, and 3 am.
   c. **Ketone monitoring**
      i. Continue monitoring blood or urine ketones until negative and then discontinue monitoring once negative.
      ii. If blood glucose is > 400 and/or patient is symptomatic of DKA, resume checking blood or urine for ketones.
   d. **IV Fluids**
      i. Heplock IV once DKA resolved.
   e. **Diabetic diet**
   f. **Diabetes education**
      i. 4 half days of education by diabetes educators.
      ii. Refer to public website for educational materials available to families.

**Known Diabetic with Diabetic Ketoacidosis**
The Office of Evidence Based Practice, 2016
Center of Clinical Effectiveness
1. Begin management of DKA as per clinical practice guidelines.
2. Upon resolution of DKA the following guidelines should be used:
   a. Patients on Pumps:
      i. Endocrinologist and/or diabetes educator should assess the pump and reconnect it to
         the patient after a new infusion set has been placed.
      ii. If the patient does not have additional infusion sets with them they should be retrieved
         from home as these are not available from our pharmacy.
      iii. A temporary basal rate of 0% will be programmed to expire approximately 24 hours
         after glargine insulin has been administered.
      iv. All further insulin administration should occur via rapid acting insulin from the pump
         once reconnected (ie basal insulin, meal boluses and correction boluses).
   b. Patients on Multiple Daily Injections (MDI):
      i. The home basal insulin (glargine or detemir) should be continued every 24 hours
         moving toward the home schedule for dosing (typically bedtime).
      ii. The home rapid acting insulin (lispro, aspart, glulisine) should be administered based
         on the insulin to carbohydrate ratios used at home for meals and snacks.
   c. Correction doses:
      i. Once pump is connected by Endocrine Team, the patient may enter their pre meal
         finger stick blood glucose results along with their grams of carbohydrate into their
         pumps for correction doses to be administered with their mealtime insulin.
      ii. Patients on MDI may use an insulin sensitivity factor (ISF) to calculate correction
         doses to be administered along with their mealtime insulin if blood glucose is
         >240mg/dL prior to a meal. If a patient’s ISF at home is 1:50, then 1 unit of rapid
         acting insulin will drop the blood glucose 50 points. To calculate a correction dose
         take the patient’s blood glucose subtract 100 (the target glucose) and divide by the
         ISF.

         Example: Patient’s blood glucose is 350 mg/dL and ISF is 1:50
         
         \[350 \text{ (current glucose)} - 100 \text{ (target glucose)} = 250\]
         \[250 \div 50 \text{ (ISF)} = 5 \text{ units of rapid acting insulin}\]
         
         Add the 5 units to the mealtime dose for the total dose.
         
         Discuss doing correction doses with the Endocrinologist on call before administering
         to patients on MDI.
      iii. If ISF is not known:
         
         \[ISF = \frac{1800}{Weight \ (kg)}\]
   d. Diabetes education:
      i. Home sick day and/or ketone management should be reviewed with the patient by a
         diabetes educator prior to discharge. Care cards with these instructions are also
         available on the public website.
      ii. Assess need for social work or psychology involvement.
Known Diabetic at Risk for Diabetic Ketoacidosis

For diabetic patients with bicarbonate level 16-19 mmol/L, glucose >240 mg/dL, and moderate to large urine ketones or blood ketones ≥ 1.5 mmol/L the following guidelines should be used:

1. Contact Endocrinologist on Call.
2. Fluids: If patient is nauseated or vomiting and unable to take oral fluids administer 10 ml/kg NS bolus over 1 hour.
3. Medications:
   a. Ondansetron
      i. Consider if patient is severely nauseated or vomiting.
         1. >2 y/o 0.1 mg/kg sublingual or IV.
         2. >40 kg give 4 mg sublingual or IV.
   b. Insulin
      i. Administer a correction dose of rapid acting insulin (aspart, lispro, glulisine) with a syringe via subcutaneous injection.
         1. 0.1 units per kg for moderate ketones.
         2. 0.2 units per kg for large ketones.
      ii. A second correction dose may be given based on above guidelines if blood glucose 2 hours post correction dose has not decreased >100 mg/dL and is > 240 mg/dL.
      iii. If patient is on an insulin pump have the patient remove their current insulin infusion set and replace it with a new infusion set in a different site (ie opposite leg, buttock, arm, etc.). If this cannot be done in the ED and patient is stable for discharge the site change should occur immediately upon discharge at home.
4. Monitoring:
   a. Blood glucose
      i. Finger stick glucose should be obtained 2 hours after a correction dose is administered.
         1. If glucose 2 hours post correction dose has decreased >100 mg/dL or is normal and patient is symptomatically improved consider discharge to home.
         2. If glucose 2 hours post correction dose has not decreased >100 mg/dL and is > 240 mg/dL repeat correction dose as above.
5. Disposition:
   a. If patient is symptomatically improved and blood glucose has decreased > 100 mg/dL or is normal after correction dose(s) contact Endocrinologist on Call for discharge to home instructions.
      i. Give appropriate care card to patient (sick day management, ketones on a pump, ketones on injections, etc.).
   b. If patient is still symptomatic and blood glucose has not significantly improved contact Endocrinologist on Call.
Guideline Preparation: This guideline was prepared by The Office of Evidence Based Practice (EBP) in collaboration with content experts at Children’s Mercy Hospitals and Clinics. Development of this guideline supports the initiative of the Department of Clinical Effectiveness to promote care standardization that builds a culture of quality and safety that is evidenced by measured outcomes. If a conflict of interest is identified, the conflict will be disclosed next to the team member’s name.

Team Members:
- **Team Leaders:**
  - Mark Clements, MD, PhD, Endocrinologist
  - Angela Turpin, MD, Endocrinologist

- **Team Members:**
  - Tiffany Addington, MD, Urgent Care Center
  - Theodore Barnett, MD, Emergency Department
  - Charleen Cunningham, RN, MSN, CPN – Education Coordinator, Emergency Department
  - Jennifer Elliott, RN, BSN, CPN, MA – Staff Nurse, 6 Henson
  - Lisa Marshall, BSJ – Center for Clinical Effectiveness, Data Analyst II
  - Brian Olsen, MD – Assistant Professor of Pediatrics, UMKC School of Medicine
  - Susette Porazik-Ball, BSN, RN, CCRN – CMS ED Critical Care Education Coordinator
  - Deanna Porter, RN, BSN, CPN – Unit Education Coordinator, 6 Henson
  - Laura Shroyer, RN, MSN, NE-BC – Department Director, 6 Henson
  - Devin Bowers, RN, MSN, NE-BC – Department Director, PICU
  - Sally Fagan, RN, BSN, CCRN – Unit Education Coordinator, PICU

- **IS Team Members:**
  - Molly Boyd, RN, BSN – PCS Clinical Informatics Manager
  - Shari Cooley, RN, MSN – Medical Informatics Manager
  - Tammy Frank, RPh – Pharmacy Informatics Analyst
  - Shelly Knowles, RN – Clinical Information System Analyst
  - Kate Vanlandingham, RHIA – Information Systems Supervisor
  - Jana Wheeler, RN, MSN, CPN – Manager, Clinical Informatics

**Office of EBP Team Members:**
- J. Bartlett, PhD, RN, Evidence Based Practice Program Manager, Team Facilitator
- T. Franklin, Data Base Coordinator
- K. Swaggart, MLIS, Medical Librarian

**Guideline development funded by:**
No external funding was obtained in the development of this guideline.

**Development Process:**
The review summary documents the following steps:
1. Review of existing internal and external guidelines and standards
   a. Internal guidelines: CMHC DKA guidelines
   b. External guidelines:

2. Review preparation  
   a. PICOT (Patient, Intervention, Comparison, Outcome, Type of question) questions established  
   b. Team leaders confirmed search terms employed by the Health Science Medical librarians, reviewed article titles and abstracts from the search, and identified articles to be read and synthesized by the Evidence Based Practice Scholars.

3. Databases searched  
   a. AHRQ National Guideline Clearinghouse  
   b. Cochrane  
   c. Medline  
   d. CINAHL

4. Critically analyze the evidence  
   a. Guidelines  
      i. AGREE criteria were used to analyze published clinical guidelines.  
   b. Single studies  
      i. The EBP Scholars used the Cochrane Collaborative’s electronic software, Review Manager 5 (RevMan), to produce systematic reviews of the evidence of the effects of healthcare and delivered these documents to the team for review. RevMan allowed the EBP Scholars to build the tables of study characteristics, tables of study biases, and analyze study data in a meta-analysis. In instances when RevMan could not be used, CASP (Critical Appraisal Skills Programme) tools were utilized to analyze the literature.  
      ii. When a meta-analysis was found in the literature search, or created in RevMan, the GRADE criteria evaluated the literature using the Cochrane Collaborative’s electronic software known as GRADEprofiler (GRADEpro). GRADEpro assesses the meta-analysis for:  
         1. Limitations in study design and execution  
         2. Inconsistency between studies  
         3. Indirectness of study outcomes  
         4. Imprecision  
         5. Publication bias  
      iii. Table 1 defines how the quality of the evidence is rated and how the recommendation is established based on the type of evidence.
**Table 1. Grading of CPG Recommendations**

<table>
<thead>
<tr>
<th>Grade of Recommendation</th>
<th>Confidence in Clarity of Benefits vs Harms, Burden, and Cost</th>
<th>Quality of Supporting Evidence</th>
<th>Implications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Strong recommendation High quality evidence</td>
<td>Desirable effects clearly outweigh undesirable effects or vice versa</td>
<td>Consistent evidence from well-performed RCTs or exceptionally strong evidence from unbiased observational studies</td>
<td>Recommendation can apply to most patients in most circumstances. Further research is unlikely to change our confidence in the estimate of effect</td>
</tr>
<tr>
<td>Strong recommendation Moderate-quality evidence</td>
<td>Desirable effects clearly outweigh undesirable effect or vice versa</td>
<td>Evidence from RCTs with important limitations (inconsistent results, methodological flaws, indirect evidence, or imprecise results) or unusually strong evidence from unbiased observational studies</td>
<td>Recommendation can apply to most patients in most circumstances. Further research (if performed) is likely to have an important effect on our confidence in the estimate of effect and may change the estimate.</td>
</tr>
<tr>
<td>Strong recommendation Low-quality evidence</td>
<td>Desirable effects clearly outweigh undesirable effect or vice versa</td>
<td>Evidence for at least 1 critical outcome from observational studies, from RCTs with serious flaws or indirect evidence</td>
<td>Recommendation may change when higher-quality evidence becomes available. Further research (if performed) is likely to have an important influence on our confidence in the estimate of effect and is likely to change the estimate.</td>
</tr>
<tr>
<td>Strong recommendation Very-low-quality evidence (Very rarely applicable)</td>
<td>Desirable effects clearly outweigh undesirable effect or vice versa</td>
<td>Evidence for at least 1 of the critical outcomes from unsystematic clinical observations or very indirect evidence</td>
<td>Recommendation may change when higher-quality evidence becomes available; any estimate of effect, for at least 1 critical outcome, is uncertain.</td>
</tr>
<tr>
<td>Recommended High-quality evidence</td>
<td>Desirable effects closely balanced with undesirable effects</td>
<td>Consistent evidence from well-performed RCTs or exceptionally strong evidence from unbiased observational studies</td>
<td>The best action may differ, depending on circumstances or patients or societal values. Further research is unlikely to change our confidence in the estimate of effect.</td>
</tr>
<tr>
<td>Recommended Moderate-quality evidence</td>
<td>Desirable effects closely balanced with undesirable effects</td>
<td>Evidence from RCTs with important limitations (inconsistent results, methodological flaws, indirect evidence, or imprecise results) or unusually strong evidence from unbiased observational studies</td>
<td>Alternative approaches likely to be better for some patients under some circumstances. Further research (if performed) is likely to have an important influence on our confidence in the estimate of effect and may change the estimate.</td>
</tr>
<tr>
<td>Recommended Low-quality evidence</td>
<td>Desirable effects closely balanced with undesirable effects</td>
<td>Evidence for at least 1 critical outcome from observational studies, from RCTs with serious flaws or indirect evidence</td>
<td>Other alternatives may be equally reasonable. Further research is likely to have an important influence on our confidence in the estimate of effect and is likely to change the estimate.</td>
</tr>
<tr>
<td>Recommended Very-low-quality evidence</td>
<td>Desirable effects closely balanced with undesirable effects</td>
<td>Evidence for at least 1 critical outcome from unsystematic clinical observations or very indirect evidence</td>
<td>Other alternatives may be equally reasonable. Any estimate of effect, for at least 1 critical outcome, is uncertain.</td>
</tr>
</tbody>
</table>
5. Recommendations for the guideline were developed by a consensus process incorporating the three principles of EBP (current literature, content experts [CPG Team], and patient and family preference [when possible]).

**Approval Process:** Guidelines are reviewed and approved by an internal, Tiffany Musick, DO, and external reviewer David Maahs MD (University of Colorado, Barbara Davis Center for Diabetes), the CPG Team comprised of content expert clinicians, the Office of EBP, Medical Executive Committee and other appropriate hospital committees as deemed suitable for the guideline’s intended use. Guidelines are reviewed and updated as necessary every 3 years within the Office of EBP at CMH&C. The CPG Team will be involved with every review and update.

**Disclaimer:**
The content experts and the Office of EBP are aware of the controversies surrounding the management of the pediatric patient in DKA. When evidence is lacking or inconclusive, options in care are provided in the guideline and the power plans that accompany the guideline.

These guidelines do not establish a standard of care to be followed in every case. It is recognized that each case is different and those individuals involved in providing health care are expected to use their judgment in determining what is in the best interests of the patient based on the circumstances existing at the time.

It is impossible to anticipate all possible situations that may exist and to prepare guidelines for each. Accordingly these guidelines should guide care with the understanding that departures from them may be required at times, although a discussion with an Endocrinologist is recommended prior to this occurring.
References


Question 1: In the pediatric patient presenting with DKA which route of insulin therapy, intravenous or subcutaneous, is most efficacious in resolving DKA as evidenced by a:
- normalized pH,
- bicarbonate,
- B-hydroxybutyrate,
- negative urine ketones,
- length of hospitalization,
- duration of treatment until resolution of DKA (hrs),
- duration of therapy until hyperglycemia < 200 - 250 mg/dL, and
- amount of insulin (units) until resolution of DKA.

**GRADEProfiler Table:**

<table>
<thead>
<tr>
<th></th>
<th>Quality assessment</th>
<th>No of patients</th>
<th>Effect</th>
<th>Quality</th>
<th>Importance</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No of studies</td>
<td>Design</td>
<td>Risk of bias</td>
<td>Inconsistency</td>
<td>Indirectness</td>
</tr>
<tr>
<td><strong>pH &gt;7.3 (h)</strong> (Better indicated by lower values)</td>
<td>2,1</td>
<td>Randomized trials</td>
<td>Very serious</td>
<td>No serious inconsistency</td>
<td>No serious indirectness</td>
</tr>
<tr>
<td><strong>Bicarbonate &gt; 15 - 18 mEq/l (h)</strong> (Better indicated by lower values)</td>
<td>2,1</td>
<td>Randomized trials</td>
<td>Very serious</td>
<td>No serious inconsistency</td>
<td>No serious indirectness</td>
</tr>
<tr>
<td><strong>B-hydroxybutyrate &lt;0.6mmol/l (h)</strong> (Better indicated by lower values)</td>
<td>1</td>
<td>Randomized trials</td>
<td>Very serious</td>
<td>No serious inconsistency</td>
<td>No serious indirectness</td>
</tr>
<tr>
<td><strong>Urine Ketone Negative (h)</strong> (Better indicated by lower values)</td>
<td>1</td>
<td>Randomized trials</td>
<td>Very serious</td>
<td>No serious inconsistency</td>
<td>No serious indirectness</td>
</tr>
</tbody>
</table>
### Hospital Stay (days) (Better indicated by lower values)

| 2.4 | Randomized trials | No serious risk of bias | No serious inconsistency | Serious | none | 35 | 35 | - | MD 0.19 lower (1.08 lower to 0.7 higher) | ☎️ ☎️ ☎️ MODERATE |

### Duration of treatment until resolution of DKA (hrs) (Better indicated by lower values)

| 2.4 | Randomized trials | No serious risk of bias | No serious inconsistency | Very serious | none | 35 | 35 | - | MD 1 lower (2.53 lower to 0.53 higher) |

### Duration of therapy until hyperglycemia < 200 - 250 mg/dL (hr) (Better indicated by lower values)

| 1.2.3.4 | Randomized trials | Serious | No serious inconsistency | No serious indirectness | Serious | none | 60 | 60 | - | MD 0.22 lower (1.42 lower to 0.97 higher) |

### Amount of insulin (units) until resolution of DKA (Better indicated by lower values)

| 1.2.3.4 | Randomized trials | Serious | No serious inconsistency | No serious indirectness | Serious | none | 60 | 60 | - | MD 6.45 lower (14.07 lower to 1.16 higher) |

---

5. For the Ersoz (2006) and Fisher (1977) articles the author's did not describe how risk of bias was minimized.
6. The combined sample size between the Ersoz (2006) and Fisher (1977) articles is 50 which could lead to statistical imprecision.
7. Same as footnote 5.
8. Same as footnote 6.
9. Ersoz (2006) did not describe how risk of bias was minimized.
10. The sample size (N=20) is small which could compromise statistical precision.
11. Same as footnote 9.
12. Same as footnote 10.
13. Between the two studies the sample size (N=70) is small which could compromise statistical precision.
15. Ersoz, 2006; Fisher 1977 did not describe how risk of bias was minimized while the other two articles (Umpierrez, Cuervo, 2004; Umpierrez, Latif, 2004) did describe how risk of bias was minimized.
16. Between the four studies the sample size (N=120) which is smaller than the standardized Cochrane acceptable sample size (N=400); with smaller sample sizes statistical precision can be compromised.
17. Same as footnote 15.
18. Same as footnote 16.

**Synthesis Author(s):** EBP Scholars (Bartlett, J. A., Dusin, J. D., Gutierrez, C. L., & Shubat, S. J.)

**Date:** 2011-11-23
Forest Plots of Comparisons

Subcutaneous Insulin vs. Continuous Intravenous Insulin, outcome: pH > 7.3 (h).

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Experimental Mean</th>
<th>SD</th>
<th>Control Mean</th>
<th>SD</th>
<th>Mean Difference IV, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ersoz 2006</td>
<td>6.8</td>
<td>5.7</td>
<td>8.2</td>
<td>5.6</td>
<td>-1.40 [-6.35, 3.55]</td>
</tr>
<tr>
<td>Fisher 1977</td>
<td>8.7</td>
<td>4.11</td>
<td>6.219</td>
<td>15</td>
<td>2.70 [0.34, 5.06]</td>
</tr>
</tbody>
</table>

Total (95% CI) 25 100.0% 1.94 [-0.19, 4.07]

Heterogeneity: Chi² = 2.15, df = 1 (P = 0.14); I² = 53%
Test for overall effect: Z = 1.79 (P = 0.07)

Subcutaneous Insulin vs Continuous Intravenous Insulin, outcome: Bicarbonate > 15 - 18 mEq/l (h).

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Subcutaneous Mean</th>
<th>SD</th>
<th>Control Mean</th>
<th>SD</th>
<th>Mean Difference IV, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ersoz 2006</td>
<td>14.8</td>
<td>7</td>
<td>10 13.2</td>
<td>7.5</td>
<td>22.3% 1.60 [-4.76, 7.96]</td>
</tr>
<tr>
<td>Fisher 1977</td>
<td>10.8</td>
<td>3.01</td>
<td>15 13.02</td>
<td>6.02</td>
<td>77.7%-2.20 [-5.61, 1.21]</td>
</tr>
</tbody>
</table>

Total (95% CI) 25 100.0% 1.35 [-4.36, 1.65]

Heterogeneity: Chi² = 1.07, df = 1 (P = 0.30); I² = 6%
Test for overall effect: Z = 0.88 (P = 0.38)

Subcutaneous Insulin vs Continuous Intravenous Insulin, outcome: B-hydroxybutyrate <0.6mmol/l (h).

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Experimental Mean</th>
<th>SD</th>
<th>Control Mean</th>
<th>SD</th>
<th>Mean Difference IV, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ersoz 2006</td>
<td>15.3</td>
<td>8.7</td>
<td>10 11.2</td>
<td>4.9</td>
<td>100.0% 4.10 [-2.09, 10.29]</td>
</tr>
</tbody>
</table>

Total (95% CI) 10 100.0% 4.10 [-2.09, 10.29]

Heterogeneity: Not applicable
Test for overall effect: Z = 1.30 (P = 0.19)
Subcutaneous Insulin vs Continuous Intravenous Insulin, outcome: Urine Ketone Negative (h).

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Experimental--Drip Mean</th>
<th>Control--SQ Mean</th>
<th>Mean Difference</th>
<th>Study or Subgroup</th>
<th>Mean</th>
<th>SD</th>
<th>Mean</th>
<th>SD</th>
<th>Mean Difference</th>
<th>Mean Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total (95% CI)</td>
<td>10.9</td>
<td>10.9</td>
<td>-0.00</td>
<td>-2.93</td>
<td>13.13</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>10.9</td>
<td>10.9</td>
<td>-0.00</td>
<td>-2.93</td>
<td>13.13</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: Not applicable</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 1.24 (P = 0.21)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Subcutaneous Insulin vs Continuous Intravenous Insulin, outcome: Hospital Stay (days).

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Experimental--Drip Mean</th>
<th>Control--SQ Mean</th>
<th>Mean Difference</th>
<th>Study or Subgroup</th>
<th>Mean</th>
<th>SD</th>
<th>Mean</th>
<th>SD</th>
<th>Mean Difference</th>
<th>Mean Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total (95% CI)</td>
<td>10.9</td>
<td>10.9</td>
<td>-0.00</td>
<td>-2.93</td>
<td>13.13</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>10.9</td>
<td>10.9</td>
<td>-0.00</td>
<td>-2.93</td>
<td>13.13</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: Chi² = 0.83, df = 1 (P = 0.36); I² = 0%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 0.42 (P = 0.68)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Subcutaneous Insulin vs Continuous Intravenous Insulin, outcome: Duration of treatment until resolution of DKA (hrs).

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Experimental--Drip Mean</th>
<th>Control--SQ Mean</th>
<th>Mean Difference</th>
<th>Study or Subgroup</th>
<th>Mean</th>
<th>SD</th>
<th>Mean</th>
<th>SD</th>
<th>Mean Difference</th>
<th>Mean Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total (95% CI)</td>
<td>10.9</td>
<td>10.9</td>
<td>-0.00</td>
<td>-2.93</td>
<td>13.13</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>10.9</td>
<td>10.9</td>
<td>-0.00</td>
<td>-2.93</td>
<td>13.13</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: Chi² = 0.00, df = 1 (P = 1.00); I² = 0%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 1.28 (P = 0.20)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Subcutaneous Insulin vs Continuous Intravenous Insulin, outcome: Duration of therapy until hyperglycemia < 200 - 250 mg/dL (hr).

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Experimental--Drip</th>
<th>Control--SQ</th>
<th>Mean Difference</th>
<th>Mean Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ersoz 2006</td>
<td>12.7</td>
<td>7.5</td>
<td>10 9.4 8.9 10</td>
<td>2.7%3.30 [-3.91, 10.51]</td>
</tr>
<tr>
<td>Fisher 1977</td>
<td>6 3.83</td>
<td>10 5.6 2.46</td>
<td>15 15 28.6% 0.40 [-1.90, 2.70]</td>
<td></td>
</tr>
<tr>
<td>Umpierrez Cuervo 2004.7.1</td>
<td>5 6.9</td>
<td>4 15</td>
<td>15 13.5% 0.20 [-3.04, 3.44]</td>
<td></td>
</tr>
<tr>
<td>Umpierrez Latif 2004</td>
<td>7 20</td>
<td>3 20</td>
<td>20 56.9% 0.00 [-1.58, 1.58]</td>
<td></td>
</tr>
</tbody>
</table>

Total (95% CI) 60 60 100.0% 0.22 [-0.97, 1.42] 

Heterogeneity: $\chi^2 = 0.80$, df = 3 ($P = 0.85$); $I^2 = 0$

Test for overall effect: $Z = 0.37$ ($P = 0.71$)

Subcutaneous Insulin vs Continuous Intravenous Insulin, outcome: Amount of insulin (units) until resolution of DKA.

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Experimental--Drip</th>
<th>Control--SQ</th>
<th>Mean Difference</th>
<th>Mean Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ersoz 2006</td>
<td>65.2</td>
<td>12.7</td>
<td>10 61.7 10.9 10</td>
<td>53.9% 3.50 [-6.87, 13.87]</td>
</tr>
<tr>
<td>Fisher 1977</td>
<td>100 30.12</td>
<td>15 85 21.91</td>
<td>15 16.3% 15.00 [-3.85, 33.85]</td>
<td></td>
</tr>
<tr>
<td>Umpierrez Cuervo 2004.82</td>
<td>28 15</td>
<td>85 33</td>
<td>15 12.1% 3.00 [-24.90, 18.90]</td>
<td></td>
</tr>
<tr>
<td>Umpierrez Latif 2004</td>
<td>98 26</td>
<td>84 32</td>
<td>20 17.7% 14.00 [-4.07, 32.07]</td>
<td></td>
</tr>
</tbody>
</table>

Total (95% CI) 60 60 100.0% 6.45 [-1.16, 14.07] 

Heterogeneity: $\chi^2 = 2.49$, df = 3 ($P = 0.48$); $I^2 = 0$

Test for overall effect: $Z = 1.66$ ($P = 0.10$)

Search strategy implemented:

Medline performed October 22, 2010:

http://www.ncbi.nlm.nih.gov/sites/myncbi/collections/public/18WEaBXD-u1n3n7ziwXvxqjQh/
Characteristics of included studies

Ersoz 2006

Methods  Randomized Control Trial
Participants Twenty patients with mild or moderate DKA (mean age 43.8 ± 19.0 years, 11 women and nine men) were enrolled in the study.
Interventions After a complete physical and laboratory evaluation, patients with a diagnosis of mild or moderate DKA were enrolled in the study. The patients were randomly assigned into two groups. Following a bolus injection of 0.15 U/kg IV regular insulin, group L received half of this dose as hourly SC insulin lispro, while group R was treated conventionally with standard IV regular insulin infusion. Insulin dose was titrated according to serum glucose and pH levels. Both treatments were continued until all follow-up parameters became normal.
Outcomes Evaluate the efficacy and safety of hourly subcutaneous insulin lispro administration in the treatment of diabetic ketoacidosis in comparison with intravenous regular insulin treatment. Time needed for normalization of serum glucose, B-hydroxybutyrate, blood pH and urine ketone.
Notes Patients with severe ketoacidosis were not included in the study population.

Risk of bias table

<table>
<thead>
<tr>
<th>Bias</th>
<th>Scholars' judgment</th>
<th>Support for judgment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random sequence generation (selection bias)</td>
<td>Unclear Risk</td>
<td>Sequence generation was not described.</td>
</tr>
<tr>
<td>Allocation concealment (selection bias)</td>
<td>Unclear Risk</td>
<td>Allocation was not described.</td>
</tr>
<tr>
<td>Blinding (performance bias and detection bias)</td>
<td>High Risk</td>
<td>Unable to blind patients or practitioners.</td>
</tr>
<tr>
<td>Incomplete outcome data (attrition bias)</td>
<td>Unclear Risk</td>
<td>None discussed.</td>
</tr>
<tr>
<td>Selective reporting (reporting bias)</td>
<td>Unclear Risk</td>
<td>None discussed.</td>
</tr>
<tr>
<td>Other bias</td>
<td>Unclear Risk</td>
<td>None discussed.</td>
</tr>
</tbody>
</table>

Fisher 1977

Methods  After initial evaluation and lab work in the ER, patients were brought to the Clinical Research Center where they were treated by low-dose insulin therapy given either intramuscularly, subcutaneously, or by continuous intravenous infusion according to a previously established randomized protocol. All insulin injections, subsequent blood chemical tests and medical procedures were carried out in the Clinical Research Center of the University of Tennessee Center for the Health Sciences.

Participants For admission to the protocol, patients had to meet all the following criteria: plasma glucose greater than 300mg per deciliter; blood acetone positive at more than 1:2 dilution; blood pH less than 7.3; serum bicarbonate less than 15 mEq per liter; glycosuria
Initial April 29, 2013; Revisions: 4/13; 1/14; 9/14; 12/14; 12/15, 12/16

(3+ test or greater) with ketonuria. Informed consent was obtained in all cases before the patients were admitted to the Clinical Research Center. A total of 45 patients were admitted to this protocol from October, 1975 through September, 1976.

**Interventions**

Venous blood was drawn at regular intervals for measurement of glucose, electrolytes, ketone bodies, cortisol, glucagon, pyruvate and lactate, and arterial specimens were obtained for blood gases and pH. In patients who had not previously received insulin, blood was obtained for measurement of immunoreactive insulin at the outset and during insulin therapy at 10-minute intervals for the first hour and once every hour thereafter. The initial dose of crystalline insulin was administered, based on body weight (0.33 units per kg), regardless of the initial plasma glucose as a bolus in a peripheral vein for the intravenous group. The other groups received intramuscular and subcutaneous injections in the deltoid area with 3.8-cm and 1.3-cm needles, respectively. Patients who failed to have at least a 10% fall in plasma glucose by the end of the first hour received repeat "loading" doses on a weight basis hourly until a 10% decline in plasma glucose occurred. Thereafter, the dose of insulin in all three groups were arbitrarily set at 7 units per hour until the plasma glucose reached 250mg per deciliter. The intravenous group received insulin as a continuous infusion in 0.9% sodium chloride solution containing 2.5% human albumin. The intramuscular and subcutaneous groups received 7 units of regular insulin hourly by the respective routes. Once plasma glucose reached 250mg per deciliter, dextrose in water or in saline was substituted for the sodium chloride solution. If the ketoacidosis was still not under control (control being defined as bicarbonate concentration higher than 15 mEq per liter, pH above 7.3 and plasma acetone negative at 1:2 dilution), 4 to 12 units of regular insulin was given every two hours by the same route as previously administered according to the amount of hyperglycemia or glycosuria. No insulin was administered if the plasma glucose was less than 150mg per deciliter even in the presence of glycosuria.

Intravenous fluid and electrolyte replacement and the use of sodium bicarbonate was kept as similar as possible in all groups. Potassium replacement was administered half as potassium chloride and half as potassium phosphate. All patients were kept in the Clinical Research Center for 24 hours, even if the DKA was under control, to evaluate for hypoglycemia, hypokalemia or other complications. Venous blood samples were obtained just before hourly insulin therapy and analyzed using a Beckman glucose AutoAnalyzer. Serum acetone in serial dilution was measured by the nitroprusside method. Insulin was assayed by the double-antibody radioimmunoassay method, glucagon by the use of Unger's 30-K antiserum, and cortisol by the fluorometric method. Ketone bodies, pyruvate and lactate were measured by enzymatic procedures. All other chemical measurements were performed by the Clinical Chemistry Laboratory. Calculation of statistical significance was by the Student t-test.

**Outcomes**

As a result of the random assignment of patients on admission to one of the three treatment groups the average initial chemical profile was remarkably similar, as were mean weights and ages. There was no significant difference in the number of hours required to reach various biochemical endpoints. Little difference noted in the amount of fluid replacement or insulin therapy administered. Of note is the significant increase observed in the rate of fall of both glucose and ketone bodies with intravenous as compared to subcutaneous and intramuscular therapy during the first two hours. The ketone bodies actually rose during the first hour of therapy in the latter two groups. Nine of forty-five patients failed to have at least a 10% fall in plasma glucose by the end
of the first hour, requiring a second loading dose of insulin (two in the intravenous group, three in the subcutaneous, and six in the intramuscular group), whereas two patients, both in the intramuscular group, needed a third loading dose to achieve an adequate initial response. After the second hour, however, no significant differences were observed in either the glucose or ketone-body levels among the three routes of insulin administration.

Notes
none

Risk of bias table

<table>
<thead>
<tr>
<th>Bias</th>
<th>Scholars' judgment</th>
<th>Support for judgment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random sequence generation</td>
<td>Unclear Risk</td>
<td>No description given.</td>
</tr>
<tr>
<td>Allocation concealment</td>
<td>Unclear Risk</td>
<td>No description given.</td>
</tr>
<tr>
<td>Blinding</td>
<td>Unclear Risk</td>
<td>No description given.</td>
</tr>
<tr>
<td>Incomplete outcome data</td>
<td>Unclear Risk</td>
<td>No description given.</td>
</tr>
<tr>
<td>Selective reporting</td>
<td>Unclear Risk</td>
<td>No description given.</td>
</tr>
<tr>
<td>Other bias</td>
<td>Unclear Risk</td>
<td>No description given.</td>
</tr>
</tbody>
</table>

Umpierrez Cuervo 2004

Methods  
Prospective, randomized, open trial

Participants  
45 consecutive adult patients with DKA

Interventions  
Patients were randomly assigned in the emergency department to receive SC aspart insulin every hour (SC-1h, n=15) or every 2 h (SC-2h, n=15), or to receive IV regular insulin (n=15).

Patients treated with SC-1h received an initial injection of 0.3 units/kg body wt, followed by 0.1 units kg⁻¹ X h⁻¹ until blood glucose reached 13.8 mmol/l (250 mg/dL). At that time, insulin dose was reduced reduced to 0.05 units kg⁻¹ X h⁻¹, and the IV fluids were changed to D5% 0.45 saline to maintain blood glucose at 11.1 mmol/l (200 mg/dL) until resolution of DKA.

Patients treated with SC-2h received an initial dose of 0.3 units/kg followed by 0.2 units/kg 1 h later and every 2 h until blood glucose reached 13.8 mmol/l (250 mg/dL). At that time, insulin dose was reduced to 0.1 units/kg every 2 h, and the IV fluids were changed to D5% 0.45 saline to keep blood glucose at 11.1 mmol/l (200 mg/dL) until resolution of DKA. [This group’s data is not reported in this review.]

Patients treated with IV regular insulin received an initial bolus of 0.1 units/kg, followed by a continuous infusion of regular insulin calculated to deliver 0.1 units X kg⁻¹ X h⁻¹ until blood glucose levels were 13.8 mmol/l (250 mg/dL). At that time, insulin dose was reduced to 0.05 units kg⁻¹ X h⁻¹, and the IV fluids were changed to D5% 0.45 saline to maintain blood glucose at 11.1 mmol/l (200 mg/dL) until resolution of DKA.
Outcomes
1. Duration of treatment until resolution of hyperglycemia and ketoacidosis
2. Total length of hospitalization
3. Amount of insulin administration until resolution of hyperglycemia and ketoacidosis
4. Number of hypoglycemic events.

Notes
The diagnosis of DKA was established in the emergency department. Patients with: a plasma glucose level of 13.8 mmol/l (250 mg/dL), a serum bicarbonate level 15 mmol/l, a venous pH 7.30, and a positive serum ketone level at a dilution 1:4 by the nitroprusside reaction, and/or a serum -hydroxybutyrate level 3.0 mmol/l. Patients excluded had: persistent hypotension (systolic blood pressure 80 mmHg) after the administration of 1 liter of normal saline and patients with acute myocardial ischemia, end-stage renal or hepatic failure, anasarca, dementia, or pregnancy.

Because of hospital regulations that did not allow the use of IV insulin drips outside the ICU, patients treated with IV regular insulin were admitted to the ICU, whereas patients treated with SC aspart were managed in the general medicine floor or in a step-down unit.

The authors did not define DKA resolution.

Risk of bias table

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors' judgment</th>
<th>Support for judgment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random sequence generation</td>
<td>Unclear Risk</td>
<td>Insufficient information about the sequence generation process to permit judgment</td>
</tr>
<tr>
<td>Allocation concealment</td>
<td>Unclear Risk</td>
<td>Insufficient information about the sequence generation process to permit judgment</td>
</tr>
<tr>
<td>Blinding (performance bias and</td>
<td>Low Risk</td>
<td>Though blinding did not occur the outcome and the outcome measurement were not likely to be influence by lack of blinding</td>
</tr>
<tr>
<td>detection bias)</td>
<td></td>
<td>No missing outcome data</td>
</tr>
<tr>
<td>Incomplete outcome data (attrition bias)</td>
<td>Low Risk</td>
<td>All of the study's pre-specified outcomes that were of interest were reported</td>
</tr>
<tr>
<td>Selective reporting (reporting bias)</td>
<td>Low Risk</td>
<td>The study seems to be free of other sources of bias</td>
</tr>
<tr>
<td>Other bias</td>
<td>Low Risk</td>
<td></td>
</tr>
</tbody>
</table>

Umpierrez Latif 2004

Methods
Randomized Control Trial

Participants
The sample comprised 40 patients with diabetic ketoacidosis who were recruited from the Atlanta Medical Center and the University of Tennessee Health Science Center. [40 patients with DKA were assigned in the emergency department to receive subcutaneous insulin lispro or intravenous regular insulin following a computer-generated randomization table. The diagnosis of diabetic ketoacidosis was established in the
emergency department using a plasma glucose level 250 mg/dL (13.9 mmol/L), a serum bicarbonate level 15 mEq/L, a blood pH 7.3, a positive serum ketone level at a dilution 1:4 by the nitroprusside reaction, and a serum -hydroxybutyrate level 31 mg/dL (3 mmol/L). Pts were excluded who had persistent hypotension (systolic blood pressure 80 mm Hg) after the administration of 1 liter of normal saline, comatose state (loss of consciousness), acute myocardial ischemia, heart failure, end-stage renal disease, anasarca, dementia, or pregnancy. Due to hospital regulations disallowing the use of intravenous insulin outside the intensive care unit, patients treated with intravenous insulin were admitted to the intensive care unit, while patients treated with subcutaneous lispro were managed on a general medicine floor or in a stepdown unit.

Interventions

**Insulin therapy arms:**
1) Subcutaneous lispro every hour: Initial dose subcutaneously: 0.3 unit/kg of body weight, followed by Subcutaneous lispro insulin at 0.1 unit/kg/h. When blood glucose levels 250 mg/dL, change intravenous fluids to dextrose 5% in 0.45% saline and reduce rate to 0.05 unit/ kg/h to keep glucose levels 200 mg/dL (11.1 mmol/L) until resolution of diabetic ketoacidosis.
2) Intravenous regular insulin: a) Initial intravenous bolus: 0.1 unit/kg body weight, followed by. b) Continuous insulin infusion at 0.1 unit/kg/h. When blood glucose levels 250 mg/dL, change intravenous fluids to dextrose 5% in 0.45% saline and reduce rate to 0.05 unit/ kg/h to keep glucose levels 200 mg/dL (11.1 mmol/L) until resolution of diabetic ketoacidosis.

Outcomes

Compare the efficacy and safety of subcutaneous insulin lispro with that of low-dose continuous intravenous regular insulin in the treatment of patients with uncomplicated diabetic ketoacidosis. Ketoacidosis was considered resolved when serum bicarbonate levels were ≥18 mEq/L and venous pH was ≥7.3.

Notes

Subcutaneous insulin lispro pts were managed in regular medicine wards or an intermediate care unit, while intravenous protocol group were managed in the intensive care unit.

**Risk of bias table**

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors' judgment</th>
<th>Support for judgment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random sequence generation (selection bias)</td>
<td>Low risk</td>
<td>Computer generated.</td>
</tr>
<tr>
<td>Allocation concealment (selection bias)</td>
<td>High risk</td>
<td>Unable to conceal allocation.</td>
</tr>
<tr>
<td>Blinding (performance bias and detection bias)</td>
<td>High risk</td>
<td>Though blinding did not occur the outcome and the outcome measurement were not likely to be influence by lack of blinding</td>
</tr>
<tr>
<td>Incomplete outcome data (attrition bias)</td>
<td>Low risk</td>
<td>All of the study's pre-specified outcomes that were of interest were reported</td>
</tr>
<tr>
<td>Selective reporting (reporting bias)</td>
<td>Low risk</td>
<td>None reported.</td>
</tr>
</tbody>
</table>

The Office of Evidence Based Practice, 2016
Center of Clinical Effectiveness
Other bias

Low risk

None reported.

**Characteristics of excluded studies**

**Kitabchi 1976**

Reason for exclusion: comparison groups were IV and subcutaneous insulin versus IM insulin
Appendix B

Question 2: In the pediatric patient presenting with DKA does point of care ketone analysis correlate with serum ketone analysis?

DKA Team Recommendations:

We recommend the use of point of care ketone analysis for children to manage children with DKA. We placed a high value on equitable and patient-centered care through the use of ketonemia monitoring which would enable providers to deliver safe, effective, timely and efficient care through prompt resolution of symptoms and reduction in cost of treatment.

In addition to the data below, comparative values for point-of-care (POC) βOHB and serum bicarbonate (CO$_2$) were evaluated at Children’s Mercy Hospital and the POC βOHB value corresponding to the CO$_2$ value < 16 was established (Ferguson et al., 2015). Receiver Operating Characteristic (ROC) analysis indicated that a POC βOHB value of 3.3 mmol/L predicts DKA with 92.5% sensitivity and 76.2% specificity. The ROC-AUC (area under the curve) was 0.922 with an efficiency of 85%. To assess the stability of the estimated cutoff of 3.3 mmol/L, the data was bootstrap sampled 1,000 times with the results supporting the POC βOHB serum value 3.3 mmol/L as achieving the highest efficiency when predicting DKA.
Figure 1. Optimal Cutoff for DKA Diagnosis by POC βOHB

### Statistical Analysis

<table>
<thead>
<tr>
<th></th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Area under the ROC curve (AUC)</td>
<td>0.922</td>
</tr>
<tr>
<td>Asymptotic Std Error of AUC</td>
<td>0.021</td>
</tr>
<tr>
<td>Asymptotic Gaussian 95% CI</td>
<td>0.88 to 0.96</td>
</tr>
<tr>
<td>AUC significantly better than chance?</td>
<td>Z = 9.51, Probability (2-tail) &lt; 0.001</td>
</tr>
</tbody>
</table>

Probability > 0.05 means the test is not significantly better than chance.
Synthesis Author(s): EBP Scholars (Bartlett, J. A., Collum, K., Dusin, J. D., Gutierrez, C. L., Pirvu, D. & Shubat, S. J.)
Date: 2011-11-23

Rewers 2006

Clinical features and settings
Children's Hospital in Denver, CO: Emergency Department and Inpatient Units

Participants
Type 1 diabetes mellitus and age less than 18 years.

Study design
Prospective, investigator-initiated study

Target condition and reference standard(s)
DKA in children; Reference: Serum samples were measured using a reference laboratory method (Cobas Mira Plus; Roche Diagnostics, Indianapolis, IN). Routine laboratory values (pH, pCO2, plasma glucose, electrolytes, bicarbonate, and BUN).

Index and comparator tests
Index: β-OHB levels were assessed in 30 s on 10 L of whole venous blood sample applied to an electrochemical strip using an electrochemical blood ketone sensor (Precision Xtra meter).
Comparator: Serum samples were measured using a reference laboratory method (Cobas Mira Plus; Roche Diagnostics, Indianapolis, IN). Routine laboratory values (pH, pCO2, plasma glucose, electrolytes, bicarbonate, and BUN).

Follow-up
Laboratory parameters were measured hourly for the first 3 h and every 2–3 h thereafter.

Notes
The correlation gives you a good idea of how well the observed value of a variable (capillary β-OHB) retains the true rank order of subjects. Correlations >0.90 are needed to retain reasonable order in the ranking. The bedside meter β-OHB levels were significantly correlated with pH (r=0.63; P<0.0001), bicarbonate (r=0.74; P<0.0001), and pCO2 (r=0.55; P<0.0001) at all points of measurement during the treatment (unadjusted Pearson correlations). The correlation coefficients were similar for the bedside meter and the reference laboratory method. A strong correlation was found between the bedside meter and the reference laboratory values of β-OHB (r=0.92; P<0.0001).
Assessment of methodological quality table

<table>
<thead>
<tr>
<th>Item</th>
<th>Scholar's judgment</th>
<th>Support for judgment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Representative spectrum?</td>
<td>Yes</td>
<td>Serum samples were measured using a reference laboratory method (Cobas Mira Plus; Roche Diagnostics, Indianapolis, IN). Routine laboratory values (pH, pCO2, plasma glucose, electrolytes, bicarbonate, and BUN).</td>
</tr>
<tr>
<td>Acceptable reference standard?</td>
<td>Unclear</td>
<td>Serum samples were measured using a reference laboratory method (Cobas Mira Plus; Roche Diagnostics, Indianapolis, IN). Routine laboratory values (pH, pCO2, plasma glucose, electrolytes, bicarbonate, and BUN).</td>
</tr>
<tr>
<td>Acceptable delay between tests?</td>
<td>Yes</td>
<td>Laboratory parameters including β-0HB were measured hourly for the first 3 h and every 2–3 h thereafter.</td>
</tr>
<tr>
<td>Partial verification avoided?</td>
<td>Yes</td>
<td>Did not report</td>
</tr>
<tr>
<td>Differential verification avoided?</td>
<td>Yes</td>
<td>Did not report</td>
</tr>
<tr>
<td>Incorporation avoided?</td>
<td>Yes</td>
<td>Did not report</td>
</tr>
<tr>
<td>Reference standard results blinded?</td>
<td>Unclear</td>
<td>Did not report</td>
</tr>
<tr>
<td>Index test results blinded?</td>
<td>Unclear</td>
<td>Did not report</td>
</tr>
<tr>
<td>Relevant clinical information?</td>
<td>Yes</td>
<td>Did not report</td>
</tr>
<tr>
<td>Uninterpretable results reported?</td>
<td>Yes</td>
<td>Did not report</td>
</tr>
<tr>
<td>Withdrawals explained?</td>
<td>Yes</td>
<td>Did not report</td>
</tr>
</tbody>
</table>

Voulgari 2010

**Clinical features and settings**

**Participants**

Type 2 Diabetics presenting to the ER with capillary glucose level >13.9

**Study design**

Prospective cohort comparison of a simultaneous measurement of capillary blood ketones

**Target condition and reference standard(s)**

DKA; serum β-0HB using enzymatic end-point spectrophotometric method

**Index and comparator tests**

Precision-Xtra Device (Abbott Laboratories, Abingdon, UK) was the index test and Serum β-0HB levels were measured by an enzymatic end-point spectrophotometric method
of Evidence Based Practice, 2016
Center of Clinical Effectiveness

Initial April 29, 2013; Revisions: 4/13; 1/14; 9/14; 12/14; 12/15, 12/16

Notes

all Type 2 Diabetics presenting to the ER with a capillary blood glucose level >13.9 mmol/L
Authors report capillary ketonemia (β-OHB >3.0mmol/L) had the highest performance (sensitivity 99.87%, specificity 92.89%, positive predictive value 92.89%) for the diagnosis of DKA compared with serum ketonemia (sensitivity 90.45%, specificity 88.65%, positive predictive value 87.76%) or ketonuria (sensitivity 89.89%, specificity 52.73%, positive predictive value 41.87%). Unable to corroborate these numbers due to lack of data.
Serum and capillary β-OHB values determined by the Precision-Xtra were highly correlated (r=0.99, P<0.001).

Assessment of methodological quality table

<table>
<thead>
<tr>
<th>Item</th>
<th>Scholar's judgment</th>
<th>Support for judgment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Representative spectrum?</td>
<td>No</td>
<td>50 patients (26 men and 24 women, mean age 60.28.2 years) had DKA</td>
</tr>
<tr>
<td>Acceptable reference standard?</td>
<td>Yes</td>
<td>β-OHB was determined using an enzymatic end-point spectrophotometric method</td>
</tr>
<tr>
<td>Acceptable delay between tests?</td>
<td>Yes</td>
<td>The capillary blood for the determination of glucose and β-OHB was obtained simultaneously with the venous blood sample used for the determination of glucose, biochemical parameters, and β-OHB levels.</td>
</tr>
<tr>
<td>Partial verification avoided?</td>
<td>Yes</td>
<td>it was one to one testing</td>
</tr>
<tr>
<td>Differential verification avoided?</td>
<td>Yes</td>
<td>it was one to one testing</td>
</tr>
<tr>
<td>Incorporation avoided?</td>
<td>Yes</td>
<td>two separate tests</td>
</tr>
<tr>
<td>Reference standard results blinded?</td>
<td>Unclear</td>
<td>did not report</td>
</tr>
<tr>
<td>Index test results blinded?</td>
<td>Unclear</td>
<td>did not report</td>
</tr>
<tr>
<td>Relevant clinical information?</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>Uninterpretable results reported?</td>
<td>Unclear</td>
<td>did not report</td>
</tr>
<tr>
<td>Withdrawals explained?</td>
<td>No</td>
<td></td>
</tr>
</tbody>
</table>
Search Strategy / Bibliography:


http://www.ncbi.nlm.nih.gov/sites/myncbi/collections/public/1ZgGxv6audfkW_e3uQiBkfekW/ resulted in 61 citations and 6 additional citations found through google and related citations in Pubmed

http://www.ncbi.nlm.nih.gov/sites/myncbi/collections/public/1v1pldqxmjz8ui76XfpIq65S5v/; two citations answered the question