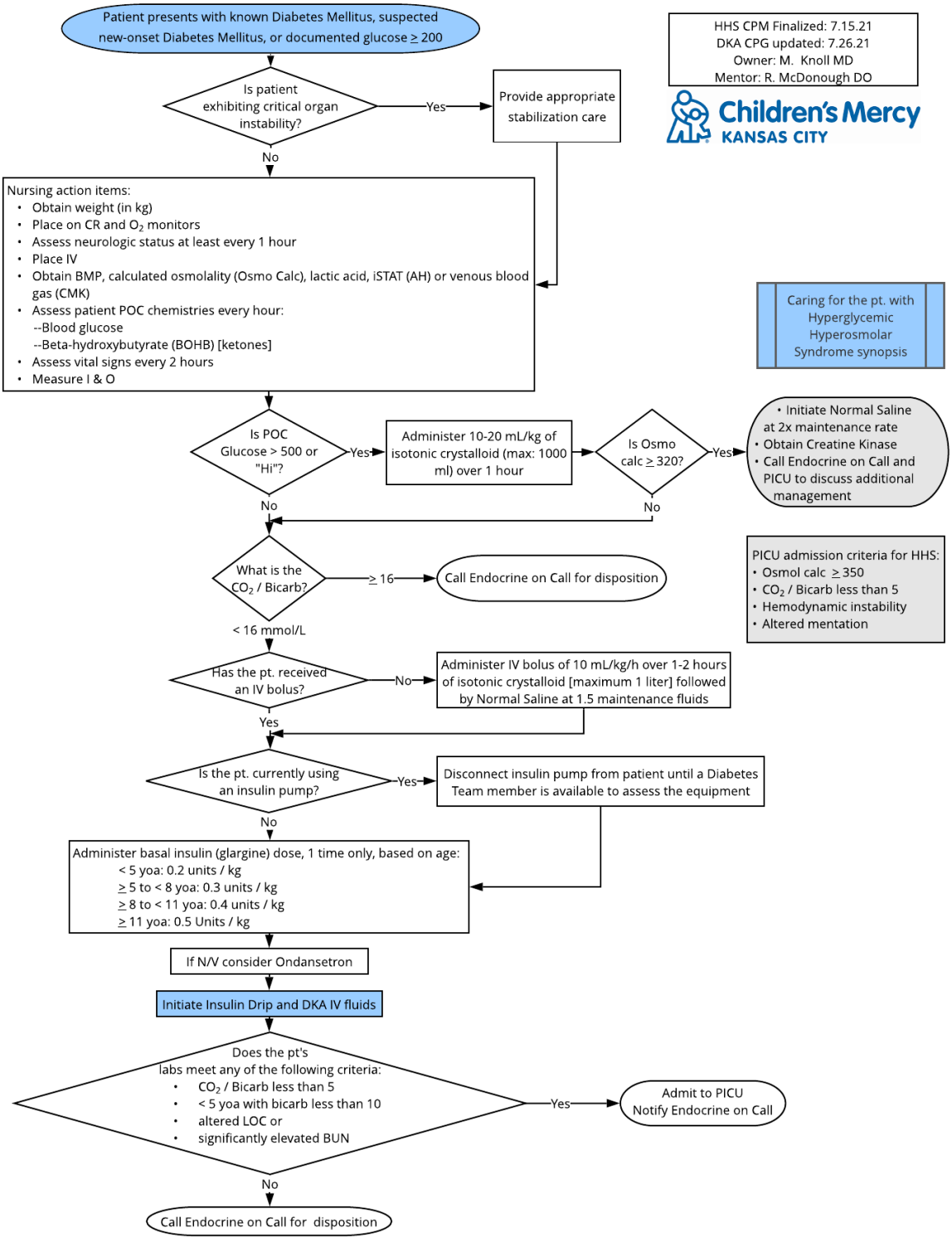
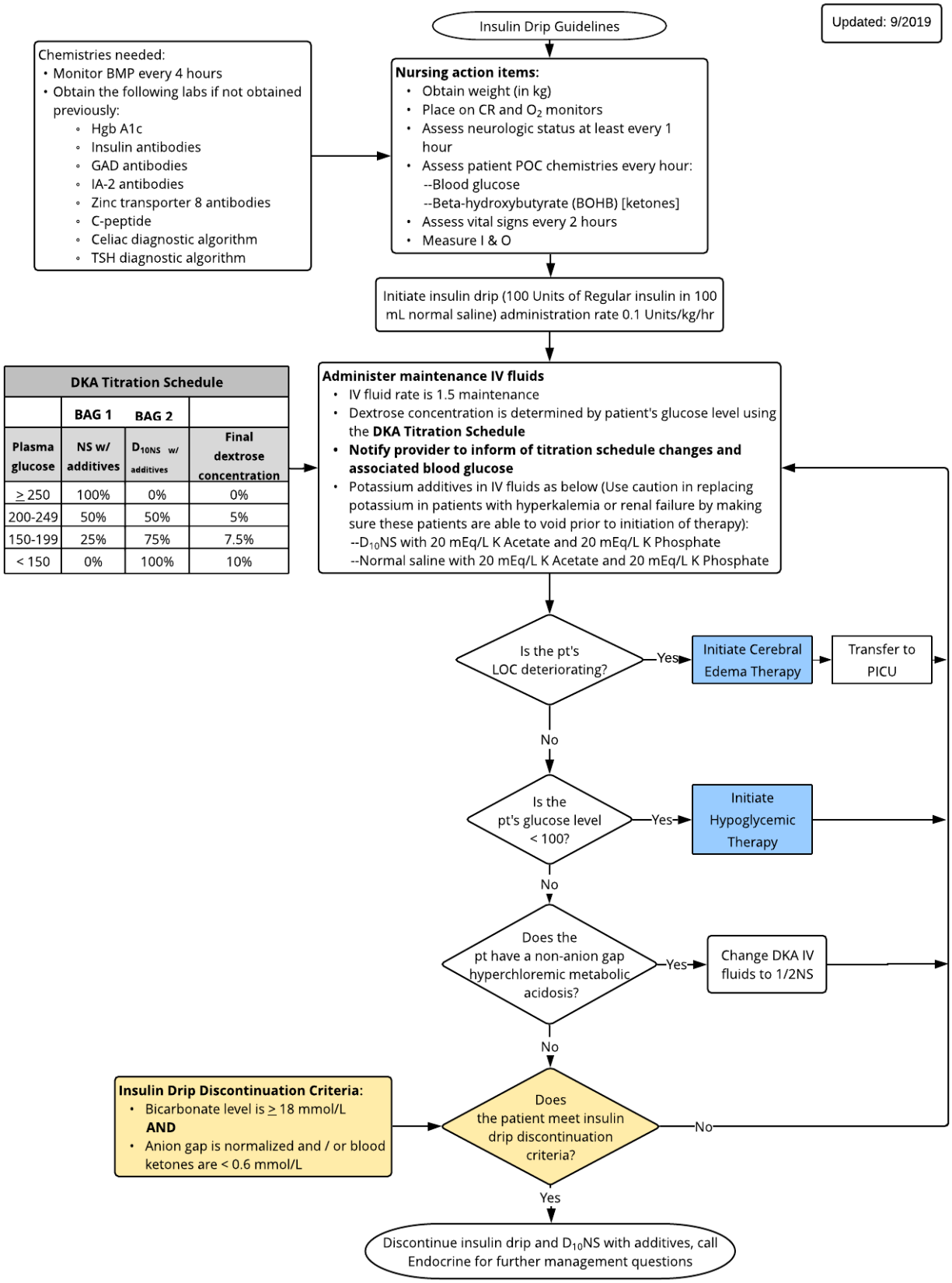
Children's Mercy Hospitals and Clinics
Evidence Based Practice

Diabetic Ketoacidosis Clinical Practice Guideline with Hyperglycemic Hyperosmolar Syndrome Care Process Model

Algorithm:



Insulin Drip Algorithm



Epidemiology:
In most western countries, type 1 diabetes accounts for over 90% of childhood and adolescent diabetes, 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 1 per 500-600 with the T1D incidence doubling every 20 years (Rogers, Kim, Banerjee & Lee, 2017). 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.

Linkage to specific combinations of alleles at the DRB1, DQA1 and DQB1 loci, with both susceptible and 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 Mendelian pattern of inheritance. The concordance rates in the 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 fathers with diabetes (3.6–8.5%) compared with mothers with diabetes (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 has known or presumed diabetes mellitus (here to referred to as "diabetes") a CO2 <16 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?

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 hourly POC blood β-hydroxybutyrate
- Hourly capillary blood glucose for patients on insulin drips and those receiving every 2-hour correction doses of subcutaneous insulin.
- Bicarbonate level (from BMP, iSTAT or VBG) will assist emergency department clinicians in determining patient placement. Ongoing monitoring of 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
- BUN level significantly elevated.

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.
   - 1.5x 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.
   - 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".
   - 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. This injection aids in the transition to subcutaneous dosing at DKA resolution, and only plays a small role in DKA treatment

- **New-onset diabetes–** 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 diabetes patient –** if patient is connected to an insulin pump, it should be disconnected. Then administer glargine insulin based on the above "new-onset diabetes" recommendations. If patient is on injections administer home dose of glargine or use above "new-onset diabetes" 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 D_{10} NS with additives fluids based on blood glucose.

DKA Titration Schedule			
	BAG 1	BAG 2	
	Given as Percentages		
Plasma Glucose	**NS w/ additives**	**D_{10} NS w/ additives**	**Final Dextrose Concentration**
> 250	100%	0%	0%
200-249	50%	50%	5%
150-199	25%	75%	7.5%
< 150	0%	100%	10%

- If blood glucose drops between 80 to 99 mg/dL decrease IV insulin to 0.05units/kg/hour and contact the Supervising Physician.
- If blood glucose drops < 80 mg/dL stop IV insulin, follow hypoglycemia protocol located under supportive documents (see page 13), and contact Supervising Physician.
- Continue IV insulin infusion until bicarbonate level is ≥18mmol/L AND 1) anion gap is normalized, or 2) POC 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.**

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.
   - 1.5x maintenance fluids should be changed to NS with 20 mEq/L K Acetate and 20 mEq/L K Phosphate as soon as available.
   - An additional IVF bag of D_{10} 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".
   - NPO with ice chips initially. If patient clinically appears well and would like to eat, they may do so, but they must receive the appropriate dose of insulin for carbohydrates consumed. This dose may be found in their diabetes clinic visit or inpatient consultation records.
2. **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. This injection aids in the transition to subcutaneous dosing at DKA resolution, and only plays a small role in DKA treatment
      - **New-onset diabetes–** 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 diabetes patient –** if patient is connected to an insulin pump, it should be disconnected. Then administer glargine insulin based on the above "new-onset diabetes" recommendations. If patient is on injections administer home dose of glargine or use above "new-onset diabetes" 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 D_{10} NS with additives fluids based on blood glucose.

DKA Titration Schedule			
	BAG 1	BAG 2	
	Given as Percentages		
Plasma Glucose	**NS w/ additives**	**D_{10} NS w/ additives**	**Final Dextrose Concentration**
> 250	100%	0%	0%
200-249	50%	50%	5%
150-199	25%	75%	7.5%
<150	0%	100%	10%

- 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 (see page 13), and contact Supervising Physician.
- Continue IV insulin infusion until bicarbonate level is ≥18mmol/L AND either 1) anion gap is normalized, or 2) 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.**

c. 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 D_{10} NS with additives fluids based on blood glucose.

DKA Titration Schedule			
	BAG 1	BAG 2	
	Given as Percentages		
Plasma Glucose	**NS w/ additives**	**D_{10} NS w/ additives**	**Final Dextrose Concentration**
> 250	100%	0%	0%
200-249	50%	50%	5%
150-199	25%	75%	7.5%
< 150	0%	100%	10%

- If blood glucose drops < 80 mg/dL follow hypoglycemic protocol located under supportive documents (see page 13) 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 AND either 1) anion gap is normalized, or 2) 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, very elevated BUN at presentation, use of bicarbonate for treatment of acidosis, fluid bolus volume over 40 mL/kg given in the first 4 hours of treatment, a n d 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 to ½
            - Begin medication therapy with one of the two options below
                - Mannitol 0.5-1 g/kg IV over 20 minutes
                - Hypertonic saline (3%), 5-10 mL/kg over 30 minutes
            - Obtain CT head **after** treatment has been started to rule out other possible intracerebral causes of neurologic deterioration (thrombosis or hemorrhage). ***If cerebal edema is suspected treatment should precede imaging studies***!
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 (see page 13)
4. **Hypophosphatemia**
5. **Pancreatitis**

Discharge Criteria for DKA:

- **Resolution of DKA**: bicarbonate ≥18mmol/L OR venous pH >7.3, WITH normal (closed) 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 number 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.

Supporting tools

Informational Tools: ***Types of Insulin see Table 1.***

Table 1. **Types of Insulin**

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

Procedures:

1. *Hypoglycemia* (see page 13)
2. *New Onset Diabetes* (see page 14)
3. *Known Diabetic with Diabetic Ketoacidosis* (see page 15)
4. *Known Diabetic at Risk for Diabetic Ketoacidosis* (see page 16)

Hypoglycemia

1. Patients currently in DKA on IV insulin drip:
    a. Blood glucose < 80 mg/dL
        i. Stop insulin drip. Maximize D_{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 $D_{10}W$ 5 mL/kg bolus IV through peripheral IV, if central line present may administer $D_{25}W$ 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 can 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 $D_{10}W$ 5 ml/kg bolus IV through peripheral IV. If central line present may administer $D_{25}W$ 2 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 (IA-2 Ab, GAD-65 Ab, zinc transporter Ab, insulin Ab), c-peptide, TSH Diagnostic Algorithm, and Celiac Diagnostic Algorithm
3. If patient is not in 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. For patients presenting in DKA, basal insulin doses are as above
            1. < 5 yoa: 0.2 units/kg every 24 hours
            2. 5 to 10 years: 0.25 units/kg every 24 hours
            3. > 10 years: 0.3 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 above prescribed threshold prior to a meal administer a correction dose of subcutaneous rapid acting (lispro, aspart, glulisine) insulin based on insulin sensitivity factor (ISF).

$$\text{ISF} = \frac{1800}{Lantus\ dose\ X2}$$

            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 monitor only for BG > 240 mg/dL or with vomiting/abdominal pain
    d. IV Fluids
        i. Saline lock IV once DKA resolved.
    e. Carbohydrate Counting Diet
    f. Diabetes education
        i. Provided in either the ambulatory or inpatient settings depending on patient circumstances. Discuss with endocrinologist on-call to determine education disposition.
        ii. Refer to public website for educational materials available to families.

Known Diabetic with Diabetic Ketoacidosis

Begin management of DKA as per clinical practice guidelines.

1. 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, 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 last dose of insulin glargine has been administered.
        iv. All further insulin administration should occur via rapid acting insulin from the pump once reconnected (for example basal insulin, meal boluses and correction boluses).
    b. Patients on Multiple Daily Injections (MDI):
        i. The home basal insulin (glargine, detemir, degludec) 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 and insulin sensitivity factors 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 (current glucose)-100 (target glucose) = 250 250÷50 (ISF) = 5 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:

$$\text{ISF} = \frac{1800}{Total\ Daily\ Dose\ of\ Insulin}$$

    d. Diabetes education:
        Home sick day and/or ketone management should be reviewed with the patient by a diabetes educator prior to discharge.
        i. 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/kg for moderate ketones.
            2. 0.2 units/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 remains > 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. Ketone/DKA correction doses ***MAY NOT*** be given through insulin pump.
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 remains > 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 The Children's Mercy Hospitals. 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.

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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:
      International Diabetes Federation. (2010). Global IDF/ISPAD guidelines for Type 1 diabetes in childhood and adolescence. Retrieved from http://www.fdgdiabete.it/public/draft_idf_2010.pdf

Wolfsdorf, J., Glaser, N., & Sperling, M. A. (2006). Diabetic ketoacidosis in infants, children, and adolescents: A consensus statement from the American Diabetes Association. *Diabetes Care, 29*(5), 1150-1159. doi: 29/5/1150 [pii] 10.2337/diacare.2951150

2. Review preparation
   a. PICOT (***P***atient, ***I***ntervention, ***C***omparison, ***O***utcome, ***T***ype 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
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 the CPG Team comprised of content expert clinicians, the Office of EBP, 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

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Ferguson, A. M., Michael, J., Bartlett, J. A., Barnes, M., DeLurgio, S., Turpin, A., Garg, U., & Clements, M. (2015, July 26-30). Establishing a point-of-care β-Hydroxybutyrate concentration to initiate treatment of pediatric diabetic ketoacidosis. American Association for Clinical Chemistry: 2015 Annual Meeting & Clinical Lab Expo. Atlanta, GA.

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Appendix A

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:

	Quality assessment						No of patients		Effect	Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Subcutaneous Insulin	Continuous Intravenous Insulin	Absolute	
pH >7.3 (h) (Better indicated by lower values)										
2[1,2]	RCT	Very serious[5]	No serious inconsistency	No serious indirectness	Serious[6]	reporting bias	25	25	MD 1.94 lower (4.07 lower to 0.19 higher)	⊕OOO VERY LOW
Bicarbonate > 15 - 18 mEq/l (h) (Better indicated by lower values)										
2[1,2]	RCT	Very serious[7]	No serious inconsistency	No serious indirectness	Serious[8]	reporting bias	25	25	MD 1.35 lower (4.36 lower to 1.65 higher)	⊕OOO VERY LOW
B-hydroxybutyrate <0.6mmol/l (h) (Better indicated by lower values)										
1[1]	RCT	Very serious[9]	No serious inconsistency	No serious indirectness	Serious[10]	none	10	10	MD 4.1 lower (10.29 lower to 2.09 higher)	⊕OOO VERY LOW
Urine Ketone Negative (h) (Better indicated by lower values)										
1[1]	RCT	Very serious[11]	No serious inconsistency	No serious indirectness	Serious[12]	none	10	10	MD 5.1 lower (13.13 lower to 2.93 higher)	⊕OOO VERY LOW

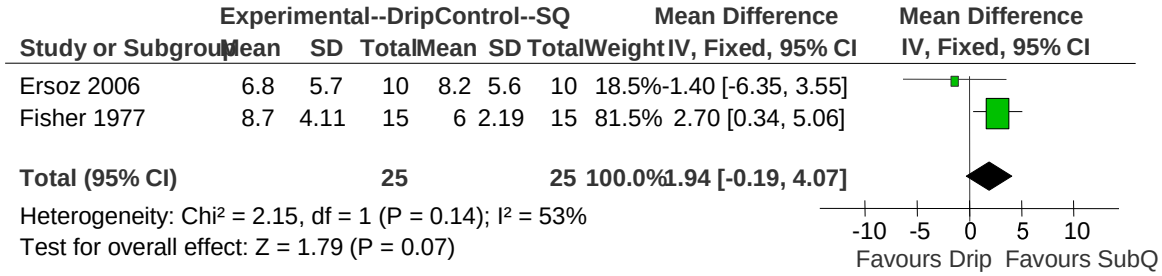
Hospital Stay (days) (Better indicated by lower values)										
2[3,4]	RCT	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[13]	none	35	35	MD 0.19 lower (1.08 lower to 0.7 higher)	⊕⊕⊕O MODERATE
Duration of treatment until resolution of DKA (hrs) (Better indicated by lower values)										
2[3,4]	RCT	No serious risk of bias	No serious inconsistency	No serious indirectness	Very serious[14]	none	35	35	MD 1 lower (2.53 lower to 0.53 higher)	Low
Duration of therapy until hyperglycemia < 200 - 250 mg/dL (hr) (Better indicated by lower values)										
4[1,2,3,4]	RCT	Serious[15]	No serious inconsistency	No serious indirectness	Serious[16]	none	60	60	MD 0.22 lower (1.42 lower to 0.97 higher)	Low
Amount of insulin (units) until resolution of DKA (Better indicated by lower values)										
4[1,2,3,4]	RCT	Serious[17]	No serious inconsistency	No serious indirectness	Serious[18]	none	60	60	MD 6.45 lower (14.07 lower to 1.16 higher)	Low

[1] Ersoz (2006).
[2] Fisher (1977).
[3] Umpierrez Cuervo (2004).
[4] Umpierrez Latif (2004).
[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.
[14] Same as footnote 13.
[15] Two of the articles (Ersoz, 2006; Fisher 1977) did not describe how risk of bias was minimized while the other two articles (Umpierrex, Cuervo, 2004; Umpierrez, Latif, 2004) did describe how risk of bias was minimimized.
[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.

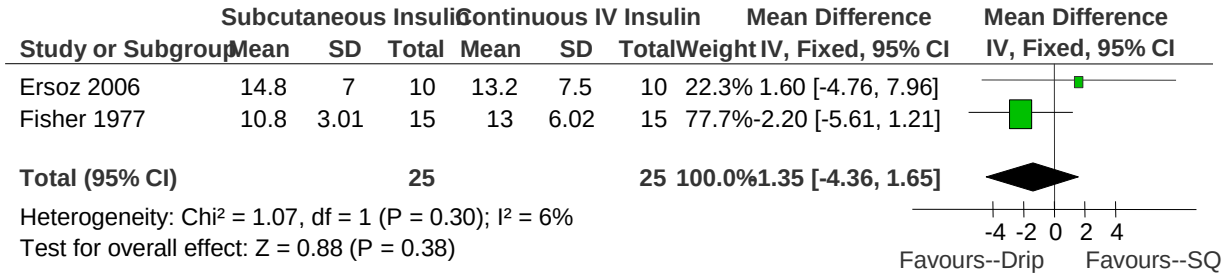
Synthesis Author(s): EBP Scholars (Bartlett, J. A., Dusin, J. D., Gutierrez, C. L., & Shubat, S. J.)
Date: 2011-11-23

Forest Plots of Comparisons

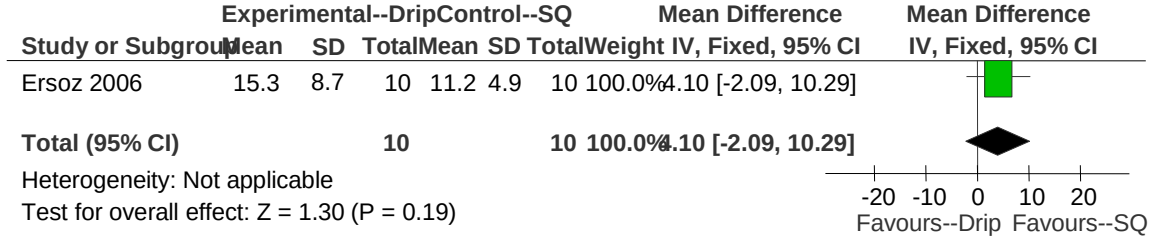
Subcutaneous Insulin vs. Continuous Intravenous Insulin, outcome: pH >7.3 (h).



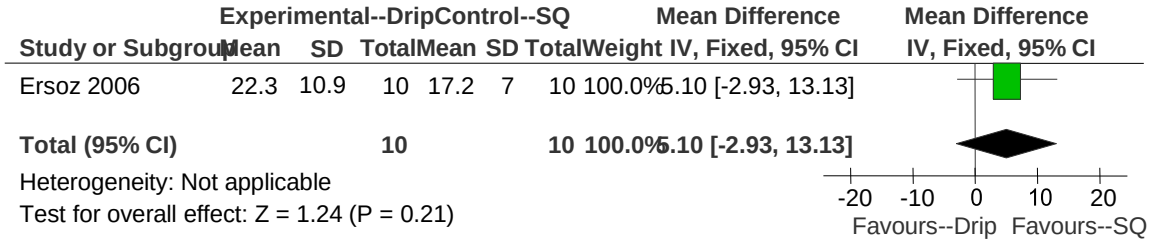
Subcutaneous Insulin vs Continuous Intravenous Insulin, outcome: Bicarbonate > 15 - 18 mEq/l (h).



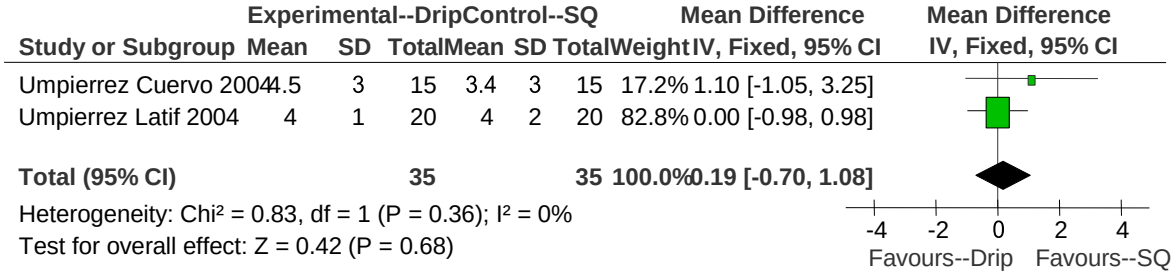
Subcutaneous Insulin vs Continuous Intravenous Insulin, outcome: B-hydroxybutyrate <0.6mmol/l (h).



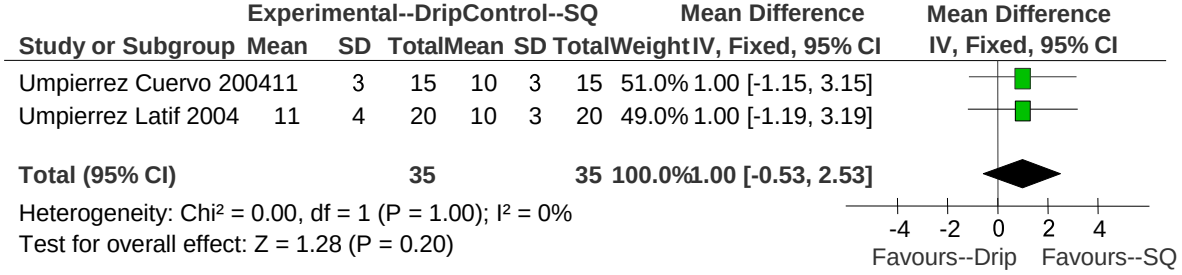
Subcutaneous Insulin vs Continuous Intravenous Insulin, outcome: Urine Ketone Negative (h).



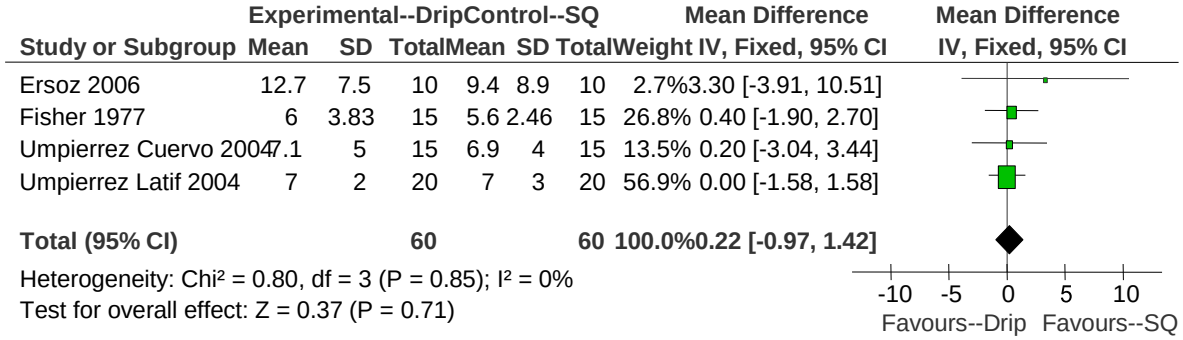
Subcutaneous Insulin vs Continuous Intravenous Insulin, outcome: Hospital Stay (days).



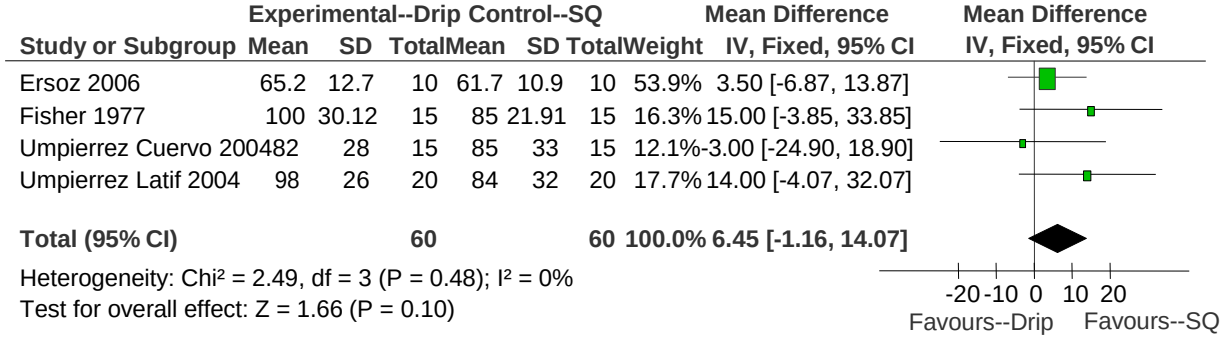
Subcutaneous Insulin vs Continuous Intravenous Insulin, outcome: Duration of treatment until resolution of DKA (hrs).



Subcutaneous Insulin vs Continuous Intravenous Insulin, outcome: Duration of therapy until hyperglycemia < 200 - 250 mg/dL (hr).



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



Search strategy implemented:

PubMed performed October 22, 2010:

"Diabetic Ketoacidosis/drug therapy"[Majr] AND ("Insulin/administration and dosage"[Mesh] AND ("Infusions, Intravenous"[Mesh] OR "Injections, Subcutaneous"[Mesh])) AND ("humans"[MeSH Terms] AND (systematic[sb] OR (Meta-Analysis[ptyp] OR Randomized Controlled Trial[ptyp] OR Comparative Study[ptyp])) AND English[lang]) 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 lispo 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

Bias	Scholar's judgement	Support for judgement
Random sequence generation (selection bias)	Unclear Risk	Sequence generation was not described.
Allocation concealment (selection bias)	Unclear Risk	Allocation was not described
Blinding (performance bias and detection bias)	High Risk	Unable to blind patients or practitioners.
Incomplete outcome data (attrition bias)	Unclear Risk	None discussed.
Selective reporting (reporting bias)	Unclear Risk	None discussed.
Other bias	Unclear Risk	None discussed.

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 (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 above7.3 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.

Risk of bias table

Bias	Scholar's judgement	Support for judgment
Random sequence generation (selection bias)	Unclear Risk	No description given.
Allocation concealment (selection bias)	Unclear Risk	No description given.
Blinding (performance bias and detection bias)	Unclear Risk	No description given.
Incomplete outcome data (attrition bias)	Unclear Risk	No description given.
Selective reporting (reporting bias)	Unclear Risk	No description given.
Other bias	Unclear Risk	No description given.

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 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 3. 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

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

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 level250 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 level31 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

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