DKA, HHS, and Hypoglycemia
Approaches for Diabetes Management
February 2, 2019
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Disclosures

I have no conflicts of interest or other disclosures relevant to this presentation.
Learning Objectives

1. Discuss three acute complications of diabetes with treatment approaches

2. Summarize clinical findings, management, and complications of DKA, HHS and hypoglycemia

3. Recognize the similarities and differences between DKA and HHS

4. Define prevention strategies for hypoglycemia in diabetes

Case 1

18 year-old man presented to the emergency department with 2 days of vomiting, diarrhea, abdominal pain and malaise

He had prior symptoms of polyuria and polydipsia

He has been drinking Gatorade to try to stay hydrated.

He had not had any recent medical care

An initial blood sugar by POC fingerstick is >600
Case 1

Chemistry

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<thead>
<tr>
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- WBC’s 12,000; + urine ketones
- VBG: pH 7.02, PCO₂ 30, HCO₃ 8

Hyperglycemic Crisis: DKA vs. HHS

Hyperglycemic Crisis

- NATIONAL DIABETES STATISTICS REPORT, 2017
  207,000 ER visits for hyperglycemic crisis in 2014
  - 9.5 per 1000 persons with diabetes (95% CI)

- 168,000 admissions for DKA in 2014
  - 7.7 out of every 1000 persons with diabetes

- HHS in children has increased by 52.4% from 1997 to 2009

- TRENDS IN DKA HOSPITALIZATIONS, 2000-2014
  - DKA in persons < 45 years is 27 X the rate for persons ≥ 65 years.

CDC National Diabetes Statistics Report 2017; Benoît 2018; Dessai 2018; Pasquel 2014
Diabetic Ketoacidosis (DKA)

Uncontrolled hyperglycemia
Metabolic acidosis
Increased ketones

<table>
<thead>
<tr>
<th></th>
<th>Mild DKA</th>
<th>Moderate DKA</th>
<th>Severe DKA</th>
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</thead>
<tbody>
<tr>
<td>Anion-gap acidosis</td>
<td>pH 7.25-7.30</td>
<td>pH 7.00-7.24</td>
<td>pH &lt; 7.00</td>
</tr>
<tr>
<td>Bicarb</td>
<td>&lt;15-18</td>
<td>10 to &lt;15</td>
<td>&lt;15</td>
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<tr>
<td>Anion gap</td>
<td>&gt;10</td>
<td>&gt;12</td>
<td>&gt;12</td>
</tr>
<tr>
<td>Hyperglycemia</td>
<td>&gt;250</td>
<td>&gt;250</td>
<td>&gt;250</td>
</tr>
<tr>
<td>Ketonemia/ketonuria</td>
<td>Present</td>
<td>Present</td>
<td>Present</td>
</tr>
<tr>
<td>Mental Status</td>
<td>Alert</td>
<td>Alert/drowsy</td>
<td>Stupor/coma</td>
</tr>
</tbody>
</table>

Kitabchi, 2009

Hyperosmolar Hyperglycemic State (HHS)

PREVIOUSLY KNOWN AS:
Hyperglycemic hypersomolar nonketotic coma (HONK) or hyperglycemic hyperosmolar nonketotic state (HHNK)

Endogenous insulin is enough to prevent lipolysis and ketogenesis but inadequate to facilitate glucose utilization

Dehydration >>> than in DKA
- Total body water deficit usually 7-12 liters

Maletkovic, 2013; Gouveia, 2013; Pasquel 2014
Pathogenesis of DKA and HHS

Absolute insulin deficiency
Stress
Infection
Insufficient Insulin
Relative insulin deficiency
Insufficient Insulin
Glucagon
Cortisol
Catecholamines
Growth hormone
Proteolysis
Adipose tissue
Lipolysis
FFA’s
Liver
Ketone body production
Gluconeogenesis
Hyperketonemia
Glucosuria
Dehydration
Hyperglycemia
Reduced glucose utilization
Minimal ketones
Impaired renal function
Hyper-osmolarity

Pathogenesis of DKA

Absolute insulin deficiency
Stress
Infection
Insufficient Insulin
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Pathogenesis of HHS

Stress
Infection
Insufficient Insulin

Glucagon
Cortisol
Catecholamines
Growth hormone

Relative insulin deficiency

Proteolysis

Minimal ketones

Peripheral tissues

Reduced glucose utilization

Gluconogenesis

Hyperglycemia

Glucosuria

Hyperosmolarity

Dehydration

Impaired renal function

HHS

Pathogenesis of DKA and HHS

Absolute insulin deficiency

Lipolysis

FSA's

Adipose tissue

Hyperketonemia

Glucagon
Cortisol
Catecholamines
Growth hormone

Proteolysis

Peripheral tissues

Reduced glucose utilization

Gluconogenesis

Hyperglycemia

Glucosuria

Hyperosmolarity

Dehydration

Impaired renal function

DKA

HHS

DKA and HHS

Polyuria and polydipsia
Nausea and vomiting
Anorexia
Fatigue/malaise

Precipitating factors
- Infection
- Extreme physical stress
- Missed or inadequate insulin therapy (including insulin pump malfunction)
- Medications
  - Corticosteroids
  - Pentamidine
  - Terbutaline
  - Anti-psychotics
- Cocaine
- Religious fasting
- Cannabis—hyperemesis syndrome
- DKA: SGLT2-inhibitors—70% of reported cases in literature were euglycemic

Maletkovic, 2013; Gallo, 2016; Goldenberg 2016;
### DKA vs. HHS

<table>
<thead>
<tr>
<th>Timing</th>
<th>DKA</th>
<th>HHS</th>
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<tbody>
<tr>
<td>Develops over hours to days</td>
<td>Develops over days to weeks</td>
<td></td>
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<table>
<thead>
<tr>
<th>Hyperventilation</th>
<th>DKA</th>
<th>HHS</th>
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<tr>
<td>+ (Kussmaul breathing)</td>
<td>-</td>
<td></td>
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<table>
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<tr>
<th>Abdominal pain</th>
<th>DKA</th>
<th>HHS</th>
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<th>Mental status change</th>
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**Anion-gap acidosis**
- DKA: pH < 7.3
- HHS: pH > 7.3

**Bicarbonate**
- DKA: < 15
- HHS: > 18

**Osmolality**
- DKA: < 320
- HHS: > 320

**Hyperglycemia**
- DKA: > 250
- HHS: > 600

**Ketoneemia/ketonuria**
- DKA: Present
- HHS: Rare

**Mortality**
- DKA: 2%
- HHS: 20%

Maletkovic, 2013

Kitabchi, 2009; Maletkovic, 2013
Approach to Patient with Hyperglycemic Crisis

STABILIZE PATIENT

Airway
Ventilation & Oxygenation
IV Access
Cardiac Monitor
Urinary Catheter

Maletkovic, 2013

Evaluation of Patient with Hyperglycemic Crisis

HISTORY AND PHYSICAL EXAM

History
- Precipitating factors
- Symptoms of infection
- Missed insulin

Physical Exam
- Mental status
- Respiration (Kussmaul)
- Fruity breath
- Signs of infection
- Signs of dehydration

Maletkovic 2013; English 2004
Case 1

Exam:
- T 38.4°C (101 F); BP 112/57; HR 146, RR 60 (Kussmaul respirations)
- Obtunded: GCS 9
- Obese, BMI 33 kg/m²
- Acanthosis nigricans of neck
- Pupils sluggish, dry mucous membranes

Evaluation of Patient with Hyperglycemic Crisis

LABORATORY EVALUATION

- Glucose, Metabolic Panel, Phosphate, Magnesium, ABG
- CBC, Serum Ketones, Urinalysis, Cardiac Enzymes, A1C, Coagulation profile, Urine Pregnancy Test
- Consider also Urine & Blood Cultures, Lumbar Puncture, Amylase and Lipase, CPK
Evaluation of Patient with Hyperglycemic Crisis

OTHER STUDIES AND IMAGING

- EKG
- Chest Radiograph
- Additional Imaging of Chest, Abdomen, Brain

Interpretation of Labs

Calculating Anion Gap:
- \((\text{Serum sodium}) - (\text{Chloride} + \text{bicarbonate})\)

Sodium: osmotic forces drive water into vascular spaces
- Corrected sodium: Add 1.6 mEq/L for every 100 points glucose is elevated
- Some laboratories will reflect additional decreases in sodium measurement due to pseudohyponatremia from elevated lipids

Serum Osmolality
- \((2 \times \text{serum sodium}) + (\text{glucose in mg/dL divided by 18}) + (\text{BUN in mg/dL divided by 2.8})\)
- Effective Osmolality
  \((2 \times \text{serum sodium}) + (2 \times \text{potassium}) + (\text{glucose in mg/dL divided by 18})\)
### Case 1

**Chemistry**

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- WBC’s 12,000; + urine ketones
- VBG: pH 7.02, PCO₂ 30, HCO₃ 8

Hyperglycemic Crisis: DKA vs. HHS

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### Interpretation of Labs

*Calculating Anion Gap:*

\[(\text{Serum sodium}) - (\text{Chloride} + \text{bicarbonate})\]

**Case 1**

\[138 - (112 + 9) = 138 - 121 = 17\]

Maletkovic, 2013
Interpretation of Labs

Sodium: osmotic forces drive water into vascular spaces
- Corrected sodium: Add 1.6 mEq/L for every 100 points glucose is elevated

**Case 1**

**Sodium 138 but glucose 1600**...

**Step 1:** 1600 - 100 = 1500
**Step 2:** 1500 ÷ 100 = 15
**Step 3:** 15 x 1.6 = 24
**Step 4:** 138 + 24 = 162

Maletkovic, 2013

Interpretation of Labs

**Serum Osmolality**
- \((2 \times \text{serum sodium}) + (\text{glucose in mg/dL divided by 18}) + (\text{BUN in mg/dL divided by 2.8})\)
  - **Case 1**
  - \((2 \times 138) + (1600/18) + (38/2.8) =\)
  - \(276 + 88.9 + 13.6 =\)
  - \(378\)

- Effective Osmolality (does not include BUN since it does not affect osmotic gradient)
  - \((2 \times 138) + (2 \times 6.4) + (1600/18) =\)
  - \(276 + 12.8 + 88.9 =\)
  - \(378\)

Maletkovic, 2013
### Case 1: DKA versus HHS

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<td>pH &lt; 7.3</td>
<td>pH &gt; 7.3</td>
</tr>
<tr>
<td><strong>Bicarbonate</strong></td>
<td>&lt;15</td>
<td>&gt;18</td>
</tr>
<tr>
<td><strong>Anion gap</strong></td>
<td>&gt;10</td>
<td>variable</td>
</tr>
<tr>
<td><strong>Osmolality</strong></td>
<td>&lt;320</td>
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</tr>
<tr>
<td><strong>Hyperglycemia</strong></td>
<td>&gt;250</td>
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<td><strong>Ketonemia/ketonuria</strong></td>
<td>Present</td>
<td>Rare</td>
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#### Anion-gap Acidosis
- **DKA**: pH < 7.3, Anion gap > 10, Osmolality < 320, Hyperglycemia > 250, Ketonemia/ketonuria Present, Bicarbonate < 15. Risk of Mortality is 20% (5% in elderly).
- **HHS**: pH > 7.3, Anion gap variable, Osmolality > 320, Hyperglycemia > 600, Ketonemia/ketonuria Rare, Bicarbonate > 18. Risk of Mortality is 2%.

#### Protocol for management of adult patients with DKA or HHS

1. **Initial Evaluation**
   - Check capillary glucose and serum/urine ketones to confirm hyperglycemia and ketonemia/ketonuria. Obtain blood for metabolic profile: Start iv fluids: 1 L of 0.9% NaCl per hour.
   - Determine hydration status (severely, moderately, mildly).
   - Evaluate corrected serum Na+ values: high, normal, low.
   - 0.45% NaCl (250-500 ml/hr) depending on hydration status.
   - When serum glucose reaches 200 mg/dl (DKA) or 300 mg/dl (HHS), change to 5% dextrose with 0.45% NaCl at 150-250 ml/hr.

2. **Insulin Administration**
   - **DKA**: When serum glucose reaches 200 mg/dl, reduce regular insulin infusion to 0.02-0.05 U/kg/hr, or give rapid-acting insulin at 0.5 U/kg SC every 2 hrs. Keep serum glucose between 150 and 200 mg/dl until resolution of DKA.
   - **HHS**: When serum glucose reaches 300 mg/dl, reduce regular insulin infusion to 0.02-0.05 U/kg/hr. Keep serum glucose between 200 and 300 mg/dl until patient is markedly alert.

3. **Ketone Management**
   - **DKA**: Present and rare.
   - **HHS**: Rare.

4. **Potassium Management**
   - **DKA**: Administer adequate renal function (urate output = 10 ml/hr).
   - **HHS**: Monitor serum K+ every 2 hrs.

5. **Final Adjustments**
   - **DKA**: Give 20-30 mEq K+ in each liter of IV. Read to keep serum K+ between 3-3.5 mEq/L.
   - **HHS**: Do not give K+ but check serum K+ every 2 hrs.

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Kitabchi, 2009; Maletkovic, 2013; Cardoso, 2016

**Copyright © 2011 American Diabetes Association, Inc.**

Kitabchi A E et al. Dia Care 2009;32:1335-1343
Treatment of DKA and HHS

Fluid replacement
- Start normal saline at **10-20 ml/kg**
  - Patients under 18—no evidence that less rapid or isotonic saline protects from cerebral edema
  - Once euvoelma is achieved, may change to ⅓ NS for those with normal sodium or hypernatremia
  - In HHS, some experts recommend continuing isotonic saline unless osmolality is not falling despite adequate fluid resuscitation
- Dextrose should be added at glucose of **<250 mg/dL in DKA or <300 mg/dL in HHS**
  - Two-bag system may be used: one with needed electrolytes and no dextrose; one with needed electrolytes and 10% dextrose
  - Proportion of rate from 2-bag methods determines dextrose infusion and allows for easy adjustment for maintaining glucose in target range
  - Used primarily in Pediatric DKA but used effectively in adults with DKA as well with faster resolution of anion gap and reduced hypoglycemia

Maletkovic 2013, Glaser 2005; Fluid regimes for DKA 2018; Glaser 2018; Munir 2017

Hydration status
- Severe hypovolemia
- Mild dehydration
- Cardiogenic shock
- Evaluate corrected serum Sodium
- Serum Na⁺ high or Normal
- Serum Na⁺ low
- Hemodynamic Monitoring/pressors

1 Liter/Hr 0.9% NaCl

0.45% NaCl 250-500 ml/h

When glucose is 200-250 mg/dL (DKA) or 300 mg/dL (HHS), change to D5 with 0.45% NaCl at 150-250 ml/hr

0.9% NaCl 250-500 ml/h

Kitabchi 2009; Cardosa 2016
Treatment of DKA and HHS

Fluid Replacement Goals

- Total fluid replenishment over 24-48 hours (or more slowly if baseline kidney failure or heart failure)
- Avoid rapid correction of osmolality
- Keep change of corrected sodium to ≤0.5 mg/dl per hour and ≤10 mg/dl per 24 hours


Treatment of DKA and HHS

Potassium
- Total body depletion of potassium due to urinary and gastrointestinal losses
  - Glucosuria may result in 70mEq/L loss of potassium
- Shift of potassium out of cells from insulin deficiency, acidosis, and proteolysis will reverse with fluids and insulin
- Start potassium supplementation at potassium of <5.3mEq/L
- Monitor for arrhythmias

Maletkovic, 2013, Glaser 2005
Potassium

Establish adequate renal function
UOP 50ml/hr

- K+ <3.3
  - Hold insulin; Give 20-30 mEq K+ until K+ is >3.3
- K+ 3.3-5.2
  - 20-30 mEq K+/L
- K+ >5.2
  - Do not give K+
  - Check K+ every 2h


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Treatment of DKA and HHS

Insulin
- Start after initial fluid resuscitation; delay if potassium is <3.3 mEq/L
- Initial insulin bolus does not offer significant benefit
- Regular insulin via IV is preferred therapy (0.1 unit/kg/hr in DKA); rapid analogs may be used but higher cost
- Delay or reduce insulin rate in HHS in favor of hydration to avoid rapid osmotic shifts
- Intramuscular injection of rapid-acting analogues has been studied as well—may reduce cost if performed on general floor instead of ICU
- Insulin should continue until resolution of anion gap in DKA, not resolution of hyperglycemia

Maletkovic 2013; Glaser 2005; Cardosa 2015
Insulin:

- **Regular IV Route (DKA and HHS)**
  - 0.1 Unit/Kg as IV bolus
  - 0.1 Unit/Kg as IV continuous infusion

  If glucose does not fall 10% in 1st hour, give 0.14 Unit/Kg as bolus and resume infusion.

- **Regular IV Route (DKA and HHS)**
  - 0.14 Unit/kg as IV continuous infusion

  HHS: Reduce insulin to 0.02-0.05 Units/kg/hr once Glucose is 300 mg/dL

  DKA: Reduce insulin to 0.02-0.05 Units/kg/hr when glucose reaches 200 mg/dL

  HHS: Keep glucose between 150-200 mg/dL until resolution of DKA

  DKA: Keep glucose 200-300 until mentally alert

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**Treatment of DKA and HHS**

**Insulin**
- Check electrolytes, BUN, venous pH, Creatinine, glucose every 2-4 hours until stable
- After resolution of DKA or HHS and when able to eat, may initiate subcutaneous insulin regimen:
  - Continue IV infusion for 1-2 hours after subcutaneous insulin is given
  - In insulin naïve patients, start 0.5-0.8 Unit/Kg per day
  - Children: (0.5-1 Unit/kg/day)
  - Look for precipitating causes
- Continuation of basal insulin
  - Continuation of basal insulin during intravenous infusion of insulin may result decreased rebound hyperglycemia after insulin infusion is discontinued
  - In one small pediatric study (13), it reduced time to DKA resolution

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Maletkovic 2013; Glaser 2005; Cardosa 2016

Maletkovic, 2013; Glaser 2005; Cardosa 2015; Hsia, 2012
Treatment of DKA and HHS

BICARBONATE

Administration is controversial and limited to severe acidosis
- Risks of hypokalemia, hypernatremia, paradoxical CNS acidosis
- Children with DKA treated with bicarbonate were more likely to have cerebral edema

Maletkovic, 2013; Glaser, 2005; Glaser, 2001; Cardosa, 2016

Maletkovic 2013; Glaser 2005; Cardosa 2016
Treatment of DKA and HHS

PHOSPHATE

- Not clearly beneficial in all patients
- Risk of hypocalcemia

Maletkovic, 2013; Glaser, 2005; Glaser, 2001

Phosphate

Consider with Phos < 1 mg/dL
OR
Cardiac dysfunction, anemia, or respiratory distress

20-30 mmol/L/day K$_2$PO$_4$
(max rate of 4.5 mmol/h and 90 mmol per day)

Cardosa 2016
Case 1: Review Question #1

Which lists the proper treatment and order of treatment for this patient?

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<td>B</td>
<td>Insulin</td>
<td>Bicarbonate</td>
<td>Fluids</td>
<td>Potassium</td>
</tr>
<tr>
<td>C</td>
<td>Insulin</td>
<td>Fluids</td>
<td>Potassium</td>
<td>No bicarbonate</td>
</tr>
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Case 1

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Hyperglycemic Crisis: DKA vs. HHS
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Normal saline bolus, followed by 250-500 ml/hr of NS or 0.45 NS depending on sodium and osmolality trend
Insulin IV at 0.05 to 0.1 unit/kg/hr
Potassium once potassium is less than 5.3 and UOP has been established
No bicarbonate indicated; pH is not <6.9

Case 1: Clinical Course

He was admitted to the ICU
Given NS bolus over the first hour
Given NS of 250 ml/hr
Developed cardiac arrhythmia due to hyperkalemia in first 3 hours
- Insulin started at 0.03 units/kg/h along with dextrose
Developed status epilepticus and was intubated in first 12 hours
Insulin infusion and dextrose were carefully titrated to bring about slow correction of glucose and sodium
Case 1: Clinical Course

CT scan was normal (no edema)
Seizures resolved day 2
He developed rhabdomyolysis and pancreatitis
He has persistent hypertension
He was extubated day 4
He was transitioned to subcutaneous insulin

Complications of DKA and HHS

- Thrombosis—Particularly in HHS
- Cardiac arrhythmias
- Hypotension
- Cerebral edema
- Cerebral hemorrhage
- Pulmonary edema
- Renal failure
- Intestinal necrosis
- Pancreatitis
- Hypoglycemia
- Hypokalemia

Maletkovic, 2013; Glaser 2005
## Complications of DKA and/or HHS

<table>
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| Cerebral edema in children with DKA (0.3-1%) with mortality of 21-24% in those who develop cerebral edema and permanent neurologic morbidity in 21-26% | Malignant hyperthermia-like syndrome  
- Hyperpyrexia and rhabdomyolysis |
| Prompt administration mannitol (0.25-1g/kg) may be beneficial | |
| Hypertonic saline (3%) has grown in favor but increased mortality over mannitol seen in retrospective analysis | |

Maletkovic 2013; Glaser 2005, DeCourcey 2013

## Prevention of DKA and HHS

Education regarding sick day management for patient and caregivers  
- Early contact with health care team  
- Education about importance of insulin during illness  
- In pediatric cases, responsible adult assuming role of administering insulin  
- Initiation of easily digestible liquid diet containing carbohydrates and salt when needed  

Use of home ketone monitoring

Kitabchi 2009; Lewis 2013; Wolsdorf 2018
Prevention of DKA and HHS

Assess economic factors, social, and psychological factors
- Lack of resources to afford insulin or regular diabetes care
- Cutting insulin to facilitate weight loss
- Psychological reasons for missing insulin: depression, or other mood disorder:
  - 58% of patient with recurrent DKA at MUSC Children's Hospital had psychological diagnosis (depression, ADHD, bipolar disorder)

Kitabchi 2009; Lewis 2013; Wolsdorf 2018

Transition from Acute Care Setting

A structured discharge plan tailored to the individual's needs
- Outpatient follow-up with diabetes care provider within 1 month or 1-2 weeks if glycemic control is not optimized prior to leaving the hospital of
- Clear communication with outpatient providers (directly or via discharge summary)
- Medication reconciliation
- Prescriptions filled and reviewed with patient before discharge
- Follow-up is enhanced if inpatient team schedules outpatient follow-up
- Educational assessment and review of glucose self-monitoring, hypoglycemia and hyperglycemia, medication plan, healthy meal planning, sick-day management

ADA Standards of Care, 2019
Case 1:
Review Question #2
Which of the following would you NOT recommend for this patient’s tailored diabetes discharge plan?
A. Education on glucose monitoring, hypoglycemia, hyperglycemia, sick-day management, and insulin administration
B. Follow-up appointment in 6 weeks
C. Dietary counseling/education
D. Written discharge summary faxed to outpatient provider
E. Assessment of any economic barriers to ongoing care and address as needed
F. Outpatient prescriptions filled and reviewed with patient prior to discharge

Learning Objectives
1. Discuss three acute complications of diabetes with treatment modalities
2. Summarize clinical findings, management, and complications of DKA, HHS and hypoglycemia
3. Recognize the similarities and differences between DKA and HHS
4. Define prevention strategies for hypoglycemia in diabetes
Case 2
A 77 year old man with type 1 diabetes for 50 years is admitted to the hospital after a severe hypoglycemic event at home where he was found unconscious by his wife
- Initial glucose reading on home meter was 37
- His wife called EMS who gave D50 (25g)
- His blood sugar on arrival to the emergency room was 212
- A1C 8.2%
- He manages his diabetes with an insulin pump
- His wife notes that the patient has increased forgetfulness and repeated episodes of severe hypoglycemia, often without preceding symptoms

Hypoglycemia
- Occurs in 35-42% of Type 1 diabetes patients
- ER visits: 245,000 in adults in the US in 2014
  - 11.2 per 1000 persons with diabetes (95% CI 10.4-12.1)
- Higher rates of severe hyperglycemia if longer duration of diabetes
  - >15 years vs. >5 years: rates of 46% vs. 22%
- Cause of significant loss of productivity and hospital stays

Hypoglycemia Symptoms

<table>
<thead>
<tr>
<th>Adrenergic Symptoms</th>
<th>Neuroglycopenic Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pallor</td>
<td>Confusion</td>
</tr>
<tr>
<td>Diaphoresis</td>
<td>Slurred Speech</td>
</tr>
<tr>
<td>Shakiness</td>
<td>Irrational behavior</td>
</tr>
<tr>
<td>Hunger</td>
<td>Disorientation</td>
</tr>
<tr>
<td>Anxiety</td>
<td>Loss of consciousness</td>
</tr>
<tr>
<td>Irritability</td>
<td>Seizures</td>
</tr>
<tr>
<td>Headache</td>
<td>Pupillary Sluggishness</td>
</tr>
<tr>
<td>Dizziness</td>
<td>Decreased response to noxious stimuli</td>
</tr>
</tbody>
</table>

Kaira, 2013

Hypoglycemia Classification

<table>
<thead>
<tr>
<th>Level</th>
<th>Description</th>
</tr>
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<tbody>
<tr>
<td>Level 1</td>
<td>Glucose $&lt;70 \text{ mg/dL}$ and $\geq 54 \text{ mg/dL}$</td>
</tr>
<tr>
<td>Level 2</td>
<td>Glucose $&lt;54 \text{ mg/dL}$</td>
</tr>
<tr>
<td>Level 3</td>
<td>A severe even characterized by altered mental status and/or physical status requiring assistance</td>
</tr>
</tbody>
</table>

ADA Standards of Medical Care 2019
Hypoglycemia Treatment

Level 1 or Level 2 Hypoglycemia
- 15-20 g of carbohydrate in the form of glucose tablets (3-4), or other glucose-containing food/beverage; sources high in fat or protein are not recommended

Level 3 Hypoglycemia
- Glucagon 1 mg SQ or IM
  - Nausea and vomiting, hyperglycemia
  - Provide to all patients at risk for level 2 hypoglycemia
- IV Glucose 25g followed by glucose infusion

Sulfonylurea overdose may lead to prolonged hypoglycemia

Cryer, 2009; ADA Standards of Medical Care 2019

Case 2

A 77 year old man with type 1 diabetes for 50 years is admitted to the hospital after a severe hypoglycemic event at home where he was found unconscious by his wife
- Initial glucose reading on home meter was 37
- His wife called EMS who gave D50 (25g)
- His blood sugar on arrival to the emergency room was 212
- A1C 6.8%
- He manages his diabetes with an insulin pump
- His wife notes that the patient has increased forgetfulness and repeated episodes of severe hypoglycemia

How would you classify his Hypoglycemia?
### Hypoglycemia Classification

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</table>

### Causes of Hypoglycemia

<table>
<thead>
<tr>
<th>Too Much Insulin</th>
<th>Not Enough Glucose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incorrect amount of insulin</td>
<td>Inadequate carbohydrate intake or absorption</td>
</tr>
<tr>
<td>Increased insulin sensitivity</td>
<td>Decreased endogenous glucose production</td>
</tr>
<tr>
<td>Decreased insulin clearance</td>
<td>Increased utilization of carbohydrates and/or depletion of hepatic glycogen stores</td>
</tr>
<tr>
<td>Delayed gastric emptying: mismatch of timing of insulin and carbohydrate absorption</td>
<td></td>
</tr>
</tbody>
</table>

Kalra, 2013

ADA Standards of Medical Care 2019
### Hypoglycemia Risk Factors

<table>
<thead>
<tr>
<th>Risk Factors</th>
<th>Endocrine deficiencies</th>
</tr>
</thead>
<tbody>
<tr>
<td>◦ Duration of diabetes and age</td>
<td>◦ Hypothyroidism</td>
</tr>
<tr>
<td>◦ C-peptide negativity</td>
<td>◦ Hypopituitarism</td>
</tr>
<tr>
<td>◦ History of severe hypoglycemia</td>
<td>◦ Primary adrenal insufficiency</td>
</tr>
<tr>
<td>◦ Impaired awareness of hypoglycemia</td>
<td>◦ Growth hormone deficiency</td>
</tr>
<tr>
<td>◦ Strict glycemic control</td>
<td></td>
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<tr>
<td>◦ Sleep/general anesthesia or other sedation</td>
<td></td>
</tr>
<tr>
<td>◦ Reduced oral intake; emesis</td>
<td></td>
</tr>
<tr>
<td>◦ Critical illness</td>
<td></td>
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<tr>
<td>◦ Unexpected travel after rapid-acting insulin</td>
<td></td>
</tr>
<tr>
<td>◦ Sudden reduction in corticosteroid dose</td>
<td></td>
</tr>
<tr>
<td>◦ Reduced IV dextrose administration</td>
<td></td>
</tr>
<tr>
<td>◦ Interruption of enteral feedings or TPN</td>
<td></td>
</tr>
<tr>
<td>◦ Drug dispensing error</td>
<td></td>
</tr>
<tr>
<td>◦ Renal and hepatic dysfunction</td>
<td></td>
</tr>
</tbody>
</table>

Kalra, 2013
Hypoglycemia Outcomes

Functional brain failure reversed by correction of glucose levels

Long term cognitive effects seen in children (< 5, particularly vulnerable)

Prolonged hypoglycemia can cause brain death

Increased dementia, cerebral ataxia, cognitive problems in elderly

Glucose reperfusion in rat studies suggest that extreme hyperglycemia after hypoglycemia may contribute to neuronal death


Hypoglycemia may lead to sudden cardiac death from arrhythmia

“Dead in bed” syndrome: death in young Type 1 patients likely due to prolonged QT and arrhythmia (Accounts for 5-6% of deaths in this demographic)

Increase mortality in ACCORD (Action to Control Cardiovascular Risk in Diabetes) study in intensive group (goal a1C <6.5%) and 3 fold higher incidence of hypoglycemia

In the LEADER study, participants with type 2 DM with severe hypoglycemia (267 of 9,340) had increased risk of major cardiac events, CV death, and all-cause death

Cryer, 2009; Hallimi 2010, Kalra, 2013; Zinman 2018
Hypoglycemia and Alcohol

- Alcohol impairs endogenous glucose release
- May cause delayed hypoglycemia with increased risk lasting also long as 24 hour after ingestion
- Alcohol may also...
  - Blunt ability of patient to respond appropriately to early symptoms of hypoglycemia
  - Impair counter-regulatory response
  - May enhance cognitive deficits caused by hypoglycemia
- Hypoglycemic symptoms may be mistaken by others as intoxication

Choudhary, 2011; Richardson, 2005; Tetzchner, 2017

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Hypoglycemia and Alcohol

- Advise to patients:
  - Don’t include alcohol in their carb coverage/carb counting
  - Eat with ingestion of alcohol
  - Be prepared to monitor frequently
  - Target blood sugar of 100-140 before bed

Choudhary, 2011; Richardson, 2005
Hypoglycemia Unawareness

- Loss of adrenergic symptoms prior to onset of neuroglycopenic symptoms
- Hypoglycemia-associated autonomic failure (HAAF):
  - Defective counter-regulatory decrease in insulin and increase in glucagon and attenuated epinephrine release
  - May be reversed at least partially by avoidance of hypoglycemia, is maintained by recurrent hypoglycemia
  - 25-fold increased risk of severe hypoglycemia during intensive diabetes management

Seaquist 2013; Moheet 2013

Case 2

What additional information would you like to know about this patient?

- Current pump settings and review of insulin use
- History of recent hypoglycemic patterns
- History of reduced oral intake, emesis, or diarrhea
- History of increased activity
- Renal impairment, recent change of medications, symptoms of adrenal insufficiency, symptoms of hypothyroidism, weight loss
- Alcohol intake
Case 2

- Review of patient’s insulin pump shows large bolus of insulin just before the hypoglycemic event occurred
  - Patient does not recall giving this bolus and his wife is adamant that he was not eating during that time and she does not participate in his pump management
- No other changes in eating pattern, activity pattern were noted; he has not had a change in his pump settings or other medications
- His wife has concerns about his insulin pump management given is increasing forgetfulness

Technology and Hypoglycemia

Predict low suspend features of integrated continuous glucose monitors with insulin pumps can reduce hypoglycemia

Continuous glucose monitoring can reduce hospitalizations for severe hypoglycemia, reduce work absenteeism, and reduce fear of hypoglycemia

Continuous glucose monitoring can be a useful tool to monitor glucose trends while driving

Abraham, 2018; Charleer 2018
Driving Safety

- Patients with diabetes demonstrate a 12-19% increased risk of motor vehicle accident

- Main factor: hypoglycemia
  - Peripheral neuropathy and visual impairment should also be considered

Prospective multi-center study:
- 185 (41%) participants reported 503 episodes of moderate hypoglycemia
- 23 (5%) participants reported 31 episodes of severe hypoglycemia while driving

Lorber, 2013; Cox 2013

Driving Safety

Patient counseling:
- Be prepared: meter, source of quick-acting sugar, snacks providing complex carbohydrate in the vehicle

- Start out right: Blood sugar target before driving: 100 or greater

- STOP vehicle with any symptoms of low blood sugar: Measure and treat

- Wait: do not resume driving until cognition and blood sugar have recovered (20-30 minutes)

- Check again: recheck blood sugars periodically if driving for extended period of time

Lorber, 2013; Choudhary, 2011
Hypoglycemia Prevention

- Monitoring and goal setting
  - Glucose self-monitoring, A1C goals, use of CGM
- Patient education
  - How to prevent and treat hypoglycemia
- Dietary intervention and counseling
  - Regular eating patterns, alcohol intake
- Exercise counseling
  - Monitoring, use of carbohydrate intake around exercise, reduced insulin dosing around exercise

Seaquist, 2013; Cryer, 2009; Choudhary, 2011

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Hypoglycemia Prevention

- Medication adjustment
  - Evaluate regimen, consider agents without hypoglycemic potential if appropriate
- Evaluation for additional underlying causes
  - Kidney impairment or liver disease
  - Endocrine deficiencies
  - Celiac disease; malabsorption
  - Insulin binding antibodies

Seaquist, 2013; Cryer, 2009; Choudhary, 2011
Case 2

- The patient was taken off of his insulin pump and placed on a conservative basal bolus insulin regimen by injection
- His wife was provided diabetes education to assist in co-management of his diabetes, and she was trained on administration of glucagon
- He was discharged with plan for outpatient assessment of dementia
- Consideration for a continuous glucose monitor was discussed with patient and his wife

Related Cases

Admission for severe hypoglycemia in patient with diet-controlled type 2 diabetes
- Evaluation showed elevated insulin and C-peptide; + sulfonylurea screening
- Patient mistakenly took sulfonylurea (had been prescribed in past) instead of pain medication post-operatively
- No further episodes

Recurrent severe hypoglycemia in adolescent on insulin pump for type 1 diabetes
- Bolus history unrevealing
- “Priming” history on pump scrutinized—priming with site connected as a way to manipulate insulin

Unexplained fasting hypoglycemia of 40 on meter download in patient with type 1 diabetes being seen for the first time as an outpatient; all other morning values at target or above target
- After counseling patient about effect of alcohol on blood sugars, he refers back to meter download and reports—“yeah, I was drinking the night before that.”
Conclusions

Acute diabetes complications associated with hyperglycemia include diabetic ketoacidosis (DKA) and hyperosmolar hyperglycemic state (HHS)

DKA and HHS have some unique characteristics and treatment approaches

Patients may have a mixed picture of DKA and HHS

Hypoglycemia is common in diabetes and can result in significant morbidity as well as mortality

Prevention of acute diabetes complications requires adequate patient education, assessment of patient risk, an individualized treatment approach, and sometimes some very careful investigation

Questions?

Thank You!
References


Fluid regimes for DKA. Arch Dis Child. 2018;103(9):867.


References


Standards of Medical Care in Diabetes—2019; Diabetes care; January 01 2019; volume 42 issue Supplement 1, 2019.

References


References


