DKA, HHS, and Hypoglycemia

Approaches for Diabetes Management
February 2, 2019
Katherine Lewis, MD, MSCR
Associate Professor
MUSC Division of Endocrinology and Metabolic Disorders
MUSC Division of Pediatric Endocrinology

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

138	112	38	1600
6.4	9	3.2	

- **WBC's 12,000; + urine ketones**
- **VBG: pH 7.02, PCO_2 30, HCO_3 8**

Hyperglycemic Crisis: DKA vs. HHS

Hyperglycemic Crisis

- **NATIONAL DIABETES STATISTICS REPORT, 2017**

207,000 ER visits for hyperglycemic crisis in 2014

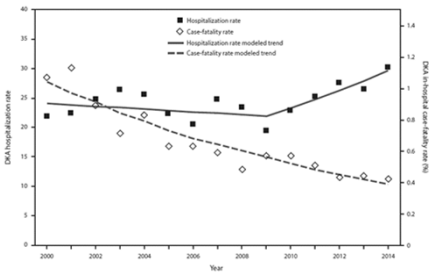
- **9.5 per 1000 persons with diabetes (95% CI)**

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.

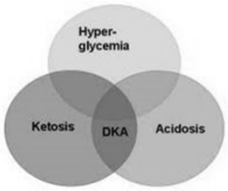
CDC National Diabetes Statistics Report 2017; Benoit 2018; Desai 2018; Pasquel 2014

Diabetic Ketoacidosis (DKA)

Uncontrolled hyperglycemia

Metabolic acidosis

Increased ketones



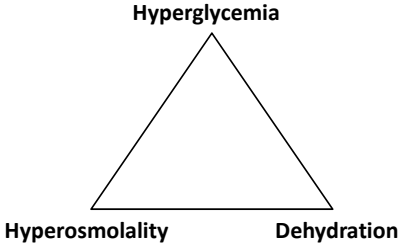
	Mild DKA	Moderate DKA	Severe DKA
Anion-gap acidosis	pH 7.25-7.30	pH 7.00- <7.24	pH < 7.00
	Bicarb <15-18	Bicarb 10 to <15	Bicarb <10
	Anion gap >10	Anion gap >12	Anion gap >12
Hyperglycemia	>250	>250	>250
Ketonemia/ketonuria	Present	Present	Present
Mental Status	Alert	Alert/drowsy	Stupor/coma

Kitabchi, 2009

Hyperosmolar Hyperglycemic State (HHS)

PREVIOUSLY KNOWN AS:

Hyperglycemic hypersomolar nonketotic coma (HONK) or hyperglycemic hyperosmolar nonketotic state (HHNK)



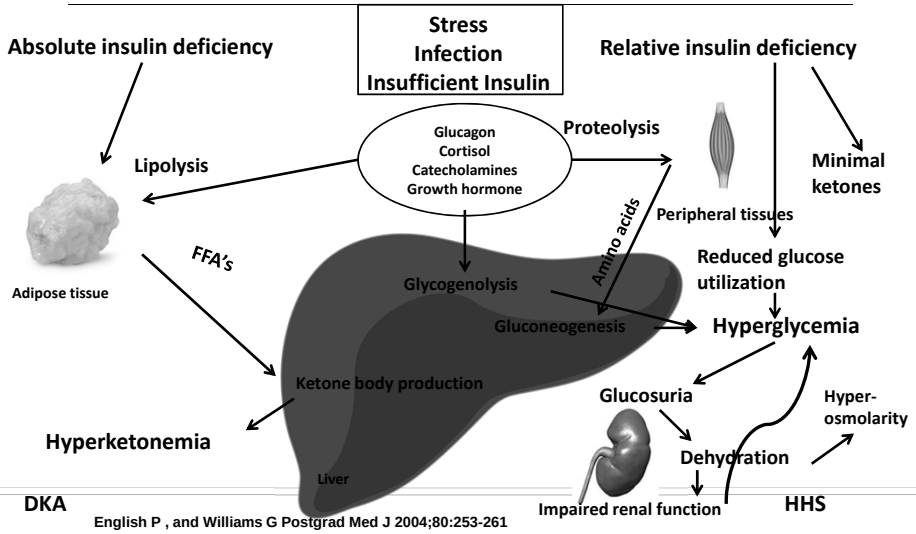
Endogenous insulin is enough to prevent lipolysis and ketogenesis but inadequate to facilitate glucose utilization

Dehydration >>> than in DKA

- **Total body water deficit usually 7-12 liters**

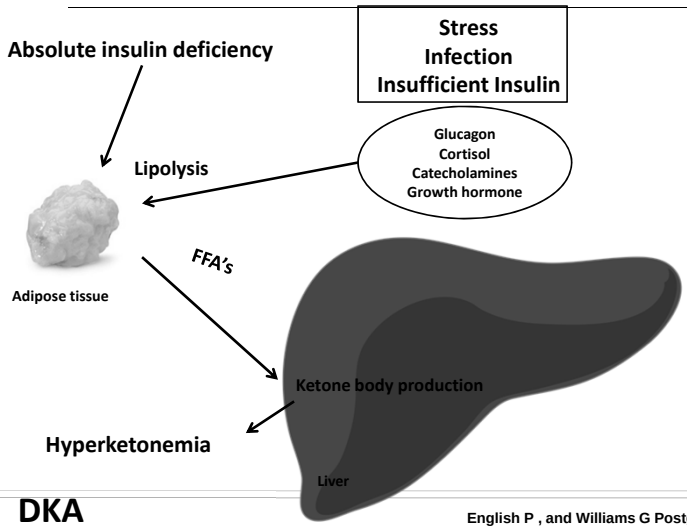
Maletkovic, 2013; Gouveia, 2013; Pasquel 2014

Pathogenesis of DKA and HHS



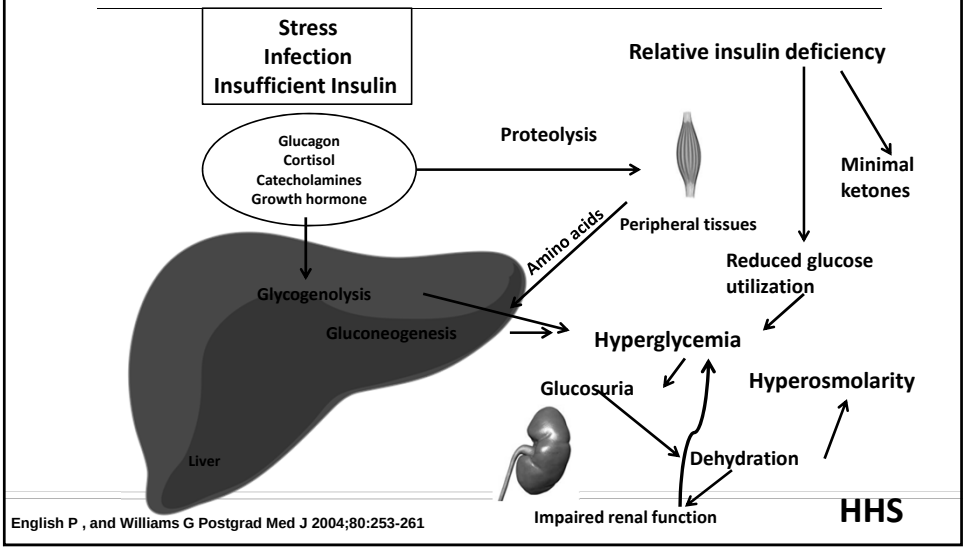
English P , and Williams G Postgrad Med J 2004;80:253-261

Pathogenesis of DKA



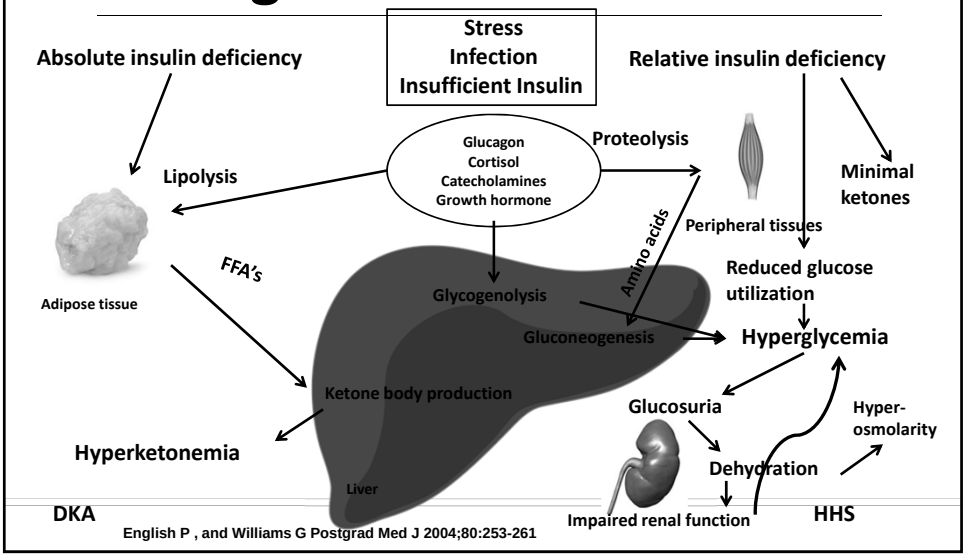
English P , and Williams G Postgrad Med J 2004;80:253-261

Pathogenesis of HHS



English P , and Williams G Postgrad Med J 2004;80:253-261

Pathogenesis of DKA and HHS



English P , and Williams G Postgrad Med J 2004;80:253-261

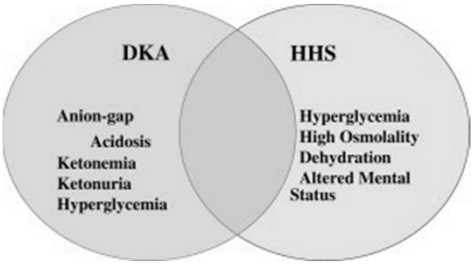
DKA and HHS

Polyuria and polydipsia

Nausea and vomiting

Anorexia

Fatigue/malaise

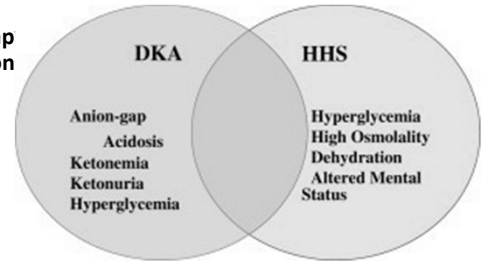


Maletkovic, 2013

DKA and HHS

Precipitating factors

- **Infection**
- **Extreme physical stress**
- **Missed or inadequate insulin therap (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**

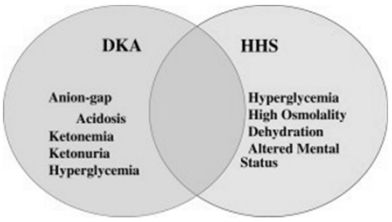


Maletkovic, 2013; Gallo, 2016; Goldenberg 2016;

DKA vs. HHS

	DKA	HHS
Timing	Develops over hours to days	Develops over days to weeks
Hyperventilation	+ (Kussmaul breathing)	-
Abdominal pain	+	-
Mental status change	+/-	+
Dehydration	+	++

Type 1 DM >Type 2 DM



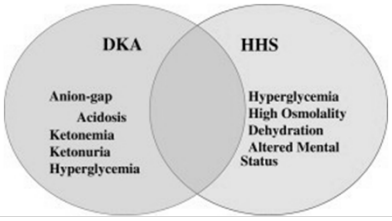
Type 2 DM >>Type 1 DM

Maletkovic, 2013

DKA vs. HHS

	DKA	HHS
Anion-gap acidosis	pH <7.3	pH >7.3
	Bicarbonate <15	Bicarbonate >18
	Anion gap >10	Anion-gap variable
Osmolality	<320	>320
Hyperglycemia	>250	>600
Ketonemia/ketonuria	Present	Rare

Mortality 2%
(5% in elderly)



Mortality 20%

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**

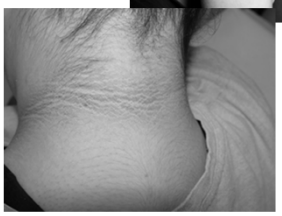
Physical Exam
- **Mental status**
- **Respirations (Kussmaul)**
- **Fruity breath**
- **Signs of infection**
- **Signs of dehydration**

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

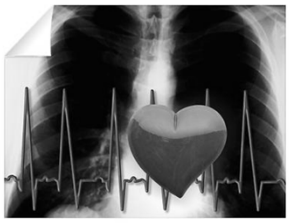
- **Glucose, Metabolic Panel, Phosphate, Magnesium, ABG**
- **CBC, Serum Ketones, Urinalysis, Cardiac Enzymes, A1C, Coagulation profile, Urine Pregnancy Test**
- **Consider also Urine & Blood Cultures, Lumbar Puncture, Amylase and Lipase, CPK**

Maletkovic, 2013

Evaluation of Patient with Hyperglycemic Crisis

OTHER STUDIES AND IMAGING

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



Maletkovic, 2013

Interpretation of Labs

Calculating Anion Gap:

- **(Serum sodium)- (Chloride +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 x serum sodium) + (glucose in mg/dL divided by 18) + (BUN in mg/dL divided by 2.8**
- **Effective Osmolality**

(2 x serum sodium) + (2 x potassium) + (glucose in mg/dL divided by 18)

Maletkovic, 2013; Baldrighi, 2018; Cardosa, 2016

Case 1

Chemistry

138	112	38	1600
6.4	9	3.2	

- **WBC's 12,000; + urine ketones**
- **VBG: pH 7.02, PCO_2 30, HCO_3 8**

Hyperglycemic Crisis: DKA vs. HHS

Interpretation of Labs

Calculating Anion Gap:

- **(Serum sodium)- (Chloride +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

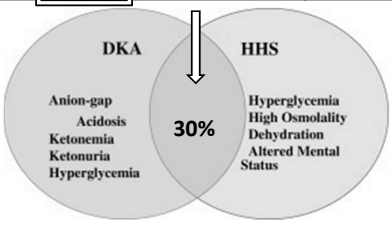
- **(2 x serum sodium) + (glucose in mg/dL divided by 18) + (BUN in mg/dL divided by 2.8)**
  - **Case 1**
  - **(2 x 138) + (1600/18) + (38/2.8) =**
  - **276 + 88.9 + 13.6 =**
  - **378**

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

Maletkovic, 2013

Case 1: DKA versus HHS

	DKA	HHS
Anion-gap acidosis	pH <7.3	pH >7.3
	Bicarbonate <15	Bicarbonate >18
	Anion gap >10	Anion-gap variable
Osmolality	<320	>320
Hyperglycemia	>250	>600
Ketonemia/ketonuria	Present	Rare



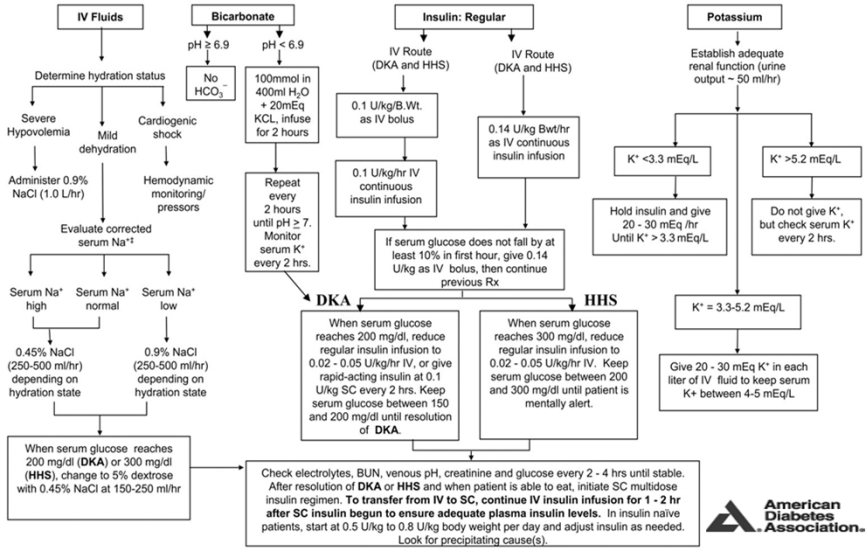
Mortality 2%
(5% in elderly)

Mortality 20%

Kitabchi, 2009; Maletkovic, 2013; Cardoso, 2016

Protocol for management of adult patients with DKA or HHS

Complete initial evaluation. Check capillary glucose and serum/urine ketones to confirm hyperglycemia and ketonemia/ketonuria. Obtain blood for metabolic profile. Start IV fluids: 1.0 L of 0.9% NaCl per hour.†



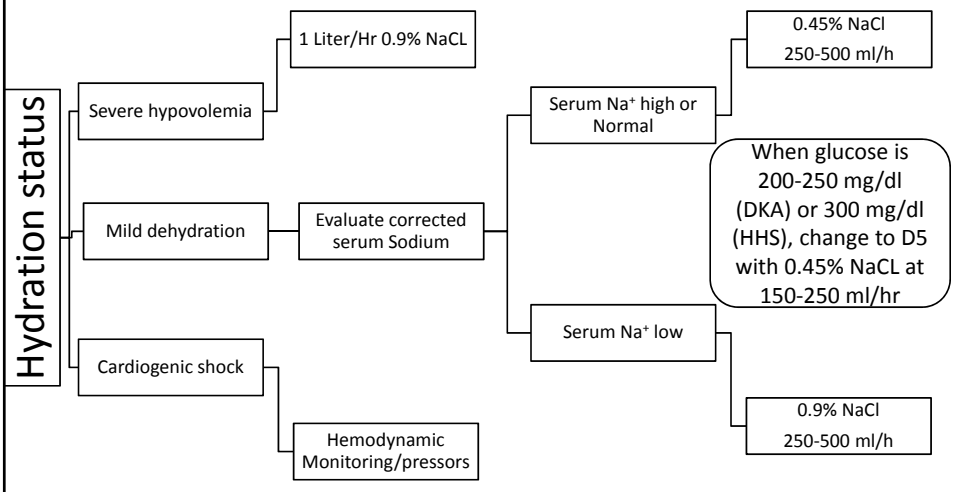
Kitabchi A E et al. Dia Care 2009;32:1335-1343

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 euvolemia is achieved, may change to ½ 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



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**

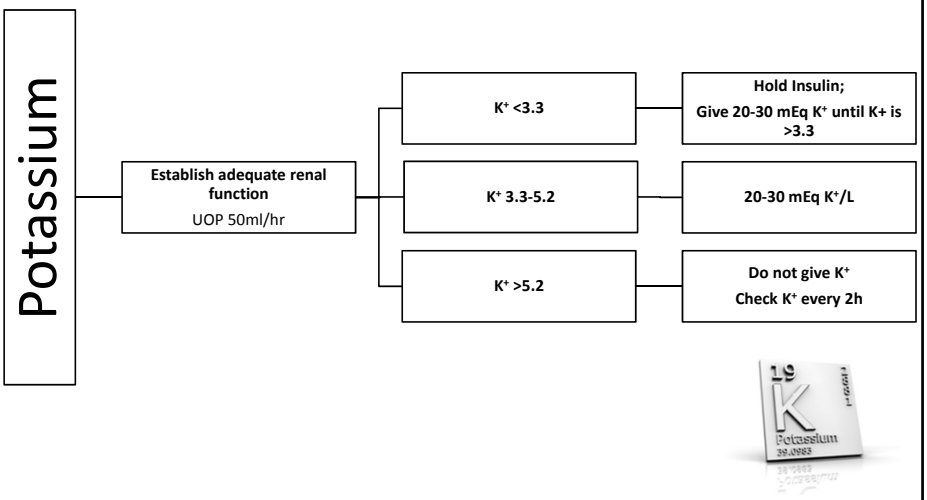
Maletkovic, 2013, Glaser 2005; Cardosa,2016

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 arrythmias**

Maletkovic, 2013, Glaser 2005



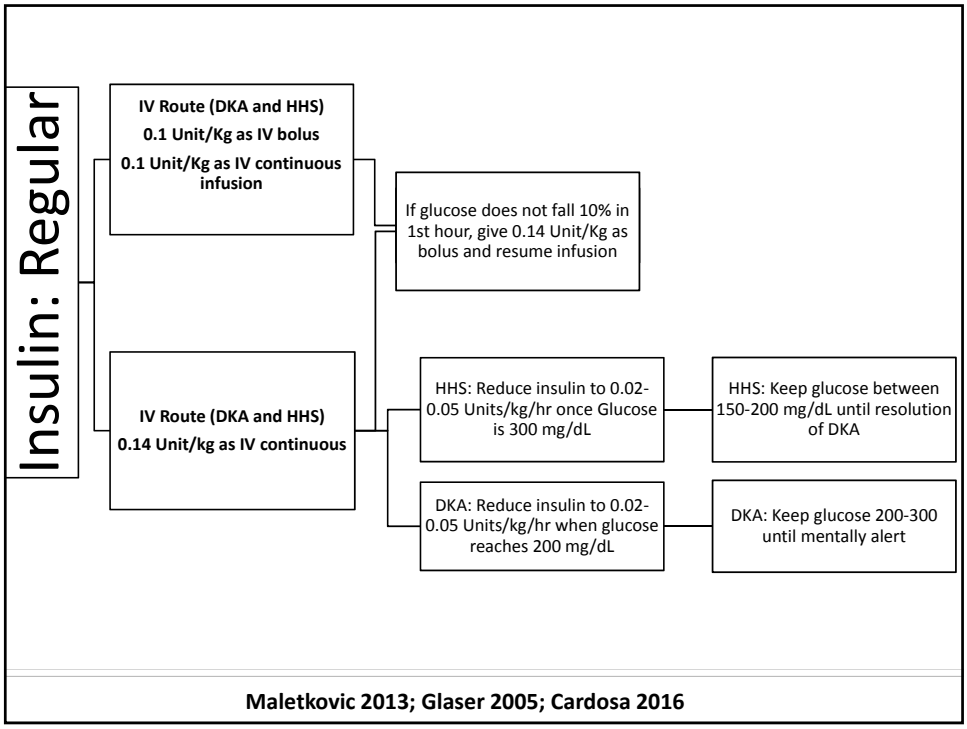
Maletkovic, 2013, Glaser 2005; Cardosa,2016

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



Maletkovic 2013; Glaser 2005; Cardosa 2016

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**

Maletkovic, 2013; Glaser 2005; Cardosa 2015; Hsia, 2012

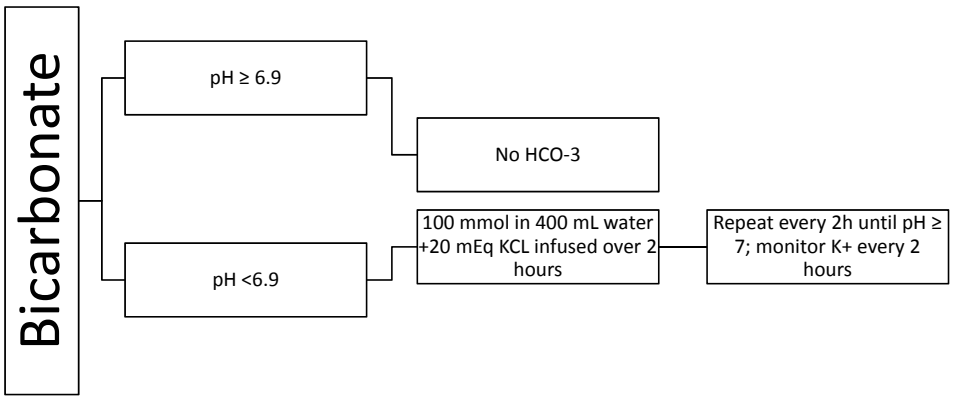
Treatment of DKA and HHS

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_2PO_4 (max rate of 4.5 mmol/h and 90 mmol per day)

Cardosa 2016

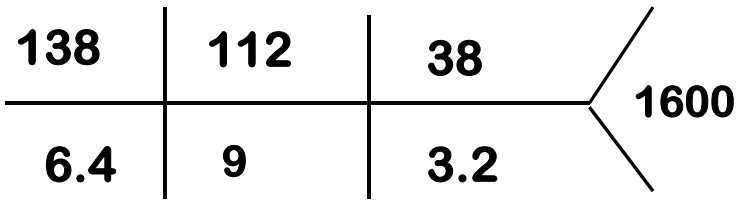
Case 1:
Review Question #1

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

A	**Fluids**	**Potassium**	**Insulin**	**Bicarbonate**
B	**Insulin**	**Bicarbonate**	**Fluids**	**Potassium**
C	**Insulin**	**Fluids**	**Potassium**	**No bicarbonate**
D	**Fluids**	**Insulin**	**Potassium**	**No bicarbonate**

Case 1

Chemistry



- **WBC's 12,000; + urine ketones**
- **VBG: pH 7.02, PCO_2 30, HCO_3 8**

Hyperglycemic Crisis: DKA vs. HHS

Case 1:
Review Question #1

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

A	**Fluids**	**Potassium**	**Insulin**	**Bicarbonate**
B	**Insulin**	**Bicarbonate**	**Fluids**	**Potassium**
C	**Insulin**	**Fluids**	**Potassium**	**No bicarbonate**
D	**Fluids**	**Insulin**	**Potassium**	**No bicarbonate**

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

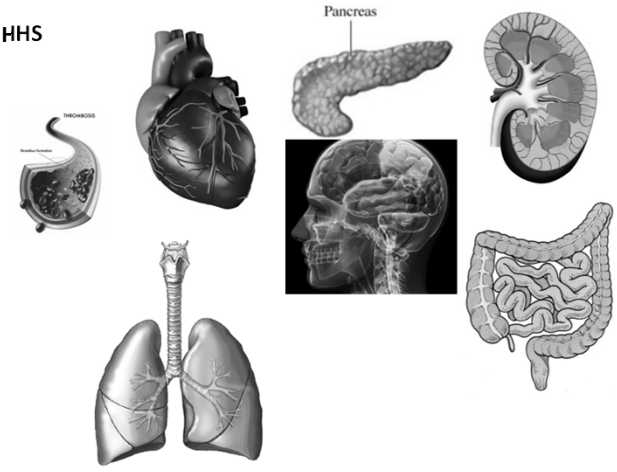
He has persistent hypertension

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

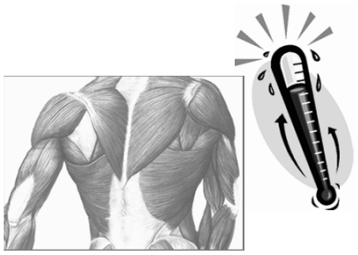
Complications of DKA and/or HHS

DKA

- 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%
  - 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

HHS

- Malignant hyperthermia-like syndrome
  - Hyperpyrexia and rhabdomyolysis



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**

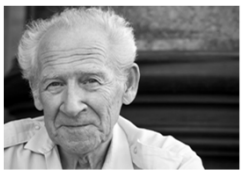
3. **Recognize the similarities and differences between DKA and HHS**

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**

Cryer, 2009; CDC National Diabetes Statistics Report 2017, using data from 2014 National Inpatient Sample, Agency for Healthcare Research and Quality

Hypoglycemia Symptoms

Adrenergic Symptoms	Neuroglycopenic Symptoms
Pallor	Confusion
Diaphoresis	Slurred Speech
Shakiness	Irrational behavior
Hunger	Disorientation
Anxiety	Loss of consciousness
Irritability	Seizures
Headache	Pupillary Sluggishness
Dizziness	Decreased response to noxious stimuli

Kalra, 2013

Hypoglycemia Classification

Level	Description
Level 1	Glucose <70 mg/dL and ≥ 54 mg/dL
Level 2	Glucose <54 mg/dL
Level 3	A severe even characterized by altered mental status and/or physical status requiring assistance

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

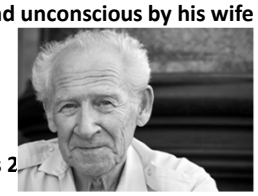
- **Glucagon 1 mg SQ or IM**
  - Nausea and vomiting, hyperglycemia
  - Provide to all patients at risk for level 2 hypoglycemia
- **IV Glucose 25g** followed by glucose infusion

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 2**
- **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

Level	Description
Level 1	Glucose <70 mg/dL and ≥ 54 mg/dL
Level 2	Glucose <54 mg/dL
Level 3	A severe even characterized by altered mental status and/or physical status requiring assistance

ADA Standards of Medical Care 2019

Causes of Hypoglycemia

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

Kalra, 2013

Hypoglycemia Risk Factors

- Duration of diabetes and age
- C-peptide negativity
- History of severe hypoglycemia
- Impaired awareness of hypoglycemia
- Strict glycemic control
- Sleep/general anesthesia or other sedation
- Reduced oral intake; emesis
- Critical illness
- Unexpected travel after rapid-acting insulin

Kalra, 2013

Hypoglycemia Risk Factors

- Sudden reduction in corticosteroid dose
- Reduced IV dextrose administration
- Interruption of enteral feedings or TPN
- Drug dispensing error
- Renal and hepatic dysfunction

Endocrine deficiencies

- Hypothyroidism
- Hypopituitarism
- Primary adrenal insufficiency
- Growth hormone deficiency

Kalra, 2013

Hypoglycemia Outcomes

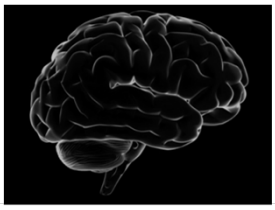
Functional brain failure reversed by correction of glucose levels

Prolonged hypoglycemia can cause brain death

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

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

Increased dementia, cerebral ataxia, cognitive problems in elderly



Cryer, 2009; Halimi 2010, Kalra, 2013, Seaquist 2013, Ebadi 2018

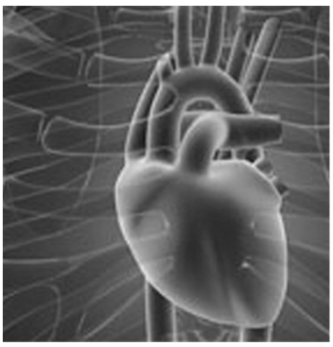
Hypoglycemia Outcomes

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

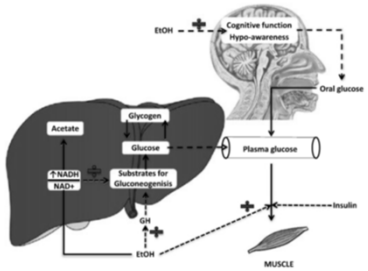
In the LEADER study, participants with type 2 DM with severe hypoglycemia (267 of 9,340) had increased risk of major cardiac events, CV death, and all-cause death



Cryer, 2009; Halimi 2010, Kalra, 2013; Zinman 2018

Hypoglycemia and Alcohol

- Alcohol impairs endogenous glucose release
- 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
- May cause delayed hypoglycemia with increased risk lasting also long as 24 hour after ingestion



Choudhary, 2011; Richardson, 2005; Tetzschner, 2017

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

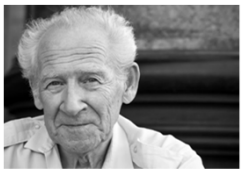
- Loss of adrenergic symptoms prior to onset of neuroglycopenic symptoms

- 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

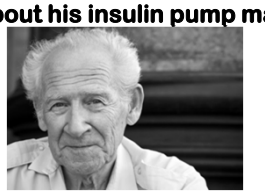
What additional information would you like to know about this patient?



- 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

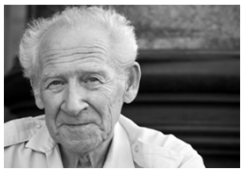
Hypoglycemia Prevention

- **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

CDC National Diabetes Statistics Report 2017 https://www.cdc.gov/diabetes/pdfs/data/statistics/national-diabetes-statistics-report.pdf

Benoit SR, Zhang Y, Geiss LS, Gregg EW, Albright A. Trends in Diabetic Ketoacidosis Hospitalizations and In-Hospital Mortality - United States, 2000-2014. MMWR Morb Mortal Wkly Rep. 2018;67(12):362-365.

Desai D, Mehta D, Mathias P, Menon G, Schubart UK. Health Care Utilization and Burden of Diabetic Ketoacidosis in the U.S. Over the Past Decade: A Nationwide Analysis. Diabetes Care. 2018;41(8):1631-1638.

Pasquel FJ, Umpierrez GE. Hyperosmolar hyperglycemic state: a historic review of the clinical presentation, diagnosis, and treatment. Diabetes Care. 2014;37(11):3124-3131.

Kitabchi AE, Umpierrez GE, Miles JM, Fisher JN. Hyperglycemic crises in adult patients with diabetes. Diabetes Care. 2009;32(7):1335-1343.

Maletkovic J, Drexler A. Diabetic ketoacidosis and hyperglycemic hyperosmolar state. Endocrinol Metab Clin North Am. 2013;42(4):677-695

Gouveia CF, Chowdhury TA. Managing hyperglycaemic emergencies: an illustrative case and review of recent British guidelines. Clin Med (Lond). 2013;13(2):160-162.

English P, Williams G. Hyperglycaemic crises and lactic acidosis in diabetes mellitus. Postgrad Med J. 2004;80(943):253-261.

Gallo T, Shah VN. An Unusual Cause of Recurrent Diabetic Ketoacidosis in Type 1 Diabetes. Am J Med. 2016;129(8):e139-140.

References

Goldenberg RM, Berard LD, Cheng AYY, et al. SGLT2 Inhibitor-associated Diabetic Ketoacidosis: Clinical Review and Recommendations for Prevention and Diagnosis. Clin Ther. 2016;38(12):2654-2664.e2651.

Baldrighi M, Sainaghi PP, Bellan M, Bartoli E, Castello LM. Hyperglycemic Hyperosmolar State: A Pragmatic Approach to Properly Manage Sodium Derangements. Curr Diabetes Rev. 2018;14(6):534-541.

Cardoso L, Vicente N, Rodrigues D, Gomes L, Carrilho F. Controversies in the management of hyperglycaemic emergencies in adults with diabetes. Metabolism. 2017;68:43-54.

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

Glaser, N., *Pediatric diabetic ketoacidosis and hyperglycemic hyperosmolar state.* Pediatr Clin North Am, 2005. 52(6): p. 1611-35.

Halimi, S; Acute consequences of hypoglycaemia in diabetic patients. Diabetes Metab., 2010, Oct; 36 Suppl 3: S75-83.

Glaser N, Kuppermann N. Fluid treatment for children with diabetic ketoacidosis: How do the results of the pediatric emergency care applied research network Fluid Therapies Under Investigation in Diabetic Ketoacidosis (FLUID) Trial change our perspective? Pediatr Diabetes. 2019;20(1):10-14.

References

Munir I, Fargo R, Garrison R, et al. Comparison of a 'two-bag system' versus conventional treatment protocol ('one-bag system') in the management of diabetic ketoacidosis. BMJ Open Diabetes Res Care. 2017;5(1):e000395.

Hsia DS, Tarai SG, Alimi A, Coss-Bu JA, Haymond MW. Fluid management in pediatric patients with DKA and rates of suspected clinical cerebral edema. Pediatr Diabetes. 2015;16(5):338-344.

Glaser, N., et al., *Risk factors for cerebral edema in children with diabetic ketoacidosis. The Pediatric Emergency Medicine Collaborative Research Committee of the American Academy of Pediatrics.* N Engl J Med, 2001. 344(4): p. 264-9.

Decourcey DD, Steil GM, Wypij D, Agus MS. Increasing use of hypertonic saline over mannitol in the treatment of symptomatic cerebral edema in pediatric diabetic ketoacidosis: an 11-year retrospective analysis of mortality*. Pediatr Crit Care Med. 2013;14(7):694-700.

Lewis KA, MD, F Dixon, R Paulo, D Bowlby: *Dazed and Konfused Adolescents: Recurrent DKA in Girls with Mental Health Concerns*. Poster Presentation at the Pediatric Academic Societies/Pediatric Endocrine Society Meeting, May, 2013

Wolfsdorf JI, Glaser N, Agus M, et al. ISPAD Clinical Practice Consensus Guidelines 2018: Diabetic ketoacidosis and the hyperglycemic hyperosmolar state. Pediatr Diabetes. 2018;19 Suppl 27:155-177.

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

References

Cryer, P.E., et al., *Evaluation and management of adult hypoglycemic disorders: an Endocrine Society Clinical Practice Guideline.* J Clin Endocrinol Metab, 2009. 94(3): p. 709-28.

Kalra, S., et al., *Hypoglycemia: The neglected complication.* Indian J Endocrinol Metab, 2013. 17(5): p. 819-34.

Seaquist, E.R., et al., *Hypoglycemia and diabetes: a report of a workgroup of the American Diabetes Association and the Endocrine Society.* Diabetes Care, 2013. 36(5): p. 1384-95.

Ebadi SA, Darvish P, Fard AJ, Lima BS, Ahangar OG. Hypoglycemia and cognitive function in diabetic patients. Diabetes Metab Syndr. 2018;12(6):893-896.

Zinman B, Marso SP, Christiansen E, et al. Hypoglycemia, Cardiovascular Outcomes, and Death: The LEADER Experience. Diabetes Care. 2018;41(8):1783-1791.

Choudhary, P. and S.A. Amiel, *Hypoglycaemia: current management and controversies.* Postgrad Med J, 2011. 87(1026): p. 298-306.

Richardson, T., et al., *Day after the night before: influence of evening alcohol on risk of hypoglycemia in patients with type 1 diabetes.* Diabetes Care, 2005. 28(7): p. 1801-2.

References

R, Norgaard K, Ranjan A. Effects of alcohol on plasma glucose and prevention of alcohol-induced hypoglycemia in type 1 diabetes-A systematic review with GRADE. Diabetes Metab Res Rev. 2018;34(3).

Moheet, A., et al., *Hypoglycemia associated autonomic failure in healthy humans: Comparison of 2 vs 3 periods of hypoglycemia on hypoglycemia-induced counterregulatory and symptom response 5 days later.* J Clin Endocrinol Metab, 2013: p. jc20133493.

Abraham MB, Nicholas JA, Smith GJ, et al. Reduction in Hypoglycemia With the Predictive Low-Glucose Management System: A Long-term Randomized Controlled Trial in Adolescents With Type 1 Diabetes. Diabetes Care. 2018;41(2):303-310.

Charleer S, Mathieu C, Nobels F, et al. Effect of Continuous Glucose Monitoring on Glycemic Control, Acute Admissions, and Quality of Life: A Real-World Study. J Clin Endocrinol Metab. 2018;103(3):1224-1232.

Lorber, D., et al., *Diabetes and driving.* Diabetes Care, 2013. 36 Suppl 1: p. S80-5.

Cox, D.J., H. Singh, and D. Lorber, *Diabetes and driving safety: science, ethics, legality and practice.* Am J Med Sci, 2013. 345(4): p. 263-5.