Hyperglycemic Emergencies: DKA and Hyperglycemic Hyperosmolar

Hyperglycemic Crises

- **DKA**
  - Most common hyperglycemic emergency in patients with type 1 and type 2 diabetes
  - DKA accounts for 4%-9% of all hospital discharge summaries among patients with diabetes
  - Annual average of ~135,000 hospitalizations for DKA in the United States
  - Most common mortality rate <2%

- **HHS**
  - Hospitalization rate lower than DKA, approximately <1% of all primary diabetic admissions
  - Mortality rates ~15%

DKA Incidence from NHDS

<table>
<thead>
<tr>
<th>Year</th>
<th>Number (in Thousands)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2006</td>
<td>134,663 episodes</td>
</tr>
</tbody>
</table>

Type 1 Diabetes Accounts for the Majority of Primary* DKA Episodes

<table>
<thead>
<tr>
<th>Type 1 Diabetes Accounts for the Majority of Primary* DKA Episodes</th>
<th>T1D - Children</th>
<th>T1D - Adults</th>
<th>T2D</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary DKA Episodes</td>
<td>134,637,2488</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T1D - Children</td>
<td>18%</td>
<td>48%</td>
<td>34%</td>
</tr>
<tr>
<td>T1D - Adults</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T2D</td>
<td></td>
<td></td>
<td></td>
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</tbody>
</table>

- 34% of episodes are T2D
- Longer hospital stays with T2D
- 4.2 days with T2D vs average of 3.5 days with T1D

T2D accounts for 34% of primary DKA cases and more than 50% of secondary causes

DKA-related Mortality Rates Have Been in Decline Since the 90s

Mortality due to DKA (per annum)

Overall 2006 mortality rate for DKA: 0.41%
Pathogenesis of Hyperglycemic Crises

Insulin Deficiency
Counterregulatory Hormones

Increased glucose production
Decreased glucose uptake
Lipolysis - Increased FFA
Metabolic acidosis
Hypertonicity

Hyperglycemia osmotic diuresis
Dehydration


Diagnostic Criteria for DKA and HHS

<table>
<thead>
<tr>
<th></th>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
<th>HHS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma glucose (mg/dL)</td>
<td>&gt;250</td>
<td>&gt;250</td>
<td>&gt;250</td>
<td>&gt;600</td>
</tr>
<tr>
<td>pH</td>
<td>7.25-7.3</td>
<td>7.0-7.24</td>
<td>7.0</td>
<td>7.30</td>
</tr>
<tr>
<td>Bicarbonate (mEq/L)</td>
<td>15-18</td>
<td>10- &lt;15</td>
<td>&lt;10</td>
<td>&lt;15</td>
</tr>
<tr>
<td>Urine ketones*</td>
<td>positive</td>
<td>positive</td>
<td>positive</td>
<td>small</td>
</tr>
<tr>
<td>Serum ketones*</td>
<td>positive</td>
<td>positive</td>
<td>positive</td>
<td>small</td>
</tr>
<tr>
<td>Effective serum Osmol (mOsm/kg)?</td>
<td>variable</td>
<td>variable</td>
<td>variable</td>
<td>&gt;320</td>
</tr>
<tr>
<td>Alteration in sensoria or mental obtundation</td>
<td>alert</td>
<td>alert†</td>
<td>stupor†</td>
<td>coma</td>
</tr>
</tbody>
</table>

* Nitroprusside reaction method
† Calculation: 2[measured Na (mEq/L)] + glucose (mg/dL)/18

Useful Formulas for the Evaluation of DKA

1. Calculation of anion gap (AG):
   \[ AG = [\text{Na}^+] - ([\text{Cl}^- + \text{HCO}_3^-]) \] (normal <12 mEq/L)

2. Total and effective serum osmolality:
   \[ \text{Total} = 2[\text{Na}^+] + \text{glucose} \text{ (mg/dL)} + \text{BUN} \text{ (mg/dL)} \]
   \[ \text{Effective} = 2[\text{Na}^+] + \text{glucose} \text{ (mg/dL)} \]
   (normal 275-295 mmol/L)
   \[ \text{Effective} = \frac{2[\text{Na}^+] + \text{glucose} \text{ (mg/dL)}}{18} \]

Precipitating Causes for DKA and HHS

<table>
<thead>
<tr>
<th>Case</th>
<th>DKA (n=144)</th>
<th>HHS (n=23)</th>
</tr>
</thead>
<tbody>
<tr>
<td>New diabetes</td>
<td>25 (17)</td>
<td>4 (17)</td>
</tr>
<tr>
<td>Failure to take insulin</td>
<td>59 (41)</td>
<td>9 (32)</td>
</tr>
<tr>
<td>Infection</td>
<td>40 (28)</td>
<td>8 (35)</td>
</tr>
<tr>
<td>Medical illness</td>
<td>14 (10)</td>
<td>3 (13)</td>
</tr>
<tr>
<td>Unknown</td>
<td>6 (4)</td>
<td>0</td>
</tr>
</tbody>
</table>

*Data are reported as number (percentage) of patients. DKA indicates diabetic ketoacidosis; HHS, hyperglycemic hyperosmolar nonketotic syndrome.

Euglycemic Diabetic Ketoacidosis
A Potential Complication of Treatment with Sodium-Glucose Co-transporter 2 Inhibition

Case Study

18-year-old African American male admitted with a 3 week hx. of polyuria, polydipsia, and 20-lb weight loss. One day prior to admission, developed nausea, vomiting, and diffuse abdominal pain.

Physical exam: 100/80 mmHg, HR: 112/min, RR: 24/min
Weight: 160 lb, BMI: 22 kg/m²
Lethargic with Kussmaul breathing; otherwise, PE was WNL; no end-organ complications of DM

Venous pH: 7.18
B-OH-B: 8.7 MM
U/A: + ketones
HbA1c: 13.2%
SGLT2-I and Risk of Ketoacidosis in T1D
Potential Mechanisms

Clinical Presentation of DKA

Symptoms
- Polydipsia
- Polyuria
- Weakness
- Weight loss
- Nausea
- Vomiting
- Abdominal pain

Signs
- Hypothermia
- Tachycardia
- Tachypnea
- Kussmaul breathing
- Ileus
- Acetone breath
- Altered sensorium

The onset of DKA is usually relatively short, ranging from hours to a day or two.

Mental Status at Presentation in DKA

Level of Consciousness

Serum Osmolality (mOsm/L)

Alert: <300 mOsm/L
Stupor or coma: ≥320 mOsm/L

Initial Laboratory Studies

- Immediate determination of blood glucose by finger stick and serum ketones (B-OH-B) or urinary ketones
- Laboratory studies:
  - Venous or arterial pH (ABG’ss)
  - CBC with differential
  - CMP (glucose, electrolytes, bicarbonate, PO4, Mg, BUN, creatinine)
  - Serum ketones
  - Urinalysis
  - Bacterial cultures*
  - Cardiac enzymes*

* If clinically indicated

Managing Hyperglycemic Emergencies

Blood β-OHβ Levels in DKA Detection and Treatment

- β-OHβ concentrations >0.5 mmol/L are considered "abnormal"
- Patients presenting with DKA can range between 3-12 mmol/L β-OHβ
  - β-OHβ ≤1.0 mmol/L — treat blood glucose level appropriately
  - β-OHβ 1.1 to 3.0 mmol/L — insulin and fluids; retest in 1 hour and, if no improvement, contact physician
  - β-OHβ >3.0 mmol/L — insulin, fluids, urgent medical attention

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Management of DKA

- Replacement of fluid losses
- Correction of hyperglycemia/metabolic acidosis
- Replacement of electrolyte losses
- Detection and treatment of precipitating causes
- Conversion to a maintenance diabetes regimen (prevention of recurrence)

Fluid Therapy in DKA

- Normal saline, 1-2 L over 1-2 h
- Calculate corrected serum sodium
- Normal or high serum sodium: ½ NS at 250-500 mL/h
- Low serum sodium: NS at 250-500 mL/h
- Glucose <250 mg/dL: Change to D5% NS or 1/2NS

Management after Resolution of DKA

- Patients with DKA should be treated with IV insulin or rapid-acting SC insulin until ketoacidosis is resolved
- Criteria for resolution of DKA
  - BG ≤250 mg/dL
  - Serum bicarbonate level ≥18 mEq/L
  - Venous pH ≥7.3
  - (B-OH-B, anion gap)
Transition to Subcutaneous Insulin after Resolution of DKA

- After initial IV or SQ therapy (pH >7.3, HCO3 >18, AG < 14)
- Give SQ basal insulin 2-4 hours before stopping IV insulin
- Start multi-dose insulin (basal bolus) regimen
  - Insulin analogs are preferred over human insulin
  - Basal: glargine / detemir
  - Rapid-acting insulin analogs (lispro, aspart, glulisine)
- Analogs result in similar BG control, but less hypoglycemia than human insulin (15% vs 41%)
- Use of ‘early’ glargine insulin during treatment of DKA may prevent rebound hypoglycemia during insulin infusion

Summary

- DKA is a common, serious, and expensive complication in patients with type 1 and type 2 diabetes
- Prevention of metabolic decompensation through patient education, strict surveillance of glucose homeostasis, and aggressive diabetes management might reduce the high morbidity and mortality
- Recent treatment protocols have improved clinical outcomes in patients with DKA

Definitions: Hypoglycemia

Hypoglycemia: “all episodes of abnormally low plasma glucose concentration that expose the individual to potential harm”

1. Severe hypoglycemia: An event requiring assistance of another person to actively administer carbohydrate, glucagon, or other resuscitative actions (definitions vary)
2. Documented symptomatic hypoglycemia: An event during which typical symptoms of hypoglycemia are accompanied by a low measured BG concentration

Rates of Hypoglycemia

- 30%-40% of individuals with T1D have 1-3 episodes of severe hypoglycemia/ year
- Rates in insulin-treated T2D ~1/3rd as common
- Rates of mild hypoglycemia ~50 times more common
- Use of SUs, a glinide, or insulin and increased duration of diabetes increase the risk for hypoglycemia of any kind
Hypoglycemia: Impact on Healthcare Resources

- Analysis of healthcare resource use during severe hypoglycemia events (requiring external assistance) from 15 trials of T1 and T2DM using insulin (degludec; degludec/aspart; glargine, biphasic aspart, detemir)
- 536 severe hypoglycemia events
  - 29.3% involved an ambulance/emergency team
  - 11.9% led to hospital/emergency room attendance of ≤24 hours
  - 6.7% required hospital admission (>24 hours)
  - Those receiving basal-oral therapy had greater risk for hospitalization (47.6%)
- Once a severe episode occurred, the tendency to utilize healthcare resources was higher in T2 vs T1DM

Economic Impact of Severe and Non-severe Hypoglycemia Episodes

- Review of 14 studies on T1 and T2DM
- Direct cost associated per hypoglycemia episodes requiring assistance from a healthcare practitioner: $116

<table>
<thead>
<tr>
<th>Indirect costs associated with:</th>
<th>T1DM</th>
<th>T2DM</th>
</tr>
</thead>
<tbody>
<tr>
<td>severe hypoglycemia requiring non-medical assistance</td>
<td>$242</td>
<td>$579</td>
</tr>
<tr>
<td>severe hypoglycemia requiring medical assistance</td>
<td>$160</td>
<td>$176</td>
</tr>
<tr>
<td>non-severe hypoglycemia</td>
<td>$11</td>
<td>$11</td>
</tr>
</tbody>
</table>

Case 1: Hypoglycemia

- SV is a 35-year-old female with a 30-year history of type 2 diabetes. She has diabetic retinopathy, but no other complications.
- She is very physically active working in a preschool.
- She also trains for running 10 Ks and runs 5 days per week.
- Recently she has been having episodes of severe hypoglycemia, twice overnight when her husband treated her with glucagon and once while at school when paramedics had to be called.
- Her target A1c is 6%.

Case 1: Hypoglycemia (cont)

- On questioning, her insulin dosing has not changed.
- However, she no longer senses her lows regularly.
- Currently, she is taking 10 units of long-acting insulin at bedtime and gives 1 unit for every 20 grams of carbs and a correction (or sensitivity) factor of 50.
- Her CGM tracing follows.
- What would you recommend and why?
Risk of CV Events and Death in Patients With vs Without Severe Hypoglycemia: (ADVANCE)

Study inclusion criteria: T2DM + major vascular disease or ≥1 CV risk factor

<table>
<thead>
<tr>
<th>Risk</th>
<th>Macrovacular events</th>
<th>Death—any cause</th>
<th>Death—CV cause</th>
<th>Death—non-CV cause</th>
</tr>
</thead>
<tbody>
<tr>
<td>81</td>
<td>3.45 (2.34-5.08); P&lt;0.001</td>
<td>3.30 (2.31-4.72); P&lt;0.001</td>
<td>3.78 (2.34-6.11); P&lt;0.001</td>
<td>2.86 (1.67-4.86); P&lt;0.001</td>
</tr>
</tbody>
</table>

Adjusted Hazard Ratio (95% CI)

Macrovascular events


Summary of ACCORD, ADVANCE, VADT

Severe Hypoglycemia and Mortality Risk

<table>
<thead>
<tr>
<th>Study</th>
<th>Intensive</th>
<th>Standard</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACCORD</td>
<td>3.1%</td>
<td>1.1%</td>
</tr>
<tr>
<td>ADVANCE</td>
<td>0.7%</td>
<td>0.4%</td>
</tr>
<tr>
<td>VADT</td>
<td>12.0%</td>
<td>4.0%</td>
</tr>
</tbody>
</table>


Hypoglycemia Associated Autonomic Failure (HAAF)

- Defined as attenuation of the sympathoadrenal response to hypoglycemia that leads to impaired awareness of hypoglycemia, which increases the risk for severe hypoglycemia
- It is often induced by antecedent hypoglycemia
- The diagnosis is generally made clinically, based on the patient’s subjective sense of a reduction in symptoms of hypoglycemia avoidance
- This impaired awareness is reversible by 2-3 weeks of hypoglycemia avoidance
- Educational programs exist to help patients restore their sense of lows


Recommendations of the International Hypoglycemia Study Group

People with diabetes treated with a sulfonylurea, a glinide, or insulin should:

- Be educated about hypoglycemia
- Treat SMPG levels ≤70 mg/dL (3.9 mmol/L) to avoid progression to clinical iatrogenic hypoglycemia
- Regularly be queried about hypoglycemia, including the glucose level at which symptoms develop; those developing symptoms at a glucose level ≤55 mg/dL (3.0 mmol/L) should be considered at risk

SMPG = self-monitored plasma glucose

When hypoglycemia becomes a problem, the diabetes healthcare provider should:

- Consider each conventional risk factor and those indicative of compromised glucose counter-regulation
- Avoid sulfonylureas (and glinides) if possible, using insulin analogs when insulin is required, and consider using CSII, CGM, and CSII + CGM in selected patients
- Provide structured education and, in patients with impaired awareness of hypoglycemia, prescribe short-term scrupulous avoidance of hypoglycemia
- Seek to achieve the lowest A1c level that does not cause severe hypoglycemia and preserves awareness of hypoglycemia with an acceptable number of less-than-severe episodes of hypoglycemia, provided that benefit from glycemic control can be anticipated

**Rule of 15 for Treating Hypoglycemia**

**Guide for Patients**

- If BG is 50-70 mg/dL – take 15 grams of simple sugar, such as 4 oz of juice or 4 glucose tablets.
- Then eat a snack with 15 grams of carbohydrates and a protein. You can use a carton of yogurt; an apple with cheese; 6 to 7 crackers with cheese or peanut butter, a KindPlus Bar. You must combine these additional carbohydrates with a protein. It is important to drink lots of water when you are low.
- If less than 50 mg/dL – take 30 grams of simple sugar, such as 8 oz of juice or 8 glucose tablets. Then use the same instructions as above for your snack. Drink lots of water.

**Conclusions**

- Hypoglycemia is common in people with diabetes treated with sulfonylurea agents, glinides, and insulin
- Mild hypoglycemia is much more common than severe hypoglycemia
- Severe hypoglycemia is associated with an increased risk of mortality
- HAAF increases the risk for severe hypoglycemia
- Approaches to prevent and treat hypoglycemia need to be employed