Hyperosmolar Hyperglycemic State (HHS)

Erica Kretchman DO
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Speaker for Valeritas, Medtronic, AstraZenica, Boehringer Ingelheim. These do not influence this presentation
Objective

- Review and understand diagnosis of Hyperosmolar Hyperglycemic State (HHS) and differentiating from Diabetic Ketoacidosis
- Treatment of HHS
- Complications of HHS
Question 1

• Which of the following is NOT a typical finding in HHS?
  1. Blood PH <7.30
  2. Dehydration
  3. Mental Status Changes
  4. Osmotic diuresis
Question 2

• Hypertonic fluids, such as 3% saline, are the first line of treatment to correct dehydration in HHS
  1. True
  2. False
Question 3

• Which of the following statements is INCORRECT about Hyperosmolar Hyperglycemic State?
  1. HHS occurs mainly in type 2 diabetics.
  2. This condition presents without ketones in the urine.
  3. Metabolic alkalosis presents in severe HHS.
  4. Intravenous Regular insulin is used to treat hyperglycemia.
Hyperosmolar Hyperglycemic State (HHS)

• HHS and DKA are two of the most serious complications from Diabetes
  • Hospital admissions for HHS are lower than the rate for DKA and accounts for less than 1 percent of all primary diabetic admissions
  • Mortality rate for patients with HHS is between 10 and 20 percent, which is approximately 10 times higher than that for DKA
    • Declined between 1980 and 2009
    • Typically from precipitating illness - rare from HHS itself
PRECIPITATING FACTORS

• The most common events are infection (often pneumonia or urinary tract infection) and discontinuation of or inadequate insulin therapy.

• Acute major illnesses such as myocardial infarction, cerebrovascular accident, renal failure, sepsis, or pancreatitis.

• Drugs that affect carbohydrate metabolism, including glucocorticoids, higher-dose thiazide diuretics, sympathomimetic agents and second-generation "atypical" antipsychotic agents.

• Compromised water intake due to underlying medical conditions, particularly in older patients, can promote the development of severe dehydration and HHS.

• Undiagnosed Diabetes
PRECIPITATING FACTORS - DRUGS

- Beta-adrenergic blockers
- Calcium-channel blockers
- Chlorpromazine
- Chlorthalidone
- Cimetidine
- Clozapine
- Diazoxide
- Ethacrynic acid
- Immunosuppressive agents
- L-asparaginase
- Loxapine
- Phenytoin
- Propranolol
- **Steroids**
- Thiazide diuretics
- Total parenteral nutrition
Death Rates for Hyperglycemic Crises as Underlying Cause

Rate per 100,000 Persons with Diabetes By Age, United States, 2009

Deaths per 100,000

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Rate per 100,000 Persons with Diabetes</th>
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</thead>
<tbody>
<tr>
<td>0-44</td>
<td>20.7</td>
</tr>
<tr>
<td>45-64</td>
<td>11.1</td>
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<tr>
<td>65-71</td>
<td>6.5</td>
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<tr>
<td>≥75</td>
<td>14.8</td>
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</table>

Hyperosmolality and Mortality in Hyperglycemic Crises

- 1,211 patients with Hyperglycemic crises
- Combined DKA-HHS in 27%
- DKA-HHS was independently associated with 2.4 fold increased mortality

Case Definition of Hyperglycemic Crises
1) HHS: BG >600 mg/dL, effective osmolality ≥300 mOsm/L, bicarbonate >18 mEq/L
2) DKA: ICD-code for DKA and bicarbonate ≤18 mEq/L
3) Combined DKA-HHS: DKA criteria + effective osmolality ≥300 mOsm/kg

Pathogenesis

- Two main hormonal dysfunction
  - Insulin deficiency or resistance
  - Glucagon excess
- Also increase in counterregulatory hormones like cortisol, Growth hormone and catecholamines

So Why are ketones typically present in DKA but not HHS?
It’s All About the Benjamins
Pathogenesis of diabetic ketoacidosis and hyperosmolar hyperglycemic state

**Absolute insulin deficiency**
- Lipolysis
  - FFA to liver
  - Ketogenesis
  - Alkali reserve
- **Ketoacidosis**
  - Triacylglycerol
  - Hyperlipidemia

**Counterregulatory hormones**
- Protein synthesis
- Proteolysis
- Absent or minimal ketogenesis
- **Gluconeogenic substrates**
- Gluconeogenesis
- **Glucosuria (osmotic diuresis)**
- Loss of water and electrolytes
  - Decreased fluid intake
  - Dehydration
  - Impaired renal function
  - Impaired renal function

**Relative insulin deficiency**

**Hyperglycemia**

**Hyperosmolarity**

**DKA**: diabetic ketoacidosis; **HHS**: hyperosmolar hyperglycemic state.

++: Accelerated pathway.

Case Presentation

• 71 year old women with T2DM for 10 years with weight of 100 Kg.
  • Takes Lantus 45 units daily
  • Humalog 15 units actid
  • At the pharmacy her insulin was to cost 523 dollars so she has not taken any insulin for the last 4 weeks. She stopped monitoring her glucose when she read HI.
  • She was found on the floor by daughter moaning with loss of bladder function.
Case Presentation

- VS – BP 110/50, HR 98, O2 sat 94
- Sodium – 135 mg/dL
- K – 4.5 mg/dL
- Glucose – 1200 mg/dL
- HCO3 – 20 mEq/L
- PH 7.35
- Anion Gap 12
- Urine ketones – Neg
- Serum OSM – 320 mmol/L
Hyperosmolar Hyperglycemic State

- Seen in Type 2 Diabetes Mellitus
- More neurologic symptoms: altered mental status or coma (25-50% of cases)
- Marked hyperglycemia
  - Seen in levels above 600 mg/dL but typically > 1000 mg/dL
- Plasma osmolality may reach 380 mosmol/kg
- Usually normal anion gap and no serum ketones – mild ketosis may exist
- Volume depletion is severe (8-10 L)/ Average fluid deficit = 25% of total body water.
- pH > 7.3
- Bicarb > 18-20
Presentation of Diabetic Ketoacidosis

- Seen in Type 1 Diabetes Mellitus
  - Crossover to Type 2 ketosis prone
- Hyperglycemia typically above 250 mg/dL.
  - Can see with normal glucose if patient treats at home with insulin or in case of use of SGLT2 inhibition
- Variable osmolality
- Abnormal anion gap
- Volume depletion
- pH < 7.3
- Bicarb < 18
- Ketones present in urine and blood
### Typical laboratory characteristics of DKA and HHS*

<table>
<thead>
<tr>
<th></th>
<th>DKA</th>
<th></th>
<th></th>
<th>HHS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mild</td>
<td>Moderate</td>
<td>Severe</td>
<td></td>
</tr>
<tr>
<td><strong>Plasma glucose (mg/dL)</strong></td>
<td>&gt;250</td>
<td>&gt;250</td>
<td>&gt;250</td>
<td>&gt;600</td>
</tr>
<tr>
<td><strong>Plasma glucose (mmol/L)</strong></td>
<td>&gt;13.9</td>
<td>&gt;13.9</td>
<td>&gt;13.9</td>
<td>&gt;33.3</td>
</tr>
<tr>
<td><strong>Arterial pH</strong></td>
<td>7.25 to 7.30</td>
<td>7.00 to 7.24</td>
<td>&lt;7.00</td>
<td>&gt;7.30</td>
</tr>
<tr>
<td><strong>Serum bicarbonate (mEq/L)</strong></td>
<td>15 to 18</td>
<td>10 to &lt;15</td>
<td>&lt;10</td>
<td>&gt;18</td>
</tr>
<tr>
<td><strong>Urine ketones</strong></td>
<td>Positive</td>
<td>Positive</td>
<td>Positive</td>
<td>Small</td>
</tr>
<tr>
<td><strong>Serum ketones - Nitroprusside reaction</strong></td>
<td>Positive</td>
<td>Positive</td>
<td>Positive</td>
<td>≤ Small</td>
</tr>
<tr>
<td><strong>Serum ketones - Enzymatic assay of beta hydroxybutyrate (normal range &lt;0.6 mmol/L)³</strong></td>
<td>3 to 4 mmol/L</td>
<td>4 to 8 mmol/L</td>
<td>&gt;8 mmol/L</td>
<td>&lt;0.6 mmol/L</td>
</tr>
<tr>
<td><strong>Effective serum osmolality (mOsm/kg)⁶</strong></td>
<td>Variable</td>
<td>Variable</td>
<td>Variable</td>
<td>&gt;320</td>
</tr>
<tr>
<td><strong>Anion gap⁷</strong></td>
<td>&gt;10</td>
<td>&gt;12</td>
<td>&gt;12</td>
<td>Variable</td>
</tr>
<tr>
<td><strong>Alteration in sensoria or mental obtundation</strong></td>
<td>Alert</td>
<td>Alert/drowsy</td>
<td>Stupor/coma</td>
<td>Stupor/coma</td>
</tr>
</tbody>
</table>

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HHS

- Type 2 DM
- Severe hyperglycemia
  Glucose > 600 mg/dL
- Osm > 320 mOsm/kg

DKA

- Type 1 DM
- Glucose > 250 mg/dL
- pH < 7.3
- Anion Gap
- Bicarb deficient
Initial evaluation

- Airway, breathing, and circulation (ABC) status
- Mental status
- Possible precipitating events (eg, source of infection, myocardial infarction)
- Volume status
- The initial laboratory evaluation of a patient with suspected DKA or HHS should include determination of:
  - Serum glucose
  - Serum electrolytes (with calculation of the anion gap), blood urea nitrogen (BUN), and plasma creatinine
  - Complete blood count (CBC) with differential
  - Urinalysis and urine ketones by dipstick
  - Plasma osmolality (Posm)
  - Serum ketones (if urine ketones are present)
  - Arterial blood gas if the serum bicarbonate is substantially reduced or hypoxia is suspected
  - Electrocardiogram
- Additional testing, such as cultures of urine, sputum, and blood, serum lipase and amylase, and chest radiograph should be performed on a case-by-case basis.
- Measurement of glycated hemoglobin (A1C) may be useful in determining whether the acute episode is the culmination of an evolutionary process in previously undiagnosed or poorly controlled diabetes or a truly acute episode in an otherwise well-controlled patient.
## Electrolyte and Fluid Deficits in DKA and HHS

<table>
<thead>
<tr>
<th>Parameter</th>
<th>DKA*</th>
<th>HHS*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Water, mL/kg</td>
<td>100 (7 L)</td>
<td>100-200 (10.5 L)</td>
</tr>
<tr>
<td>Sodium, mmol/kg</td>
<td>7-10 (490-700)</td>
<td>5-13 (350-910)</td>
</tr>
<tr>
<td>Potassium, mmol/kg</td>
<td>3-5 (210-300)</td>
<td>5-15 (350-1050)</td>
</tr>
<tr>
<td>Chloride, mmol/kg</td>
<td>3-5 (210-350)</td>
<td>3-7 (210-490)</td>
</tr>
<tr>
<td>Phosphate, mmol/kg</td>
<td>1-1.5 (70-105)</td>
<td>1-2 (70-140)</td>
</tr>
<tr>
<td>Magnesium, mmol/kg</td>
<td>1-2 (70-140)</td>
<td>1-2 (70-140)</td>
</tr>
<tr>
<td>Calcium, mmol/kg</td>
<td>1-2 (70-140)</td>
<td>1-2 (70-140)</td>
</tr>
</tbody>
</table>

* Values (in parentheses) are in mmol unless stated otherwise and refer to the total body deficit for a 70 kg patient.

Treatment

- Fluids, Fluids, Fluids
- Electrolyte replacement
- Regular insulin infusion
- Address underlying cause
Fluids

- Start IV fluids 0.9NS at 1L/hr
- Determine hydration status
  - Severe hypovolemia maintain 1L/hr
  - Mild hypovolemia – monitor corrected sodium
    - Measured sodium + \[1.6 \text{ (glucose - 100)} / 100\]
    - Sodium normal or high – 250-500mL/hr of 0.45 NS
    - Low – 250-500mL/hr of NS
- When Serum Glucose reaches below 300 mg/dL switch to D5 0.45 NS at 150-250 mL/Hr
- Check BUN, Electrolytes creatinine every 2-4 hours
Potassium

- $K^+ > 5.3$ mEq/L
  - Do not give $K^+$ initially, but check serum $K^+$ with basic metabolic profile every 2 h
  - Establish urine output ~50 mL/hr

- $K^+ < 3.3$ mEq/L
  - Hold insulin and give $K^+$ 20-30 mEq/hr until $K^+ > 3.3$ mEq/L

- $K^+ = 3.3-5.2$ mEq/L
  - Give 20-30 mEq $K^+$ in each L of IV fluid to maintain serum $K^+$ 4-5 mEq/L
Insulin

• Regular insulin infusion
  • 0.1 unit/kg initial IV bolus with continued 0.1 unit/kg/hr rate of infusion
    • Alternate 0.14 unit/kg/hr rate without bolus
  • If not declining by 50 mg/dL in the first hour double dose of infusion
  • Once 300 mg/dL is reached decrease infusion to 0.02 units/kg/hr

• Keep serum glucose around 250-300 mg/dL unit patient is mentally alert.

• Monitor glucose every 1-2 hours
Treatment

• Phosphorous
  • Generally replacement is not recommend
    • Dose not improve clinical outcomes in DKA – no clinical trials with HHS
    • Increased risk of hypocalcemia.
  • In cases with cardiac dysfunction, anemia, respiratory depression when phosphorous < 1.0 consider changing potassium replacement to Kphos at 20-30 mEq
Complications

- Hypoglycemia
- Hypokalemia
- Hyperglycemia
- Cerebral Edema
  - Limited data of occurrence in HHS in adults – more risky in children with DKA.
  - Close monitoring of serum electrolytes and fluid replacement.
  - If occurs limited data on the use of mannitol or 3% saline to raise plasma osmolality and shift free water out of brain cells
- Vascular Occlusions – MI, DIC, Mesenteric artery occlusion are <2% with aggressive treatment.
RESOLUTION

- Mentally alert
- Plasma osmolality is <315 mOsmol/kg
- Tolerating diet

**Transition off IV insulin**

- Patient can be transitioned to subcutaneous insulin when above goals were met and serum glucose is <250-300 mg/dL.
- SQ injection of basal insulin/intermediate acting insulin – Humalog nutritional and correctional insulin. Insulin infusion can be discontinued in 2 hours.
Predischarge Checklist

- Diet information
- Glucose monitor and strips (and associated prescription)
- Medications, insulin, needles (and associated prescription)
- Treatment goals
- Contact phone numbers
- “Medic-Alert” bracelet
- “Survival Skills” training
What to we need to consider?

• Our case study already couldn’t afford insulin – what can we do to help?
  • Formulary
    • Long Acting (Basal)
      • Basaglar (glargine)
      • Lantus (glargine)
      • Levemir (detemir)
      • Toujeo (glargine) and Toujeo Max
      • Tresiba (degludec) and Tresiba U200
    • Rapid Acting (Bolus)
      • Ademelog (lispro)
      • Apidra (glulisine)
      • Humalog (lispro) and Humalog U200
      • Novolog (aspart)
      • Fiasp (aspart- ultra rapid acting)
What to we need to consider?

- Our case study already couldn’t afford insulin – what can we do to help?
  - Formulary
    - Long Acting (Basal)
      - Basaglar (glargine) $234.16
      - Lantus (glargine) $287.27
      - Levemir (detemir) $446.08
      - Toujeo (glargine) $295.26 and Toujeo Max $503.53
      - Tresiba (degludec) $489.84 and Tresiba U200 $586.10
    - Rapid Acting (Bolus)
      - Ademelog (lispro) $472.38
      - Apidra (glulisine) $423.51
      - Humalog (lispro) $338.47 and Humalog U200 $271.17
      - Novolog (aspart) $542.25
      - Fiasp (aspart- ultra rapid acting) $563.47

Average cost $419.49 per box
Cost per unit in pens (based on Good RX)

- **Long Acting (basal)**
  - Basaglar (glargine) $0.15
  - Lantus (glargine) $0.19
  - Levemir (detemir) $0.29
  - Toujeo (glargine) $0.21 and Toujeo Max $0.27
  - Tresiba (degludec) $0.32 and Tresiba U200 $0.32

- **Rapid Acting (Bolus)**
  - Ademelog (lispro) $0.31
  - Apidra (glulisine) $0.28
  - Humalog (lispro) $0.22 and Humalog U200 $0.22
  - Novolog (aspart) $0.45
  - Fiasp (aspart- ultra rapid acting) $0.37

Average cost $0.27 per unit
What to do with the rising cost of insulin?

The list price of Humalog insulin keeps going up

Since 1996, there have been more than two dozen price increases on a vial of Humalog insulin. Adjusted for inflation, the current price is 700% higher than it was 20 years ago.

Note: List price is in unadjusted dollars and does not reflect rebates or discounts

Source: Truven Health Analytics
How do we help the individual

- Choose the right insulin on formulary
- Vouchers if able
- Discussion on cost
- Low income subsidiary (extra help)
  - Your resources must be limited to $14,100 for an individual or $28,150 for a married couple living together.
  - Your annual income must be limited to $18,210 for an individual or $24,690 for a married couple living together.
- Patient financial assistance
### Annual 2017 Poverty Guidelines for the 48 Contiguous States

<table>
<thead>
<tr>
<th>Household/Family Size</th>
<th>100%</th>
<th>138%</th>
<th>250%</th>
<th>300%</th>
<th>400%</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>12,060</td>
<td>16,643</td>
<td>30,150</td>
<td>36,180</td>
<td>48,240</td>
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<td>2</td>
<td>16,240</td>
<td>22,411</td>
<td>40,600</td>
<td>48,720</td>
<td>64,960</td>
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<tr>
<td>3</td>
<td>20,420</td>
<td>28,180</td>
<td>51,050</td>
<td>61,260</td>
<td>81,680</td>
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<td>4</td>
<td>24,600</td>
<td>33,948</td>
<td>61,500</td>
<td>73,800</td>
<td>98,400</td>
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<td>5</td>
<td>28,780</td>
<td>39,716</td>
<td>71,950</td>
<td>86,340</td>
<td>115,120</td>
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<tr>
<td>6</td>
<td>32,960</td>
<td>45,485</td>
<td>82,400</td>
<td>98,880</td>
<td>131,840</td>
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<td>7</td>
<td>37,140</td>
<td>51,253</td>
<td>92,850</td>
<td>111,420</td>
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<td>8</td>
<td>41,320</td>
<td>57,022</td>
<td>103,300</td>
<td>123,960</td>
<td>165,280</td>
</tr>
</tbody>
</table>

Financial Aid Programs Available: GSK SANOFI Lilly Novo AstraZenica Merck

### Monthly 2017 Poverty Guidelines for the 48 Contiguous States

<table>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>1,005</td>
<td>1,387</td>
<td>2,513</td>
<td>3,015</td>
<td>4,020</td>
</tr>
<tr>
<td>2</td>
<td>1,353</td>
<td>1,868</td>
<td>3,383</td>
<td>4,060</td>
<td>5,413</td>
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<tr>
<td>3</td>
<td>1,702</td>
<td>2,348</td>
<td>4,254</td>
<td>5,105</td>
<td>6,807</td>
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<tr>
<td>4</td>
<td>2,050</td>
<td>2,829</td>
<td>5,125</td>
<td>6,150</td>
<td>8,200</td>
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<tr>
<td>5</td>
<td>2,398</td>
<td>3,310</td>
<td>5,996</td>
<td>7,195</td>
<td>9,593</td>
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<td>2,747</td>
<td>3,790</td>
<td>6,867</td>
<td>8,240</td>
<td>10,987</td>
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<td>4,271</td>
<td>7,738</td>
<td>9,285</td>
<td>12,380</td>
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<td>3,443</td>
<td>4,752</td>
<td>8,608</td>
<td>10,330</td>
<td>13,773</td>
</tr>
</tbody>
</table>
Cheaper Alternatives

• Human insulin
  • Novolin Products (vials)
    • Regular $0.025 per unit
    • NPH $0.026 per unit
    • 70/30 (NPH/Regular) $0.024 per unit
  • Humulin Products (Vials)
    • Regular $0.099 per unit
    • NPH $0.099 per unit
    • 70/30 (NPH/Regular) $0.099 per unit
    • RU500 $0.148 per unit
How to Convert Insulins

- Rapid acting to Regular insulin
  - Unit for unit
  - Be cautious for longer duration of action of Regular insulin. More likely to have insulin stacking/hypoglycemia.
  - Ideally dosed 30 minutes before meals.
How to Convert Insulins

• Long Acting to Intermediate acting (NPH)
  • Unit for unit conversion
  • NPH should be split twice daily
    • 50:50
    • 2/3 in AM and 1/3 before dinner or at bedtime
  • Consider insulin peak effect with NPH and increased risk of hypoglycemia
  • Request that individual is regular in dosing medication and meal times/balance
How to Convert Insulins

• Basal/Bolus to Pre mixed 70/30
  • Calculate total daily dose (Basal+prandial)
    • Reduce total daily dose of all insulin by 20–30%.
    • Split dosing
      • 50/50 to give you the starting dose of premix insulin at breakfast and evening meal.
      • Or 2/3 dose before breakfast and 1/3 dose before dinner.

• Special consideration
  • Patient should be adherent to regular schedule, meal times, meal balance and frequent glucose monitoring due to increased risk of hypoglycemia and glycemic variability
  • Time injection 30 minutes before meals
## Pharmacokinetics of the most commonly used insulin preparations

<table>
<thead>
<tr>
<th>Insulin type</th>
<th>Approximate onset of action</th>
<th>Peak effect</th>
<th>Approximate duration of action*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lispro, aspart, faster aspart, glulisine</td>
<td>3 to 15 minutes</td>
<td>45 to 75 minutes</td>
<td>2 to 4 hours</td>
</tr>
<tr>
<td>Regular</td>
<td>30 minutes</td>
<td>2 to 4 hours</td>
<td>5 to 8 hours</td>
</tr>
<tr>
<td>NPH</td>
<td>2 hours</td>
<td>4 to 12 hours</td>
<td>8 to 18 hours, with usual duration of action around 12 hours</td>
</tr>
<tr>
<td>Insulin glargine</td>
<td>2 hours</td>
<td>No peak</td>
<td>20 to &gt;24 hours</td>
</tr>
<tr>
<td>Insulin detemir</td>
<td>2 hours</td>
<td>3 to 9 hours</td>
<td>6 to 24 hours*</td>
</tr>
<tr>
<td>NPL</td>
<td>2 hours</td>
<td>6 hours</td>
<td>15 hours</td>
</tr>
<tr>
<td>Insulin degludec</td>
<td>2 hours</td>
<td>No peak</td>
<td>&gt;40 hours</td>
</tr>
</tbody>
</table>

NPH: neutral protamine hagedorn; NPL: neutral protamine lispro.

* Glucose-lowering action may vary considerably in different individuals or within the same individual.

† Duration of action is dose dependent. At higher doses (≥0.8 units/kg), mean duration of action is longer and less variable (22 to 23 hours).
Question 1

• Which of the following is NOT a typical finding in HHS?
  1. Blood PH <7.30
  2. Dehydration
  3. Mental Status Changes
  4. Osmotic diuresis
Question 2

- Hypertonic fluids, such as 3% saline, are the first line of treatment to correct dehydration in HHS
  1. True
  2. False
Question 3

• Which of the following statements is INCORRECT about Hyperglycemic Hyperosmolar Syndrome?
  1. HHS occurs mainly in type 2 diabetics.
  2. This condition presents without ketones in the urine.
  3. Metabolic alkalosis presents in severe HHS.
  4. Intravenous Regular insulin is used to treat hyperglycemia.
Question 4

• How do we help with insulin cost
  1. Choose the right formulary insulin
  2. Check for patient financial assistance
  3. Look for low cost alternatives
  4. Advocate for lower insulin costs
  5. All of the above
References

• AACE guidelines Diagnosis and Management of Hyperglycemic Crises: Diabetic Ketoacidosis and the Hyperglycemic Hyperosmolar State
• Good RX (insulin cost)
• https://www.ssa.gov/pubs/EN-05-10525.pdf (Low income subsidery)
Thank you!