IN THE NAME OF GOD
Diabetic ketoacidosis and hyperosmolar hyperglycemic state in adults

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**DKA AND HHS**

- Diabetic ketoacidosis (DKA) and hyperosmolar hyperglycemic state (HHS, also known as hyperosmotic hyperglycemic nonketotic state [HHNK]) are two of the most serious acute complications of diabetes.
DEFINITIONS of DKA & HHS

• Differ clinically according to the presence of:
  
• Ketoacidosis
  
• The degree of hyperglycemia
Diabetic Ketoacidosis

• (DKA) develops most commonly in:
  • patients with **T1DM** (approximately 2.5 cases per 100 T1DM patients per year).

• It also can occur in those with **T2DM**, especially during acute illness (severe infection, medical illness, cardiovascular or trauma), and in a subset of *ketosis-prone* T2DM patients (less often).
**DKA is present in**

- approximately 25% of T1DM patients at diagnosis

- patients with known T1DM stop taking prescribed insulin
DKA
Lifethreatening condition

• mortality rate: 2.5%
• most deaths resulting from:
• complicating or precipitating medical conditions
• rather than the metabolic disturbances of DKA itself
PATHOGENESIS OF DKA

• Two hormonal abnormalities:
  – Insulin deficiency and/or resistance.
  – Glucagon excess – required???
    • increased secretion of catecholamines and cortisol
Liver → Increased Hepatic Glucose Production → HYPERGLYCEMIA → Osmotic Diuresis → Volume Depletion

Peripheral Tissue → Decreased Glucose Utilization

Adipose Tissue → Released FFA → KETOACIDOSIS → Decreased Alkali Reserve → Metabolic Acidosis

Liver → Increased Ketogenesis
<table>
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<th>Predisposing or precipitating factors for diabetic ketoacidosis</th>
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<tr>
<td>Inadequate insulin treatment or noncompliance</td>
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<td>New onset diabetes (20 to 25 percent)</td>
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<td>Acute illness</td>
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<td>Infection (30 to 40 %) (pneumonia/UTI/gastroenteritis/sepsis)</td>
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<td>Infarction (cerebral, coronary, mesenteric, peripheral)</td>
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<td>Acute pancreatitis, Appendicitis</td>
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<td>Pregnancy</td>
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<td>Drugs</td>
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<td>Glucocorticoids</td>
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<td>Clozapine or Olanzapine</td>
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<td>Cocaine</td>
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<td>Lithium</td>
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<tr>
<td>Terbutaline</td>
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</table>
Symptoms of DKA

- Nausea/vomiting
- Thirst/polyuria
- Polydipsia
- Shortness of breath
- Weight loss (especially in new-onset diabetes)
- Recent blurred vision
- Weakness
- Anorexia
- Abdominal pain (which can mimic acute abdomen)
- Mental status changes varying from somnolence to coma
Physical Findings of DKA (1)

- **Dehydration** (decreased skin turgor, dry axillae and oral mucosa, tachycardia, hypotension, low jugular venous pressure)

- The **skin may be warm and dry** from the vasodilating effects of acidosis, and marked hypotension should generate concern for impending **vascular collapse**
Physical Findings of DKA (2)

• Tachypnea/Kussmaul

• Abdominal tenderness (may resemble acute pancreatitis or surgical abdomen)

• Lethargy/obtundation/cerebral edema/possibly coma
Onset of DKA

• Symptoms usually evolve over 2 to 4 days

• but can have an onset of less than 12 hours in patients using insulin pumps.
The prognosis of DKA

- Is substantially worse at the:
  - 1-extremes of age
  - 2-coma
  - 3-hypotension.
Diagnosis OF DKA

• (1) BS >250 mg/dL
• (2) moderate to severe ketonemia:
  – (β-hydroxybutyrate >5 mmol/L or positive ketone levels by Ketostix at a serum dilution of 1 : 2 or higher)
• (3) acidosis(pH <7.3 or plasma bicarbonate ≤15 mEq/L)

• Measurements of urine ketones may be misleading, because urinary ketones can be positive during fasting in the absence of DKA.
HSS

• T2DM
• One third of whom have not been previously diagnosed
• Elderly
• Compromised renal function (frequently)
• Insulin deficiency, often exacerbated by insulin resistance
• Some endogenous insulin secretion suppresses lipolysis and ketogenesis enough to prevent ketoacidosis
Diagnosis OF HHS

- Glucose (600–1200) (mg/dL)
- Osmolality 330–380 (mOsm/Kg)
- Plasma ketones +/-
- Serum bicarbonate Normal to slightly ↓
- Arterial pH >7.3
  - and neurologic abnormalities are frequently present (including coma in 25 to 50 percent of cases)
The physical examination of HSS

- profound dehydration
- hypotension
- tachycardia
- altered mental status
- Notably absent are symptoms of DKA
- HHS is often precipitated by a serious, concurrent illness
- Compromises water intake
Mortality attributed to HHS

• Is higher than that of DKA, with rates ranging from 5 to 20 percent; as in DKA

• Mortality is most often due to the:
  – underlying illness comorbidity.
# Predisposing or precipitating factors for HHS

<table>
<thead>
<tr>
<th>HHS</th>
<th>Endocrine</th>
<th>Drugs/therapy</th>
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</thead>
<tbody>
<tr>
<td><strong>Inadequate insulin treatment or noncompliance (21 to 41 percent)</strong></td>
<td>Acromegaly</td>
<td>Beta-Adrenergic blockers</td>
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<tr>
<td><strong>Acute illness</strong></td>
<td>Thyrotoxicosis</td>
<td>Calcium-channel blockers</td>
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<tr>
<td>Infection (32 to 60 percent)</td>
<td>Cushing's syndrome</td>
<td>Chlorpromazine</td>
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<tr>
<td>Pneumonia</td>
<td></td>
<td>Chlorthalidone</td>
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<td>Urinary tract infection</td>
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<td>Cimetidine</td>
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<td>Sepsis</td>
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<td>Clozepine</td>
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<td>Cerebral vascular accident</td>
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<td>Diazoxide</td>
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<td>Myocardial infarction</td>
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<td>Ethacrynic acid</td>
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<td>Acute pancreatitis</td>
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<td>Imunosuppressive agents</td>
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<td>Acute pulmonary embolus</td>
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<td>L-asparaginase</td>
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<td>Intestinal obstruction</td>
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<td>Loxapine</td>
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<td>Dialysis, peritoneal</td>
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<td>Olanzapine</td>
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<td>Mesenteric thrombosis</td>
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<td>Phenytoin</td>
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<td>Renal failure</td>
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<td>Propranolol</td>
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<td>Heat stroke</td>
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<td>Steroids</td>
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<td>Hypothermia</td>
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<td>Thiazide diuretics</td>
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<tr>
<td>Subdural hematoma</td>
<td><strong>Previously undiagnosed diabetes</strong></td>
<td>Total parenteral nutrition</td>
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<tr>
<td>Severe burns</td>
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Pathophysiology of HSS

• Relative insulin deficiency

• inadequate fluid intake
<table>
<thead>
<tr>
<th></th>
<th>DKA Mild</th>
<th>Moderate</th>
<th>Sever</th>
<th>HSS</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>
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<tr>
<td>Arterial pH</td>
<td>7.25-7.30</td>
<td>7.00-7.24</td>
<td>&lt;7.00</td>
<td>&gt;7.30</td>
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<tr>
<td>Serum bicarbonate (mEq/L)</td>
<td>15-18</td>
<td>10 to &lt;15</td>
<td>&lt;10</td>
<td>&gt;18</td>
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<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 osmolality (mOsm/kg) •</td>
<td>Variable</td>
<td>Variable</td>
<td>Variable</td>
<td>&gt;320</td>
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<tr>
<td>Anion gap Δ</td>
<td>&gt;10</td>
<td>&gt;12</td>
<td>&gt;12</td>
<td>Variable</td>
</tr>
<tr>
<td>Alteration in sensoria or mental obtundation</td>
<td>Alert</td>
<td>Alert/drowsy</td>
<td>Stupor/coma</td>
<td>Stupor/coma</td>
</tr>
</tbody>
</table>
Treatment of DKA and HHS
| Hour | | | | | |
|---|---|---|---|---|

**Mental status**

**Vital signs**
- Temperature
- Pulse
- Respiration (rate & depth)*
- Blood pressure

**Chemistries**
- Serum glucose
- Serum ketones
- Urine ketones
- Serum Na⁺ (mEq/L)
- Serum K⁺ (mEq/L)
- Serum Cl⁻ (mEq/L)
- Serum HCO₃⁻ (mEq/L)
- Serum BUN (mg/dL)
- Effective osmolalityΔ
- Anion gap

**Blood gases**
- pH Specify venous (V) or arterial (A)
- pO₂
- pCO₂
- O₂ sat

**Insulin (units in past hour)**
- Route
  - IV
  - SC
  - IM

**Fluid/Metabolites (past hour)**
- 0.45 percent NaCl (ml)
- 0.9 percent NaCl (ml)
- 5 percent dextrose (ml)
- Other

**Output**
- Urine (ml)
- Other
Treatment of DKA and HHS

• is similar, including correction of the:
  • Fluid
  • Electrolyte abnormalities
    – Metabolic acidosis [in DKA]
  • Insulin
  • Predisposing or precipitating factors
The first step in the treatment of DKA or HHS

- Infusion of isotonic saline to expand extracellular volume and stabilize cardiovascular status
- ↑Insulin responsiveness by:
  - ↓Plasma osmolality (Posm)
  - ↓Vasoconstriction and improving perfusion
  - ↓Stress hormone levels
Complete initial evaluation. Check capillary glucose and serum/urine ketones to confirm hyperglycemia and ketonemia/ketonuria. Start IV fluids: 1.0 L of 0.9 percent NaCl per hour.*

**IV fluids**
- Determine hydration status
  - Severe hypovolemia
    - Administer 0.9 percent NaCl (1.0 L/hr)
  - Mild hypovolemia
    - Evaluate corrected serum Na⁺
    - Hemodynamic monitoring/pressors
  - Cardiogenic shock
    - 0.45 percent NaCl (250-500 mL/hr) depending on volume state

**Insulin**
- IV route
  - Insulin: Regular 0.1 U/kg as IV bolus
  - 0.1 U/kg IV continuous insulin infusion
- Uncomplicated DKA-SC route
  - Rapid-acting insulin: 0.3 U/kg, then 0.2 U/kg one hour later
  - Rapid-acting insulin: 0.2 U/kg SC every two hrs

If serum glucose does not fall by 50-70 mg/dL in first hour, double IV or SC insulin bolus

**Potassium**
- Establish adequate renal function (urine output ~50 mL/hr)
  - If serum K is <3.3 mEq/L, hold insulin and give 20-40 mEq K/hr until K ≥2.2 mEq/L
  - Rapid-acting insulin: 0.2 U/kg SC every two hrs

If serum K is >5.3 mEq/L, do not give K but check serum K every two hrs

**Assess need for bicarbonate**
- Dilute NaHCO₃ (100 mmol) in 400 mL H₂O with 20 mEq KCl. Infuse over two hrs.
  - pH <6.9
    - Repeat NaHCO₃ administration every two hrs until pH >7.0. Monitor serum K every two hrs.
  - pH ≥6.9
    - No HCO₃

When serum glucose reaches 200 mg/dL, reduce regular insulin infusion to 0.02-0.05 U/kg/hr IV, or give rapid-acting insulin at 0.1 U/kg SC every two hours. Keep serum glucose between 150 and 200 mg/dL until resolution of DKA.

If K is 3.3-5.3 mEq/L, give 20-30 mEq/K in each liter of IV fluid to keep serum K between 4-5 mEq/L

Check electrolytes, BUN, venous pH, creatinine and glucose every 2-4 hrs until stable. After resolution of DKA and when patient is able to eat, initiate SC multidose insulin regimen. Continue IV insulin infusion for 1-2 hr after SC insulin begun to ensure adequate plasma insulin levels. In insulin naïve patients, start at 0.5 U/kg to 0.3 U/kg body weight per day and adjust insulin as needed. Look for precipitating cause(s).
Complete initial evaluation. Check capillary glucose to confirm hyperglycemia. Start IV fluids: 1.0 L of 0.9 percent NaCl per hour.

**IV Fluids**
- Determine hydration status
  - **Severe Hypovolemia**
    - Administer 0.9 percent NaCl (1.0 L/hr)
  - **Mild dehydration**
    - Evaluate corrected serum Na*¹
  - **Cardiogenic shock**
    - Hemodynamic monitoring/pressors
    - Serum Na* low
      - 0.45 percent NaCl (250-500 ml/hr) depending on hydration state
    - Serum Na* normal
      - 0.9 percent NaCl (250-500 ml/hr) depending on hydration state
  - Serum Na* high
    - 0.45 percent NaCl (250-500 ml/hr) depending on hydration state

**Insulin**
- IV regular insulin
  - Insulin: 0.1 U/kg body weight as IV bolus
  - 0.1 U/kg/hr IV continuous insulin infusionΔ
  - If serum glucose does not fall by 50-70 mg/dl in first hour, double insulin dose
  - When serum glucose reaches 300 mg/dl, change to 5 percent dextrose with 0.45 percent NaCl at 150-250 ml/hr

**Potassium**
- Establish adequate renal function (urine output ~50 ml/hr)
  - K⁺ <3.3 mEq/L
    - Hold insulin and give 20-30 mEq K⁺/hr until K⁺ > 3.3 mEq/L
  - K⁺ = 3.3-5.3 mmEq/L
    - Give 20-30 mEq K⁺ in each liter of IV fluid to keep serum K⁺ between 4-5 mEq/L
  - K⁺ >5.3 mEq/L
    - Do not give K⁺, but check serum K⁺ every two hrs.

- Check electrolytes, BUN, creatinine and glucose every 2-4 hrs until stable. After resolution of HHS and when patient is able to eat, initiate SC multidose insulin regimen. Continue IV insulin infusion for 1-2 hrs after SC insulin begun to ensure adequate plasma insulin levels. In insulin naive patients, start at 0.5-0.8 U/kg per day and adjust insulin as needed. Look for precipitating cause(s).
Low-dose intravenous (IV) insulin

- Should be administered to all patients with moderate to severe DKA who have a serum potassium $\geq 3.3$ mEq/L.

- K$<3.3$ mEq/L, insulin therapy should be delayed until potassium replacement has begun and the serum potassium concentration has increased.
Identification and treatment of any precipitating events
SGLT2 inhibitors

• SGLT2 inhibitors, which can precipitate DKA, should be discontinued
Protocol for the management of adult patients with DKA

- DKA diagnostic criteria: Serum glucose >250 mg/dL, arterial pH <7.3, serum bicarbonate <18 mEq/L, and at least moderate ketonuria or ketonemia. Normal laboratory values vary; check local lab normal ranges for all electrolytes.
- BUN: blood urea nitrogen; DKA: diabetic ketoacidosis; HCO₃⁻: bicarbonate; IV: intravenous; K: potassium; Na: sodium; NaCl: sodium chloride; NaHCO₃: sodium bicarbonate; SC: subcutaneous.
  * After history and physical exam, obtain capillary glucose and serum or urine ketones. Begin one liter of 0.9 percent NaCl over one hour and draw arterial blood gases, complete blood count with differential, urinalysis, serum glucose, BUN, electrolytes, chemistry profile, and creatinine levels STAT. Obtain electrocardiogram, chest radiograph, and specimens for bacterial cultures, as needed.
  ¶ Serum Na⁺ should be corrected for hyperglycemia (for each 100 mg/dL glucose >100 mg/dL, add 2.0 mEq to sodium value for corrected serum sodium value).
  Δ An alternative IV insulin regimen is to give a continuous intravenous infusion of regular insulin at 0.14 units/kg/hour; at this dose, an initial intravenous bolus is not necessary.
  ◊ 100 mmol sodium bicarbonate = 100 mEq sodium bicarbonate.
  § Please refer to the topic on DKA for the definition of DKA resolution.

Protocol for the management of adult patients with HHS

- HHS diagnostic criteria: serum glucose >600 mg/dL, arterial pH >7.3, serum bicarbonate >15 mEq/L, and minimal ketonuria and ketonemia. Normal laboratory values vary; check local lab normal ranges for all electrolytes.
- BUN: blood urea nitrogen; HHS: hyperosmolar hyperglycemic state; IV: intravenous; K: potassium; Na: sodium; NaCl: sodium chloride; SC: subcutaneous.
  * After history and physical exam, obtain capillary glucose and serum or urine ketones (nitroprusside method). Begin one liter of 0.9 percent NaCl over one hour and draw arterial blood gases, complete blood count with differential, urinalysis, serum glucose, BUN, electrolytes, chemistry profile and creatinine levels STAT. Obtain electrocardiogram, chest radiograph, and specimens for bacterial cultures, as needed.
  ¶ Serum Na⁺ should be corrected for hyperglycemia (for each 100 mg/dL glucose >100 mg/dL, add 2.0 mEq to sodium value for corrected serum sodium value).
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- Graphic 67368 Version 3.0
Volume repletion

• ↓ BS by 35 to 70 mg/dL per hour due to:
• ECF expansion and dilution
• Increased urinary losses resulting from improved renal perfusion and glomerular filtration
• an amelioration of the high "stress hormone" levels, which oppose the effects of insulin, as ECF volume is restored.
Bicarbonate administration is also controversial

• reduce the hyperventilatory drive → raise the blood $P_{CO_2}$ → across the blood brain barrier

• The administration of alkali may slow the rate of recovery of the ketosis

• Alkali administration can lead to a posttreatment metabolic alkalosis
Alkali therapy

• Patients with an arterial pH ≤6.9 in whom decreased cardiac contractility and vasodilatation can impair tissue perfusion

• Patients with potentially life-threatening hyperkalemia
Phosphate depletion

- Do not recommend the routine use of phosphate replacement in the treatment of DKA or HHS
phosphate replacement

• Severe hypophosphatemia occurs (serum phosphate concentration below 1.0 mg/dL or 0.32 mmol/L), especially if

• cardiac dysfunction

• hemolytic anemia

• and/or respiratory depression develop

• When needed, potassium or sodium phosphate 20 to 30 mEq can be added to 1 L of IV fluid.
phosphate replacement

• Consequently, routine replacement is not indicated.

• When the patient stabilizes, phosphate-rich food such as dairy products and almonds may be recommended.
MONITORING

- serum glucose → every hour until stable
- serum electrolytes, blood urea nitrogen (BUN), creatinine, and venous pH (for DKA) should be measured every two to four hours
Repeat arterial blood gases are unnecessary during the treatment of DKA.

Venous pH, which is approximately 0.03 units lower than arterial pH.

An alternative to monitoring venous pH is to monitor the serum bicarbonate concentration.
Bedside ketone meters

• measure capillary blood beta-hydroxybutyrate may be another convenient method for monitoring the response to treatment

• When bedside meters are not available, monitoring venous pH and/or the venous bicarbonate and anion gap is sufficient.
Resolution of ketoacidosis in DKA

- BS <200 mg/dL
- Serum anion gap <12 mEq/L (or at the upper limit of normal for the local laboratory)
- Serum bicarbonate ≥15 mEq/L
- Venous pH >7.30
- The patient is able to eat
Resolution of HSS

- BS< 250 to 300 mg/dL
- Mentally alert
- The plasma effective osmolality has fallen below 315 mOsmol/kg
- The patient is able to eat.
Urinary ketone levels

- Although assessments of urinary or serum ketone levels by the nitroprusside method can be used for the initial diagnosis of ketoacidosis, it should not be used for monitoring resolution of DKA.
Converting to subcutaneous insulin

• If the patient is unable to eat, it is preferable to continue the IV insulin infusion

• In insulin-naive patients, a multidose insulin regimen should be started at a dose of 0.5 to 0.8 units/kg per day, including bolus and basal insulin until an optimal dose is established
COMPLICATIONS of THE TREATMENT of DKA and HHS
• Hypoglycemia and hypokalemia (the most common)
• Hyperglycemia may recur
• Cerebral edema
• Noncardiogenic pulmonary edema
Cerebral Edema

• Cerebral edema in uncontrolled diabetes mellitus (usually DKA, with only occasional reports in HHS) is primarily a disease of children, and almost all affected patients are younger than 20 years old.
Cerebral edema

• Symptoms typically emerge within 12 to 24 hours of the initiation of treatment for DKA but may exist prior to the onset of therapy.
Clinical Manifestation of Cerebral Edema

- Headache (earliest clinical manifestation)
- Lethargy and decreased arousal
- Seizures, incontinence, pupillary changes, bradycardia, and respiratory arrest can develop.
- Symptoms progress if brainstem herniation occurs, and the rate of progression may be so rapid that clinically recognizable papilledema does not develop.
preventive measures may reduce the risk of cerebral edema

- Gradual replacement of sodium and water deficits in patients who are hyperosmolar.
- Dextrose should be added to the saline solution.
Treatment of cerebral edema in children with diabetic ketoacidosis

- Case reports and small series in children suggest benefit from prompt administration of **mannitol** (0.25 to 1.0 g/kg) intravenously over 20 minutes.
- Hypertonic (3 percent) saline (5 to 10 mL/kg over 30 min).
- The mannitol dose may be repeated in two hours, if there is no initial response.
Treatment of cerebral edema in children with diabetic ketoacidosis

- Until further data are available, we suggest using 3 percent saline only as a secondary intervention in patients with progressive symptoms of cerebral edema and no response to mannitol.
• DKA-associated cerebral edema has a mortality rate of 20 to 40 percent
Following treatment of DKA

• the physician and patient should review
• the sequence of events that led to DKA to prevent future recurrences.

• Foremost is patient education about the symptoms of DKA, its precipitating factors, and the management of diabetes during a concurrent illness.
Following treatment of DKA

- During illness or when oral intake is compromised, patients should
- (1) frequently measure the capillary blood glucose
- (2) measure urinary ketones when the serum glucose is > 300 mg/dL
- (3) drink fluids to maintain hydration
- (4) continue or increase insulin
- (5) seek medical attention if dehydration, persistent vomiting, or uncontrolled hyperglycemia develop.

Using these strategies, early DKA can be prevented or detected and treated appropriately on an outpatient basis.