بنام خداوند بخشنده مهربان

# DIABETIC KETOACIDOSIS

# Introduction AND Epidemiology

- Acute , life-threatening complication of DM
- Occurs predominantly in patients with type 1 DM
- Annual incidence in developed countries is between 13.4 and 14.9 cases per 1000 type 1 DM
- There has been an increased number of DKA cases in patients with newly diagnosed type 2 DM
- Over the past decade in the US , frequency of DKA has increased by 30%
- Approximately 25% of all episodes occur in patients whose diabetes was previously undiagnosed
- Mortality is higher in patients from developing countries , those with comorbidities and the elderly

# Pathophysiology

- A response to cellular starvation brought on by relative *insulin deficiency* and *counter-regulatory hormone excess*
- May be caused by cessation of insulin intake or by physical or emotional stress , despite continued insulin therapy
- Complete or relative absence of insulin and excess counter-regulatory hormones result in :

  Hyperglycemia , Osmotic diuresis , Prerenal azotemia , Ketone formation ,

  High anion gap metabolic acidosis , Dehydration , Electrolyte imbalance
-

- Cells decrease amino acid uptake and accelerate proteolysis so that large amounts of amino acids are released and converted to two-carbon fragments .
- Insulin deficiency results in activation of a hormone-sensitive lipase that increases FFA .
- FFAs are oxidized and converted to acetoacetate and β-hydroxybutyrate .
- Adipose tissue fails to clear circulation of lipids

- Increased ketone production with decreased ketone use leads to ketoacidosis .
- Acidotic patient attempts to increase lung ventilation to rid the body of excess acid with Kussmaul breathing .
- Bicarbonate is consumed .
- Acidosis compounds the effects of ketosis and hyperosmolality to depress mental status .

- *Acidemia* is not invariably present , even with significant ketoacidosis
- Ketoalkalosis : Diabetic patients vomiting for several days and in some with severe dehydration and hyperventilation
- Alkalemia : Should prompt consideration of alcoholic ketoacidosis ( alkalemia is much more common )

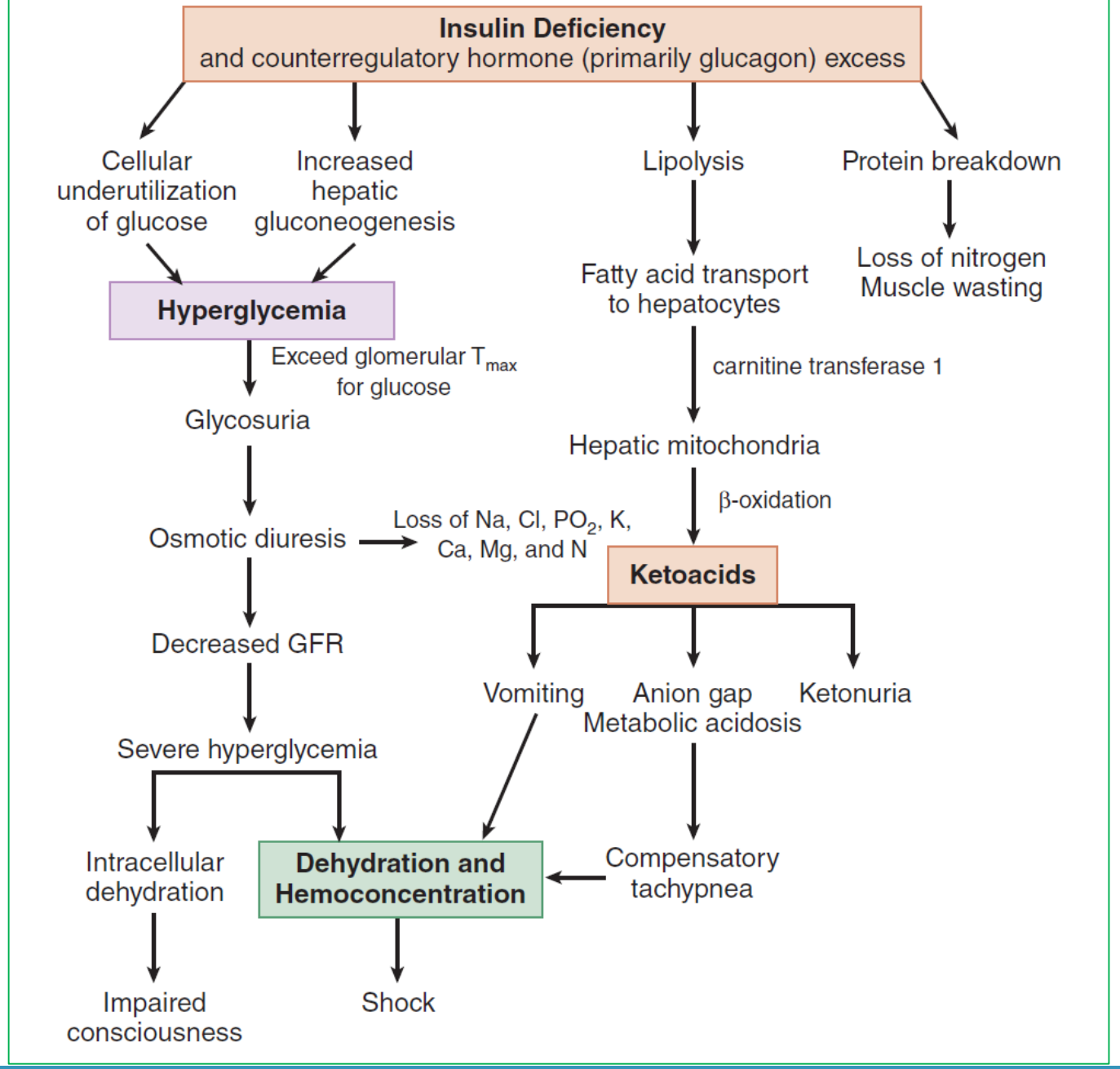

Insulin Deficiency
and counterregulatory hormone (primarily glucagon) excess
Cellular underutilization of glucose
Increased hepatic gluconeogenesis
Lipolysis
Protein breakdown
Hyperglycemia
Fatty acid transport to hepatocytes
Loss of nitrogen
Muscle wasting
Exceed glomerular $T_{max}$ for glucose
carnitine transferase 1
Glycosuria
Hepatic mitochondria
β-oxidation
Osmotic diuresis
Loss of Na, Cl, $PO_2$, K, Ca, Mg, and N
Ketoacids
Decreased GFR
Vomiting
Anion gap Metabolic acidosis
Ketonuria
Severe hyperglycemia
Intracellular dehydration
Dehydration and Hemoconcentration
Compensatory tachypnea
Impaired consciousness
Shock

**TABLE 225-1 Important Causes of Diabetic Ketoacidosis**

- Omission or reduced daily insulin injections
- Dislodgement/occlusion of insulin pump catheter
- Infection
- Pregnancy
- Hyperthyroidism, pheochromocytoma, Cushing's syndrome
- Substance abuse (cocaine)
- Medications: steroids, thiazides, antipsychotics, sympathomimetics
- Heat-related illness
- Cerebrovascular accident
- GI hemorrhage
- Myocardial infarction
- Pulmonary embolism
- Pancreatitis
- Major trauma
- Surgery

# Clinical Features

- Clinical manifestations are related directly to *Hyperglycemia* , *Volume depletion*, *Acidosis* .
- Metabolic alterations tend to evolve within 24 hours .
- Osmotic diuresis gradually leads to volume loss in addition to renal losses of sodium , chloride, potassium……
- Initially, patients may compensate by increasing fluid intake, and polyuria and polydipsia are usually the only symptom

- As acidosis progresses, ventilation is stimulated physiologically by acidemia to diminish Pco2 and to counter metabolic acidosis.

## 20.14 Clinical features of diabetic ketoacidosis

### Symptoms

- Polyuria, thirst
- Weight loss
- Weakness
- Nausea, vomiting
- Leg cramps
- Blurred vision
- Abdominal pain

### Signs

- Dehydration
- Hypotension (postural or supine)
- Cold extremities/peripheral cyanosis
- Tachycardia
- Air hunger (Kussmaul breathing)
- Smell of acetone
- Hypothermia
- Delirium, drowsiness, coma (10%)

Approximately 50% of these patients, especially children, report abdominal pain

In adults abdominal pain more often signifies actual abdominal disease that may be triggering DKA

- Alteration of consciousness seems to correlate better with elevated serum osmolality ( >320 mmol/kg) than with severity of metabolic acidosis .

- Absence of fever does not exclude infection
- Hypothermia is present occasionally because of peripheral vasodilation

- Abdominal pain and tenderness generally correlate with the level of acidosis .
- Pain can be due to gastric dilatation , ileus , or pancreatitis , but any other acute abdominal disorder can also develop.

- Due to frequency of abdominal pain and presence of an elevated serum amylase or lipase level in both DKA and pancreatitis, distinguishing these two conditions may be difficult . An elevated serum lipase level is *more specific* to pancreatitis .

# Physical examination

- Alteration of consciousness
- Tachypnea with Kussmaul breathing
- Tachycardia
- Frank hypotension or orthostatic blood pressure changes
- Odor of acetone on the breath
- Signs of dehydration
- An elevated temperature is rarely caused by DKA itself and suggests an inciting infection

# DIAGNOSIS

- Blood glucose > 250 milligrams/dL , Anion gap >10 - 12 mEq/L , Bicarbonate <15 mEq/L , and Ph < 7.3 with moderate ketonuria or ketonemia constitute the diagnosis of DKA .

- DKA is divided into mild , moderate , and severe

- *Mild DKA :* Arterial pH  7.25 - 7.3 , Bicarbonate 15 - 18 mEq/L , Anion gap >10 mEq/L
- *Moderate DKA* : Arterial pH 7.0 - 7.24 , Bicarbonate 10 - 15 mEq/L , Anion gap >12 mEq/L
- *Severe DKA :* Arterial pH < 7.00 , Bicarbonate <10 mEq/L , Anion gap >12 mEq/L

## TABLE 115.4 Typical Laboratory Values in Diabetic Ketoacidosis and Hyperglycemic Hyperosmolar State

| | DKA | HHS |
|---|---|---|
| Glucose (mg/dL) | >350 | >700 |
| Sodium (mEq/L) | Low 130s | 140s |
| Potassium (mEq/L) | ≈4.5–6.0 | ≈5 |
| Bicarbonate (mEq/L) | <10 | >15 |
| Blood urea nitrogen (mg/dL) | 25–50 | >50 |
| Serum ketones | Present | Absent |

Euglycemic DKA (blood glucose level ≤ 300 mg/dL) has been reported in up to 18% of patients

# Differential Diagnosis

**TABLE 225-3 Differential Diagnosis for Diabetic Ketoacidosis**

- Alcoholic ketoacidosis
- Starvation ketoacidosis
- Renal failure
- Lactic acidosis
- Ingestions
  - Salicylates
  - Ethylene glycol
  - Methanol

Alcoholic ketoacidosis accounts for approximately 20% of all cases of ketoacidosis

# Laboratory Testing

- Serum glucose , Electrolyte , VBG
- Serum ketoacid ( Although frequently measured , they are not necessary to diagnose DKA )
- EKG ( MI , Hyperkalemia or Hypokalemia )
- Basic metabolic panel
- Urinalysis
- Blood or urine cultures

- All laboratory determinations must be interpreted with caution
- *Creatinine* level may be falsely elevated
- *Leukocytosis* more closely reflects the degree of ketosis than the presence of infection
- Only the elevation of *band neutrophils* has been demonstrated to indicate the presence of infection
- Current literature demonstrating greater specificity of *lipase* for the diagnosis of pancreatitis .

# ABG or VBG

- If determination of  pH is the sole concern , VBG correlate well with arterial pH and are preferable .

- If there is concern about the degree of respiratory compensation and better assessment of ventilation is required , then ABG should be obtained .

# Potassium

- Total-body potassium is depleted
- In most patients measured serum potassium level is normal or elevated ( acidisis , dehydration )
- Decrease in serum potassium during therapy is about 1.5 mEq/L and parallels the drop in glucose and dose of insulin .
- ECG changes of hyperkalemia or hypokalemia may be seen .

# Serum sodium level

- In 95% of patients total sodium level is normal or low .
- Is often misleading ( Dilutional hyponatremia , Pseudohyponatremia )
- It is often low in the presence of significant dehydration because it is strongly affected by hyperglycemia , hypertriglyceridemia, salt-poor fluid intake, increased GI and renal losses, and insensible loss .
- True value of sodium level : 1.6 mEq/L to sodium value on laboratory report for every 100-mg/dL glucose above norm .

## TABLE 115.3 Average Fluid and Electrolyte Deficits in Severe Diabetic Ketoacidosis[a]

| Weight | Water (mL/kg) | Sodium (mEq/L) | Potassium (mEq/L) | Chloride (mEq/L) | Phosphorus (mEq/L) |
|---|---|---|---|---|---|
| ≤10 kg | 100–120 | 8–10 | 5–7 | 6–8 | 3 |
| 10–20 kg | 80–100 | 8–10 | 5–7 | 6–8 | 3 |
| ≥20 kg | 70–80 | 8–10 | 5–7 | 6–8 | 3 |

# TREATMENT

- Diagnosis of DKA should be suspected at triage.
- Goals of therapy are :

Volume repletion

Reversal of metabolic consequences of insulin insufficiency

Correction of electrolyte and acid-base imbalances

Recognition and treatment of precipitating causes

Avoidance of complications

- Place patients on a cardiac monitor and begin at least one large-bore IV infusion of isotonic crystalloid
- A second IV line with 0.45% normal saline at minimal rate to keep the IV line open
- Order of therapeutic priorities :

  Volume first and foremost

  Correction of potassium deficits

  Insulin administration

- Metabolic disturbances should be corrected at approximate rate of occurrence or over 24 to 36 hours

- Monitoring every 2 hours of electrolytes ( glucose, potassium, anion gap), vital signs , level of consciousness, and volume input/output until recovery .

- Goal of treatment :

  Glucose <200 milligrams/dL

  Bicarbonate ≥18 mEq/L

  Venous pH >7.3

# VOLUME REPLETION

- Restore intravascular volume and normal tonicity , perfuse vital organs , improve GFR , lower serum glucose and ketone levels .
- Rehydration improves response to low-dose insulin and may help lower hyperglycemia .
- Mean plasma glucose concentration has been noted to drop by 18% after administration of saline solution without insulin .
- Average adult patient has a water deficit of 100 mL/kg (5 to 10 L) and a sodium deficit of 7 to 10 mEq/kg .

- It is reasonable to select either normal saline , lactated ringer's , or a commercially available balanced crystalloid

- There is no consensus on the best fluid choice in DKA .

- After initial resuscitation with isotonic crystalloid , change fluids to 0.45% normal saline once corrected serum sodium is normal or elevated .

- Based on clinical suspicion alone and before initial electrolyte results , administer initial fluid bolus of isotonic crystalloid at a rate of 15 to 20 mL/kg/h during the first hour .

- Rate of hydration should depend on hemodynamic stability , hydration status, urine output , serum electrolytes

- After the initial bolus, administer normal saline at 250 to 500 mL/h in hyponatremic patients, or give 0.45% normal saline at 250 to 500 mL/h for eunatremic and hypernatremic patients .

- In general :

  The first 2 L over 0 to 2 hours

  The next 2 L over 2 to 6 hours

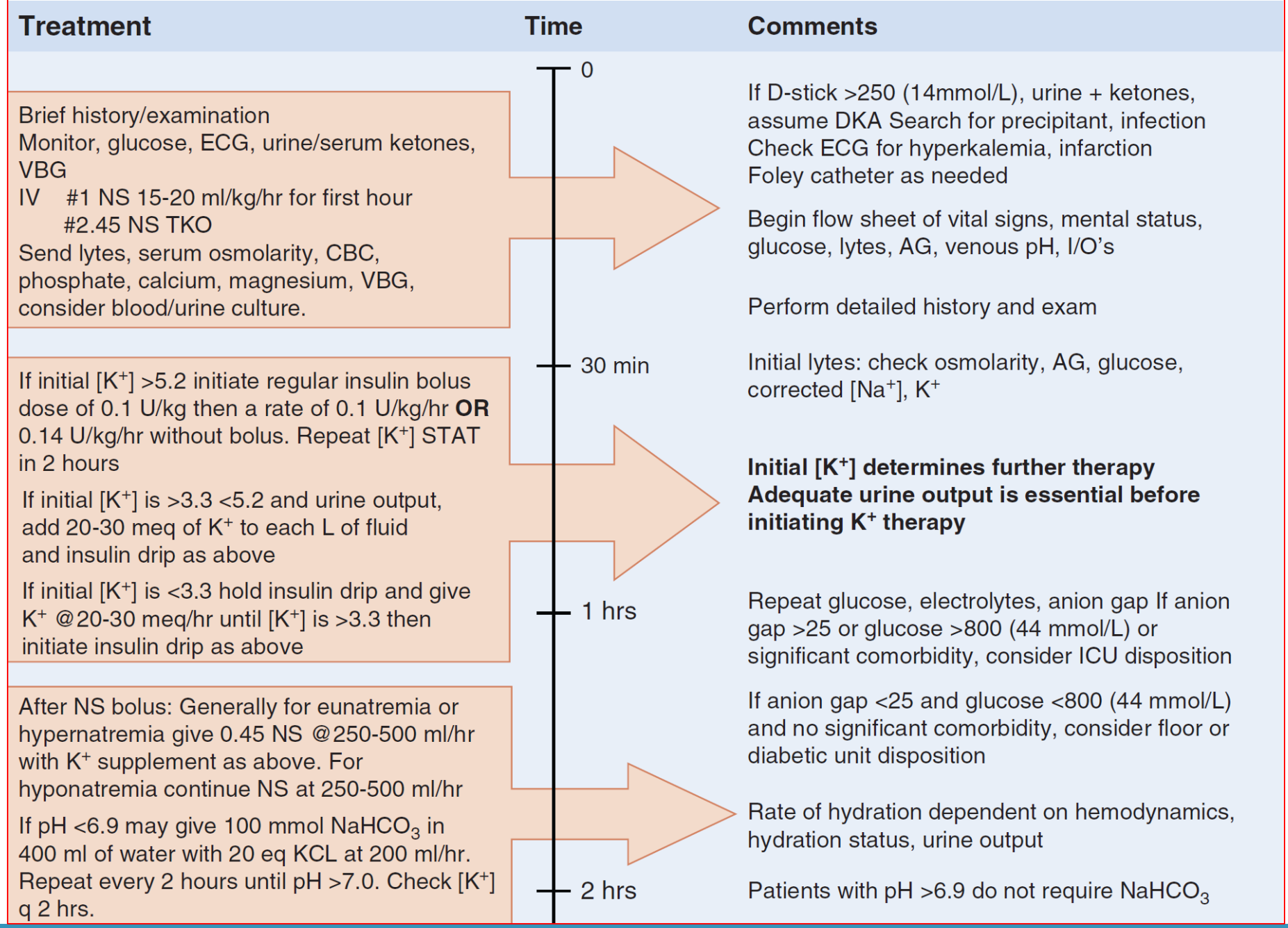
  Additional 2 L over 6 to 12 hours

- This replaces approximately 50% of the total water deficit over the first 12 hours , with the remaining 50% water deficit to be replaced over the subsequent 12 hours .
- When the blood glucose level falls to about 250 milligrams/dL , change to 5% dextrose in 0.45% normal saline.

- Patients without extreme volume depletion can be managed with a more modest fluid replacement regimen such as 250 to 500 mL/h for 4 hours .

- Closely monitor the volume status in the elderly or in those with heart or renal disease .

- Excess fluid may contribute to the development of adult respiratory distress syndrome and cerebral edema .


Treatment
Time
Comments
0
Brief history/examination
Monitor, glucose, ECG, urine/serum ketones, VBG
IV #1 NS 15-20 ml/kg/hr for first hour
#2.45 NS TKO
Send lytes, serum osmolarity, CBC, phosphate, calcium, magnesium, VBG, consider blood/urine culture.
If D-stick >250 (14mmol/L), urine + ketones, assume DKA Search for precipitant, infection
Check ECG for hyperkalemia, infarction
Foley catheter as needed
Begin flow sheet of vital signs, mental status, glucose, lytes, AG, venous pH, I/O's
Perform detailed history and exam
30 min
If initial [K+] >5.2 initiate regular insulin bolus dose of 0.1 U/kg then a rate of 0.1 U/kg/hr OR 0.14 U/kg/hr without bolus. Repeat [K+] STAT in 2 hours
If initial [K+] is >3.3 <5.2 and urine output, add 20-30 meq of K+ to each L of fluid and insulin drip as above
If initial [K+] is <3.3 hold insulin drip and give K+ @20-30 meq/hr until [K+] is >3.3 then initiate insulin drip as above
Initial lytes: check osmolarity, AG, glucose, corrected [Na+], K+
Initial [K+] determines further therapy
Adequate urine output is essential before initiating K+ therapy
1 hrs
Repeat glucose, electrolytes, anion gap If anion gap >25 or glucose >800 (44 mmol/L) or significant comorbidity, consider ICU disposition
After NS bolus: Generally for eunatremia or hypernatremia give 0.45 NS @250-500 ml/hr with K+ supplement as above. For hyponatremia continue NS at 250-500 ml/hr
If pH <6.9 may give 100 mmol NaHCO3 in 400 ml of water with 20 eq KCL at 200 ml/hr. Repeat every 2 hours until pH >7.0. Check [K+] q 2 hrs.
If anion gap <25 and glucose <800 (44 mmol/L) and no significant comorbidity, consider floor or diabetic unit disposition
Rate of hydration dependent on hemodynamics, hydration status, urine output
2 hrs
Patients with pH >6.9 do not require NaHCO3

**Active Goals:**
-Adequate fluid infusion
-Insulin infusing
-Maintain [$K^+$] 3.3-5.2
-Lower glucose by 75 milligram/dl/hr
-Maintain adequate electrolytes (Ca, Mg, Phos)

When glucose approaches 200 (11 mmol/L), change IV to D51/2NS with 20-40 meq KCL/L. Decrease insulin rate to 0.02-0.05 U/kg/hr

Re-check glucose, lytes, AG, VBG, mental status, I/O's, check results of initial phosphate, magnesium, calcium. **Check lytes every 2 hrs initially in ED. Check glucose hourly**

If glucose does not decrease by 10% after one hour of insulin therapy, give 0.14 U/kg bolus then resume previous rate

3-12 hrs

If glucose decreasing faster than 50-75 milligrams/dl/hr, (2.8-4.2 mmol/L) decrease insulin drip in half. Check glucose hourly

Correct estimated fluid deficits in the first 24-36 hours

In young and new onset diabetics avoid excess free water, monitor carefully for development of cerebral edema, and have mannitol at the bedside

Maintain serum glucose 180-200 (10-11mmol/L) and continue insulin drip for at least 12 h or until DKA resolves: glucose <200 (11 mmol/L) and Anion Gap normal, pH >7.3 and $HCO_3$>15

Re-check lytes, glucose, AG: repeat in 4 hr
If taking PO, consider oral K, Phos, Mg replacement as needed

Feed patient. Start SC insulin regimen (0.5-0.8 U/kg in insulin naïve patients). Continue IV insulin for 1-2 hrs **AFTER** SC insulin started

12-48 hrs

**Late complications:**
Refractory acidosis (sepsis)
Cerebral edema
Vascular thrombosis (rare)
ARDS

- Marked dehydration in the absence of clinical shock or heart failure : 1 L of fluid may be administered in the first hour .

- In general, 2 L of fluid resuscitation during the first 1 to 3 hours is followed by a slower infusion of a hypotonic solution , such as 0.45% normal saline solution

- Patients without extreme volume depletion may be successfully treated with a lower volume of IV fluid replacement

- Fluid rate should be adjusted according to age, cardiac status, and degree of dehydration to achieve a urine output of 1 to 2 mL/kg/h .

- Acidosis decreases after fluid infusion

- Increased renal perfusion promotes renal hydrogen ion loss, and the improved action of insulin in the better-hydrated patient inhibits ketogenesis

- Although fluid administration decreases serum glucose concentration and improves acidosis, underlying deficiency in DKA requires administration of insulin for correction of ketoacidosis

# POTASSIUM REPLACEMENT

- Patients usually present with profound total-body potassium deficits in the range of 3 to 5 mEq/kg .
- Initial serum concentration is usually normal or high .
- Initial hypokalemia indicates severe total-body potassium deficits .
- For each 0.1 decrease in pH, serum potassium concentration rises approximately 0.5 mEq/L .

- Rapid development of severe hypokalemia is potentially the most life-threatening electrolyte derangement during the treatment of DKA.

- As a general guideline : An initial serum potassium level >3.3 mEq/L but <5.2 mEq/L calls for 20 to 30 mEq/L for at least 4 hours to keep potassium between 4 and 5 mEq/L .

- Measure plasma potassium level initially every 2 hours .

- Initial hypokalemia (<3.3 mEq/L) necessitates a more aggressive replacement before insulin therapy .
- Give potassium IV at 20 to 30 mEq/h and hold insulin until K is ≥3.5 mEq/L

- Oral potassium replacement is safe and effective and is the preferred route of replacement as soon as the patient can tolerate oral fluids .

- General approach is a rate no faster than 10 mEq/h via peripheral IV or 20 mEq/h via central line access

- Continuous cardiac monitoring is generally recommended while replacing potassium in the severely hypokalemic patient

# Insulin

- DKA cannot be reversed without insulin
- Insulin therapy should be initiated as soon as the potassium level is determined to be adequate or potassium has been repleted .
- IV bolus before the infusion is no longer recommended
- Current initial therapy of choice , is regular insulin infused at 0.1 units/kg/h up to 5 to 10 units/h, mixed with IV fluids

# Magnesium

- Magnesium deficiency is a common problem in these patients
- Both initial pathophysiologic process and therapy for DKA induce profound magnesium diuresis
- Magnesium deficiency may exacerbate vomiting and mental changes , promote recalcitrant hypokalemia and hypocalcemia , or induce fatal cardiac dysrhythmia
- If there is a concern for hypomagnesemia , we recommend adding magnesium to the IV fluids, with the typical adult patient requiring 1 to 3 g for repletion

# Sodium Bicarbonate

- Acidotic patients routinely recover from DKA without alkali therapy .
- Severe metabolic acidosis is associated with numerous cardiovascular and neurologic complications .
- Decision to use bicarbonate should be based on clinical condition and pH of the patient
- Adults with a pH < 6.9 can be given 100 mEq of sodium bicarbonate in 400 mL of water with 20 mEq KCl at 200 mL/h for 2 hours until the venous pH > 7.0

# Complications

- Precipitating causes of DKA may have associated morbidity and mortality rates equal to or worse than those of DKA itself .
- Mortality in treated DKA is approximately 5% to 7%
- Infection and MI are the main contributors to mortality .
- Morbidity in DKA is largely iatrogenic : Hypokalemia , Hypoglycemia , Alkalosis , Pulmonary edema

# Potential Pitfalls During Treatment of DKA

**TABLE 225-4** Potential Pitfalls During Treatment of DKA

| Pitfall | Guideline (See Text for Details) |
|---|---|
| Delay in diagnosis | Blood glucose may be 250–300 milligrams/dL (13.9–16.6 mmol/L); urine ketones may initially be negative |
| Unrecognized precipitating illness | Check ECG for infarction; examine patient for site of infection |
| Inadequate fluids | Majority of adult patients tolerate 15–20 mL/kg/h normal saline for first hour (1–2 L normal saline), additional fluids by clinical condition/serum $Na^+$ |
| Unrecognized low $K^+$ | Check $K^+$ prior to insulin; $K^+$ supplement before insulin for $[K^+] < 3.3$ |
| Overemphasis on insulin | Follow insulin guidelines |
| Hypoglycemia | Goal for glucose decrease 50–75 milligrams/dL/h (2.8–4.2 mmol/L); add dextrose when glucose <250 milligrams/dL (<13.9 mmol/L) |
| Unrecognized electrolyte derangements | During first 6 h of treatment, check glucose hourly and electrolytes every 2 h; check $QT_c$ intervals |
| Overzealous use of bicarbonate and phosphate | $NaHCO_3$ not indicated for pH >6.9; no routine indication for phosphate supplementation |
| Recurrent DKA | Avoid stopping insulin drip before anion gap resolves. Give SC insulin, feed patient, then stop insulin drip 1–2 h later |
| Cerebral edema **NOT** recognized early | See **TABLE 225-5**. Very young and new-onset patients at risk; perform frequent neurologic checks for mental status change |


pix2pix.org