Diabetic Ketoacidosis

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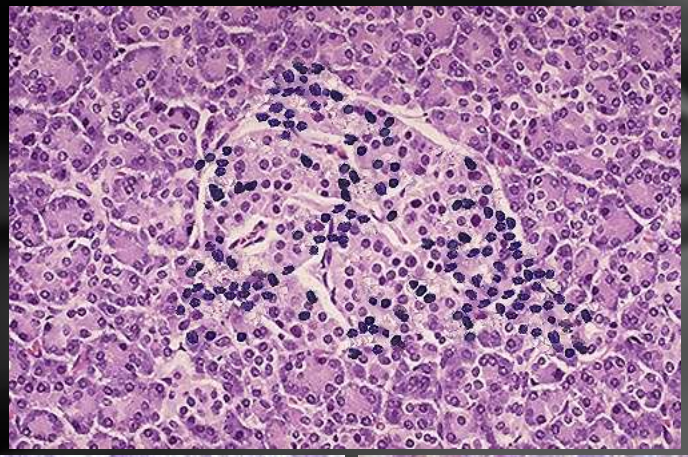
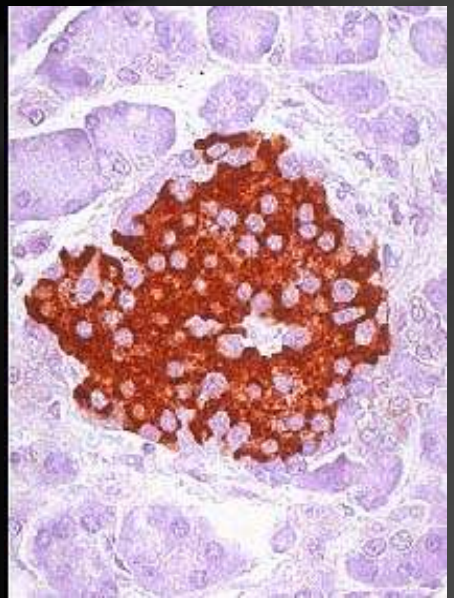
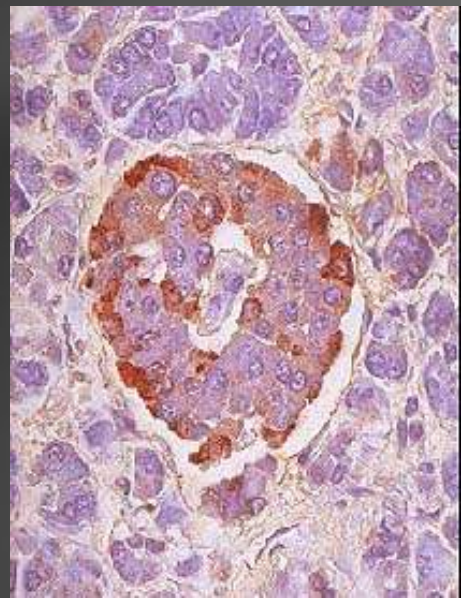
Type 1 DM

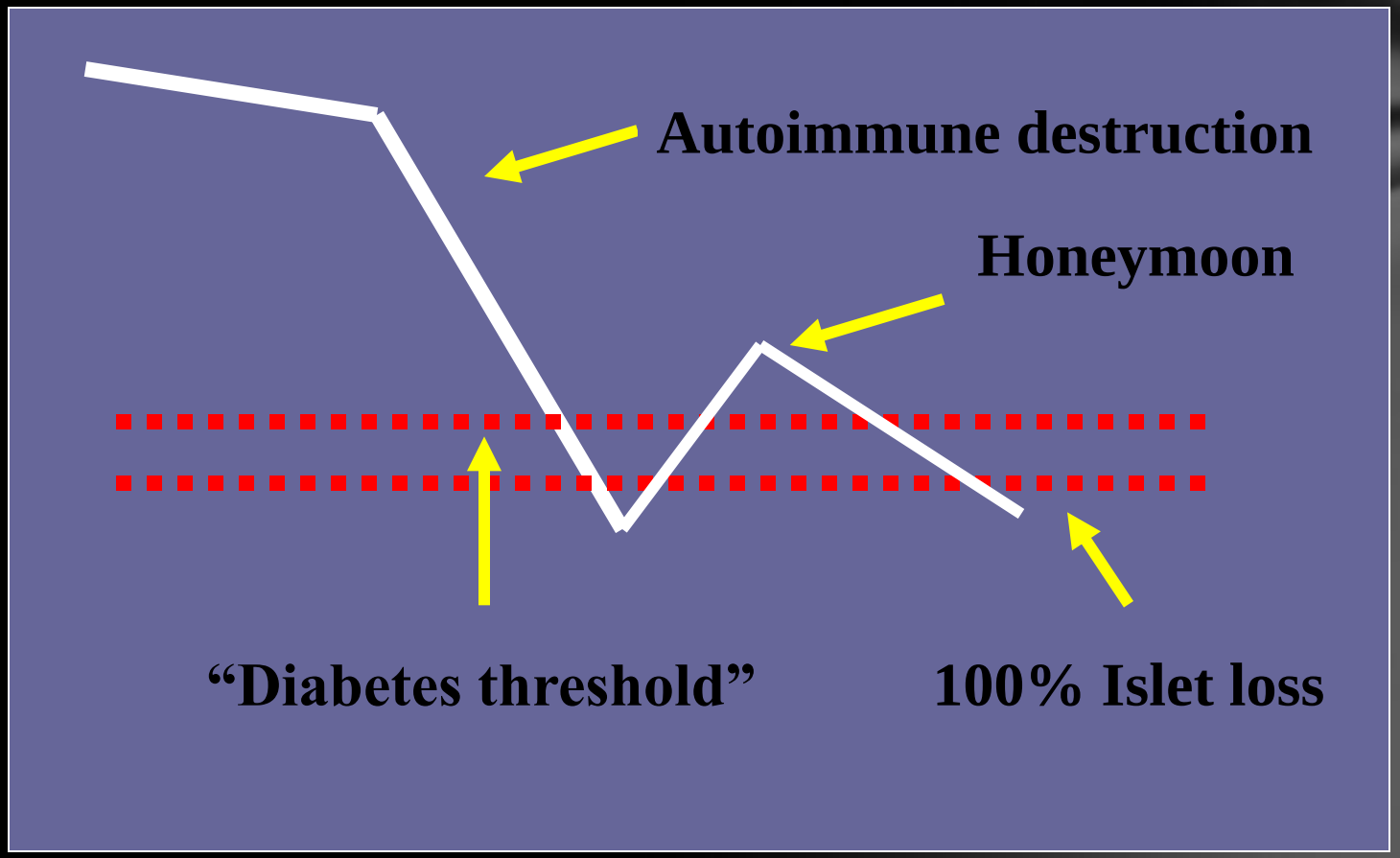
- Autoimmune destruction of the pancreatic islet cell
- Hallmark = lymphocytic infiltration of islets
- Progresses over years
- Leads to insulin deficiency
- Later may be associated with glucagon deficiency as well







Progression to Type 1 DM



Hyperglycemic States

Metabolic decompensation in Diabetes is classified into two main syndromes:

1. **DKA** – generally seen in type 1 diabetics, but increasingly preseinting in obese type 2 patients

2. **Hyperosmolar Hyperglycemic States (HHS)** – generally seen in type 2 diabetics

Definition of DKA

- It is a life threatening but reversible complication of type 1 diabetes due to absolute insulin deficiency.
- **DKA** is defined as hyperglycemia with metabolic acidosis resulting from generation of ketones in response to insulin deficiency and elevated counter-regulatory hormones such as glucagon

Definition of Ketoacidosis

- **Ketoacidosis**: High anion gap metabolic acidosis due to excessive blood concentration of ketone bodies (Ketoanion).

Diagnostic Criteria

- Blood glucose > 250 mg/dl
- pH < 7.35
- HCO_3 < 20 mEq/L
- Anion Gap > 12
- ketonemia

Epidemiology

- Annual incidence in U.S.
  - 5-8 per 1000 diabetic subjects
- 2.8% of all diabetic admissions are due to DKA
- Overall mortality rate ranges from 2-10%
  - Higher is older patients

Epidemiology

- 15-30% of new diabetics present in DKA
  - < 4 yrs of age = 40% with DKA @ diagnosis
- Most common cause of death in diabetics less than 20 years of age
  - 70% of related deaths in diabetics less than 10 yrs of age
- Mortality: 5-15% (1-2% at MEDCEN)
- Preventable

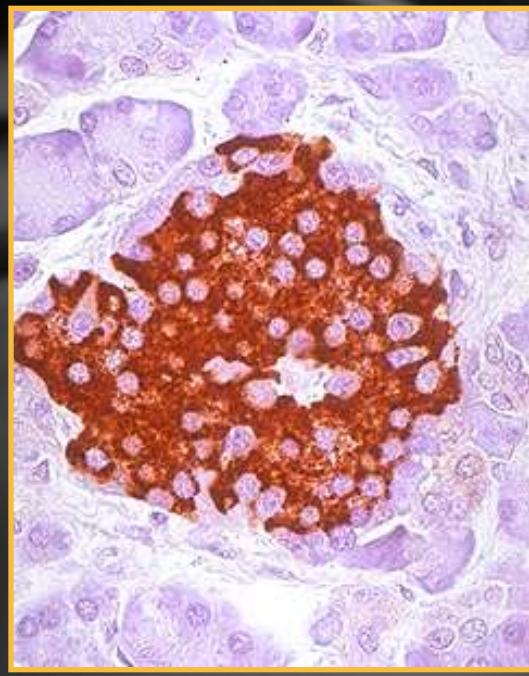
Diabetic Ketoacidosis

- One of the most serious acute metabolic complications of diabetes
  - Occurs more commonly in patients with insulin-dependent diabetes mellitus (IDDM)
  - Mortality rate was 100% in 1922 but has since come down to 5% with improvements in health care

Kitabchi, A. E., Wall, B. M., ***Diabetic Ketoacidosis****, 1995, Medical Clinics of North America, Vol. 79, 1, pg 9*

Role of Insulin

- Required for transport of glucose into
  - Muscle
  - Adipose
  - Liver
- Inhibits lipolysis
- Absence of insulin
  - Glucose accumulates in the blood
  - Liver
- Uses amino acids for gluconeogenesis
- Converts fatty acids into ketone bodies
  - Acetone, Acetoacetate, β-hydroxybutyrate
- Increased counterregulatory hormones



Etiology

- DKA violates rules of common sense
  - Increased insulin requirement despite decreased food intake
  - Marked urine output in setting of dehydration
  - Catabolic state in setting of hyperglycemia and hyperlipidemia

Pathophysiology

- Lack of insulin → increased lypolysis → oxidation of fatty acids → production of ketone bodies → high anion gap metabolic acidosis
- Hepatic glucose production and decreased peripheral utilization→ hyperglycemia

Counterregulatory Hormones - DKA

	Increases insulin resistance	Activates glycogenolysis and gluconeogenesis	Activates lipolysis	Inhibits insulin secretion
Epinephrine	X	X	X	X
Glucagon		X		
Cortisol	X	X		
Growth Hormone	X		X	X

Pathogenesis: Alterations in metabolism

Caused by

1. **Ineffectiveness of insulin**
2. **Elevations in glucagon, catecholamines & cortisol**

- Hepatic gluconeogenesis, glycogenolysis, and lipolysis are affected by this hormone imbalance
- Fat, liver and muscle can survive without glucose
- Brain must maintain use of glucose for starvation

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Pathogenesis: Alterations in metabolism

Catecholamines (unopposed)

1. Promote triglyceride breakdown to FFA and glycerol
2. Stimulates gluconeogenesis

Insulin

1. Inhibits gluconeogenesis

Pathogenesis: Alterations in metabolism

Hyperglycemia results from

1. Increased gluconeogenesis
2. Conversion of glycogen to glucose
3. Inadequate use of glucose by peripheral tissues

Ketone bodies result from

1. Beta oxidation of FFA
2. Decreased concentrations of malonyl coA (an inhibitor of ketogenesis)

Pathogenesis: Alterations in metabolism

Hyperglycemia leads to

1. Glycosuria
2. Polyuria (osmotic diuresis)
3. Polydipsia
4. Polyphagia
5. Weight loss
6. Dehyrdation

Ketone bodies lead to

1. Metabolic acidosis

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Pathogenesis: Fluid and Electrolytes

Major cause of electrolyte loss is due to osmotic diuresis

- Brought on by excess excretion of glucose
  - Glucose is restricted to extracellular space pulling water from intracellular space
- NaCl, K are excreted in the urine followed by massive amounts of water

Kitabchi, A. E., Wall, B. M., ***Diabetic Ketoacidosis****, 1995, Medical Clinics of North America, Vol. 79, 1, pg 17*

Pathogenesis: Fluid and Electrolytes

Initially plasma sodium concentrations are low or normal despite water losses due to osmotic shift of water

- **Correction of sodium**
  - Add 1.6 mEq to plasma sodium for every 100 mg of glucose over 100 mg/dl
  - (i.e. Corrected Na+ = (Plasma glucose-100) / 100 * 1.6)

Pathogenesis: Fluid and Electrolytes

Total body potassium depletion

Loss equals 5-10 mEq / kg body weight

- Plasma concentrations may be normal or elevated at time of presentation of DKA
  - Water and K are shifted from intracellular to extracellular space
  - Acidosis also causes potassium shift
  - Lack of insulin (a promoter of K uptake)
- Secondary hyperaldosteronism can increase potassium loss

Serum K during DKA:

Usually high (hyperkalemia) secondary to:

1-Shift of **K** from intracellular to extracellular compartment due to:

-Insulin deficiency and hyperglycemia.

-Extracellular hyperosmolarity.

-Acidosis.

-↑ Catabolism and breakdown of cellular protein.

2-Impaired cellular uptake of K.

Pathogenesis: Fluid and Electrolytes

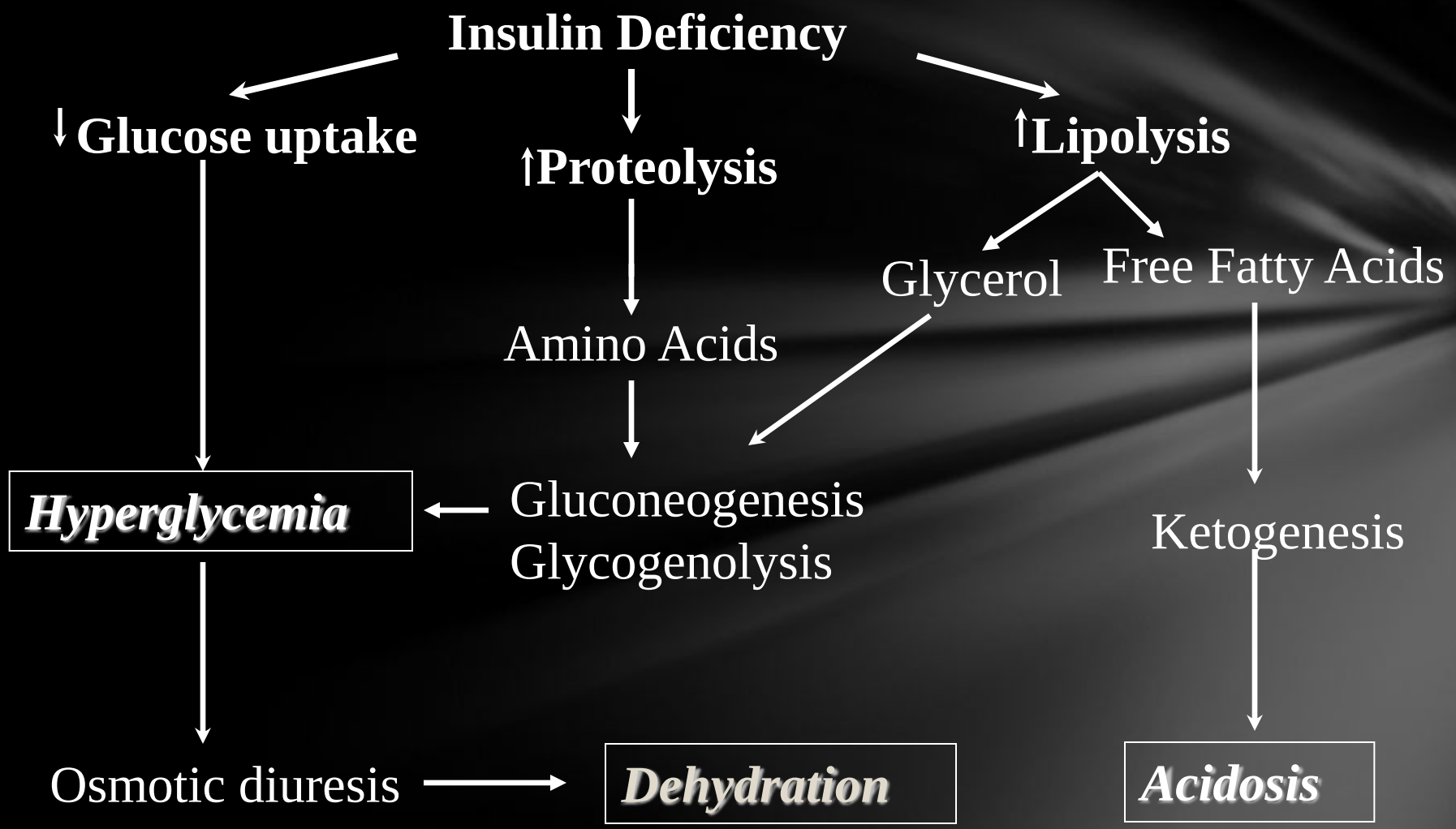
Metabolic acidosis

Caused by buffer deficit

- Induced by ketoacid dissociation at physiologic pH
  - H+ ions are buffered by HCO3
    - Bicarbonate concentration decreases

75% - 85% of ketoanions are reabsorbed

- Ketouria
- Reabsorbtion is directly related to GFR
  - Patients who take in fluids and NaCl at onset of DKA will have better renal function and more ketoanion excretion
- Metabolism of ketoacids produces HCO3
  - Therefore, excretion of ketoacids results in loss of potential HCO3


Insulin Deficiency
↓Glucose uptake
↑Proteolysis
↑Lipolysis
Glycerol
Free Fatty Acids
Amino Acids
Hyperglycemia
Gluconeogenesis
Glycogenolysis
Ketogenesis
Osmotic diuresis
Dehydration
Acidosis

DKA Precipitating Factors

Failure to take insulin

Failure to increase insulin

- Illness/Infection
  - Pneumonia
  - MI
  - Stroke
- Acute stress
  - Trauma
  - Emotional

Medical Stress

- Counterregulatory hormones
  - Oppose insulin
  - Stimulate glucagon release

Hypovolmemia

- Increases glucagon and catecholamines
  - Decreased renal blood flow
  - Decreases glucagon degradation by the kidney

What does DKA mean?

- **D**iabetic – hyperglycemic state with glucose >250 mg/dL
- **K**etosis – production of ketone bodies (betahydroxybutyrate, acetoacetate, acetone)
- **A**cidosis – pH < 7.3, anion gap metabolic acidosis

…And don't forget to ask WHY?

- **Infection, Infection, Infection (30-50%) –** think UTI, PNA, intrabdominal process
- **Inadequate insulin treatment (20-40%) –**
- non-compliance, insulin pump failure, undertreatment
- **Myocardial ischaemia/Infarction (3-6%)**
- **Other things …**
- Alcohol, CVA, renal failure, severe burns, PE, pancreatitis

When do I think about DKA?

- Weakness/lethargy
- Nausea/vomiting
- Polyuria/polydipsia
- Abdominal pain, classically periumbilical
- History of deterioration over a few days, sx related to a precipitating event (chest pain, dysuria, fever, cough…)

Signs and Symptoms of DKA

Polyuria, polydipsia

- Enuresis

Dehydration

- Tachycardia
- Orthostasis

Abdominal pain

- Nausea
- Vomiting

Fruity breath

- Acetone

Kussmaul breathing

Mental status changes

- Combative
- Drunk
- Coma

Diagnosis of DKA – History and physical

Clinical presentation

- Polyuria, polydipsia, weight loss
- Nausea, vomiting, abdominal pain

Physical examination

- Signs of volume depletion

Physical signs of DKA:

a-General signs: Ill appearance and disturbed consciousness.

b-Signs of dehydration:

- -Skin: Dry, hot, flushed, and loss of skin turgor.
- -Tongue: Dry (sometimes woody tongue).
- -Eyes: Sunken eyes and dark circles under the eyes.

c-Vital signs:

- -Tachycardia, hypotension and tachypnea.

d-Specific signs:

- **-Ketotic breath:** A strong, fruity breath odour (similar to nail polish remover or acetone).
- **-Acidotic breath** (Kussmaul's respiration): deep and rapid.
- -Abdominal tenderness.

Definitive diagnosis - initial workup

- Blood chemistry
- Glucose by finger stick
- Blood and urine ketones (nitroprusside)
- CBC w/ differential
- Arterial blood gas
- UA
- Infusion of 1 L of 0.9% NaCl

Kitabchi, A. E., Wall, B. M., ***Diabetic Ketoacidosis****, 1995, Medical Clinics of North America, Vol. 79, 1, pg 17*

Lab Findings

- Hyperglycemia
- Anion gap acidosis
  - **(Na + K) – (Cl + Bicarb) >12**
  - **Bicarbonate <15 mEq/L**
  - **pH <7.3**
- Positive urine and serum ketones
- Hyperosmolarity

Diagnostic Criteria for DKA and HHS

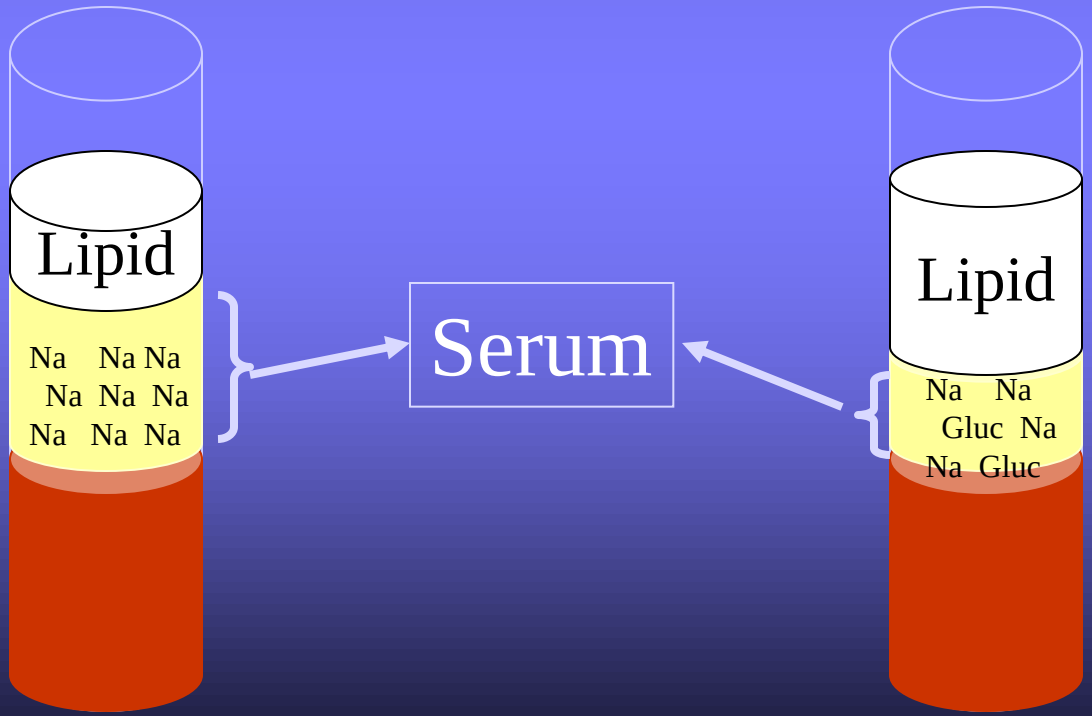
	Mild DKA	Moderate DKA	Severe DKA	HHS
Plasma glucose (mg/dL)	> 250	> 250	> 250	> 600
Arterial pH	7.25-7.30	7.00-7.24	< 7.00	> 7.30
Sodium Bicarbonate (mEq/L)	15 – 18	10 - <15	< 10	> 15
Urine Ketones	Positive	Positive	Positive	Small
Serum Ketones	Positive	Positive	Positive	Small
Serum Osmolality (mOsm/kg)	Variable	Variable	Variable	> 320
Anion Gap	> 10	> 12	> 12	variable
Mental Status	Alert	Alert/Drowsy	Stupor/Coma	Stupor/Coma

Misleading Labs
Sodium

- Na^+ depressed 1.6 mEq/L per 100 mg% glucose
- Corrected Na^+ = measured Na +
  1.6 meq/L x (glucose-100)/100))
- Example:
  - Na^+ = 123 meq/L and Glucose = 1,250 mg/dl
  - 1,250 – 100 = 1,150 / 100 = 11.5 x 1.6 = 18 meq/L
  - Corrected Na^+ = 123 + 18 = 141 meq/L

Misleading Labs
Sodium

- Triglycerides also artificially lower Na



Misleading Labs
Potassium

- Acidosis leads to flux of K^+ out of cells as H^+ enters cells to buffer
- Dehydration and volume depletion
  - ↑ Aldosterone → ↑ Na reabsorption and K^+ wasting
- Serum K^+ usually normal or high, but total body K^+ is low

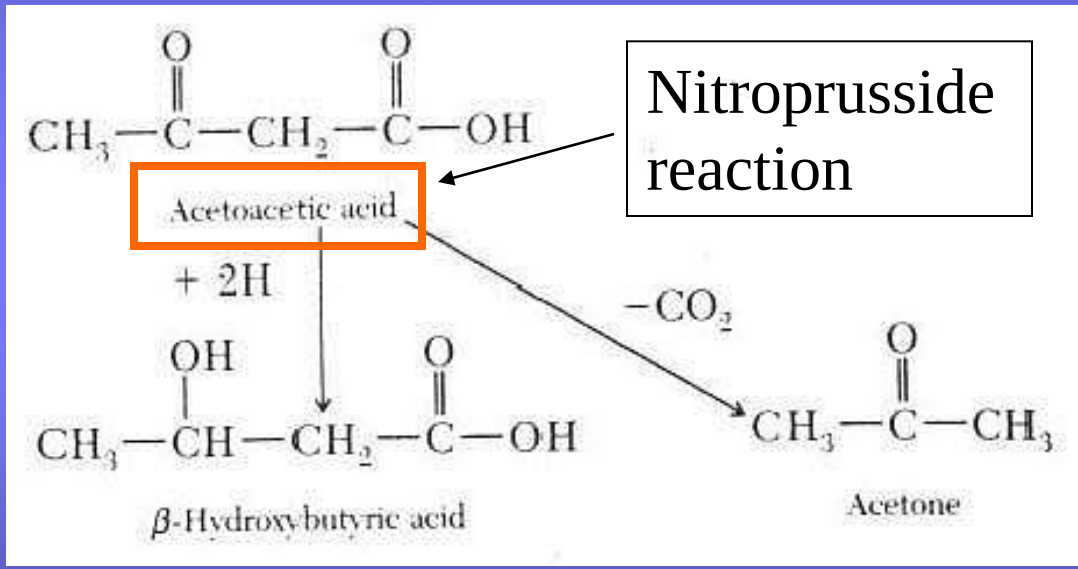
DKA- Risks of Therapy

Hypokalemia/Hyperkalemia

- With insulin therapy
  - K^+ moves into cells (1 meq/L ↓ / 0.1 unit pH ↑)
- Even with ↑ K^+ you must
  - Give large doses (40 meq/L) K^+
  - Monitor K^+ levels and EKG
    - High K - tall peaked T, long PR, wide QRS
    - Low K - depressed ST, diphasic T, Prom U-wave
  - Cardiac dysrythmia

Misleading Labs
Ketones

- In the absence of insulin, FFA go to the liver, and into mitochondria via carnitine
- ß-oxidation → excess acetylCoA



- Acetyl-CoA condenses to acetoacetate
- ↓ Insulin prevents utilization of acetoacetate
- so levels ↑ and shunt to ß-hydroxybutyrate and acetone

Misleading Labs

Screening for Ketonemia

- Urine Dip stick vs. anion gap/serum bicarb

	Sensitivity	Specificity
DKA	99 %	69 %

- Diabetic with minor signs and symptoms and negative urine ketone dip stick is unlikely to have acidosis

  = high negative predictive value for excluding DKA

Am J Emer Med 34: 1999

Misleading Labs
WBC count

- N = 247 DKA admissions over 6 years
  - Mean WBC = 17,519/mm3 (+/- 9,582)
  - 69% without infection
  - 17.8% presumed viral infection
  - 12.9% bacterial infection - more common in children < 3 years of age

 All need to be evaluated and re-evaluated if persistent acidosis

Am J Emer Med 19: 270-3, 2001

Urine testing during DKA

1- Urine glucose conc. Is poorly correlated with BG levels.

2- Renal threshold for glucose and ketones are increased in DKA & HHS.

3- Most of the available laboratory urine tests (nitroprusside test) detect only acetoacetate & acetone but not beta–HB.

4- Beta-HB is the predominant ketones in severe untreated DKA cannot be measured or recognized by the standard nitroprussid test .

Urine testing during DKA

5- When the clinical condition improves with treatment , the urine test results become positive due to the returning predominance of acetoacetate .

6- So, during follow up of patients with DKA urine test for ketones is better avoided.

7- Now blood ketone measurements are available and detect beta-HB.

Differential Diagnosis of Anion Gap Acidosis

- Alcoholic ketoacidosis
- Lactic acidosis
- Renal failure
- Ethylene glycol or methyl alcohol poisoning
- Starvation in late pregnancy or lactation (rare)

Atypical Presentations

DKA can be present with BS <300

- Impaired gluconeogenesis
  - Liver disease
  - Acute alcohol ingestion
  - Prolonged fasting
  - Insulin-independent glucose is high (pregnancy)
- Chronic poor control but taking insulin

Bedside urine ketones false negatives

- Measure acetoacetate not β-hydroxybutyrate
- Send blood to lab

…and what does it look like?

- Signs of volume depletion, you know these
- dry mocusa, skin tenting, flat neck veins, orthostasis, and decreased axillary sweat
- Sweet smell on patient's breath (ketones)
- Tachycardia
- Kussmaul respirations (deep, rapid)

Diagnosis is the easy part..

- Finger stick → BG >250
- ABG → pH <7.3 (don't fall victim to a concomitant acid-base disorder, usually metabolic alkalosis due to vomiting, will alter the pH)
- Renal Function Panel (includes phos and albumin) → high anion gap, low bicarb
- CBC with diff
- Serum ketones (betahydroxybutyrate)

Again, don't forget ask why

- UA, urine cx, blood cx
- AMI panel and ECG
- Chest xray
- LFT's, lipase
- Other imaging if indicated (CT chest for PE, CT abd, RUQ u/s etc..)

Treatment

IMET 2000 Pal
International Medical Education Trust 2000 - Palestine

Treatment - goals

1. Improve circulatory volume and perfusion
2. Decrease serum glucose
3. Clear serum of ketoacids at steady rate
4. Correct electrolyte imbalances

Kitabchi, A. E., Wall, B. M., ***Diabetic Ketoacidosis****, 1995, Medical Clinics of North America, Vol. 79, 1, pg 17*

Initiation of treatment:

1-General measures:

-Airway and O2 inhalation if needed.

-IV line.

-Urinary Foley's catheter (if in shock).

-NGT (Nasogastric Tube): to avoid gastric dilatation and protection from aspiration .

-Thrombosis prophylaxis: 5000 units of heparin SC/12 hours.

-Empiric use of 3rd generation cephalosporin antibiotics.

Initiation of treatment:

2-Specific measures:

Successful therapy of hyperglycemic crises requires the administration of:

a-Fluids:

1- Correct volume deficit and hypotension.

2- Improve tissue perfusion.

3-Improve insulin sensitivity (↓insulin counterregulatory hormones).

4-Improve glomerular filtration rate:

i-↑ excretion of large amount of glucose in urine.

ii-Clears hyperketonemia.

5- Correct metabolic acidosis.

Initiation of treatment:

b-Insulin:

Reversal of metabolic abnormalities :

i-Corrects hyperglycemia.

ii-Inhibits ketogenesis.

c-Potassium:

Prevents complications associated with hypokalemia.

Treatment - goals

Fluid and electrolytes

- Initial fluid
  - Isotonic saline (restricted to extracellular space)
    - 1 L 0.9% saline in first hour
  - Plasma osmolality can be used to estimate severity of dehydration
    - 2 (Na+) (mEq/L) + glucose (mg/dL) / 18 + BUN (mg/dL) / 2.8
    - Stupor and coma can occur w/ osmolality > 340 mOsm/kg H20

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Treatment - goals

Fluid and electrolytes

- Subsequent fluid replacement
  - Hypotonic saline (0.45% NaCl) at 200 to 1000mL/h
    - In DKA, H20 loss exceeds NaCl loss
    - Hypotonic saline is similar to fluids lost in DKA
    - Both compartments will gradually be replaced
  - Dextrose should be added to fluids if glucose < 200 mg/ dL
    - Allow for continued insulin administration until ketonemia is controlled
  - Some studies show that fluid replacement before insulin does not effect the severity of DKA
    - Allows for reductions in blood glucose and potassium concentrations before insulin therapy

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Treatment – Fluids and electrolytes

Fluid and electrolytes

Advantages of early rehydration

1. Restores circulatory volume
2. Diminish concentration of catecholamines, glucagon

Complications of fluid therapy

1. Excessive therapy may result in ARDS
2. Cerebral edema
3. Hyperchloremic acidosis

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Normal saline (0.9% sodium chloride)

- ***Advantages:***

  -Available all the time.

  -Rapid expansion of extracellular compartment.

  -Slow decline of extracellular osmolarity.

  -Slow rate of cerebral edema evolution.

- ***Disadvantages:***

  - May accentuate hypernatrimia if present.

- ***Indications:***

  -All cases of DKA.

  -Initial (1st 2 liters) in NKHH state.

Half strength saline (0.45% sodium chloride)

Used only if serum corrected sodium is high >145 mEq/L.

- ***Corrected sodium level*** = measured sodium + corrected value.
- ***Corrected value*****:** For every 100 mg/dl BG above the normal baseline of BG 100 mg/dl, Add 1.6 mEq/l Na to the measured serum sodium.
- ***Example*****:** Measured Na = 134 mEq/L, BG= 400mg/dl.

Corrected Na value: 3 x 1.6 mEq/L=4.8 mEq/L.

The serum corrected Na is: 134+4.8 = 138.8 mEq/L.

Typical Fluids Therapy

- 10% dehydration is standard estimate (use weight if known)
- Bolus: treat shock, usual 20-30cc/kg given 10cc/kg at a time
- Replace deficit over 48-72 hours

  = maintenance + 42cc/hr x 48 hours

Treatment – Insulin therapy

- Conscious, non-obtunded patient
  - Initial priming dose
    - 0.3 to 0.4 U / kg
      - ½ given IV
      - ½ given SC
  - Subsequent insulin
    - ER
      - 7 units / hour IV
    - General floor
      - Hourly injections of insulin SC
      - Ensures that nurse sees patient on hourly basis
    - ICU
      - 7 units/ hour IV per hour

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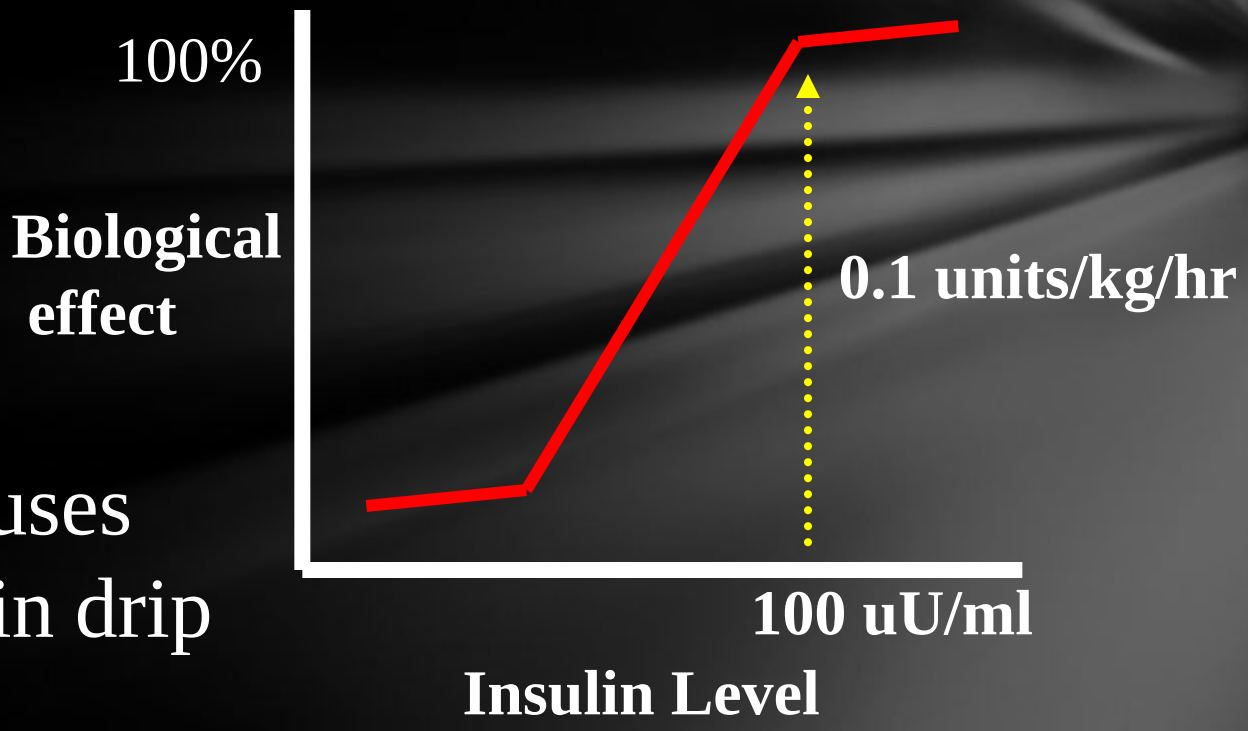
DKA – Risks of Therapy

Insulin



Current therapy uses continuous insulin drip

 Drop glucose 50-100 mg/dl/hr

Typical Insulin Therapy

- 0.1 unit/kg/hr continuous drip (regular)
- Flush tubing with 50 ml
- 250 units regular in 250 cc NS (1.0 units/ml)

= 0.1 u/kg/hr = 0.1 ml/kg/hr

Treatment – Potassium therapy

- Potassium decreases after insulin therapy

1. Insulin causes potassium to enter cells
2. Extracellular fluid volume expansion
3. Resolution of acidemia
4. Negative potassium balance from DKA

Hypokalemia is life threatening

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Treatment – Potassium therapy

- Potassium should not be added to initial first liter of saline (0.9%)
  - Patients are initially hyperkalemic
  - Addition of K+ without insulin can cause a dangerous increase in extracellular potassium
    - Cardiac arrythmias

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Treatment – Potassium therapy

- Requirements for potassium therapy
  - Patient is making urine
  - Serum potassium is less than 5.5
- Potassium replacement
  - 20 to 30 mEq per L of IV fluid
  - 2/3 KCL, 1/3 KP04 to replace phosphorus
  - Patients with severe hypokalemia at admission may need more aggressive potassium replacement
    - May need potassium added to first liter of fluid
    - Do not exceed 40 mEq/ hour
  - Check potassium level every 1 to 2 hours initially

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Treatment – Bicarbonate therapy

- Controversial
- Most literature shows no benefit to using bicarbonate with patients who have DKA
  - No differences in reduction of glucose or ketoanion
  - May increase hypokalemia
- For patients with pH < 7.0, they may benefit from bicarbonate therapy
  - pH 6.9-7.0 may give 44 mEq of bicarb
  - pH <6.9, may give 88 mEq of bicarb

DKA – Risks of Therapy

Bicarbonate Administration

- Administration to acidotic patient generates rapid rise in CO_2
- CO_2 enters CNS rapidly
- HCO_3^- is delayed by blood-brain barrier
- Increased CNS CO_2 exacerbates cerebral acidosis

$$CO_2 + H_2O \rightarrow H_2CO_3 \rightarrow H^+ + HCO_3^-$$

- May also reduce partial pressure of O_2 in CSF vasoconstriction brain hypoxia/ischemia

DKA – Risks of Therapy

Bicarbonate Administration

- Multi-center study from 10 pediatric centers, USA and Melbourne, Australia over 15 yr period
  - 6977 DKA hospitalizations: 61 cases cerebral edema (0.9%)
- Presentation:

	$PaCO_2$	BUN	Glucose	Bicarb
Cerebral Edema	11.3	27	758	23/61 (32%)
Controls	15.1	21	700	43/174 (23%)

- ≠ fluid, insulin, or sodium administration, nor rate of fall in glucose was associated

NEJM 344:264-269, 2001

DKA – Risks of Therapy

Bicarbonate Administration

- Variations in treatment exacerbate an on-going pathologic process
- Brain ischemia is major underline etiology
  - Hyperglycemia increases extent of neurologic damage
  - Extreme dehydration, hypocapnia
  - Concept of idiogenic osmotically active substances not supported (no relationship to change in glucose, rate of fluid or Na administration)

 Risk related to duration and severity of DKA

NEJM 344:264-269, 2001

Treatment – Phosphate therapy

- At presentation serum phosphate may be normal or increased
- Total body phosphate is decreased by approximately 1 mmol / kg in DKA
- Phosphate reenters the intracellular space with introduction of insulin
- Complications of hypophosphatemia
  - Respiratory depression
  - Skeletal muscle weakness
  - Hemolytic anema
  - Cardiac dysfunction

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Treatment – Phosphate therapy

- Studies have been unable to prove that replacement of phosphate is beneficial to patients with DKA
- Certain patients may benefit from phosphate therapy
  - Patients with anemia
  - Congestive heart failure
  - Pneumonia
  - Hypoxia
- Any patient with phosphate concentrations less than 1.0 mg / dL should receive phosphate therapy

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Treatment – Consideration in management

- Check blood glucose every hour for first few hours
  - Helps identify insulin resistant individuals
- Fingerstick every 4 hours as long as patient with DKA is receiving IV fluids
- Avoid overhydration
- Note: Nitroprusside can be used to detect ketones but is not accurate
  - Does not measure b-hydroxybutyrate which is the most concentrated ketone
  - As therapy continues acetoacetate (AA) is converted to b-OHB which paints a picture of worsening ketonemia
  - A few drops of hydrogen peroxide will convert b-OHB to AA (uptodate online)

Kitabchi, A. E., Wall, B. M., ***Diabetic Ketoacidosis****, 1995, Medical Clinics of North America, Vol. 79, 1, pg 17*

Initial evaluation (perform immediately):

- History and physical examination
- Laboratory tests: arterial blood gases, complete blood count with differential, urinalysis, blood glucose, blood urea nitrogen, creatinine, electrolytes (chem 7)
- Electrocardiogram
- Chest radiograph and cultures as needed
- Start IV fluid: 1 L of 0.9% sodium chloride per hour initially (15 to 20 mL/kg/hour).

Diagnostic criteria for diabetic ketoacidosis:

- Blood glucose level >250 mg/dL (13.9 mmol/L)
- Arterial pH <7.3
- Serum bicarbonate level <15 mEq/L
- Moderate ketonuria and ketonemia

IV fluids

Determine hydration status

- Hypovolemic shock → Administer 0.9% sodium chloride (1 L/hour) and/or plasma expander
- Mild hypotension
- Cardiogenic shock → Hemodynamic monitoring

Evaluate corrected serum sodium level

- Serum sodium level high
- Serum sodium level normal → Administer 0.45% sodium chloride (7 to 14 mL/kg/hour), depending on hydration status
- Serum sodium level low → Administer 0.9% sodium chloride (7 to 14 mL/kg/hour), depending on hydration status

Insulin

- IV route → Administer regular insulin, 0.15 U/kg as IV bolus → Administer regular insulin, 0.1 U/kg/hour as IV infusion
- SC/IM route → Administer regular insulin, 0.3 U/kg, with one half given as IV bolus and one half given SC or IM → Administer regular insulin, 0.1 U/kg/hour SC or IM

If blood glucose level does not fall by 50 to 70 mg/dL (2.8 to 3.9 mmol/L) in the first hour:

- Double insulin infusion hourly until blood glucose level falls by 50 to 70 mg/dL
- Give hourly IV 10-U insulin bolus until blood glucose level falls by 50 to 70 mg/dL

Potassium

If serum potassium level is <3.3 mEq/L, hold insulin and give 40 mEq of potassium per hour (two thirds as potassium chloride and one third as potassium phosphate) until potassium level is ≥3.3 mEq/L

If serum potassium level is ≥5.5 mEq/L, do not give potassium but check level every 2 hours

If serum potassium level is ≥3.3 mEq/L but <5.5 mEq/L, give 20 to 30 mEq of potassium in each liter of IV fluid (two thirds as potassium chloride and one third as potassium phosphate) to keep serum potassium level at 4.0 to 5.0 mEq/L

When serum glucose reaches 250 mg/dL (13.9 mmol/L):

Change to 5% dextrose in 0.45% saline administered at 100 to 200 mL/hour, with adequate insulin (0.05 to 0.1 U/kg/hour as IV infusion or 10 U SC every 2 hours) given to keep blood glucose level between 150 and 200 mg/dL (8.3 and 11.1 mmol/L) until metabolic control is achieved

- Check chem 7 every 2 to 4 hours until patient is stable
- Look again for precipitating causes
- After resolution of diabetic ketoacidosis, obtain blood glucose level every 4 hours, and give sliding-scale regular insulin SC in 5-U increments for every 50 mg/dL increase above 150 mg/dL to a maximum of 20 U

When do you stop the drip?

NOT UNTIL THE ANION GAP CLOSES

MAINTANCE INSULIN THERAPY HAS BEEN INITIATED

(Drip should be continued for 1-2 hours after SC insulin has been administered)

Monitor

- ICU - pH < 7.3 and/or HCO_3 < 15
- Available staff
- Strict I/O (NPO)
- Fluid calculations must account for ongoing losses – vomiting, diarrhea, excessive urine
- ? If > 4 L/m^2/day
- CNS activity - headache, change in sensorium

Monitor

- Vitals - sudden drop in HR, tachypnea
- Neurologic checks - q30-60 minutes
- Weight - bid
- Labs
  - dstick q1 hour
  - Urine dip q void - resolution of ketonuria may lag behind clinical improvement

Monitor

- Labs
- Lytes, VBG q 2-4 hours
  - Drop in Na - increase risk of cerebral edema, ? SIADH vs. cerebral salt wasting
  - HCO_3^- / pH in first 2-3 hours may drop further due to re-perfusion of tissue, lactic acidosis

What happens when BG reaches 250-300…

- Decrease the rate of insulin gtt to 0.05-0.1 u/kg/hr (goal is to keep BS in this range until the gap closes)
- Add dextrose to the fluids, rate should be 150-250/hr
- And again, don't stop the drip until

GAP IS CLOSED

- Start maintance sc insulin therapy once gap is closed, can start home dose, if new diabetic calculate daily insulin dose (0.5 – 1 unit/kg/day)

Remember…

Typical DEFECTIS

- Water 5 – 10 L (osmotic diuresis)
- Potassium 3 – 5 MEQ/kg body weight (don't be fooled by hyperkalemia, remember urine electrolyte losses are high and insulin drives K into cells
- Phosphate: routine supplementation in adults has not been shown to affect outcome, replete if < 1

Last piece of the puzzle…ELECTROLYTES

POTASSIUM

If initial K > 5.5 check ECG, treat hyperkalemia if changes present, recheck in 2 hours

If K < 5.5 and adequate urine output add KCL to the fluids –

4.5 – 5.4 add 20 mEq/L

3.5 – 4.4 add 30 mEq/L

<3.5 add 40 mEq/L

BICARB

If pH >7, usually no indication for repletion

Use of bicarb for pH of 6.9 – 7.1 is controversial, can use 1 amp of Sodium Bicarb over 1 hour

If pH < 6.9, 2 amps of Sodium Bicarb over 2 hours

CAUTION

- Enemy is acidosis, not hyperglycemia
- Avoid hypoglycemia
- Cerebral edema (typically seen in children) occurs with overaggressive correction of hypoglycemia or administration of hypotonic solution
- Avoid Hypokalemia
- Pulmonary edema – remember to adjust fluid administration if patient has CHF or ESRD (will not have osmotic diuresis if anuric)

Complications of DKA

1-Complications of associated illnesses e.g. sepsis or MI.

2-Adult respiratory distress syndrome.

3-Thromboembolism (elderly).

4-Complications of treatment:

a-Hypokalemia: Which may lead to:

-Cardiac arrhythmias.

-Cardiac arrest.

-Respiratory muscle weakness.

Complications of DKA

b-Hypoglycemia.

c-Overhydration and acute pulmonary edema:

particularly in:

-Treating children with DKA.

-Adults with compromised renal or cardiac function.

-Elderly with incipient CHF.

Complications of DKA

d-Neurological complications: Cerebral Edema.

-It occurs only in children with DKA.

-Very dangerous and increases mortality.

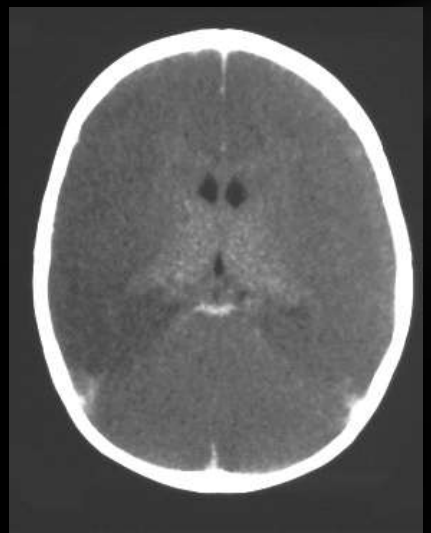
-The risk is related to the severity, duration and rapid correction of DKA.

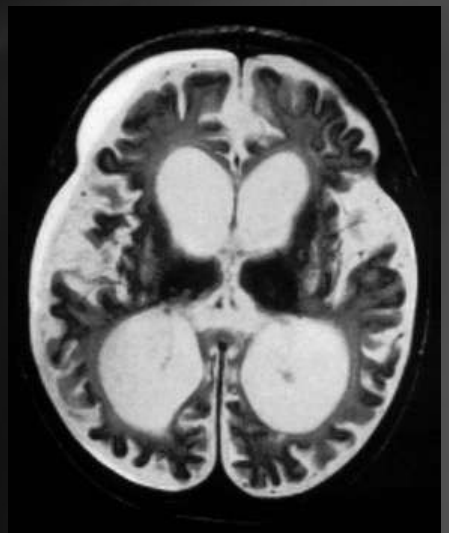
***Mechanism*:** The brain adapts by producing intracellular osmoles (idiogenic osmoles) which stabilize the brain cells from shrinking while the DKA was developing. When the hyperosmolarity is rapidly corrected, the brain becomes hypertonic towards the extracellular fluids → water flows into the cells → cerebral edema

DKA – Controversy

Cerebral Edema - Truths ?

- Idiogenic osmoles in CNS accumulate fluid
- Cerebral edema – present in 100% of patients prior to therapy
- Treatment exacerbates cerebral edema
  - Vigorous fluid administration
  - Hypotonic fluids
  - Bicarbonate





Late Sequelae

DKA – Cerebral Edema

Actualities

- Etiology is not known
- Occurs exclusively in pediatric patients
- Mortality Rate = 21%
- Morbidity Rate = 27% (permanent neurologic sequelae)

 Difficulty is relatively rare occurrence (1-3 %) with subsequent small numbers of patients in retrospective or prospective studies

DKA – Cerebral Edema
Actualities

- NEJM - Jan 2001
  - N = 6977 DKA patients from 10 centers over 15 years
  - 61 developed cerebral edema (0.9%)
- Pediatrics - Sep 2001
  - N = 520 DKA patients over 5 1/2 years
  - 2 developed cerebral edema

DKA – Cerebral Edema

Total Fluids

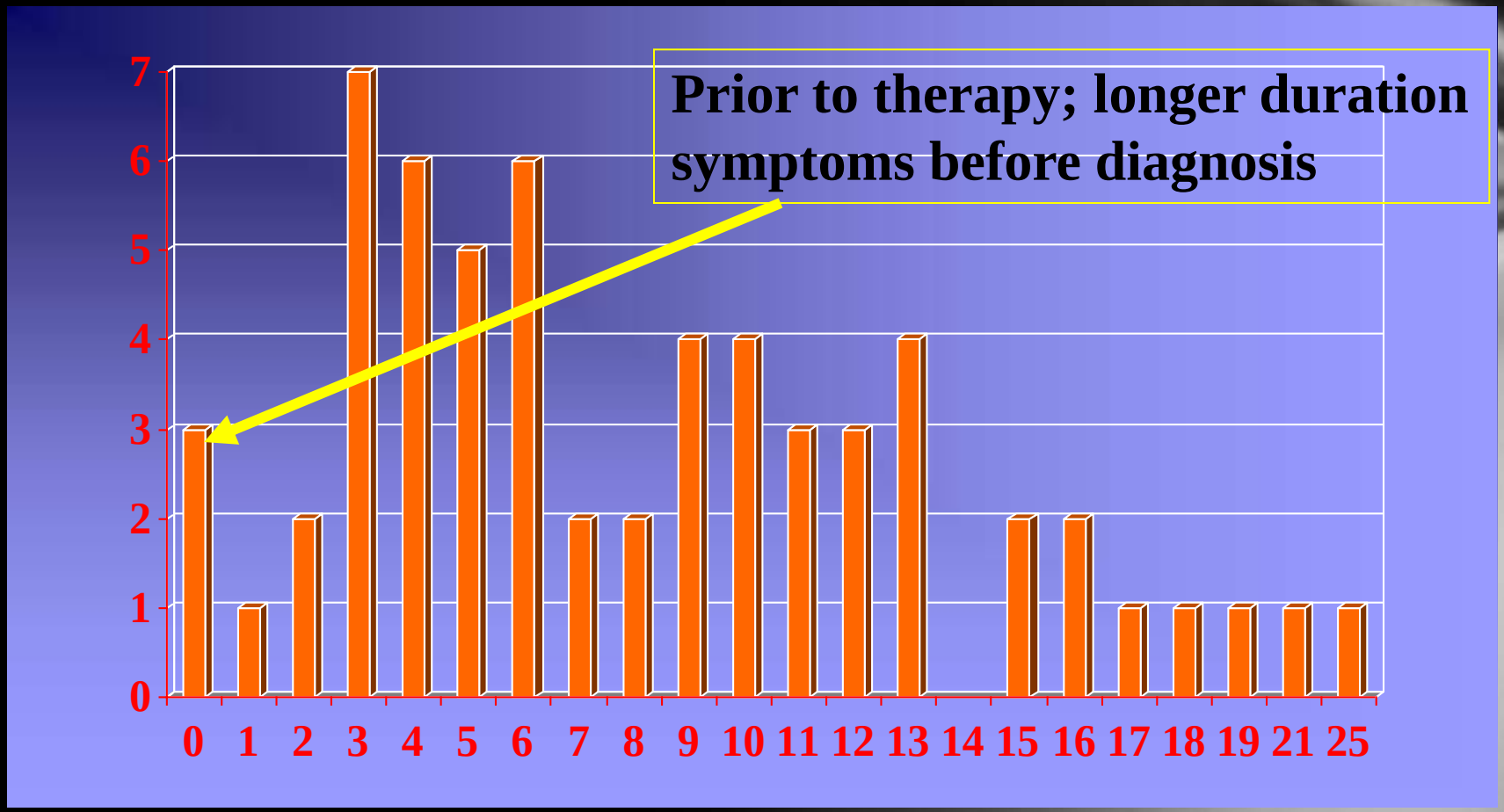
- > 4 L/m^2/day, or > 50 ml/kg in first 4 hrs ⍺ hyponatremia ⍺ herniation
- May occur in patients that receive less
- Of 52 patients with neurologic complications 21 had either a rise of serum Na or fall less than 4 mmol/L

 Attention to fluid rate and tonicity is essential, but may not be sufficient to predict subset that will develop neurologic complications

JCEM 85:509-513, 2000 J Peds 113:10-14, 1988

DKA – Cerebral Edema

Variable Time of Onset



NEJM 344:264-69, 2001

DKA – Cerebral Edema

Other

- Hypoxemia
- Children's brains have higher oxygen requirement, 5.1 mL/100g vs. 3.3 mL/100g
- Hypophosphatemia with resultant decreased 2,3-DPG decreases O_2 delivery to brain cells
- Mannitol - earliest effects are related to decreased viscosity, not to shift of fluid from extravascular space

JCEM 85: 509-13, 2000

DKA – Cerebral Edema

Signs and Symptoms

1. Sudden and persistent drop in heart rate
   - not bradychardia - not assoc with HTN
   - not related to hydration status
2. Change in sensorium
3. Headache
4. Emesis
5. Incontinence
6. Unexplained tachypnea
7. Fall in serum Na, or failure to rise

JCEM 85:509-513, 2000

DKA – Cerebral Edema

Evaluation

- CT may be non-diagnostic at time of symptoms
- 9 of 30 - no edema, 6 read as normal
- 5 of 9 - 2.5 to 8 hours after onset of coma, read as normal

Cerebral Edema is a clinical diagnosis.
Need to treat **BEFORE** imaging.

JCEM 85:509-513, 2000

A word about HHS

- Management is slimilar
- BG >600
- Serum osmolality > 320
- pH >7.3
- Anion gap is vairiable
- Typically in Type 2 DM, and change in mental status
- Goal is to continue insulin drip until serum osm drop below 310

A patient presents w/ DKA and a glucose of 700, Na+ of 132. What is the corrected Na+?

- Add 1.6 to every 100 mg /dL of glucose over 100
- Subtract 100 from 700
- Divide by 100
- Multiply by 1.6
- Add it to 132
  - (700-100) / 100 * 1.6 = (600/100) * 1.6 = 9.6
  - 132 + 9.6 = **141.6**

True or false

- 1 L of Normal saline is appropriate initial fluid therapy
- It is vital to correct bicarbonate in DKA patients
- Dextrose should be added to patients with glucose < 200 who still have ketonemia
- ARDS can occur from poor rehydration
- Nitroprusside is an accurate way to calculate ketone concentration
- A patient that is admitted with DKA and elevated serum potassium has elevated total body potassium

Cases

23 yo F with no PMH p/w diffuse abdominal pain for 1 day. PE is significant for HR of 120, BP 100/68, fruity odor to her breath, and tender but non-surgical abdomen. On presentation Na is 136, BG 551, Cl 101, K is 5.6 and bicarb is 7, serum ketones are present. 3 hours after intiation of IVF and IV insulin the labs are -

140/106/30

----------<190

4.1/14/1.3

What is the next appropriate step?

A. Measure another serum ketone level before making further changes

B. Discontinue insulin infusion and administer subcutaneous insulin

C. Discontinue insulin infusion and begin D5NS

D. Discontinue NS and begin D5NS

Cases

23 yo F with no PMH p/w diffuse abdominal pain for 1 day. PE is significant for HR of 120, BP 100/68, fruity odor to her breath, and tender but non-surgical abdomen. On presentation Na is 136, BG 551, Cl 101, K is 5.6 and bicarb is 7, serum ketones are present. 3 hours after intiation of IVF and IV insulin the labs are a

140/106/30

----------<190

4.1/14/1.3

What is the next appropriate step?

A. Measure a follow up serum ketone level before making any further changes

B. Discontinue insulin infusion and administer subcutaneous insulin

C. Discontinue insulin infusion and begin D5NS

D. Discontinue NS and begin D5NS

Cases

34 yo M p/w with fever, tachycardia and DKA. Labs are as follows:

WBC 16K, BG 600, BUN 15, Cr 1.7,

Na 130, K 3, ca 9, Phos 2.5, ph 7, Bicarb 5, Cl 100

What is the best first step?

A. Ns 1L + 40 MEQ KCL
B. Regular insulin 10 units IV bolus and 10 units IM stat
C. NS at 200ml/hr
D. Bicarb 50 mmol + 15 MEQ KCL over 2 hours
E. Empiric antibiotics

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Case

- A 10 y/o male (~30 kg) presents to the ED with a one-day history of emesis and lethargy.
- Vitals show T 37C, HR 110, RR 25 BP 99/65. Patient is lethargic, but oriented x 3. Exam reveals the odor of acetone on the breath, dry lips, but otherwise unremarkable
- Labs: pH 7.05 $PaCO_2$ 20, PaO_2 100, BE -20, Na^+ 133, K^+ 5.2, Cl 96 CO_2 8. Urine shows 4+ glucose and large ketones

Case

- How much fluid would you administer as a bolus?
- Would you administer bicarbonate?
- What is the “true” serum sodium?
- How much insulin would you administer?
- What IVF would you start? At what rate?

Answers

- 10 - 20 cc/kg bolus of NS would be adequate. Though the patient is dehydrated (dry lips), his hemodynamics are good, with acceptable vitals and good perfusion. There would be no reason to administer more than 20 cc/kg fluids.

- While this patient is clearly acidemic, he is NOT in impending cardiovascular collapse and therefore there is no justification for the administration of bicarbonate. In fact, administration of bicarbonate has been associated with the development of cerebral edema.

- The "true" serum sodium is 143 133 + 0.016[700-100]

- Insulin is generally started at 0.1 u/kg/hr. Therefore, in this 30 kg patient, an insulin infusion of 3 u/hr of regular insulin should be initiated.

- IVF of 2/3 NS or NS should be started at ~ 2400 cc/m^2/day, which is approximately 1.5 x maintenance

Case

- A 4 y/o female in the PICU is undergoing treatment for new onset IDDM and DKA. She is on an insulin infusion at 0.1 u/kg/hr, and fluids are running at 2400 cc/m2/day.
- Over the last hour, she has been complaining about increasing headache. She is now found to be unresponsive with bilateral fixed and dilated pupils, HR is 50 with BP 150/100.
- What is your next step in management?

Answers

- This patient is exhibiting cerebral edema, the most feared and lethal complication of DKA.

- Management at this point consists of securing the airway by endotracheal intubation and hyperventilating the patient. Mannitol 0.5 - 1 g/kg and or hypertonic saline (~5cc/kg 3% NaCl) should be administered as well.

- It would not be appropriate to stop the insulin infusion, or to bolus the patient with glucose. It should be noted that even patients receiving proper management for DKA (like this patient) may nonetheless develop cerebral edema.

Case

- A 72-year old female with a history of diabetes mellitus, hypertension, GERD and obstructive sleep apnea, presents to the emergency room with nausea/vomiting and lethargy. Patient states that she skipped “a few” doses of her lantus, but has otherwise been good about her insulin. She admits to blurred vision, and some mild abdominal discomfort.

Case

- Physical Exam:
- 38.1, 110/78, 110, 22, 99% on RA
- Gen: Obese female, alert and oriented x 3; in NAD
- HEENT: very dry mucus membranes
- CV: RRR
- Resp: LCTA bilaterally
- Abd: soft, mildly tender diffusely, no rebound/guarding
- Ext: no LE edema

Case

Labs:

- Sodium: 130
- Potassium: 5.9
- Chloride: 102
- Bicarbonate: 18
- BUN: 38
- Cr: 1.9
- Glucose: 602
- WBC: 14.3
- Hgb: 13.9
- Hct: 42
- Platelets: 291
- Urinalysis:
  - Trace ketones
  - Trace blood
  - Leuk. Est: 4 +
  - WBC > 50

Case

What does this patient have?

How should you acutely treat this patient?

What other tests would you send?

What do you do when the patient's glucose falls below 200?

Case

- A 32-year old woman is admitted to the hospital in a semi-comatose, volume-depleted state, exhibiting marked air hunger. She has had type 1 diabetes mellitus for 12 years and ran out of insulin 3 days ago.
- Labs:
  - Glucose: 1075 mg/dL Serum bicarbonate: 4.5 mEq/L

    Potassium: 3.8
  - ABG: pH 6.90, PCO_2: 23 mm Hg

Case

- After 4 hours of treatment that includes standard doses of insulin (10 units/h) fluids, intravenous potassium chloride (10 mEq/L) plus 150 meq/L of sodium bicarbonate, the patient's pH increases to 7.10. However, she suddenly develops respiratory failure followed by cardiac arrest.

Case

- What is the most likely therapeutic misjudgement?

(A) She was given too much potassium chloride and had suppression of all cardiac pacemaker activity.

(B) She was given too little potassium chloride and developed respiratory muscle paralysis followed by ventricular fibrillation.

(C) She was given too little insulin in the face of an unusually high plasma glucose concentration and developed cerebral edema.

(D) She was given too much bicarbonate, which led to cerebrospinal fluid acidosis and suppression of the brain stem respiratory center.

(E) She should have been given her potassium as potassium phosphate in order to prevent respiratory muscle paralysis from hypophosphatemia caused by insulin administration.

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Thank you for your attention

Raed Abu Sham'a, M.D