


The American Association of Clinical Endocrinologists
presents

**Management of Inpatient
Hyperglycemia 2012**

Today's Session

Hyperglycemia Crisis Conditions



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Disclosure

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**Diagnosis and Management of
Hyperglycemic Crises**

Diabetic Ketoacidosis (DKA)
Hyperglycemic Hyperosmolar State (HHS)



Diagnosis & Management of Hyperglycemic Crises

1. Overview
2. Pathogenesis and Pathophysiology
3. Focus on Acidosis
4. Patient Presentation
5. Treatment Recommendations
6. Finding the Cause and Preventing Recurrence



DKA and HHS are Life -Threatening Emergencies

- Classification as Diabetic Ketoacidosis (DKA):
DKA is suggested by plasma glucose > 250 mg/dL, arterial pH < 7.3, bicarbonate < 15, anion gap > 12 meq/L, and moderate ketonuria or ketonemia.
- Classification as Hyperglycemic Hyperosmolar State (HHS):
HHS is suggested by plasma glucose > 600 mg/dL, serum osmolality > 320 mosm/L, arterial pH > 7.3, bicarbonate > 15 meq/L, and minimal ketonuria and ketonemia.

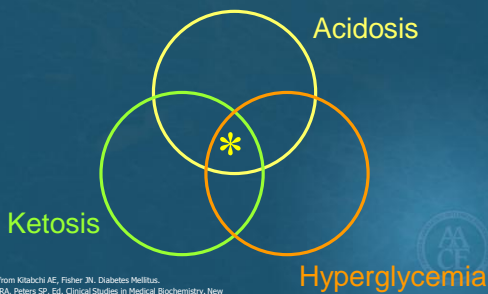


Characteristics of DKA and HHS

- DKA (Diabetic Ketoacidosis)
 - Absolute (or near- absolute) insulin deficiency, resulting in severe hyperglycemia, ketone body production, and systemic acidosis
 - Evolution over hours to 1- 2 days
 - Presentation most common in Type 1 diabetes, but increasingly seen in Type 2 diabetes
- HHS (Hyperglycemic Hyperosmolar State)
 - Severe relative insulin deficiency, resulting in profound hyperglycemia and hyperosmolality (from urinary free water losses), but no significant ketone production or acidosis
 - Evolution over days to weeks; higher mortality rate
 - Presentation typically in Type 2 or previously unrecognized diabetes



Definition of Diabetic Ketoacidosis*

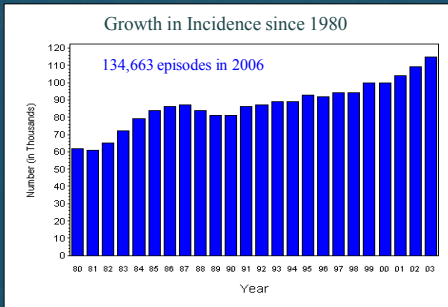


Hospital Discharges for Diabetic Ketoacidosis (DKA) in the US

- In 2005, diagnosis of DKA was present on
 - 120,000 discharges
 - 7.4 discharges per 1000 DM patient population
- There was a higher rate of DKA for persons < age 45
 - 55.4 discharges / 1000 DM patient population (1987)
 - 31.6 discharges / 1000 DM patient population (2005)

Diabetes Data and Trends. Hospitalization. [cited 2010 December 24]; Available from: http://www.cdc.gov/diabetes/statistics/hospitalization_national.html#5

Hospital DKA Discharges in the US



CDC/NCHS, National Hospital Discharge Survey (NHDS). [cited 12/2008]; Available from: <http://www.cdc.gov/nchs/about/hdsad/nhds.htm>

Diagnosis & Management of Hyperglycemic Crises

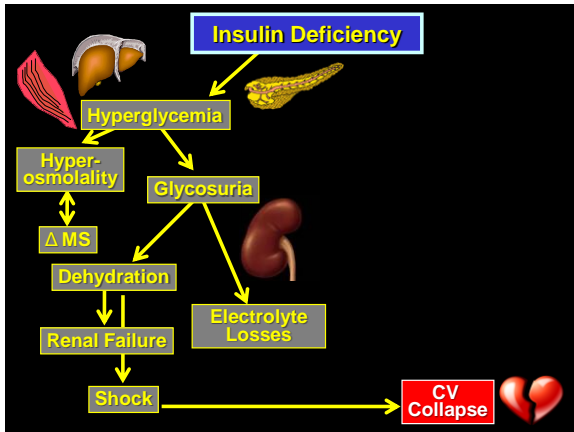
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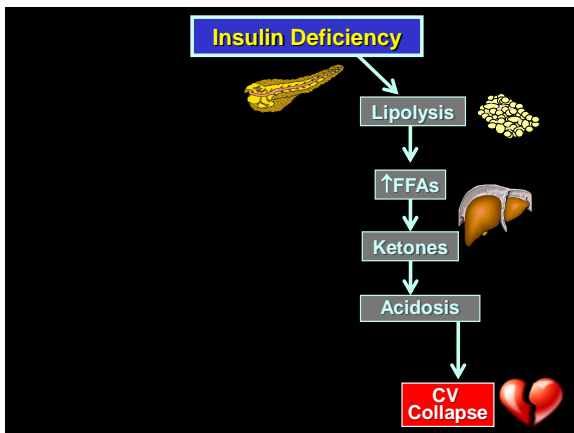
Diabetic Ketoacidosis: Pathophysiology

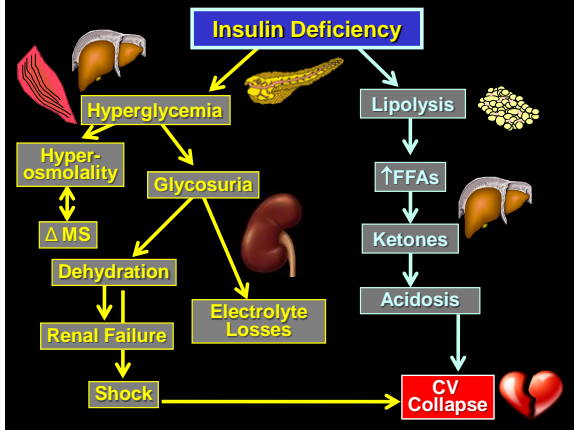
- Unchecked gluconeogenesis → *hyperglycemia*
- Osmotic diuresis → *dehydration*
- Unchecked ketogenesis → *ketosis*
- Dissociation of ketone bodies into hydrogen ion & anions → *anion-gap metabolic acidosis*

Often a precipitating event is identified (infection, lack of insulin administration)









Hyperosmolar Hyperglycemic State: Pathophysiology

- Unchecked gluconeogenesis → hyperglycemia
- Osmotic diuresis → dehydration
- Presentation commonly with renal failure
- Insufficiency of insulin for prevention of hyperglycemia but sufficiency for suppression of lipolysis and ketogenesis
- Absence of significant acidosis
- Often identifiable precipitating event (infection, MI)

Diabetic Hyperglycemic Crises

overlap syndromes

<h2 style="color: green;">DKA</h2> <ul style="list-style-type: none"> • Younger, Type 1 • Acidosis • Volume Depletion • Electrolyte Disturbances • <u>No</u> Hyperosmolality 	<h2 style="color: yellow;">HHS</h2> <ul style="list-style-type: none"> • Older, Type 2 • Volume Depletion • Hyperosmolality • Electrolyte Disturbances • <u>No</u> Acidosis
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Predictors of Future Near-Normoglycemic Remission in Adults with DKA

- African-American, Hispanic and other minorities
- Newly diagnosed diabetes
- Obesity
- Family history of type 2 diabetes mellitus
- Negative islet autoantibodies
- Fasting C-peptide levels > 0.33 nmol /L within 1 week or > 0.5 nmol /L during follow-up

Umpeirez G E et al. Ann Intern Med 2006;144:350-357

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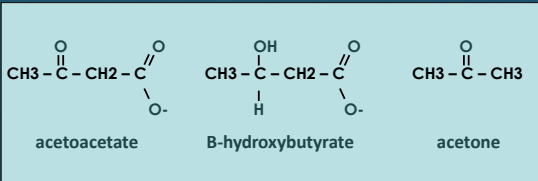
Anion Gap Metabolic Acidosis

- The normal **anion gap** in meq/L is calculated as:
 $[Na] - [Cl + HCO_3]$.
- The normal gap is < 12 meq /L.
- Causes of anion gap acidosis (unmeasured anions) include:
 - Ketoacidosis* (diabetic, alcoholic)
 - Lactic acidosis* (lactate [underperfusion, sepsis])
 - Uremia* (phosphates, sulfates)
 - Poisonings / overdoses* (methanol, ethanol, ethylene glycol, aspirin, paraldehyde)
- In ketoacidosis, the "delta" of the anion gap above 12 meq/L is composed of anions derived from keto-acids

Hyperchloremic Metabolic Acidosis (Non-Anion Gap)

- Due to fluid replacement with saline (NaCl) and renal loss of HCO₃⁻, during recovery from DKA a hyperchloremic acidosis is commonplace ('expansion acidosis').
- Following successful treatment of DKA, a non-anion-gap acidosis may persist after the ketoacidosis has cleared (i.e., after closing of the anion gap).
- "Closing" of the anion gap is a better sign of recovery from DKA than is correction of metabolic acidosis.

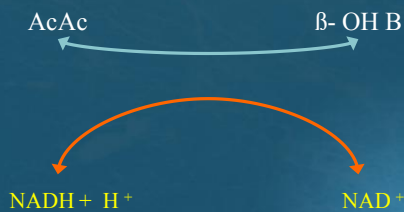
Ketone Bodies in DKA



Unless β-hydroxybutyrate (β-OH B) is specifically ordered, the ketone bodies are estimated by the nitroprusside reaction in the lab, which measures only acetone and acetoacetate (AcAc).

(Acetone is not an acid.)

Ketone Body Equilibrium in DKA



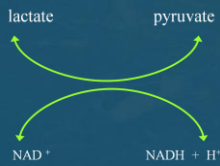
In DKA, the dominant keto-acid is β-hydroxybutyric acid (especially in case of poor tissue perfusion / lactic acidosis); during recovery the balance shifts to acetoacetic acid.

Significance of Ketone Measurements

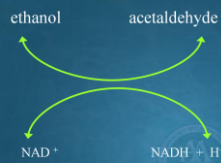
- Unless you have a special meter or in-house assay, or use a send-out lab, you can't measure the main player, β -hydroxybutyrate.
- During recovery, using the nitroprusside test, you might wrongly think the ketone concentration is not improving or is even getting worse.
- Your best biochemical indicator of resolution of keto-acid excess is simply the anion gap.
- There is no rationale for follow-up ketone measurements after the initial measurement has returned high.

Co-existing Conditions (Altered Redox States) Drive Balance Toward \uparrow NADH & \uparrow β -OH B

lactic acidosis



alcoholic ketoacidosis



Fulop M, et al. Arch Int Med 1976;136:987-990.
 Mariss E, et al. N Engl J Med 1970;283(18):978-80
 Levy et al. Ann Int Med 1973;79:213-219.
 Werns, K. et al. Am J Med 1991;91:119.

Molar Ratio of β -OH B : AcAc

Normal health	2 to 1
DKA	3 - 4 to 1
DKA with high redox state	7.7 - 7.8 to 1

Significance? Increase of measured ketones may be misleadingly small in DKA with coexisting lactic acidosis and /or alcoholism.

Mariss 1970

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Clinical Presentation of DKA

History

- Thirst
- Polyuria
- Abdominal pain
- Nausea / vomiting
- Profound weakness

Physical exam

- Kussmaul respirations
- Fruity breath
- Relative hypothermia
- Tachycardia
- Supine hypotension, orthostatic drop of BP
- Dry mucous membranes
- Poor skin turgor

Lab Findings in DKA

- Severe hyperglycemia
- Increased blood and urine ketones
- Low bicarbonate
- High anion gap
- Low arterial pH
- Low PCO₂ (respiratory compensation)

Potassium Balance in DKA

- Potassium is dominantly intracellular.
- Urinary losses occur during evolution of DKA (due to glycosuria).
- Total body potassium stores are greatly reduced in any patient with DKA.
- During insulin deficiency, in presence of high blood glucose, and as cells buffer hydrogen ion, potassium moves from inside the cell into the extracellular space (plasma).
- Blood levels of potassium prior to treatment are usually high, but may drop precipitously during therapy.

Hyperglycemic Hyperosmolar State (HHS)

- Compared to DKA, in HHS there is greater severity of :
 - dehydration
 - hyperglycemia
 - hypernatremia
 - hyperosmolality
- Because some insulin typically persists in HHS, ketogenesis is absent to minimal, insufficient to produce significant acidosis.

HHS: Typical Patient Profile (c/w DKA)

- Older patients
- Prior history of T2DM, which may have been unrecognized
- More insidious development (weeks vs. hours/days)
- Greater osmolality and mental status changes
- Dehydration presenting with a shock -like state
- Patients with more co -morbidityes

Electrolyte & Fluid Deficits in DKA vs. HHS

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

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

Chalson et al, Can Med Assoc J. 2003; 168(7):859-866

Initial Lab Evaluation of Hyperglycemic Emergencies

- ✓ Comprehensive metabolic profile
- ✓ Serum osmolality
- ✓ Serum and urine ketones
- ✓ Arterial blood gases
- ✓ Lactate (?)
- ✓ CBC
- ✓ Urinalysis
- ✓ ECG
- ✓ ? Blood cultures



Laboratory Diagnostic Criteria of DKA & HHS

Parameter	Normal range	DKA	HHS
Plasma glucose, mg/dl	76 – 115	≥ 250	≥ 600
Arterial pH*	7.35 – 7.45	≤ 7.30	> 7.30
Serum bicarbonate, mmol/L	22 – 28	≤ 15	> 15
Effective serum osmolality, mmol/kg	275 – 295	≤ 320	> 320
Anion gap†, mmol/L	< 12	> 12	Variable
Serum ketones	Negative	Mod to high	None or trace
Urine ketones	Negative	Mod to high	None or trace

* If venous pH is used, a correction of 0.03 must be made
 † Calculation: Na⁺ - (Cl⁻ + HCO₃⁻)

after Chalson et al, Can Med Assoc J. 2003; 168(7):859-866

Formula for Estimating Serum Osmolality & Effective Osmolality

OSMOLALITY

$$2 \times [\text{Na}^+ \text{ meq/L}]$$

$$+ [\text{glucose mg /dL}] / 18$$

$$+ [\text{BUN mg /dL}] / 2.8$$

$$= \text{Sosm (mosm /Kg H}_2\text{O)}$$

EFFECTIVE OSMOLALITY

$$2 \times [\text{Na}^+ \text{ meq/L}]$$

$$+ [\text{glucose mg /dL}] / 18$$

$$= \text{Sosm (mosm /Kg H}_2\text{O)}$$

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Treatment with IV Fluids and Dextrose

- For severe hypovolemia, during the first 1-2 hours (in absence of cardiac compromise), give 1 - 1.5 liters 0.9% NaCl.
- After initial volume resuscitation, or for more mild dehydration, use intravenous fluid rate of 250- 500 mL/hr.
- Compute corrected serum Na (for every 100 mg/dL BG elevation, add 1.6 mEq/L to Na value);
 - use 0.45% NaCl if corrected Na normal,
 - use 0.9 % NaCl if corrected Na < 135.
- When BG reaches 200 mg/dL (DKA) or 300 mg/dL (HHS), change to 5% dextrose with 0.45% NaCl at 150- 250 mL/hr ('clamping blood glucose' until anion gap has closed in DKA).

Conventional Insulin Guidelines

- Initiate the correction of hypovolemic shock with fluids, and correct hypokalemia if present, before starting insulin.
- When starting insulin, infuse 0.1 to 0.14 units • kg⁻¹• hr⁻¹ initially.
- If plasma glucose does not decrease by 50 – 75 mg in the 1st hour, increase the infusion rate of insulin.
- Continue insulin infusion until anion gap closes.
- Initiate subcutaneous insulin at least 2 hr before interruption of insulin infusion.

adapted from Kitabchi AE et al. Diabetes Care. 2009 Jul;32(7):1335-43.



Rationale for a Dynamic Insulin Protocol for DKA and HHS (to be shown in tabular form, with column change rules)

- Even with the use of low dose insulin therapy, hypokalemia and hypoglycemia continue to occur; and failure to reduce insulin infusion rate as the blood glucose approaches target may be associated with hypoglycemia.
 - Umpierrez GE, et al. Archives of Internal Medicine. 1997;157(6):669-75
 - Burghen GA, et al. Diabetes Care. 1980 Jan-Feb;3(1):15-20
- The effects of a revision of intravenous insulin infusion rate will not be expressed until a lag time has elapsed.
 - Mudaliar S et al. Diabetes Care. 2002; 25(9):1597-602



A Dynamic Insulin Protocol for DKA

PHYSICIAN ORDERS FOR DKA : target blood glucose 150-199 mg/dL until recovery					
Default is Col 3	<input type="checkbox"/> Column 1	<input type="checkbox"/> Column 2	<input type="checkbox"/> Column 3	<input type="checkbox"/> Column 4	<input type="checkbox"/> Column 5
BG mg/dL	Insulin units/hr	Insulin units/hr	Insulin units/hr	Insulin units/hr	Insulin units/hr
<90	0.1	0.1	0.1	0.1	←
90 – 129	0.2	0.3	0.3	0.4	←
130 – 149	0.4	0.6	0.8	1.0	←
150 – 169	0.6	1.1	1.5	1.8	2.5
170 – 179	0.8	1.6	2.3	3.0	4.3
180 – 199	1.0	2.0	3.0	4.0	6.0
200 – 229	1.1	2.2	3.3	4.4	6.5
230 – 259	1.3	2.5	3.8	5.0	7.5
260 – 289	1.4	2.8	4.2	5.6	8.4
290 – 319	1.5	3.1	4.6	6.2	9.3
320 – 359	1.7	3.4	5.1	6.8	10.2
360 – 399	1.8	3.7	5.5	7.4	11.1
≥ 400	2.0	4.0	6.0	8.0	12.0

Devi R et al. Diabetes Management 2011; 1 (4): 397-412.



Cerebral Edema

- Cerebral edema is a dreaded complication of DKA in childhood.
 - Muir AB, et al. Diabetes Care 2004;27(7):1541-6
- Mortality may be 24%, with significant morbidity among survivors.
 - Edge JA et al. Arch Dis Child. 2001 Jul;85(1):16-22
- One pediatric study found that rates of fluid administration and insulin administration were not associated with cerebral edema.
 - Glaser N. et al. N Engl J Med 2001;344(4):254-9
- In another case control pediatric study, insulin dose in first 2 hrs was significantly associated with the risk of cerebral edema.
 - Edge J, et al. Diabetologia. 2006;49(9):2002-9



Potassium Repletion in DKA

- Life-threatening hypokalemia can develop during insulin treatment.
- Potassium re-enters cells with insulinization and correction of acidosis.
- The small extracellular compartment experiences a precipitous drop of potassium concentration.
- Anticipatory potassium replacement during treatment of DKA is almost always required.



Potassium Repletion in DKA

- For $K^+ > 5.2$ mEq/L, do not give K^+ initially, but check serum K^+ with basic metabolic profile every 2 hr. Establish urine output ~ 50 mL/hr.
- For $K^+ < 3.3$ mEq/L, hold insulin and give K^+ 20 - 30 mEq/hr until $K^+ > 3.3$ mEq/L.
- When $K^+ = 3.3 - 5.2$ mEq/L, give 20 - 30 mEq K^+ in each liter of IV fluid to keep serum K^+ 4-5 mEq/L.



Phosphorous Repletion in DKA

- A sharp drop of serum phosphorus can also occur during insulin treatment.
- It is not common that treatment is required.
- The caregiver can give some of K+ as K- Phos.



Fluid & Electrolyte Management in HHS

- Treatment requires more free water and greater volume replacement than for patients with DKA.
- To avoid heart failure, caution is required in the elderly with pre-existing heart disease.
- Potassium is usually not significantly elevated on admission (unless in renal failure); during treatment, potassium replacement is required.



Causes of Morbidity & Mortality in DKA

- | | |
|-----------------------------------|--------------------------------------------------------------------------------|
| • Shock | • Acute renal failure |
| • Hypokalemia during treatment | • Adult respiratory distress syndrome |
| • Hypoglycemia during treatment | • Vascular thrombosis |
| • Cerebral edema during treatment | • Precipitating illness, including MI, stroke, sepsis, pancreatitis, pneumonia |
| • Hypophosphatemia | |



DKA Management Pitfalls

1. Not assessing for and/or treating underlying cause of the DKA
2. Not watching K⁺ closely enough and / or not replacing K⁺ aggressively enough
3. Following serial serum ketone concentrations
4. Following serum bicarbonate instead of the anion gap, with misinterpretation of expansion acidosis as "persistent ketoacidosis"
5. Interrupting IV insulin too soon (e.g., patient not yet eating, anion gap not yet closed)

DKA Management Pitfalls (continued)

6. Occurrence of rebound ketosis consequent to inadequate insulin dosing at transition (e.g. failure to give SQ insulin when glucose is "low" or injudicious use of sliding scale insulin)
7. Inappropriate extension of the hospitalization to "fine-tune" an outpatient regimen
8. Inadequate patient education / training
9. Inadequate follow-up care

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Search for Precipitating Cause / Factors

- ? Non-compliance / psychiatric issues *
- ? Insulin error / insulin pump malfunction *
- ? Poor "sick-day" management *
- ? Infection (pneumonia, pyelonephritis, flu, intra-abdominal, cutaneous infection, etc.)
- ? Steroid therapy, other drugs / substances

(to be continued)



* in patients with established T1DM

Search for Precipitating Cause / Factors (cont.)

- ? Dehydration
- ? Renal insufficiency
- ? Myocardial infarction, stroke
- ? Pancreatitis
- ? Other endocrinopathy (*rare*)
- ? Other causes



Pre -discharge Checklist



1. Diet information
2. Monitor / strips (& Rx)
3. Rx for / supplies of meds, insulin, needles
4. Treatment goals
5. Contact phone numbers
6. "Medic -Alert" bracelet
7. "Survival Skills" training



Education in T1DM to Prevent DKA

- Recognize symptoms and findings that require contact with a health care provider.
- Prevent ketoacidosis through self-management skills:
 - glucose testing
 - appropriate use of urine acetone testing
 - appropriate maintenance of insulin on sick days
 - use of supplemental insulin during illness.
- Address social factors.



Summary

- DKA and HHS are life-threatening emergencies.
- Management involves attention to precipitating cause, fluid and electrolyte management, insulin therapy, patient monitoring, prevention of metabolic complications during recovery, and transition to long term therapy.
- Patient education and discharge planning should aim at prevention of recurrence.



Questions