Diagnosis and Management of Hyperglycemic Crises

Diabetic Ketoacidosis

Hyperglycemic Hyperosmolar State

OVERVIEW

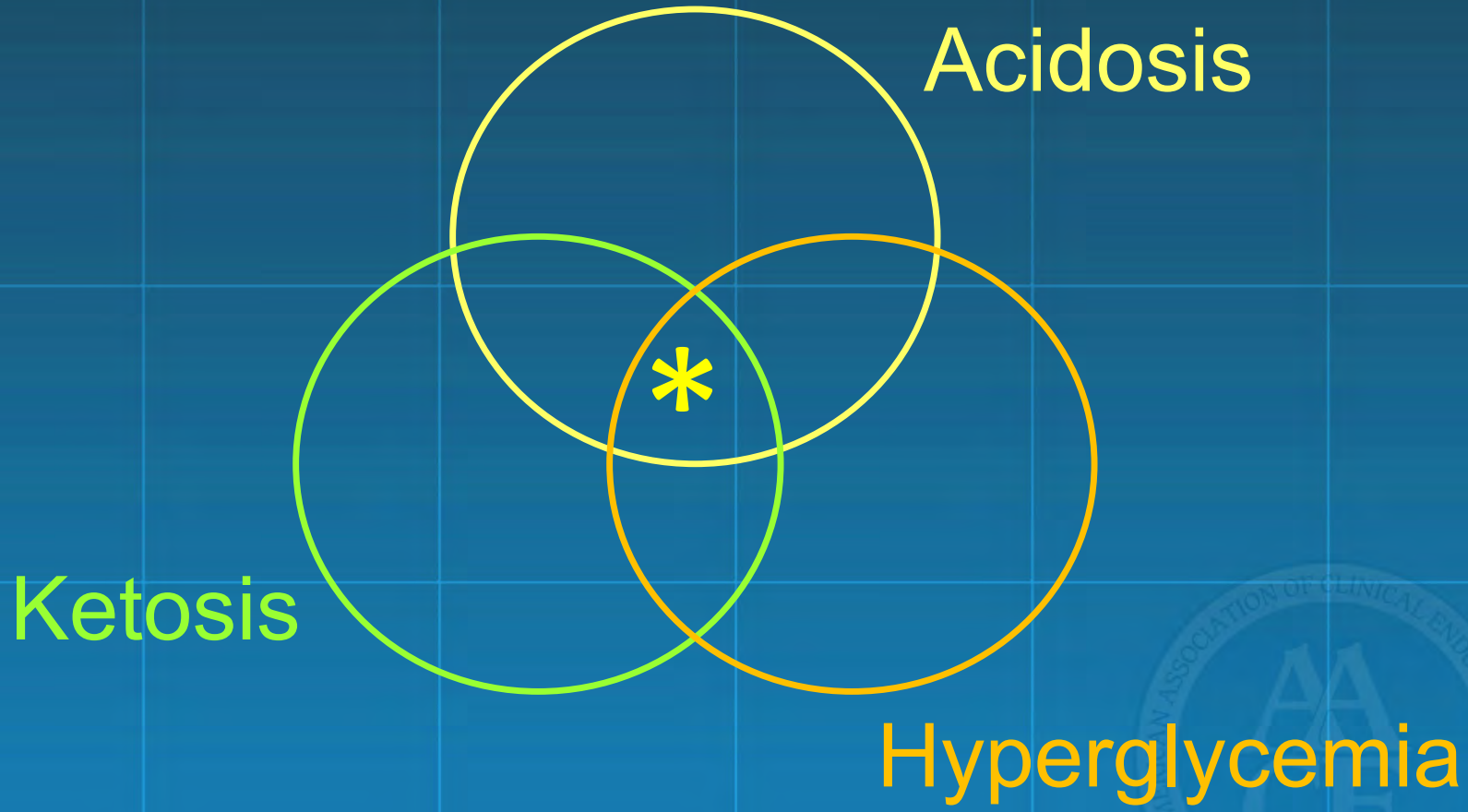
DKA and HHS Are Life-Threatening Emergencies

Diabetic Ketoacidosis (DKA)	Hyperglycemic Hyperosmolar State (HHS)
Plasma glucose >250 mg/dL	Plasma glucose >600 mg/dL
Arterial pH <7.3	Arterial pH >7.3
Bicarbonate <15 mEq/L	Bicarbonate >15 mEq/L
Moderate ketonuria or ketonemia	Minimal ketonuria and ketonemia
Anion gap >12 mEq/L	Serum osmolality >320 mosm/L

Characteristics of DKA and HHS

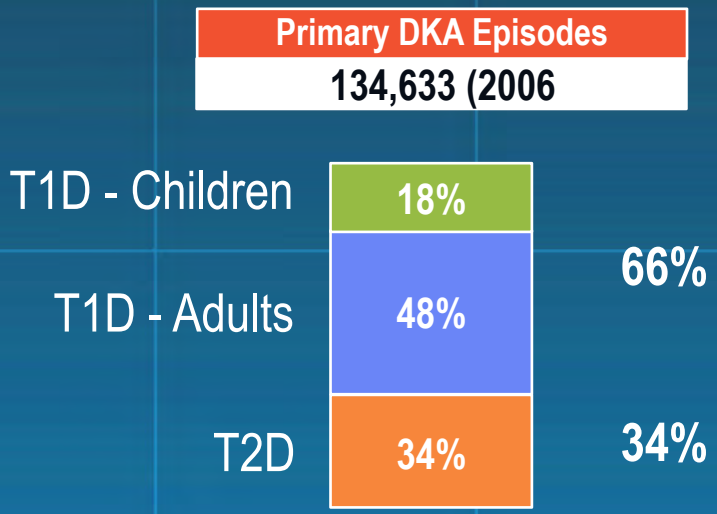
Diabetic Ketoacidosis (DKA)	Hyperglycemic Hyperosmolar State (HHS)
Absolute (or near-absolute) insulin deficiency, resulting in • Severe hyperglycemia • Ketone body production • Systemic acidosis	Severe relative insulin deficiency, resulting in • Profound hyperglycemia and hyperosmolality (from urinary free water losses) • No significant ketone production or acidosis
Develops over hours to 1-2 days	Develops over days to weeks
Most common in type 1 diabetes, but increasingly seen in type 2 diabetes	Typically presents in type 2 or previously unrecognized diabetes
	Higher mortality rate

Definition of Diabetic Ketoacidosis*



Adapted from Kitabchi AE, Fisher JN. Diabetes Mellitus. In: Glew RA, Peters SP, ed. *Clinical Studies in Medical Biochemistry*. New York, NY: Oxford University Press; 1987:105.

Type 1 Diabetes Accounts for the Majority of Primay DKA Episodes



- 34% of episodes are Type 2
  ⇒*~46,000 cases*
- ⇒Longer Hospital Stays
  ⇒*4.2 vs average of 3.5*
- Very few have CV issues or serious infections => *Less than 15%*

T2D accounts for 34% of primary DKA cases and more than 50% of secondary causes

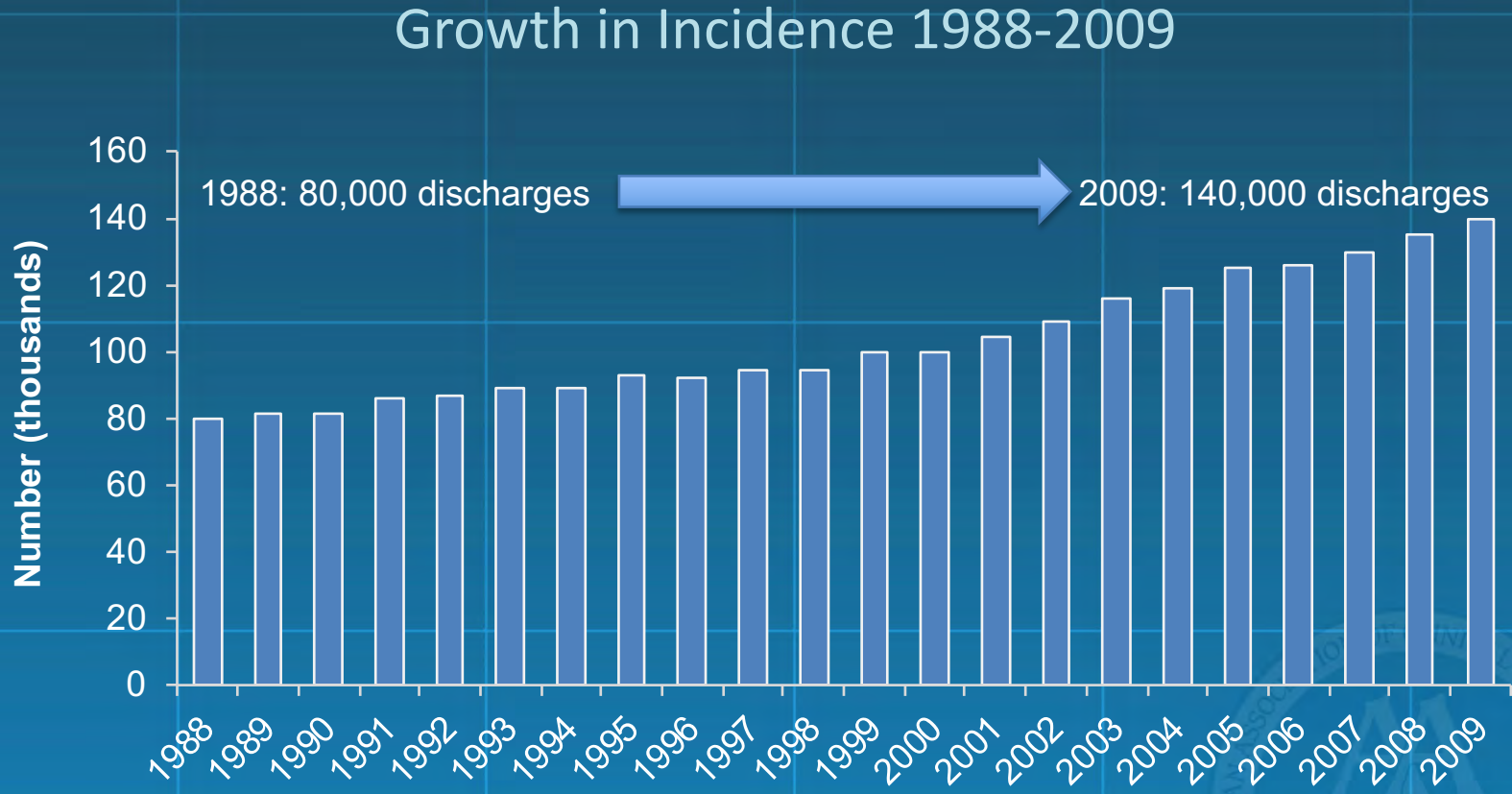
National Hospital Discharge Survey. 2006.

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)

CDC. Diabetes Data and Trends. Hospitalization. Available from: http://www.cdc.gov/diabetes/statistics/hospitalization_national.htm#5

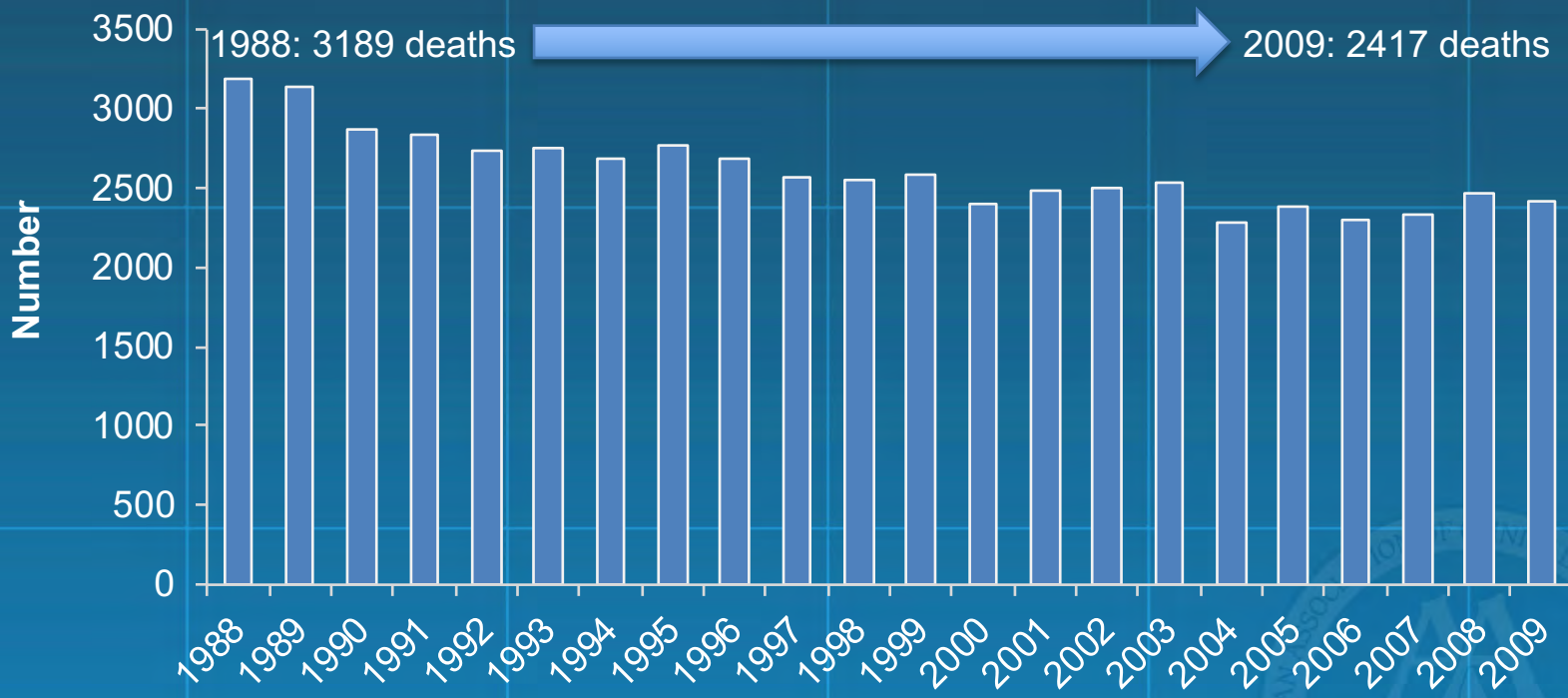
DKA Hospital Discharges in the US



CDC. Diabetes data and trends. Hospitalization: DKA. Available from: https://www.cdc.gov/diabetes/statistics/dkafirst/fig1.htm

DKA Mortality in the US

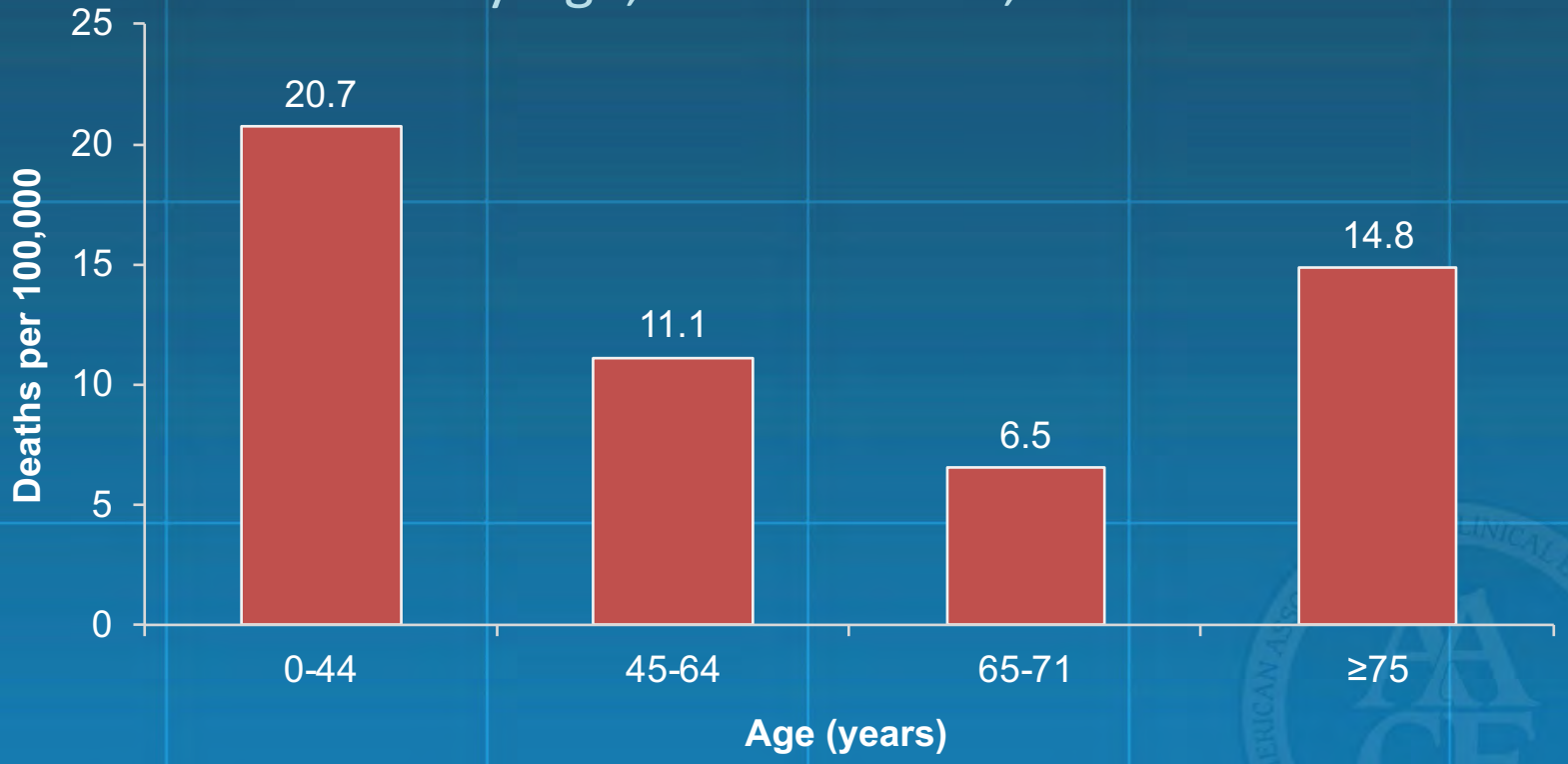
Decline in Incidence 1988-2009



CDC. Diabetes data and trends. DKA mortality. Available from: https://www.cdc.gov/diabetes/statistics/mortalitydka/fnumberofdka.htm.

Death Rates for Hyperglycemic Crises as Underlying Cause

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

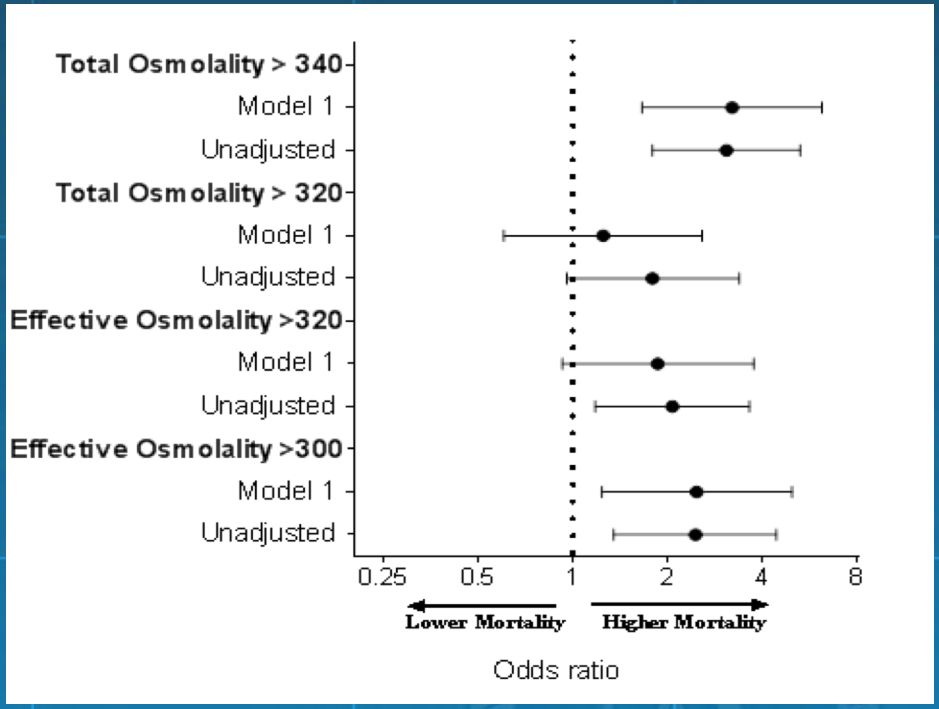


CDC. Diabetes complications. Mortality due to hyperglycemic crises. Available from: https://www.cdc.gov/diabetes/statistics/mortalitydka/fratedkadiabbyage.htm.

Hyperosmolality and Mortality in Hyperglycemic Crises

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

Odds Ratios for Mortality



Case Definition of Hyperglycemic Crises

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

Pasquel FJ, et al. Presented at 76th Annual ADA Scientific Sessions, New Orleans, LA. June 10-14, 2016. Abstr 1482-P.

Causes of Morbidity and Mortality in DKA

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

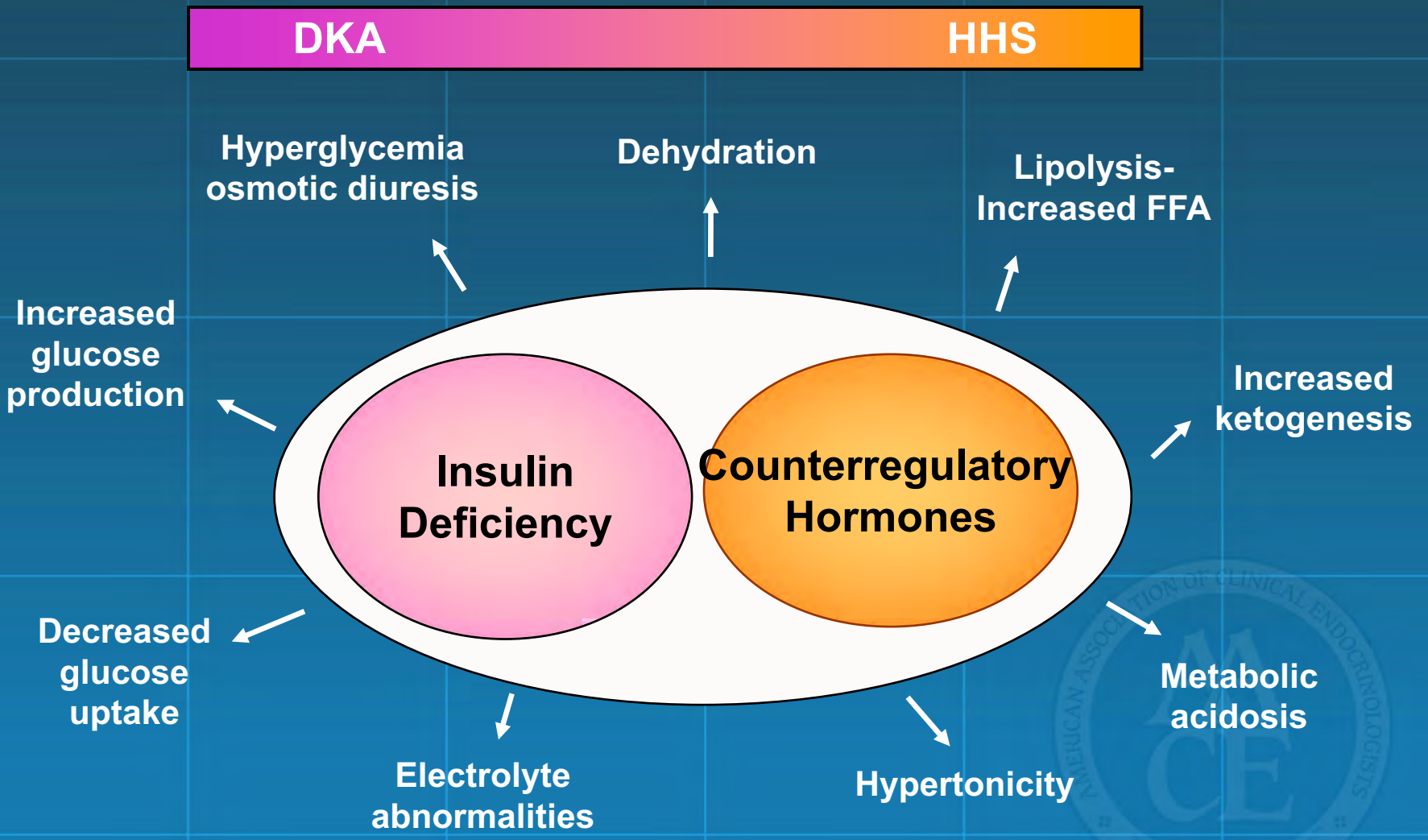
PATHOGENESIS AND PATHOPHYSIOLOGY

Diabetic Ketoacidosis: Pathophysiology

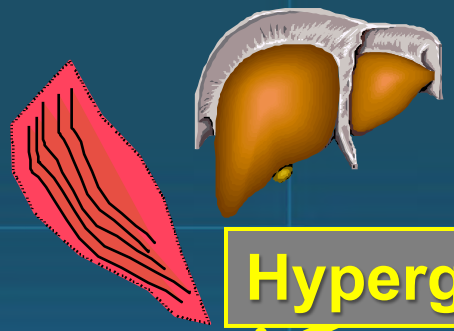
Unchecked gluconeogenesis	→	Hyperglycemia
Osmotic diuresis	→	Dehydration
Unchecked ketogenesis	→	Ketosis
Dissociation of ketone bodies into hydrogen ion and anions	→	Anion-gap metabolic acidosis

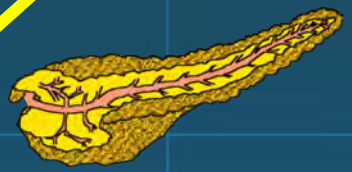
Often a precipitating event is identified
(infection, lack of insulin administration)

Pathogenesis of Hyperglycemic Crises



Umpierrez G, Korytkowski M. *Nat Rev Endocrinol*. 2016;12:222-232.





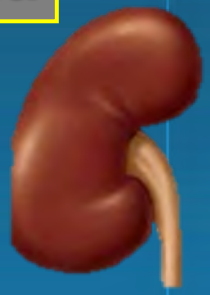
Insulin Deficiency

Hyperglycemia

Hyper-osmolality

Δ MS

Glycosuria



Dehydration

Renal Failure

Shock

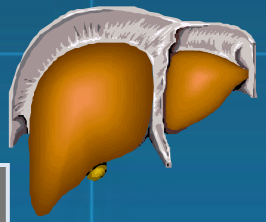
Electrolyte Losses

CV Collapse

Insulin Deficiency

Lipolysis

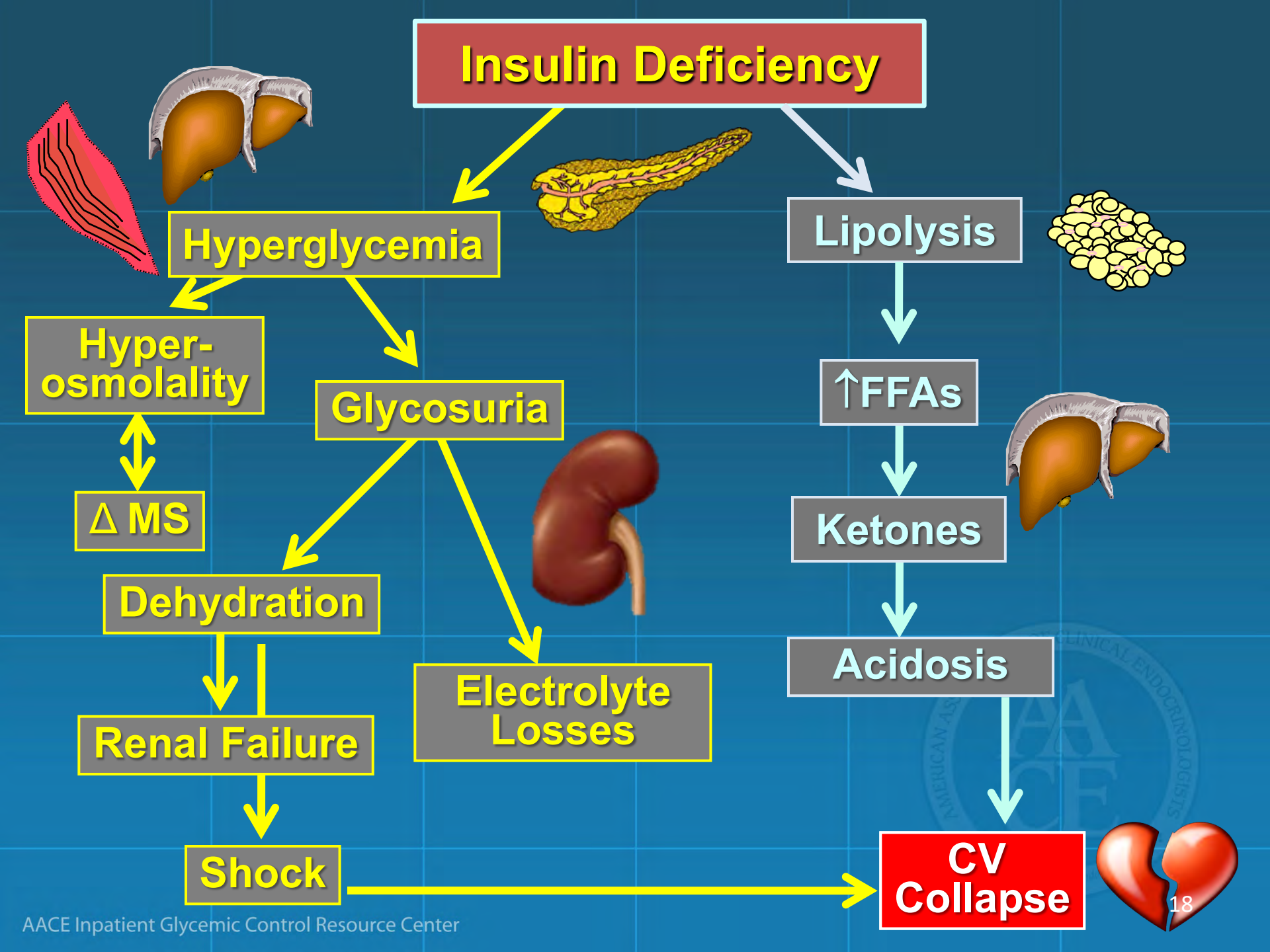
↑FFAs



Ketones

Acidosis

CV Collapse

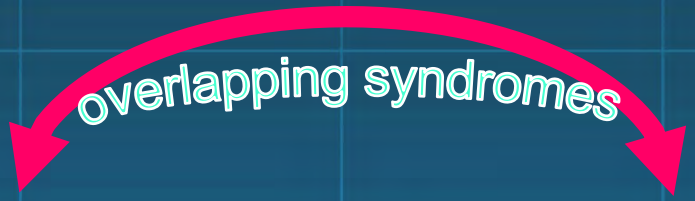

Insulin Deficiency
Hyperglycemia
Hyper-
osmolality
Δ MS
Glycosuria
Dehydration
Renal Failure
Shock
Electrolyte
Losses
Lipolysis
↑FFAs
Ketones
Acidosis
CV
Collapse

Hyperosmolar Hyperglycemic State: Pathophysiology

Unchecked gluconeogenesis	→	Hyperglycemia
Osmotic diuresis	→	Dehydration

- Presents commonly with renal failure
- Insufficient insulin for prevention of hyperglycemia but sufficient insulin for suppression of lipolysis and ketogenesis
- Absence of significant acidosis
- Often identifiable precipitating event (infection, MI)

Diabetic Hyperglycemic Crises



Diabetic Ketoacidosis (DKA)	Hyperglycemic Hyperosmolar State (HHS)
Younger, type 1 diabetes	Older, type 2 diabetes
No hyperosmolality	Hyperosmolality
Volume depletion	Volume depletion
Electrolyte disturbances	Electrolyte disturbances
Acidosis	No acidosis

Predictors of Future Near-Normoglycemic Remission in Adults With DKA

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

  or
  - >0.5 nmol/L during follow-up

Umpierrez GE, et al. *Ann Intern Med.* 2006;144:350-357.

FOCUS ON ACIDOSIS

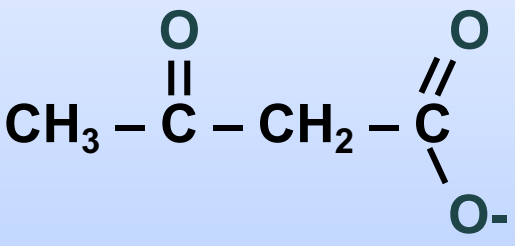
Anion Gap Metabolic Acidosis

- 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

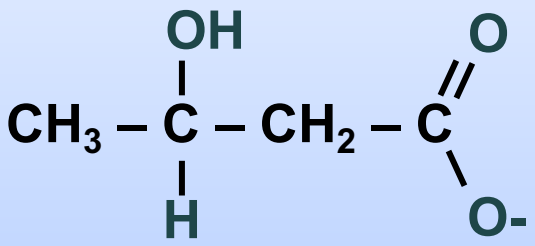
Hyperchloremic Metabolic Acidosis (Non-anion Gap)

- Hyperchloremic acidosis (ie, expansion acidosis) is common during recovery from DKA due to
  - Fluid replacement with saline (NaCl)
  - Renal loss of HCO_3
- Following successful treatment of DKA, a non-anion–gap acidosis may persist after the ketoacidosis has cleared (ie, 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

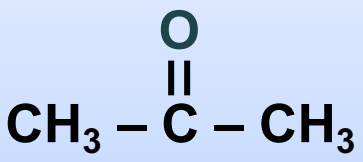
Ketone Bodies in DKA



Acetoacetate



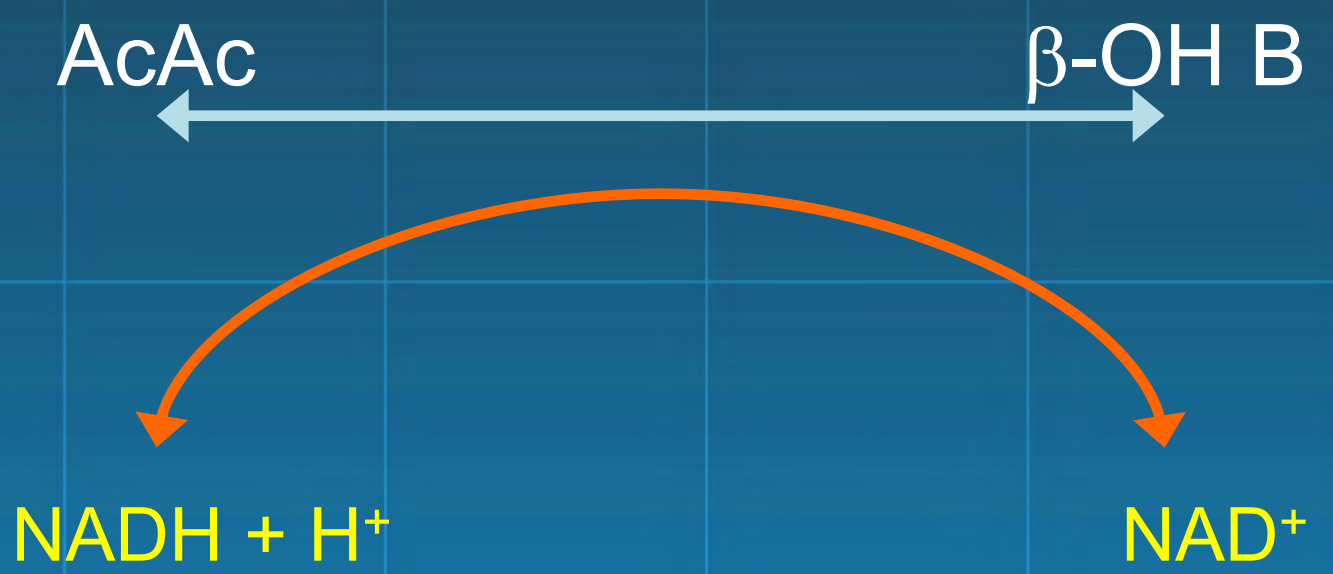
β-Hydroxybutyrate



Acetone

- 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



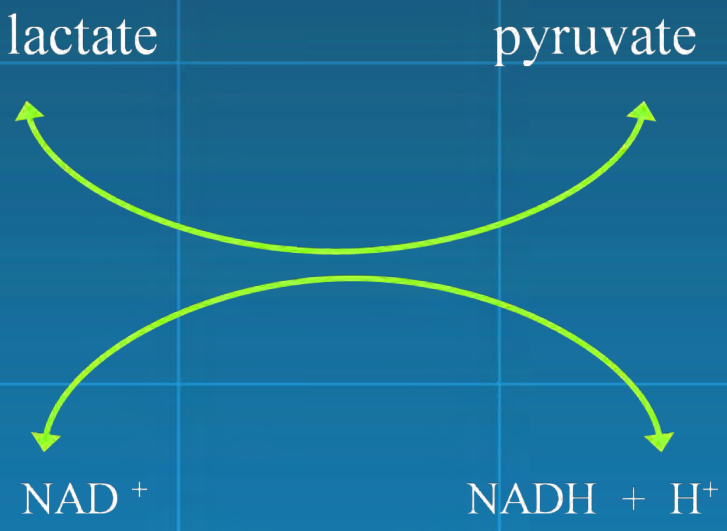
- In DKA, the dominant ketoacid is β-hydroxybutyric acid (β-OH B), especially in cases of poor tissue perfusion/lactic acidosis
- During recovery, the balance shifts to acetoacetic acid (AcAc)

Significance of Ketone Measurements

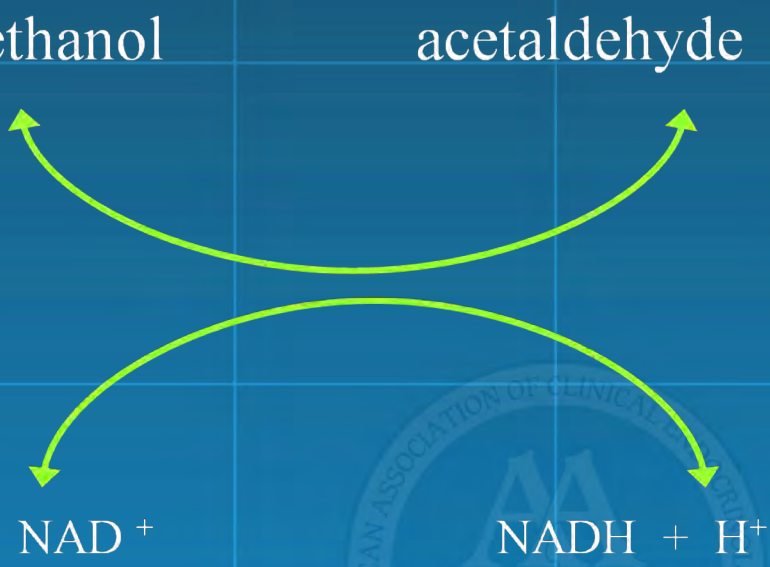
- β-hydroxybutyrate can only be measured using specialized equipment not available in most in-house laboratories
- During recovery, results from the nitroprusside test might wrongly indicate that the ketone concentration is not improving or is even getting worse
- The best biochemical indicator of resolution 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

Coexisting Conditions (Altered Redox States) Drive Balance Toward ↑ NADH and ↑ β-OH B

Lactic Acidosis



Alcoholic Ketoacidosis



Fulop M, et al. *Arch Intern Med.* 1976;136:987-990; Marliss EB, et al. *N Engl J Med.* 1970;283:978-980; Levy LJ, et al. *Ann Intern Med.* 1973;79:213-219; Wrenn KD, et al. *Am J Med.* 1991;91:119-128.

Molar Ratio of β-OH B to 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

Marliss EB, et al. *N Engl J Med.* 1970;283:978-980.

PATIENT PRESENTATION

Clinical Presentation of Diabetic Ketoacidosis

History

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

Physical Exam

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

Patients with any form of diabetes who present with abdominal pain, nausea, fatigue, and/or dyspnea should be evaluated for DKA.

Handelsman Y, et al. *Endocr Pract*. 2016;22:753-762.

Lab Findings in DKA

- Hyperglycemia
  - Usually >250 mg/dL
  - Lower blood glucose values possible, especially under metabolically stressful conditions (eg, prolonged fasting, carbohydrate avoidance, extreme sports/physical exertion, myocardial infarction, stroke, severe infection, surgery)
- Increased blood and urine ketones
- High β-hydroxybutyrate
- High anion gap
- Low arterial pH
- Low PCO_2 (respiratory compensation)

Handelsman Y, et al. *Endocr Pract*. 2016;22:753-762.

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
- Potassium moves from inside the cell to the extracellular space (plasma)
  - During insulin deficiency
  - In presence of high blood glucose
  - As cells buffer hydrogen ions
- Blood levels of potassium prior to treatment are usually high but may drop precipitously during therapy

Clinical Presentation of Hyperglycemic Hyperosmolar State

- 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 and is insufficient to produce significant acidosis

Clinical Presentation of Hyperglycemic Hyperosmolar State

Patient Profile

- Older
- More comorbidities
- History of type 2 diabetes, which may have been unrecognized

Disease Characteristics

- More insidious development than DKA (weeks vs hours/days)
- Greater osmolality and mental status changes than DKA
- Dehydration presenting with a shock-like state

Electrolyte and Fluid Deficits in DKA and 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.

Chaisson JL, et al. *CMAJ*. 2003;168:859-866.

Initial Laboratory 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 and HHS

Parameter	Normal range	DKA	HHS
Plasma glucose, mg/dL	76-115	≥250*	≥600
Arterial pH†	7.35-7.45	≤7.30	>7.30
β-Hydroxybutyrate, mg/dL	4.2-5.2	≥31 (children) ≥40 (adults)	
Serum bicarbonate, mmol/L‡	22-28	≤18	>15
Effective serum osmolality, mmol/kg	275-295	≤320	>320
Anion gap,§ mmol/L	<10	>10	Variable
Serum ketones¶	Negative	Positive	None or trace
Urine ketones‡	Negative	Moderate to high	None or trace

*May occur at lower glucose values, especially under physiologically stressful conditions.
† If venous pH is used, a correction of 0.03 must be made.
‡ Suggestive but not diagnostic of DKA.
§ Calculation: $(Na^+) – [Cl^- + HCO_3^-$ (mEq/L)].
¶ Nitroprusside reaction method.

Chaisson JL, et al. *CMAJ*. 2003;168:859-866. Handelsman Y, et al. *Endocr Pract*. 2016;22:753-762. Haw SJ, et al. In: *Managing Diabetes and Hyperglycemia in the Hospital Setting: A Clinician's Guide*. Draznin B, ed. Alexandria, VA: American Diabetes Association; 2016;284-297.

ADA Diagnostic Criteria for DKA and HHS

Parameter	DKA			HHS
	Mild	Moderate	Severe	
Plasma glucose, mg/dL	>250	>250	>250	>600
Arterial pH	7.25-7.3	7.0-7.24	<7.0	>7.30
Serum bicarbonate, mmol/L	15-18	10 to <15	<10	>15
Serum ketones†	Positive	Positive	Positive	Small
Urine ketones†	Positive	Positive	Positive	Small
Effective serum osmolality,* mOsm/kg	Variable	Variable	Variable	>320
Alteration in sensoria or mental obtundation	Alert	Alert/drowsy	Stupor/coma	Stupor/coma

*Calculation: 2[measured Na^+ (mEq/L)] + glucose (mg/dL)/18.
† Nitroprusside reaction method.

ADA. *Diabetes Care.* 2003;26:S109-S117.

Formulas for Estimating Serum Osmolality and Effective Osmolality

Osmolality

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

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

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

$= \text{Sosm (mosm/Kg } H_2O)$

Effective Osmolality

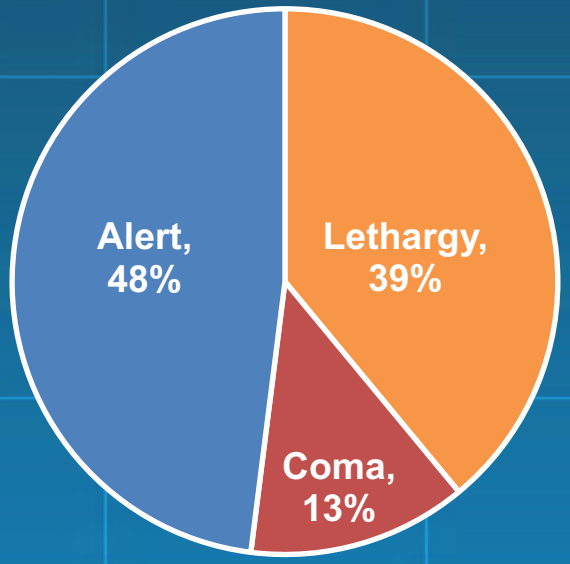
$2 \times [Na^+ \text{ mEq/L}]$

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

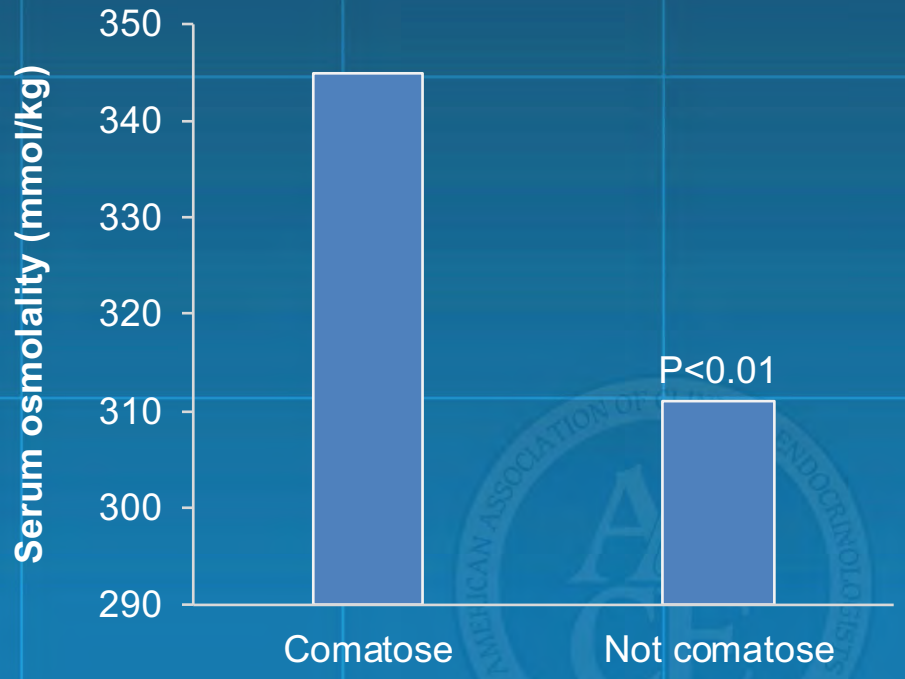
$= \text{Sosm (mosm/Kg } H_2O)$

Mental Status at DKA Presentation

Level of Consciousness



Mental Status and Osmolality



Umpierrez GE, et al. *Arch Intern Med*. 1997;157:669-675.

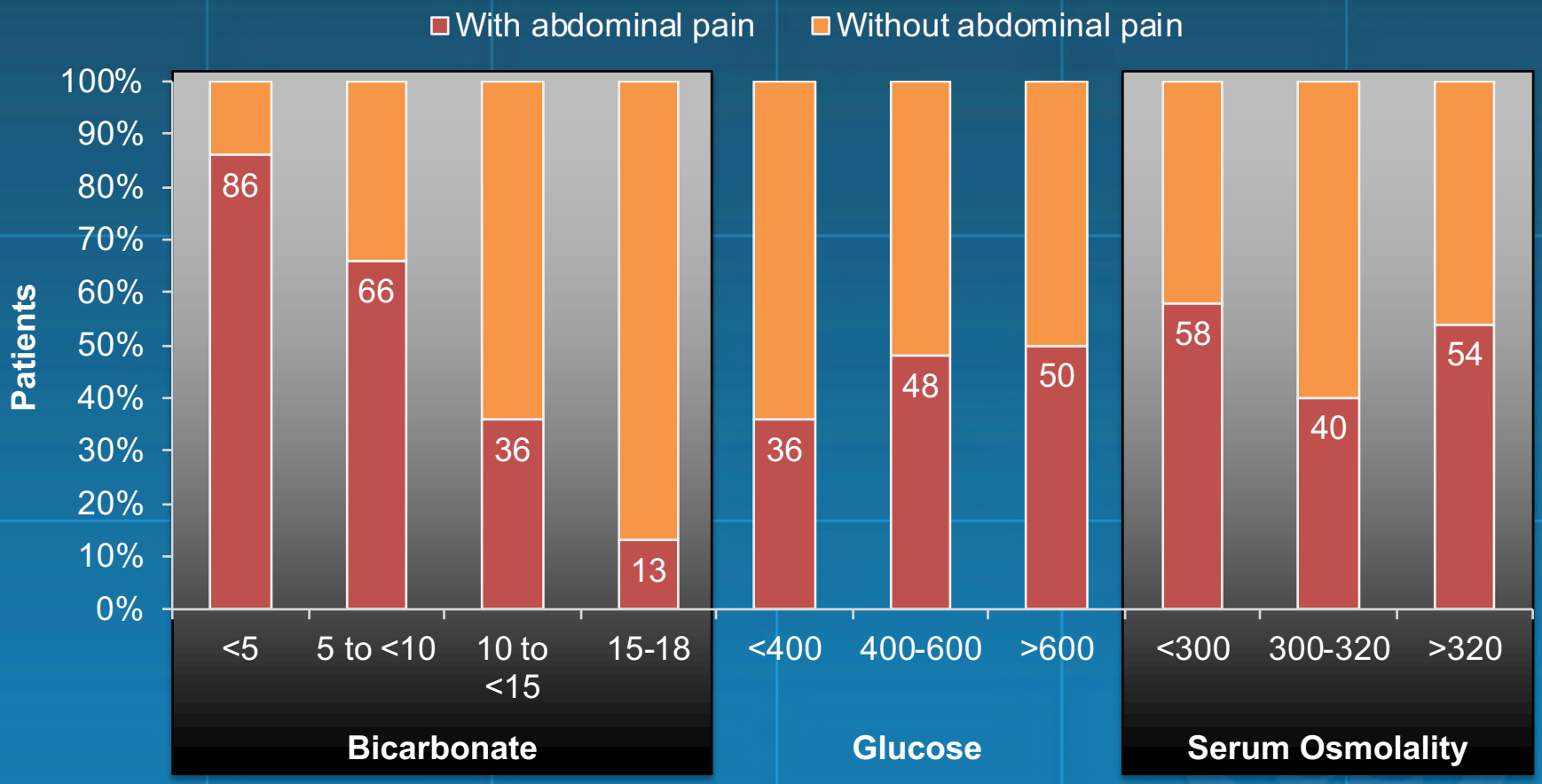
DKA and Abdominal Pain

Characteristic	Presenting With Abdominal Pain (n=86)	Presenting Without Abdominal Pain (n=103)
Age, years	37 ± 1†	41 ± 2
Male gender, n	47	64
History of alcohol use, %	51*	24
History of cocaine use	13‡	2
Blood glucose, mg/dL	596	586
Bicarbonate, mmol/L	9 ± 1*	15 ± 1
Ph	7.12 ± 0.02*	7.24 ± 0.09
Sodium, mmol/L	133 ± 1	133 ± 1
Serum osmolality, mmol/L	307 ± 2	307 ± 2

*$P<0.05$. †$P<0.01$. ‡$P<0.0001$.

Umpierrez G, Freire AX. *J Crit Care*. 2002;17:63-67.

Clinical Characteristics of DKA Patients Presenting With Abdominal Pain



*$P<0.05$. †$P<0.01$. ‡$P<0.0001$.

Umpierrez G, Freire AX. *J Crit Care*. 2002;17:63-67.

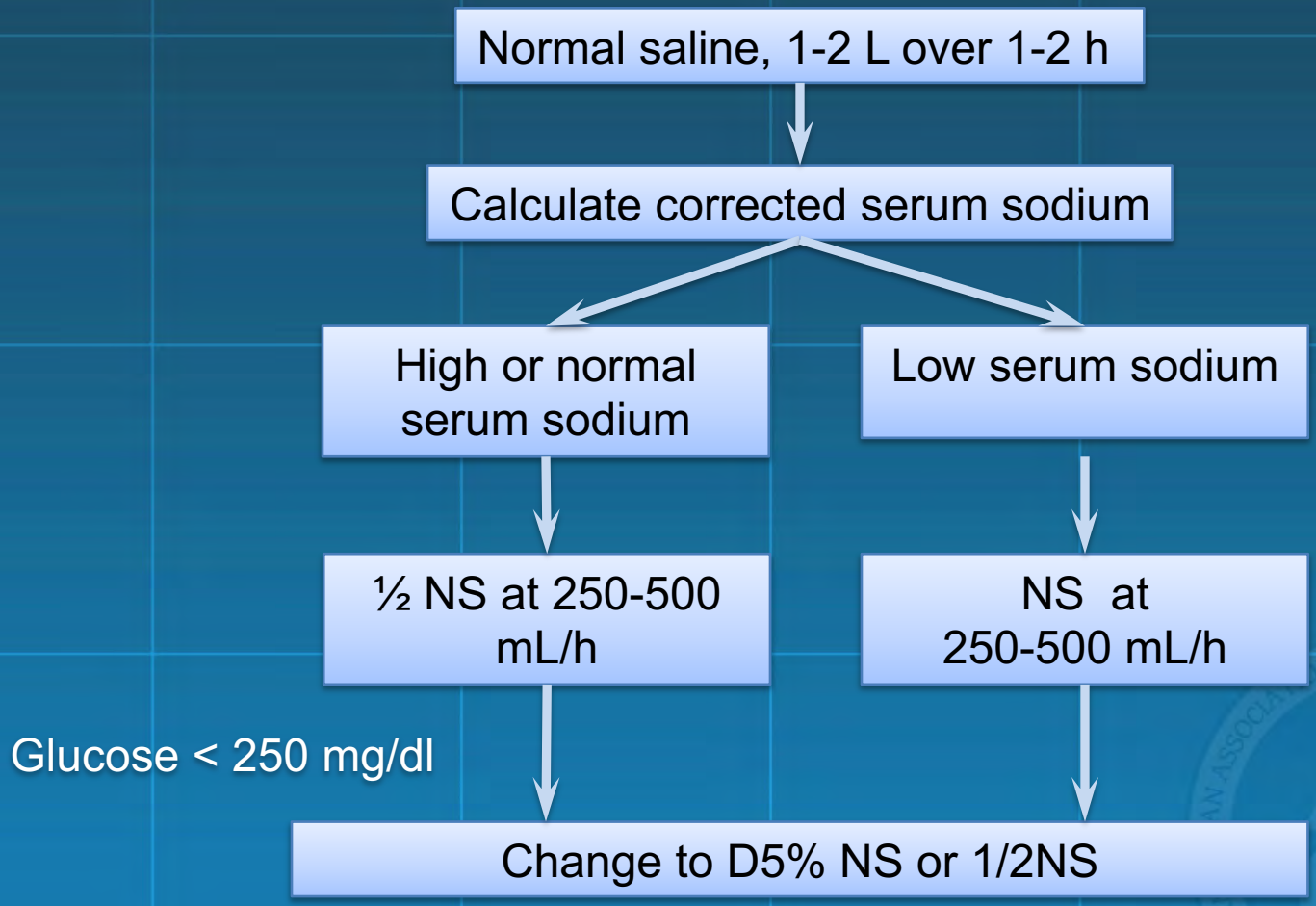
TREATMENT RECOMMENDATIONS

Management of DKA and HHS

- Replacement of fluids losses
- Correction of hyperglycemia/metabolic acidosis
- Replacement of electrolytes losses
- Detection and treatment of precipitating causes
- Conversion to a maintenance diabetes regimen (prevention of recurrence)

Kitabchi AE, et al. *Diabetes Care*. 2009;32:1335-1343.

Fluid Therapy in DKA



ADA. *Diabetes Care.* 2003;26:S109-S117.

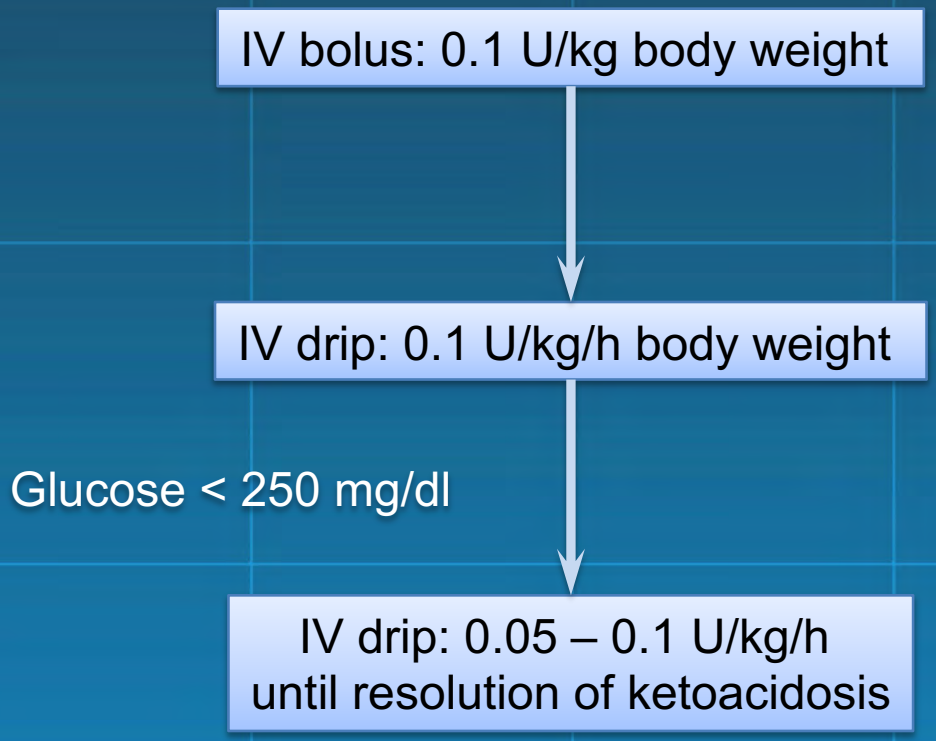
Suggested Initial Rate of Fluid Replacement*

Hours	Volume
1st hour	1000 – 2,000 mL
2nd hour	1000 mL
3rd-5th hours	500 – 1000 mL/hour
6th-12th hours	250 – 500 mL/hour

*Average replacement after initial hemodynamic resuscitation with normal saline when indicated

Chaithongdi N et al. *Hormones* (Athens). 2011;10:250-260.

Intravenous Insulin Therapy in DKA



ADA. *Diabetes Care.* 2003;26:S109-S117.

Potassium Repletion in DKA

- Life-threatening hypokalemia can develop during insulin treatment
- Potassium reenters 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 Replacement

- K^+ = > 5.5 mEq/L: no supplemental is required
- K^+ = 4 - 5 mEq/L: 20 mEq/L of replacement fluid
- K^+ = 3 - 4 mEq/L: 40 mEq/L of replacement fluid

If admission K^+ = <3 mEq/L give 10-20 mEq/h until K^+ >3 mEq/L, then add 40 mEq/L to replacement fluid

ADA. *Diabetes Care.* 2003;26:S109-S117.

Potassium Repletion in DKA

- K^+ >5.2 mEq/L
  - Do not give K^+ initially, but check serum K^+ with basic metabolic profile every 2 h
  - Establish urine output ~50 mL/hr
- K^+ <3.3 mEq/L
  - Hold insulin and give K^+ 20-30 mEq/hr until K^+ >3.3 mEq/L
- K^+ = 3.3-5.2 mEq/L
  - Give 20-30 mEq K^+ in each L of IV fluid to maintain serum K^+ 4-5 mEq/L

Phosphorus Repletion in DKA

- A sharp drop of serum phosphorus can also occur during insulin treatment
- Treatment is usually not required
  - Caregiver can give some K^+ as K^- phos

Bicarbonate Administration

- pH > 7.0: no bicarbonate
- pH < 7.0 and bicarbonate < 5 mEq/L:
  44.6 mEq in 500 mL 0.45% saline over 1 h until pH > 7.0

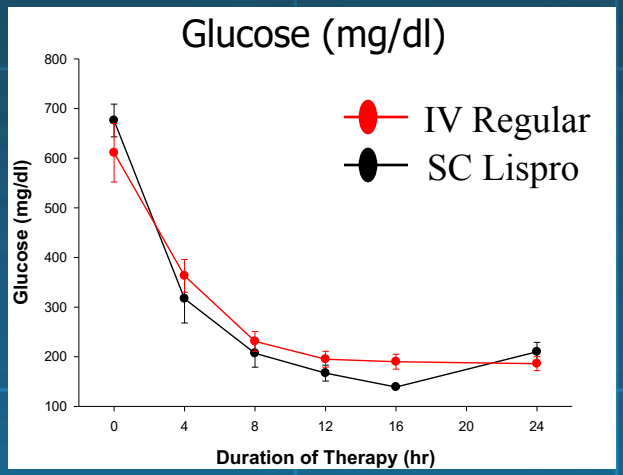
ADA. *Diabetes Care.* 2003;26:S109-S117.

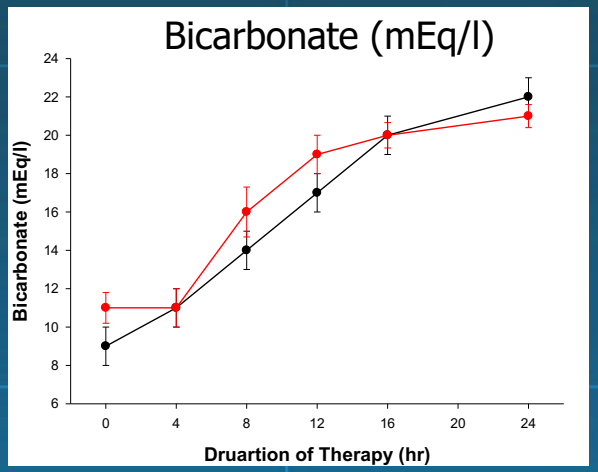
Phosphorus Administration

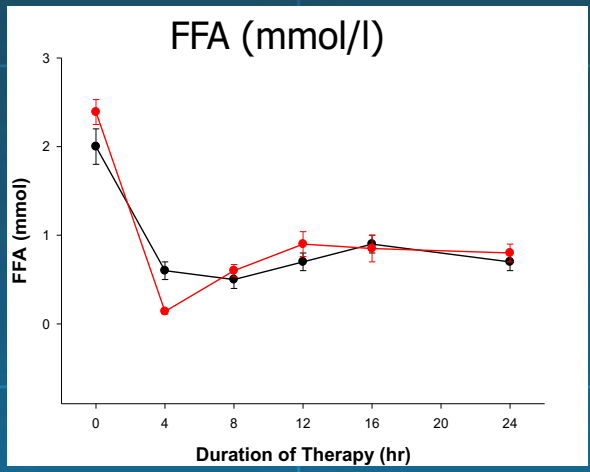
- Not routinely recommended
- If serum phosphorus < 1 mg/dL: 30-40 mmol K-Phos over 24 h
- Monitor serum calcium level

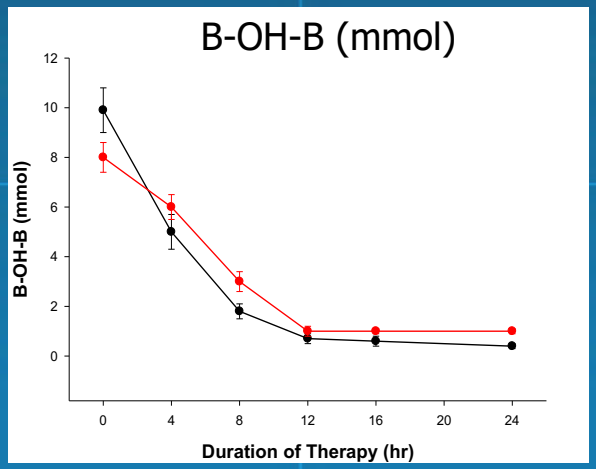
ADA. *Diabetes Care.* 2003;26:S109-S117.

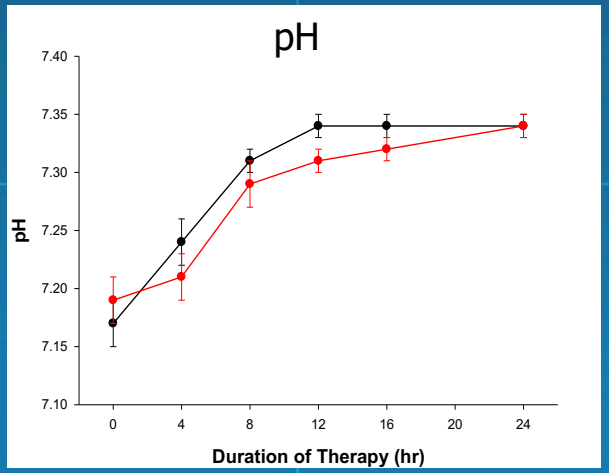
Changes in Metabolic and Acid-Base Parameters During Treatment of DKA

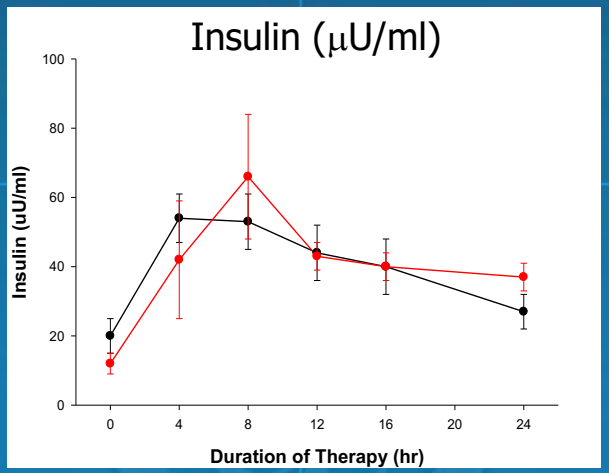












Umpierrez G et al. *Am J Med.* 2004;117:291-296.

Conventional Insulin Guidelines

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

Kitabchi AE, et al. *Diabetes Care*. 2009;32:1335-1343.

Subcutaneous Rapid Acting Insulin or Intravenous Regular Insulin for DKA Treatment

Systematic Review
(N=5 RCTs)

- No substantial difference in time to resolution of DKA between SC lispro or aspart vs IV regular insulin in adults
  - In single study including children and adolescents, DKA resolution slower with SC rapid acting analogs than with IV regular insulin
- Rates of hypoglycemia and duration of hospital stay comparable between rapid acting insulin analogs and regular insulin in adults and children

Andrade-Castellanos CA, et al. *Cochrane Database Syst Rev*. 2016 Jan 21;(1):CD011281.

Subcutaneous Insulin Protocols

Rapid Acting Insulin Every 1 Hour

- Initial dose
  - 0.2 U/kg of body weight, followed by 0.1 U/kg/h
- When BG <250 mg/dL
  - Change IVF to D5%-0.45% saline
  - Reduce rapid acting insulin to 0.05 unit/kg/h
  - Keep glucose ≈ 200 mg/dL until resolution of DKA

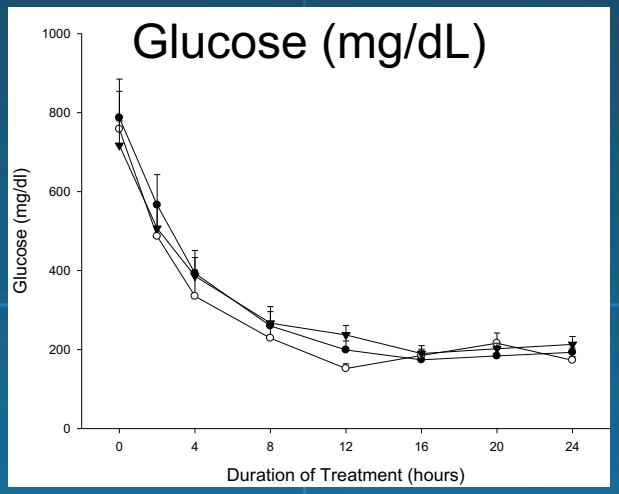
Rapid Acting Insulin Every 2 Hours

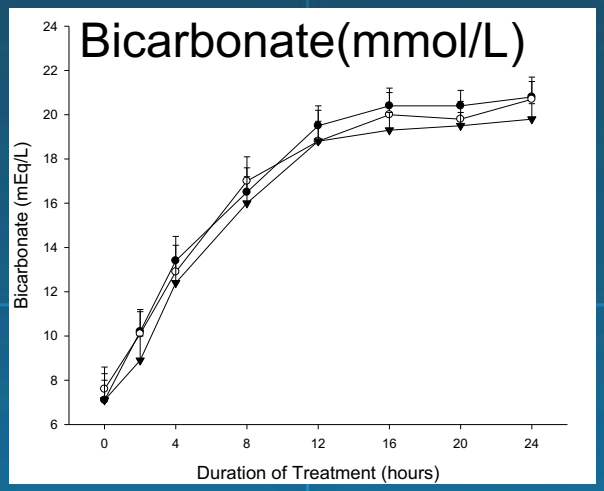
- Initial dose
  - 0.3 U/kg of body weight, followed by 0.2 U/kg 1 h later, then
  - Rapid acting insulin at 0.2 U/kg every 2 h
- When BG <250 mg/dL
  - Change IVF to D5%-0.45% saline
  - Reduce rapid acting insulin to 0.1 U/kg every 2 h
  - Keep glucose ≈ 200 mg/dL until resolution of DKA

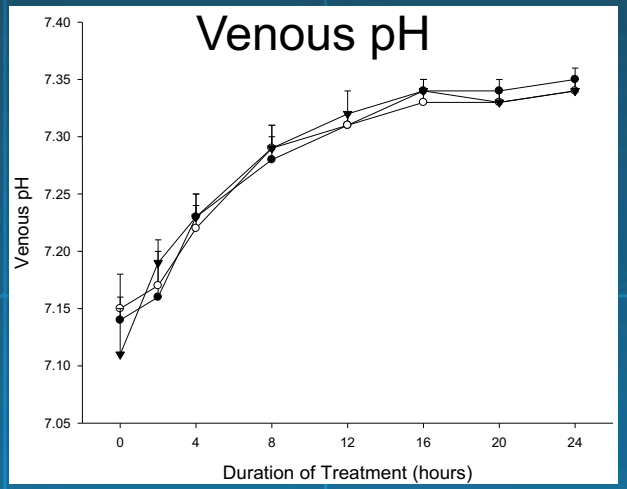
Haw SJ, et al. In: *Managing Diabetes and Hyperglycemia in the Hospital Setting: A Clinician's Guide*. Draznin B, ed. Alexandria, VA: American Diabetes Association; 2016;284-297.

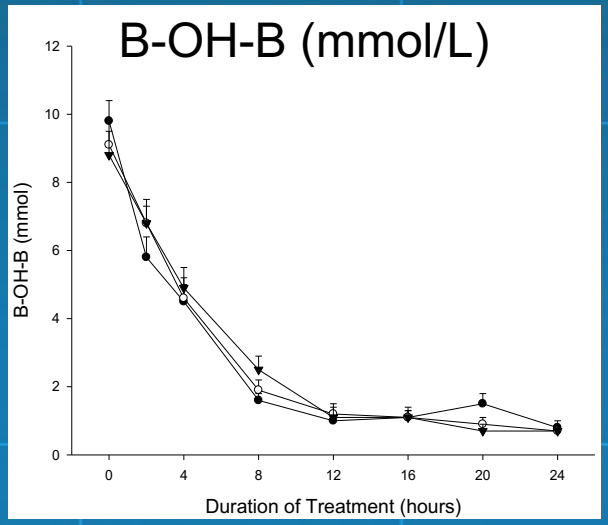
Changes in Metabolic Profile in Patients Treated with Aspart SC-1hr and SC-2hr or with IV Regular Insulin

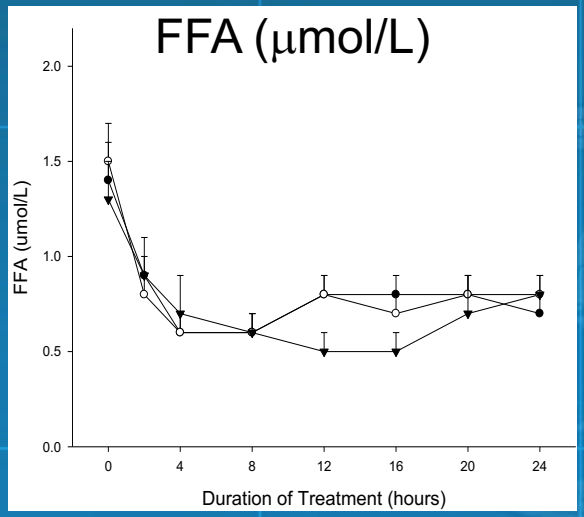
Aspart SC-1hr Aspart SC-2hr Regular IV











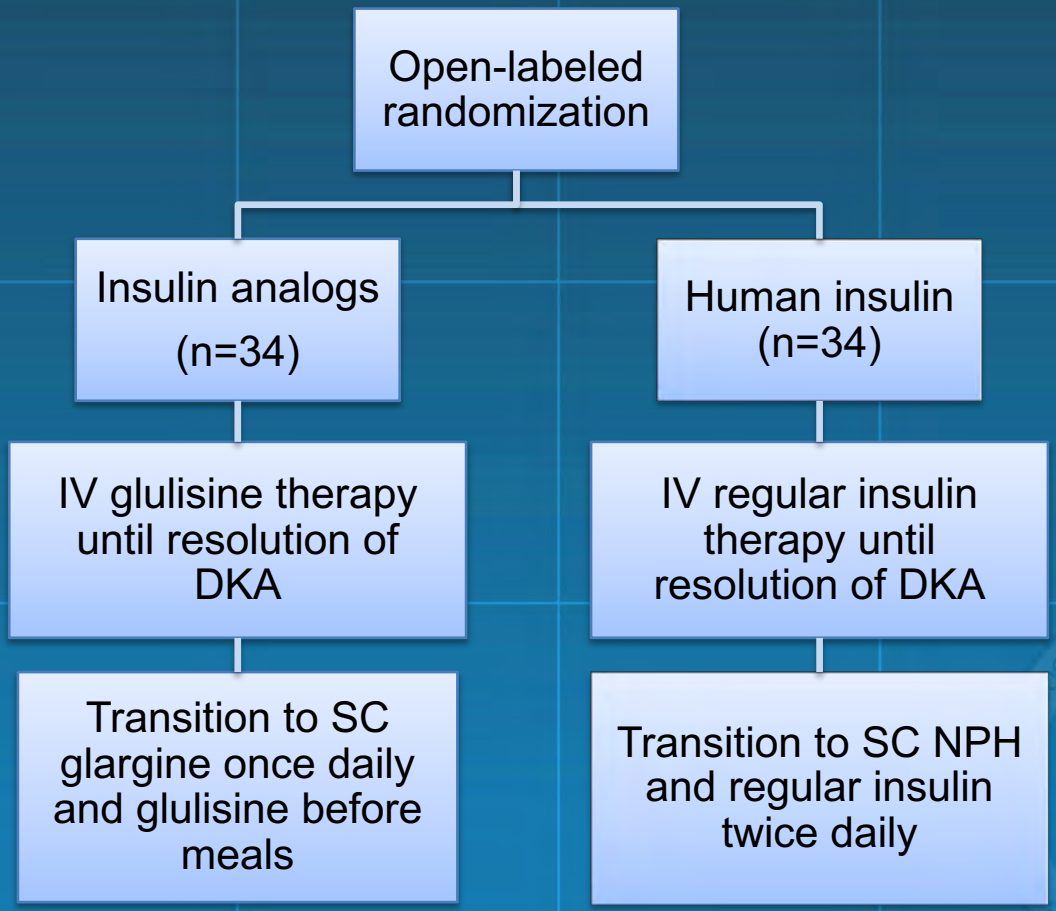
Umpierrez G et al. *Diabetes Care.* 2004;27:1873-1878.

Response to Medical Treatment and Cost of Hospitalization for DKA

	SC aspart Every 1 h	SC aspart Every 2 h	IV regular insulin
Length of stay, days	3.4±0.8	3.9±1.3	4.5±0.8
Duration of therapy until BG <250 mg/dL, h	6.9±1.1	6.1±1.0	7.1±1.0
Duration of therapy until resolution of DKA, h	9.9±0.7	10.7±0.8	11±0.7
Insulin required to reach BG <250 mg/dL, units	67±4	65±7	62±8
Insulin required for resolution of DKA, units	85±4	94±8	82±9
Episodes of hypoglycemia	1	1	1
Hospitalization costs	$10,733±$2017	$10,473±$1738	$16,828±$2563

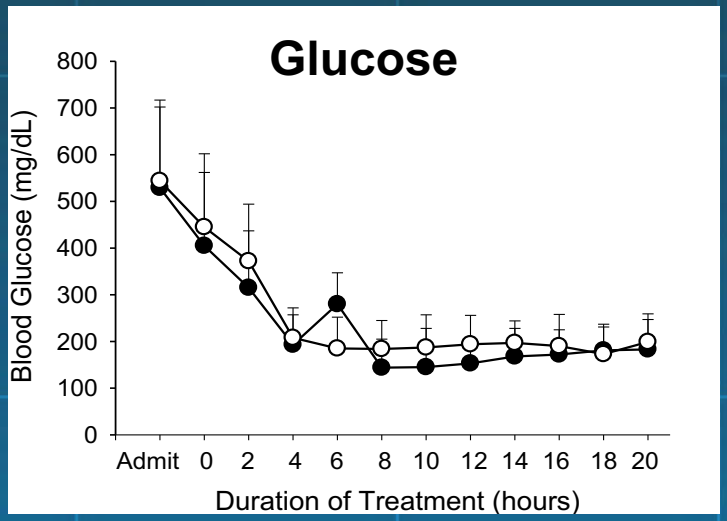
Umpierrez G et al. Presented at 63rd ADA Scientific Sessions, New Orleans, LA; June 14, 2003.

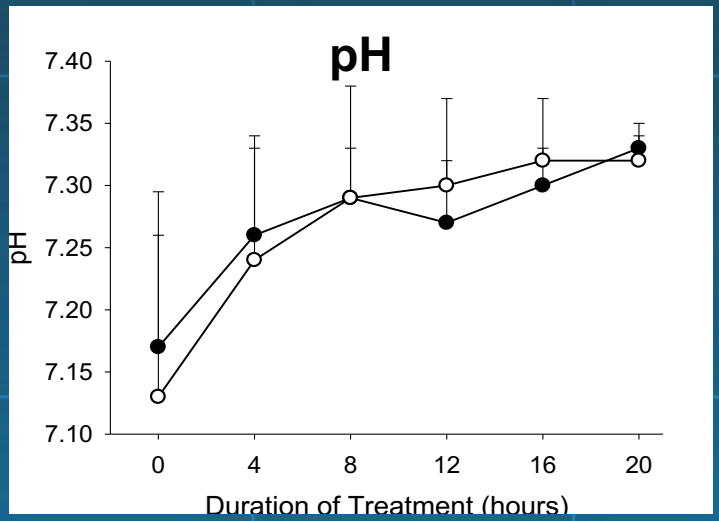
Insulin Analogs vs Human Insulin in the Treatment of Patients with DKA

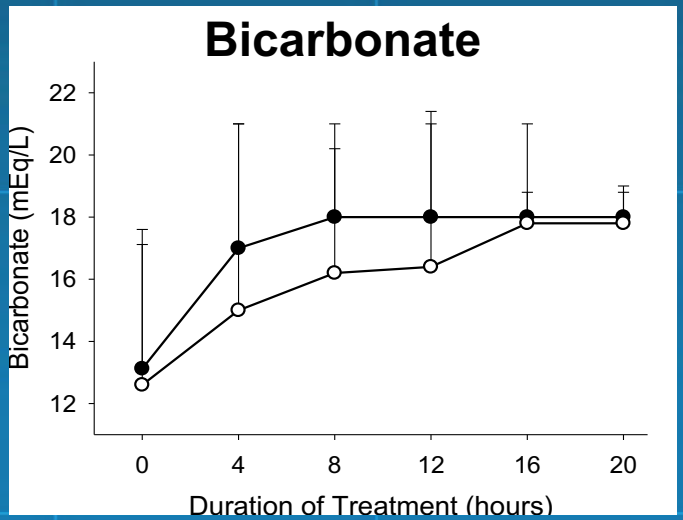


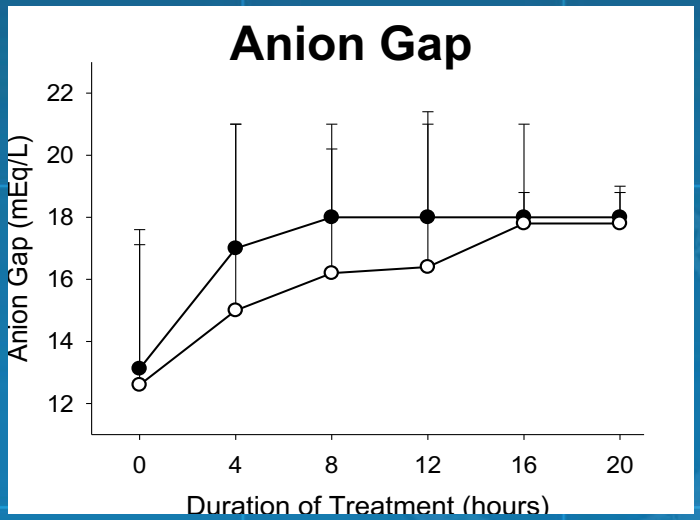
Umpierrez G et al, *Diabetes Care.* 2009;32:1164-1169.

Insulin Glulisine vs Regular Insulin









Umpierrez G et al, *Diabetes Care.* 2009;32:1164-1169.

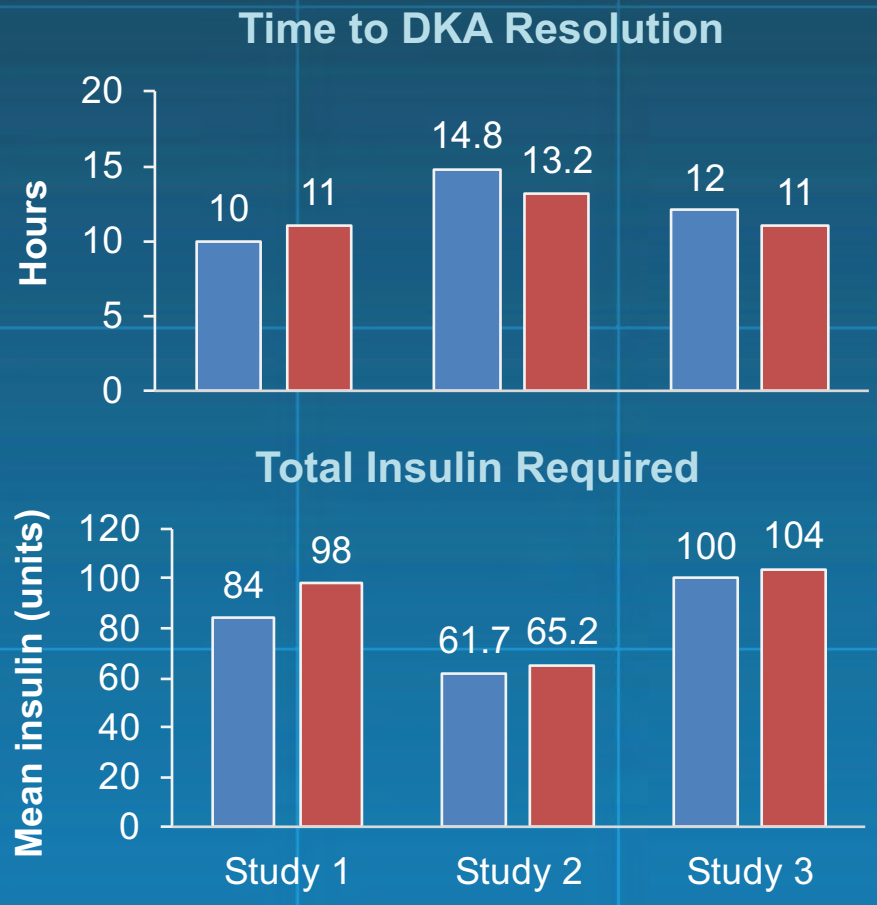
Mean Daily Glucose and Hypoglycemia During Transition to SC Insulin

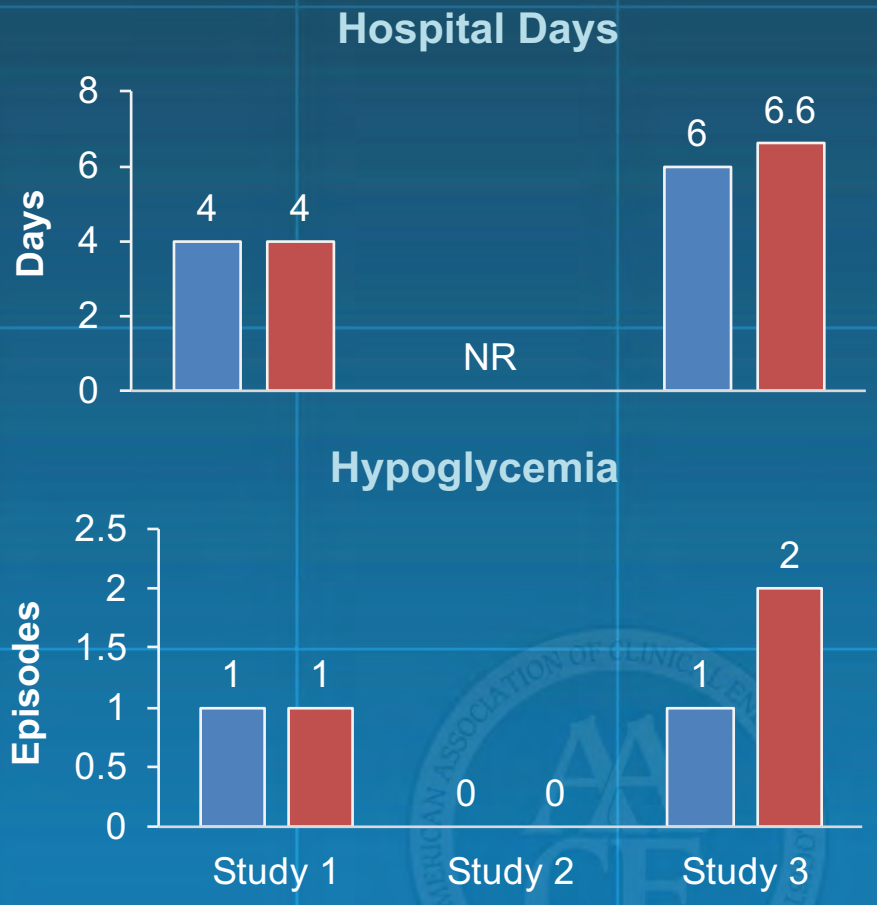
Mean daily glucose	NPH/ regular	Glargine/ glulisine	P value
Day 1	188 ± 61	213 ± 76	0.234
Day 2	206 ± 71	220 ± 61	0.370
Day 3	207 ± 86	180 ± 80	0.417
Day 4	211 ± 63	158 ± 44	0.068
Day 5	190 ± 45	124 ± 41	0.068
Hypoglycemia	**NPH/ regular**	**Glargine/ glulisine**	**P value**
Patients with BG <70 mg/dl, n (%)	14 (41)	5 (15)	0.03
Episodes of BG <70 mg/dl, n	26	8	0.019
Patients with BG <40 mg/dl, n (%)	2 (6)	1 (3)	NS
Episodes of BG <40 mg/dl, n	2	1	NS

Data for glucose levels are means ± SD.

Umpierrez G et al, *Diabetes Care.* 2009;32:1164-1169.

Subcutaneous Lispro vs Intravenous Regular Infusion for DKA





NR, not reported.; Study 1: USA, N=40; Study 2: Turkey: N=20; Study 3: India, N=50.

Vincent M, Nobécourt E. *Diabetes Metab*. 2013;39:299-305.

Rationale for a Dynamic Insulin Protocol for DKA and HHS

- Even with low-dose insulin therapy[1,2]
  - Hypokalemia and hypoglycemia may continue to occur
  - Failure to reduce insulin infusion rate as the blood glucose approaches target may lead to hypoglycemia
- There is a lag between the change in intravenous insulin infusion rate and the resulting effects[3]

1. Umpierrez GE, et al. *Arch Intern Med*. 1997;157:669-675.
2. Burghen GA, et al. *Diabetes Care*. 1980;3:15-20.
3. Mudaliar S, et al. *Diabetes Care*. 2002;25:1597-1602.

A Dynamic Insulin Protocol for DKA

Physician orders for DKA: target blood glucose 150-199 mg/dL until recovery					
Maintenance rate* (units/h)	1.0	2.0	3.0	4.0	6.0
BG mg/dL	**Insulin units/h**	**Insulin units/h**	**Insulin units/h**	**Insulin units/h**	**Insulin units/h**
<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

*Assigned when the blood glucose is close to 184 mg/dL.
DKA, diabetic ketoacidosis.

Devi R, et al. *Diabetes Manage*. 2011;1:397-412. Devi R, et al. *Diabetes Technol Ther*. 2014;16:208-218.

A Dynamic Insulin Protocol for HHS

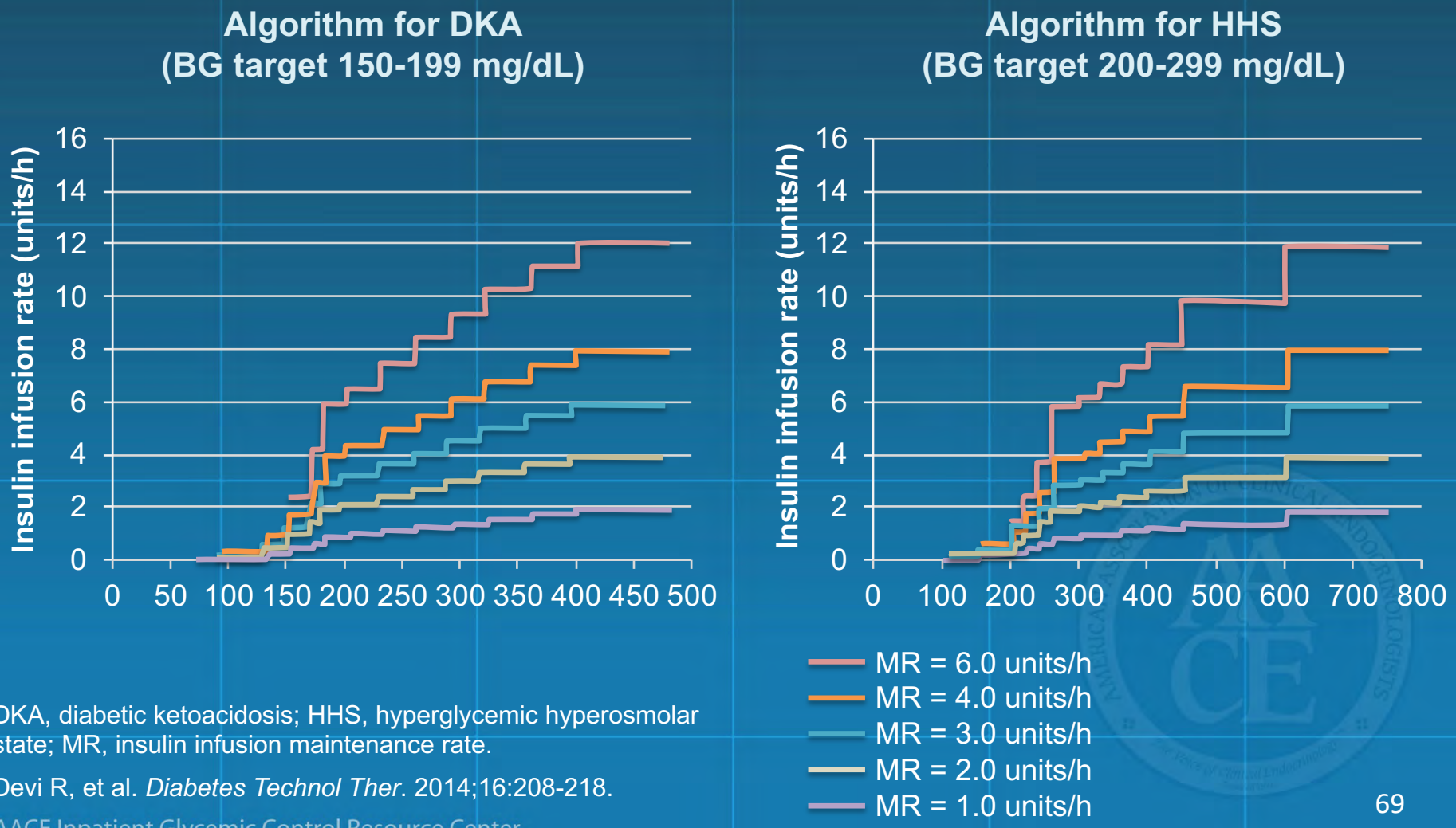
Physician orders for HHS: target blood glucose 200-299 mg/dL until recovery					
Maintenance rate* (units/h)	1.0	2.0	3.0	4.0	6.0
BG mg/dL	**Insulin units/hr**	**Insulin units/hr**	**Insulin units/hr**	**Insulin units/hr**	**Insulin units/hr**
<100	0.1	0.1	0.1	0.1	←
100-149	0.2	0.2	0.3	0.3	←
150-199	0.3	0.5	0.6	0.7	←
200-219	**0.5**	**0.8**	**1.1**	**1.3**	**1.7**
220-239	**0.6**	**1.1**	**1.5**	**1.9**	**2.6**
240-259	**0.8**	**1.5**	**2.1**	**2.7**	**3.9**
260-299	**1.0**	**2.0**	**3.0**	**4.0**	**6.0**
300-329	1.1	2.1	3.2	4.2	6.3
330-359	1.1	2.3	3.4	4.6	6.9
360-399	1.3	2.5	3.8	5.0	7.5
400-449	1.4	2.8	4.2	5.6	8.3
450-599	1.6	3.3	4.9	6.6	9.9
≥600	2.0	4.0	6.0	8.0	12.0

*Assigned when the blood glucose is close to 271 mg/dL.
HHS, hyperglycemic hyperosmolar state.
Devi R, et al. *Diabetes Manage.* 2011;1:397-412. Devi R, et al. *Diabetes Technol Ther*. 2014;16:208-218.

Continuation of physician orders for DKA and HHS
Initiation of insulin drip, monitoring of BG, and termination of insulin drip
Initiate IV insulin infusion using selected or default column assignment. Reassignment to a higher column before 4 hours of treatment requires an MD order. If BG fails to fall each hour during hrs 1-4, notify MD
Adjust column assignment for DKA or HHS based on column change rules, and adjust drip rate based on BG level
Measure BG every 1 hour (fingerstick or capillary blood sample using point-of-care glucose monitor)
If BG is within target range x 4hrs, then measure BG q 2 h. If column reassignment occurs, measure q 1 h
Record BG results, insulin drip rate changes, and column reassignments on the ICU flow sheet
Obtain order for SQ insulin to be administered q 1-2 h before discontinuing IV insulin
Algorithm for order to treat patient if BG <70 mg/dL
If BG is <70 mg/dL, administer 25 ml of D50 by IV
Adjust column assignment to next lower column and use pretreatment BG to assign row
Recheck BG in 5 minutes. If BG is <70 mg/dL, repeat administration of 25 ml of D50 by IV
Column change rules after 4 hours of treatment of DKA
If BG ≥200 mg/dL and not falling after 3 successive hourly tests (or for 2 h) on the same column, move to next higher column
If BG <180 mg/dL after 3 successive hourly tests (or for 2 h) on the same column during infusion of fluids containing D5W, or if any BG <150 mg/dL, move to next lower column
Column change rules after 4 hours of treatment of HHS
If BG ≥300 mg/dL and not falling after 3 successive hourly tests (or for 2 h) on the same column, move to next higher column
If BG <280 mg/dL after 3 successive hourly tests (or for 2 h) on the same column during infusion of fluids containing D5W, or if any BG <200 mg/dL, move to next lower column

Devi R, et al. *Diabetes Manage.* 2011;1:397-412.

Dynamic Insulin Infusion Rates as a Function of Blood Glucose



DKA, diabetic ketoacidosis; HHS, hyperglycemic hyperosmolar state; MR, insulin infusion maintenance rate.

Devi R, et al. *Diabetes Technol Ther*. 2014;16:208-218.

Transition to Subcutaneous Insulin After Resolution of DKA

After Initial IV or SC therapy
(pH>7.3, HCO3 >18, AG < 14)

↓

Give SC basal insulin 2–4 hours before stopping IV insulin

↓

Start multi-dose insulin (basal bolus) regimen

- Insulin analogs are preferred over human insulin
  - Basal: glargine or detemir
  - Rapid-acting insulin analogs (lispro, aspart, glulisine)
- Analogs result in similar blood glucose control but less hypoglycemia than human insulin (15% vs 41%)

↓

Use early glargine insulin during treatment of DKA may prevent rebound hyperglycemia during insulin infusion

Umpierrez G, Korytkowski M. *Nat Rev Endocrinol*. 2016;12:222-232.

When to Transition From IV Insulin Infusion to SC Insulin

DKA

- BG <200 mg/dL and 2 of the following
  - HCO_3 ≥15 mEq/L
  - Venous pH >7.3
  - Anion gap ≤12 mEq/L

HHS

- Normal osmolality and regaining of normal mental status
- Allow an overlap of 1-2 h between subcutaneous insulin and discontinuation of intravenous insulin

Kitabchi AE, et al. *Diabetes Care*. 2009;32:1335-1343.

Cerebral Edema

- Cerebral edema is a dreaded complication of DKA in childhood[1]
- Mortality may be 24%, with significant morbidity among survivors[2]
- One pediatric study found that rates of fluid administration and insulin administration were not associated with cerebral edema[3]
- In another case control pediatric study, insulin dose in first 2 h was significantly associated with the risk of cerebral edema[4]

1. Muir AB, et al. *Diabetes Care.* 2004;27:1541-1546. 2. Edge JA, et al. *Arch Dis Child*. 2001;85:16-22.
3. Glaser N, et al. *N Engl J Med.* 2001;344:264-269. 4. Edge J, et al. *Diabetologia*. 2006;49:2002-2009.

Fluid and Electrolyte Management in HHS

- Treatment of HHS requires more free water and greater volume replacement than needed for patients with DKA
- To avoid heart failure, caution is required in the elderly with preexisting heart disease
- Potassium
  - Usually not significantly elevated on admission (unless in renal failure)
  - Replacement required during treatment

DKA Management Pitfalls

- Not assessing for and/or treating underlying cause of the DKA
- Not watching K^+ closely enough and/or not replacing K^+ aggressively enough
- Following serial serum ketone concentrations
- Following serum bicarbonate instead of the anion gap, with misinterpretation of expansion acidosis as “persistent ketoacidosis”
- Interrupting IV insulin too soon (eg, patient not yet eating, anion gap not yet closed)

DKA Management Pitfalls

- Occurrence of rebound ketosis consequent to inadequate insulin dosing at transition (eg, failure to give SC insulin when glucose is “low” or injudicious use of sliding scale insulin)
- Inappropriate extension of hospitalization to “fine-tune” an outpatient regimen
- Inadequate patient education and training
- Inadequate follow-up care

FINDING THE CAUSE AND PREVENTING RECURRENCE

Possible Precipitating Causes or Factors in DKA: Type 1 Diabetes

- Nonadherence to insulin regimen or psychiatric issues
- Insulin error or insulin pump malfunction
- Poor “sick-day” management
- Infection (intra-abdominal, pyelonephritis, flu)
- Myocardial infarction
- Pancreatitis
- Other endocrinopathy (rare)
- Steroid therapy, other drugs or substances

Possible Precipitating Causes or Factors in DKA: Type 2 Diabetes

- Nonadherence to medication regimen
- Poor “sick-day’ management
- Dehydration
- Renal insufficiency
- Infection (intra-abdominal, pyelonephritis, flu)
- Myocardial infarction, stroke
- Other endocrinopathy (rare)
- Steroid therapy, other drugs or substances

DKA and SGLT2 Inhibitor Therapy

AACE Recommendations

Findings

- In T1D and T2D, metabolic changes shift substrate metabolism from carbohydrate to fat metabolism, predisposing patients to development of ketonemia and DKA during SGLT2 inhibitor use
- Normal or modestly elevated BG does not exclude the diagnosis of DKA during SGLT2 inhibitor use

Recommendations

- Stop SGLT2 inhibitor immediately
  - Symptoms of DKA
  - Emergency surgery
- Stop SGLT2 inhibitor ≥24 hours before
  - Planned invasive procedures
  - Anticipated stressful physical activity (eg, marathon)
- Measure blood rather than urine ketones for DKA diagnosis
- Advise patients taking SGLT2 inhibitors to avoid excess alcohol and low-carbohydrate/ ketogenic diets

Handelsman Y, et al. *Endocr Pract*. 2016;22:753-762.

Predischarge Checklist

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

Education in Type 1 Diabetes to Prevent DKA

- Recognize symptoms and findings that require contact with a healthcare 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
  - Transition to long-term therapy
- Patient education and discharge planning should aim at prevention of recurrence