Endocrine Emergencies

David DeAtkine, Jr., MD, F.A.C.E.

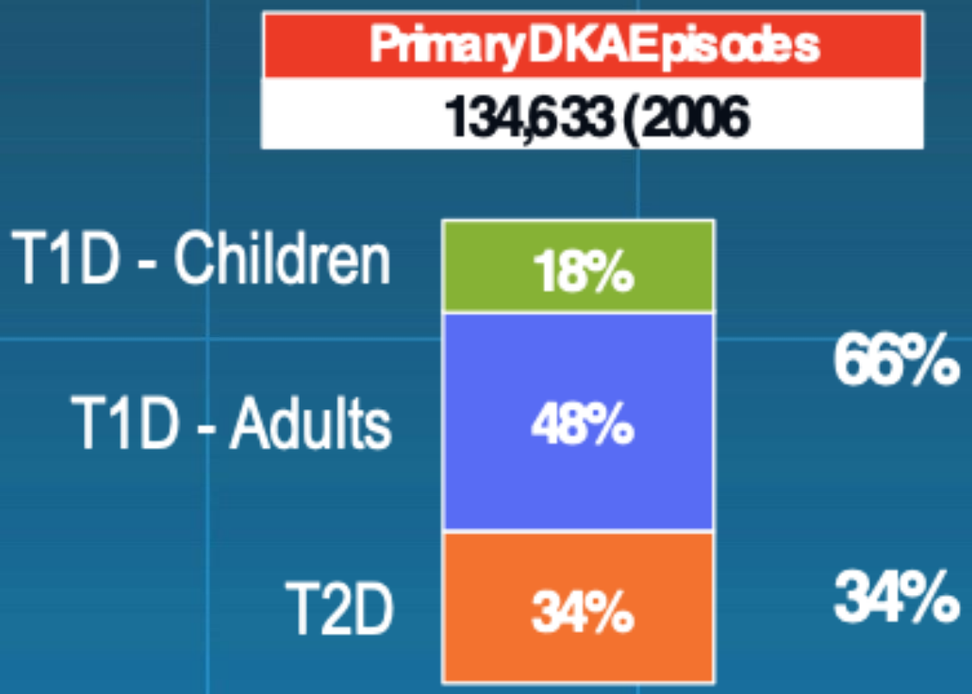
Review:

- DKA
- Myxedema Coma
- Thyroid Storm
- Acute Adrenal Insufficiency
- Pituitary Apoplexy
- Hypercalcemic Crisis
- Hypocalcemia

Diabetic Ketoacidosis

- -characterized by: Ketosis, Acidosis, and Hyperglycemia
- in the era of SGLT-2 inhibitors, ketoacidosis can occur in the setting of near normoglycemia, and unexpectedly, in T2DM

Type 1 Diabetes Accounts for the Majority of Primary DKA Episodes



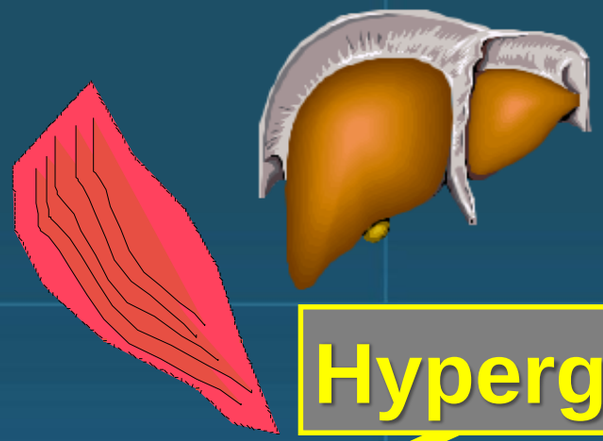
- 34% of episodes are Type 2
  ⇒*~46,000 cases*
- ⇒Longer Hospital Stays
  ⇒*4.2 vs average of 3.5*
- Very few have CV issues or serious infections ⇒*Less than 15%*

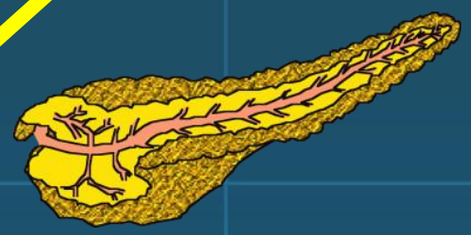
T2D accounts for 34% of primary DKA cases and more than 50% of secondary causes

National Hospital Discharge Survey. 2006.

PATHOGENESIS AND PATHOPHYSIOLOGY

Insulin Deficiency



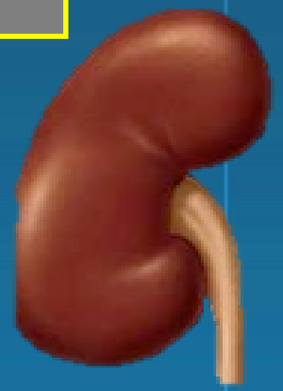


Hyperglycemia

Hyper-osmolality

Δ MS

Glycosuria



Dehydration

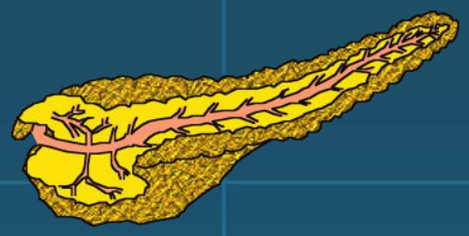
Renal Failure

Shock

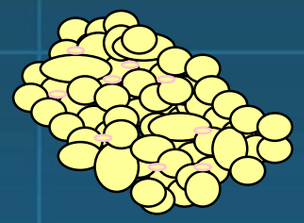
Electrolyte Losses

CV Collapse

Insulin Deficiency



Lipolysis



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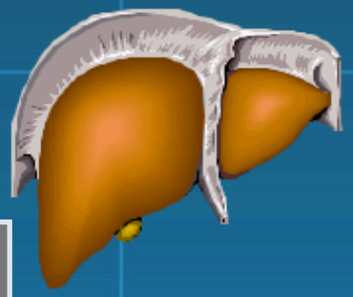
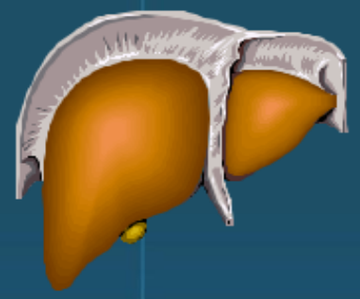


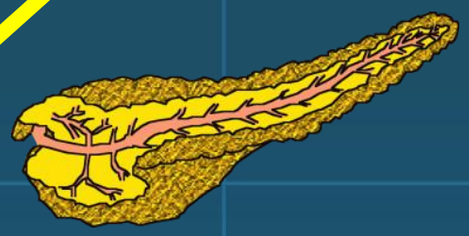
Ketones

Acidosis

CV Collapse

Insulin Deficiency





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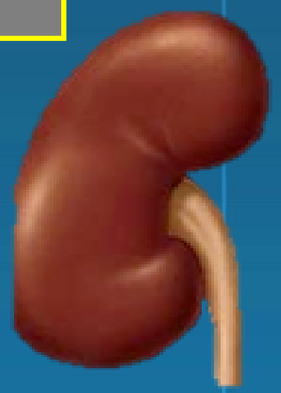

Dehydration

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Shock

Electrolyte Losses

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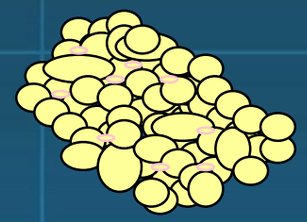

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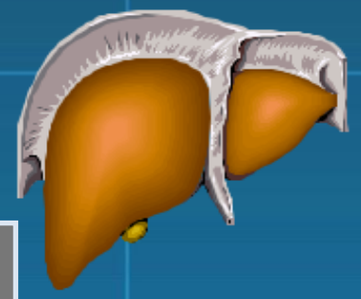


Ketones

Acidosis

CV Collapse

Diabetic Hyperglycemic Crises

overlapping syndromes

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

FOCUS ON ACIDOSIS

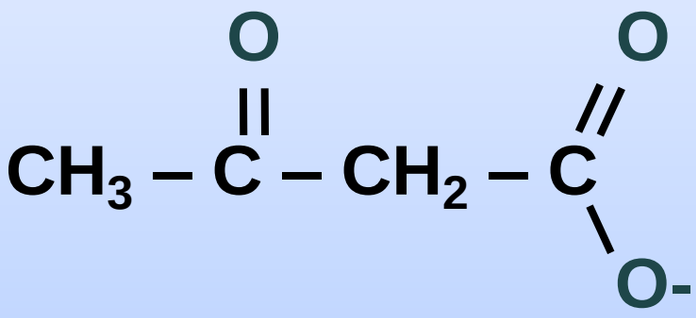
Anion Gap Metabolic Acidosis

- 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

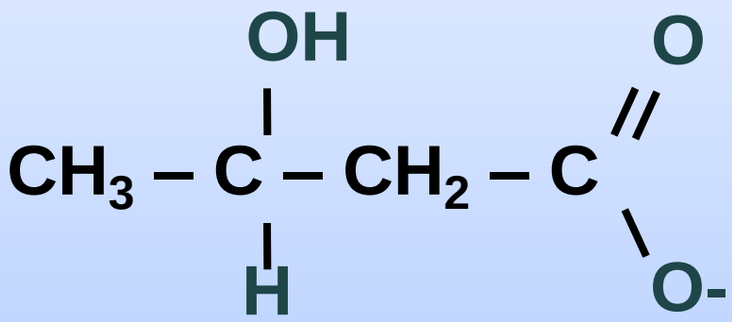
Hyperchloremic Metabolic Acidosis (Non-anion Gap)

- 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

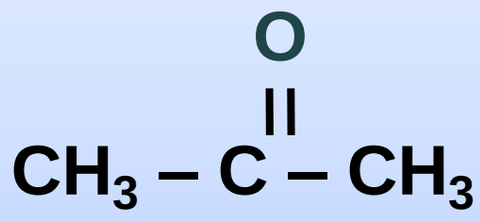
Ketone Bodies in DKA



Acetoacetate



®-Hydroxybutyrate

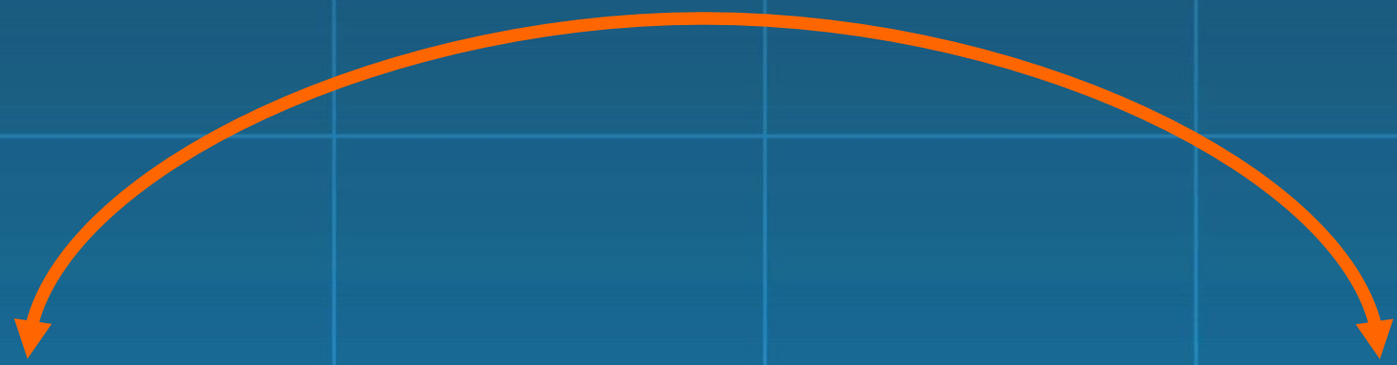


Acetone

- Unless ®-hydroxybutyrate (®-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

AcAc ⇌ ®-OH B



$NADH + H^+$ NAD^+

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

Significance of Ketone Measurements

- ®-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

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…EXCEPT in the case of SGLT-2 use!!
  - 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 ®-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

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.

Formulas for Estimating Serum Osmolality and Effective Osmolality

Osmolality

2 x [Na^+ mEq/L]

+ [glucose mg/dL] / 18

+ [BUN mg/dL] / 2.8

= Sosm (mosm/Kg H_2O)

Effective Osmolality

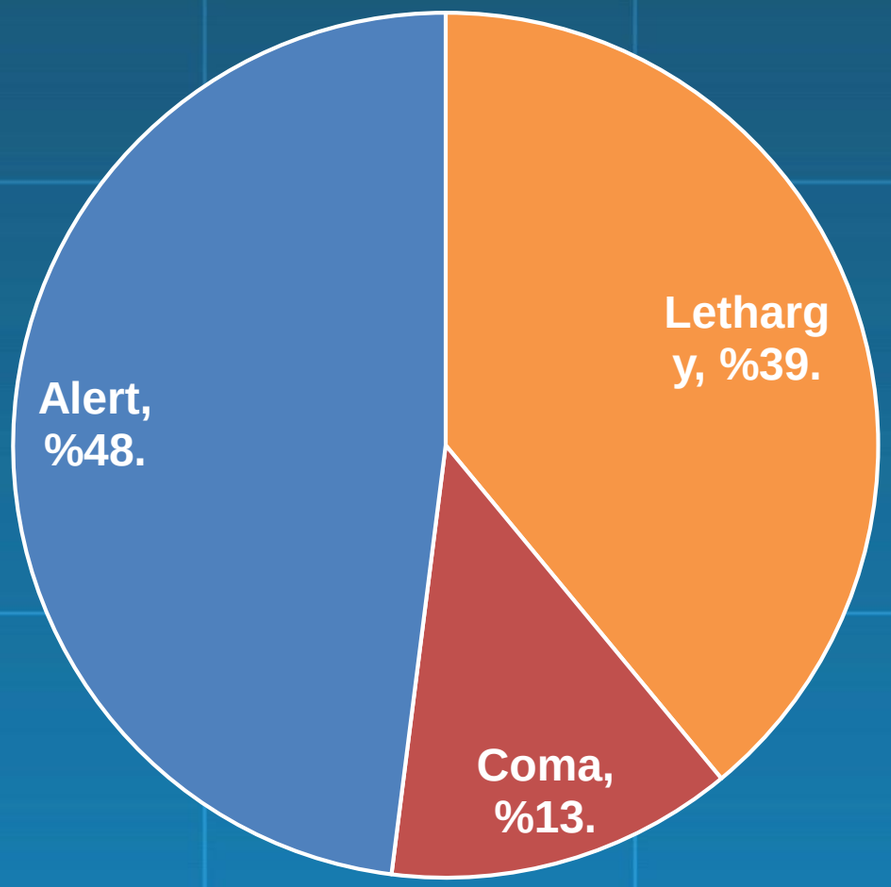
2 x [Na^+ mEq/L]

+ [glucose mg/dL] / 18

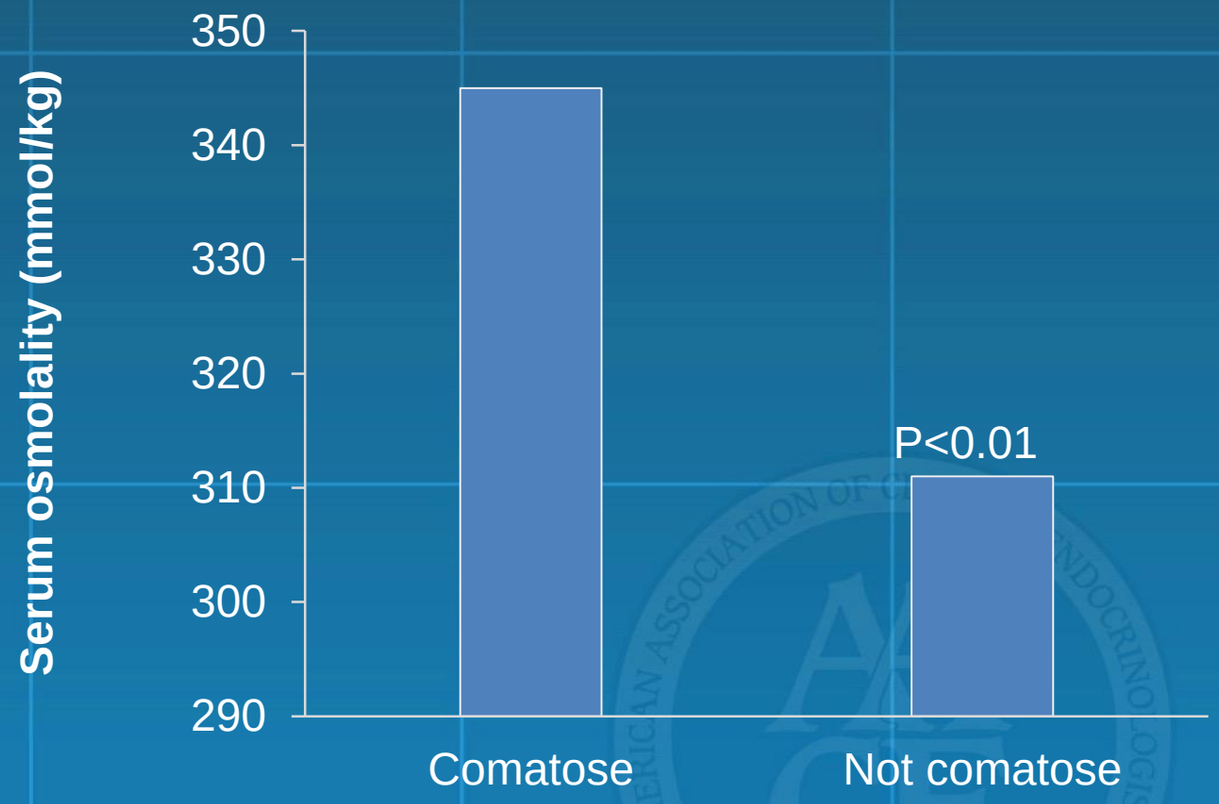
= Sosm (mosm/Kg H_2O)

Mental Status at DKA Presentation

Level of Consciousness



Mental Status and Osmolality



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

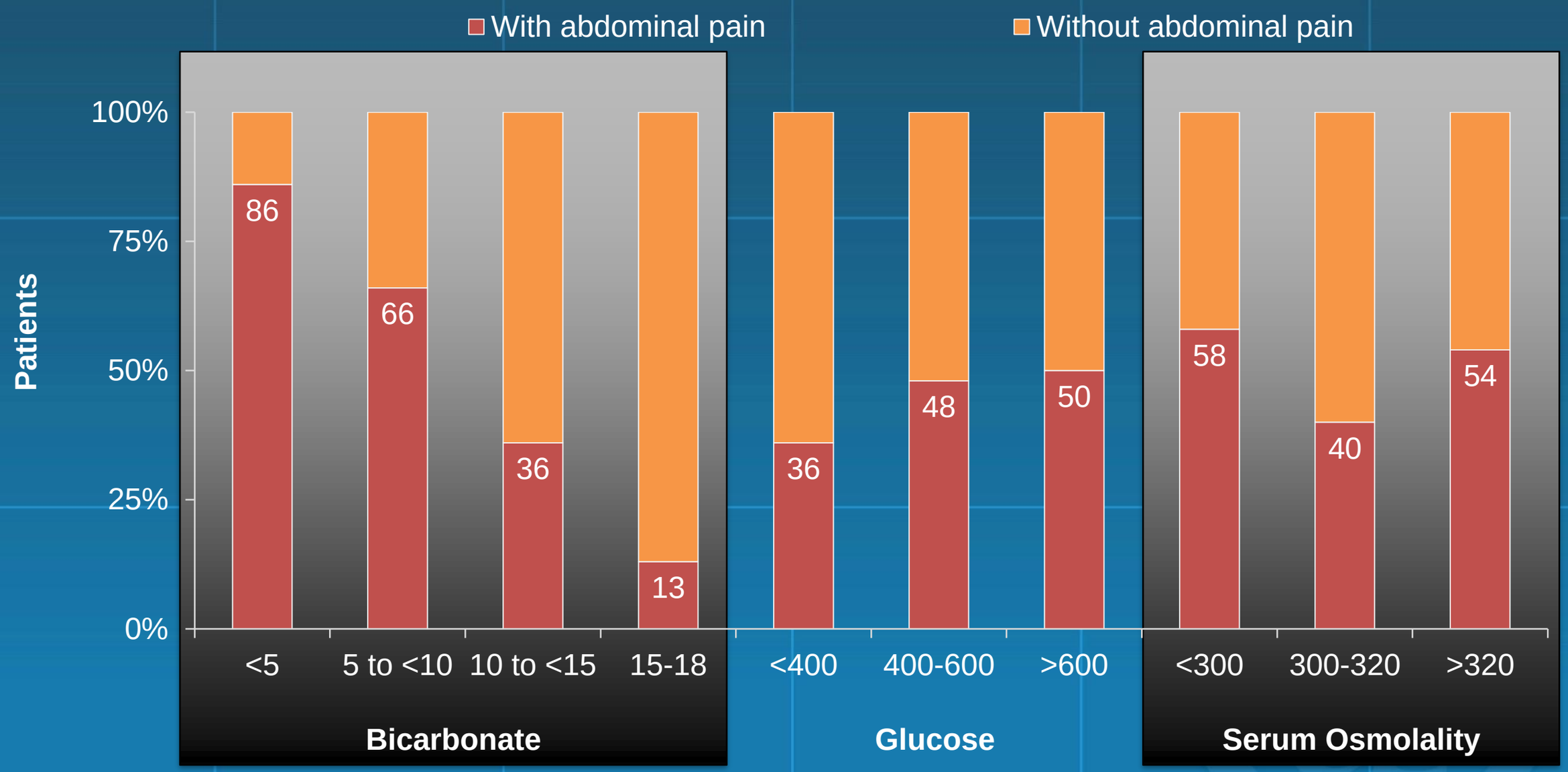
DKA and Abdominal Pain

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.

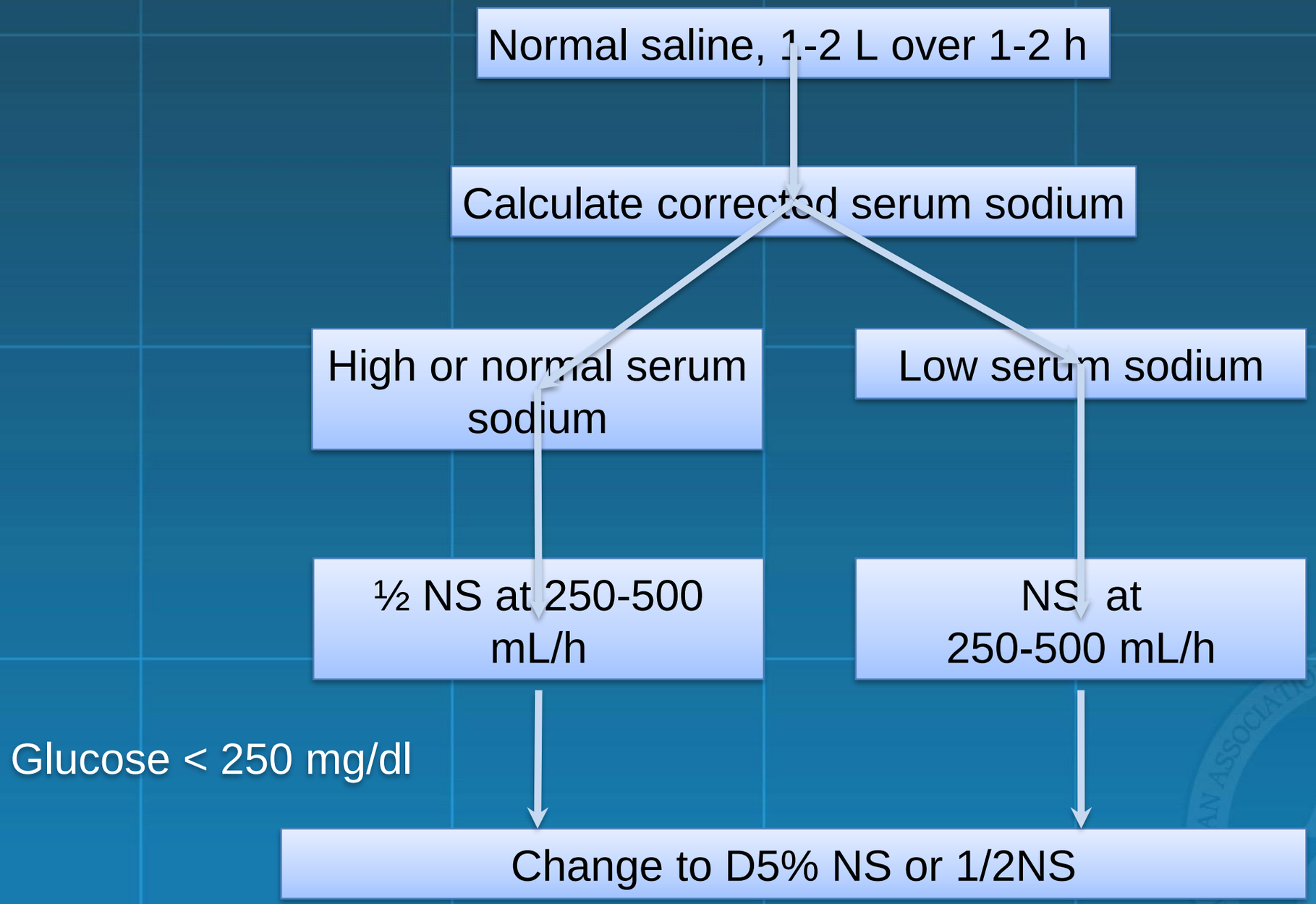
TREATMENT RECOMMENDATIONS

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

IV bolus: 0.1 U/kg body weight

IV drip: 0.1 U/kg/h body weight

Glucose < 250 mg/dl

IV drip: 0.05 – 0.1 U/kg/h
until resolution of ketoacidosis

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

St Vincent's System

- implementing a system wide protocol using ADA clinical guidelines
- IV insulin initiated at 0.1 u/kg/hr
- bolus IV insulin based on sliding scale and hourly blood glucose checks

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.

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.

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)
- Inadequate patient education and training
- Inadequate follow-up care

Precipitating Factors

- infection (pneumonia, gastroenteritis, UTI, skin and soft tissue, periodontal, perirectal)
- MI, CHF
- stress, physiologic or psychologic
- noncompliance
- sedation due to other drugs
- SGLT-2 inhibitors (?glucagon or catecholamine excess)

Myxedema coma

Myxedema Coma

- End stage of untreated or insufficiently treated hypothyroidism
- Typical clinical picture:
  - Elderly obese (female more common than male)
  - increasingly withdrawn, lethargic, sleepy, confused
  - Slips into a coma
- History:
  - Previous thyroid surgery
  - Radioiodine
  - Default thyroid hormone therapy

Precipitating Events

Myocardial infarction

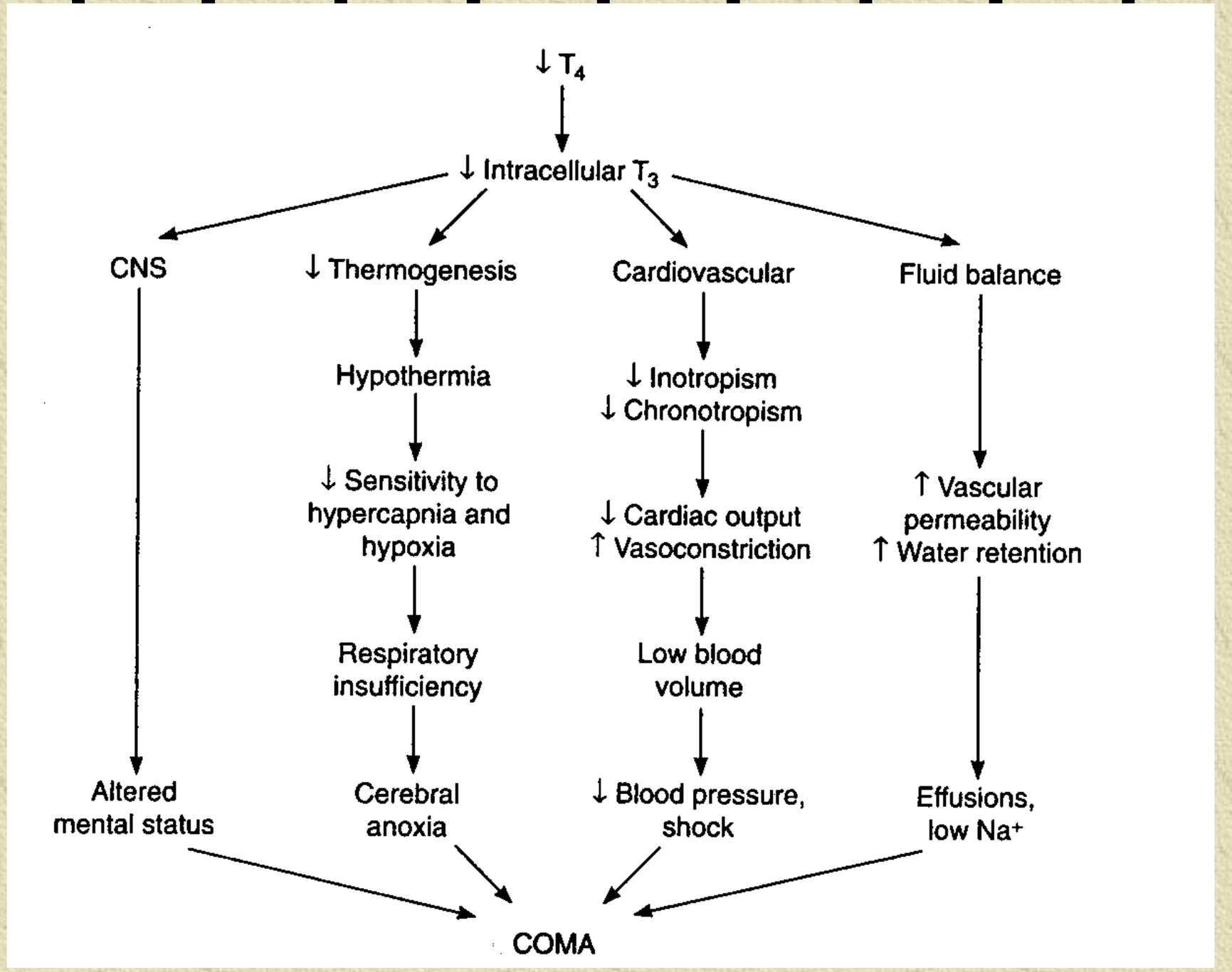
Infection
- UTI
- Pneumonia

Gastrointestinal hemorrhage

Acute trauma

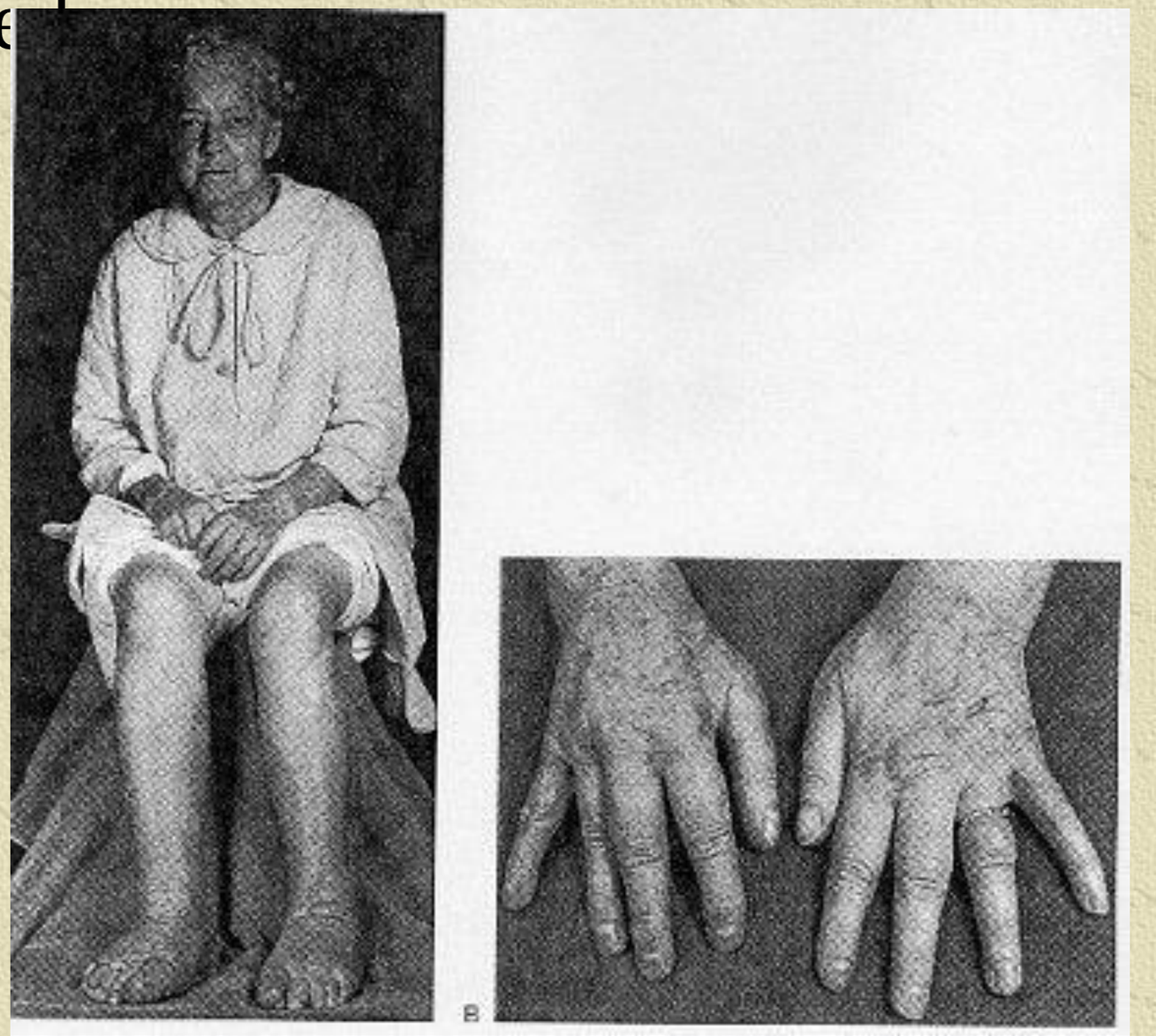
Administration of sedative, narcotic or potent diuretics

Pathogenesis of Myxedema



Physical Findings

- Comatose or obtunde
- Dry coarse skin
- thick tongue
- Hoarse voice
- Thin dry hair
- Delayed reflex relaxation time
- Hypothermia
- Pericardial, pleural effusions, ascites



Lab Tests

FT4 low, FT3 low and TSH high

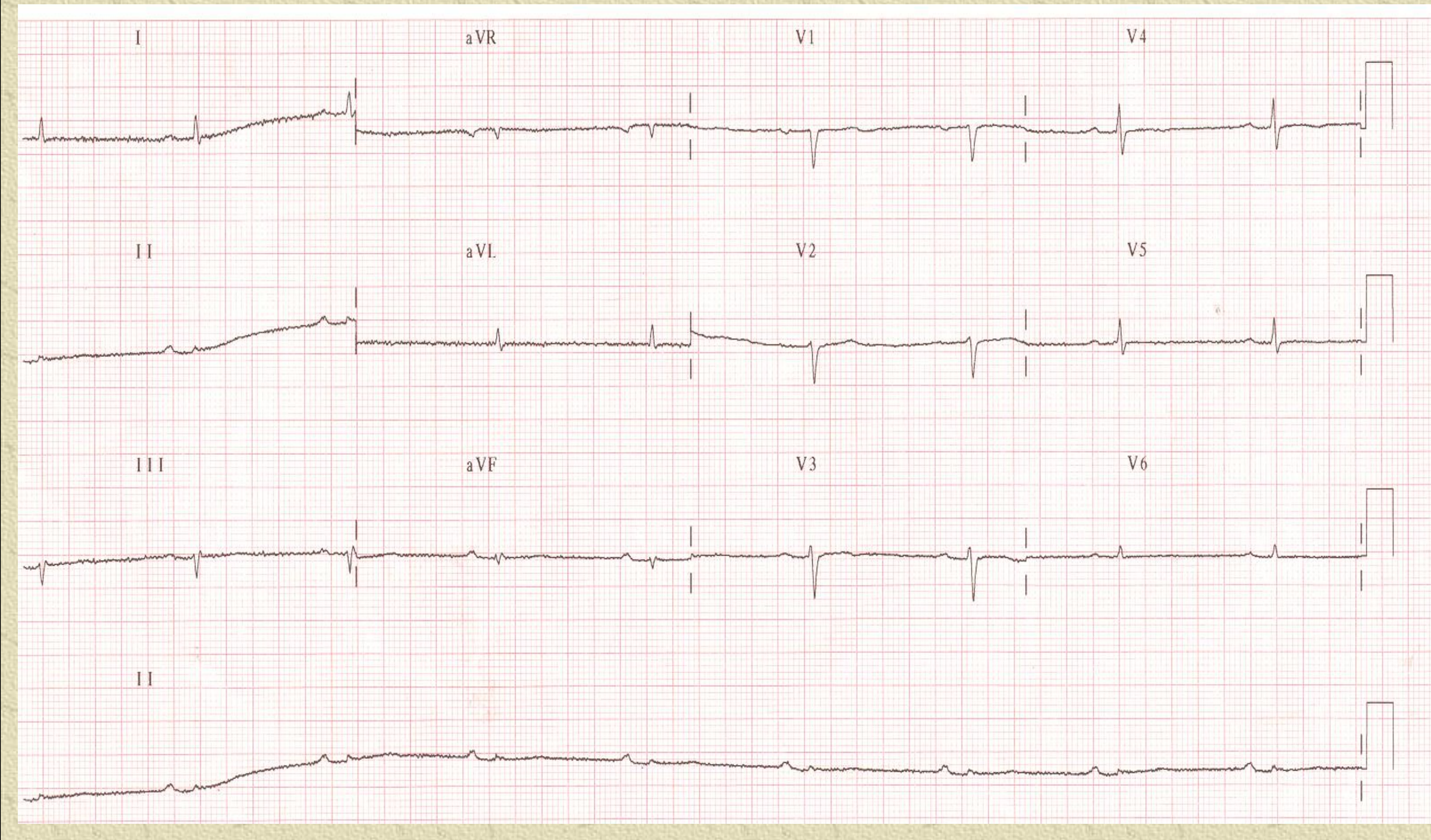
If the T4 is low and TSH low normal consider pituitary hypothyroidism

Blood gasses

Electrolytes and creatinine

Distinguish from euthyroid sick syndrome
Low T3, Normal or low TSH, normal free T4

ECG in Patient with Myxedema Coma



Management of Myxedema (1)

ICU admission may be required for ventilatory support and IV medications

Parenteral thyroxine (expensive)

Loading dose of 300 – 400 µg

Then 50-100µg daily

at St Vincent's — 3 day course

Electrolytes

consider fluid restriction for hyponatremia, or replace with NS if hypovolemic

Avoid fluid overload

Avoid sedation

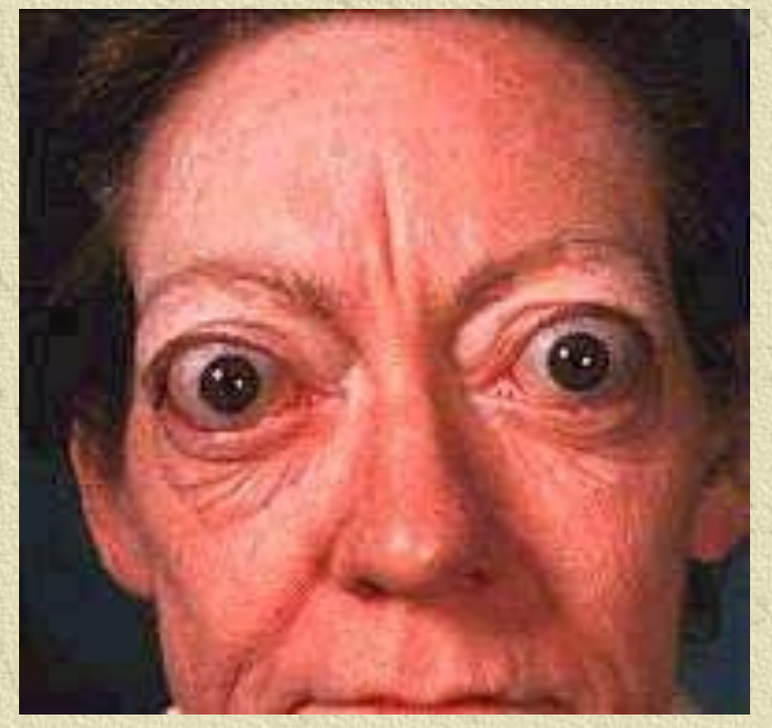
Glucocorticoids

Controversial but necessary in hypopituitarism or polyglandular failure

Dose: Hydrocortisone 40 – 100 mg q6 for 1 week, then taper

Prognosis of Myxedema

- Mortality is 20%, and is mostly due to underlying and precipitating diseases



Thyroid Storm

Acute life threatening exacerbation of thyrotoxicosis

Clinical Setting

most common underlying cause is untreated or inadequately managed Grave's disease

in addition to the typical signs of hyperthyroidism one sees:

fever (>40 ^{0}C)

profound hyperdynamic cardiac output or even:

high-output congestive heart failure

profound irritability or psychosis

Precipitating factors

Withdraw of antithyroid drugs
Severe infection
DKA
MI
Cardiac failure
Surgery
Trauma

Diagnosis

Free T4, free T3 elevated

TSH suppressed

Note that findings are not different than that of hyperthyroidism, but the difference is in the setting

Treatment of Thyroid Storm

©Sympathetic outflow

Triangle of Treatment

©Production and release of thyroid hormone

©Peripheral conversion (T4 □ T3)

Management of Thyroid Storm (1)

Supportive care
- Fluids, containing Glucose
- Oxygen
- Cooling
- If indicated antibiotics or digoxin
- Avoid Aspirin — it can displace thyroid hormone from inert binding sites and increase available thyroid hormone(!)

Management of Thyroid Storm (2)

Specific Measures

Propranolol 40 – 80 mg 6 hourly or IV esmolol drip or IV propranolol push intermittently

Methimazole 20 mg 6 hourly (pr of po)

Lugol's Iodine 5 drops (250 mg) orally bid

Dexamethasone 2 mg 6 hly

Cholestyramine 20 – 30 g/d

Prognosis

- Mortality dropped since the 1920's from 100% to 20 – 30%
- Mortality most frequently associated with serious underlying medical conditions

Acute Adrenal Insufficiency

Causes of Acute Adrenal insufficiency (1)

Usually presents as an acute process in a patient with underlying chronic adrenal insufficiency

Causes of Primary adrenal insufficiency

- Auto-immune
- TB of adrenals
- Metastatic malignancy to adrenals
- adrenal hemorrhage in patients on anticoagulants
- opportunistic infections associated with HIV

Causes of Acute Adrenal insufficiency (2)

Causes of secondary adrenal insufficiency
- Pituitary or hypothalamic disease, HIV associated with secondary adrenal insufficiency

Acute destruction of the adrenals can occur with
- bleeding in the adrenals
- Sepsis
  - DIC or
- complication of anticoagulant therapy

Precipitating Events (1)

Omission of medication

Precipitating illness
- Severe infection
- Myocardial infarction
- Surgery without adrenal support (by especially aware of this risk with adrenalectomy— even unilateral)
- Severe trauma

Withdrawal of steroid therapy in a patient on long term steroid therapy (adrenal atrophy)

Precipitating Events (2)

Administration of drugs impairing adrenal hormone synthesis e.g.. Ketoconazole

Using drugs that increase steroid metabolism e.g. Phenytoin and rifampicin

Clinical Presentation

Nausea and vomiting

Hyperpyrexia

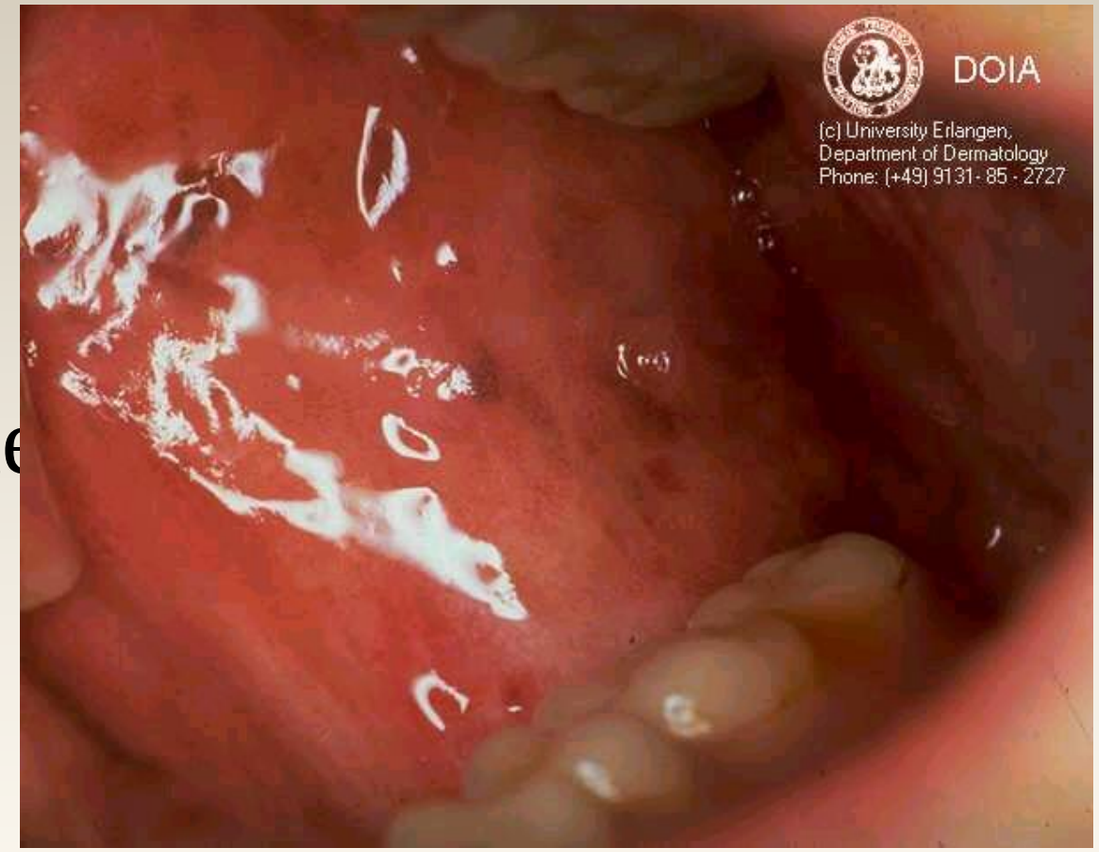
Abdominal pain

Dehydration

Hypotension and shock

Clues to Underlying Chronic Adrenal Insufficiency

- Pigmentation in unexposed areas of the skin
  - Creases of hands
  - Buccal mucosa
  - Scars
- Consider adrenal insufficie
  not respond to pressors



Lab Diagnosis (1)

- Hyponatremia and hyperkalemia (Hyponatremia might be obscured by dehydration)
- Random cortisol is not helpful unless it is very low (<5 mg/L) during a period of great stress

Lab Diagnosis (2)

ACTH (cosyntropin) stimulation test
  Failure of cortisol to rise above 552 nmol/L or 20ug/dl 30 min after administration of 0.25 mg of synthetic ACTH IV

Basal ACTH will be raised in primary adrenal insufficiency but not in secondary

CT of abdomen will reveal enlargement of adrenals in patents with adrenal hemorrhage, active TB or metastatic malignancy

Management of Acute Adrenal Insufficiency (1)

Hydrocortisone
- 100 mg IV stat then 50-100mg IV q6-8for 24 h
- Taper slowly over the next 72 h
- When oral feeds is tolerated change to oral replacement therapy
- Overlap the first oral and last IV doses

Replace salt and fluid losses with 5% dextrose in normal saline IV

Management of Acute Adrenal Insufficiency (2)

- Patients with primary adrenal insufficiency may require mineralocorticoid therapy (fludrocortisone) when shifted to oral therapy
- Treat precipitating diseases

Pituitary Apoplexy

Clinical Setting

- Sudden crisis in a patient with known or previously unknown pituitary tumor

- It may occur in a normal gland during and after child birth, or with head trauma (especially basilar skull injury), or in patient on anticoagulation therapy

Symptoms and Signs

Severe headache and visual disturbance

Syncope

Bitemporal hemianopsia

CN III palsy

Meningeal symptoms with neck stiffness

Symptoms of acute secondary adrenal insufficiency
    Nausea vomiting , hypotension and collapse

Diagnosis

—CT scan of head and pituitary

—Hormonal studies — acutely FT3, FT4, cortisol may be of help —but don’t delay therapy

—Assessment of pituitary function after acute stage has settled

Management of Pituitary Apoplexy

management

- steroids— stress dose— IV hydrocortisone 100mg IV q6-8.
- thyroid hormone replacement can be oral or via NGT
- acute neurosurgical consultation re: decompression
- long term assessment for GH, sex hormone, thyroid, adrenal, and even anti-diuretic hormone therapy

Diabetes Insipidus

- * hypernatremia with dilute urine/polyuria >3 L/day (urine osm < serum osm — inappropriately dilute urine) — typically therapy initiated at Na of 150 or so

- * DDAVP 1-2 ug sq or IV BID (parenteral dose is 1/10 of intranasal dose)

Hypercalcalcemic Crisis

Most Common Causes

Endocrine:

- Hyperparathyroidism
- MEN IIa
- PTHrp by solid tumors

Neoplastic:

- aggressive bone metastases
- Myeloma

Granulomatous (also hormonal, mediated by 1,25 (OH)2D :

- Sarcoidosis
- Tuberculosis

Clinical Features

-History of polyuria and polydipsia

-Dehydration

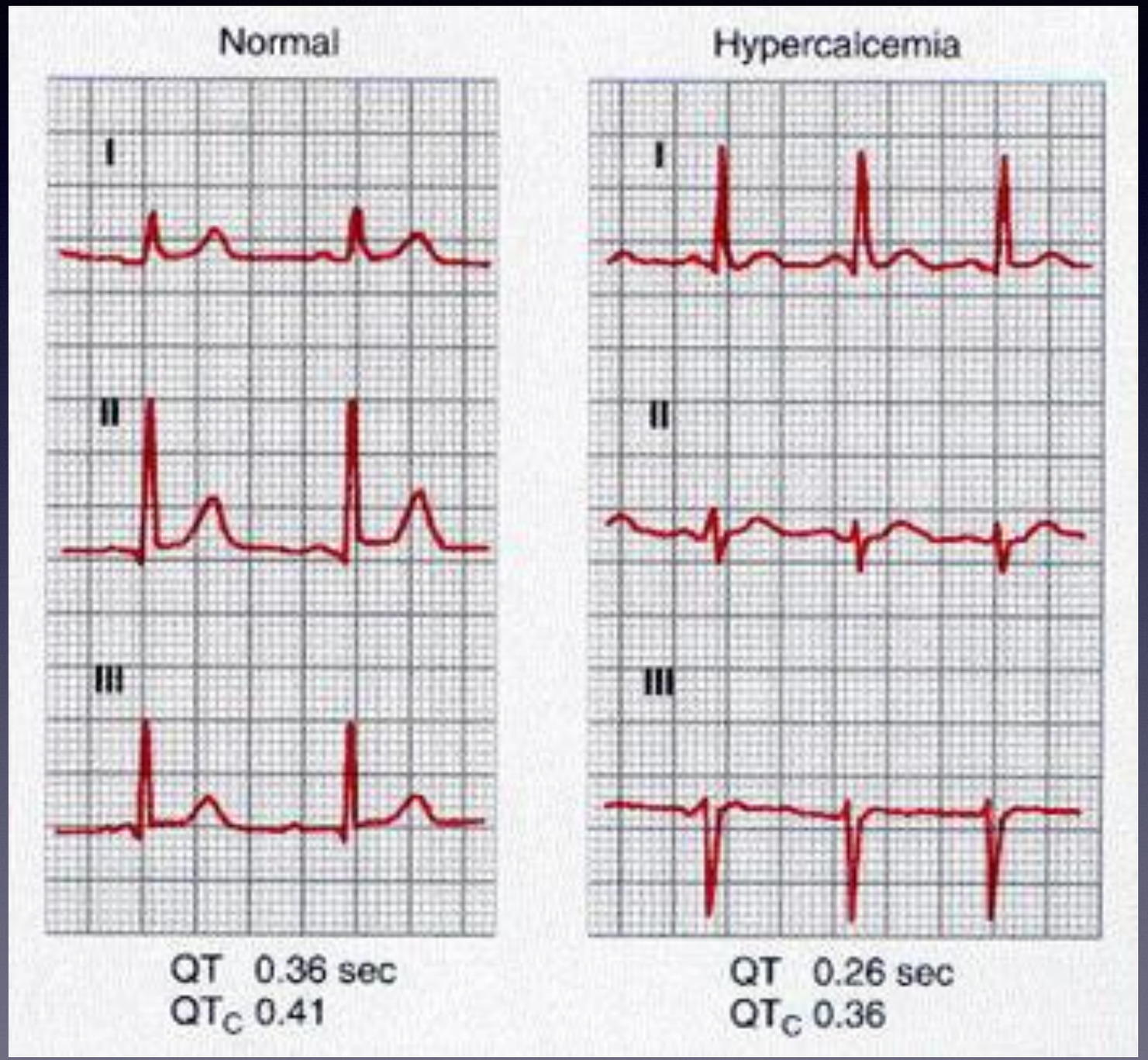
-Bone pain

-Confusion, psychosis, obtundation

-Anorexia

-Constipation

ECG Hypercalcemia



S – Ca high

PTH high *

PTH low

Workup

Primary hyperparathyroidism

Malignancy or other Cause

beware of the “inappropriately normal” PTH

- parathyroid adenomas act like normal glands with a different set point

- at high enough calcium levels, they will suppress PTH production

- accurate assessment may require rehydration and rechecking levels

Treatment of Hypercalcaemia

Volume repletion/expansion
NaCl 0.9% 4 L in first 24 h

Bisphosphonates IV (Pamidronate 60-90mg IV over 2 hours) or (Zoledronic acid 4mg over 15 minutes)

Calcitonin (4 u/kg) - less commonly used …may be useful in vit A toxicity

Corticosteroids (prednisone 30 – 60 mg daily) are the drugs of choice if granulomatous disease vit D intoxication is the cause

Hemodialysis

Acute Hypocalcaemia

Causes of Acute Hypocalcaemia (1)

Hypoparathyroidism

Destruction of parathyroids

- Most commonly surgical – parathyroid resection or accidental—relates to absence of PTH
- Acute hypomagnesemia

Reduced 1,25(OH)vit D

Chronic renal insufficiency

Acute systemic illness

Drugs: ketoconazole, doxorubicin, cytarabine, anti-epileptics

Causes of Acute Hypocalcemia (2)

Increased uptake of Ca in bone
- Osteoblastic metastases
- Hungry bone syndrome — acute hypocalcemia associated with hypophosphatemia related to large amounts of unmineralized osteoid matrix rapidly acquiring calcium — can occur with parathyroid and even thyroid surgery

Complexing of Ca from the circulation
- □ albumin binding in alkalosis
- Acute pancreatitis with formation of Ca soaps
- Transfusion related citrate complexing

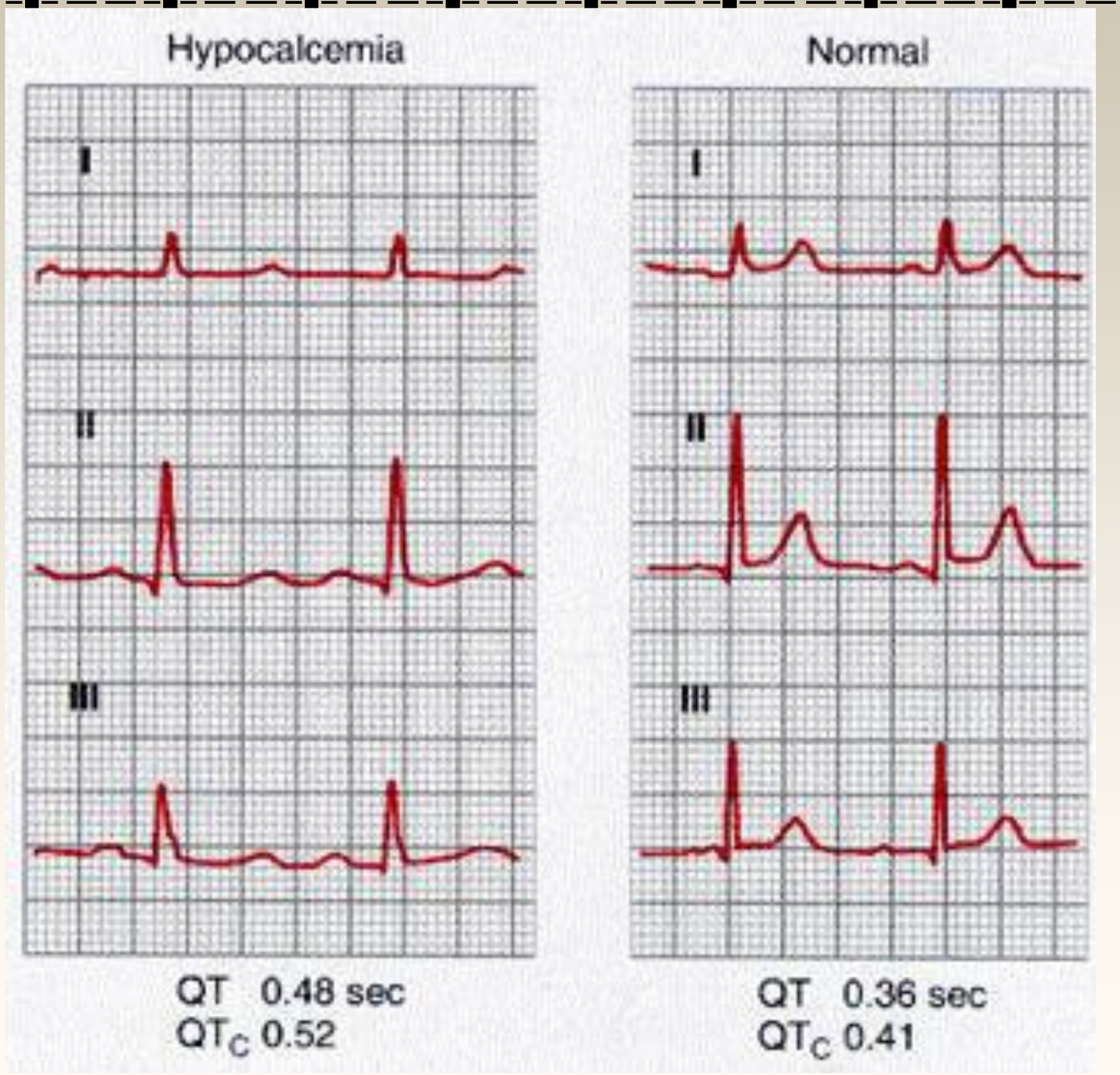
Clinical Picture of Acute Hypocalcaemia

Symptoms

Perioral numbness
Tingling parasthesias
Muscle cramps
Carpopedal spasm
Seizures

Trousseau sign

ECG in Hypocalcemia



WORKUP INCLUDES:

Serum total Ca^{++}, Albumin and Ionized Ca^{++}

Serum PO_4^{++}

Serum Mg^{++}

Plasma PTH

- Low in hypoparathyroidism
- High in hungry bones syndrome

$25(OH)D_3$ and $1,25\ (OH)D_3$

Serum Amylase and Lipase

Treatment of Hypocalcemia

First correct low Mg^{++}

Calcium gluconate 10 ml of 10% solution IV over 5 – 10 min and repeat as necessary in cases with frank generalized tetany — usually 2 amps of calcium gluconate is appropriate and repeated every few hours as necessary

Slower continuous infusion of Calcium gluconate in less acute cases

address underlying cause (vit D deficiency, vit D resistance, etc.)

Questions