Endocrinology Emergencies & Glycemic Control in the ICU

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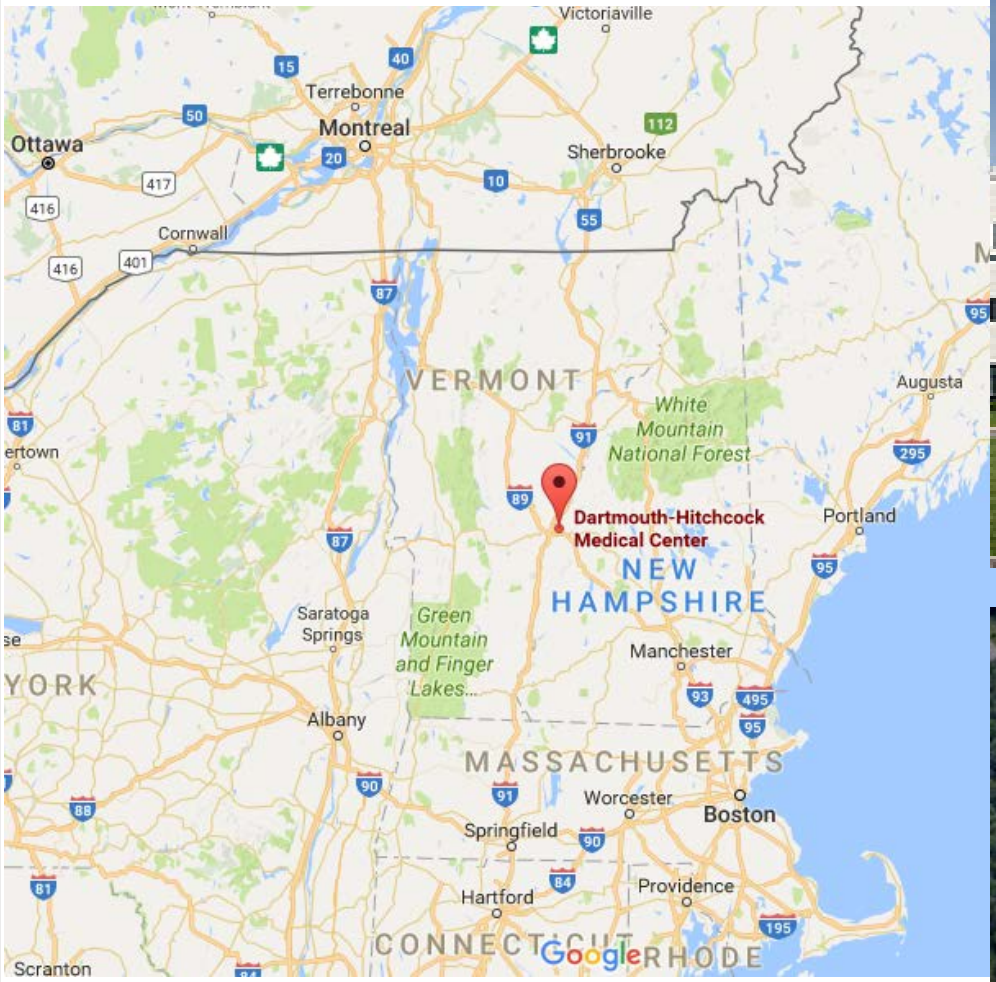
Objectives

- Recognize and understand the treatment options for thyroid storm and thyroid (myxedema) coma
- Recognize and understand the treatment of adrenal crisis
- Recognize the diagnostic and treatment differences between DKA and HONC/HHS
- Understand the rationale for glycemic control in critically ill patients



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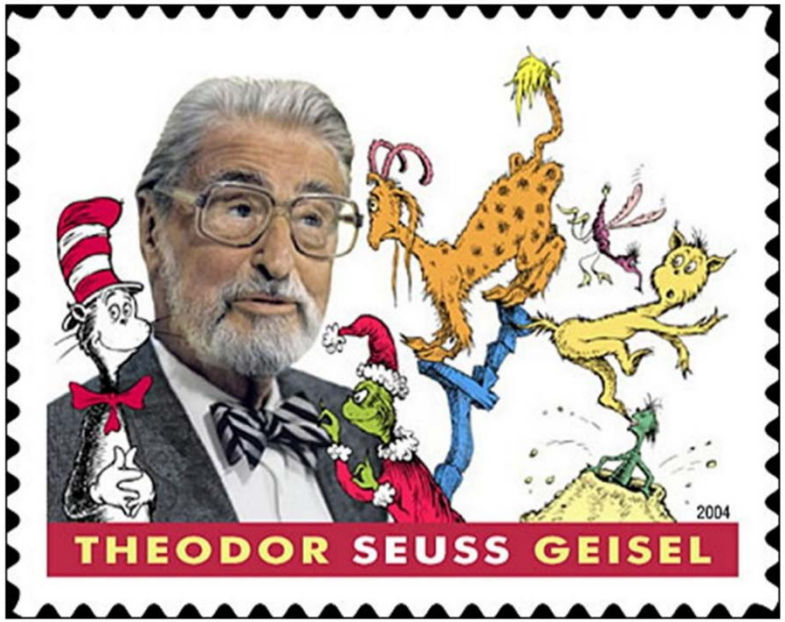

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Overview

- Thyroid storm
- Thyroid coma
- Adrenal insufficiency (adrenal crisis)
- Pheochromocytoma
- Hyperosmolar hyperglycemic state (aka HONC)
- DKA
- Glycemic control

Thyroid storm - Background

- Not usually due to untreated hyperthyroidism (i.e. new tumor or Grave's disease)
- Usually have a precipitating event such as trauma, surgery, infection, surgery (doesn't need to be thyroid), acute iodine intoxication
- Higher levels of circulating thyroid hormone aren't directly-related to severity of condition
- Unclear pathophysiology: rapid rate of increase in serum thyroid hormone levels, increased responsiveness to catecholamines, or enhanced cellular responses to thyroid hormone
- Very rare, but can be life-threatening

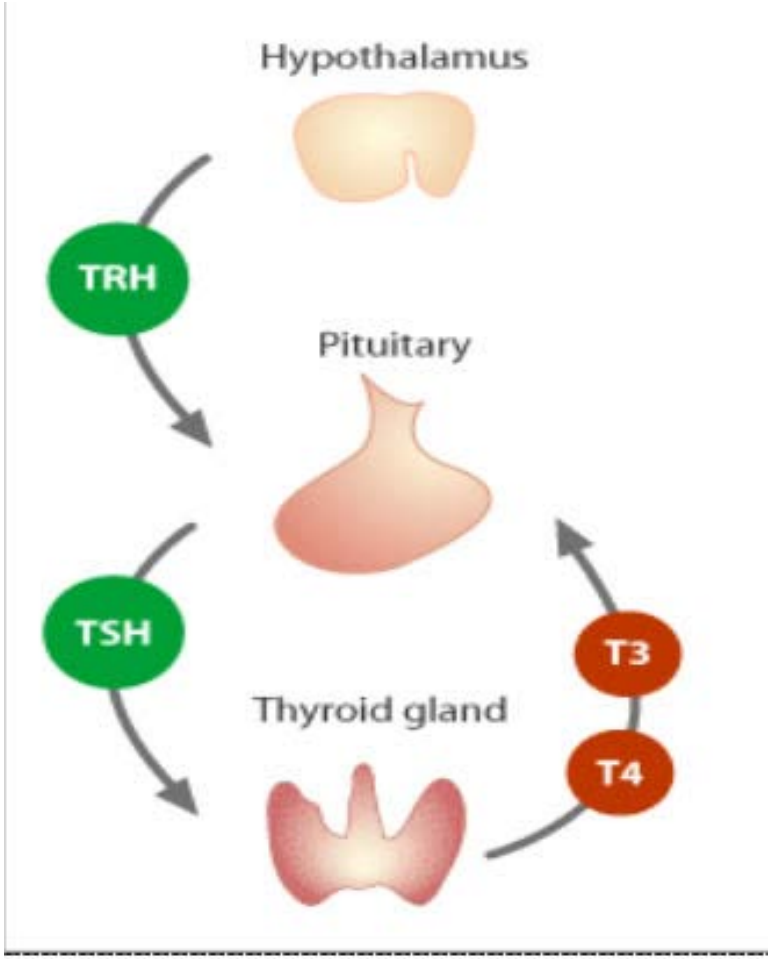
Thyroid storm – Symptoms

- Exaggerated symptoms of hyperthyroidism
- Pyrexia (>104°)
- Arrhythmia, tachycardia (>140 beats/min), CHF
- Anxiety, agitation, psychosis, delirium
- Nausea, vomiting, diarrhea
- Tremors
- Usual symptoms of hyperthyroidism (exophthalmos, goiter, warm/moist skin)

Thyroid storm - Diagnosis

- Thyroid studies are similar to those for hyperthyroidism
- Elevated free T3 and free T4, low TSH
- May have hypercalcemia or hyperglycemia (due to catecholamine release)

Review of thyroid function



Thyroid storm - Treatment

- Beta-blocker to control the symptoms and signs induced by increased adrenergic tone
- Thionamide to block new hormone synthesis
  - Propylthiouracil (PTU) vs. methimazole
  - PTU preferred - blocks T4 to T3 conversion and safe in pregnancy
  - Methimazole preferred for longer term use of thyroid suppression
  - PTU 200mg q4hr or methimazole 20mg q4-6hr PO/via NGT
- An iodine solution to block the release of thyroid hormone
  - SSKI, 5 drops [20 drops/mL, 38 mg iodide/drop] PO q6hr, or Lugol's solution, 10 drops [20 drops/mL, 8 mg iodine/drop] q8hr (rarely used as free iodine toxic to GI tract)
- Glucocorticoids to reduce T4-to-T3 conversion, promote vasomotor stability, and possibly treat an associated relative adrenal insufficiency

Lugol's Solution

- Developed by Jean Guillaume Auguste Lugol in the 1820s
- Combination of elemental iodine and KI
- Intended as a therapy for TB
- Main benefit is that it's readily available for emergency treatment of drinking water and of radiation exposure (used as a disinfectant usually)

Thyroid storm - Treatment

- Initial treatment
  - Propranolol 80mg
  - PTU 200mg or methimzole 20mg (can be given rectally)
  - Hydrocortisone 100mg IV
  - Consider SSKI 1 hr after PTU given as the iodine in SSKI could be used to synthesize new thyroid hormone

Thyroid (Myxedema) Coma

- Very rare in setting of easy TSH testing
- Due to very long term hypothyroidism
- Can be acutely worsened by an new insult (infection, surgery, trauma, etc.)
- Elderly people, women, those w/ cardiac disease are more susceptible
- Mortality as high as 30-40% (review of 23 patients from 1999-2007)

Thyroid (Myxedema) Coma - Symptoms

- Symptoms include those of hypothyroidism, but more severe: decreased mental status, hypothermia, hypotension, bradycardia, hyponatremia, hypoglycemia
- Puffiness of the hands and face, a thickened nose, swollen lips, and an enlarged tongue may occur secondary to nonpitting edema with abnormal deposits of mucin in the skin and other tissues (myxedema)

Thyroid (Myxedema) Coma - Diagnosis

- Elevated TSH (can be VERY high), low free T4 and T3 levels
- If due to secondary hypothyroidism, TSH may be normal or low

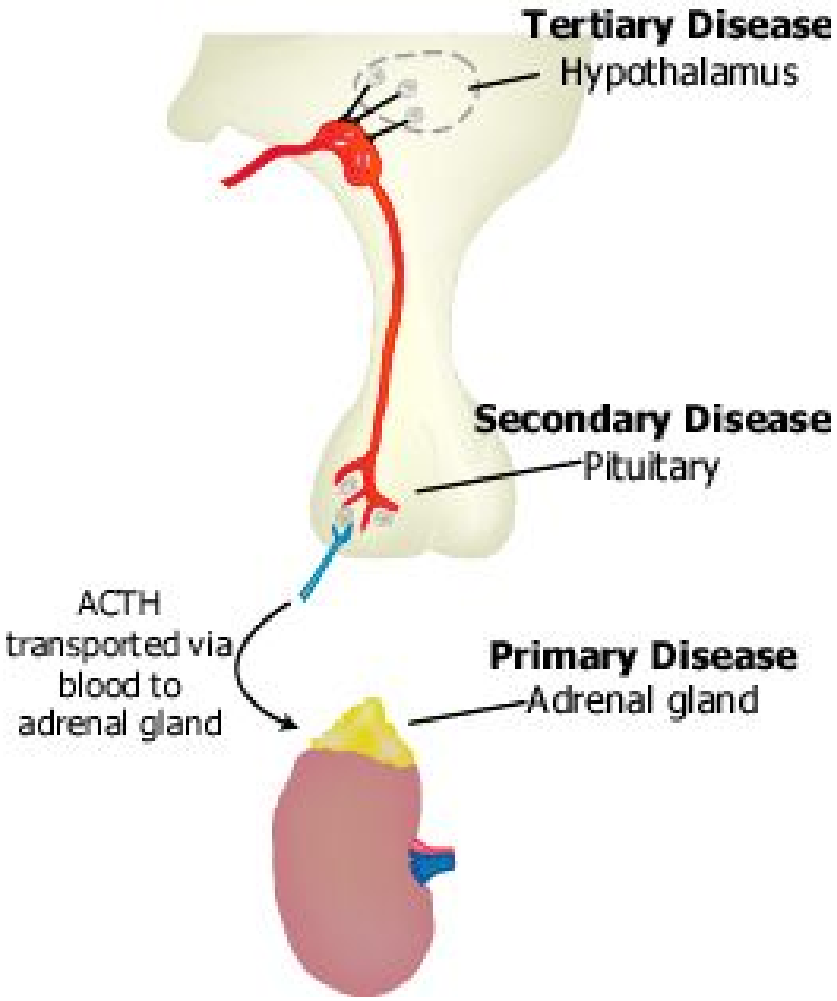
Thyroid (Myxedema) Coma - Treatment

- Very little data on optimal therapy
- T4 (usually loaded w/ 500mcg dose and then 100mcg qd)
- Supportive measures are needed (warming, fluids, vent, etc)
- Some endocrinologists also recommend T3 as it is more biologically active and has a more rapid onset
  - 5-20mcg load and then 2.5-20mcg q8hr until nl T4 level
- Give stress dose hydrocortisone as adrenal insufficiency is common w/ 2° hypothyroidism
  - Should check for adrenal insufficiency before hydrocortisone

Adrenal Insufficiency (Crisis)

- Presents with shock (hypotension) in those with:
  - New primary disease – Addison's Disease (can have a tanned look - ACTH effect, hyperkalemia, hyponatremia, peripheral eosinophilia)
  - Physiologic stress during steroid replacement therapy
  - Stopping steroid replacement therapy
  - Adrenal hemorrhage or trauma more rare
  - Secondary adrenal insufficiency (postoperative pituitary patients is a common cause) unlikely to have shock as mineralocorticoid axis intact

Adrenal Function



Adrenal crisis - Diagnosis

- 6am (peak level) serum cortisol <5 mcg/dL had 99% specificity, but only 36% sensitivity in one review
- Salivary cortisol level at 8 AM > 5.8 ng/mL excludes adrenal insufficiency

- Cosyntropin (synthetic ACTH) stim test is gold standard
  - After 250mcg IV bolus, serum cortisol should rise by >9mcg/dl

Adrenal crisis - Therapy

- Hydrocortisone 100mg q8hr
- Longer term – PO administration
- Treat underlying condition (i.e. surgery for tumor)

Pheochromocytoma

- Catecholamine secreting tumor of the adrenal gland
- 24% of pheos are associated w/ familial syndromes –MEN2
- 10% are malignant
- Very rare

Pheochromocytoma - Diagnosis

- 24 hr urine fractionated metanephrines and catecholamines
- 98% specificity and sensitivity based on Mayo review
- Spot plasma levels have great sensitivity, but poor specificity

Pheochromocytoma - Treatment

- Phenoxybenzamine 1st (alpha-adrenergic blocker) – 20-100mg/d
  - Side effects of orthostasis, nasal congestion, and fatigue
- Longer-term alpha blockade w/ terazosin, prazosin, etc due to side-effect profile
- Beta-blockade 2nd (peripheral vasodilatory beta-blockade w/ unopposed alpha stimulation will lead to increased BP)
- Adrenalectomy

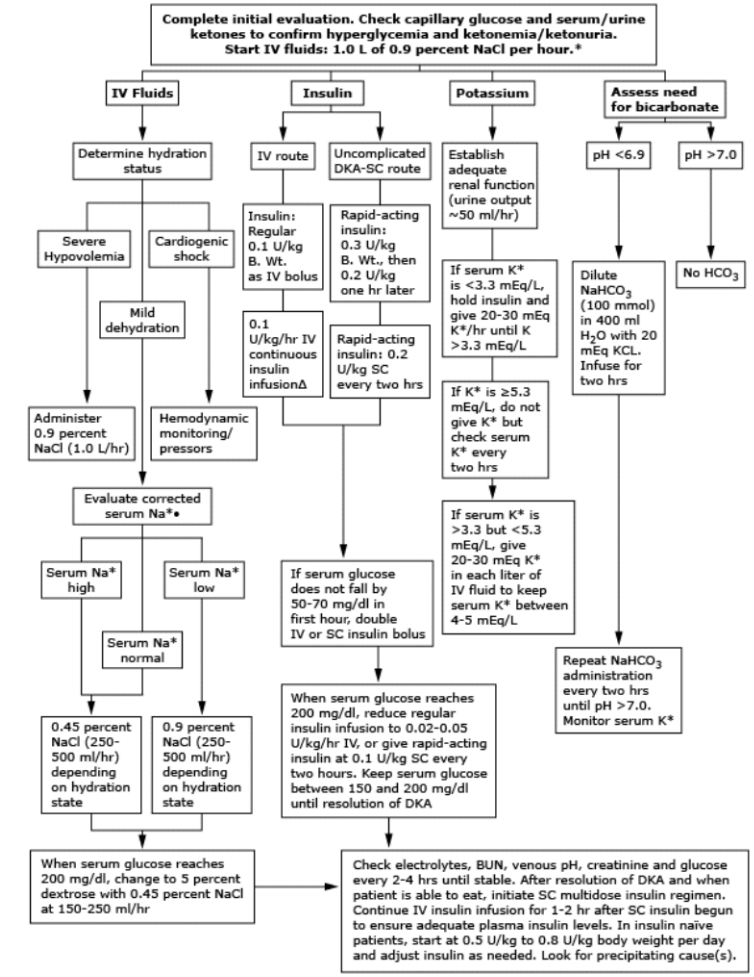
DKA - Characteristics

- Mainly Type 1 DM and must be insulin dependent, so younger patients
- Trigger (usually infection, but MI, CVA, pancreatitis, drug abuse, eating disorders, new onset Type 1 DM) vs. noncompliance
- Presence of ketones (BOHB, acetoacetone, acetone)
- Dehydration (role of osmotic diuresis)
- Potassium deficit – insulin promotes K uptake into cell and dehydration (usually K is high or normal)

DKA - Therapy

- Insulin
  - IV insulin infusion 1st (bolus usually indicated)
  - When ketones no longer present, gap closed, and able to take PO, start SQ insulin
- Aggressive hydration
- Close monitoring of electrolytes, ketones, anion gap
- No evidence of benefit from HCO3 infusion (reserved for profound acidosis – pH <7)
- Electrolyte repletion
  - Replete K when <5meq/dL
  - Replete phos when below nl range (little evidence for aggressive repletion)

Protocol for the management of adult patients with DKA



DKA diagnostic criteria: serum glucose >250 mg/dl, arterial pH <7.3, serum bicarbonate <18 mEq/l, and moderate ketonuria or ketonemia. Normal laboratory values vary; check local lab normal ranges for all electrolytes.

IV: intravenous; SC: subcutaneous.

* After history and physical exam, obtain capillary glucose and serum or urine ketones (nitroprusside method). Begin one liter of 0.9 percent NaCl over one hour and draw arterial blood gases, complete blood count with differential, urinalysis, serum glucose, BUN, electrolytes, chemistry profile, and creatinine levels STAT. Obtain electrocardiogram, chest X-ray, and specimens for bacterial cultures, as needed.

• Serum Na^+ should be corrected for hyperglycemia (for each 100 mg/dl glucose >100 mg/dl, add 1.6 mEq to sodium value for corrected serum sodium value).

Δ An alternative IV insulin regimen is to give a continuous intravenous infusion of regular insulin at 0.14 units/kg/hour; at this dose, an initial intravenous bolus is not necessary.

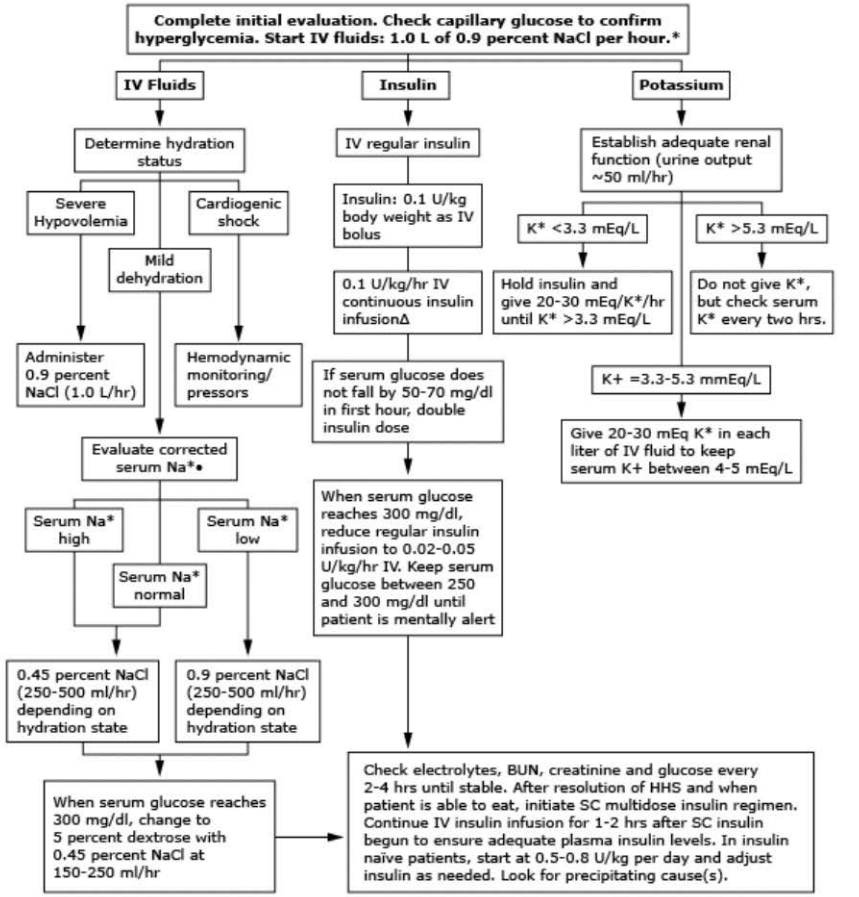
HHS - Characteristics

- Type 2 DM w/ at least partial insulin secretion
- Older patients b/c Type 2 DM
- Triggers like DKA, but also dehydration more of a cause than a symptom
- No ketones

HHS - Therapy

- Aggressive IV hydration, fluid needs usually higher than in DKA
- Insulin infusion similar to DKA
- Replete K as per DKA
- Resolution when mentally alert, osm <315

Protocol for the management of adult patients with HHS



HHS diagnostic criteria: serum glucose >600 mg/dl, arterial pH >7.3, serum bicarbonate >15 mEq/l, and minimal ketonuria and ketonemia. Normal laboratory values vary; check local lab normal ranges for all electrolytes.

IV: intravenous; SC: subcutaneous.

* After history and physical exam, obtain capillary glucose and serum or urine ketones (nitroprusside method). Begin one liter of 0.9 percent NaCl over one hour and draw arterial blood gases, complete blood count with differential, urinalysis, serum glucose, BUN, electrolytes, chemistry profile and creatinine levels STAT. Obtain electrocardiogram, chest X-ray, and specimens for bacterial cultures, as needed.

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Δ An alternative IV insulin regimen is to give a continuous intravenous infusion of regular insulin at 0.14 units/kg per hour; at this dose, an initial intravenous bolus is not necessary.

DKA vs. HHS - Diagnosis

- DKA
  - Ketones present in urine/blood
  - Glu rarely >800mg/dL
  - Low HCO3 (metabolic acidosis)
  - Respiratory compromise more likely
  - Rapid onset (<24hrs)
- HHS
  - No to minimal ketones
  - Usally HCO3 >20mEq/L (minimal acidosis)
  - Glu commonly >800mg/dL
  - Slower onset (several days)
  - Dehydration more trigger than symptom
  - Elevated osm more common, i.e. obtundation

DKA vs. HHS - Treatment

- DKA
  - Insulin and IVF needed
  - More likely to need mechanical ventilation for acidosis
  - Reserve HCO_3 infusion for severe acidosis only
- HHS
  - Rehydration more critical

Glycemic Control in the ICU

- Critical illness leads to hyperglycemia
- Increased cortisol, insulin resistance, catecholamines, glucagon

Hyperglycemia in the ICU - Mortality

- Increased mortality in all sub groups
- Compared to patients who survived, those who died had significantly higher admission blood glucose levels (175 vs 151 mg/dL mean blood glucose levels (172 vs 138 mg/dL and maximum blood glucose levels (258 vs 177 mg/dL).
- Graded effect, with higher mortality among patients who had higher blood glucose levels. Mortality ranged from 10 percent in patients with a mean blood glucose between 80 and 99 mg/dL (4.4 and 5.5 mmol/L) to 43 percent in patients with a mean blood glucose greater than 300 mg/dL (16.6 mmol/L).

Krinsley JS. Association between hyperglycemia and increased hospital mortality in a heterogeneous population of critically ill patients. Mayo Clin Proc 2003; 78:1471.

Leuven Surgical Trial

- Single center, 1548 surgical ICU patients (some were actually medical) to receive intensive insulin therapy (IIT) or conventional blood glucose management
- Randomized to IIT (target blood glucose of 80 to 110 mg/dL) or conventional glucose control (target blood glucose of 140 to 180 mg/dL)
- Patients in both arms were given 200 to 300 g of IV glucose during 1st day in ICU and most were on both parenteral and enteral nutrition to achieve caloric goals
- The mean blood glucose was significantly lower in the IIT group (103 versus 153 mg/dL [5.7 versus 8.5 mmol/L]).
- ICU mortality was significantly lower in the IIT group (4.6 versus 8.0 percent). The magnitude of the benefit was greatest among patients who were in the ICU for five days or longer.
- Hospital mortality was significantly lower in the IIT group (7.2 versus 10.9 percent).
- IIT decreased critical illness polymyoneuropathy, acute renal failure, transfusion requirement, and blood stream infections.
- Hypoglycemia (blood glucose <40 mg/dL) was more frequent in the IIT group (5.1 versus 0.8 percent).

Leuven Surgical Trial

- Most patients were adult (mean age 63 years) males (71 percent) who had undergone cardiac surgery (63 percent) and were not severely ill (mean Acute Physiologic and Chronic Health Evaluation [APACHE II] score was 9).
- Control group ICU mortality was 8 percent and hospital mortality was 11 percent. These mortality rates are higher than the 1.5 to 3.5 percent reported for most patients undergoing routine cardiac surgery
- High mortality rate leads to a possible harmful intervention in the control group (IV glucose infusion without aggressive rescue as in the IIT group
- Dedicated nurse for insulin infusion therapy, not practical outside of a study

van den Berghe G, Wouters P, Weekers F, et al. Intensive insulin therapy in critically ill patients. N Engl J Med 2001; 345:1359.

Leuven Medical Trial

- Single center, 1200 medical ICU patients
- Randomized to IIT (target blood glucose of 80 to 110 mg/dL) or conventional glucose control (target blood glucose of 140 to 180 mg/dL)
- Same IV glucose infusion
- Mean blood glucose was lower in the IIT group than the conventional therapy group (105 versus 160 mg/dL)
- IIT did not change overall hospital mortality (37.3 versus 40.0 percent in the control group)
- IIT significantly reduced ICU length of stay, hospital length of stay, duration of mechanical ventilation, and acute kidney failure
- Hypoglycemia was significantly more common in the IIT group (18.7 versus 3.1 percent)

Van den Berghe G, Wilmer A, Hermans G, et al. Intensive insulin therapy in the medical ICU. N Engl J Med 2006; 354:449.

GLUCONTROL

- 1101 critically ill medical and surgical patients
- Randomized to IIT (target blood glucose of 80 to 110 mg/dL) or conventional glucose control (target blood glucose of 140 to 180 mg/dL)
- Terminated early due to numerous protocol violations
- IIT group had higher rate hypoglycemia (8.7% vs. 2.7%)
- No difference in mortality

Preiser JC, Devos P, Ruiz-Santana S, et al. A prospective randomised multi-centre controlled trial on tight glucose control by intensive insulin therapy in adult intensive care units: the Glucontrol study. Intensive Care Med 2009; 35:1738.

VISEP

- Volume Substitution and Insulin Therapy in Severe Sepsis (VISEP)
- Multicenter two-by-two factorial trial conducted in medical and surgical ICU patients with severe sepsis (other treatment was pentastarch for resuscitation)
- IIT (target blood glucose of 80 to 110 mg/dL) vs. conventional control (target blood glucose of 180 to 200 mg/dL
- IIT arm was stopped after 488 patients (planned enrollment of >1000) because IIT had higher rate of hypoglycemia (12.1% vs. 2.1%)
- Hypoglycemia (blood glucose ≤40 mg/dL) was significantly more common in the IIT group (17 versus 4.1 percent)
- There was no significant difference in 28 day mortality (24.7 versus 26.0 percent in the conventional glucose control group), morbidity, or organ failures
- There was a nonstatistically significant increase in 90 day mortality in the IIT group (39.7 versus 35.4 percent)

Brunkhorst FM, Engel C, Bloos F, et al. Intensive insulin therapy and pentastarch resuscitation in severe sepsis. N Engl J Med 2008; 358:125.

NICE-SUGAR

- Normoglycemia in Intensive Care Evaluation Survival Using Glucose Algorithm Regulation – largest trial
- 6104 medical and surgical ICU patients randomized to either IIT (target blood glucose level of 81 to 108 mg/dL) or conventional glucose control (target blood glucose of <180 mg/dL) The IIT group had a significantly lower time-weighted blood glucose (115 versus 144 mg/dL)
- The IIT group had a significantly higher 90 day mortality (27.5 versus 24.9 percent, odds ratio 1.14, 95% CI 1.02-1.28)
- The IIT group had a significantly higher incidence of severe hypoglycemia (6.8 versus 0.5 percent), defined as a blood glucose <40 mg/dL
- In the subgroup of 2232 operative patients, those who received IIT had a significantly higher mortality than those who received conventional glycemic control (24.4 versus 19.8 percent, odds ratio 1.31, 95% CI 1.07-1.61).

NICE-SUGAR Study Investigators, Finfer S, Chittock DR, et al. Intensive versus conventional glucose control in critically ill patients. N Engl J Med 2009; 360:1283.

Summary of Glycemic Control

- NICE-SUGAR was last large study
- 140-180mg/dL is now considered standard of care for goal glycemic control in a critically-ill patient
- We put everyone (non-diabetics as well) on q4 or q6 sliding scale insulin

Thank you – Questions?

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