Brigham and Women's Hospital
Founding Member, Mass General Brigham

Endocrine Emergencies in the ICU

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CONTINUING MEDICAL EDUCATION
DEPARTMENT OF MEDICINE

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TEACHING HOSPITAL

Financial Disclosures

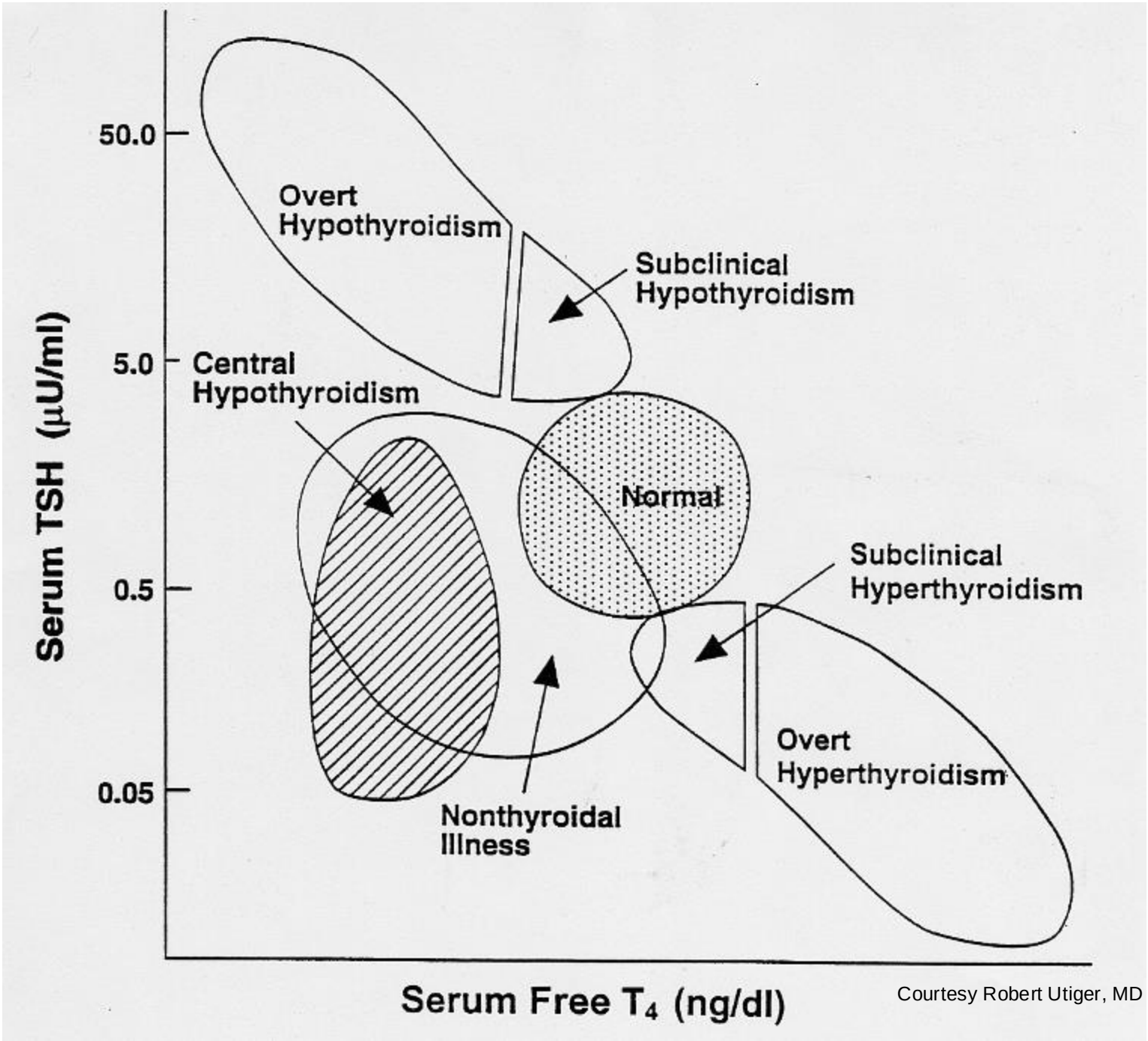
- None

Outline

- Thyroid Storm
- Myxedema coma
- Adrenal insufficiency
- Hypercalcemic crisis
- Hyperglycemic crises

Thyroid Function Tests in the ICU

Diagnosis	TSH	Free T4	Total T3
1° Hyperthyroidism	↓↓↓	↑	↑
1° Hypothyroidism	↑	↓	↔↓
2° Hypothyroidsm	↔↓	↓	↔↓
Non-thyroidal illness	↔↓	↔↓	↓↓↓



Courtesy Robert Utiger, MD

Thyroid Storm: Criteria

- Thyroid storm is a **clinica**l diagnosis
  - based on a combination of symptoms, physical findings and laboratory studies
- In setting of elevated thyroid function tests, no specific level distinguishes hyperthyroidism from thyroid storm
- Non-specific findings may include hypercalcemia, hyperglycemia and azotemia

TABLE 2

Burch-Wartofsky Point Scale

Temperature (°F)	
99-99.9	5 points
100-100.9	10
101-101.9	15
102-102.9	20
103-103.9	25
≥ 104.0	30
Central nervous system effects	
Absent	0
Mild (agitation)	10
Moderate (delirium, psychosis, extreme lethargy)	20
Severe (seizure, coma)	30
Gastrointestinal-hepatic dysfunction	
Moderate (diarrhea, nausea/vomiting, abdominal pain)	10
Severe (unexplained jaundice)	20

Cardiovascular dysfunction	
Tachycardia (beats/min)	
99-109	5
110-119	10
120-129	15
130-139	20
≥ 140	25
Atrial fibrillation	10
Heart failure	
Mild (pedal edema)	5
Moderate (bibasilar rales)	10
Severe (pulmonary edema)	15
Precipitant history	
Positive	0
Negative	10

Total: < 25, storm unlikely; 25 – 45, impending storm; > 45, thyroid storm

Source: Burch, Wartofsky. *Endocrinol Metab Clin North Am.* 1993.[2]

Thyroid Storm

- Mortality remains a problem: 8%-25% in recent series
- Precipitants
  - Infection
  - Surgery
  - I 131 treatment or contrast exposure
  - Abrupt cessation of anti-thyroid medication
  - Toxemia

Endocrine Practice 17:457, 2011
JCEM 100:451, 2015

Thyroid Storm: Treatment

- Inhibit production of thyroid hormone by inhibiting organification of iodide (thionamide)
- PTU vs methimazole
  - PTU preferred over methimazole because of greater inhibition of peripheral conversion of T4 to T3
  - Dosing 500-1000mg loading dose po then 250 mg q 4 hours
  - Concerns for liver dysfunction with PTU chronically but not acutely

Thyroid 26: 1343-142 , 2016

Thyroid Storm: Treatment

- Administer iodine
  - Iodine blocks release of pre-formed thyroid hormone
  - If possible, start after initial dose of PTU is given
  - Start SSKI 5 drops q 6 hour
- Administer corticosteroids
  - Will suppress thyroiditis if present
  - Decrease T4 to T3 conversion, and support stress response
  - Dose 8 mg qd dexamethasone or hydrocortisone 100mg iv q 8
- Administer beta-blocker
  - This will slow tachycardia
  - Decreases T4 to T3 conversion
  - Use propranolol 60-80 mg q 4 h or esmolol infusion
  - If beta-blockers are contra-indicated, consider diltiazem

Thyroid Storm: Treatment

- Supportive measures
  - Acetaminophen is preferred over salicylates for pyrexia: asa ↑ free hormone levels
  - Avoid external cooling as shivering may raise core temperature
  - Correct dehydration
  - Cautious treatment of heart failure with diuretics if necessary
- When all else fails: case reports
  - Plasmapheresis or dialysis
  - Cholestyramine

Myxedema Coma

- Severe thyroid hormone deficiency (actual coma is not necessary)
- Mortality: Mortality rate reported at 30%-50%
- Precipitating factors
  - Medication non-compliance
  - Cold weather
  - Infection
  - MI/CVA
  - CNS depressant medications: narcotics, anesthetics, sedatives

Table 4
Diagnostic Scoring System for Myxedema Coma[a]

Thermoregulatory dysfunction (temperature, °C)	
>35	0
32-35	10
<32	20
Central nervous system effects	
Absent	0
Somnolent/lethargic	10
Obtunded	15
Stupor	20
Coma/seizures	30
Gastrointestinal findings	
Anorexia/abdominal pain/constipation	5
Decreased intestinal motility	15
Paralytic ileus	20
Precipitating event	
Absent	0
Present	10

Cardiovascular dysfunction	
Bradycardia	
Absent	0
50-59	10
40-49	20
<40	30
Other EKG changes[b]	10
Pericardial/pleural effusions	10
Pulmonary edema	15
Cardiomegaly	15
Hypotension	20
Metabolic disturbances	
Hyponatremia	10
Hypoglycemia	10
Hypoxemia	10
Hypercarbia	10
Decrease in GFR	10

Abbreviations: EKG = electrocardiogram; GFR = glomerular filtration rate.

[a] A score of 60 or higher is highly suggestive/diagnostic of myxedema coma; a score of 25 to 59 is suggestive of risk for myxedema coma, and a score below 25 is unlikely to indicate myxedema coma.

[b] Other EKG changes: QT prolongation, or low voltage complexes, or bundle branch blocks, or nonspecific ST-T changes, or heart blocks.

Endocr Pract. 2014;20:808-817

Myxedema Coma: Diagnosis

- In appropriate clinical setting, thyroid function tests consistent with severe hypothyroidism are sufficient
- 95% of cases will be due to 1° hypothyroidsm and TSH will be elevated
- 5% of cases may be due to central hypothyroidism and TSH will not be elevated
- The level of the TSH elevation does not necessarily correlate with the presence of myxedema coma

Myxedema Coma: Supportive Treatment

- Avoid:
  - Active re-warming
  - Hypotonic fluids
- Consider:
  - Ventilatory support
  - Empiric antibiotics
  - Hypertonic saline if sodium is below 120 mEq/L

Myxedema Coma: Treatment

- Administer:
  - Glucocorticoids
    - Prudent to administer hydrocortisone 50-100 mg tid for several days
    - 1° or 2° adrenal insufficiency may coexist: screen prior to Rx, if possible, with cortisol level

Myxedema Coma: Treatment

Administer:

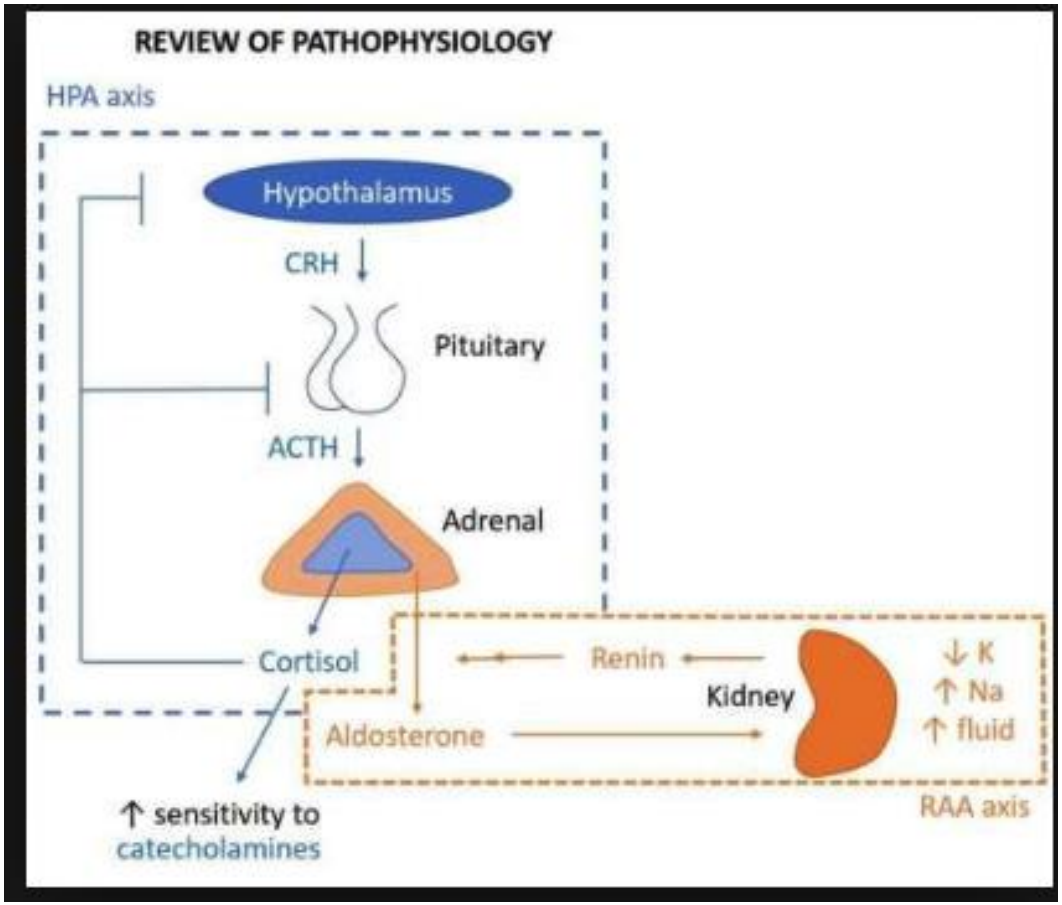
- Thyroid hormone
  - 300-500 µg T4 given iv followed by 100 µg iv qd
  - **OR** Combination of T4(at 50% of dose) and T3 10µg iv q 8 hours
  - When patient alert and taking po, switch to oral replacement
  - Dosing rule of thumb: 1.6 mcg/kg/day for ideal body weight levothyroxine orally
  - Improvement in mentation, temperature, pulse and Na occur quickly
  - TSH response will be gradual

J Endocrinol. 2004;180(2):347

Myxedema Coma: Treatment

- Special Consideration: CAD
  - CAD is common in patients with hypothyroidism
  - Untreated hypothyroidism may mask symptoms of CAD
  - If CAD is suspected, T4 replacement may be safer at dose of 200-250 µg iv as one time dose to reverse neurologic impairment followed by 25-50 µg T4 iv qd

Hypothalamic/Pituitary/Adrenal Axis



Basicmedical Key

Steroid Action

- Some effects of cortisol
  - Maintain blood pressure by sensitizing vascular smooth muscle to catecholamine pressor effects
  - Antagonize effect of ADH on free water excretion and suppress ADH secretion
  - Increase hepatic gluconeogenesis
- Effects of aldosterone
  - Na retention
  - Potassium excretion
  - Maintain extracellular volume
  - Increase vascular resistance

Types of Adrenal Insufficiency

- Primary adrenal insufficiency
  - Destruction of the adrenal glands
  - Cortisol and aldosterone will be deficient
- Secondary adrenal insufficiency
  - Pituitary, hypothalamic disease, or *chronic steroid use*
  - Adrenal glands are not destroyed
  - Aldosterone axis will remain intact
  - Cortisol producing cells will atrophy over time

Definition of Acute Adrenal crisis: 3 components required

- Symptoms/signs of Adrenal crisis
  - Fatigue/lethargy/nausea
  - Fever
  - Hypotension
  - Labs: hyponatremia, hypoglycemia, hyperkalemia
- Low cortisol level
- Clinical improvement in response to parenteral glucocorticoid(hydrocortisone)

Ther Adv Endocrinol Metab
2019, Vol. 10: 1–12

Precipitants of acute adrenal crisis

- Acute stress in patient with undiagnosed chronic adrenal insufficiency (infection or dehydration)
- Primary adrenal insufficiency
  - Bilateral adrenal hemorrhage
  - Autoimmune destruction
  - Infiltrative(TB, bilateral metastasis)
- Secondary Adrenal insufficiency
  - Abrupt cessation of glucocorticoids or failure to increase dose in setting of stress
  - Pituitary infarction, mass
- Medications inhibiting cortisol production:
  - Etomidate, ketoconazole, megestrol
- Check-point inhibitor therapy(primary and secondary from hypophysitis)

ACTH Stim Test for Diagnosis of Adrenal Insufficiency

- Baseline ACTH level if available
  - ACTH levels require special conditions to be accurate such a being drawn and immediately placed on ice
- If reliable ACTH not available, consider baseline renin and aldosterone levels
- Measure cortisol level at baseline
- Give 250 µg cosyntropin(synthetic ACTH) iv
- Measure cortisol between 30 and 60 minutes
- ACTH stim can be done ***any*** time of the day

BMJ Open. 2018; 8(5): e019273

J Clin Endocrinol Metab. 2016 Feb; 101(2): 364–389

Testing the HPA axis

STATIC TEST (morning)

- Morning cortisol (**and ACTH**)
- An "appropriate" AM cortisol should ideally be >13-14 µg/dL, reflecting a morning peak
- An AM cortisol <5 mcg/dL is highly suggestive of adrenal insufficiency
- AM cortisol levels between 5-13 can be difficult to interpret and can be repeated

PROVOCATIVE TEST (any time)

- 250 µg cosyntropin stimulation test
- Stimulated cortisol <14* mcg/dL highly suggestive of primary adrenal insufficiency

*18 mcg/dL is the traditional cutoff. New cortisol immunoassays and LC-MS/MS assays have lower thresholds

Slide courtesy of Anand Vaidya, MD

Measuring steroids

- Cortisol levels may be falsely elevated by cross-reactivity with administered drugs
  - Steroids which will cross-react
    - Hydrocortisone
    - Prednisolone, prednisone (to a moderate degree)
  - Steroid which does not cross-react in assays
    - Dexamethasone
    - Give dexamethasone if necessary while performing ACTH stim testing

Acute Adrenal Insufficiency: Treatment

- Infuse normal saline or D5NS 1-3 liters over 12-24 hours
- Hydrocortisone 100 mg iv bolus X 1
- 200 mg iv continuous infusion of hydrocortisone q 24 hours tapered to physiologic replacement as indicated or 50 mg iv hydrocortisone q 6 hours
- Saline will be adequate to replace mineralocorticoid needs acutely until diagnosis established
- Average maintenance dose
  - Hydrocortisone 10-15 mg qam and 5-10 mg qpm
  - Fludrocortisone .1 mg qd (if there is mineralocorticoid deficiency)

Anesthesia 75: 654-663, 2020
JCEM 105:2262-2274, 2020

Hypercalcemic Crisis

- Definition
  - Corrected* serum calcium over 14 mg/dl
  - Evidence of organ dysfunction
- Symptoms
  - Polyuria, dehydration due to concentrating defect
  - Nausea, vomiting, abdominal pain
  - Confusion, somnolence, coma

*Correction for low albumin is increase of .8mg/dl calcium for each 1 mg/dl below 4 mg/dl of albumin

Hypercalcemic crisis: Findings

Renal impairment
Pancreatitis
Ectopic calcifications including nephrocalcinosis
EKG changes including:
- shortened QTc interval,
- heart block,
- ventricular arrythmias

Hypercalcemic crisis: Causes

- Malignancy: 50%
- Parathyroid hormone mediated : 25%
  - Primary hyperparathyroidism
  - Parathyroid cancer(rare)
- Vitamin D excess (elevated 25-OH vitamin D)
- Granulomatous disease (elevated 1,25-OH vitamin D)
- Miscellaneous: hyperthyroid, vitamin A excess, immobilization

Suggested Initial Labs

- PTH level
  - If normal or high suggests primary hyperparathyroidism in setting of hypercalcemia
  - Low phosphorus is a clue to hyperparathyroidism
- If PTH low
  - Look for malignancy and check PTH related protein (PTHrp)
  - If no malignancy, consider granulomatous disease or vitamin D or A toxicity

Hypercalcemic crisis: Treatment

- Vigorous IV saline hydration to maintain urine output over 100-150 cc/hour
- Furosemide only in fluid overload
- Calcitonin 4-8 U/kg SQ q 12 hrs can be quick but effect wears off after a few days
- IV bisphosphonate should be used early on, but response is delayed (avoid if GFR<30)
  - pamidronate 60-90 mg iv over 2 hours
  - zoledronic acid 4 mg iv over 15 minutes (preferred if available)

Hormone Met Res 2019, 51: 770

Hypercalcemic crisis: Additional options for treatment failure

- Cinacalcet 30-90 mg PO 1-2 x per day for 1° HPT as bridge to surgery
- Glucocorticoids (prednisone 40 mg qd)if vitamin D toxicity, granulomatous disease or myeloma is suspected
- Denosumab 120 mg sc weekly if malignancy is suspected
- Dialysis for severe renal failure

Diagnostic Categories: Hyperglycemic Emergencies

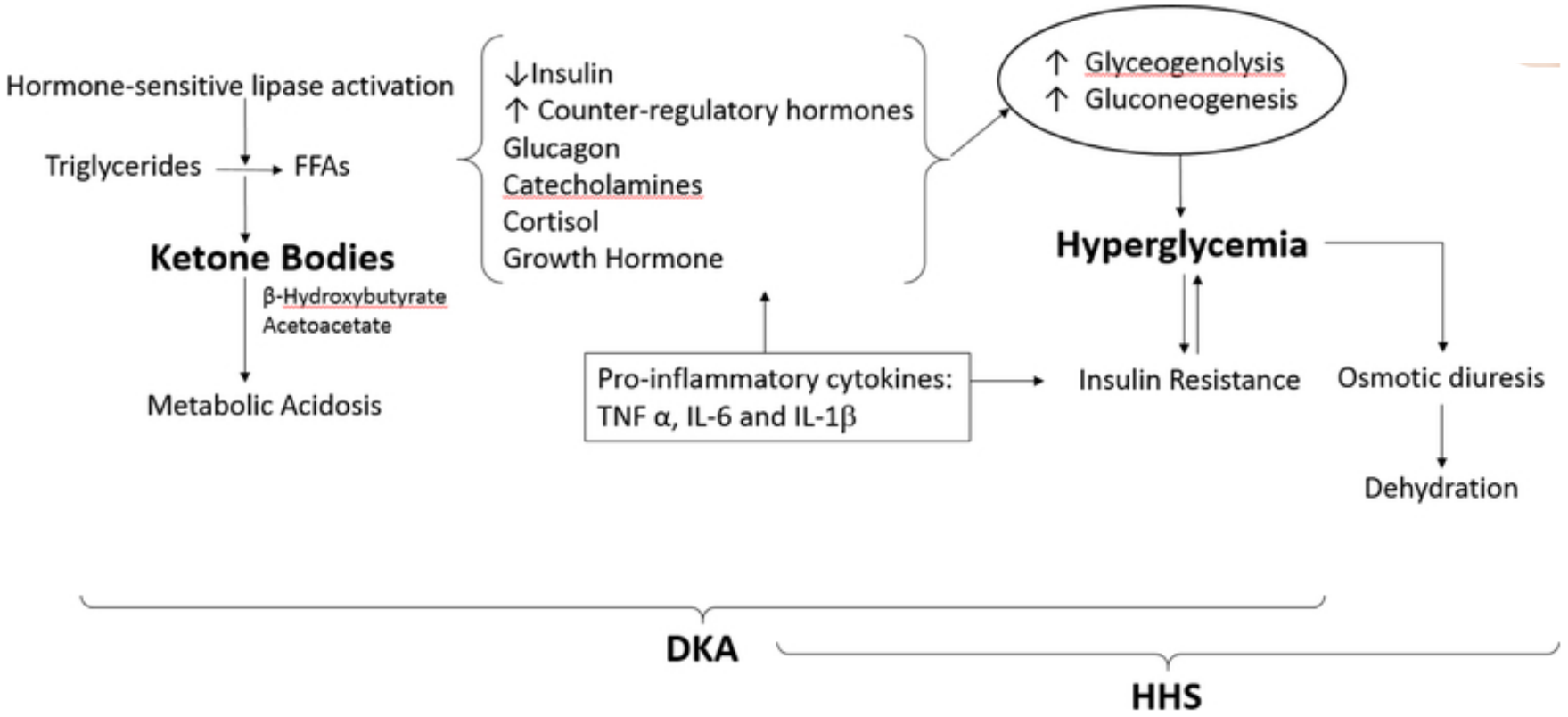
- *Diabetic ketoacidosis*
  - Predominant abnormality is ketosis with acidosis in setting of hyperglycemia
- *Hyperosmolar Hyperglycemic Syndrome*
  - Predominant abnormality is dehydration due to hyperglycemia in absence of acidosis
- Ketoacidosis and hyperosmolarity can occur together
- This is more a *spectrum* than a *dichotomy* for diagnosis
- They can occur in type 1 and type 2 diabetes

Diagnostic Criteria

Measure	DKA			HHS
	Mild	Moderate	Severe	
Plasma glucose (mg/dL)	>250	>250	>250	>600
Arterial pH	7.25 to 7.30	7.00 to <7.24	<7.00	>7.30
Serum bicarbonate (mEq/L)	15 to 18	10 to < 15	<10	>18
Urine or serum ketones [a]	Positive	Positive	Positive	Small
Urine or serum β-hydroxybutyrate (mmol/L)	>3.0	>3.0	>3.0	<3.0
Effective serum osmolality [b]	Variable	Variable	Variable	>320 mOsm/kg
Anion gap	>10	>12	>12	Variable
Mental status	Alert	Alert/drowsy	Stupor/coma	Stupor/coma

Medical Clinics of North America, 2017-05-01, Volume 101, 587-606,

Pathogenesis of DKA/HHS



Medical Clinics of North America, 2017-05-01,
Volume 101, Issue 3, Pages 587-606,

Epidemiology and Mortality Of DKA/HHS

Age Group	% of total DM hospitalizations	Increase from 2007 to 2014	Mortality in 2014
18-44	4.5%	32%	2.3%
45-64	1.4%	55%	5.9%
Over 64	.5%	67%	11.8%

Higher rates seen in ethnic minority populations and lower socio-economic class
High mortality in part due to underlying medical illnesses

Recent Danish study found 17% in-hospital mortality from HHS

Cureus. 2019 Apr 1;11(4):e4353
DC 47:272, 2024.

Precipitating Factors for DKA/HHS

- New onset diabetes 50%
- Medication non-compliance 25%
- Infection 20-25%
- Cardiovascular event 2-5%
- Pancreatitis 5%
- New drugs: steroids, newer anti-psychotics, SGLT2-inhibitors
- Substance abuse co-exists in 25-50%

Nature Reviews Endocrinology 12:222, 2016

Clinical Features

Condition	Symptoms	Signs	Presentation
DKA	Polydipsia	Hypothermia	Acute onset (hours-days)
	Polyuria	Tachycardia	More common in T1D than T2D
	Weakness	Tachypnea	
	Weight loss	Kussmaul breathing	
	Nausea	Ileus	
	Vomiting	Acetone breath	
	Abdominal pain	Altered sensorium	
HHS	Polydipsia	Hypothermia	Insidious onset (days-weeks)
	Polyuria	Hypotension	Older age
	Weakness	Tachycardia	More common in T2D than T1D
	Weight loss	Altered sensorium	

Initial Labs to Order

- Plasma glucose(actual, measured as POC not accurate at high values)
- BUN, creatinine, electrolytes
- Serum β-OH butyrate or serum ketones and urine ketones
- Arterial or venous pH
- CBC
- Any indicated labs or imaging to determine cause

Handy Formulas

1. Anion Gap: Normal ~ 10-16 meq/L
   Na – (HCO_3 + Cl)
   Our patient: 121 – (15 + 80) = 26

2. Effective serum osmolality: Normal 275-299
   2[measured Na(meq/l)] + glucose(mg/dl)/18

3. "Corrected Na": Normal 135-145
   Na(measured) + .016X[glucose(mg/dl) -100]
   corrected Na helps put measured Na in context when glucose very high

Am J Med 1999 Apr;106(4):399-403

Other Metabolic Disorders Presenting with Anion Gap or Ketosis

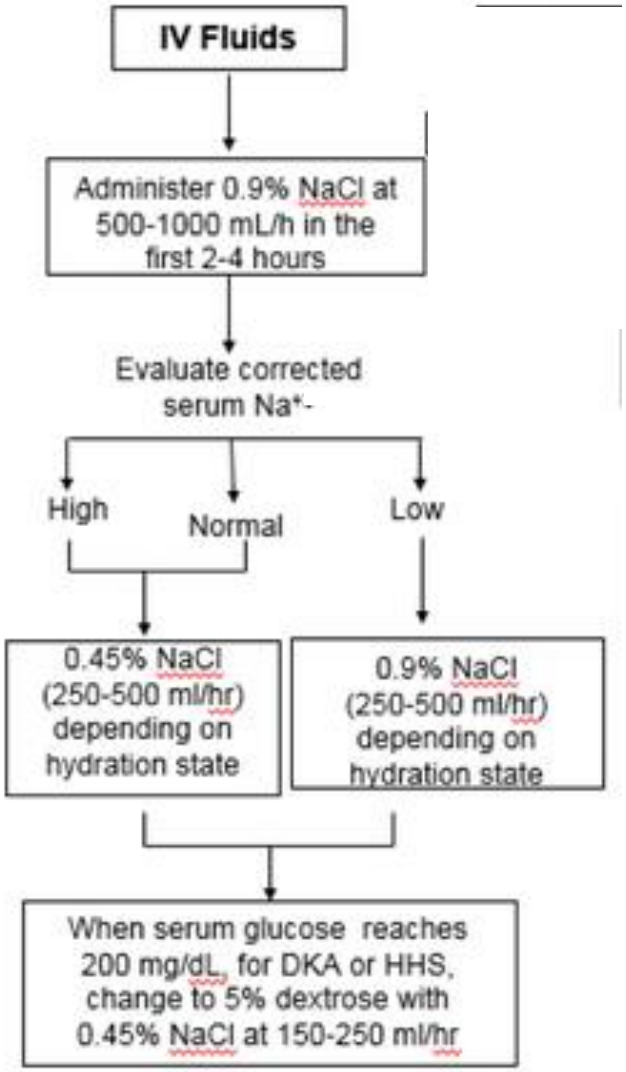
- Anion Gap Acidosis
  - Lactic acidosis
  - Toxin ingestion
  - Aspirin overdose
  - Uremia
- Ketosis
  - Alcoholic ketoacidosis
  - Starvation ketosis

Treatment: Four-Pronged Approach

- Fluids
- Electrolytes
- Insulin
- Cause
  - Causation should be investigated simultaneously with initiation of treatment

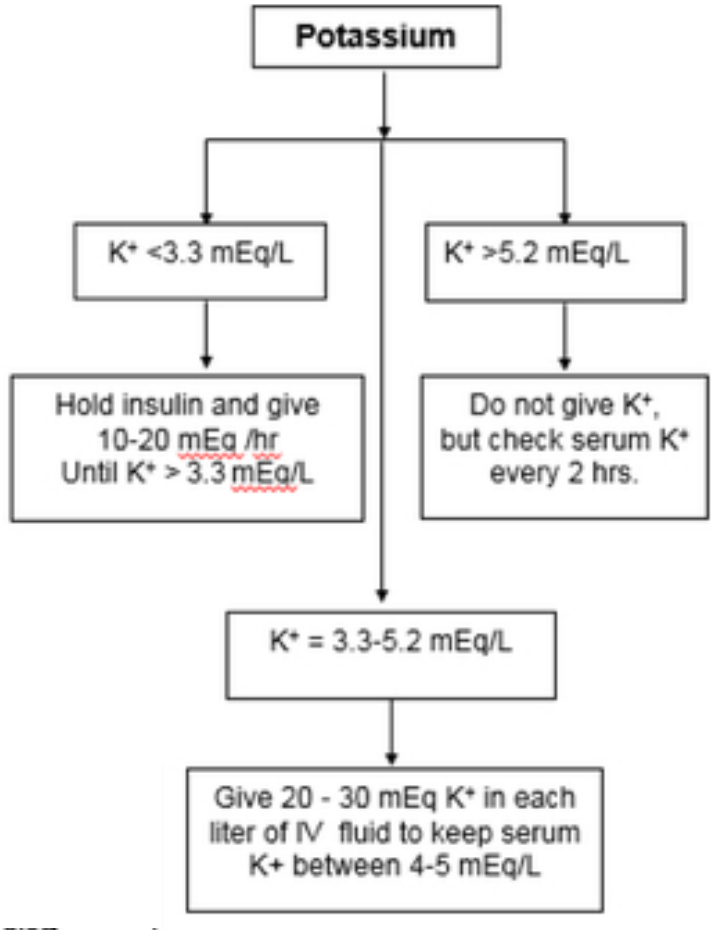
Treatment of DKA/HHS: Fluids

- Fluid deficits can be substantial
  - DKA up to 3-5 liters
  - HHS 5-9 liters
- Fluids should initially be replaced with normal saline
  - 1 liter/hour or 15-20 ml/kg/hour for at least 1 hour
- Use caution in CHF and ESRD



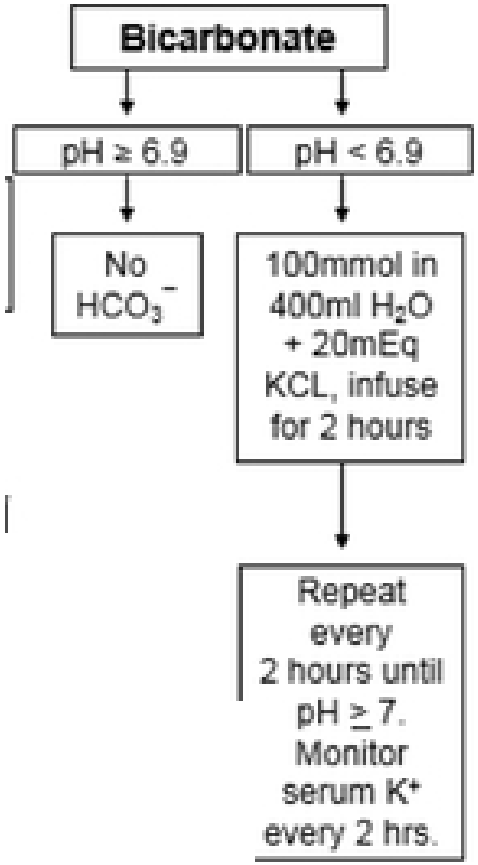
Treatment of DKA/HHS: Potassium

- Insulin and sodium bicarbonate can lower potassium significantly
- Never administer insulin or bicarbonate until potassium level is available
- Assume potassium depletion exists except in ESRD
- Fluids will help to lower glucose initially



Treatment of DKA/HHS: Bicarb and Phosphate

- Bicarbonate
  - In general, supplementation with bicarbonate is not necessary and may worsen hypokalemia
  - Consider supplementation if pH ≤6.9
- Phosphate
  - Insulin and fluid replacement will lower phosphate
  - Replacement not necessary unless phosphate<1.0 mg/dl
  - Milk is a good source of phosphate when patient is eating



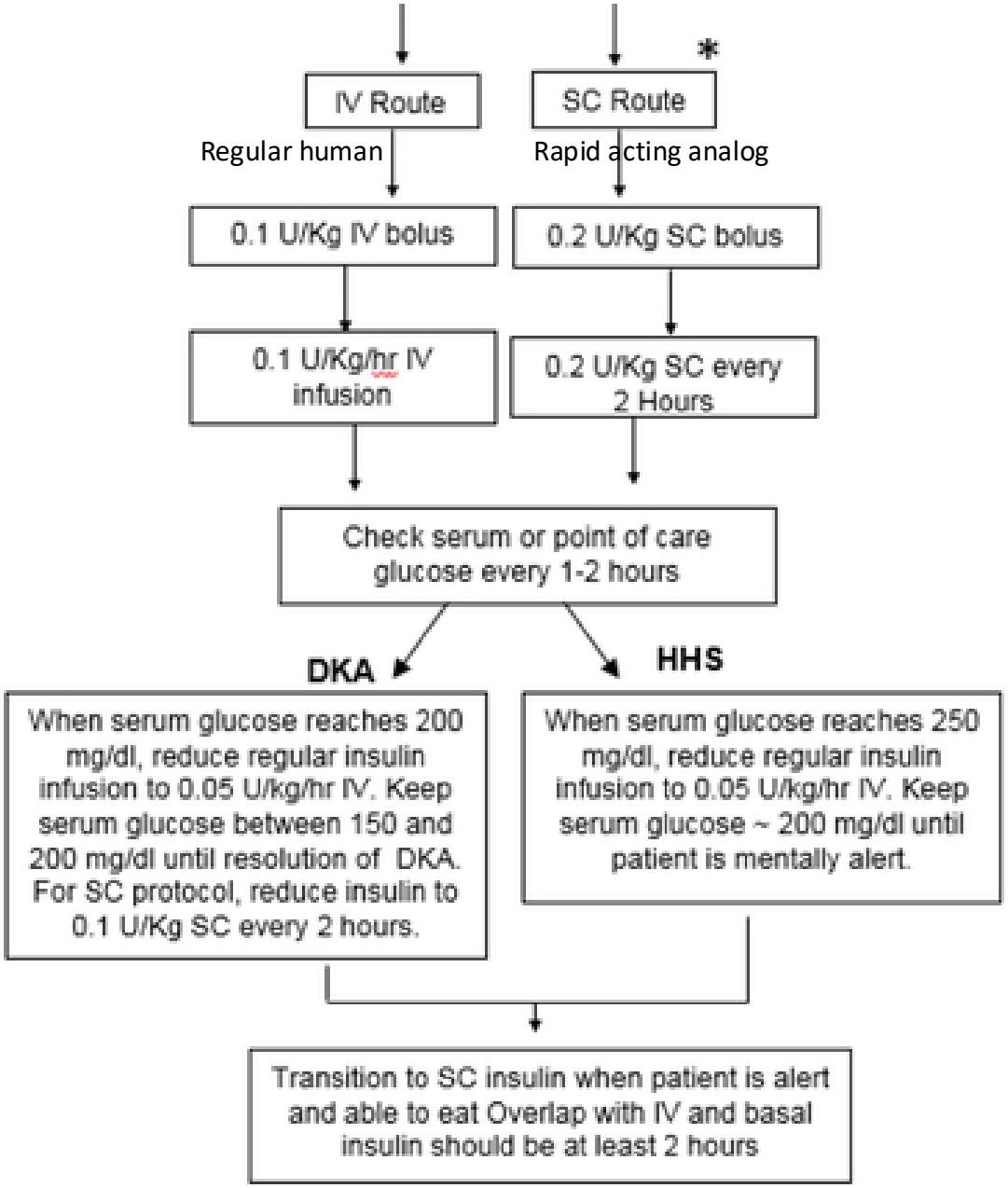
Initiating Insulin

- IV insulin is most commonly used for management
- Regular human insulin should be used(not analog insulin)
- Initial bolus should be .1 units/kg iv
- Initial drip rate should be .1 units/kg/hour
- Drip rate should not be adjusted unless glucose fails to decrease
- Glucose should be checked every 1-2 hours.
- POC testing generally is not valid if glucose is over 500 and sample will need to be sent to lab

What About SC Insulin?

- Subcutaneous regimens are available for mild to moderate DKA
- Do not use in severe or complicated DKA or HHS
- Do not use if patient is significantly dehydrated
- Use a rapid-acting analog insulin such as aspart or lispro

INSULIN


IV Route
SC Route
*
Regular human
Rapid acting analog
0.1 U/Kg IV bolus
0.2 U/Kg SC bolus
0.1 U/Kg/hr IV infusion
0.2 U/Kg SC every 2 Hours
Check serum or point of care glucose every 1-2 hours
DKA
HHS
When serum glucose reaches 200 mg/dl, reduce regular insulin infusion to 0.05 U/kg/hr IV. Keep serum glucose between 150 and 200 mg/dl until resolution of DKA. For SC protocol, reduce insulin to 0.1 U/Kg SC every 2 hours.
When serum glucose reaches 250 mg/dl, reduce regular insulin infusion to 0.05 U/kg/hr IV. Keep serum glucose ~ 200 mg/dl until patient is mentally alert.
Transition to SC insulin when patient is alert and able to eat Overlap with IV and basal insulin should be at least 2 hours

Treatment of DKA/HHS: Transition to sc insulin

- Patient should be clinically stable
- Resolution of episode by laboratory tests
  - DKA
    - Glucose <250mg/dl and 2 of 3: bicarbonate≥18meq/L mEq/l, venous pH >7.3, AG<12
    - NaCl containing fluids can lead to a phase of hyperchloremic acidosis with no AG
  - HHS
    - Serum osms <310, glucose <250mg/dl and baseline mental status

Transition to sc insulin

- Weight based dose calculation
  - Calculate total daily dose: 0.5 units/kg/day split 50% basal(long-acting) and 50% divided among meals(rapid acting)
  - Insulin resistance can exist and doses as high as 0.6 units/kg/day have been suggested
- Continue insulin drip for *at least* 2 hours after initial sc insulin dose given (give rapid acting and basal) and 4 hours if giving basal alone
- Correctional insulin(sliding scale) to start after drip stopped
- Patients with established insulin doses can be restarted as appropriate based on home dosing

Nature Reviews Endocrinology 12:222, 2016

Treatment of DKA/HHS:Complications

- Hypokalemia can be dangerous
- Hypoglycemia is avoidable with adequate monitoring
- Hypophosphatemia usually does not require treatment
- Hyperchloremic acidosis due to use of normal saline will resolve on its own
- Cerebral edema occurs in up to 1% of children but is rare in adults
    - Actual cause not known
    - Avoid rapid lowering of plasma osmolality
    - Mortality up to 70%

Take Home Messages

- Thyroid Storm
  - Diagnosis requires clinical suspicion in appropriate setting
  - Prompt treatment includes anti-thyroid medication, iodine,dexamethasone and beta-blockers
- Myxedema Coma
  - Diagnosis requires clinical suspicion in appropriate setting
  - Treatment includes iv steroid replacement and iv thyroid hormone

Take Home Messages

- Adrenal insufficiency
  - Diagnosis can be confirmed by ACTH stimulation testing
  - Treatment includes glucocorticoid replacement; mineralocorticoid replacement if primary adrenal insufficiency present
- Hypercalcemia
  - Fluid replacement with saline initial therapy
  - Iv bisphosphonate therapy if adequate renal function
  - Identify etiology

Take Home Messages

- Hyperglycemic crises (DKA/HHS)
  - Fluids and insulin are mainstay of treatment
  - K management very important
  - Identify etiology is equally important
  - Transition to subcutaneous insulin when appropriate