**Academic Half Day – Endocrine Emergencies**

**Facilitator Guide**

Agenda:

1:10 – 1:20 pm Theory Burst

1:20 – 2:15 pm Small Groups: Case 1

2:15 – 2:30 pm Questions with the Expert

2:30 – 2:40 pm Break

2:40 – 3:20 pm Small Groups: Cases 2 & 3

3:20 – 3:30 pm Questions with the Expert

**Case 1**

A 65 yo man with HTN, CVA, and recent diagnosis of atrial fibrillation 2 months ago presents with 1 month of progressive generalized weakness and dizziness that is now affecting his ability to do his ADLs. He has lost 10 lbs during this time. He has a history of tobacco use with a 40-pack year smoking history. He has a family history of lung cancer. He is taking warfarin, diltiazem ER, lisinopril, and simvastatin.

Brief exam: BP 84/60, irregular HR 105/min, appears generally fatigued and drowsy

Labs: Hgb 10.6, Na 131, K 5.0, INR of 7.3. CXR normal. Blood cultures are pending.

**What else do you want to look for on the exam? Provide the information below as requested by the learners.**

HEENT: Lips dry and cracked, hyperpigmentation of gums and lips   
CV: No murmurs, no JVD, warm and well perfused  
Resp: CTAB, no crackles   
Abd: soft, nontender, no CVA tenderness  
Neuro: Follows simple commands, moves all extremities

## **Discuss your diagnostic schema for shock. What general diagnoses are you considering and why?**

* + Shock differential includes cardiogenic, hypovolemic, distributive (septic, anaphylactic, adrenal crisis), obstructive (tamponade, PE), and neurogenic.
  + DDX may be broad in this patient, including
    - Lung cancer with SIADH (given hyponatremia)
    - Pericardial tamponade (malignant)
    - PE
    - Hypovolemic: hemorrhage (supratherapeutic INR) vs non-hemorrhagic.
    - Adrenal crisis: Mix hypovolemic + distributive
      * Volume loss from hypoaldosteronism
      * Warfarin – adrenal hemorrhage
  + In cases of non-specific symptoms in the setting of critical illness, low threshold to consider Adrenal Insufficiency (see below for the underlying differential).
    - Non-specific symptoms: Weakness, fatigue, anorexia, nausea, vomiting, weight loss, abdominal pain, orthostatic hypotension
  + Physical exam findings that are suggestive: hyperpigmentation (ACTH hypersecretion POMC, mechanism reviewed in Q3), hypotension, tachycardia if in adrenal crisis
    - ADRENAL **CRISIS** IS AN **EMERGENCY**!

## **What are the different types of adrenal insufficiency? How will their clinical phenotypes differ?**

Adrenal Insufficiency: Partial or complete lack of production/secretion of adrenocortical steroids. Can be Primary, Central, or Iatrogenic:

* + Primary Insufficiency – failure/disease of the adrenal gland itself
    - There are three layers of the adrenal cortex which secrete three distinct classes of corticosteroids under separate regulatory mechanisms (APPENDIX NUMBER 3).
      * Zona Glomerulosa (Salt) – Mineralocorticoids  Aldosterone
        + RAAS regulation – not affected by pituitary malfunction or central AI
      * Zona Fasciculata (Sugar) – Glucocorticoids  Cortisol
        + Hypothalamus – Pituitary axis regulation
      * Zona Reticularis (Sex) – Sex hormone  DHEA/DHEAS
        + Hypothalamus – Pituitary axis regulation
    - *When the adrenal gland is affected, all cortex layers are affected, so you see glucocorticoid deficiency as well as mineralocorticoid deficiency (hyperkalemia, hyponatremia, hypotension, salt craving)*
    - In US, majority caused by autoimmune destruction (21-hydroxylase antibodies positive)
    - US = Addison’s Disease; Worldwide = TB
  + Central Adrenal Insufficiency
    - Secondary (pituitary) – Diminished ACTH by process destroying pituitary corticotrophs
    - Tertiary (hypothalamus) – diminished CRH due to hypothalamic disease
* Decreased stimulation of Z. Fasciculata via decreased CRH/ACTH, therefore decreased cortisol production
* *Z. Glomerulosa is not affected because it is under control of RAAS. Therefore, central AI is less likely to cause mineralocorticoid deficiency and associated s/sx.*
  + Iatrogenic - #1 cause in adults – exogenous glucocorticoids (a form of central AI)
    - Exogenous steroid suppresses CRH and ACTH via negative feedback, leading to atrophy of Z. Fasciculata and Reticularis, impaired ability to secrete cortisol under stress
    - Aldosterone production is not largely affected

## **Explain the mechanism of hyperpigmentation, hyponatremia, and hyperkalemia in this patient. Based off these labs and physical exam findings, which type of adrenal insufficiency is he likely to have?**

* + Primary adrenal insufficiency (PAI)
  + **Hyperpigmentation**: the lack of cortisol on the negative feedback loop causes an excessive amount of CRH/ACTH released from HP axis  POMC (proopiomelanocortin)  ACTH, MSH  increased melanin production
    - Remember, in central AI, ACTH and its precursors are low, so this is not seen in secondary or tertiary AI.
  + **Hyponatremia & Hyperkalemia:** The Zona Glomerulosa is affected so aldosterone is not secreted. Therefore, the kidney is not retaining sodium and secreting potassium appropriately.
    - May see mild hyponatremia due to cortisol deficiency in central AI leading to CRH production with some stimulation of ADH. \*\*This is how euvolemic hyponatremia happens and why we rule out AI when working up SIADH.
    - *Refer to Appendix number 4 for Aldosterone mechanism of action*

## **What is the differential for the underlying cause of adrenal insufficiency?**

|  |  |
| --- | --- |
| Primary AI | Central AI |
| Autoimmune adrenalitis – Addison’s Disease | Exogenous Glucocorticoid Therapy |
| Infection: TB, fungal, bacterial, HIV, Neisseria | Hypothalamic/pituitary diseases – granulomatous (sarcoid), infectious, infiltrative (amyloid, hemochromatosis), malignancy (lymphoma, pituitary carcinoma versus other brain mets) |
| Metastatic cancer to adrenals: lung, breast, melanoma, GI (destroy most of gland to be  symptomatic) | Cranial Irradiation or surgery which damages the pituitary stalk |
| Adrenal Hemorrhage/infarction – Meningococcemia (Waterhouse-Friderichsen syndrome), anticoagulant therapy puts at high risk, antiphospholipid syndrome, post-op, HIT, DIC | Pituitary apoplexy (infarct), Sheehan’s Syndrome (when significant peri/post-partum bleeding leads to hypotension and pituitary ischemia) |
| Meds: ketoconazole, etomidate, fluconazole -> inhibit steps in cortisol synthesis | Chronic drugs: long-term Megestrol in cachectic patients (has glucocorticoid activity and thus suppresses H-P axis), opiates (unclear mechanism, something to do with tonic inhibition of the HPA axis as many pain receptors are in the hypothalamus and pituitary  expert question? |

1. **How will you make your diagnosis?**
   * Measure baseline morning serum **cortisol** (cut-offs vary depending on resource and lab). Why measure in the AM? Cortisol has a diurnal variation, highest in the AM. Also keep in mind stressors at the time of measurement can falsely elevated cortisol.
     + Less < 3 mcg/dL – highly suggestive
     + >15 makes AI unlikely, would revisit other diagnoses (sepsis, hemorrhage)
     + 3-15 indeterminate – requires a stimulation test
     + Remember, cortisol is 90% protein bound to CBG and albumin

* Pregnancy increases CBG and thus cortisol total levels
* Hypoproteinemia lowers serum cortisol
  + Measure baseline **ACTH**
  + **Cosyntropin Stimulation Test** – a synthetic portion of ACTH. If the adrenal gland is diseased, giving extra ACTH will have no effect on cortisol release.
    - When given Cosyntropin, a normal adrenal gland will raise cortisol levels to >18- 20 mcg/dL after 30-60 minutes.
* Failure to reach > 18 suggests primary adrenal failure
  + - 250 mcg (standard test) is preferred by the Endocrine Society’s 2016 Clinical Practice Guidelines when compared to the low dose 1 mcg test
  + Imaging:
    - CT abdomen if thinking primary AI
    - MRI brain with pituitary protocol if thinking central AI

## **Putting it all together. What would our patient’s labs/tests/clinical presentation look like?**

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Type** | **Cortisol Level** | **Aldo level** | **Renin** | **ACTH** | **DHEA** | **Other** | **Cosyntropin Stim** |
| **Primary** | Low | Low | High | High | Low | Hyperpigmented; low Na, elevated K; more likely to be hypotensive or present in adrenal  crisis | Minimal/no response |
| **Central** | Low | NML | NML | Low | Can be low | Can have low Na but normal K | Modest response |

Our patient:

Serum ACTH: 245 (H)

Baseline serum cortisol: 0.4 ug/dL

Cosyntropin stim test: no response (probably not indicated given the significantly low cortisol level)

CT abdomen: bilateral adrenal hemorrhage, thought to be related to recent initiation of anticoagulation and supratherapeutic INR. No evidence of DIC, HIT, malignancy, embolic source.

## **But wait, I thought this was endocrine emergency half day! Why are we spending all this time on pathophysiology? You’re right – in these cases, stabilize the patient first and then start your work up. How will you treat this patient?**

* + *If you suspect adrenal crisis, treatment should NOT BE DELAYED for diagnostic tests.*
    - If you start hydrocortisone prior to obtaining a cortisol level, be aware that this will artificially elevate your cortisol level.
      * How would you make the diagnosis then? Expert question maybe?
  + Steroids – give hydrocortisone 100 mg IV bolus, then 50 mg IV q6h.
    - Continue until vital signs stabilize and has capacity to take oral medications. Typically continue IV for 1-3 days.
    - Mineralocorticoid replacement is not necessary acutely given the high doses of hydrocortisone and cross reactivity with mineralocorticoid activity.
  + IVF – bolus isotonic fluids immediately; typically 1-3 L. Often use normal saline here for the sodium load.
  + Treat underlying cause, work up sepsis, antibiotics, pressors if needed, etc.
  + \*\*In unconfirmed adrenal insufficiency presenting with concerns for concomitant hypothyroidism, must treat AI prior to initiating replacement thyroid hormones. Supplying thyroxine prior to repleting glucocorticoid deficiency can precipitate a crisis!

## **Your patient is ready for discharge. What medications would you like to discharge him on for his adrenal insufficiency? Are there any important discharge instructions that you would like to educate him about?**

## Medications:

* + - Glucocorticoids: Hydrocortisone 15-25 mg total daily dose divided into 2-3 doses with highest dose in the morning and lowest dose in the late afternoon.
      * If having difficulty with multiple daily doses, can do pred daily, but less ideal.
      * Titrate to lowest dose to relieve symptoms and avoids signs/symptoms of glucocorticoid excess.
    - Mineralocorticoid: fludrocortisone 0.05-0.1 mg/day.
      * Might need to be increased in the summer when salt loss increases.
      * If they develop primary hypertension, treat with sodium restriction and a lower dose of fludrocortisone. DO NOT USE diuretics or spironolactone, since you are counter acting the fludrocortisone.
      * Mineralocorticoid is almost never required in secondary AI.
      * Titrate based on vital signs, serum potassium, plasma renin activity.
    - Maybe stop their warfarin too? They should be on a DOAC if no contraindications for a lower bleeding risk.

## Sick Day Rules during illness and surgery

## Mild stress (i.e. a febrile illness) – increase hydrocortisone (or other steroid) by 2-3x patient’s base dose until recovery. No need to increase fludrocortisone

* + - Major stressors/surgeries:
      * Surgeries require stress dose prior/after and a taper
      * Typically: Hydrocortisone 50 mg q6h x 1 day, then 50 q12 x 1 day, then taper to base dose over 3-5 days
    - Sepsis/shock is usually treated with empiric stress dose steroids with a bolus of 100 mg hydrocortisone regardless of the cortisol level, IVF. Then start scheduled steroids - 200 mg/day in divided doses. This is how we treated our patient initially.

**Case 2**

A 31 yo female is seen in the ED for dizziness, tremors, and fatigue that started about 2 months prior. She delivered her first baby 5 months ago and states she is very sleep deprived. She is otherwise healthy and medical history is unremarkable. Her pregnancy was uneventful, and she did not have gestational diabetes. She is currently breastfeeding. She does note that she has felt slightly short of breath off and on for the past couple of weeks and has been having some colicky abdominal pain for a couple of months for which she underwent CT A/P to rule out nephrolithiasis. She told her PCP who ordered some tests last week but today was so dizzy she decided to go to the ED. She denies drugs, EtOH, tobacco use. Her only medication is prenatal vitamins.

Vitals: T 100.3, P 122, BP 118/74, RR 22, SpO2 99% on RA, Wt 120 lb (pre-baby weight)

Exam: in general, she appears alert, not in any acute distress. She has mild bilateral lid lag without conjunctival injection. She has a smooth enlarged thyroid without neck stiffness. She is tachycardic with a regular rhythm. No JVD, no edema. Lungs are clear. Abd is soft, nontender, no CVA tenderness. On neurologic exam, she is mentating normally, but has a fine tremor in bilateral UEs and has brisk DTRs.

## **What is on your differential?**

* Tachycardia, tremor, mild lid lag, brisk DTR are all concerning for hyperthyroidism/Graves’ disease, especially since today is Endocrine day.
* Additionally given that her temp is elevated and she is tachycardic, you may be concerned about sepsis, PE, toxidromes, serotonin syndrome etc
  + Toxidromes: sympathomimetics vs anticholinergic.
    - Sympathomimetic: Tachycardia, hypertension, hyperthermia, diaphoresis, tremors, dilated pupils, AMS.
      * Meds/drugs: Cocaine, ephedrine, amphetamines, ergots, caffeine
    - Anticholinergic: “Red as a beat, dry as a bone, hot as a hare, blind as a bat, mad as a hatter, full as a flask.”
* Meds/drugs: Antihistamines, antipsychotics, antispasmodics, muscle

1. **What if the patient is agitated with afib and crackles on exam? How would this change your differential?**

* In the setting of mild hyperpyrexia, with tachycardia, tremor, AMS, concerns for heart failure, you’re now more concerned for thyroid storm.
* There are no universally accepted criteria or validated clinical tools for diagnosing thyroid storm.
* Calculate the Burch-Wartofsky Score (see appendix) – high sensitivity, low specificity (higher false positives). Remember, thyroid storm is a ***clinical diagnosis*** and mortality is high if undiagnosed early on.
  + Solve this patients Burch-Wartofsky score together. Score should be: 75
  + >45 highly suggestive
  + <25 highly unlikely
  + 25-45 intermediate

## **What could precipitate thyroid storm in this patient? What are other common triggers?**

* Iodine load – this could be from contrast or amiodarone. When from contrast, this is called the Jod-Basedow Effect. The iodine is used as a substrate for producing more thyroid hormone.
* Other common precipitants – trauma, surgery, infection, MI, discontinuing thioamides, *parturition*.

## **Her TSH comes back undetectable. Free T4 is 2.8 (nl 0.9-2.4), and T3 225 (nl 70-195). Where would you like to admit this patient? Pretend you are inputting your orders into the computer. What medications would you like to start on this patient? *Try to remember as many as you can then refer to appendix number 5.***

* + Ideally, this patient should initially be managed in the ICU, especially if she is altered and starting to show signs of possible decompensated heart failure. Mortality is 8-25%.
  + Beta-blockers for adrenergic symptoms. **Be cautious if patient is in decompensated heart failure.**
    - Propranolol – 60-80 mg PO q4-6 hours to manage heart rate
    - Esmolol alternatively
    - Beta blockade with propranolol has the added benefit of blocking peripheral conversion of T4 to T3.
  + Thionamides to inhibit the synthesis of thyroid hormone.
    - PTU (200 mg PO q4h) for life-threatening thyroid storm is preferred as it has the added benefit of blocking T4 to T3 conversion, however, has worse risk of hepatotoxicity. Can be transitioned to methimazole before discharge from the hospital.
    - Methimazole (20 mg PO q4-6 hr) is preferred for severe, but not life threatening hyperthyroidism due to its longer duration of action and less common hepatotoxicity. Don’t forget agranulocytosis!
    - What if they cannot take thionamides due to side effects or allergy? Thyroidectomy is the treatment of choice. Pretreat with beta blockers, steroids, bile acid sequestrants, and SSKI for approx 5-14 days.
  + Potassium iodine to block thyroid hormone release and synthesis (Wolff-Chaikoff Effect). *Must give at least 1 hour after the first does of thionamide so that the iodine cannot be used as substrate to produce more thyroid hormone.*
  + Glucocorticoids are typically given in life threatening thyroid storm (but not in severe nonlife threatening).
    - They act by blocking T4T3 conversion. They also may theoretically help dampen the immune response in Graves’ disease.
    - Frequently recommended by experts, but the data is limited.
  + Cholestyramine to sequester thyroid hormones and block recycling
    - Thyroid hormone is metabolized by the liver, conjugated and excreted in the bile. Then they are reabsorbed. Cholestyramine interferes with the recycling of thyroid hormone.
    - Be careful when giving other drugs orally though as cholestyramine can interfere with absorption of other oral medications. Should be separate by 2 hours before and 2 hours after.
  + Symptomatic treatment – cooling, fluids
  + Treat precipitating cause

## **Over the next several days, the patient’s symptoms improve drastically. She is afebrile, in normal sinus rhythm, and has no more signs of heart failure. She is tapered off glucocorticoids and maintained on methimazole. She asks you about the plan after discharge. You discuss:**

* Close follow up with endocrinology for dose titration and monitoring of TFTs, LFTs, and CBC.
* Once stable, should undergo radioiodine ablation vs surgery for definitive management of her hyperthyroidism.

1. **What if she gets pregnant again?**

* She should avoid methimazole for the first trimester and take PTU instead. “PTU is PREFERRD in PART 1 of PREGNANCY.”

**Case 3**

A 71-year-old female with a history of HTN, HLD, DM2, depression, and low back pain is brought to the ER by her husband for AMS. She notes progressive fatigue over the past 4 months and reports she was recently diagnosed with depression by her PCP. He notes a 6 lb weight gain during this time. Over the past few days, she was having worsening difficulty rising from her chair and seemed “swollen.” She was seen at an outside ER and given low dose oxycodone to improve her pain. Over the past day, she is much more somnolent and disoriented, prompting the visit to the ER.

ROS: Positive for weight gain, fatigue, chronic constipation, mild exertional dyspnea that has progressed over the last 2 weeks, lower extremity swelling for 2 weeks as well. Difficulty ascending stairs. Mental status change as noted above. Negative for fever, chest pain, vomiting, blood in stools, focal weakness, numbness/tingling, seizures

Vitals: T 95.9, P 44, BP 90/60, R 10, Sat 94% RA

Exam: In general, she is somnolent, but arousable with verbal stimulation. Her head and neck are unremarkable. She is bradycardic, but regular rhythm. No JVD. Her lungs are clear aside from a few fine crackles at the bilateral bases. Her abd is NT/ND. 1+ bilateral lower extremity edema. No rashes.

1. **What are some diagnostic considerations and how would you work them up?**

* This patient presents with hypothermia, bradycardia, decreased perfusion, and depressed mental status. You need to consider: sepsis (from a variety of infectious sources), adrenal insufficiency, myxedema coma, decompensated heart failure, unstable bradycardia/high degree AV blocks.
* Sepsis: Reasonable to obtain CBC/diff, VBG, Blood Cultures, UA, Urine Culture, CXR and to start broad spectrum antibiotics
* Decompensated Heart Failure: Reasonable to obtain BNP, EKG, CXR
* Myxedema Coma: Obtain TSH and Total/Free T4
* Adrenal Insufficiency: Start with CMP, random & AM cortisol

Labs *(learners have these labs)*

Na 128, K 4.8, Cl 92, Bicarb 26, BUN 18, Cr 1.1, glucose 74

WBC 12, Hgb 10 (MCV 90), plt 300.

UA: Trace protein, negative LE/Nitrite

VBG: pH 7.25, pCO2 58

BNP: 50

CXR: Prominent pulmonary arteries, mild pulmonary edema, normal cardiac size

EKG: Sinus Bradycardia with 1st degree AV block PR 200, no concerning ST-T wave changes

## **Based on her GCS and concerns about airway protection, she is intubated. She is started on broad spectrum antibiotics. Subsequently, she requires pressors for hypotension. She is persistently hypothermic and bradycardic. Her TSH returns at 130. Free T4 and T3 are pending. What is her diagnosis and most likely etiology?**

* Myxedema Coma – carries a mortality rate of 30-40%.
* Defined as severe hypothyroid state and mental status changes (does not have to be coma). The most common etiology is Hashimoto’s Thyroiditis and is commonly triggered by infection, MI, stroke, trauma, surgery, sedating meds such as opiates (as in this patient) as well as medications known to cause hypothyroidism including Amiodarone and Lithium.

## **Why is this patient hyponatremic?**

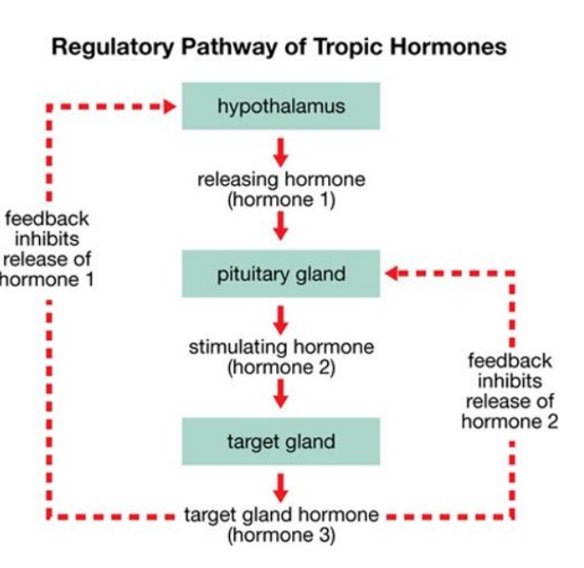
* Present in about half of patients with myxedema coma. This is typically due to impairment in free water excretion due to inappropriate AHD secretion and impaired renal function. Plus, some patients have impaired adrenal function (refer to next question for details) resulting in low aldosterone states.

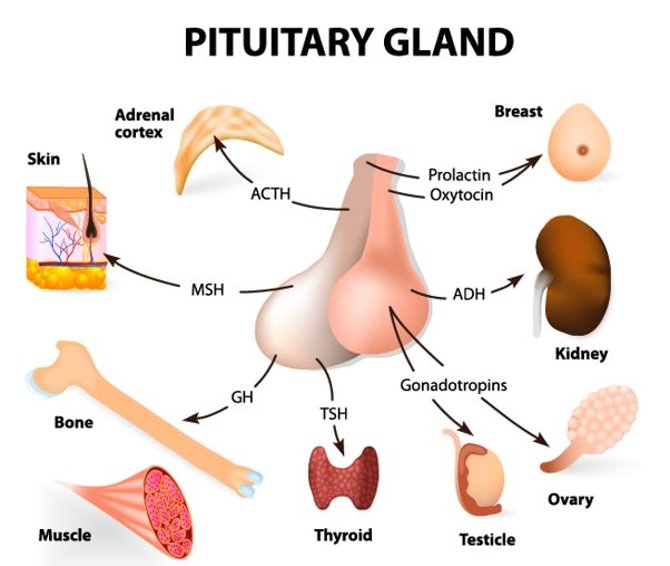
## **FT4 returns undetectable. How do you manage her condition?**

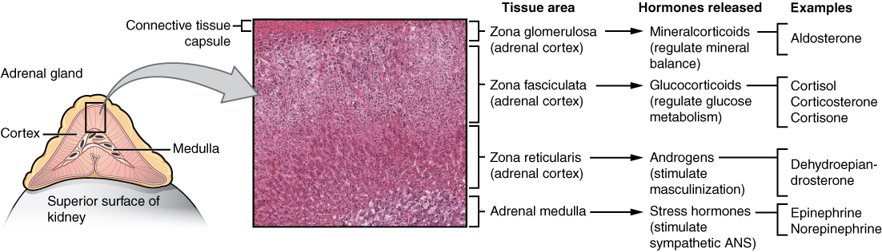
* + Always be concerned for concomitant adrenal insufficiency. This is for three reasons:

1. Patients with central hypothyroidism may have associated hypopituitarism and secondary adrenal insufficiency.
2. Autoimmune-mediated hypothyroidism may have concomitant primary adrenal insufficiency.
3. ACTH secretion may be blunted in severe hypothyroidism, resulting in subnormal cortisol response to stress
   * + Treat with stress dose steroids Hydrocortisone 100 mg IV Q8H
     + Check a cortisol level. If >18 can reasonably d/c steroids
   * Give both IV levothyroxine (T4) and IV liothyronine (T3)!
     + We give both because T3 activity is faster and conversion of T4 to T3 is impaired in acute illness (also we are giving steroids as above which interfere with T4 to T3 conversion).
     + IV Levothyroxine 200-500 ug bolus followed by 50-100 ug IV daily.
     + IV Liothyronine at the same time: 5-20 mcg bolus, then 2.5-10 mcg q8h with lower doses for elderly patient or coexisting cardiovascular disease.
     + Once stable/enteral access is obtained, can convert IV to PO levothyroxine
   * Supportive care: IV fluids (isotonic if already hyponatremic) or diuretics depending on volume status, pressor support, rewarming, dextrose, monitor for arrhythmias, and treatment of underlying cause.
     + External rewarming favored as use of active internal warming has possible association with increased vasodilation and hemodynamic collapse.
   * Monitor for cardiovascular side effects as rapidly increasing thyroid hormone can precipitate ACS and atrial arrhythmias. Should be on telemetry.
   * Measure serum T4 and T3 every 1-2 days. Be sure to measure the levels one hour BEFORE their next dose of T4/T3 are due. Clinical and biochemical improvement is usually seen within one week.

**Appendix:**







Diagram

Description automatically generated 