76 Y.O. PATIENT WITH LETHARGY AND CONFUSION

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Objectives

1. Discuss clinical presentations of severe hypothyroidism/myxedema
2. Discuss treatment guidelines and special circumstances
3. Considerations in high dose/IV thyroid hormones treatment

HPI

76 y.o. female patient was admitted with confusion and lethargy.

Per family patient with past history of post ablation hypothyroidism, noncompliant with medications and drs appointments was noted confused on the day of admission and therefore brought to the hospital.

On further questioning daughter reported patient has been off all medications for possibly many months and in the last few weeks more tired, sleeping more, admitted to cold intolerance, constipation and significant weight gain despite poor PO intake

PMHx

- Post ablative hypothyroidism (many years), per daughter LT4 dose 175mcg, however has not been taking for months
- HTN
- HFpEF
- DM II

Physical exam:

- Blood pressure 114/80, pulse 106, temperature 36.6 °C (97.9 °F), resp. rate 20, height 165.1 cm (5' 5"), weight (!) 142.4 kg (314 lb) SpO2 97 %.

  Appearance: She is obese. She is ill-appearing. Sleeping, arousable to voice, rub but not alert
- HENT: Head: Normocephalic.
- Eyes: Extraocular Movements: Extraocular movements intact. Conjunctiva/sclera: Conjunctivae normal. Pupils: Pupils are equal, round, and reactive to light.
- Neck: No neck rigidity.
- Cardiovascular: Normal rate. Pulses: Normal pulses.
- Pulmonary: Effort: Pulmonary effort is normal. Breath sounds: Normal breath sounds. No stridor.
- Abdominal: Abdomen is flat. There is distension.
- Musculoskeletal: No swelling or deformity.
- Skin: Skin is warm. Capillary Refill: Capillary refill takes less than 2 seconds.
- Neurological: No focal deficit present. Retracts to noxious stimuli in all limbs. Able to say first name but does not respond to other questions. Not currently following commands

Lab results

BASIC & COMPREHENSIVE	
Glucose, Ser/Plasma	206 *
Sodium	140
Potassium, Ser/Plasma	3.3
Chloride	92
Carbon Dioxide	28
Anion Gap	20
BUN	8
Creatinine	1.1
eGFR, Non-African ...	49 *
eGFR, African Amer...	57 *
Calcium	9.3
Inorganic Phosphate	2.1
Magnesium	2.3
Total Protein	8.0
Albumin	4.3
Bilirubin, Total	1.0
Bilirubin, Conjugated	0.2 *
Bilirubin, Unconju...	0.8
Alk Phos, Serum	58

THYROID FUNCTION	
Thyroxine, Free	<0.10 *
Thyroid Stimulatin...	64.21 *
Triiodothyronine	<20 *
Thyroxine	<0.5 *
T3, REVERSE, SERUM	

CELL COUNT & DIFF	
WBC	6.3
RBC	4.06
Hemoglobin	12.2
Hematocrit	38.8
MCV	95.6
MCH	30.0
MCHC	31.4
RBC Dist Width	14.2
Platelet Count	76 *

SARS-CoV 2 RNA ❗
POSITIVE

CK 395

Endocrinology was called for suspected myxedema coma

Thoughts?

Severe hypothyroidism/myxedema coma

- Myxedema coma is a rare life-threatening clinical condition in patients with longstanding severe untreated hypothyroidism, in whom adaptive mechanisms (chronic peripheral vasoconstriction, diastolic hypertension, and diminished blood volume developed to preserve a normal body core temperature) fail to maintain homeostasis.

Key features:

- *- Altered mental status*
- *-Defective thermoregulation: hypothermia.*
- *- Precipitating event* (bleed, inf, meds, CVA, CHF, hypoxia, raw bok choy)

Myxedema coma

- Physical exam
  - Hypothermia
  - Hypoventilation
  - Hypotension, diastolic hypertension
  - Bradycardia
  - dry coarse skin
  - Macroglossia
  - delayed deep-tendon reflexes
- Laboratory features
  - Anemia
  - Hyponatremia
  - Hypoglycemia
  - Hypercholesterolemia
  - High serum creatine kinase concentrations

Scoring system

Thermoregulatory dysfunction (Temperature °F/°C)	Points
>95/35	0
89.6-95/32-35	10
<89.6/32	20
Central Nervous System Effects	
Absent	0
Somnolent/Lethargy	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 Dysfuntion	
Bradycardia/Heart rate	
Absent	0
50-59	10
40-49	20
<40	30
Other EKG changes**	10
Pericardial/pleural effusion	10
Pulmonary edema	15
Cardiomegaly	15
Hypotension	20
Metabolic Disturbances	
Hyponatremia	10
Hypoglycemia	10
Hypoxemia	10
Hypercarbia	10
Decrease in GFR	10

*Adapted from Popoveniuc G, ChaNdra T, Sud A, et al. Endocr Pract 2014; 11:1-36.
**Other EKG changes: QT prolongation, or low voltage complex, or bundle branch blocks, or non-specific ST-T changes, or heart blocks.

Total score:
>60 highly suggestive/diagnostic of myxedema coma
25-59 supportive of diagnosis of myxedema coma
< 25 unlikely

Management

- 1. steroids precaution given COVID?

Steroids and COVID

Our Response to COVID-19 as Endocrinologists and Diabetologists

Ursula B Kaiser, Raghavendra G Mirmira, Paul M Stewart

The Journal of Clinical Endocrinology & Metabolism, Volume 105, Issue 5, May 2020, Pages 1299–1301, https://doi.org/10.1210/clinem/dgaa148

Published: 31 March 2020 **Article history**

Healio > News > Rheumatology > Practice Management

Healio Rheumatology

May 21, 2020 | 2 min read

SAVE

Moderate, high dose steroids linked to more severe COVID-19

By Jason Laday

Source/Disclosures +

1,400 cases reported by 288 organizations and more than 300 investigators

Ecancermedicalscience. 2020; 14: 1023.
Published online 2020 Mar 30. doi: 10.3332/ecancer.2020.1023

PMCID: PMC7105332
PMID: 32256706

COVID-19 and treatment with NSAIDs and corticosteroids: should we be limiting their use in the clinical setting?

Beth Russell,[1,*] Charlotte Moss,[1,*] Anne Rigg,[2] and Mieke Van Hemelrijck[1]

suggested that short course of the corticosteroid in the acute phase of infection may effectively alleviate early pro-inflammatory response, but prolonged administration may play a role in enhancing viral replication

Low-cost dexamethasone reduces death by up to one third in hospitalised patients with severe respiratory complications of COVID-19

16 June 2020

Statement from the Chief Investigators of the Randomised Evaluation of COVid-19 thERapY (RECOVERY) Trial on dexamethasone, 16 June 2020

- total of 2104 patients were randomized to receive dexamethasone 6 mg daily 10 days
- Dexamethasone reduced deaths by one-third in ventilated patients (rate ratio 0.65 [95% confidence interval 0.48 to 0.88]; p=0.0003) and by one fifth in other patients receiving oxygen only (0.80 [0.67 to 0.96]; p=0.0021). There was no benefit among those patients who did not require respiratory support (1.22 [0.86 to 1.75]; p=0.14).
- Based on these results, 1 death would be prevented by treatment of around 8 ventilated patients or around 25 patients requiring oxygen alone.

Our patient

- Did receive 1 dose of 100 mg of Dexamethasone that was not continued as serum cortisol returned at 25

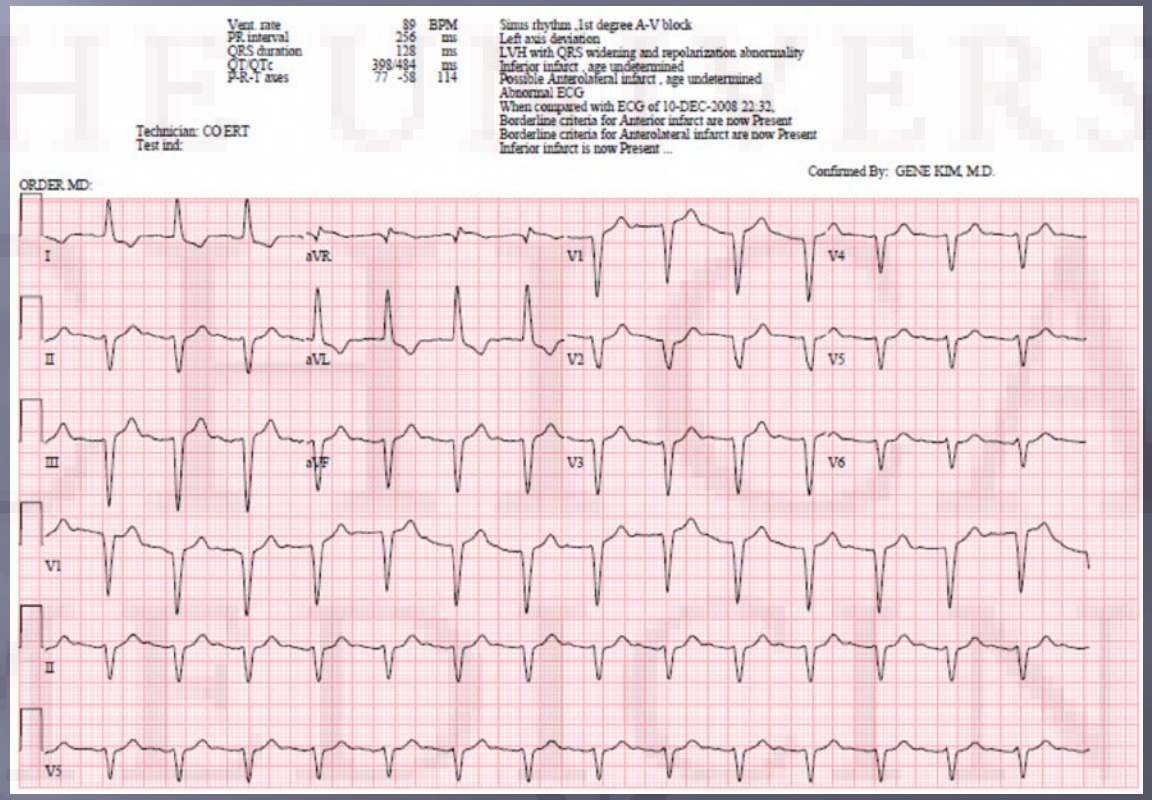
Management

- 2. LT4 dosing and adjustment?

guidelines

- ATA guidelines
  - After glucocorticoid administration
  - LT4 200-400mcg IV loading dose, followed by 75% of 1.6mcg/kg dose IV daily (170mcg/day for our patient)
  - +/- T3 bolus 5-20mcg, followed by 2.5-10 mcg Q8 h maintenance
- Others
  - Glucocorticoids
  - LT4 IV 200-400 mcg loading, followed by 50-100mcg/day
  - +/- T3 bolus 5-20mcg, followed by 2.5-10 mcg Q8 h maintenance

Given data below..



proBNP, N-Terminal		82 *
Troponin T, Quant.		
HIGH SENSITIVITY T...		47 *

Management

- 3. T3 or no T3?

T3 recommendations

- Conversion T4 to T3 likely impaired, however, this impaired conversion may sometimes be a protective mechanism to slow down metabolism in patients who are severely ill, to preserve organ function.
- May cross BBB faster
- Faster onset of action (hours)
- No clear guidelines on T3 use. By most - may be added. Some suggest adding if no expected improvement with LT4 treatment (24h after initiation)
- In some reports associated with increase mortality, especially in higher doses (> 75mcg/day)

Management

- monitoring and dose adjustment? Timing of transitioning to oral form.
- When to expect recovery?

guidelines

- Monitoring T4 and T3 Q24-48h, T3 at least 1 h after last dose
- Assure T3 is not high
- No other data on target levels
- Most patients start to improve w/i 6-36hs

Prognosis

- Mortality 30-50% despite treatment
- MCCOD sepsis, GI bleeding, respiratory failure
- Factors associated with increased mortality (Dutta et al 2008):
  - hypotension
  - bradycardia at presentation,
  - need for mechanical ventilation
  - hypothermia unresponsive to treatment
  - sepsis
  - discontinuation of L-T_4
  - intake of sedative drugs
  - lower GCS
  - higher APACHE II score
  - higher SOFA score ($r = 0.51$; $p = 0.00$)
  - High doses of LT4 (>500) and T3 (over 75mcg) as well as lower dose bolus (Yamamoto, 1999)

How common are cardiac arrhythmias and ACS with high dose and IV TH preparations?

Cardiac complications myxedema

- Sinus bradycardia
- low voltage complexes
- bundle branch blocks, complete heart blocks
- nonspecific ST-T changes.
- prolongation of the QT interval
- polymorphic ventricular tachycardia (torsades de pointes) which reversed with thyroid hormone supplementation
- Reports of hypothyroidism associated A fib, reversed with LT4 Tx
- Hypothyroid state leads sympathovagal imbalanced state, characterized by both decreased cardiovascular sympathetic and vagal modulation. The occurrence of malignant arrhythmias needs to be recognized in long-standing hypothyroidism and myxedema crisis

Incidence of cardiac complications/mortality with treatment

Table 4 Listing of Deaths in Reports Using IV Levothyroxine

Study/Lead Author	Dose of Levothyroxine and/or T3 Administered (µg)	Deaths Reported (% Mortality)
Bacci, 1981	800 µg IV levothyroxine	One death secondary to cardiac arrest 15 minutes after receiving an 800 µg IV bolus (100%)
Arlot, 1991	1000 µg IV levothyroxine	Two deaths: one due to a myocardial infarction on Day 15 after a large dose of IV levo and a second death due to sepsis on Day 9 of treatment (29%).
Yamamoto, 1999	50-1000 µg IV levothyroxine 5-200 µg T3	The highest mortality rate (60%) was seen in high dose T3 (>75 µg/day)
		cohorts. The lowest mortality rate (9%) was seen with lower doses of levothyroxine (<500 µg).
Rodriguez, 2004	100-500 µg IV levothyroxine	Four deaths were reported (36%). Mortality was in the group that received less than 500 µg compared with the group that received >500 µg.
Dutta, 2007	150-500 µg IV	Twelve patients died (12/21, 52%), with sepsis as the primary underlying factor.

FDA

J Epidemiol. 2017 Mar; 27(3): 117–122.
Published online 2017 Jan 5. doi: 10.1016/j.je.2016.04.002
PMCID: PMC5350620
PMID: 28142035

Clinical characteristics and outcomes of myxedema coma: Analysis of a national inpatient database in Japan

Yosuke Ono,[a,*] Sachiko Ono,[b] Hideo Yasunaga,[b] Hiroki Matsui,[b] Kiyohide Fushimi,[c] and Yuji Tanaka[a]

Retrospective observational study 2010-2013, 149 patients with Myxedema MC comorbidity – CAD (40%)

There were no patients with newly-diagnosed acute myocardial infarction or lethal arrhythmia after admission (four patients were diagnosed with angina pectoris, PVCs, atrial fibrillation, and one with non-sustained ventricular tachycardia). These four patients were not treated with T3

Cardiac complications with treatment

- few studies specifically examined cardiac adverse events following IV levothyroxine to treat myxedema coma (Holvey, Arlot, Ridgeway).
- Two of the articles (Holvey, Ridgeway) did not observe any negative cardiac effects following treatment with doses of IV levothyroxine below 750 µg.
- The other (Arlot) observed negative cardiac effects following high doses of levothyroxine (1000 µg).

- No incidence of cardiac complications with IV LT4 treatment reported by manufacturer
- Clinical studies with use of T3 in CHF (Malik 1999) and post MI (Pingitore, 2019 (associated with low T3 syndrome) showed safety and benefits

- ROOS ET AL. (2004) concluded that a full starting dose is safe, more convenient, and more cost effective.
- IV LT4 treatment of hypothyroidism in patients with no known preexisting CAD revealed no cardiac SE (Ladenson, 1982)

Back to our patient

	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9	Day 10	Day 11	Day 12	Day 13	Day 14	Day 15	Last
Vital S (HR)	90-120	70-90	60s	60s	60-70	70	80s. 140s	80s	80s	80s	80s	80s	80s	80s	80s	80s
Mental status	obtunded	obtunded	leth			better				confused		drowsy	AAx2	Awake, conf		
FT4	<0.01	0.34	0.38	0.55	0.65	0.64	0.43	0.54	0.85	0.69	0.76	0.79	0.9	0.99	1.07	1.4
T3	<20	25	27	35	47	46	77	124	136	107	104	100	77	92	82	73
TSH	64												24			13
Troponin	47	59	54													
Treatment (T4, T3)	200 5	50 2.5	75 2.5	75 2.5	100 2.5	100 2.5	125 5	125 5	125 5	125 5 PO	125 5 PO	125 5 PO	125 5 PO	125 5 PO	125 5 PO	PO 175

Patient's progress

- On discharge: confused and requires signif. amount of assistance
- FT4 1.4; TSH 13.98; T3 73
- Back on Metformin, however in last 3 days of hospitalization required insulin
- Started on Amlodipine during hospitalization as well

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