THE UNIVERSITY OF CHICAGO MEDICINE & BIOLOGICAL SCIENCES

69 M with Hypercalcemia

Caroline Abe, MD, MPH
Adult Endocrinology Fellow
March 13th, 2025

To earn credit for today's activity text code:

GAHTAV to 773-245-0068

Dr. Abe does not have any relevant financial relationships with any commercial interests.

Objectives

- Discuss differential of hypercalcemia
- Review mechanisms of hyperthyroidism induced hypercalcemia
- Review differential and workup of hyperthyroidism
- Review differentiating type 1 and type 2 amiodarone induced thyrotoxicosis
- Discuss management of amiodarone induced thyrotoxicosis in clinical context

HPI

- 69Yrs-old male PMH of Afib, HFrEF s/p LVAD, and HLD
- Past month, having increased drainage from driveline, fatigue, dyspnea on exertion, weakness, weight loss.
- Admitted for LVAD driveline infection, now s/p debridement, on IV antibiotics.
- Endocrine consulted since recently calcium levels have been elevated.

History and Physical Exam

Medical:

- HFrEF s/p LVAD, destination therapy
- Afib
- Chronic subdural hygroma
- HLD

Surgical:

- LVAD

Family:

- No hx calcium problems or thyroid disease

Social:

- Lives at home with family

Medications:

- Amiodarone 200 mg qD
- Doxycycline 100mg BID
- Empagliflozin 10 mg qD
- Furosemide 40 mg qD
- Losartan 25 mg qD
- Magnesium 400 mg qD
- Metoprolol ER 25 mg qD
- Pantoprazole 40 mg qD
- Pravastatin 40 mg qD
- Spironolactone 25 mg qD
- Warfarin 4 mg qD

Objective:

Vitals

T 37, HR 91 MAP 82 by doppler, RR 21, BMI 14.6

Exam

General: cachectic, fatigued
HENT: MMM. No goiter or thyroid nodules.
Eyes: EOMI, no proptosis
Pulm: no inc WOB
CV: LVAD
Abd: +wound vac over driveline
Neuro: moves all extremities, normal reflexes
Psych: answers questions appropriately
Ext: no edema, warm. No tremor.

Labs

- BMP: 139 / 3.5 / 103 / 27 / 11 / 25 / 1.21 (bl 0.7) / 97
- Ca 14.2 / alb 2.9 / Mg 1.8 / Phos 3.5 / ALP 252 (previously normal)
- CBC: 8 / 10.4 (MCV 81.5) / 166
- PTH <6
- 25-OH Vitamin D 37

		Calcium
Ref. Range & Units		8.4 - 10.2 mg/dL
11/20/24	21:01	14.2 ⌃⌃
11/20/24	17:42	14.0 ⌃⌃
11/20/24	05:28	13.9 ⌃⌃
11/19/24	05:20	13.9 ⌃⌃
11/18/24	04:55	12.8 ⌃
11/17/24	06:33	12.2 ⌃
11/16/24	06:10	11.9 ⌃
11/15/24	05:10	12.0 ⌃
11/14/24	05:43	12.3 ⌃
11/13/24	18:51	12.1 ⌃
11/13/24	11:00	12.8 ⌃
10/18/24	09:48	10.1
08/01/24	06:22	8.6
07/31/24	04:37	8.7
07/30/24	04:59	8.7
07/29/24	04:07	8.8
07/28/24	04:03	8.4
07/27/24	14:45	8.5

Review differential and workup of hypercalcemia

TABLE 3

Causes of Hypercalcemia

Parathyroid hormone-related

Primary hyperparathyroidism*

Sporadic, familial, associated with multiple endocrine neoplasia I or II

Tertiary hyperparathyroidism

Associated with chronic renal failure or vitamin D deficiency

Vitamin D-related

Vitamin D intoxication

Usually 25-hydroxyvitamin D_2 in over-the-counter supplements

Granulomatous disease sarcoidosis, berylliosis, tuberculosis

Hodgkin's lymphoma

Malignancy

Humoral hypercalcemia of malignancy* (mediated by PTHrP)

Solid tumors, especially lung, head, and neck squamous cancers, renal cell tumors

Local osteolysis* (mediated by cytokines) multiple myeloma, breast cancer

Other endocrine disorders

Hyperthyroidism

Adrenal insufficiency

Acromegaly

Pheochromocytoma

Genetic disorders

Familial hypocalciuric hypercalcemia: mutated calcium-sensing receptor

Other

Immobilization, with high bone turnover (e.g., Paget's disease, bedridden child)

Recovery phase of rhabdomyolysis

PTHrP = parathyroid hormone-related peptide.

**—The most common causes of hypercalcemia.*

Review differential and workup of hypercalcemia

TABLE 3

Causes of Hypercalcemia

Parathyroid hormone-related

Primary hyperparathyroidism*

Sporadic, familial, associated with multiple endocrine neoplasia I or II

Tertiary hyperparathyroidism

Associated with chronic renal failure or vitamin D deficiency

Vitamin D-related

Vitamin D intoxication

Usually 25-hydroxyvitamin D_2 in over-the-counter supplements

Granulomatous disease sarcoidosis, berylliosis, tuberculosis

Hodgkin's lymphoma

Malignancy

Humoral hypercalcemia of malignancy* (mediated by PTHrP)

Solid tumors, especially lung, head, and neck squamous cancers, renal cell tumors

Local osteolysis* (mediated by cytokines) multiple myeloma, breast cancer

Other endocrine disorders

Hyperthyroidism

Adrenal insufficiency

Acromegaly

Pheochromocytoma

Genetic disorders

Familial hypocalciuric hypercalcemia: mutated calcium-sensing receptor

Other

Immobilization, with high bone turnover (e.g., Paget's disease, bedridden child)

Recovery phase of rhabdomyolysis

PTHrP = parathyroid hormone-related peptide.

**—The most common causes of hypercalcemia.*

Additional workup?

Carroll, MF (2003)

Additional Workup

- Review of CT C/A/P from admission:
  - No evidence of malignancy or lung findings concerning for granulomatous disease
  - “BONES, SOFT TISSUES: Coarsening of the osseous trabecular pattern with cortical thinning likely represents Paget's disease.”

- TFTs:
  - TSH <0.01, FT4 >7.77

Learning Point - Hyperthyroidism as a Cause of Hypercalcemia

- Hypercalcemia due to thyrotoxicosis is well documented
  - Typically mild to moderate
  - Approximately 20% of patients with thyrotoxicosis
- Mechanisms include bone turnover and resorption due to direct effect of T3 on the bone
- PTH is suppressed, reducing 1,25(OH)2 vitamin D levels and renal calcium re-absorption
- Treatment with beta-blocker may reduce hypercalcemia
- Treating hyperthyroidism reverses hypercalcemia

Goltzman (2000), Chen (2017), Britto (1994), Iqbal (2003)

Learning Point - Paget's Disease as a Cause of Hypercalcemia

- Localized bone lesions with increased reabsorption and disorganized remodeling, advances very slowly
- Elevated alkaline phosphatase – first biochemical marker (1929)
- Detected with bone scan using technetium99-m labeled bisphosphonate, shows market increased uptake
- Hypercalcemia in Paget's is rare
  - May occur due to increased bone resorption in immobilization, fractures, primary hyperparathyroidism, or bone metastesis
- Treatment - ZA 5 mg IV, normalizes bone resorption and formation markers for up to 6.5 years
  - Indicated for bone pain, hypercalcemia, neuro deficits from vertebral disease, CHF, prevention of deformity/hearing loss, preparation for orthopedic surgery

Workup of Hyperthyroidism

- TSH < 0.01 (prior 4.98 in 2/2024)
- FT4 > 7.77 (total T4 27.6)
- Total T3 299

Additional workup?

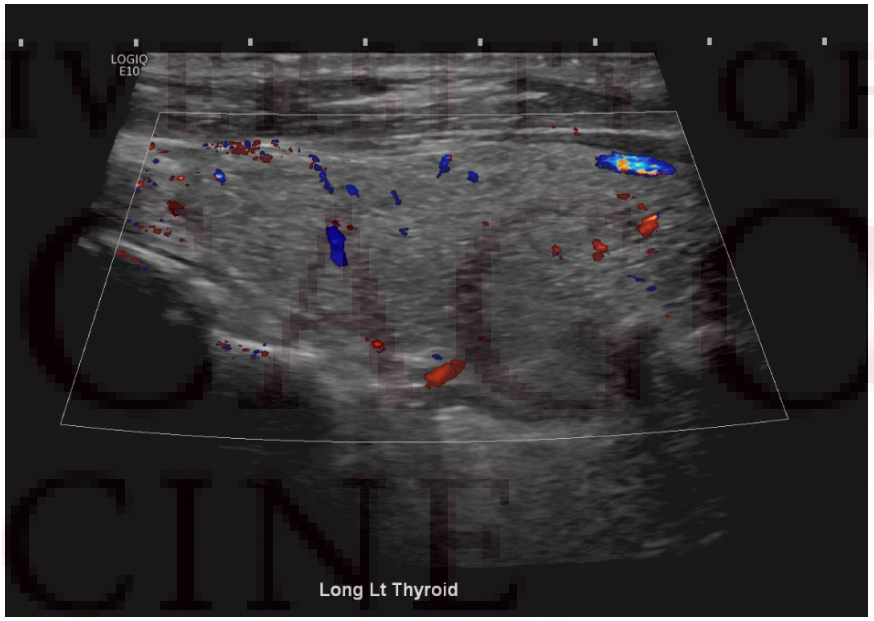
Workup of Hyperthyroidism

- TSH < 0.01 (prior 4.98 in 2/2024)
- FT4 > 7.77 (total T4 27.6)
- Total T3 299
- TSI negative, TPO negative, TgAb negative
- US Thyroid:

  IMPRESSION:

  1. Thyroid within normal limits, no evidence of nodules.

  2. No parathyroid adenoma.
- Recall: hx amiodarone since 8/2023



Type 1 vs Type 2 Amiodarone Thyrotoxicosis Overview

- Epidemiology:
  - AIT occurs in 3% of patients on amiodarone in North America (more common in low iodine countries)
  - M:F 3:1
- Signs and symptoms:
  - Not apparent in all patients, may be obscured by underlying cardiac condition
  - May present as reappearance or exacerbation of underlying cardiac disorder, such as recurrence of atrial fibrillation and palpitation, or changes in warfarin sensitivity (increased warfarin effect)
- Type 1 – abnormal thyroid gland, increased thyroid hormone synthesis due to iodine excess
- Type 2 – destructive process of gland leading to release of pre-formed hormone (intrinsic toxic effect of amiodarone)

Type 1 vs Type 2 Amiodarone Thyrotoxicosis

Table 1.

Differences between Type 1 and 2 Amiodarone Induced Thyrotoxicosis

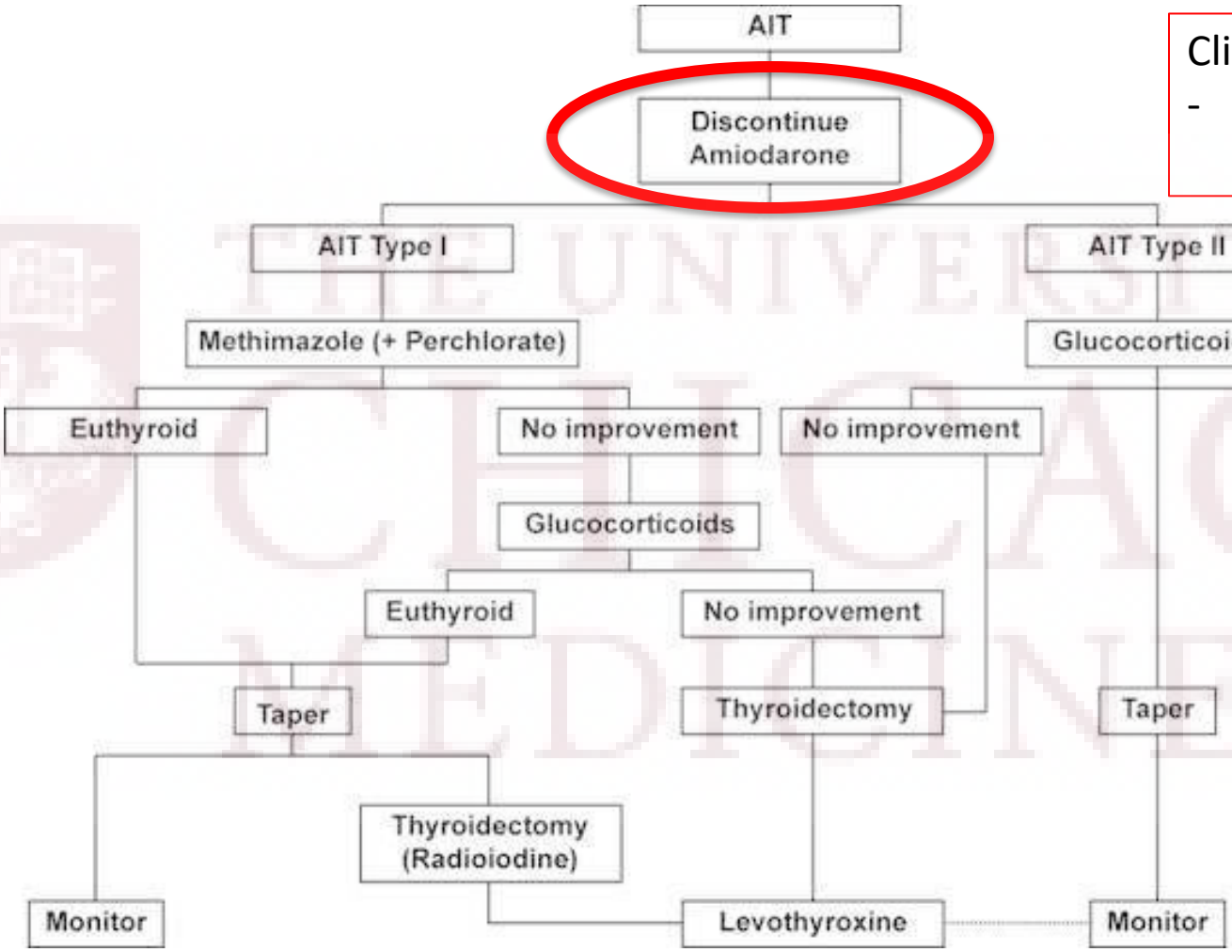
	Type 1	Type 2
Underlying thyroid disease	Yes (Multinodular goiter, Grave's)	No
Time after starting amiodarone	Short (median 3 months)	Long (median 30 months)
24-hour iodine uptake	Low-Normal (may rarely be high in iodine deficient regions)	Low to Suppressed
Thyroid Ultrasound	Diffuse or Nodular Goiter may be present	Normal or small gland
Vascularity on Echo-color Doppler ultrasound	Increased	Absent
T4/T3 ratio	Usually <4	Usually >4
TgAb / TPOAb/ TSI	May be present	Usually absent
Circulating interleukin-6	Normal to high	Sometimes markedly elevated but usually doesn't differentiate from AIT1

Macchia, PE (2000)

Diagnosis

- Amiodarone induced thyrotoxicosis
  - Likely Type 2 > Type 1
- Severe hypercalcemia
  - Due to thyrotoxicosis
  - Perhaps component of Paget's and immobility

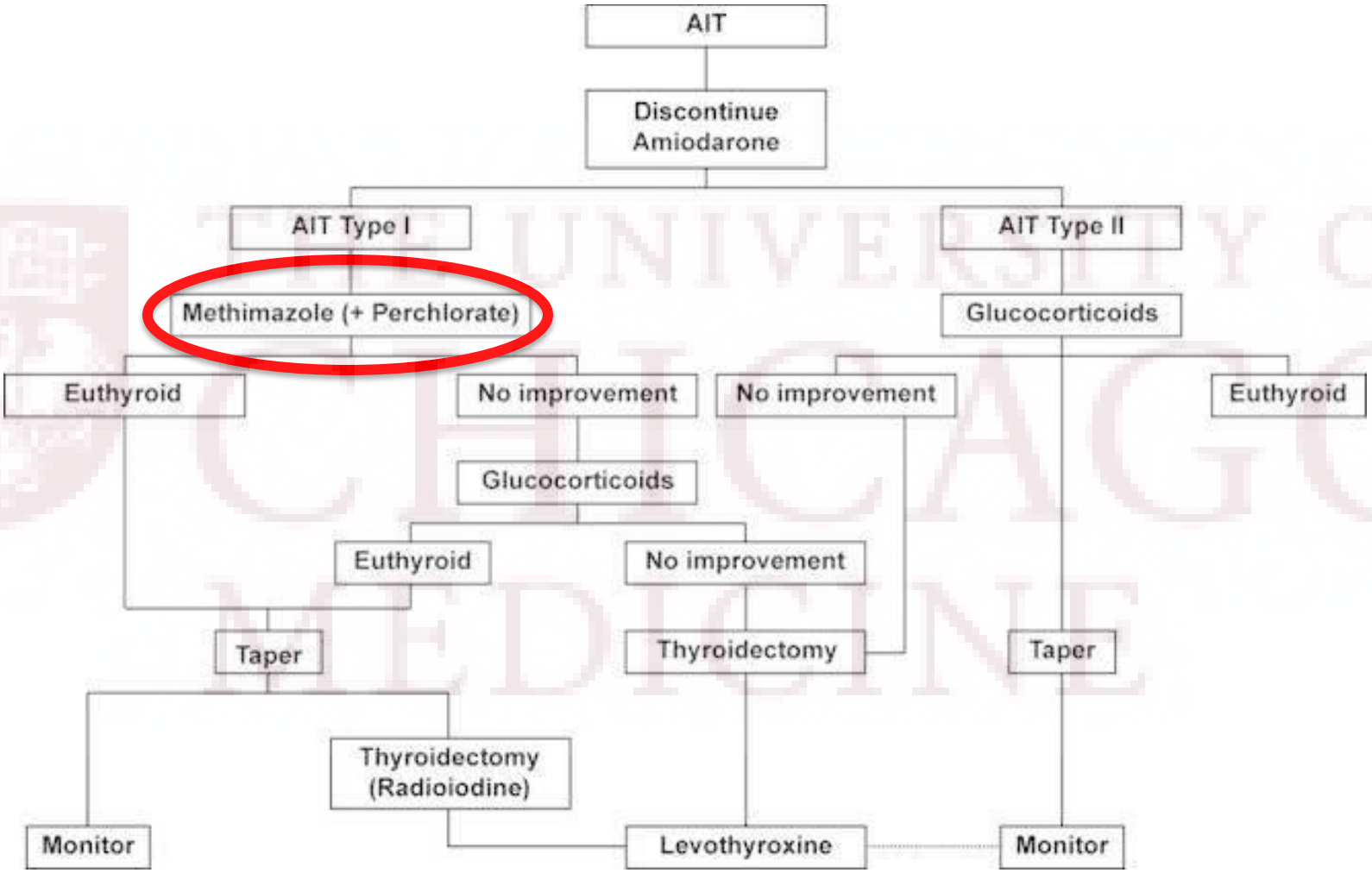
Management



Clinical factors:
- Able to digoxin load instead

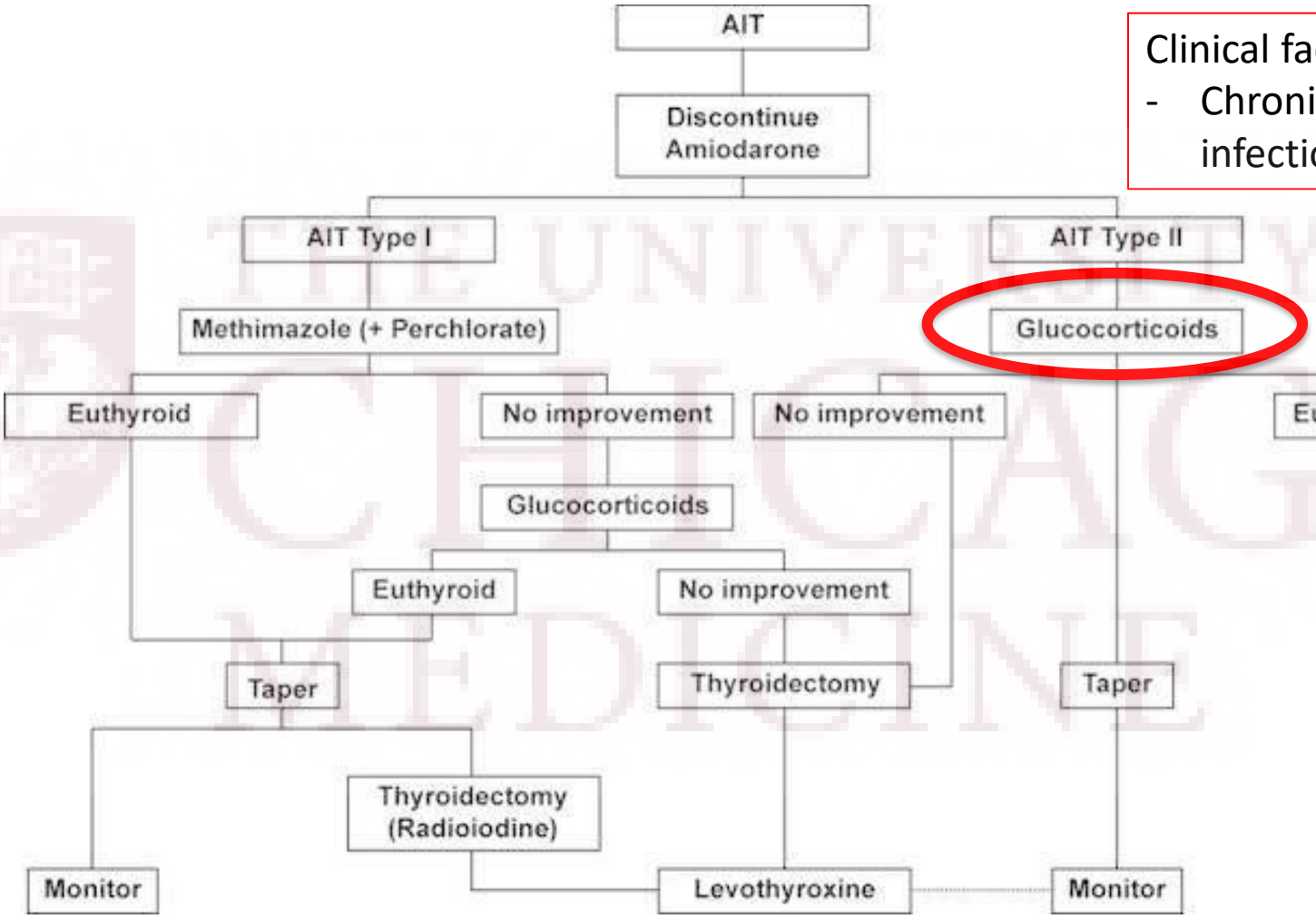
Macchia, PE (2000)

Management



Macchia, PE (2000), Lisco (2024)

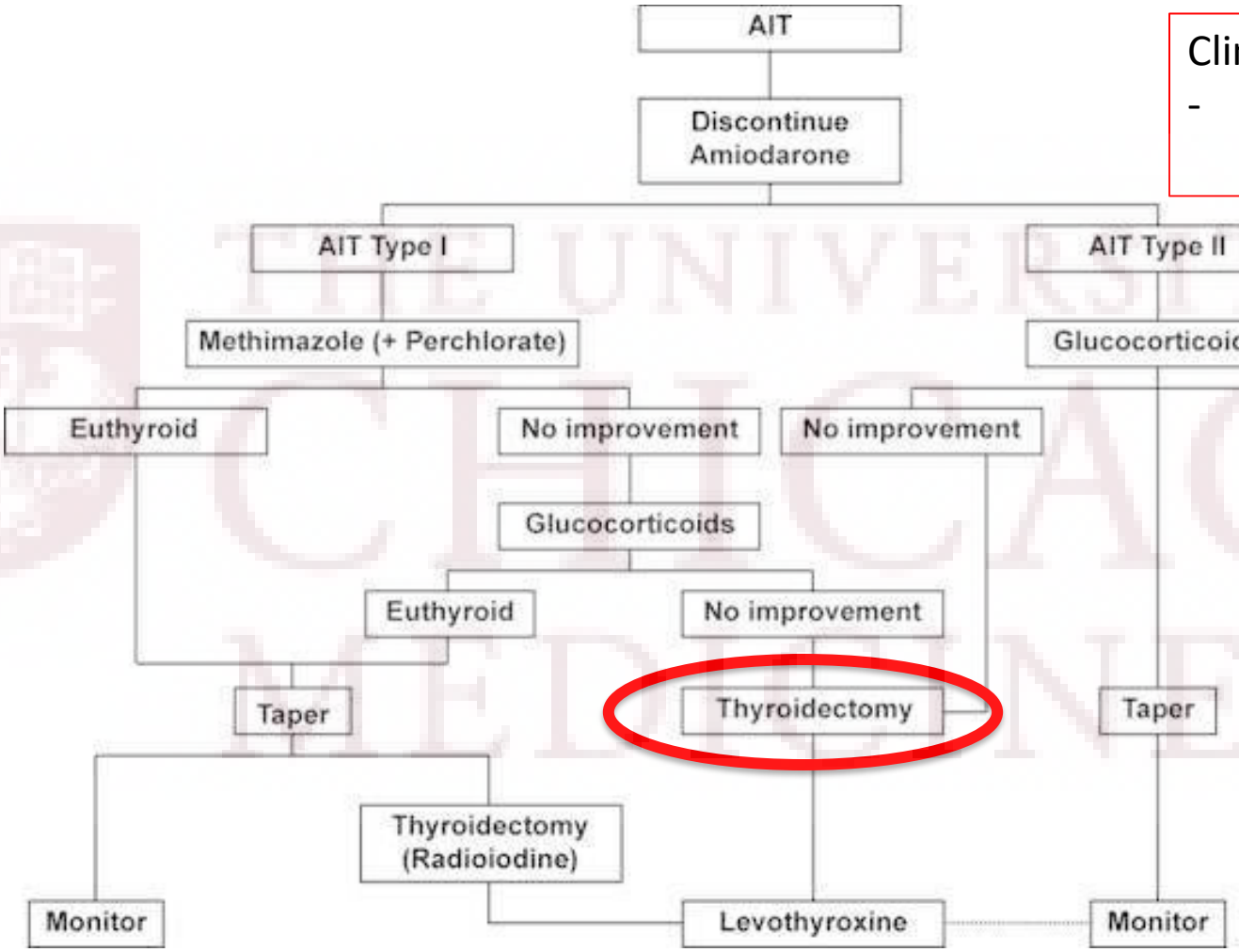
Management



Clinical factors:
- Chronic driveline infection

Macchia, PE (2000)

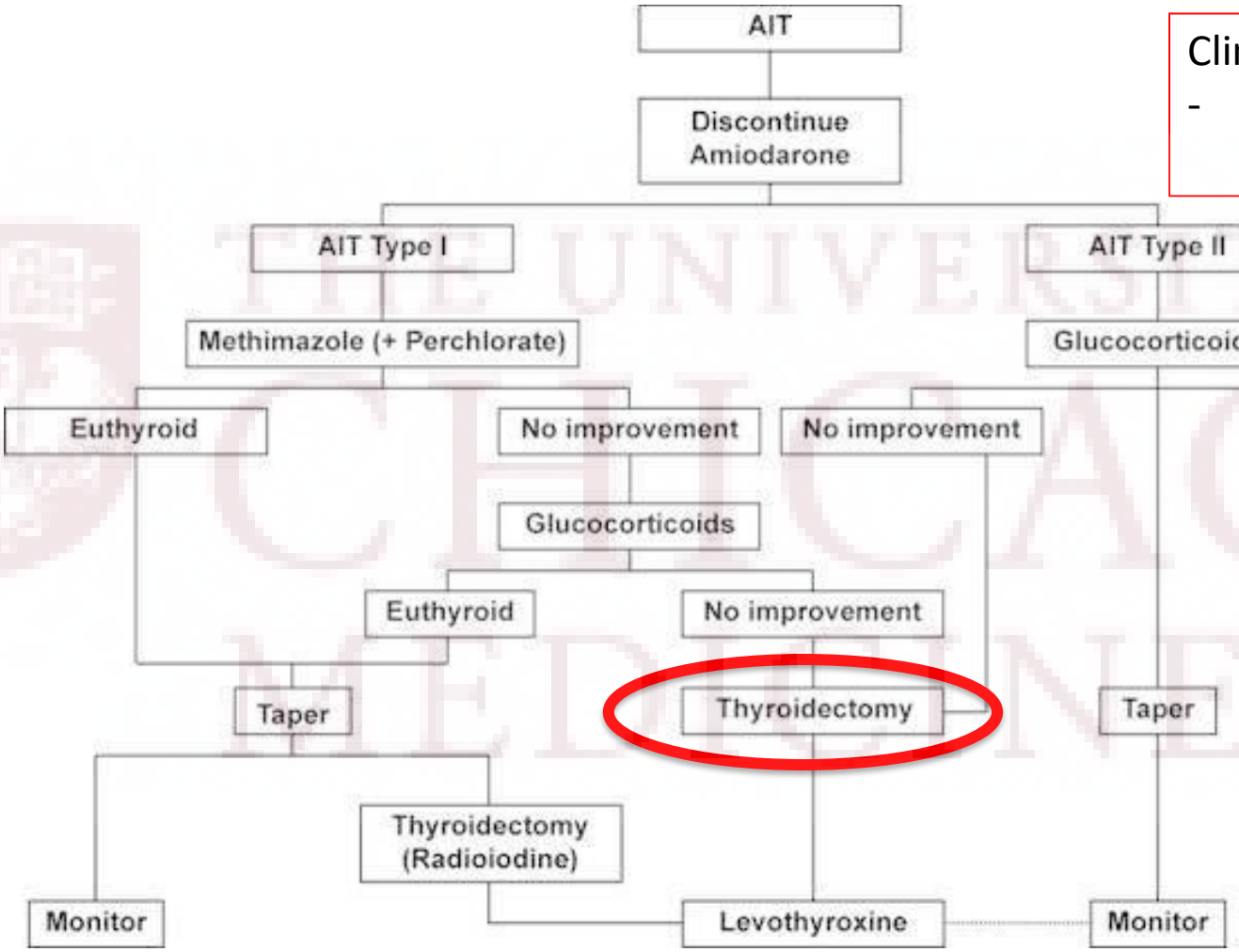
Management



Clinical factors:
- Is this patient a surgical candidate?

Macchia, PE (2000)

Management



Clinical factors:
- Is this patient a surgical candidate?

Next steps?

Management

- Complicating factors of driveline infection
  - Prednisone initially deferred due to infection
  - Methimazole 20 mg BID + cholestyramine 4 g q6
- Endocrine surgery consulted:
  - LVAD is definitive therapy, pseudomonas driveline infection likely develop abx resistance in future
  - High perioperative risk (NSQIP mortality >12%, complication >40%), but suspected higher
  - Meaningful benefit from thyroidectomy in terms of quality of life or extending life does not outweigh the risks of mortality or life-limiting/changing complications from surgery
- Discussion with cardiology and infectious disease:
  - Started prednisone 30 mg daily x3 months
  - + PJP prophylaxis

Management Hypercalcemia

- Calcitonin and fluids initially
- Zoledronic acid 4 mg IV x1

Clinical course

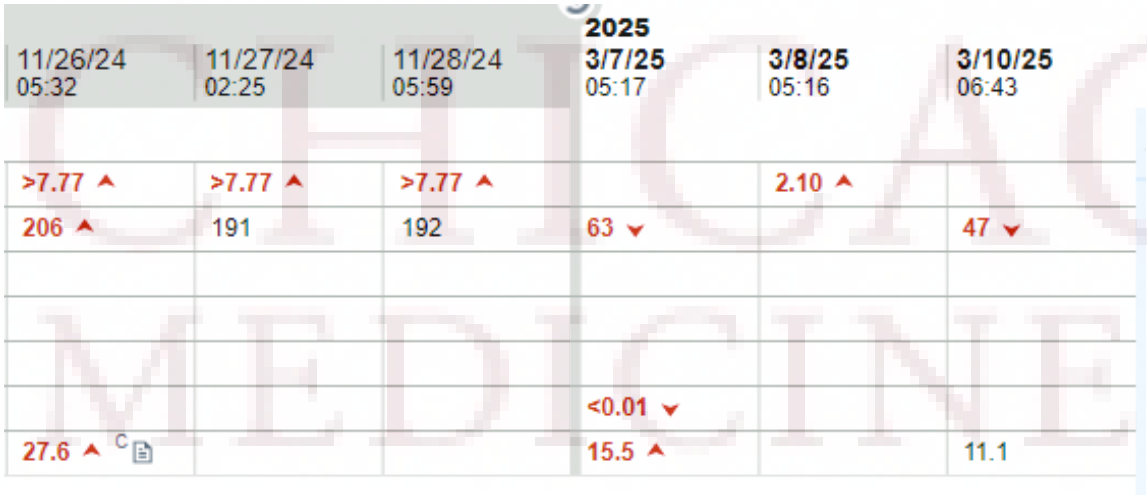
- Discharged to SNF on prednisone 30 mg daily, methimazole

Clinical course

- Discharged to SNF on prednisone 30 mg daily, methimazole
- Admitted again!
  - Coming in for supratherapeutic INR, driveline bleeding
  - Since discharge from SNF, has run out of prednisone and methimazole (past 1-2 months)

Clinical course

- Discharged to SNF on prednisone 30 mg daily, methimazole
- Admitted again!
  - Coming in for supratherapeutic INR, driveline bleeding
  - Since discharge from SNF, has run out of prednisone and methimazole (past 1-2 months)



	11/26/24 05:32	11/27/24 02:25	11/28/24 05:59	2025 3/7/25 05:17	3/8/25 05:16	3/10/25 06:43
	>7.77 ▲	>7.77 ▲	>7.77 ▲		2.10 ▲	
	206 ▲	191	192	63 ▼		47 ▼
				<0.01 ▼		
	27.6 ▲ C			15.5 ▲		11.1

  - Next TFT check in endo discharge clinic in 1 month

Take Home Points

- Hypercalcemia occurs in 20% of patients with hyperthyroidism, due to T3 mediated effect on bone
- Paget's disease rarely causes hypercalcemia, but may in certain situations
- Type 1 and type 2 amiodarone induced thyrotoxicosis can be difficult to differentiate, the latter is suggested with negative antibodies, normal appearing gland, no increased vascularity
- Type 2 AIT is treated with stopping amiodarone, steroids, or thyroidectomy
- Multidisciplinary approach is important in complex patient situations

Special thank you to Dr. Dickens and Dr. Ettleson, attendings on service!

References

- Britto JM, Fenton AJ, Holloway WR, Nicholson GC. Osteoblasts mediate thyroid hormone stimulation of osteoclastic bone resorption. Endocrinology. 1994;134(1):169-176.
- Carroll MF, Schade DS. A practical approach to hypercalcemia. Am Fam Physician. 2003;67(9):1959-1966.
- Chen K, Xie Y, Zhao L, Mo Z. Hyperthyroidism-associated hypercalcemic crisis: A case report and review of the literature. Medicine (Baltimore). 2017;96(4):e6017.
- Goltzman D. Approach to Hypercalcemia. In: Feingold KR, Anawalt B, Blackman MR, et al., eds. Endotext. South Dartmouth (MA)2000.
- Iqbal AA, Burgess EH, Gallina DL, Nanes MS, Cook CB. Hypercalcemia in hyperthyroidism: patterns of serum calcium, parathyroid hormone, and 1,25-dihydroxyvitamin D3 levels during management of thyrotoxicosis. Endocr Pract. 2003;9(6):517-521.
- Lisco G, Accardo G, Pupilli C, Malandrino P, De Geronimo V, Triggiani V. Perchlorates in the treatment of hyperthyroidism and thyrotoxicosis: a comprehensive review. Endocrine. 2024;85(1):1-10.
- Macchia PE, Feingold KR. Amiodarone Induced Thyrotoxicosis. In: Feingold KR, Anawalt B, Blackman MR, et al., eds. Endotext. South Dartmouth (MA)2000.
- Singer FR. The evaluation and treatment of Paget's disease of bone. Best Pract Res Clin Rheumatol. 2020;34(3):101506.

THE UNIVERSITY OF CHICAGO MEDICINE & BIOLOGICAL SCIENCES

ENDORAMA

March 13, 2025

Presented by:

Caroline Abe, M.D.

To earn CME credit for today's activity, UofC Faculty, Residents, Fellows, and Health Care Professionals, text code:

GAHTAV

to: **773-245-0068**