THE UNIVERSITY OF CHICAGO
MEDICINE & BIOLOGICAL SCIENCES

A 66-year-old man with thyrotoxicosis

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DUSNUG to 773-245-0068

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

Objectives

- Review the pharmacological management of severe thyrotoxicosis
- Review the side effects of antithyroid drugs
- Review the surgical management of thyrotoxicosis

HPI

- 66-year-old M with prostate cancer with mets (bones), opioid use disorder, CAD who initially was seen by UCMC Endocrinology in 8/2021
- Presented after being found down after heroin use
- In ED, found to be altered and in afib with RVR treated with β-blockers
- Denies prior history of thyroid disease or afib, recent viral illness, neck tenderness, amiodarone use.

Initial Labs

- TSH < 0.01 FT4: 2.92 TT3: 209
- CTA: Multinodular goiter with asymmetric enlargement of the right thyroid lobe

Differential?

Treatment?

<u>Short Differential</u>
- Toxic MNG/adenoma
- Graves'
- Thyroiditis

<u>Our Recommendations</u>
- Start MMI 20mg daily
- Obtain Thyroid US
- Obtain TSI and TRAb

Response:

	08/13/21	08/14/21	08/15/21	08/16/21
WBC	7.5	7.3	2.9 (L)	2.2 (L)
Hemoglobin	10.9 (L)	10.1 (L)	10.0 (L)	10.1 (L)
Hematocrit	33.9 (L)	32.5 (L)	31.5 (L)	30.7 (L)
Platelet Count	322	286	237	265
Neutrophils	81 (H)		47	45
Lymphocytes	11 (L)		29	30
Abs Neutrophils	6.05		1.32	1.02 (L)

Are we concerned?

ATDs and agranulocytosis

Definitions

Neutropenia

Mild: ANC 1000-1500

Mod: ANC 500 - 1000

Severe: ANC < 500

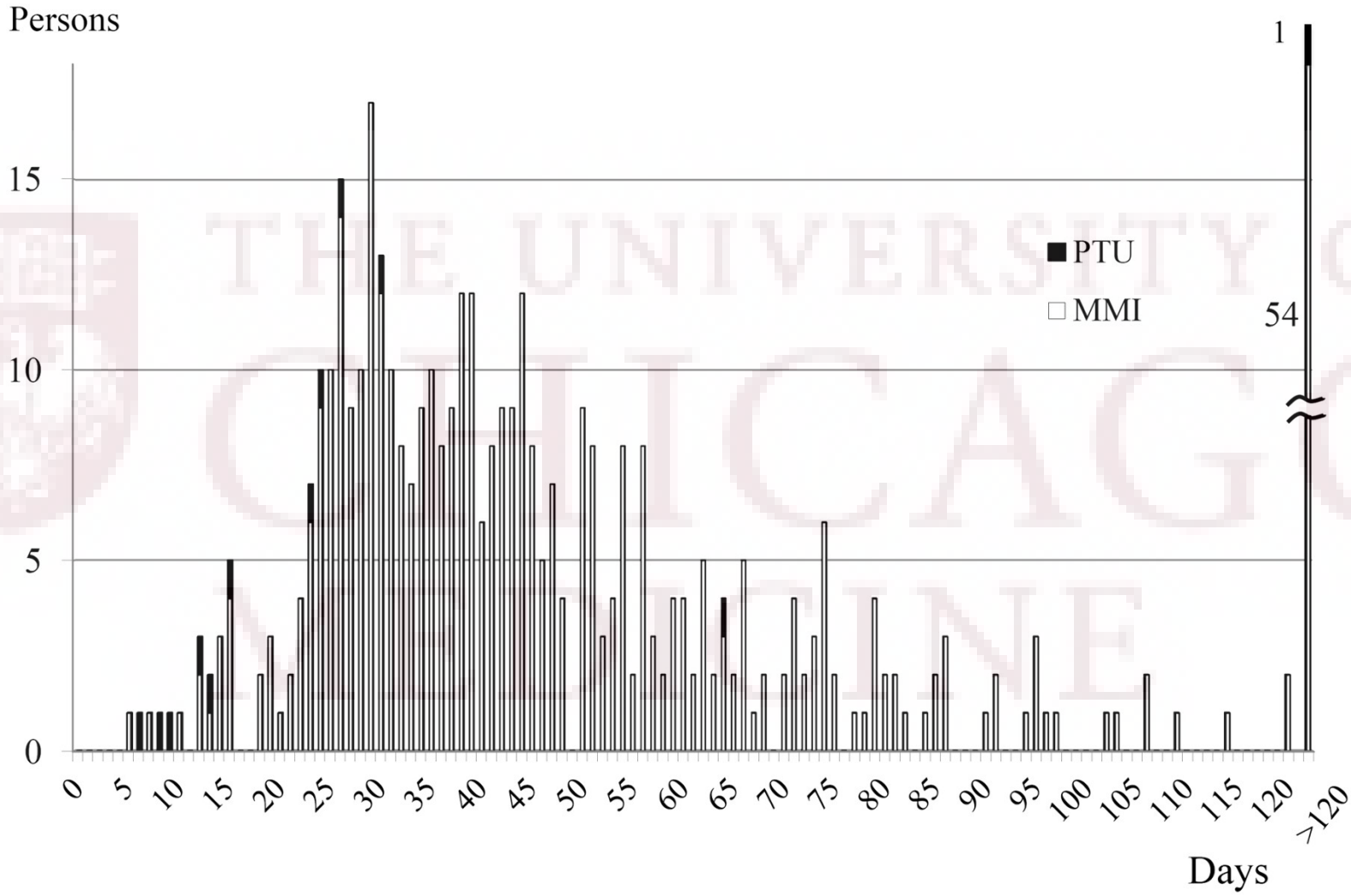
Agranulocytosis

ANC < 500 with decrease in all other WBC lines

Epidemology

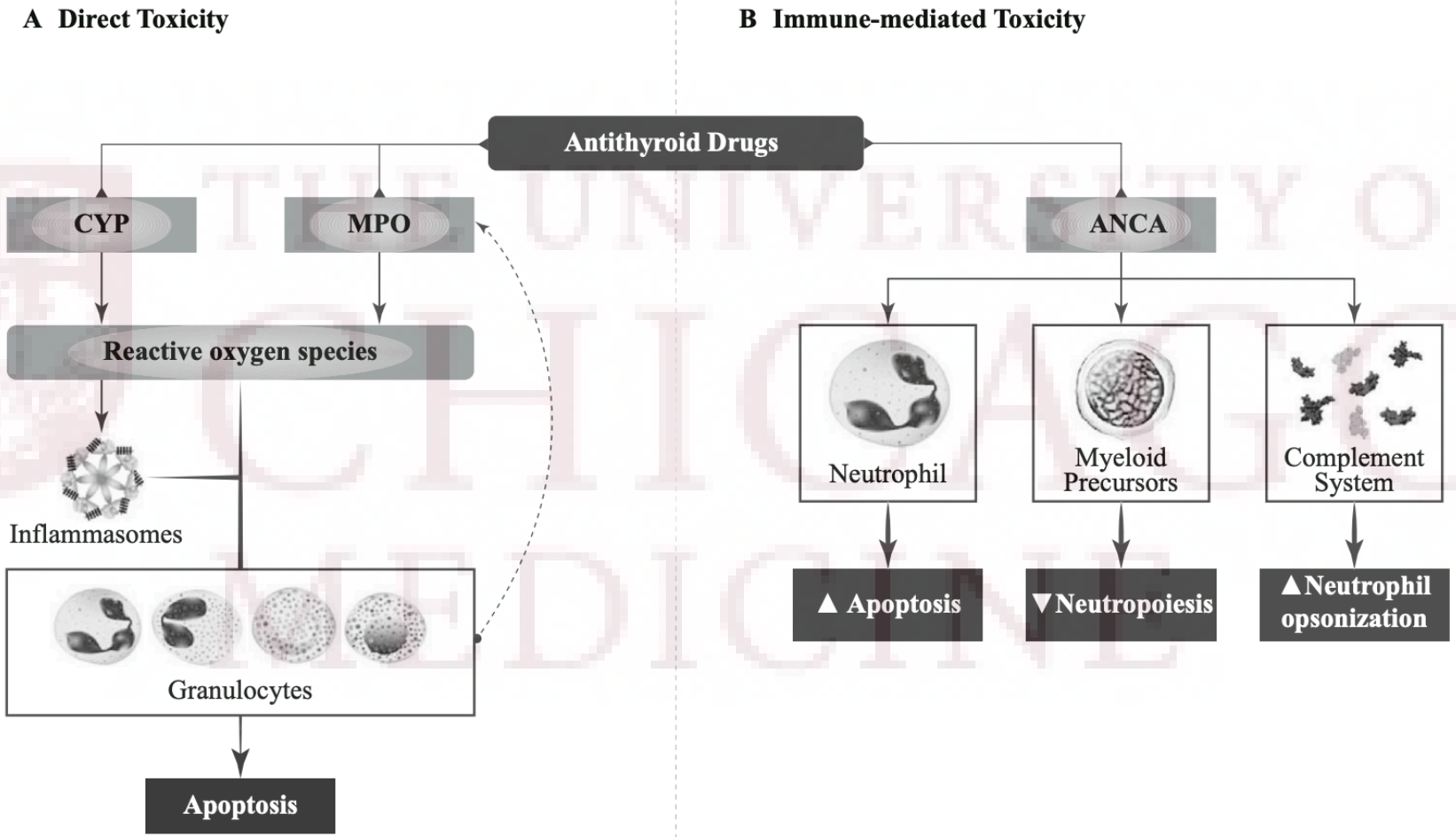
- 0.2-0.5% of patients with Graves' receiving ATDs
- highest risk in 40-50 yos
- Female > male
- MMI dose-dependent risk
- PTU: dose-independent risk
- Associated with HLA:
  - HLA-B*38:02
  - HLA-B*380201
  - HLA-DRB1*08:03
- Onset ~3 months (5 days up to 10+ years)

ATDs and agranulocytosis



(Nakamura, H et al, 2013)

MMI and agranulocytosis



(Vicente,et al, 2017)

Patient Update:

- TRAb negative
- Discontinued MMI

Patient left AMA prior to repeat TFTs or Thyroid US

FU scheduled in discharge clinic in 2-4 weeks- no show

Current admission

- Admitted at Stroger in 7/2023 for weakness (*limited records*)
  - VT and had ICD placed
    - Given amiodarone (dose unknown)
  - Diagnosed with adrenal insufficiency
    - Due to “malignant neoplasm metastatic to adrenal gland"
    - Started on hydrocortisone and fludrocortisone
- Presented this admission for ICD firing at home
  - Acute onset, over 5 shocks
  - Further VT in the ED
  - Placed on amiodarone, lidocaine, procainamide
  - Intubated, sedated, placed on norepinephrine and vasopressin

History

Medical:

- Prostate cancer
- HFrEF
- VT s/p ICD
- Opioid use disorder
- Hyperthyroidism
- Adrenal insufficiency

Surgical:

- ICD placement

Family:

- No autoimmune conditions
- No thyroid disorders

Social:

- Active drug use
- limited inter-hospitalization care

Medications:

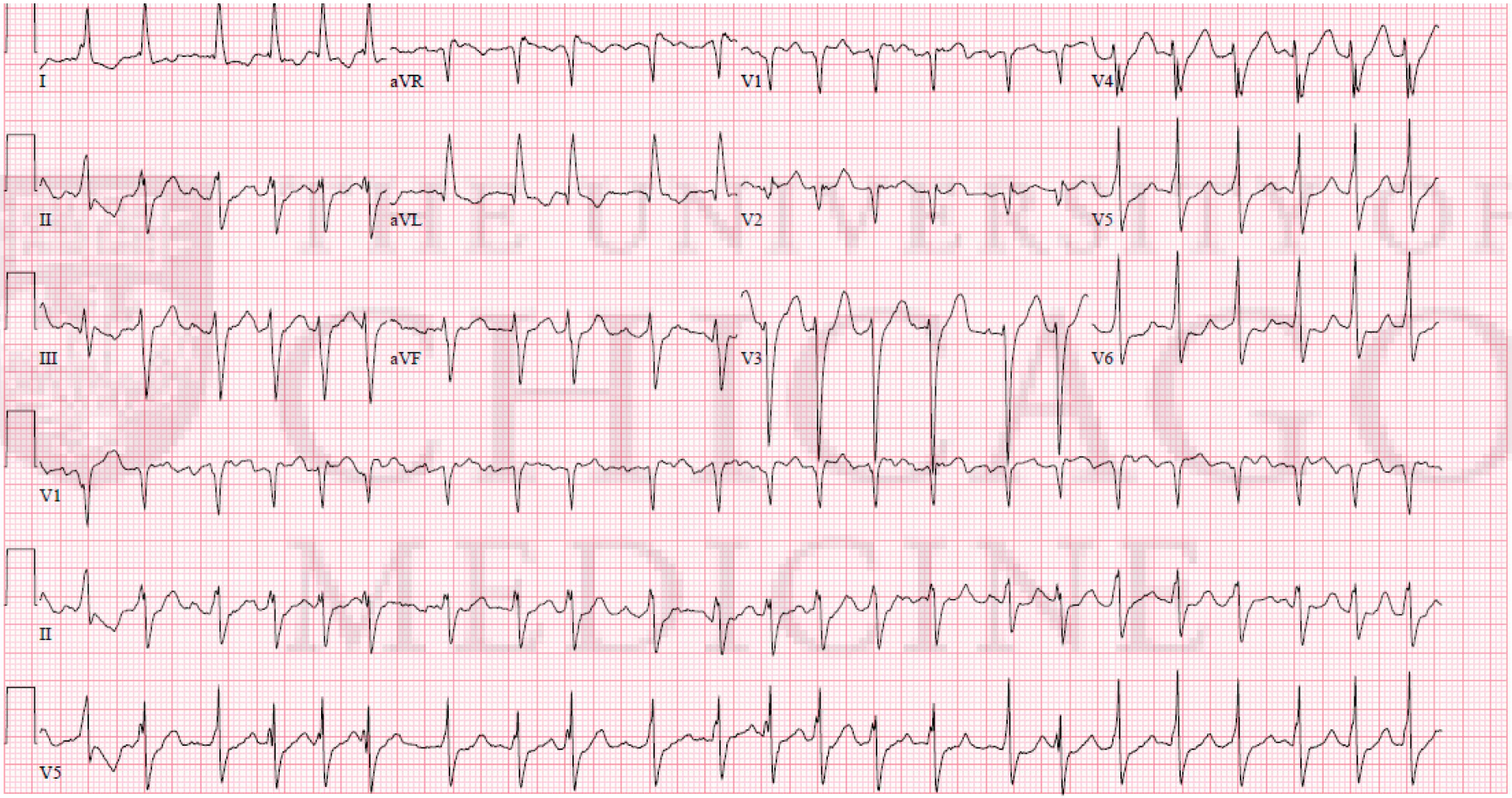
- Metoprolol ER 25mg daily
- Hydrocortisone 20mg qAM and 10mg qPM
- Fludrocortisone 0.1mg daily

Physical Exam

Vitals: BP 43-152/31-135 | Pulse 63-190 | Temp 36.9 ˚C | Resp 13 -25 | Wt 65.8 kg (145 lb) | SpO2 100% | BMI 21.3 kg/m²

General: Intubated and sedated
HEENT: ET tube in place, no proptosis
Neck: **difficult to palpate thyroid gland, no gross thyromegaly or nodules**
Cardiovascular: **Tachycardic with irregular rhythm**
Pulmonary: mechanically ventilated
Abdominal: Abdomen is soft and flat
Musculoskeletal: No edema
Skin: no diaphoresis
Neurological: Sedated, minimally responsive

Initial Results:



Initial Results:

Na: 142
K: 4.2
Cl: 106
CO2: 18
BUN: 26
Cr: 1.05
Glu: 105
Ca: 10.0
Phos: 3.7

Mg: 1.7
AST: 32
ALT: 40

TSH: < 0.01 (0.3 - 4.00 uIU/mL)
FT4: 5.35 (0.9 -1.70 ng/dL)
Free T3: 1,037 (230 - 420)

EKG: Afib with RVR with LAD, ST and T wave abnormalities (possible lateral ischemia)

Diagnosis?
Next steps?

Severe Thyrotoxicosis Management

2016 American Thyroid Association Guidelines for Diagnosis and Management of Hyperthyroidism and Other Causes of Thyrotoxicosis

Drug	*Dosing*	*Comment*
Propylthiouracil[a]	500–1000 mg load, then 250 mg every 4 hours	Blocks new hormone synthesis Blocks T_4-to-T_3 conversion
Methimazole	60–80 mg/d	Blocks new hormone synthesis
Propranolol	60–80 mg every 4 hours	Consider invasive monitoring in congestive heart failure patients Blocks T_4-to-T_3 conversion in high doses Alternate drug: esmolol infusion
Iodine (saturated solution of potassium iodide)	5 drops (0.25 mL or 250 mg) orally every 6 hours	Do not start until 1 hour after antithyroid drugs Blocks new hormone synthesis Blocks thyroid hormone release Alternative drug: Lugol's solution
Hydrocortisone	300 mg intravenous load, then 100 mg every 8 hours	May block T_4-to-T_3 conversion Prophylaxis against relative adrenal insufficiency Alternative drug: dexamethasone
Cholestyramine	4g every 6 hours	Binds thyroid hormones in the gut during enterohepatic recirculation

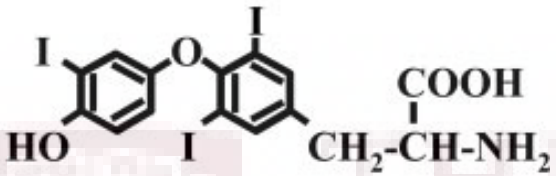
Call from the pharmacy at 2am:

"We cannot give PTU due to MMI allergy of agranulocytosis"

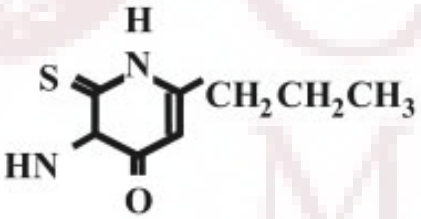
What should we do?

MMI and PTU Cross-Reactivity

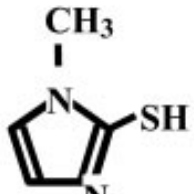
A Triiodothyronine (T3)

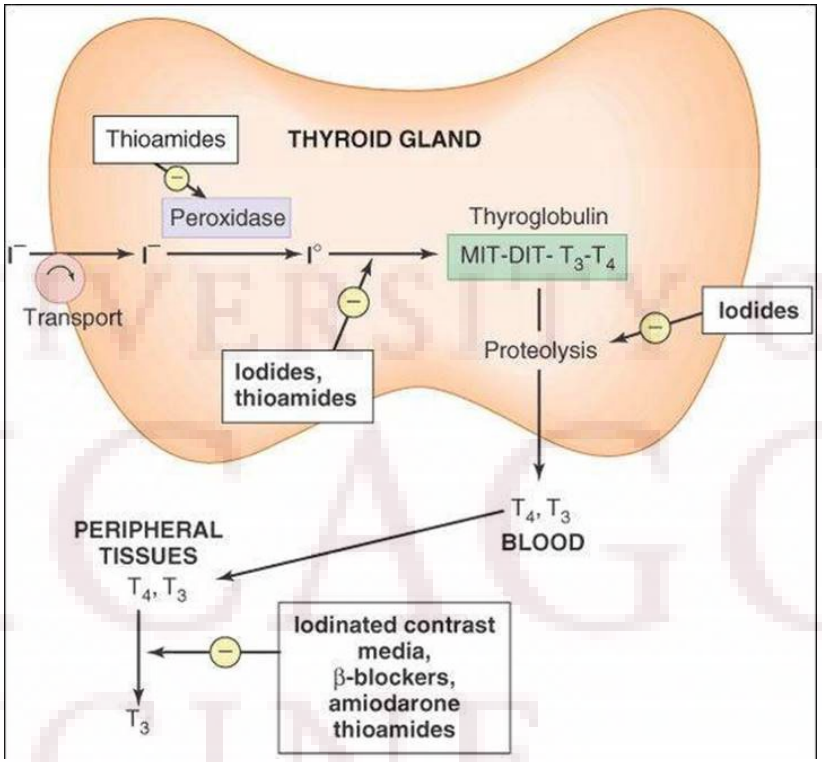


B Propylthiouracil (PTU)



C Methimazole (MMI)





Case reports of cross-reactivity of MMI and PTU
Labs studies suggest cross-reactivity of 50%

Katzung, Bertram G. *Basic and clinical pharmacology*. 2012.

Patient update:

Started on:

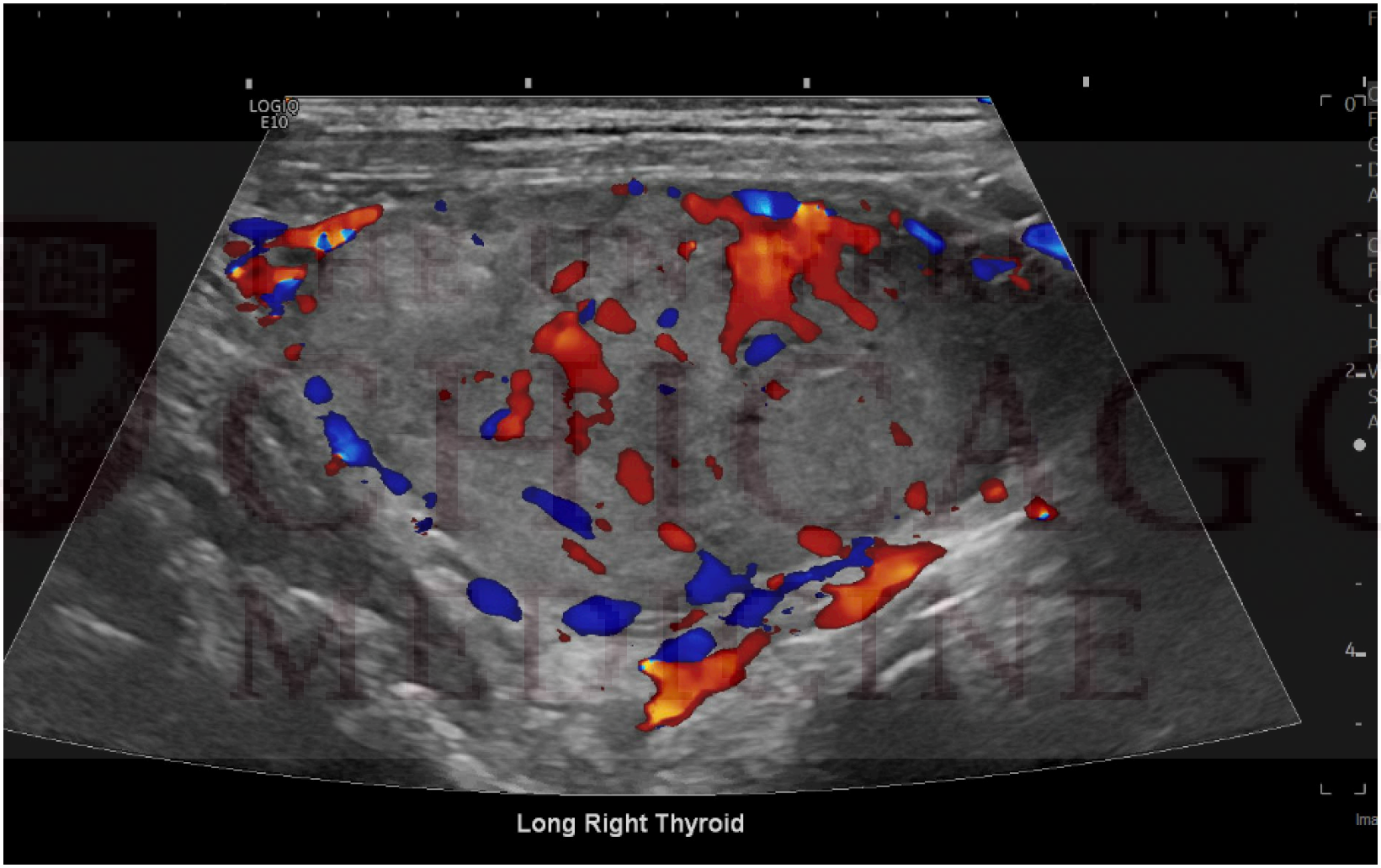
- Dexamethasone 4mg q8 hours
- Cholestyramine 4g q6 hours
- PTU 200mg q4 hours
- SSKI 250mg q hours

Trend CBC and FT4/TT3
Check TSI
Check thyroid ultrasound

Consult Endocrine Surgery or ENT for thyroidectomy

Thyroid US

Thyroid US



Thyroid US

Thyroidectomy in thyrotoxicosis

- **RECOMMENDATION 24**

  If surgery is chosen as treatment for GD, patients should be rendered euthyroid prior to the procedure with ATD pre-treatment, with or without β-adrenergic blockade. A KI-containing preparation should be given in the immediate preoperative period.

  Strong recommendation, low-quality evidence.

Thyroidectomy in thyrotoxicosis

- **RECOMMENDATION 26**

  In exceptional circumstances, when it is not possible to render a patient with GD euthyroid prior to thyroidectomy, the need for thyroidectomy is urgent, or when the patient is allergic to ATDs, the patient should be adequately treated with β-adrenergic blockade, KI, glucocorticoids, and potentially cholestyramine in the immediate preoperative period. The surgeon and anesthesiologist should have experience in this situation.

  Strong recommendation, low-quality evidence.

Thyroidectomy in uncontrolled thyrotoxicosis

Surgical Treatment of Hyperthyroidism Can Be Performed Safely Before a Euthyroid State is Achieved

TABLE 1. DEMOGRAPHICS

	Controlled (N = 134)	*Uncontrolled (N = 141)*	p
Age Median (Q1, Q3)	50.5 (37.0, 61.0)	39.0 (31.0, 55.0)	<0.001
Sex (female)	113.0 (84.3%)	108.0 (76.6%)	0.107
Pathology			
Toxic nodule(s)	43.0 (32.1%)	21.0 (14.9%)	<0.001
Graves	91.0 (67.9%)	120.0 (85.1%)	
Reason for surgery			0.008
Allergy to medications	1.0 (0.7%)	6.0 (4.3%)	
Intolerance to medications	8.0 (6.0%)	17.0 (12.1%)	
Refractory symptoms	123.0 (91.8%)	109.0 (77.3%)	
Thyroid storm	2.0 (1.5%)	9.0 (6.4%)	
Medications			
Mean no. (SD)	1.4 (0.8)	2.3 (1.0)	<0.001
Anti-thyroid drugs	97.0 (72.4%)	126.0 (89.4%)	<0.001
Beta blockade	61.0 (45.5%)	86.0 (61.0%)	<0.001
Steroids	10.0 (7.5%)	44.0 (31.2%)	<0.001
Lugol's iodine	3.0 (2.2%)	11.0 (7.8%)	0.036
Preoperative TSH (mIU/L) Median (Q1, Q3)	0.4 (0.0, 2.4)	0.0 (0.0, 0.0)	<0.001
Preoperative T4 (ng/dL) Median (Q1, Q3)	0.9 (0.7, 1.1)	3.1 (1.9, 4.4)	<0.001
Preoperative T3 (ng/dL) Median (Q1, Q3)	3.6 (3.1, 3.9)	6.2 (4.8, 12.3)	<0.001

Thyroidectomy in uncontrolled thyrotoxicosis

Surgical Treatment of Hyperthyroidism Can Be Performed Safely Before a Euthyroid State is Achieved

Jessica Fazendin,[1] Polina Zmijewski,[1] Ashba Allahwasaya,[1] Chandler McLeod,[1] Ramsha Akhund,[1] Andrea Gillis,[1] Kimberly Ramonell,[2] John Porterfield,[1] Herbert Chen,[1] and Brenessa Lindeman[1]

TABLE 2. OPERATIVE CHARACTERISTICS AND PATIENT-RELATED COMPLICATIONS

	Controlled (N = *134*)	*Uncontrolled* (N = *141*)	p
Operative time (hours)			
<1	25.0 (19.8%)	9.0 (7.3%)	0.014
1–2	57.0 (45.2%)	54.0 (43.9%)	
2–3	37.0 (29.4%)	47.0 (38.2%)	
>3	7.0 (5.6%)	13.0 (10.6%)	
Estimated blood loss (mL)			
Median (Q1, Q3)	15.0 (5.0, 30.0)	20.0 (10.0, 50.0)	0.002
Complications			
Hypocalcemia			
Temporary	6.0 (4.7%)	18.0 (13.4%)	0.013
Permanent	0.0 (0%)	4.0 (3.0%)	0.137
Hematoma (evacuation)	1.0 (0.7%)	5.0 (3.5%)	0.112
Hoarseness			
Temporary	10.0 (6.6%)	8.0 (5.0%)	0.549
Permanent	1.0 (0.8%)	1.0 (0.7%)	0.967

Thyroidectomy in AIT

Total Thyroidectomy for Amiodarone-associated Thyrotoxicosis in Patients with Severe Cardiac Disease

Jenny Gough, MBBS, Ian R. Gough, MD

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Thyroidectomy for Amiodarone-Induced Thyrotoxicosis: Mayo Clinic Experience

Anupam Kotwal, Jennifer Clark, Melanie Lyden, Travis McKenzie, Geoffrey Thompson, Marius N Stan

Journal of the Endocrine Society, Volume 2, Issue 11, November 2018, Pages 1226–1235,

Thyroidectomy in AIT

Thyroidectomy Data	All Samples (n = 17)[a]
Indications for thyroidectomy	
Medically refractory AIT (>2 wk)	12 (70.1)
Worsening cardiac status	8 (47.1)
Severe thyrotoxicosis requiring prompt resolution	6 (35.3)
Intolerance to ATD	4 (23.5)
Patient or physician preference for definitive therapy	2 (11.8)

Complications:
- Only 1 death in 31 patients
- similar surgical complication rate as euthyroid procedures

Table 4. Biochemical Response to Thyroidectomy

Laboratory Thyroid Function Tests	Immediately Presurgery	~1 wk Postsurgery	~4 wk Postsurgery	Reference Range
TSH,[a] mIU/L	0.005 (0.005–0.225)[b]	0.565 (0.03–1.1)	10 (1.425–29)	0.3–4.2
Free T4,[c] ng/dL	3.5 (2.1–8.1)	1.8 (1.15–2.55)	1.25 (0.85–1.65)	0.9–1.7
Free T3,[d] pg/mL	5.2 (4.4–55)	—	—	2–3.5
Total T3, ng/dL	73 (70–149)	—	—	80–200

Returning to our patient

THYROIDECTOMY

	Admission	Day 2	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9	Day 10	Day 11
Free T3	1,037											
FT4	5.35		5.52	5.07	3.81	3.81	2.81	2.36	2.09	1.87	1.82	1.52
TT3		251	138	107	65	65	72	49	49	29	26	26
TSH	<0.01			<0.01					<0.01			<0.01
Hgb	9.9	8.9	8.3	7.8	7.6	7.0	7.3	9.0	8.8	8.2	7.8	7.3
WBC	4.9	8.7	8.0	8.5	7.5	6.1	5.8	9.0	17.6	16.0	14.2	13.6

Returning to our patient

Surgical Pathology:

A. Right thyroid lobe; lobectomy (35.9 g):
- Predominantly microfollicular adenomatous nodule with focal intralesional fibrosis (5.2 cm)

B. Left thyroid gland; completion thyroidectomy (8.46 g):
- Macrofollicular adenomatous nodules.

Returning to our patient

	Post-op Day 0	Post op Day 1	Post-op Day 2
Calcium	9.5	8.2	8.5
Alb		3.2	
PTH, Intact	45	62	
25-Hydroxy Vitamin D	16 (L)	19 (L)	

Started on LT4 75mcg daily

Started on Vit D 2000 IU daily

Take Home Points

- Agranulocytosis is a rare, life threatening complication of ATD therapy with median onset of 3 months but can occur at any point
- Limited data on the cross-reactivity between PTU and MMI
- Thyroidectomy should be considered in AIT, especially when medical management is complicated

Special thanks to Drs. Sarne and Sam!

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- Fazendin, Jessica, et al. "Surgical Treatment of Hyperthyroidism Can Be Performed Safely Before a Euthyroid State is Achieved." *Thyroid* (2023).
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- Nakamura, Hirotoshi, et al. "Analysis of 754 cases of antithyroid drug-induced agranulocytosis over 30 years in Japan." *The Journal of Clinical Endocrinology & Metabolism* 98.12 (2013): 4776-4783.
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