35 yo F with Graves' Disease

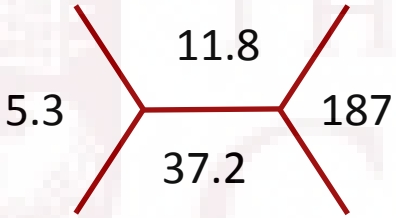
Endorama March 10, 2016
Mizuho Mimoto

PHONE CALL:

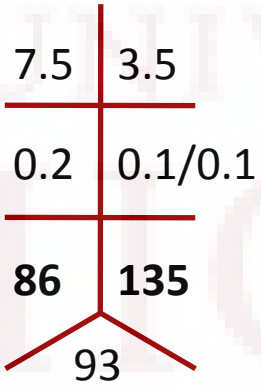
- 35 F with recently diagnosed Graves'
  - Vomiting
  - Persistent diarrhea with incontinence x 2 days
  - Tremor
  - Heart racing
  - Subjective fevers
- Come to the ED

- 6 hours goes by… and you get a call from the ED: "What would you like us to do…?"

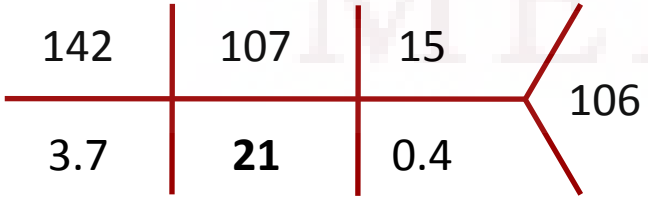
Labs

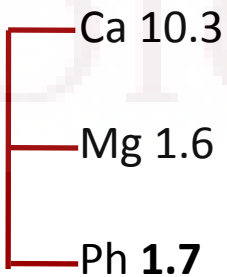


Normal differential



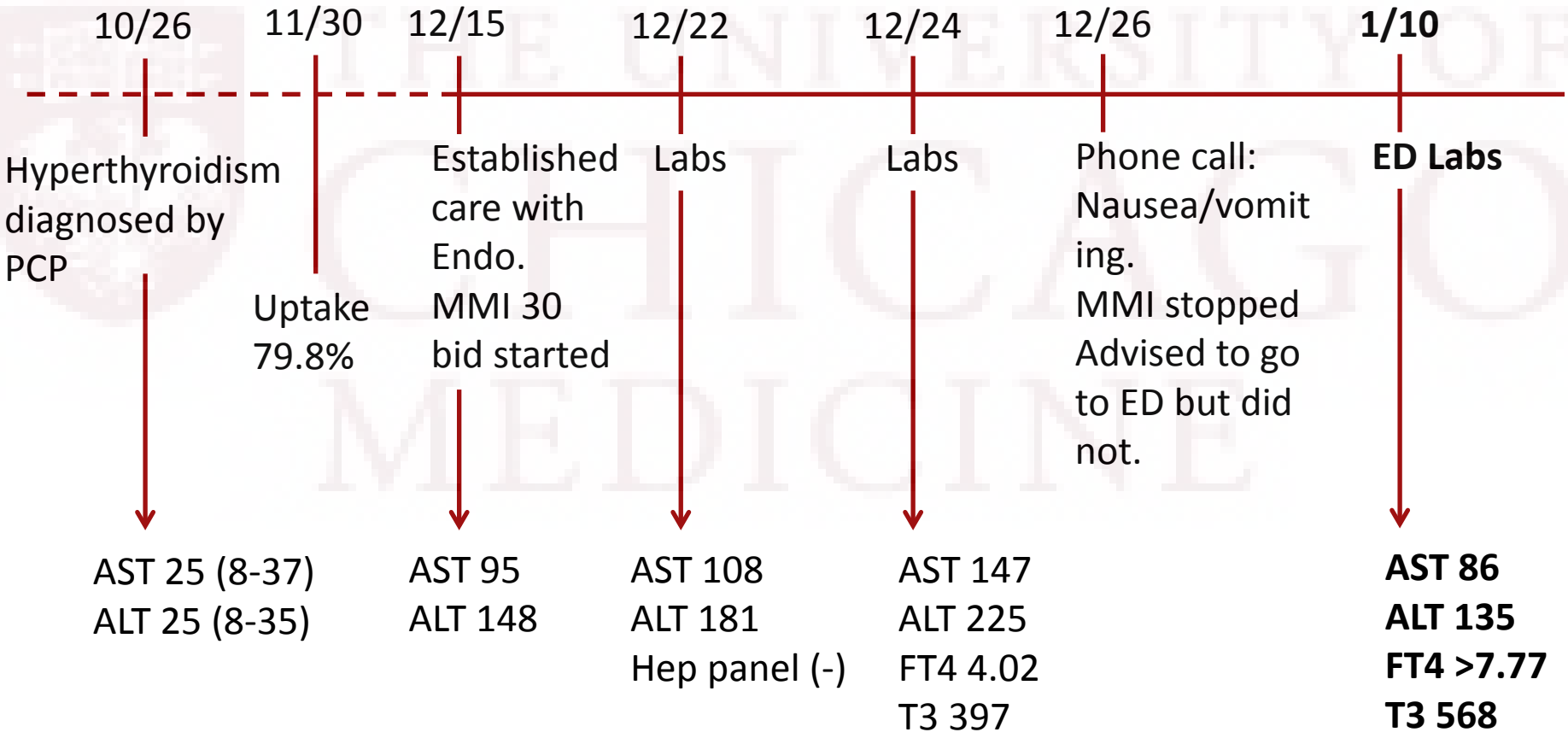
TSH: <0.01
FT4: >7.77
T3: 568





EKG: Sinus tach, HR 109 bpm

Additional HPI



ROS

Constitutional: **+Fevers, fatigue, 20# wt loss in 3 mo.** No night sweats, appetite intact
Vision: No photophobia, blurred vision, or other changes
ENT: Negative
CV: **+Palpitations, +mild DOE, +mild LE edema**. No CP, claudication.
Pulm: **+intermittent dyspnea**. No wheezing, cough
GI: +Abdominal pain, nausea, vomiting, diarrhea. No melena or hematochezia
GU: No frequency, dysuria, hematuria, discharge
ENDO: **+Heat intolerance**
MSK: **+Myalgias.** No joint pains or swelling, gait changes
Neuro: +Weakness, tremor. No HA, numbness, paresthesias
Skin: **+Rash**

Physical Exam

Vitals: T 36.3 °C, **BP 153/98, HR 118**, SpO2 98% RA, Wt 68kg
Gen: Young woman, no acute distress.
HEENT: **No proptosis or lid lag**
Neck: **Thyroid symmetrically enlarged**, no nodules
CV: **tachycardic**, regular, no murmurs, **no LE edema**
Pulm/Chest: Clear to auscultation bilaterally, no crackles
GI: **Hyperactive BS**, non-distended, soft, **mild, diffuse tenderness**, no rebound, no guarding.
MSK: **Proximal muscle weakness in bilateral UE, LE.** Normal tone.
Neuro: AOx4, no focal deficits. **Reflexes 3+ symmetric in UE, LE. Fine tremor with outstretched hands.**
Skin: **Sparse papular rash over back and chest**, no erythema, ulceration, no other rashes, hypo/hyperpigmentation, no pretibial myxedema

Past Medical History

PMH
- Asthma
- Bell's Palsy x2

PSH
- None

Social Hx
- No tobacco, EtOH
- No illicits/supplements

Medications
- Methimazole
- Propranolol (unable to afford)
- Albuterol PRN (not recently)

Allergies: NKDA

Family Hx
- Sister – Hypothyroidism
- 2 children – healthy
- No autoimmune or liver disease

Next steps in management?

1/10

ED Labs

AST 86
ALT 135
FT4 >7.77
T3 568

Would you use a thionamide?

What are your other options?

Management of hyperthyroidism

- Therapeutic Plasma Exchange
- (Alternate) Thionamide
- SSKI

- Steroids
- BB
- Cholestyramine

- RAI
- Surgery

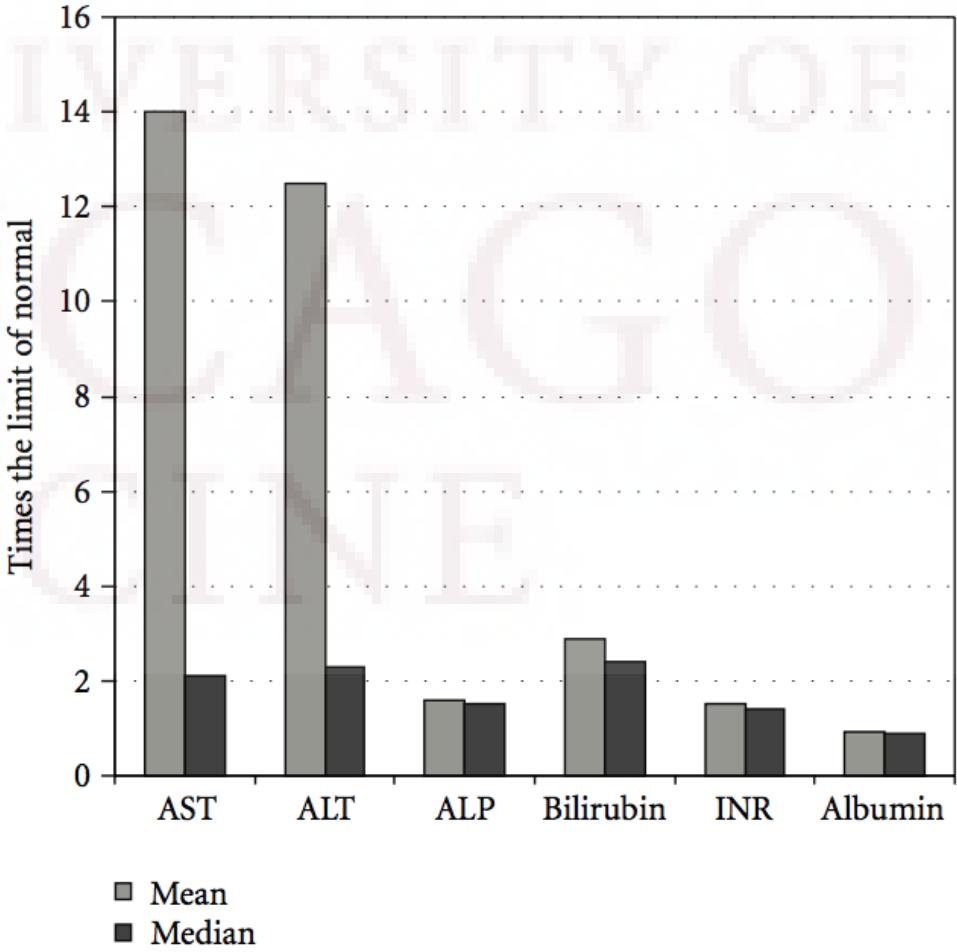
Hyperthyroidism and Hepatotoxicity

- Prevalence of coincident LFT abnormalties and hyperthyroidsim: 15-76%
- Proposed mechanisms
  - Relative ischemia
    - Increased metabolic activity relative to perfusion
    - Heart failure→hepatic congestion
- Use of Antithyroid drugs
  - PTU→hepatocellular injury pattern
  - MMI→cholestatic pattern
- Other coincident autoimmune conditions (e.g. PBC)
- One clue may be transaminitis out of proportion to decline in synthetic function

Kemichian and Fong. Gastroenterology & Hepatology 7:5 2011

How common are LFT abnormalities in thyrotoxicosis?

- Single institution retrospective review 1998-2008
- 14 patients with *de novo* thyrotoxicosis
  - LFTs available for 11 patients; of these, 9 had abnormalities
  - No correlation with thyroid indices (TSH, T4, T3, TPO or TRAb)
  - 6 patients with long-term f/u LFTs normalized an average of 8.5 mo later (median 3 mo)



Elias et al. ISRN Endocrinology. Vol 2012, Article ID 325092

Patient number	1	2	3	4	5	6	7	8	9	10	11
Age	81	50	55	21	26	23	42	42	56	55	50
Gender	F	F	F	M	F	M	M	M	M	F	F
TSH (mIU/L) [NR 0.3–5.0 mIU/L]	0.02	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	0.01	<0.01	0.01
Thyroxine (total; mcg/dL) [NR 5–12.5 mcg/dL]	NP	NP	11.5	NP	23.2	22.3	NP	NP	16.2	NP	NP
Thyroxine (free; ng/dL) [NR 0.8–1.8 ng/dL]	10	4.6	6	7.7	7	>12	5.4	9.4	3.2	5	3.6
Triiodothyronine (ng/dL) [NR 80–190 ng/dL]	NP	NP	462	385	NP	359	NP	NP	150	NP	NP
Free T3 (pg/mL) [NR 2.0–3.5 pg/mL]	20	8.6	NP	17.6	10.3	>20	17.6	NP	NP	12.3	43 (reverse)
TPO (IU/mL) [NR < 9.0 IU/mL]	<20	287	NP	>950	NP	4420	NP	3017	706	NP	NP
TRAB (%) [NR < 16%]	82	31	66	NP	NP	93	46	75	52	NP	53
TSI index (%) [NR ≤ 1.3%]	NP	NP	NP	7.3	NP	NP	NP	NP	NP	5	2.6
AST (U/L) [NR 8–48 U/L]	76	978	636	2850	39	30	82	34	99	52	69
ALT (U/L) [NR 7–55 U/L]	66	920	841	1895	41	27	102	53	70	41	44
ALP (U/L) [NR 45–115 U/L]	135	252	136	180	129	NP	97	NP	194	NP	162
Bilirubin (Total/Dir.; mg/dL) [NR 0.1–1.0/0.0–0.3 mg/dL]	NP	1.2/0.6	0.9/0.7	5.6/1.8	0.4/0.1	NP	0.7/0.2	NP	1.2/0.7	NP	3.6/2.5
INR [NR 0.8–1.2]	NP	1.2	1.4	2.4	1.1	1.0	1.0	1.0	1.1	1.7	1.7
Albumin (g/dL) [NR 3.5–5.0 g/dL]	NP	2.9	3.6	3.6	NP	NP	3.3	NP	3.4	3.1	3.0
Ascites	N	N	N	Y	N	N	N	N	Y	N	N
LVEF by ECHO	NP	48%	65%	20%	NP	NP	68%	45–50%	22%	29%	NP
Troponin T (ng/mL)	NP	12.38	0.07	<0.01	<0.01	<0.01	<0.01	0.11	<0.01	NP	NP
PTU prior to LFTs?	N	N	N	N	Y	N	N	N	N	Y	N
PTU after LFTs?	Y	Y	N	N	Y	Y	N	N	Y	Y	Y
LFTs worsened?	N	N	N/A	N/A	N	N	N/A	N/A	N	N	N

Y: yes, N: no, NP: not performed, N/A: not applicable.

Transaminitis in patients with thyrotoxicosis

Pt #	1	2	3	4	5	6	7	8	9	10	11
TSH	0.02	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	0.01	<0.01	0.01
T4	NP	NP	11.5	NP	23.2	22.3	NP	NP	16.2	NP	NP
FT4	10	4.6	6	7.7	7	>12	5.4	9.4	3.2	5	3.6
T3	NP	NP	462	385	NP	359	NP	NP	150	NP	NP
AST	76	978	636	2850	39	30	82	34	99	52	69
ALT	66	920	841	1895	41	27	102	53	70	41	44
AP	135	252	136	180	129	NP	97	NP	194	NP	162

Died

EF 20%

PTU for several months

EF 22%

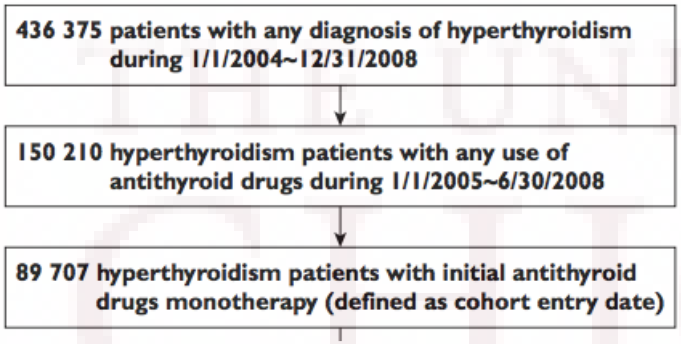
PTU for several hours
LVEF 29%

What is the relationship between thionamides and hepatotoxicity?

- PTU →Transient increase in transaminases in 1/3 of patients (up to 6x ULN), resolve with continued therapy
- MMI→usually cholestatic picture (elevated AP)
- 49 cases of thionamide hepatotoxicity
  - 28 associated with PTU (7 deaths)
  - 21 associated with MMI (3 deaths)
  - No relationship between death and dose/duration of treatment.
- US cases reported to FDA with PTU:
  - 22 cases of severe hepatotoxicity in adults (9 deaths, 5 OLT)
  - 12 cases in children (6 deaths, 6 OLT)
  - Estimated risk: 1:10,000 in adults, 1:2000 in peds
- Usually occurs within 90 days of initiation (though reported up to 1 year)
- No dose-response relationship (debated)
- MMI – tends to be cholestatic; risk of liver failure lower.

Ross, D. Uptodate (updated 11/2015)
Cooper. N Engl J Med 2005; 352:905-917

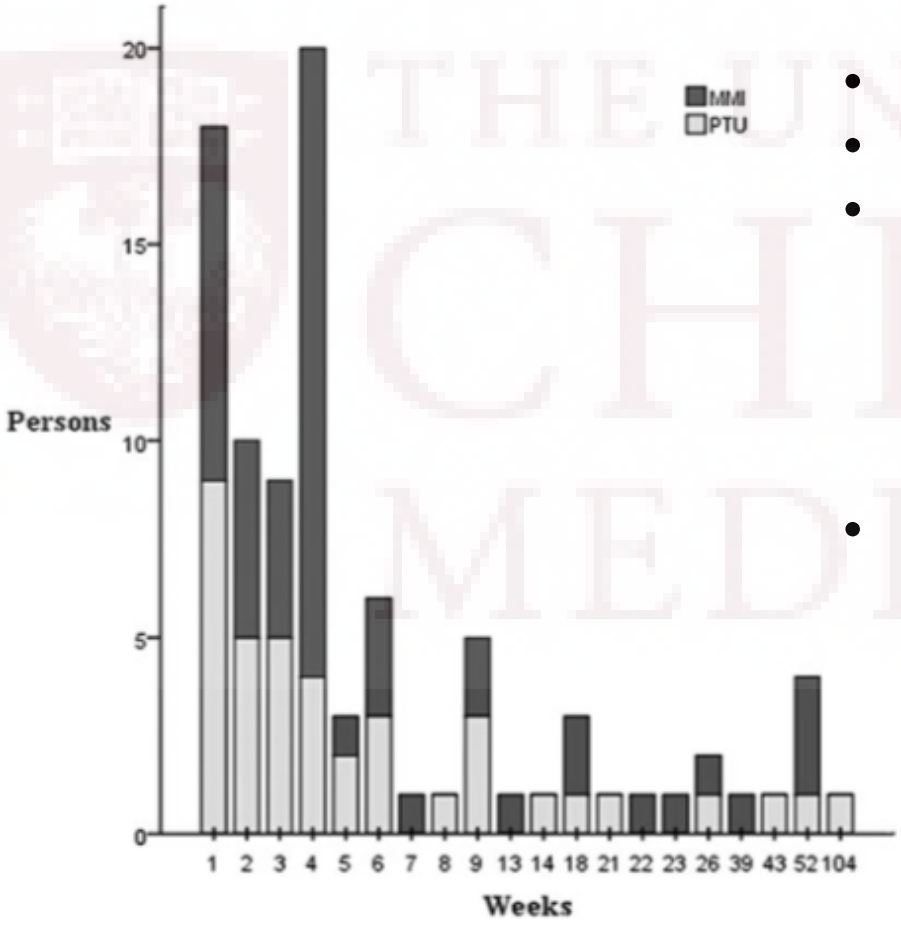
Overall incidence of hepatotoxicity with anti-thyroid drugs is low



- Median f/u: 196 days
- Hepatitis rates
  - PTU users 1.19/1000
  - MMI users 3.17/1000
- Acute liver failure
  - PTU 0.32/1000
  - MMI 0.68/1000
  - **Not significantly different**
- No increased risk of cholestasis with MMI
- Dose response with MMI only
- *(different from what was seen in other studies)*

Wang et al. Br J Clin Pharmacol / 78:3 / 619–629. 2014

ATD-induced hepatotoxicity usually occurs within the first 3 mo of therapy



- Retrospective Review (2000-2013)
- N = 8864 patients with hyperthyroidism
- 90 patients developed ATD-induced severe hepatotoxicity
  - By 4 weeks 63.3%
  - By 8 weeks 75.6%
  - By 12 weeks 81.1%
- Type of hepatotoxicity not significantly different between MMI and PTU; trend toward more cholestasis with MMI
  - MMI →Cholestasis 18/51 (35%)
  - PTU→7/39 (18%)

Yang et al. THYROID. Volume 25, Number 3, 2015

Severe hepatotoxicity with PTU is rare

- Study design:
  - Single-center Retrospective Review
  - Over hepatitis: Jaundice, hepatitis symptoms with 3x ULN LFTs
- Results
  - 912 patients with hyperthyroidism (1990-1998)
  - 497 patients included (normal TB, AST, ALT)
  - 6 (1.2%)with overt hepatitis (5 Jaundice, 2 fever, 2 rash, 1 arthralgia)
  - 14.3% pts with asymptomatic elevation of ALT
  - Timing: 12-49 days after receiving PTU

Kim et al. Am J Gastroenterol 2001;96:165–169.

PTU induced Hepatotoxicity is variable and idiosyncratic

Table 2. Maximum Hepatic Injury From PTU Administration and Type of Injury

Case	ALT (U/L)	TB (μmol/L)	ALP* (U/L)	Time† (days)	Type of Injury
1	33	731	304	14	Cholestatic
2	37	476	373	19	Cholestatic
3	169	44	289	11	Mixed
4	246	102	245	22	Mixed
5	296	8	132	9	Hepatocellur
6	64	398	259	28	Cholestatic

- 3 cholestatic, 1 hepatocellular, 2 mixed
- No difference in age, sex, PTU dose, TFTs
- LFTs normalized in all patients **16-145** days after withdrawal of PTU
- No evidence for monitoring LFTs

Kim et al. Am J Gastroenterol 2001;96:165–169.

Back to our patient

- **Initial recommendations overnight:**
  - Hold thionamide
  - Titrate propranolol for HR <100
  - Prednisone 60 mg daily
  - Cholestyramine 4 g daily

- **The following day:**
  - MMI resumed
  - Propranolol continued
  - Prednisone and cholestyramine stopped

Clinical course continued…

- Labs and clinical status improved

	1/14	1/13	1/12	1/11	1/10
Total Protein	6.8	7.4	6.9	7.5	7.7
Albumin	3.2 ▼	3.5	3.2 ▼	3.5	3.9
Bilirubin, Total	0.6	0.3	0.2	0.2	0.4
Bilirubin, Conjugated				0.1	0.1
Bilirubin, Unconju...				0.1	0.3
Alk Phos, Serum	76	85	85	93	83
AST (SGOT)	50 ▲	87 ▲	73 ▲	86 ▲	101 ▲
ALT (SGPT)	96 ▲	123 ▲	115 ▲	135 ▲	194 ▲

Thyroxine, Free	5.94 * ▲	6.93 * ▲	>7.77 * ▲
Thyrotropin	<0.01 ▼	<0.01 ▼	<0.01 ▼
Triiodothyronine	360 ▲		568 ▲

Discharged from Hospital: 1/14/16

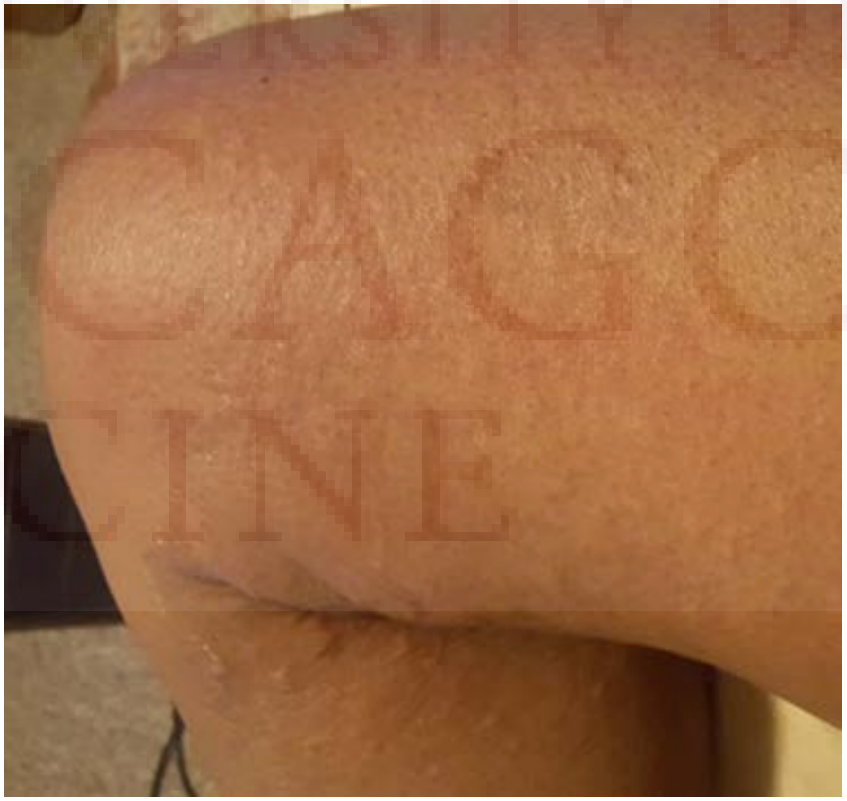
- MMI 20 mg tid
- Propranolol 30 mg q6h
- Labs in 1 weeks (LFTs, TFTs)
- F/u 1/26/16 in clinic
- ENT f/u 2/8/16 for surgical planning

ANOTHER PHONE CALL:

Sunday evening:

- Progressive hives x1 day
- Started at the feet with migration to face, involving trunk, extremities including palms and soles
- Benadryl with minimal relief
- +Abdominal pain

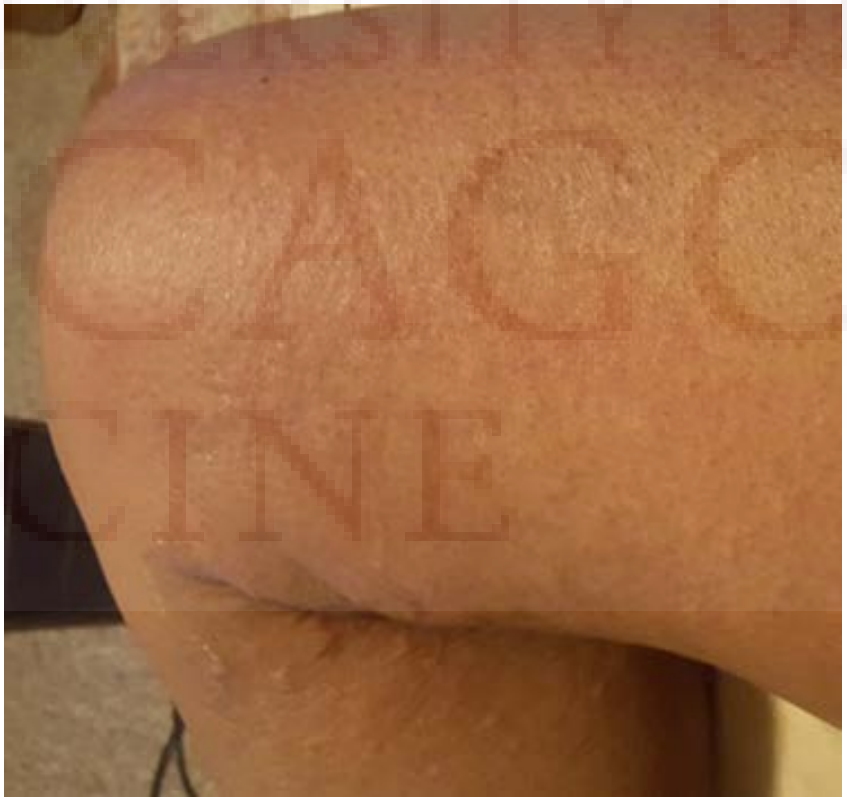
What would you like to do next?



ANOTHER PHONE CALL:

Concerning symptoms:

- Signs of serum sickness (joint pain, fever)
- Urticaria/hives
- Stevens-Johnson rash (desquamation)



Minor reactions:

- Pruritis
- Limited rash

Occur in up to 5% pts on thionamides
Mange with anti-histamine
Consider switching to alternate thionamide

ATA Guidelines

RECOMMENDATION *22*
Whenever possible, patients with GD undergoing thyroidectomy should be rendered euthyroid with methimazole. Potassium iodide should be given in the immediate preoperative period. **1/+00**

RECOMMENDATION 23
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 antithyroid medication, the patient should be adequately treated with beta-blockade and potassium iodide in the immediate preoperative period. The surgeon and anesthesiologist should have experience in this situation. **1/+00**

Bahn et al. ENDOCRINE PRACTICE Vol 17 No. 3 May/June 2011

SSKI – Lugol's

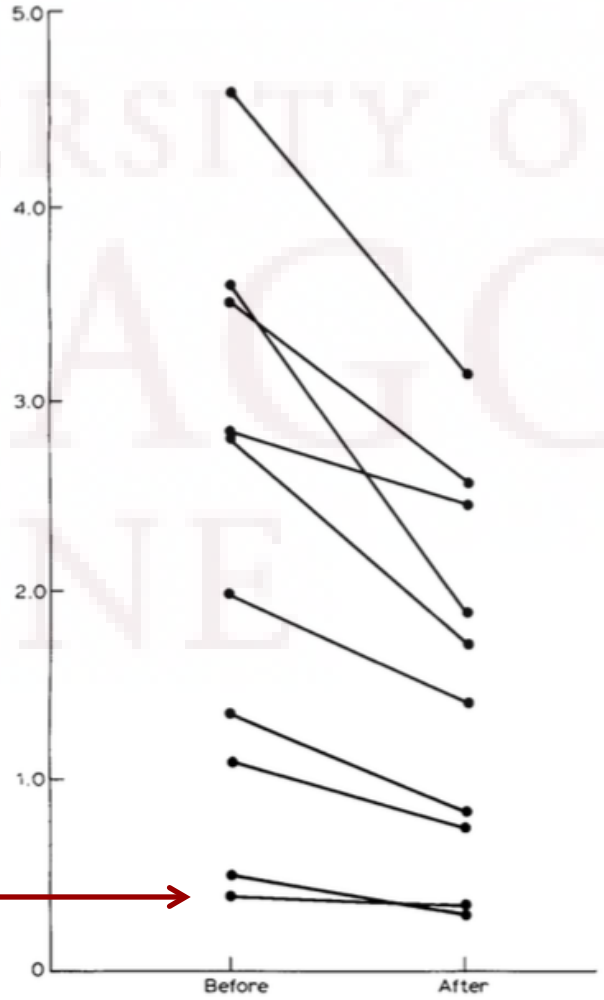
saturated solution of potassium iodide

- Elemental iodide and potassium iodide in water

- Treat iodine deficiency
- Purify drinking water
- Detects starch in biochemical assays
- Prevent radioactive iodine uptake following nuclear disaster at Chernobyl

What is the role for SSKI in thyrotoxic patients?

- N= 9 patients with Graves'
  - 6 treated with antithyroid drugs + Lugol's
  - 3 Lugol's only
  - 1 Euthyroid patient (anxiety)
- Intervention: Lugol's iodine 0.5 mL tid x 10 days



control

Figure 2 *Thallium-201 percentage uptakes before and after Lugol's iodine (P<0·005 for the nine thyrotoxic patients)*

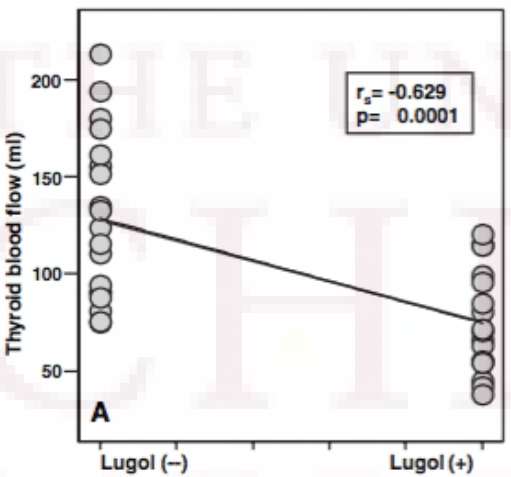
Marigold *et al.* Br. J. Surg. 1985 Vol. 72, 45-47

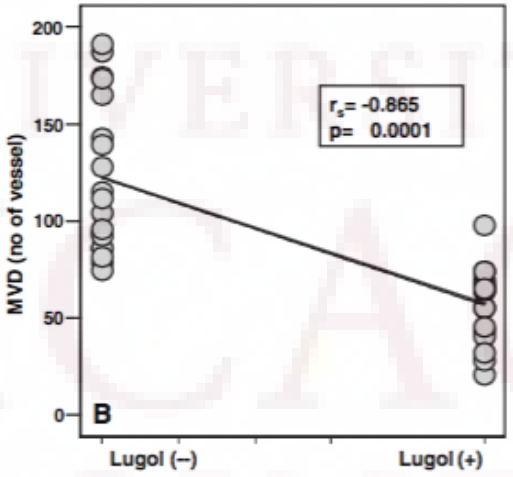
Pre-operative Iodine treatment reduces thyroid gland vascularity

- Prospective randomized trial
- 36 patients with Graves' (euthyroid)
  - 17 Lugol's (10 drops per day po tid x10 days pre-op)
  - 19 No Lugol's
- Outcomes measured
  - Blood flow through the thyroid aa. via doppler US
  - Microvessel density (CD-34 endothelial marker)
  - Thyroid weight, blood loss from gland
- Results
  - Mean blood flow, vessel density, CD-34 expression and blood loss significantly lower in pts that received Lugol's

Erbil *et al*. JCEM 92(6):2182–2189. 2007

Pre-operative Iodine treatment reduces thyroid gland vascularity





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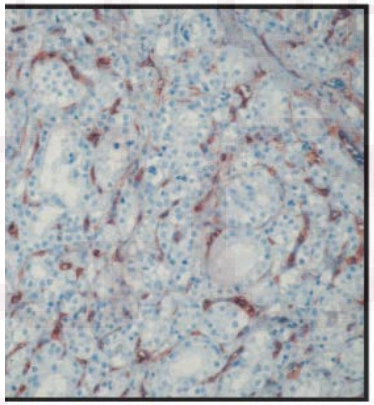

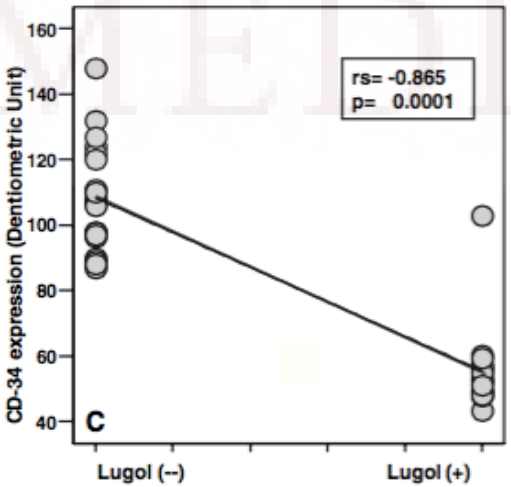

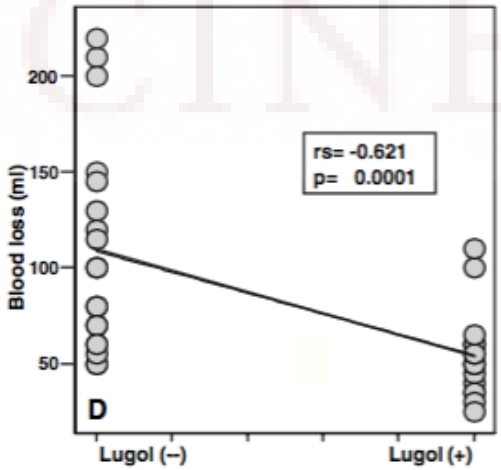

› treatment

Erbil *et al*. JCEM 2007, 92(6):2182–2189

Follow up – 2 weeks ago

- Underwent total thyroidectomy on 1/25/16
- Pre-op: TSH <0.01, fT4 4.61, TT3 369
- Immediately post-op: fT4 2.46→1.05
- Op note: "*Minimal vascularity to the thyroid gland which is a diffusely enlarged consistent with Graves"*

- Forced to leave work, lost insurance at the end of Feb, public aid application pending.
- Myalgias, nausea/vomiting, heat intolerance resolved
- Hair shedding also improved
- Regained 15 of 25 lbs lost

- Overall feeling much better

References

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