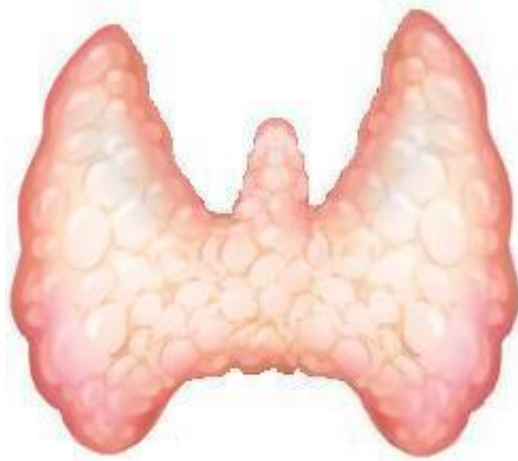


# THYROID PROBLEMS IN CRITICAL CARE PATIENTS

ประชุมวิชาการ และ อบรมระยะสั้น สมาคมเวชบำบัดวิกฤตแห่งประเทศไทย

18 ธันวาคม 2558



Brian Lee, MD

Division of Endocrinology and Metabolism

Srinakharinwirot University

# OUTLINE

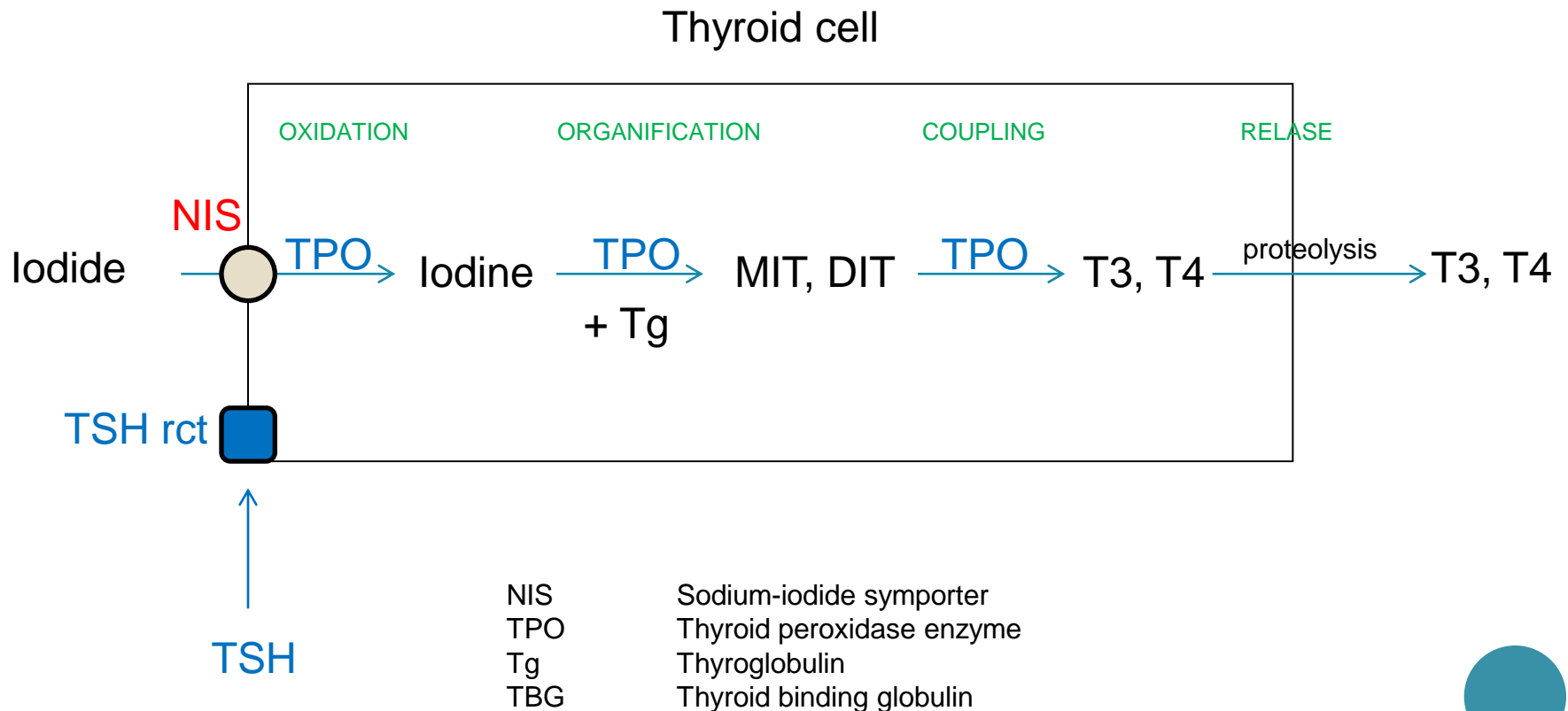
- Normal thyroid hormone physiology
- Thyroid function tests (TFT) in critical illness
- Thyroid storm
- Amiodarone-induced thyroid disorders



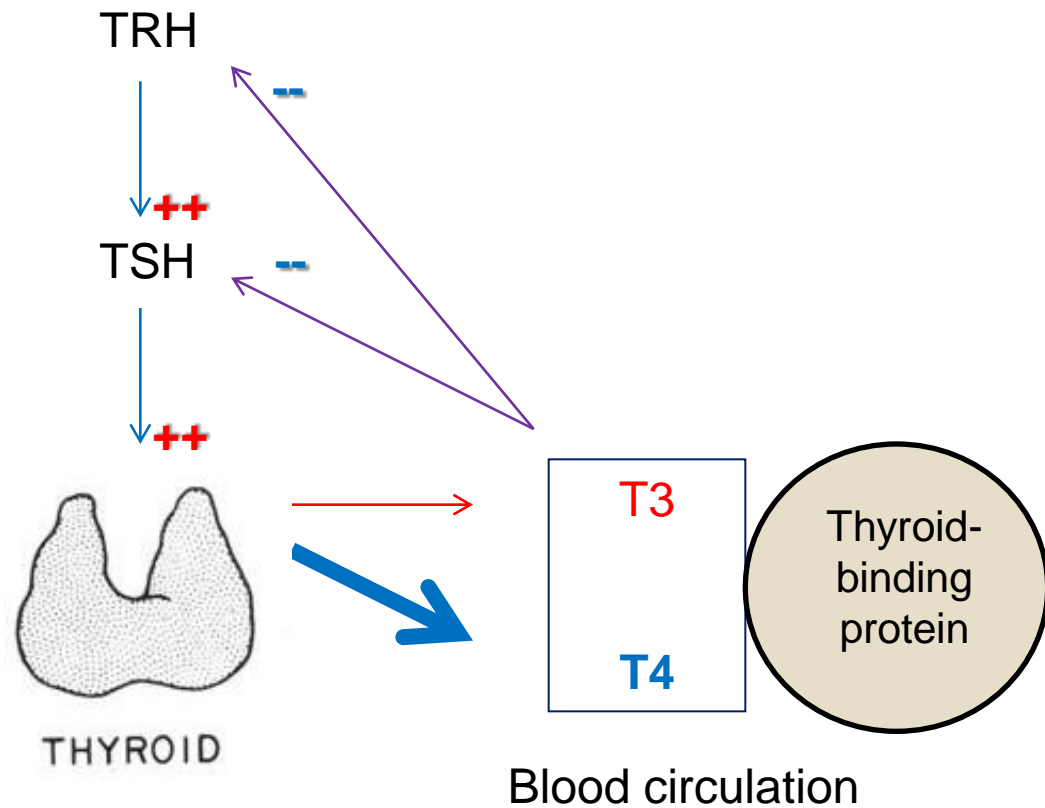
# **NORMAL THYROID PHYSIOLOGY**



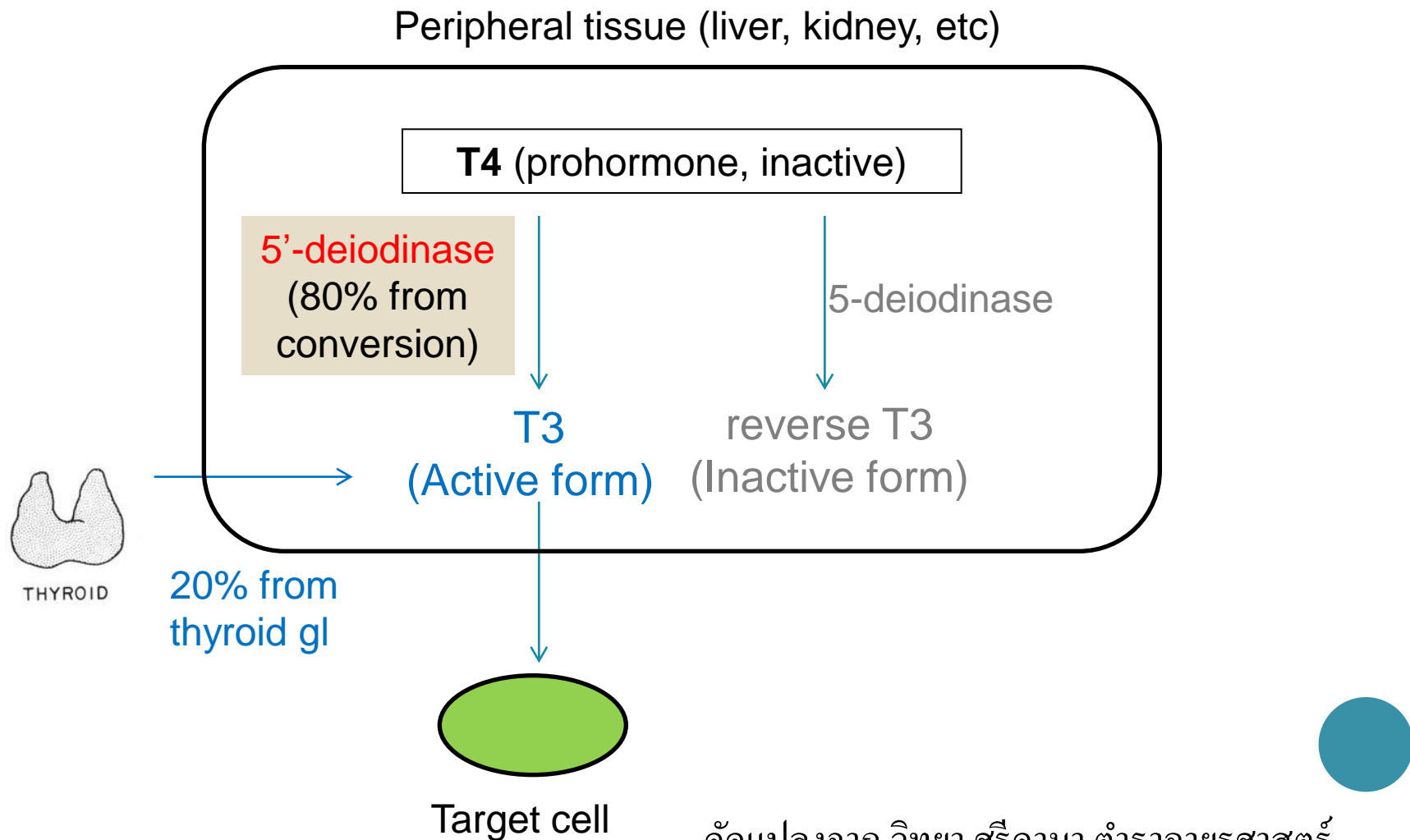
# PRODUCTION OF THYROID HORMONES



# CONTROL OF THYROID HORMONE PRODUCTION



# METABOLISM OF THYROID HORMONE



# **THYROID FUNCTION TESTS IN CRITICAL ILLNESS**



# TFT IN CRITICAL ILLNESS

- Abnormal TFT is common in critical illness
- Most patients **do not** have thyroid disease
  - **Nonthyroidal illness (NTIS)** or sick euthyroid syndrome
- Some medications may cause **hyperthyroidism or hypothyroidism**
  - **Amiodarone**
  - **Iodine-containing contrast media**





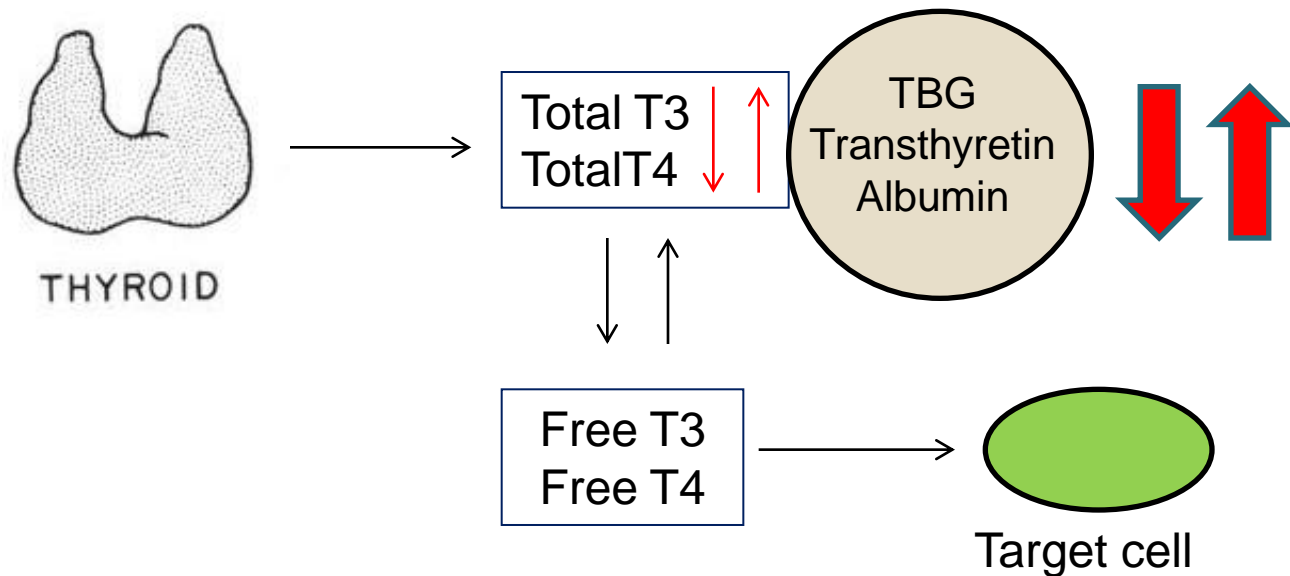
## IMPORTANT PRINCIPLES FOR TFT IN ICU:

- TFT should not be done unless there is **strong suspicion of thyroid dysfunction.**
- Serum TSH alone is inadequate for interpretation. FT4 and FT3 should be sent as well.

Crit Care Clin. 2006; 22(1): 41-45  
Clin Chem. 1996; 42(1): 188-92



# THYROID-BINDING PROTEIN AFFECTS TOTAL T3, T4



FT3, FT4 are usually not affected.

Total T3, T4 *should not* be sent in critically ill patients.

# FACTORS THAT AFFECT PROTEIN-BINDING

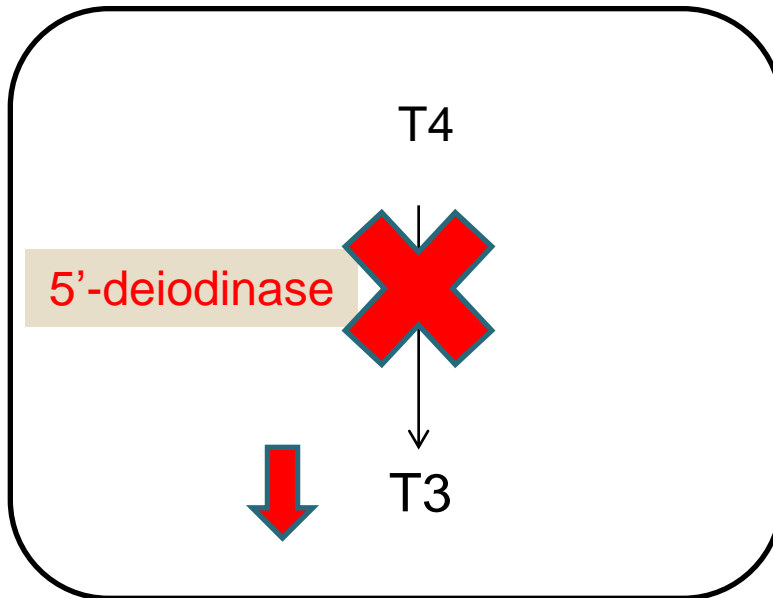
**Factors that affect TBG**    **TBG ↑ → total T3, T4 ↑**    **TBG ↓ → total T3, T4 ↓**

Disease / conditions	Pregnancy HIV infection Chronic active hepatitis Porphyria	Nephrotic syndrome Malnutrition Cirrhosis Active acromegaly
Medications	Estrogen Methadone Niacin Perphenazine	Glucocorticoids Androgen Salicylates L-asparaginase

Changes in thyroid-binding protein levels do not affect FT3, FT4.

*Total T3, T4 should not be sent in critically ill patients.*

# INHIBITION OF 5' DEIODINASE IN CRITICAL ILLNESS

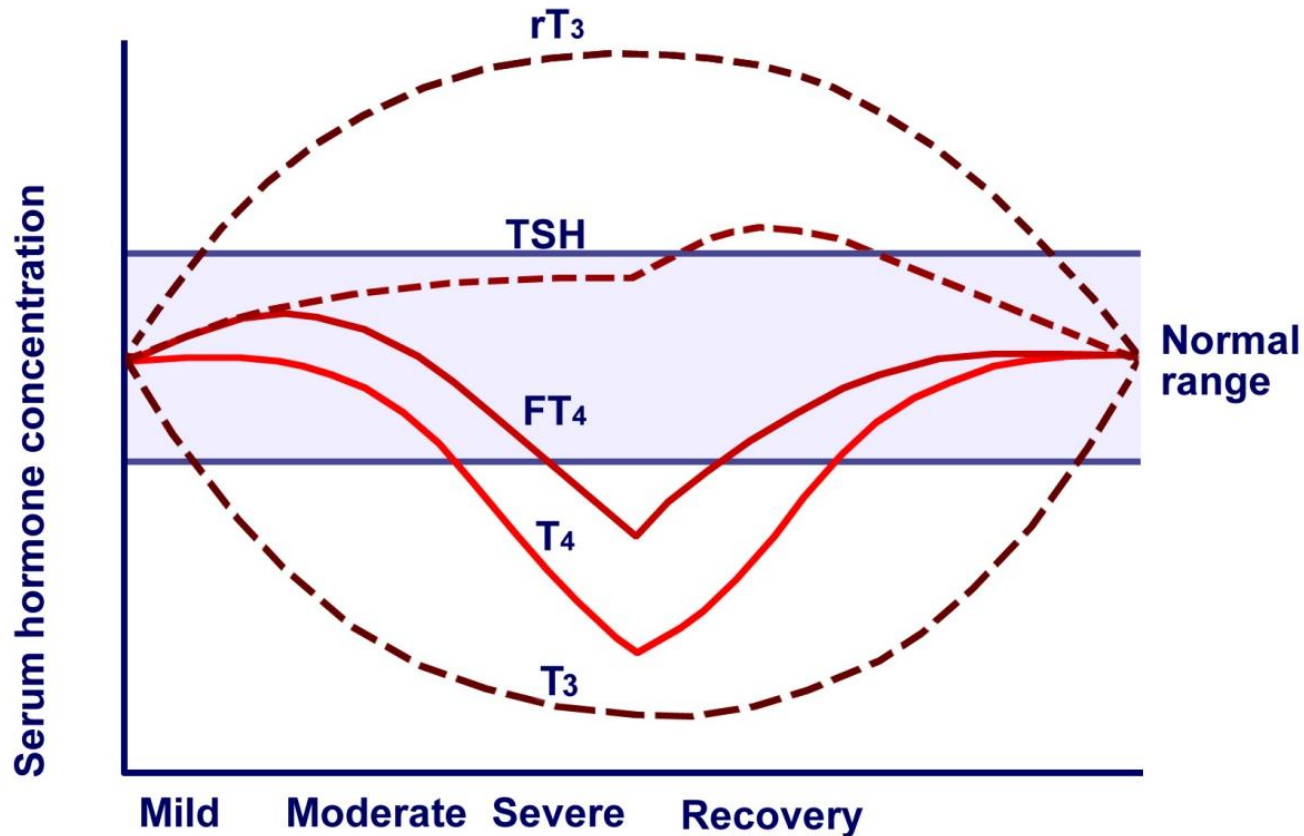


Factors that inhibit 5'-deiodinase

- Drugs: amiodarone, GC, propranolol
- Cytokines
- Free fatty acids



# CHANGES IN TFT DURING CRITICAL ILLNESS



# MEDICATIONS THAT AFFECT TFT

TFT	Medications	Effect
FT3 ↓, FT4 ↓	Rifampicin Phenytoin Phenobarbital Carbamazepine	Stimulate cytochrome P450 → increased metabolism of thyroid hormone
FT4 ↑	Heparin Salicylates Furosemide (>80 mg/d)	Compete with thyroid-binding proteins → increased free hormone
FT3 ↓, FT4 ↑	Amiodarone Glucocorticoids Propranolol (> 160 mg/d)	Inhibit 5'-deiodinase enzyme
TSH ↓	Dobutamine Dopamine (≥1mcg/kg/min) Hydrocortisone (≥100 mg/day) Dexamethasone (≥ 0.5 mg/day) Octreotide (≥100 mg/day)	Inhibit TSH secretion

# DIFFERENTIATING THYROID DISEASE FROM NONTHYROIDAL ILLNESS

Thyroid disease



Specific treatment

Non-thyroidal illness



Repeat TFT after  
recovery

# WHAT TO CONSIDER

- Clinical course
- Severity of illness
- Medications
- Underlying diseases / conditions
- History of thyroid disease and prior treatment
- Clinical signs of thyroid dysfunction in the hospital





Factors to consider

Hyperthyroidism

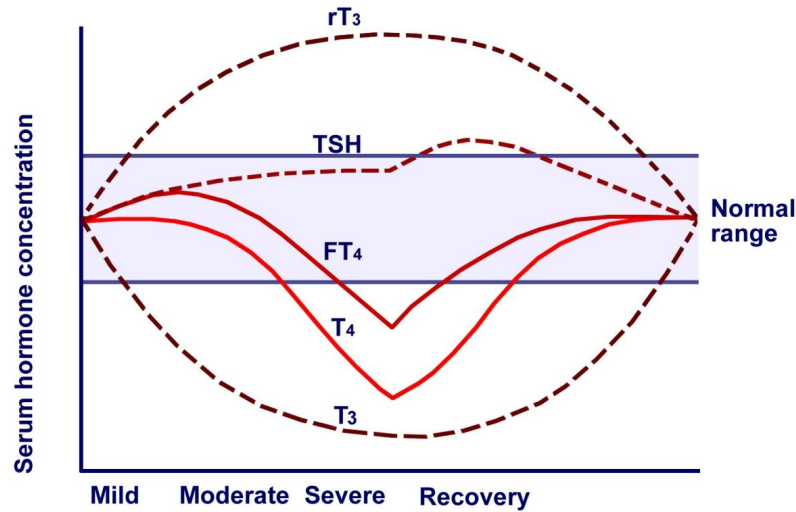


(IRAb)



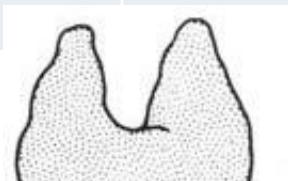
# COMMON PATTERNS OF TFTs

Thyroid status
Normal range
Primary hyperthyroidism
Primary hypothyroidism
Central hypothyroidism

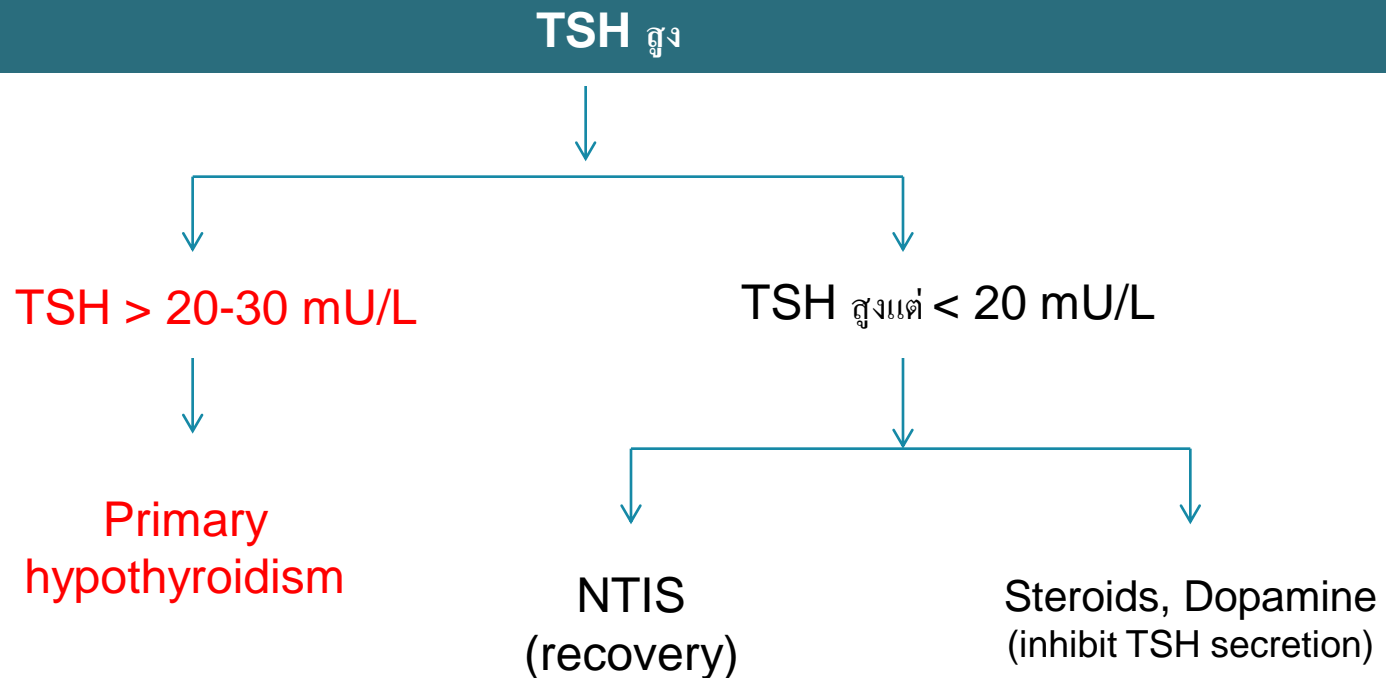


	TSH
L	0.4-4.5 mU/mL
	↓
	↑ (> 20)
	↓, NL, ↑

Nonthyroidal illness	TSH	FT3	FT4	TSH
Mild	↑↑↑	↓	↑	NL
Moderate (common)	↓	↓↓	NL	NL
Severe	↓	↓↓↓	↓	↓↓
Recovery	↑↑↑	↓	Thyroid↓ hormones	↑ (< 20)

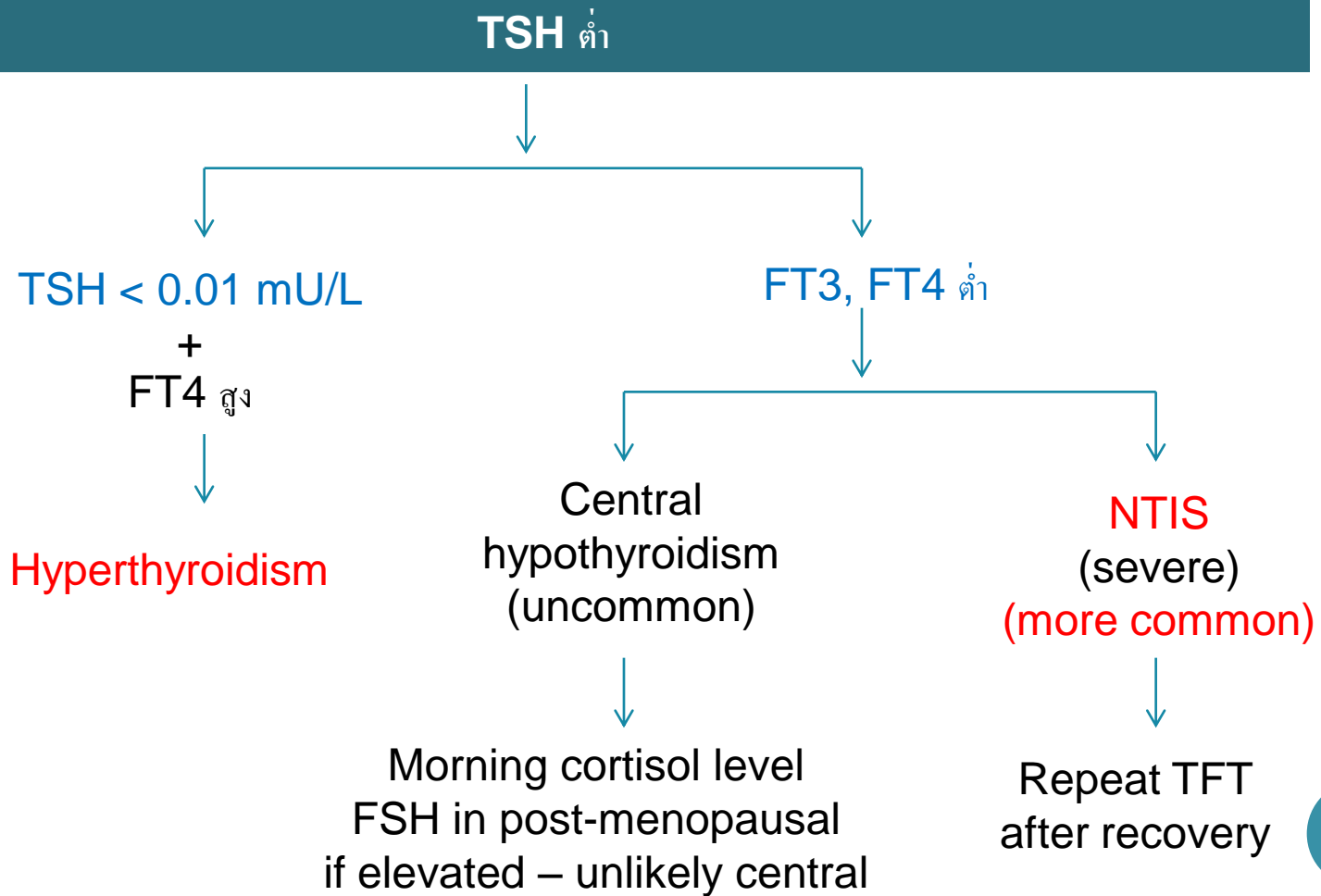


# THYROID DISEASE VS NONTHYROIDAL ILLNESS



Anti-TPO, Anti-thyroglobulin → Hashimoto's thyroiditis

# THYROID DISEASE VS NONTHYROIDAL ILLNESS

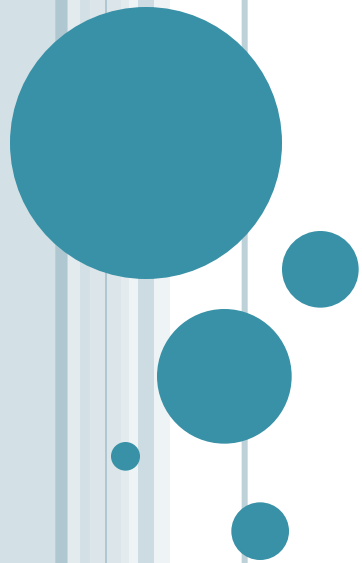


## A FINAL WORD ABOUT NONTHYROIDAL ILLNESS

- Hyperthyroidism and hypothyroidism are uncommon in ICU patients.
- Nonthyroidal illness has no proven influence on clinical outcomes.
- It seems that thyroid dysfunction have very little impact on the overall fate of critically ill patients.



# THYROID STORM



# EPIDEMIOLOGY OF THYROID STORM

- Uncommon, but serious complications
  - Incidence: 0.22% of hospital admissions for thyrotoxicosis
  - Mortality rate: 10-30%
- Usually occurs in Graves' disease  
sometimes in toxic multinodular goiter
- May be 1st clinical presentation of thyrotoxicosis



# PRECIPITATING FACTORS

- Most common: Severe infection and Discontinuation of antithyroid drugs
- Surgery: thyroid, non-thyroid
- Iodinated contrast
- I-131 ablation
- High-dose of thyroid hormone
- MI, stroke, PE
- DKA
- Trauma
- Labor / delivery





# CLINICAL MANIFESTATIONS (MULTI-SYSTEM)

## ○ Fever (nearly all pt)

- T > 38.5 °C
- Out of proportion to infection
- Excessive sweating

## ○ Neurologic signs (essential for Dx)

- Confusion, psychosis
- Seizures, coma

### Alteration of consciousness

- The only factor significantly different between Storm and non-storm

## ○ Cardiovascular (most pts)

- HR > 130-140 /min
- Tachycardia out of proportion to fever
- AF, CHF

## ○ GI/Hepatic

- Severe N/V, diarrhea
- Jaundice

## ○ Signs of Graves' disease

- Goiter, exophthalmos
- Difficult to examine in ICU pt

**Elderly** (apathetic hyperthyroidism): **weight loss, DOE, lethargy, depression, alteration of consciousness, AF, CHF; goiter may be absent**

# DIAGNOSIS

## ○ Clinical

- Burch-Wartofsky score (1993)
  - More widely-used
  - Higher sensitivity
- Japan Thyroid Association criteria (2012)
  - Good correlation with Burch-Wartofsky score
  - May miss some patients

## ○ Labs

- **TSH ↓ + FT4 ↑**  
FT3 อาจไม่สูงเนื่องจาก NTIS

ระดับการเปลี่ยนแปลง

ไม่ได้ช่วยแยก storm กับ non-storm

## ○ Other labs: non-specific

- CBC: ↑ WBC, left shift (even with no infection)
- Mild hyperglycemia
- Mild hypercalcemia
- Abnormal LFT



# BURCH-WARTOFSKY SCORE

Diagnostic parameters	Scoring points	Cardiovascular dysfunction	
<b>Thermoregulatory dysfunction</b>		Tachycardia (beats/minute)	
Temperature °F (°C)		90–109	5
99–99.9 (37.2–37.7)	5	110–119	10
100–100.9 (37.8–38.2)	10	120–129	15
101–101.9 (38.3–38.8)	15	>= 140	25
102–102.9			0
103–103.9			5
>= 104.0			10
<b>Central nervous system dysfunction</b>			15
Absent		Atrial fibrillation	
Mild (agitation)	10	Absent	0
Moderate (delirium, psychosis, extreme lethargy)	20	Present	10
Severe (seizures, coma)	30	Precipitating event	
<b>Gastrointestinal-hepatic dysfunction</b>		Absent	0
Absent	0	Present	10
Moderate (diarrhea, nausea/vomiting, abdominal pain)	10		
Severe (unexplained jaundice)	20		

**Score  $\geq$  45**

**Score 25-44**

**Score < 25**

**: highly suggestive**

**: impending thyroid storm**

**: unlikely**

# JAPAN THYROID ASSOCIATION CRITERIA

TABLE 9. FINAL CRITERIA FOR THE DIAGNOSIS OF THYROID STORM

Grade of TS	Criteria
TS1	CNS + 1 manifestation*
TS1	or
TS2	Any 3 manifestations*
TS2	* Fever $\geq 38$ C
	Tachycardia $\geq 130$ / min
	CHF: NYHA Class IV
	GI/hepatic

**Definitions**

Thyrotoxic convulsion, or

Fever:  $38^{\circ}\text{C}$  or higher.

Tachycardia:  $\geq 130$  beats/min (arrhythmias such as atrial fibrillation are evaluated by measuring the heart rate).

CHF: The patient presents with severe symptoms such as pulmonary edema, moist rales for more than half the lung field, or cardiogenic shock. The patient's CHF is categorized as Class IV by the NYHA classification or Class III or higher by the Killip classification.

GI/hepatic manifestations: The patient presents with nausea, vomiting, diarrhea, or a bilirubin of  $>3$  mg/dL.



# MANAGEMENT

- Multi-drug approach for multiple targets
- Supportive care / treat systemic decompensation
- Treat precipitating cause



# MECHANISM OF ACTION OF MEDICATIONS

Medication	Stop hormone production	Stop hormone release	↓ Conversion of T4 to T3	↓ Adrenergic symptoms
PTU	X		X	
MMI	X			
Lugol / SSKI	X	X		
Glucocorticoid			X	
B-blockers			X	X
Lithium (2 <sup>nd</sup> line)	X	X		

- PTU (preferred) more rapidly ↓ serum T3 over first few hours
- **Lugol / SSKI: must be given at least 1 hr after PTU / MMI**
- B-blocker: C/I if CHF, COPD / asthma

**Elderly, longstanding hyperthyroid, abnormal EKG / CXR – Echo before BB**

# MEDICAL TREATMENT OF THYROID STORM

Drug	Oral dose	Rectal dose
PTU	500-1000mg stat, then 250 mg q 4 h	600 mg stat, then 250 mg q 4 h
Lugol's soln 20 drops/ml, 38 mg iodide/drop	10 drops q 8 h	5-10 drops q 6-8 h
SSKI 20 drops/ml, 8 mg iodide/drop	5 drops q 6 h	250-500 mg q 6 h
Propranolol	60-80 mg po q 4-6 h	-
Esmolol	250-500 ug/kg iv stat, then iv drip 50-100 ug/kg/min	
Hydrocortisone	300 mg iv stat, then 100 mg iv q 8 h	
Dexamethasone	2 mg iv q 6 h	

- Lugol / SSKI: GI irritation, so **mix in 240 ml water** and take with food
- PTU retention enema: 400-600 mg **+ sterile water 90 ml** via Foley cath, inflate balloon in rectum for 2 hr; suppository is less uncomfortable
- Esmolol:  $T_{1/2}$  9 minutes vs. propranolol  $T_{1/2}$  2.3 hrs
- **If hypotension**, possible adrenal insuff: prefer **hydrocortisone** than dexa



# TREATMENT OF SYSTEMIC DECOMPENSATION

- Paracetamol for fever (do not use aspirin – increased free hormones)
- Dextrose soln to correct dehydration (hypoglycemia due to hepatic glycogen depletion)
- Broad-spectrum antibiotics while waiting for septic workup in patients with fever
- AF: digoxin (higher dose due to increased drug metabolism)  
If B-blocker contraindicated: amiodarone, diltiazem





# CLINICAL COURSE

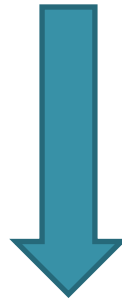
- Rapid clinical improvement in 24-48 hrs
- Normalization of serum T4 within 4-5 days

<b>Medication</b>	<b>When to stop</b>
PTU	Continue until definitive Rx
Lugol / SSKI	Stop when clinical improved, usually 5-7 days
Glucocorticoids	Stop when clinical improved, usually 5-7 days
B-blockers	Continue until euthyroid



## FAILED CONVENTIONAL MEDICAL TREATMENT

- Clinical not improved within 24-48 h
- Drug toxicity: PTU-induced agranulocytosis
- Need rapid control due to severe cardio-pulmonary comorbidities



Therapeutic plasma exchange  
Followed by total thyroidectomy



# LONG-TERM MANAGEMENT OF HYPERTHYROIDISM

- **Nonadherent patient: definitive treatment**
- **I-131 ablation**
  - Switch PTU → continue MMI as OPD pt
  - I-131 is delayed due to recent use of inorganic iodide
- **Thyroidectomy**
  - Large, obstructive goiter
- **Compliant patient**
  - Continue antithyroid drugs is acceptable
  - Switch PTU → continue MMI as OPD pt



# MEDICATIONS BLOCKING 1-131 UPTAKE

Type of medication	Recommended time of withdrawal	
	EANM	SNM
PTU, MMI	3-7 d	3 d
Lugol's soln, SSKI	1-2 wk	2-3 wk
Iodinated contrast	3-4 wk	3-4 wk
Amiodarone	1-6 mo	3-6 mo



# **AMIODARONE-INDUCED THYROID DISORDERS**



# AMIODARONE

- Highly effective anti-arrhythmic drug
- Contains 75 mg of iodine per 200 mg tablet of amiodarone
- Effects on thyroid function
  - Inhibits 5'-deiodinase: decreased conversion of T4 to T3
  - Blocks binding of T3 to nuclear receptors
  - Toxic effect on thyroid cells: destructive thyroiditis
  - Inhibit synthesis and release of thyroid hormones: Wolff-Chaikoff effect
  - Excessive thyroid hormone synthesis: Jod-Basedow effect



# PATHOGENESIS, CLINICAL FEATURES

	AIH	AIT	
		Type 1	Type 2
Mechanism	Iodine-induced persistent block of thyroid H synthesis and release	Iodine-induced excessive thyroid H synthesis	Destructive thyroiditis
Risk Fx	-High dietary iodine intake -Subclinical hypothyroidism -Anti-TPO, Tg positive	-Low dietary iodine -Pre-existing nodular goiter, autonomous nodule, latent Graves' disease	-Low dietary iodine -No underlying thyroid disease
Onset	Early Uncommon after 18 mo	Unpredictable and variable Can present after withdrawal of amiodarone	

AIH: amiodarone-induced hypothyroidism

AIT: amiodarone-induced hyperthyroidism



# DIFFERENTIATING AIT TYPE 1 AND 2

	Type 1	Type 2
Pre-existing thyroid disease	Yes	No
Neck exam	MNG, diffuse goiter	Normal or small tender goiter
Clinical course	Persistent	Transient (thyroiditis)
Color flow Doppler shows increased thyroid vascularity	Yes	No





# MONITORING PATIENTS ON AMIODARONE

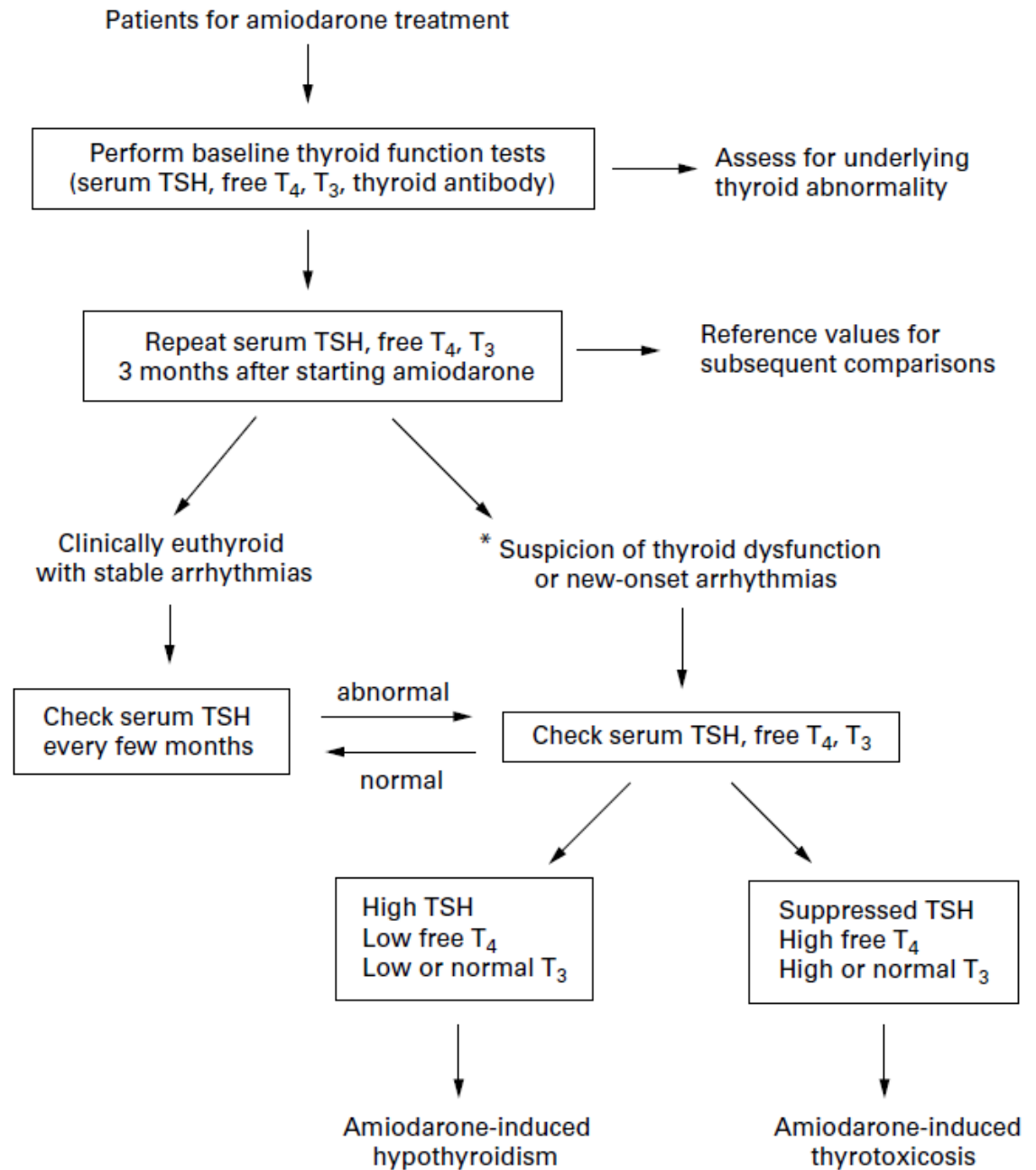


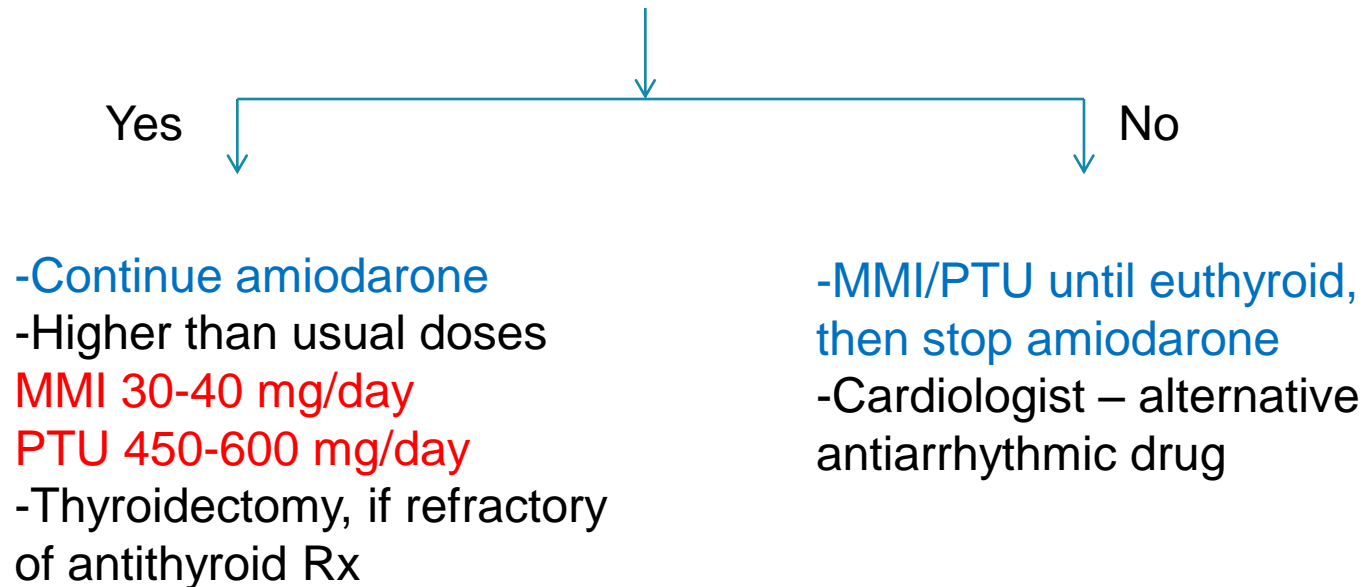
Figure 2 Algorithm for monitoring of thyroid function tests in amiodarone-treated patients

# MANAGEMENT - AIH

- Continue amiodarone.
- Give thyroid hormone replacement.  
Doses larger than normal are often required.
- Stop amiodarone if it is not effective at controlling the arrhythmia.
- Hypothyroidism usually resolves after stopping amiodarone.

# MANAGEMENT – AIT TYPE 1

- Indicated for life-threatening ventricular arrhythmia
- Effective in controlling the arrhythmia



## MANAGEMENT - AIT TYPE 2

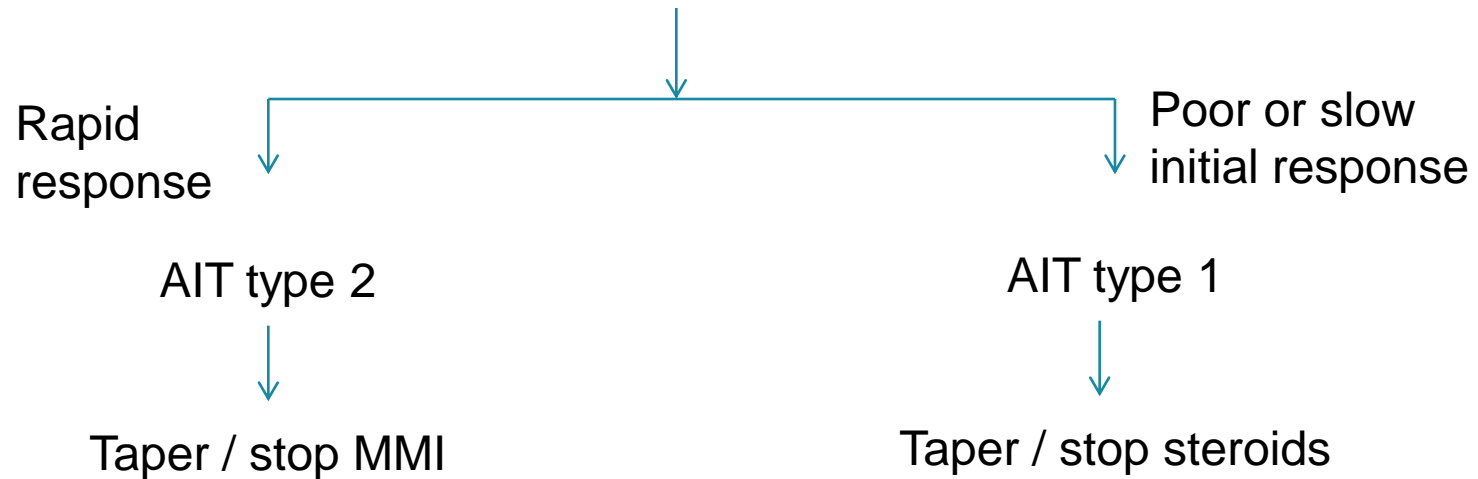
- Clinical course: hyperthyroid phase (several weeks – months) → hypothyroid phase → recovery
- Continue amiodarone if indicated and effective
- Glucocorticoids (ไม่ว่าจะกิน amiodarone ต่อหรือไม่)

**Prednisolone 40-60 mg/day for 1-2 months, then taper and stop after 3 months**



# MANAGEMENT – UNSURE TYPE 1 OR 2

- MMI 40 mg/day, combined with
- Prednisolone 40 mg/day





**THANK YOU**