CCM Board Tutorial
Endocrine emergencies in ICU: Update on management

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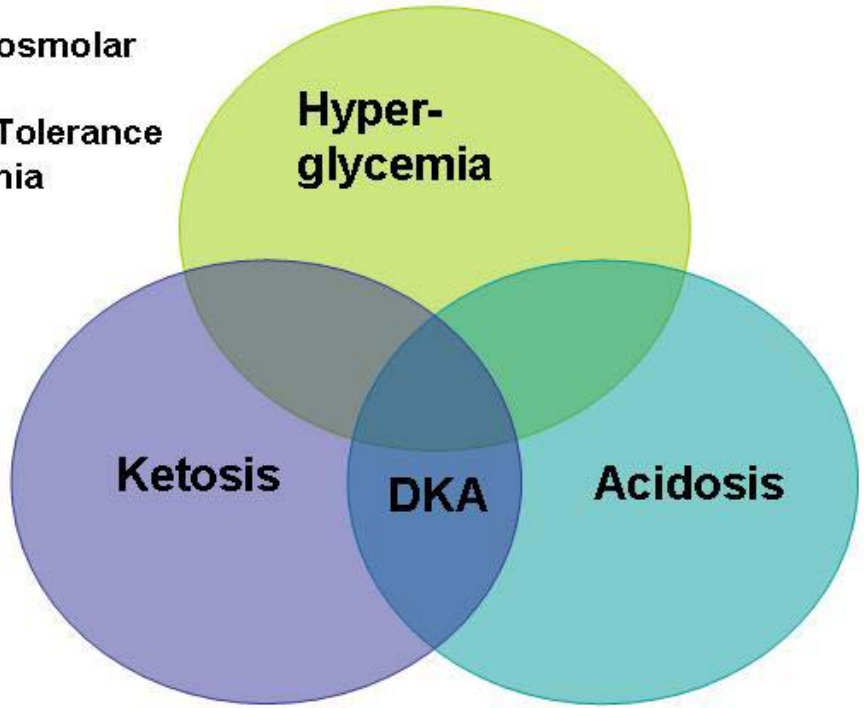
Agenda

- Diabetic Ketoacidosis (DKA) & Hyperglycaemic hyperosmolar State (HHS)
- Thyroid storm, Myoxedema coma, Sick Euthyroid syndrome
- Adrenocortical insufficiency & Addisonian crisis
- SIADH, Diabetes insipidus & Cerebral salt wasting

DKA and HHS

Diagnosis	DKA			HHS
	Mild	Moderate	Severe	
Plasma glucose (mmol/L)	> 14	> 14	> 14	>33
Arterial pH	7.25–7.30	7.00–7.24	<7.00	>7.30
Serum HCO3 (mmol/L)	15–18	10 to <15	<10	>15
Urine ketones	+	+	+	Small
Serum ketones	+	+	+	Small
Effective serum osmolality (mOsm/kg)	Variable	Variable	Variable	> 320
Mental state	Alert	Variable	Coma	Coma

Other Hyperglycemic States
Diabetes Mellitus
Non-Ketotic Hyperosmolar Coma
Impaired Glucose Tolerance
Stress Hypoglycemia



Other Ketotic States:
Ketotic Hypoglycemia
Alcoholic Ketosis
Starvation Ketosis

Other Metabolic Acidotic States
Lactic Acidosis
Hyperchloremic Acidosis
Salicysm
Uremic Acidosis
Drug-Induced Acidosis

Kitabchi AE, Umpierrez GE, Murphy MB, et al. Diabetes Care 2001; 24:131-53.

	Starvation or high fat intake	DKA	Lactic acidosis	Uremic acidosis	Alchoholic Ketosis	Salicylate intoxication	Methanol or ethyleneglycol intoxication	Hyper-osmolar coma	Hypo-Glycemic coma	Rhabdomyolysis	Isopropyl alcohol
pH	Normal	↓	↓	Mild ↓	↓↑	↓↑↑	↓	Normal	Normal	Mild ↓ Maybe ↓↓	Normal
Plasma glucose	Normal	↑	Normal	Normal	↓ Or Normal	Normal or ↓	Normal	↑↑ >500 mg/dl	↓↓ <30 mg/dl	Normal	↓
Total plasma Ketones *	Slight ↑	↑↑	Normal	Normal	Slight to Moderate ↑	Normal	Normal	Normal or slight ↑	Normal or slight ↑	Normal	↑↑
Anion gap	Slight ↑	↑	↑	Slight ↑	↑	↑	↑	Normal	Normal or Slight ↑	↑↑	Normal
Osmolality	Normal	↑	Normal	↑	Normal	Normal	↑↑	↑↑ ↑>330 mOsm/kg	Normal	Normal or slight ↑	↑
Uric Acid	Mild ↑	↑	Normal	Normal	↑	Normal	Normal	Normal	Normal	↑	Normal
Glycosuria^	Negative	++	Negative	Negative	Negative	Negative †	Negative	++	Negative	Negative	Negative
Miscellaneous		Tabs +	lactate >7 mmol/l	Serum BUN>200 mg/dl		Salycilate serum levels +	+ serum levels			Myoglobin Urin Hemoglobin Urin	

+, positive; *Acetest and Ketostix measure acetoacetic acid only: thus, misleading low values may be obtained because the majority of "ketone bodies" are β-hydroxybutyrate:
†respiratory alkalosis/metabolic acidosis; ^may get false-positive or false-negative urinary glucose caused by the presence of salicylate or its metabolites;
Adapted from reference5

Kitabchi AE, Umpierrez GE, Murphy MB, et al. Diabetes Care 2001; 24:131-53.

Clinical setting

DKA

- New-onset type 1 diabetes
- Discontinuation/inadequate insulin in established type 1 diabetes
- Young patients with type 1 diabetes
  - **psychological problems**
  - **eating disorders**

HHS

- Known type 2 DM
- 1/3 of patients do not have a prior diagnosis of diabetes
- Oral hydration usually is impaired by concurrent acute illness or chronic comorbidity (eg, dementia, immobility, vomiting)

DKA: clinical features

Symptoms, Signs	Cause
Polyuria, polydipsia	Osmotic diuresis
Anorexia, fatigue	?
Nausea, vomiting	?Ketosis
Weight loss	Protein, fat catabolism
Abdominal pain	?K^+ depletion, fluid pooling
Leg cramps	?K^+ depletion
Dehydration	Osmotic diuresis
Hypotension	Dehydration, acidemia
Tachycardia	Dehydration, acidemia
Hyperventilation	Acidemia
Gastric stasis	?K^+ depletion
Hypothermia	Peripheral vasodilation, acidemia
Impaired consciousness	Hyperosmolality

HHS: altered mental state

- Wide variety of focal & global neurologic changes
  - Drowsiness and lethargy
  - Delirium, Coma
  - Focal or generalized seizures
  - Visual changes or disturbances
  - Hemiparesis
  - Sensory deficits

Precipitating factors of DKA/HHS

- Infection
- CVA
- Alcohol abuse
- Pancreatitis
- Myocardial infarction
- Trauma
- Drugs (e.g. corticosteroid)
- Pregnancy

Who will develop DKA?

- Type 1 DM
  - 1st presentation
  - Under minor stress or missed insulin dose
- Type 2 diabetes under conditions of extreme stress (e.g. severe infection, trauma, CVD)
- Atypical diabetes or ketosis prone type 2 diabetes

Atypical Diabetes

- rare form of diabetes
- presenting with diabetic ketoacidosis
- rapidly falling requirement for insulin over the first few weeks
- spontaneous resolution of their diabetes
- May relapse within 2 years of diagnosis, requiring insulin or oral hypoglycaemic agents
- typically have negative markers of autoimmune β-cell failure

Umpierrez GE et al., Ann intern med. 2006; 144:350-357

Complications

DKA

- Hypokalaemia
- Hypoglycaemia
- APO (fluid overload) vs. ARDS (leaky capillaries)
- Acute gastric dilatation/erosive gastritis
- Hypophosphataemia
- Cerebral oedema

HHS

- Ischaemia or infarction to any organ, including heart and brain
- Thromboembolism
- ARDS/DIC or multi-organ dysfunction syndrome
- Cerebral oedema (rare)

Cerebral oedema in DKA

- Occurs 4-12 hours into treatment
- 1% of children with DKA
- Mortality rate of 21%
- Neurologic sequelae in another 21% of patients
- Less common in adult
- Related to the severity and duration of DKA, ongoing hyponatraemia. administration of bicarbonate, overaggressive or overly hypotonic fluid resuscitation

Prognosis

DKA

- The overall mortality rate is 2% or less

HHS

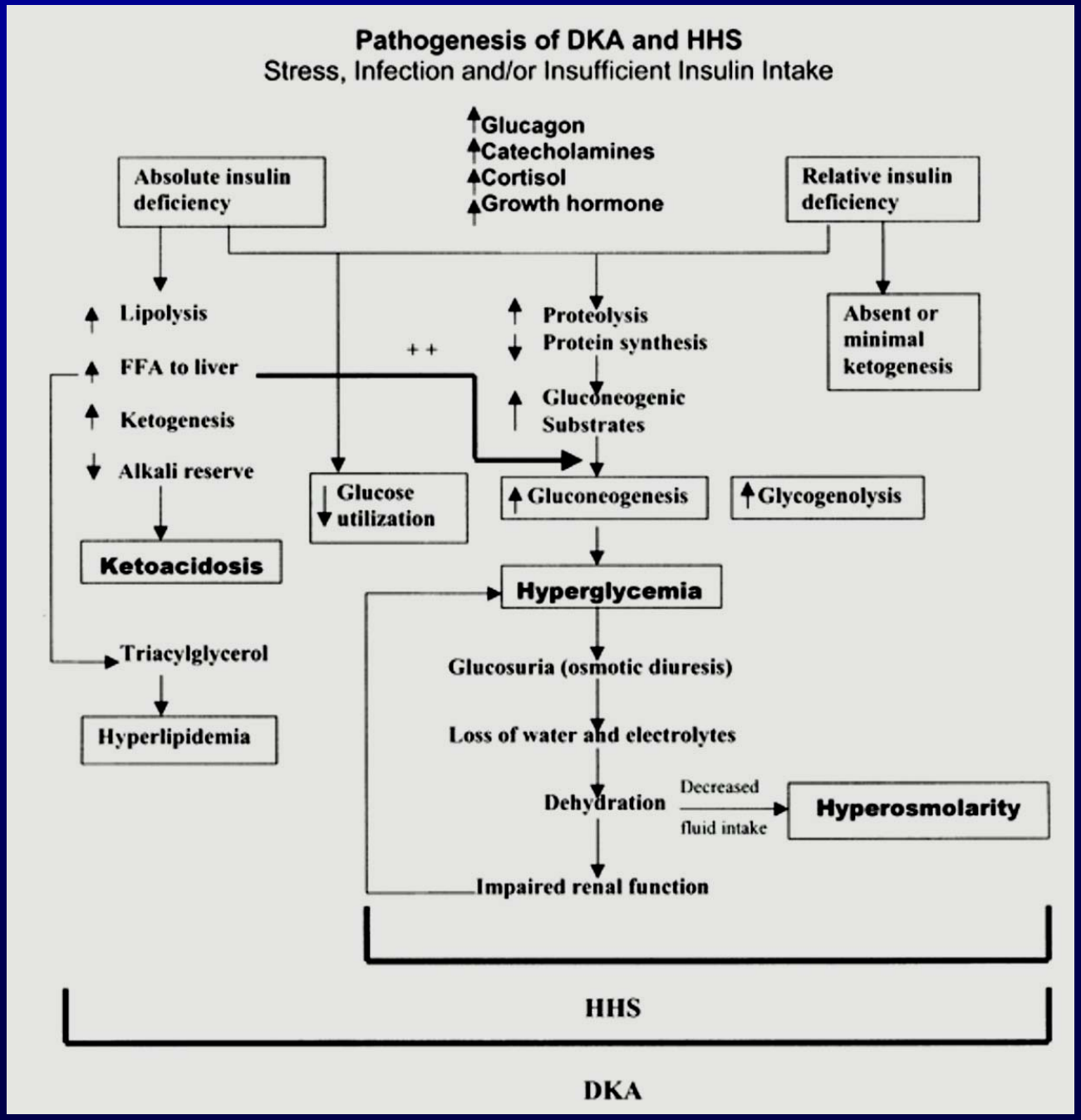
- Overall mortality rate is between 10% and 50%
- dependent on coexisting conditions and complications

Ix on admission

- Glucose
- Na/K, Ur/Cr, CPK, PO4
- CBP
- Clotting
- ABG
- Ketones
- Plasma Osmolality
- Amylase

- ECG
- CXR
- CT brain
- Sepsis work-up: urine, stool, CSF
- HbA1c

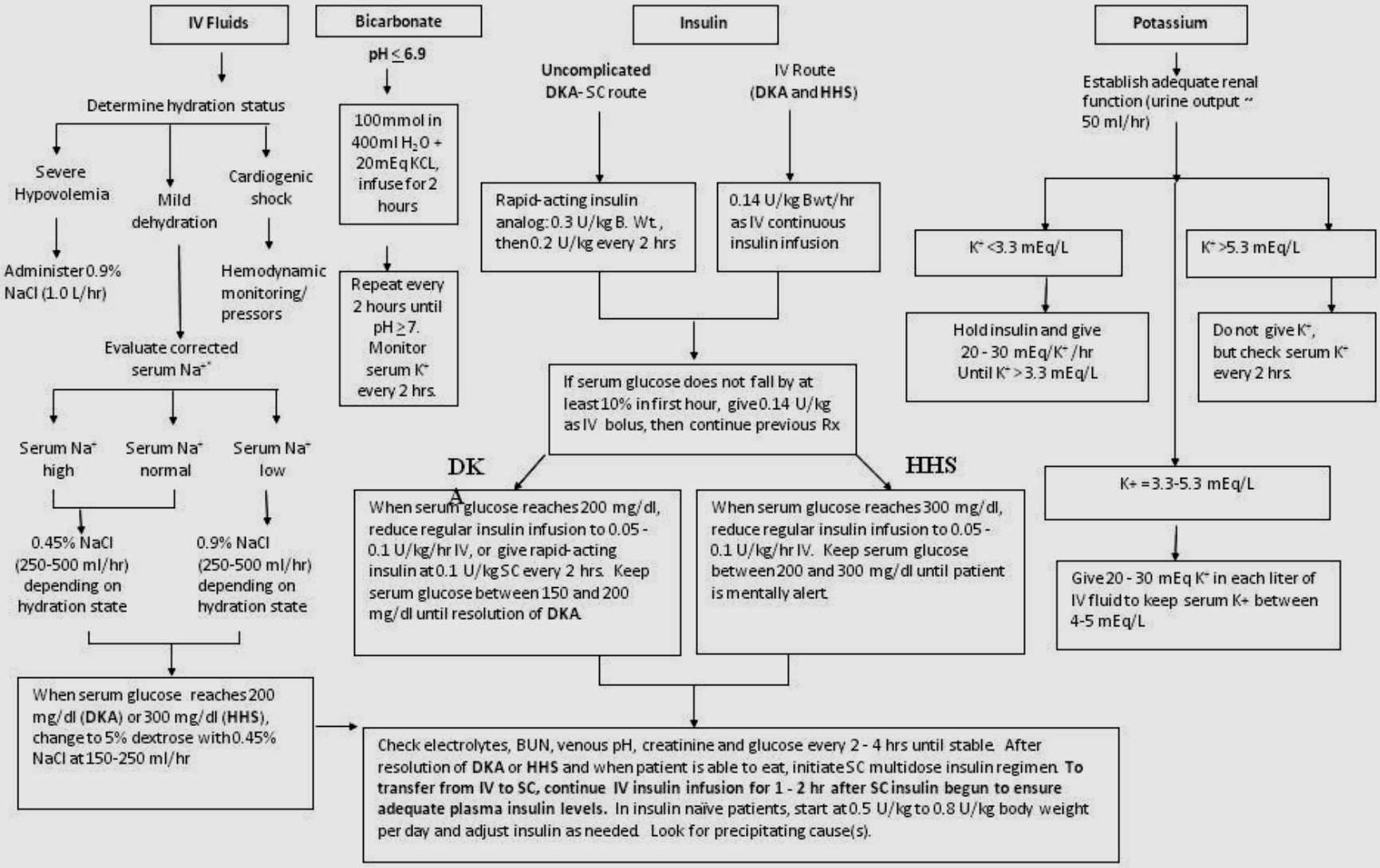
Plasma osmolality = [Na + K] x 2 + glucose + urea



Kitabchi AE, Umpierrez GE, Murphy MB, et al. Diabetes Care 2001; 24:131-53.

PROTOCOL FOR MANAGEMENT OF ADULT PATIENTS WITH DKA OR HHS*

Complete initial evaluation. Check capillary glucose and serum/urine ketones to confirm hyperglycemia and ketonemia/ketonuria. Obtain blood for metabolic profile. Start IV fluids: 1.0 L of 0.9% NaCl per hour.+



* Kitabchi et al., Diabetes Care 2006

IV Insulin: example

- IV line 1: Actapid HM 50 units in 49.5 ml Gelofusine or NS => 1 unit/ml
- Flush tubing if insulin diluted in NS
- IV line 2: D5 or D5-NS ± KCl
- Adjust according to H'stix
- Freq monitoring
- 0.15u/kg IV bolus

H'stix (mmol/L)	Actrapid (units)
< 5	0
5-8	0.5
8.1-11	1
11.1-14	2
14.1-17	3
17.1-20	4
20.1-23	5
> 23	6

Change IV to SC Insulin (1)

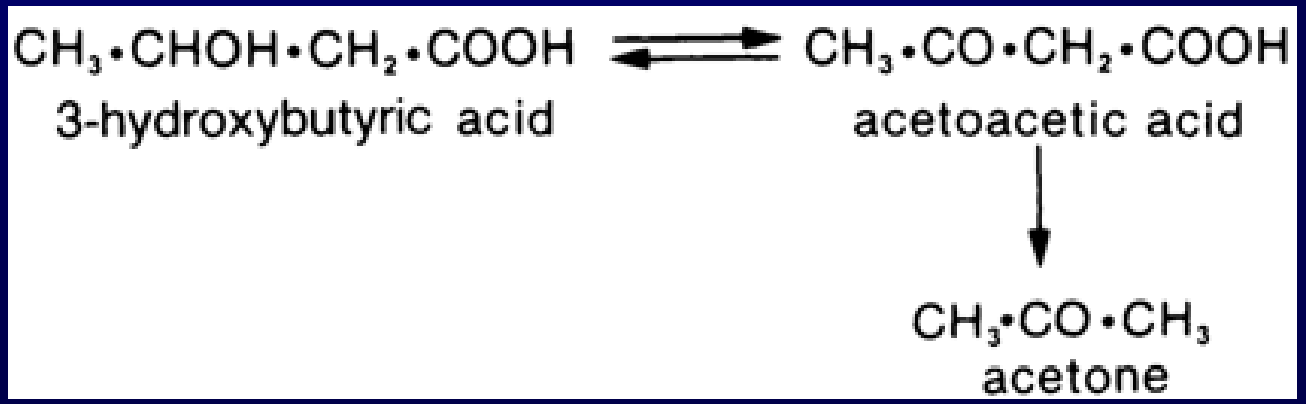
- Glucose,11 mmol/l
- Venous bicarbonate.18 mmol/l
- pH.7.30
- Able to eat and drink

Change IV to SC Insulin (2)

- Calculate the total daily dose (TDD) based on last 8-12 hr insulin infusion rate
- Give 40-50% as basal insulin given at bedtime
  - e.g. Protaphane HM or Humulin N
- Divide remaining into 3 bolus given premeals
  - e.g. Actrapid HM or Humulin R
- Stop infusion 1 hr after the 1st dose of s.c. insulin
- Consult endocrinologist for further care

Paradoxical worsening of ketosis during treatment

- Most of the laboratory tests for ketone bodies use the nitroprusside method, which detects acetoacetate, but not β hydroxybutyrate
- β hydroxybutyrate is converted to acetoacetate during treatment



Bicarbonate

- Routine use not recommended
- Problems
  - Intracellular acidosis
  - Delayed ketonion metabolism $\rightarrow$paradoxical CNS acidosis
  - Worsen hypokalaemia
  - Paradoxical rise in acetoacetate
  - Alkalosis upon reversal of ketosis
- Only indicated in severe acidosis (pH $<$7.0)

Phosphate in DKA & HHS

- Phosphate depletion in DKA is universal
- No evidence that phosphate therapy is necessary in treatment for better outcome of DKA
- In patients with potential complications of hypophosphataemia, including cardiac and skeletal muscle weakness, the use of phosphate may be considered when PO_4 < 0.35 mmol/L
- High dose PO4 administration may result in hypocalcaemia
- No studies are available on the use of phosphate in the treatment of HHS

Other measures in DKA/HHS

- Antibiotics
- Heparin/LMWH
- H2 antagonist/Proton pump inhibitor
- Close haemodynamic monitoring

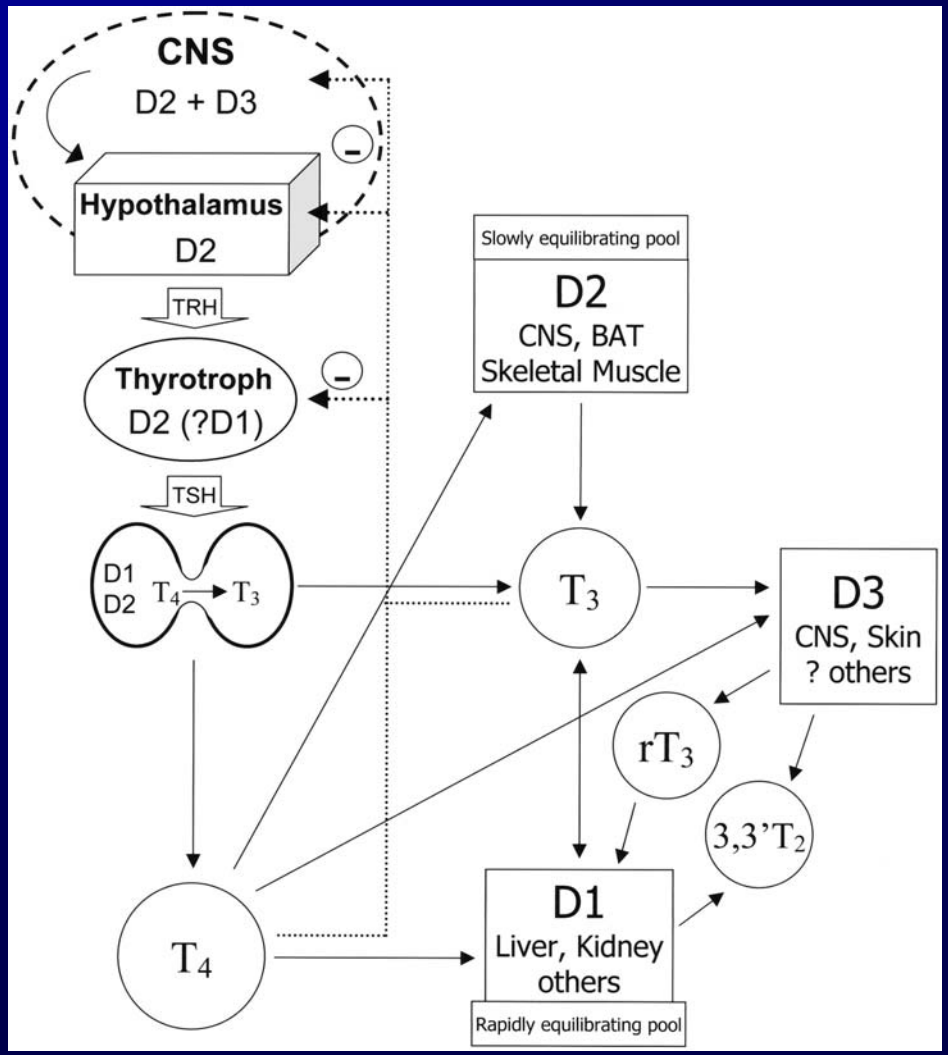
Sick Euthyroid syndrome
Nonthyroidal illness syndrome (NTIS)

Severity of illness	Thyroid-related hormones			
	Free T_4	Free T_3	Total rT_3	TSH
Mild	Normal	Reduced up to 50%	Increased up to 2-fold	Normal
Moderate	Increased	Reduced up to 90%	Increased up to severalfold	Normal
Severe	Reduced	Almost undetectable	Variable	Reduced

Hallmark is a very low free T3 in normal HPA Axis

Bianco *et al.* Endocrine Reviews, February 2002, 23(1):38–89

Decreased D2 & D3 expression in NTIS



Bianco *et al.* Endocrine Reviews, February 2002, 23(1):38–89

Sick Euthyroid syndrome
Nonthyroidal illness syndrome (NTIS)

- The abnormalities resolve upon recovery from the illness
- TSH can rise transiently above the reference range as the serum T3 and T4 normalize
- An adaptive response to conserve energy in times of stress, because tissue hypothyroidism should decrease oxygen consumption
- Maladaptive and should be treated in certain circumstances
- Severity of NTIS predicts mortality

Koenig RJ. Curr Opin Endocrinol, Diabetes Obes 2008, 15:466–469

Dx of Thyroid Emergencies

Thyroid storm

- Undetectable sTSH
- High fT4 and fT3
- T4 level does not correlate with severity

Myxoedema coma

- Very high TSH
- Very low or undetectable fT4 & fT3
- T4 level does correlate with severity
- Difficult in secondary hypothyroidism (normal TSH, low fT4)

Clinical setting: Thyroid Emergencies

- Hyper- or Hypothyroidism is COMMON
- Thyroid storm is RARE
- Myxoedema coma is EVEN RARER (?tropical climate in HK)
- Need a precipitating event to ignite the transition

Why thyroid storm?

- Poorly understood
- ? ↑ amount of free thyroid hormones
- ? ↑ in target cell beta-adrenergic receptor density or postreceptor modifications in signaling pathways

Nayak & Burman. Endocrinol Metab Clin N Am 35 (2006) 663–686

Precipitating factors

- Surgery
- Trauma
- myocardial infarction
- pulmonary embolism
- DKA
- Parturition
- Severe infection
- Withdrawal of antithyroid drugs
- Excessive iodine administration
  - eg, radiocontrast, amiodarone
- Radioiodine therapy
- Pseudoephedrine
- Salicylate use

Diagnosis of Thyroid Storm

Table 1
Diagnostic criteria for thyroid storm

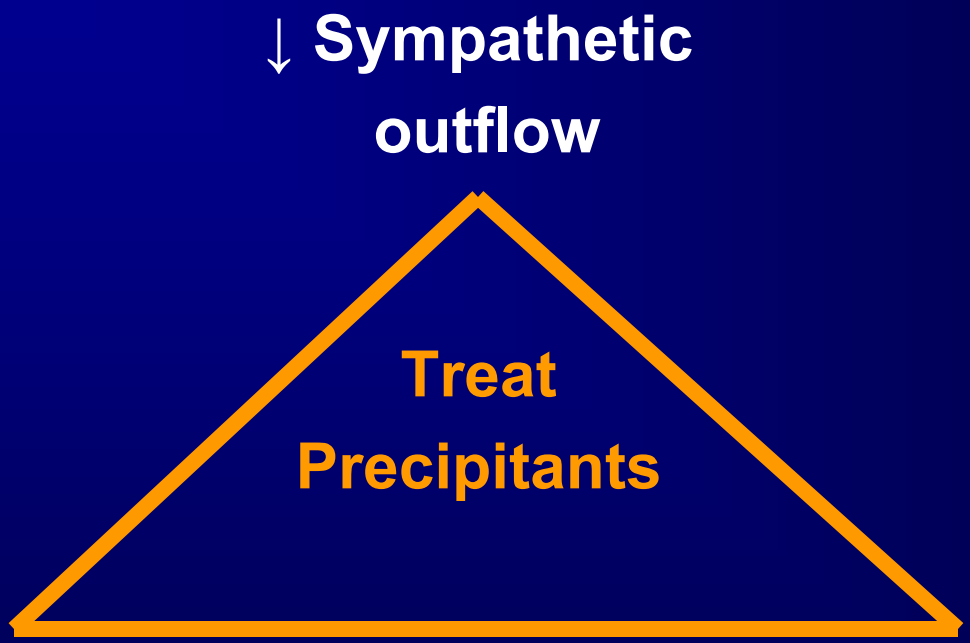
Diagnostic parameters	Scoring points
Thermoregulatory dysfunction	
Temperature	
99–99.9	5
100–100.9	10
101–101.9	15
102–102.9	20
103–103.9	25
≥104.0	30
Central nervous system effects	
Absent	0
Mild (agitation)	10
Moderate (delirium, psychosis, extreme lethargy	20
Severe (seizures, coma)	30
Gastrointestinal-hepatic dysfunction	
Absent	0
Moderate (diarrhea, nausea/vomiting, abdominal pain)	10
Severe (unexplained jaundice)	20
Cardiovascular dysfunction	
Tachycardia (beats/minute)	
90–109	5
110–119	10
120–129	15
≥140	25
Congestive heart failure	
Absent	0
Mild (pedal edema)	5
Moderate (bibasilar rales)	10
Severe (pulmonary edema)	15
Atrial fibrillation	
Absent	0
Present	10
Precipitating event	
Absent	0
Present	10

Scoring system: A score of 45 or greater is highly suggestive of thyroid storm; a score of 25–44 is suggestive of impending storm, and a score below 25 is unlikely to represent thyroid storm.

Adapted from Burch HB, Wartofsky L. Life-threatening thyrotoxicosis. Thyroid storm. Endocrinol Metab Clin North Am 1993;22(2):263–77.

- **Fever**
- CNS effect
  - Normal
  - Delirium, psychosis
  - Coma
- GI
  - Vomiting
  - Abd pain
- Cardiac
  - Tachycardia
  - AF
  - CHF

Treatment of Thyroid Storm



Supportive

1. Close monitoring : often need CVP, Swan-Ganz, cardiac monitor. ICU care if possible
2. Hyperthermia : paracetamol (not salicylate or NSAID b/c ↑ free thyroid hormone levels disproportionately), physical cooling
   - Dehydration : iv fluid (2-4 L/d)
   - iv Glucose, iv vitamin (esp. thiamine)
   - Supportive : O2 , digoxin / diuretics if CHF/AF ± inotropes
   - Treat precipitating factors and/or co-existing illness

HA Handbook of Internal Medicine, 5th edition, 2008

Specific treatment

1. Propylthiouracil 150-200 mg q4→6h po / via NG tube
   - Hydrocortisone 200 mg stat iv then 100 mg q6-8h
   - β-blockers (exclude asthma / COAD or frank CHF):
   - Propranolol 40-80 mg q4-6h po/NG or Propranolol/Betaloc 1-10 mg iv over 15 min every several hrs
   - If β-blockers contraindicated, consider diltiazem 60-120 mg q8h as alternative

HA Handbook of Internal Medicine, 5th edition, 2008

Specific treatment

4. 1 hour later, use iodide to block hormone release
   - 6-8 drops Lugol's solution / SSKI po q6-8h (0.2 g/d)
   - NaI continuous iv 0.5-1 g q12h *or*
   - Ipodate (Oragrafin) po 1-3 g/d
5. Consider LiCO3 250 mg q6h to achieve Li level 0.6-1.0 mmol/L if ATD is contraindicated
6. *Consider plasmapheresis and charcoal haemoperfusion for desperate cases*

HA Handbook of Internal Medicine, 5th edition, 2008

Thionamide

- Both Carbimazole (CMZ) & Propylthiouracil (PTU) can be used
  - Inhibits new hormone synthesis
  - Decreases T4-to-T3 conversion (PTU only)
- Normally, deiodination of T4 to T3 provides only 20% to 30% of T3 (with the remaining emanating from direct thyroid secretion)
- Provide more than 50% of T3 in the thyrotoxic state
- D1 is sensitive to inhibition by PTU

Burman K. Hyperthyroidism. In: Becker K, editor. Principles and practice of endocrinology and metabolism. 2nd edition. Philadelphia: J.B. Lipincott Company; 1995. p. 367–85

Beta-blockade

- Controlling the peripheral actions of thyroid hormone
- Relatively large doses of propranolol are required
  - Faster metabolism of the drug
  - Possibly greater quantity of cardiac β-adrenergic receptors

Iodine in hyperthyroidism

- **Wolff–Chaikoff effect**: Blocks release of hormone from gland
- Administer at least 1 hr after thionamide to avoid **Jod-Basedow effect** (hyperthyroidism following administration of iodine or iodide)
  - SSKI (1 g/mL) contains 76.4% iodine. Five drops four times a day (assuming 20 drops/mL) contain about 764 mg iodine
  - Lugol's solution (125 mg/mL of total iodine) contains, in each 100 mL, 5 g of iodine and 10 g of potassium iodide. Four drops four times a day contain about 134 mg of iodine

Glucocorticoid

- Inhibitory effect on peripheral conversion of T4 to T3
- Treat possible relative adrenal insufficiency
- possibility of undiagnosed Addison's disease or adrenal insufficiency
- Vasomotor stability

Lithium

- Can be used when thionamide therapy is contraindicated because of toxicity or adverse reactions
- Can also be used in combination with PTU or CMZ/methimazole
- Directly decreasing thyroid hormone secretion (increasing intrathyroidal iodine content)
- Inhibiting coupling of iodotyrosine residues that form iodothyronines (T4 and T3)

PTU Per Rectal (1)

TABLE 1. PHARMACOKINETIC AND EFFECTS OF ANTITHYROID DRUG GIVEN PER RECTUM IN PREVIOUS STUDIES

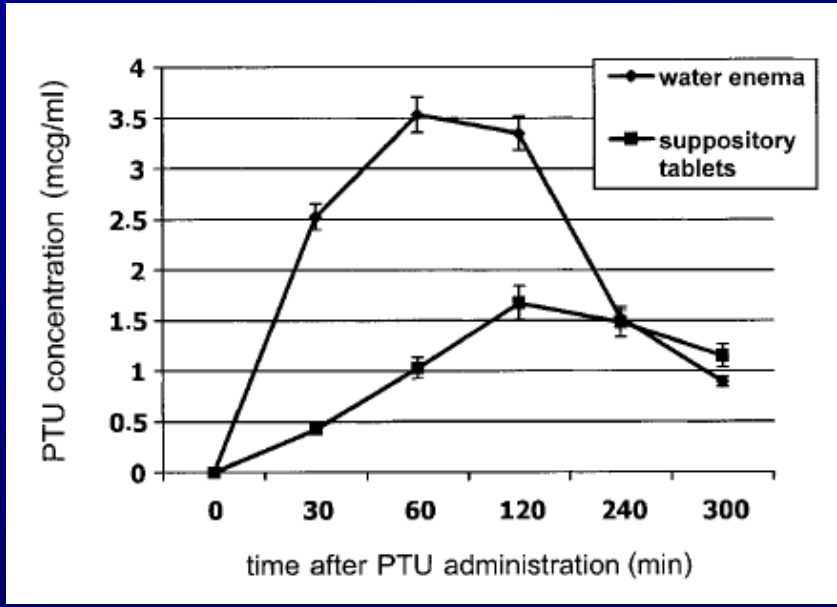
Authors	No. of subjects	Study designs	Drugs & preparations	Pharmacokinetics parameters: Peak levels (μg/mL)	Pharmacokinetics parameters: Time to peak (hour)	Thyroid hormone changes
Nabil et al. (1) 1982	6	E	MMI 60-mg suppository	1.12 ± 0.21	0.5	NA
			MMI 60-mg oral tablet	1.09 ± 0.14	1	NA
Bartle et al. (2) 1988	7	E	400-mg suppository with diethanolamine	1.2 ± 0.31	4.72 ± 0.96	↑ rT_3 20%, $p < 0.05$[a]
			400-mg suppository with Witepsol H 15	2.30 ± 0.35	2.00 ± 0.35	↑ rT_3 16%, $p < 0.05$[a]
			Oral tablet	7.12 ± 0.48	1.99 ± 0.26	↑ rT_3 25%, $p < 0.05$[a]
Walter et al. (3) 1990	1	CS	400-mg PTU in Fleet phospho soda	3	3	↓ T_4 68.8% ↓ FT_4I 68.7% at day 3 posttreatment
Yeung et al. (4) 1995	1	CS	250-mg PTU in water enema	12.9 μmol/mL	1.5	↓ FT_4 55.6% at day 2 posttreatment
Cansler et al. (5) 1997	1	CS	400-mg PTU in Fleet's enema	1.9	1	↓ T_4 22.3% at day 8 posttreatment

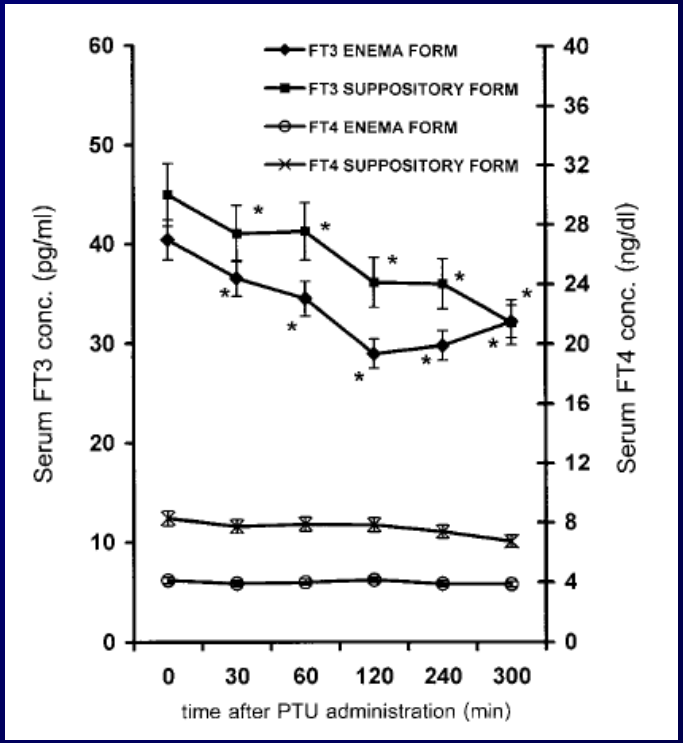
[a]Compared with basal value.

E, experimental study; CS, case report; MMI, methimazole; PTU, propylthiouracil; NA, not available; FT_4, free thyroxine; T_4, thyroxine; rT_3, reverse triiodothyronine.

Jongjaroenprasert W, Akarawut W, Chantasart D, et al. Thyroid 2002;12(7):627–31

PTU Per Rectal (2)

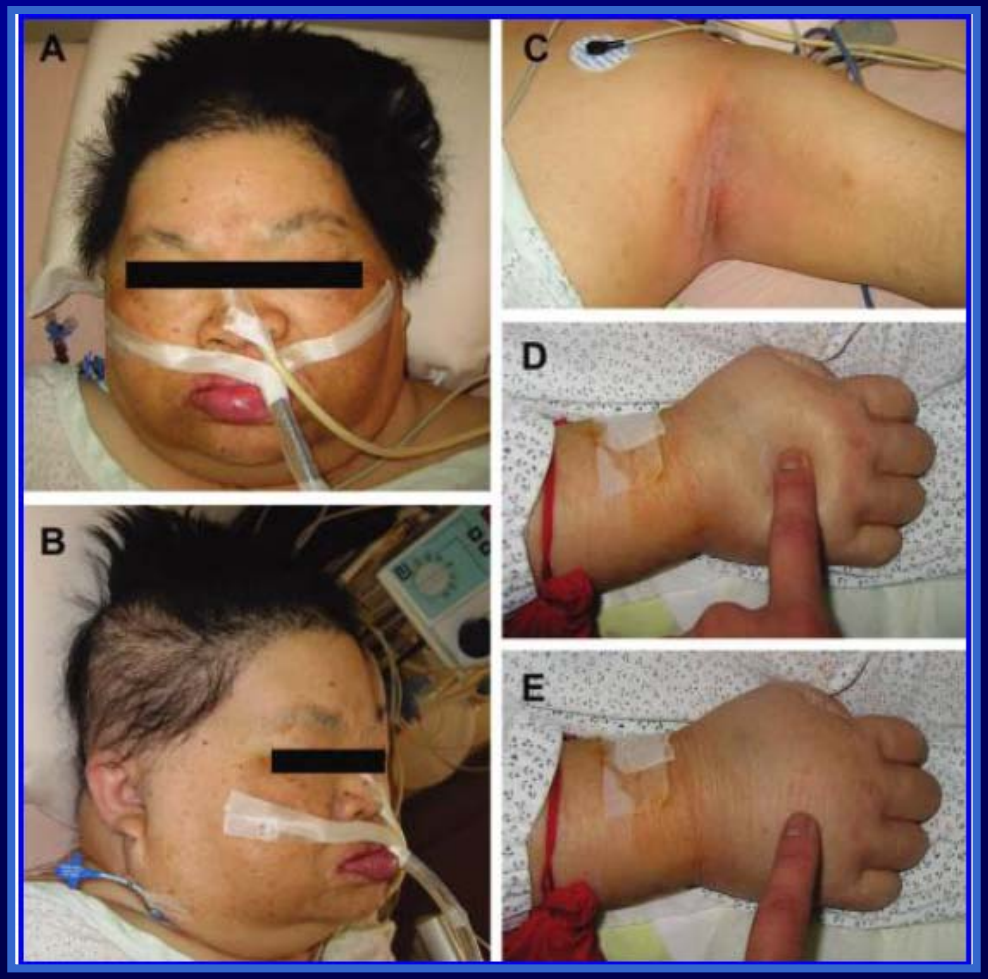




- 600 mg were dissolved in 90 mL of sterile water and administered by foley catheter inserted into the rectum, with the balloon inflated to prevent leakage

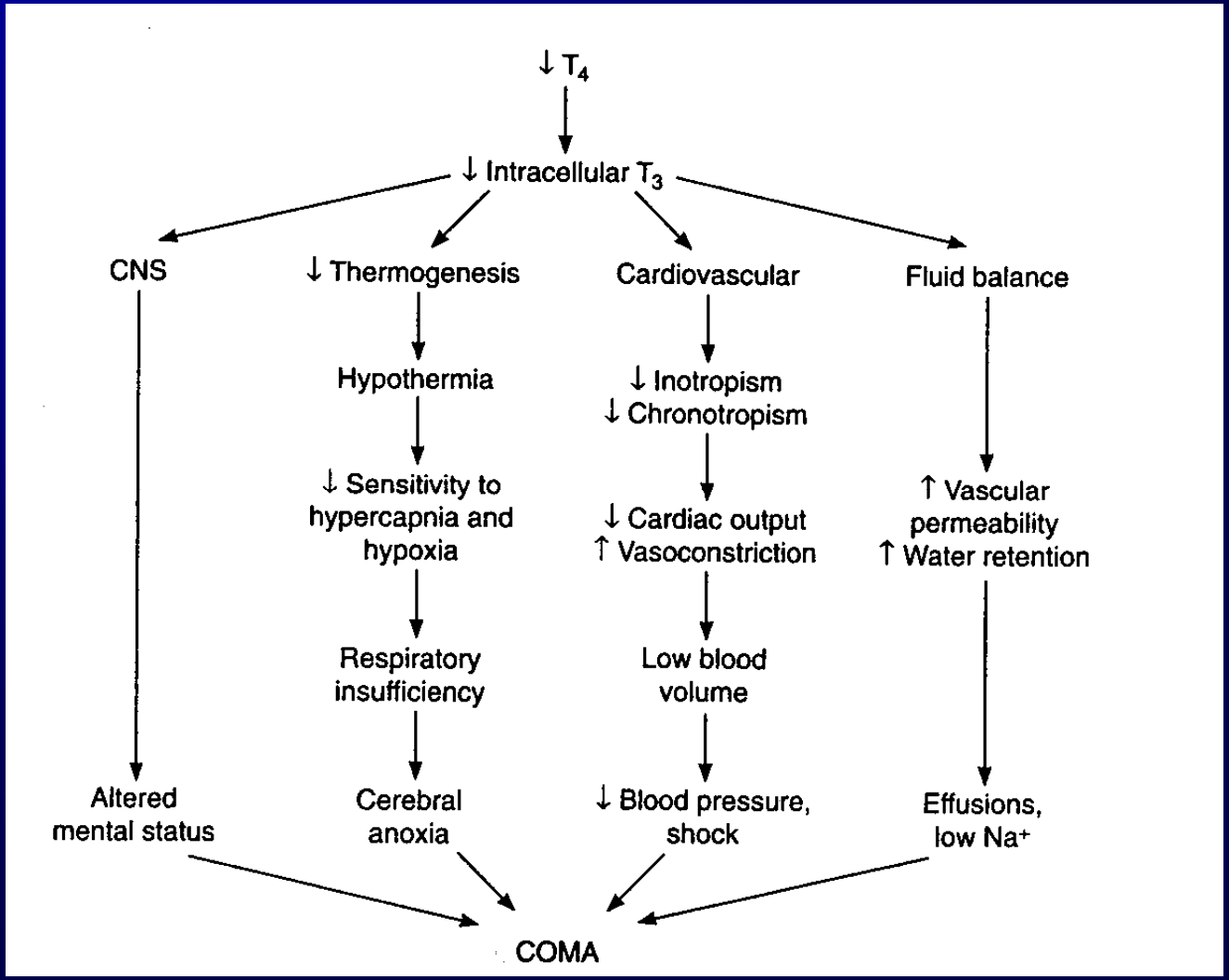
Jongjaroenprasert W, Akarawut W, Chantasart D, et al. Thyroid 2002;12(7):627–31

Myxedema coma

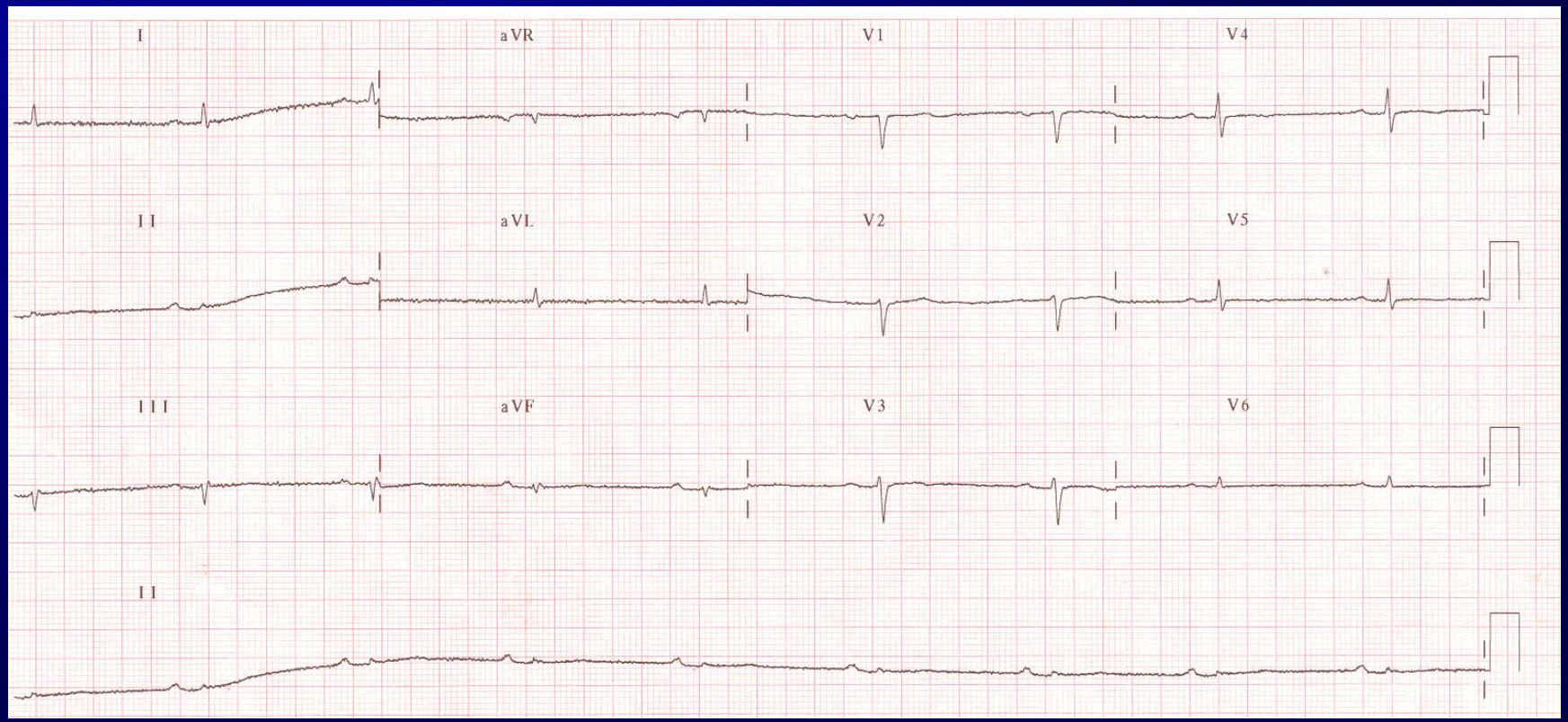


Sheu CC et al. Thyroid. 2007 Apr;17(4):371-2

Pathophysiology



Typical ECG in Myxedema coma



Clinical setting

- In the past, the overall mortality rate for myxedema coma was 60% to 70%
- Early diagnosis and advances in intensive care and management have reduced the mortality to 20% to 25%
- Elderly lady, Psychiatric patient
- Hypothermia in winter time
- History of thyroidectomy/radioactive iodine

Wartofsky L. Endocrinol Metab Clin N Am 35 (2006) 687–698

Precipitating factors Myxedema Coma

- Burns
- CO2 retention
- GI bleed
- Hypoglycaemia
- Hypothermia
- Infection
  - Pneumonia
  - Influenza
  - UTI
  - Sepsis
- Stroke
- Surgery
- Trauma
- Medications
  - Amiodarone (Cordarone)
  - Anesthesia
  - Barbiturates
  - Beta blockers
  - Diuretics
  - Lithium
  - Narcotics
  - Phenothiazines
  - Phenytoin (Dilantin)
  - Rifampin (Rifadin, Rimactane)
  - Tranquilizers

Wall CR. Am Fam Physician 2000;62:2485-90

Management of myxodema coma

- Treatment of precipitating causes
- Correct fluid and electrolytes, correct hypoglycaemia with D10
- NS 200 - 300 cc/hr ± vasopressors
- Maintain body temperature
- T4 200-500 μg po stat, then 100-200 μg po or
- T3 20-40 μg stat, then 20 μg q8h po
- Consider 5–20 μg iv T3 twice daily if oral route not
- possible
- Hydrocortisone 100 mg q6h iv

HA Handbook of Internal Medicine, 5th edition, 2008

T3 or T4 in myxoedema coma

T4

- More available
- Smoother & slower onset of action
  - > 8-14 hr
- lower risk of adverse effects
- Reduced rate of extrathyroidal T4 to T3 in sick hypothyroid patient

T3

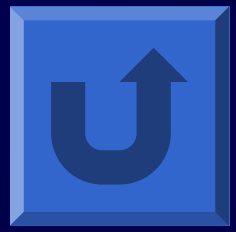
- Less Available
- Quicker onset
  - 2-3 hr (rise in Temp)
- Serum levels fluctuate more between doses
- Higher risk of CV adverse effect

Controversial

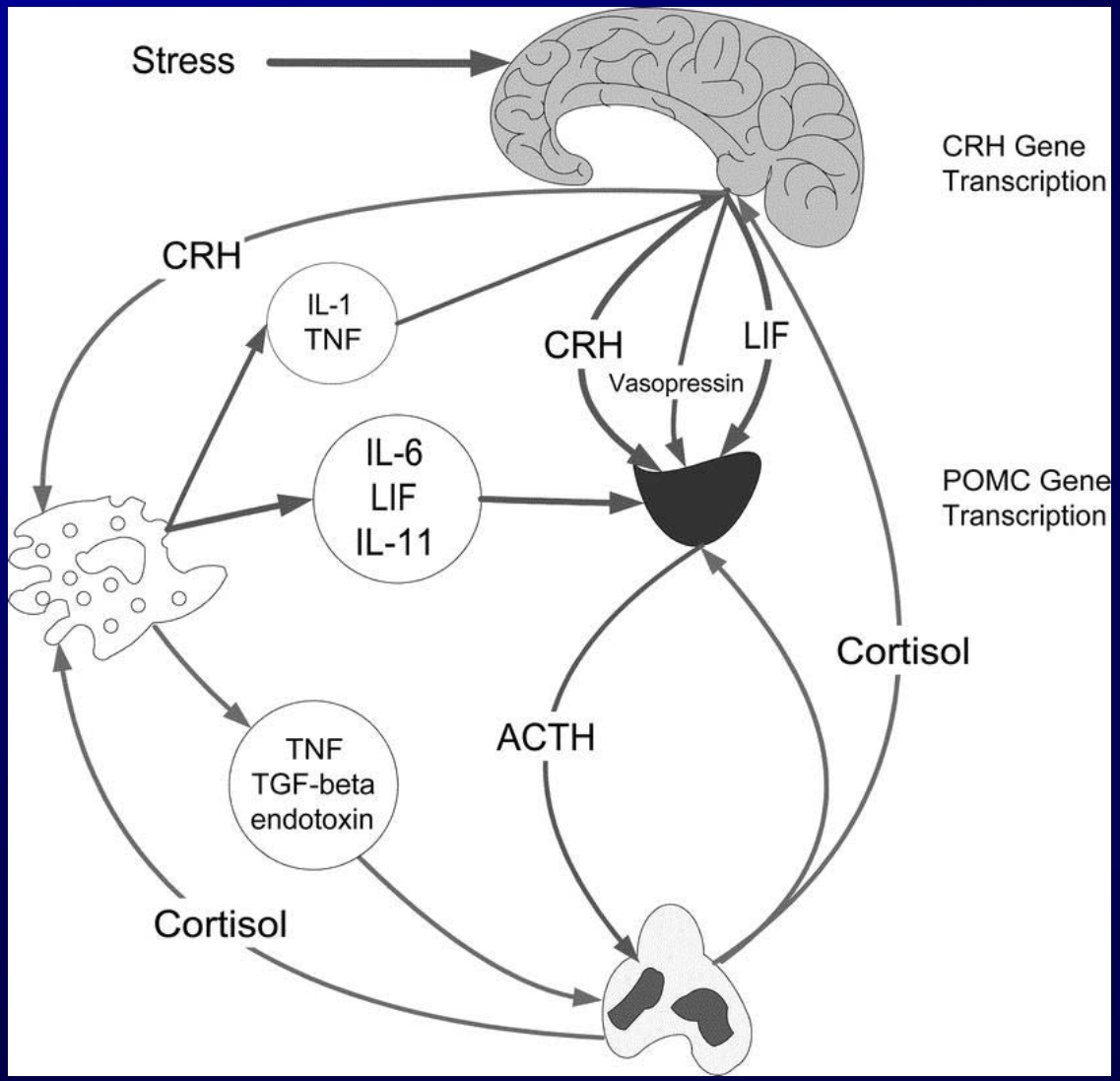
Wartofsky L. Endocrinol Metab Clin N Am 35 (2006) 687–698

Dilemma

- High mortality of untreated myxedema coma vs. risks of high-dose thyroid hormone therapy
  - May ppt atrial tachyarrhythmias or myocardial infarction
- Consider patient at a whole
  - Age
  - intrinsic cardiovascular function
  - neuropsychiatric status
  - comorbid conditions that may affect drug dosages
  - monitored closely before each dose of thyroid hormone is administered



Activation of the HPA axis by stress & interaction with inflammatory response



Marik P. Chest 2009;135;181-193

Classical Addisonian crisis

- Not common
- Usually occurs in primary adrenal insufficiency (Addison's disease)
- Rare in secondary adrenal insufficiency
  - mineralocorticoid activity maintained
- Hypoglycaemia commoner in hypopituitarism, esp. with coexisting secondary hypothyroidism

Common Etiology of Adrenal Insufficiency in ICU

Secondary adrenal insufficiency

- Following discontinuation of exogenous glucocorticoids
- Following the cure of Cushing's syndrome
- Pituitary and hypothalamic lesions
  - Pituitary apoplexy (haemorrhage or infarction)

Primary adrenal insufficiency

- Autoimmune
- Tuberculosis
- Hemorrhage (meningococcemia, anticoagulants, trauma)
- Fungal infections
- Metastatic neoplasia/infiltration
- Aquired immunodeficiency syndrome

Features supporting clinical suspicion of adrenal insufficiency

Clinical

Critical illness

- Hemorrhage (DIC, thrombocytopenia)
- Surgery (adrenalectomy, suprarenal vascular surgery)
- Disseminated infection

Drug-related factors

- Previous use of glucocorticoids
- Decreased cortisol synthesis (etomidate, ketoconazole)
- Increased cortisol metabolism (phenytoin, phenobarbital, rifampicin

General

- Fever, purpura fulminans

Hemodynamic

- Unexplained circulatory instability, hypovolemic
- shock, hyperdynamic shock

Mesotten D et al., Nat Clin Pract Endocrinol Metab. 2008 Sep;4(9):496-505

Features supporting clinical suspicion of adrenal insufficiency

Mental

- Weakness, fatigue, lethargy, agitation, apathy,
- depression, delirium, coma

Gastrointestinal

- Anorexia, nausea, vomiting, diarrhea, abdominal pain

Laboratory

- Hypoglycemia, hyponatremia, hyperkalemia,
- hypercalcemia, neutropenia, eosinophilia,
- hyperprolactinemia, hypothyroidism

Mesotten D et al., Nat Clin Pract Endocrinol Metab. 2008 Sep;4(9):496-505

Short Synacthen test (SST)

Can perform at any time of the day

250 mcg SST

- Classical test for Dx of primary adrenal failure
- May miss some partial secondary (pituitary) adrenal insufficiency
- Easy to perform
- Blood x cortisol at 0, 30, 60 mins

1 mcg SST

- More physiological stimulation → more sensitive
- R/O primary & most secondary adrenal insufficiency
- Not reliable in acute pituitary insufficiency
- Blood x cortisol at 0, 30 mins

N: Rise > 200 nmol/L or Peak cortisol level > 550 nmol/L at 30 min.

Relative Adrenal Insufficiency

- Inadequate cortisol production relative to the severity of illness
- Diagnosis difficult
  - No consensus on the cut-off point of cortisol level
  - Baseline cortisol unreliable
  - Quantitative response to ACTH stimulation variable
  - Unknown normal response
  - Dose of ACTH controversial
  - Routine cortisol assays measure total levels of the hormone, despite only the free hormone being biologically active. This issue is important given the depletion of cortisol-binding globulins during critical illness

Daily Cortisol (hydrocortisone) production

- Non-stressed daily production in adults
  - 15 to 25 mg/day
- Maximal stressed daily production
  - 200 to 350 mg/day
- Low dose
  - of 25 to 200 mg/day
- Physiologic stress-dose
  - 200 to 350 mg/day
- Supra-physiologic dose
  - 351 to 1,000 mg/day
- High dose
  - 1,000 mg/day

Thomas JP, el-Shaboury AH. Lancet 1971; 1:623–625
Marik P. Chest 2009;135;181-193

Table 3—*Regimen for Corticosteroid Treatment in Critically Ill Patients*

Indications*
Vasopressor dependent septic shock (dosage of norepinephrine or equivalent > 0.05 to 0.1 μg/kg/min) within 12 h of onset
or
Progressive ARDS after 48 h of supportive care
Dosing schedule
Hydrocortisone 50 mg IV every 6 h or 100-mg bolus then 10 mg/h continuous infusion for at least 7 d with option of treatment for 10 to 14 d. Patients should be vasopressor and ventilator "free" before taper
Hydrocortisone taper
Hydrocortisone 50 mg IV every 8 h for 3 to 4 d
Hydrocortisone 50 mg IV/po every 12 h for 3 to 4 d
Hydrocortisone 50 mg IV/po daily for 3 to 4 d
Reinstitution of full-dose hydrocortisone with recurrence of shock or worsening oxygenation
Fludrocortisone 50 μg po (optional)
Hydrocortisone and methylprednisone are considered interchangeable
Limiting complication of corticosteroid treatment
Infection surveillance: low threshold for performing blood cultures, mini-BAL. and other appropriate cultures
Hyperglycemia: monitor blood glucose, limit glycemic load, and treat with insulin as appropriate
Myopathy: monitor CPK and muscle strength, and avoid neuromuscular blocking agents

*A random cortisol or ACTH stimulation test is not required.

Marik P. Chest 2009;135;181-193

Adrenal insufficiency in ICU

- **ACTH stimulation unnecessary**
  - Adrenal under max. stimulation
  - Response to SST might not reflect the response to chronic stress
- **Consider glucocorticoid in refractory hypotension despite fluid resuscitation & vasopressors**
- When stabilized & out of stress (consult endocrinologist for proper Ix)

Diagnostic Criteria for SIADH

- Serum sodium <135 mmol/L
- Serum osmolality <280 mmol/kg
- Urine sodium >18 mmol/L
- Urine osmolality > serum osmolality
- Normal thyroid, adrenal, renal function
- Absence of peripheral edema or dehydration

Tisdall et al.,J Neurosurg Anesthesiol 2006;18:57–63

Specific Treatment of SIADH

- Fluid restriction to 1 L/day
- Results in a slow rise in sodium of 1.5 mmol/L/day
- Many patients have self-limiting disease
- Role of pharmacological treatment uncertain

Tisdall et al.,J Neurosurg Anesthesiol 2006;18:57–63

SIADH pharmacological treatment

- **Furosemide with saline or salt supplementation**
  - counteract the sodium loss that accompanies the free water loss
- **Lithium**
  - acts as a blocker of 3,5-adenosine monophosphatase & inhibits the action of ADH on the renal tubule (? Safety)
- **Demeclocycline**
  - Oral ADH antagonist
  - not available in HK

Tisdall et al.,J Neurosurg Anesthesiol 2006;18:57–63

Vasopressin receptor antagonists
Lixivaptan

- High V2 receptor affinity
- Block the physiologic actions of vasopressin
- Undergoing Phase III clinical trials
- Efficacious in the correction of hyponatraemia in SIADH, heart failure and liver cirrhosis with ascites
- Few adverse effects

Ku E et al., Expert Opin Investig Drugs. 2009 May;18(5):657-62.

Postop/post-traumatic central DI

Triphasic pattern

- Phase I : Transient DI, duration hrs to days
- Phase II : Antidiuresis, duration 2-14 days
- Phase III : Return of DI (may be permanent

HA Handbook of Internal Medicine, 5th edition, 2008

Specific treatment of Central DI

- 1-deamino-8-D-arginine vasopressin (DDAVP)
  - Give small dose 0.4 -1 mcg IV Q8H-Q12H
  - minimize the risk of an overprolonged action
  - can be repeated as required, dependent on clinical effect
- In the unconscious patient
  - fluid replacement with IV 5% dextrose or water via a nasogastric tube with concomitant DDAVP administration
- Accurate clinical assessment of volume status is required to guide treatment (BW, strict I/O)

Tisdall et al.,J Neurosurg Anesthesiol 2006;18:57–63

Problems in Central (Cranial) DI

- Excessive fluid administration given to replace high urinary output may exacerbate the problem
  - Saline solutions may aggravate the renal water loss because urine concentration cannot be achieved in the absence of ADH
- Overrapid correction of hypernatremia
  - Pulmonary and cerebral edema
  - Aim reduction in serum Na of 10 mmol/L/day
  - More rapid reduction only indicated in those who have developed hypernatremia over of a period of hours

Tisdall et al.,J Neurosurg Anesthesiol 2006;18:57–63

Cerebral Salt Wasting Syndrome (CSWS)

- Working definition: Renal loss of Na due to intracranial disease, leading to **hyponatraemia & hypovolaemia**
- First described by Peters in 1950
- Predominantly associated with SAH, also in traumatic brain injury, glioma, and tuberculous or carcinomatous meningitis

Tisdall et al.,J Neurosurg Anesthesiol 2006;18:57–63

Pathophysiology of CSWS

- Not fully understood
- Disruption of hypothalamic–renal pathways
- ↑ circulating ANP and BNP
  - At least in part, increased natriuresis and hyponatremia in acute brain injury, especially after SAH

Tisdall et al.,J Neurosurg Anesthesiol 2006;18:57–63

Specific Treatment of CSWS

- Fluid and sodium resuscitation
- Normal saline
- Hypertonic saline via CVP + frusemide
- In refractory cases
  - Prophylactic oral fludrocortisone 0.1-0.4 mg daily
  - Increasing sodium reabsorption from the renal tubule
  - Watch out for hypoK

Tisdall et al.,J Neurosurg Anesthesiol 2006;18:57–63

Summary of Na disorders

Finding	SIADH	CSWS	DI
Plasma volume	Raised	Lowered	Lowered
Sodium balance	Positive/equal	Negative	Equal
Water balance	Positive	Negative	Negative
Serum sodium	Low	Low	High
Serum osmolality	Lowered	High/normal	High
Urine sodium	High	High	Normal
Urine osmolality	High	Normal/high	Low

Normal values: plasma osmolality 278–305 mmol/kg, plasma sodium 135–145 mmol/L, urine osmolality 350–1000 mmol/kg, urine sodium 20–60 mmol/L, 100–250 mmol/24 h.

Tisdall et al.,J Neurosurg Anesthesiol 2006;18:57–63

Take home message

- All endocrine emergencies are potentially reversible
- All require supportive & close monitoring
- Clinical suspicion > lab tests
- Treat the patient, no the numbers
- Consult endocrinologist if in doubt
- NEVER reject admission in endocrine emergencies

Thank you