Tox for internist: Drug induced hyperthermia & Tox related weakness

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Part 1:
Substance induced Hyperthermia

1. Serotonin syndrome

- P: ↑ serotoninergic effect
  (↑release & synthesis, ↓break down & reuptake, direct agonist)
- Onset: hours
- Duration: hrs – usually 24 hrs(after remove cause)

1. Serotonin syndrome

- Inhibit break down
  - MAO-I: phenelzine, moclobemide, linezolid, methylene blue, St. John's wort
- Block 5-HT reuptake
  - SSRI, SNRI, TCA, MDMA, meperidine, fentanyl, tramol, dextromethorphan
- 5-HT agonist or precursor
  - LSD, L-tryptophan, high tyramine (aged cheese, red wine, liver)
- ↑5-HT release
  - Lithium, MDMA, mirtazapine

1. Serotonin syndrome

1. Dysautonomia:
   hyperthermia, BP/HR change, mydriasis,
   shivering, sweating, diarrhea
2. NM effects:
   hypereflexia, clonus, rigidity
3. CNS:
   agitated, restless, elevated mood, seizure, coma

There are criteria for diagnosis
(Hunter's criteria, Sternbach's criteria, Radomski´s criteria)

https://www.youtube.com/watch?v=oAOO5y68O-U

https://www.youtube.com/watch?v=1X-br14gCVo

1. Serotonin syndrome

- Management
  - ABCD
  - Benzodiazepine
  - 5-HT antagonist: cyproheptadine, clozapine, chlorpromazine, quetiapine
  - Supportive care
  - Non-depolarizing NM blockade, or dantrolene

2. Neuroleptic malignant syndrome

- P: Dopamine-2 receptor blockade effect at striatum (antipsychotic or sudden stop dopaminergic drug)
- Onset: days to weeks
- Duration: days to 2 weeks (after remove cause)

2. Neuroleptic malignant syndrome

1. Dysautonomia:
   hyperthermia, BP/HR change
2. NM effects:
   lead pipe rigidity (some report cog-wheel)
3. CNS:
   drowsy, depressed mood, seizure, coma

2. Neuroleptic malignant syndrome

- Management
  - ABCD
  - Benzodiazepine
  - Central dopaminergic agonist: bromocriptine (or restart dopaminergic drug)
  - Supportive care
  - Non-depolarizing NM blockade, or dantrolene

3. Malignant hyperthermia

- Autosomal dominant mutation
- Ryadonine receptor (RYR-1, chromosome 19) and L-type Ca channel (CACNA1S); locate on SR and sarcolemma
- P: general anesthetics, succinyl choline, -flurane, ethane, halothane, ether
- Onset: minutes to hrs (< 24 hr)

3. Malignant hyperthermia

- Muscle spasm
- Hyperthemia
- Dilated pupil
- Cerebral edema, coma
- Impaired cardiac function
- Areflexia
- Hyperkalemia
- Increased pCO2
- Metabolic acidosis

3. Malignant hyperthermia

- Management
  - ABCD
  - Dantrolene
  - Cooling
  - Supportive care

4. Heatstroke/ heat injury

- Heatstroke: hyperthermia c end-organ damage
- Precipitation
  1. ↑ Heat in environment
  2. ↑ Heat production: alcohol/sedative withdraw, amphetamine, hyperthyroid, muscle spasm
  3. ↓ Heat loss: anticholinergic (↓ sweating)
  4. Dehydration: diuretics
  5. Incapacitation: sedative, stroke patients
  6. ↓ CV reserve: CCB, beta blocker

4. Heatstroke/ heat injury

- Management
  - ABCD
  - Cooling (T to around 39˚c; 0.2˚c/min then slower)
    Evaporation (foggy method: artificial sweat)
    Cool saline infusion
    NG lavage
    Bladder irrigation
    Ice-water immersion
    Cool blankets & wet towels
  - Rehydration

คลื่นความร้อนรุนแรง อินเดียอุณหภูมิทะลุ 50 องศา ลมแดดคร่าชีวิตหลายศพ

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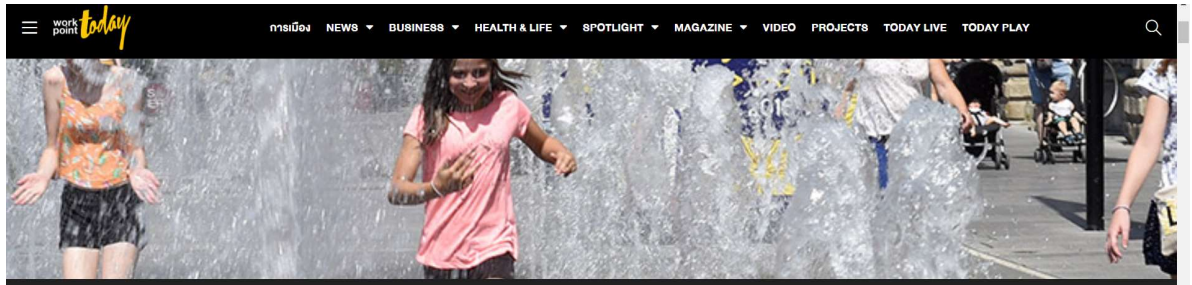

"ฝรั่งเศส" วิกฤตเตือนภัยระดับสีส้ม ปิดโรงเรียน 50 แห่ง หนีคลื่นความร้อน

ต่างประเทศ workpointTODAY | Writer 27 มิ.ย. 2562

คลื่นความร้อนคร่าชีวิตญี่ปุ่น 15 ศพ ป่วยนับหมื่น

2 ปีที่แล้ว

ที่ไหน? เผชิญคลื่นความร้อน (คร่า) ชีวิต 1.35 แสนคน

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แบ่งปัน

รู้จักคลื่นความร้อน ภัยจากสิ่งแวดล้อม ชี้ประเทศแถบยุโรป สหรัฐอเมริกา รวมทั้งอินเดีย มีผู้เสียชีวิตจำนวนมาก 135,010 คน โดยพบอุณหภูมิความร้อนต่อเนื่องกันกว่า 40 องศาเซลเซียสติดต่อกัน 3-5 วัน

5. Malignant Catatonia

- “Lethal catatonia”
- Most severe the spectrum of catatonic syndromes
- P: ↓GABA-A effect at cortex
  Change in dopaminergic system (not just D2)
  Commonly schizophrenic case who withdraw of antipsychotic
  Rarely drug induced
- Catatonia
  - Immobility, rigidity, posturing, ↑ motor activity
  - Mutism, stupor, negativism, staring, echolalia

Newcastle University

https://youtu.be/CRQMDsw02Dw?si=eoSCuoKNmfaaN3_0

5. Malignant Catatonia

1. Dysautonomia:
   hyperthermia, BP/HR change
2. NM effects:
   rigidity, waxy flexibility
3. CNS:
   negativism, stupor, coma

5. Malignant Catatonia

- Management
  - ABCD
  - Benzodiazepine
  - Electroconvulsive treatment (ECT)
  - Others: Neuroleptics (atypical), Reserpine, TCAs, Lithium, Carbamazepine, Barbiturates
  - Supportive care
  - Non-depolarizing NM blockade

6. Sympathomimetic toxidrome

- Sympathomimetics
  - Methamphetamine, MDMA, Cocaine, Theophylline, Thyroids
  - Sedative withdrawal, alcohol withdrawal
- CNS: agitated, confused, seizure
- NM effects: tremor, choreoathetosis
- ANS: sweating, mydriasis, ↑BP, ↑HR, ↑T

6. Sympathomimetic toxidrome

- Management
  - Control agitation: benzodiazepines, phenobarbital, propofol
  - Control hypertension:
    Vasodilators: nicardipine, nitroprusside, phentolamine, hydralazine
  - Control tachycardia:
    Antiarrhythmics: diltiazem, verapamil
  - Monitor EKG (Wide QRS in cocaine)
  - Control temperature: evaporation, tepid sponge
  - Treat complications

7. Anticholinergic toxidrome

- Antimuscarinics
  - Pure: atropine, scopolamine, hyoscyamine, jimson weed, angel trumpet, BZ gas
  - Plus sedation: antihistamine, TCAs, antipsychotics
- CNS: delirium
- NM effects: none, or picking things in the air
- ANS: dry skin, dry mucosa, flushing, ↓BS, urinary retention mydriasis, ↑BP, ↑HR, ↑T

https://youtu.be/u12SZAyMp54?si=l4QrXx2A9trruId7

7. Anticholinergic toxidrome

- Management
  - Supportive care
  - If full bladder → on Foley catheter
  - Physostigmine (ChE inhibitor)
  - Benzodiazepine
  - Check EKG (Wide QRS in TCAs)

	SS	NMS	MH	Heat stroke	Malignant catatonia	Anticholinergic	Sympathomimetic
Substance	SSRI, MAO-I, TCAs, MDMA	Antipsychotic, Dopa WD	general anesthetics, succinyl choline,	hot envi, impaire heat loss incapacity, exertion	Antipsychotic WD	Atropine, Angel trumpet, Antihis, TCAs	Methamphet, Cocaine, Alcohol WD
Onset	few hours	days to weeks	mins	variable	variable	mins to hours	mins to hours
Dysautonomia	yes	yes	yes	yes	yes	Yes	yes
CNS	euphoria, confused, agitated	drowsy, confused	coma	variable	negativism, mutism, staring	Delirium	agitated, confused
NM effect	↑reflexes, clonus, rigidity	rigidity, tremor	muscle spasm, rigidity	none	rigidity, posturing, waxy flexibility	none, picking things in the air	tremor, choreoathetosis
Specific Mx	Cyproheptadine	Bromocriptine	Dantrolene	Cooling	Bz, ECT	Physostigmine, Bz	Lots of Bz

8. Propofol infusion syndrome (PRIS)

- Uncoupler of oxidative phosphorylation
  - hyperthermia
  - ↓ATP production: cellular dysfunction, lactic acidosis
- Inhibits the conversion of free fatty acids to acyl-coA
  - failure of fatty acid oxidation
  - ↓ATP production

- Interaction between dose, duration, and patients' condition
  Risk infusion: >=4mg/kg/h OR infusion duration >=48h
  Other risks: steroid, catecholamine, critically ill

Mirrakhimov AE, et al. Crit Care Res Pract. 2015;2015:260385.

Kam PCA, Cardone D. Anaesthesia. 2007; 62: 690–701.

Krajčová et al. Critical Care. 2015;19:398.

8. Propofol infusion syndrome (PRIS)

Clinical effects

- Rhabdomyolysis
- Hepatic injury
- Renal injury
- Metabolic acidosis
- Cardiac arrhythmia
- Pulmonary edema
- Fever
- Hypertriglyceridemia

Management

- Discontinue propofol
- Supportive care

Mirrakhimov AE, et al. Crit Care Res Pract. 2015;2015:260385.

Kam PCA, Cardone D. Anaesthesia. 2007; 62: 690–701.

Krajčová et al. Critical Care. 2015;19:398.

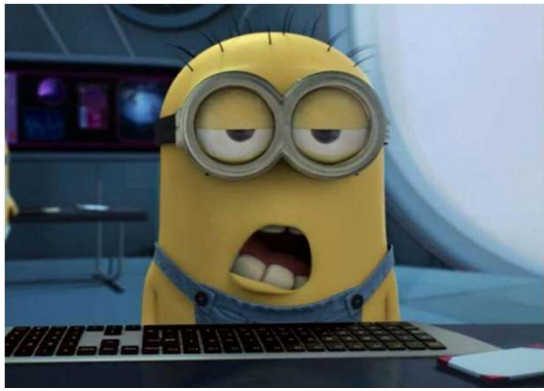
Part 2:
Toxin and weakness

Botulinum Toxin

Botulism

- Life threatening paralytic illness
  Slurred speech, drooping eyes, weakness, total paralysis

- Caused by “BOTULINUM TOXIN”



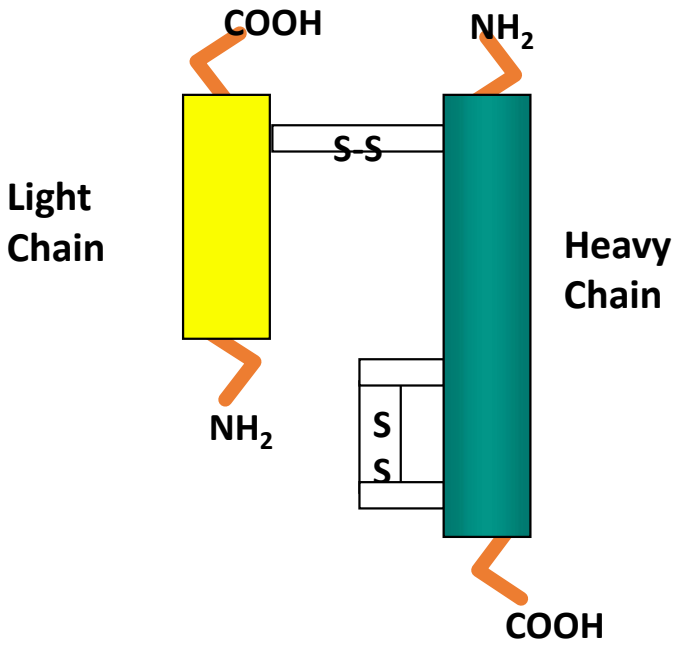
Botulinum toxin

- Enzyme produced by *Clostridium botulinum*.
- Obligate anaerobic, motile, gram-positive rod with oval, subterminal spores
- Spores is HEAT-RESISTANT.

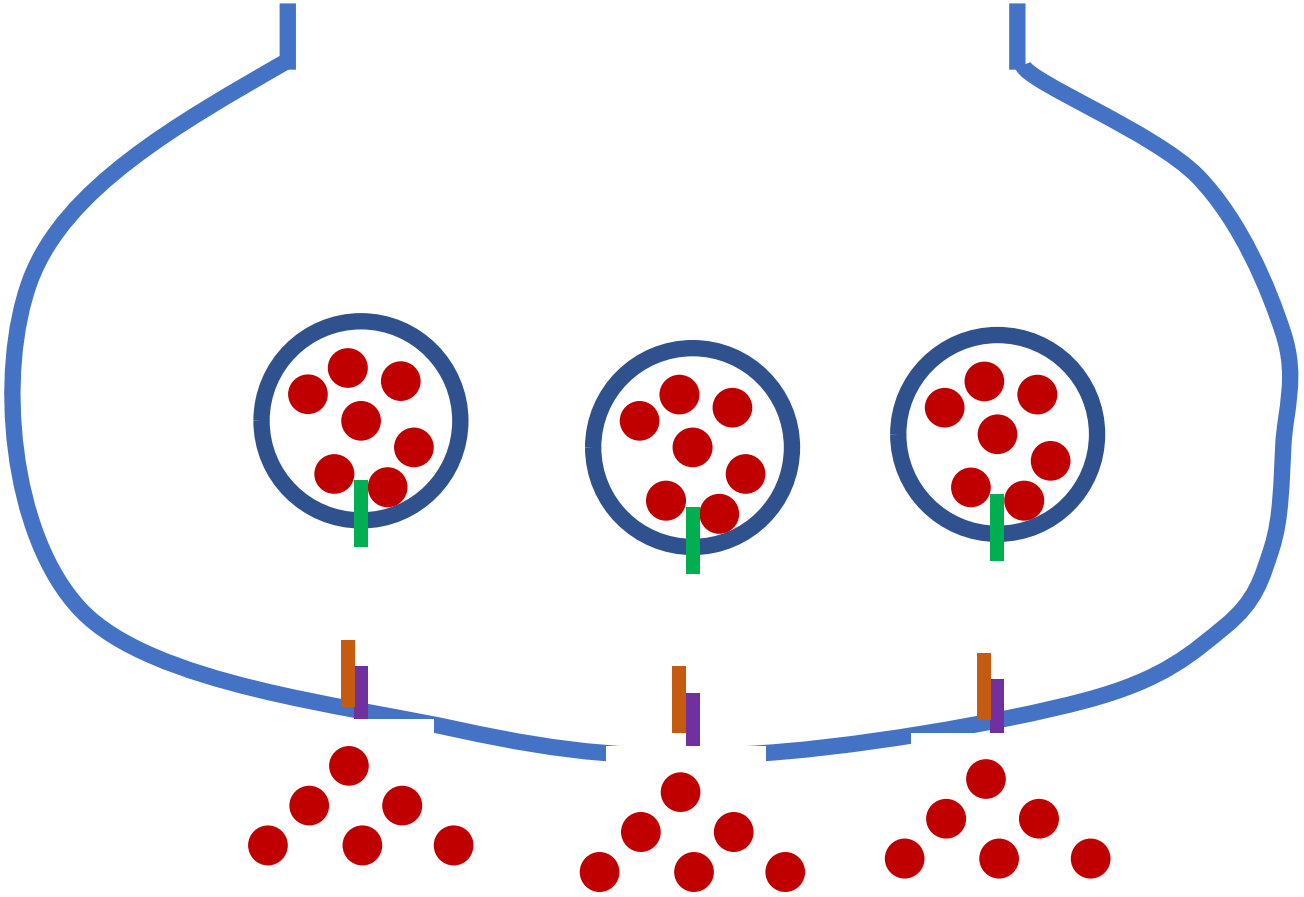
Clostridium botulinum

Botulinum toxin

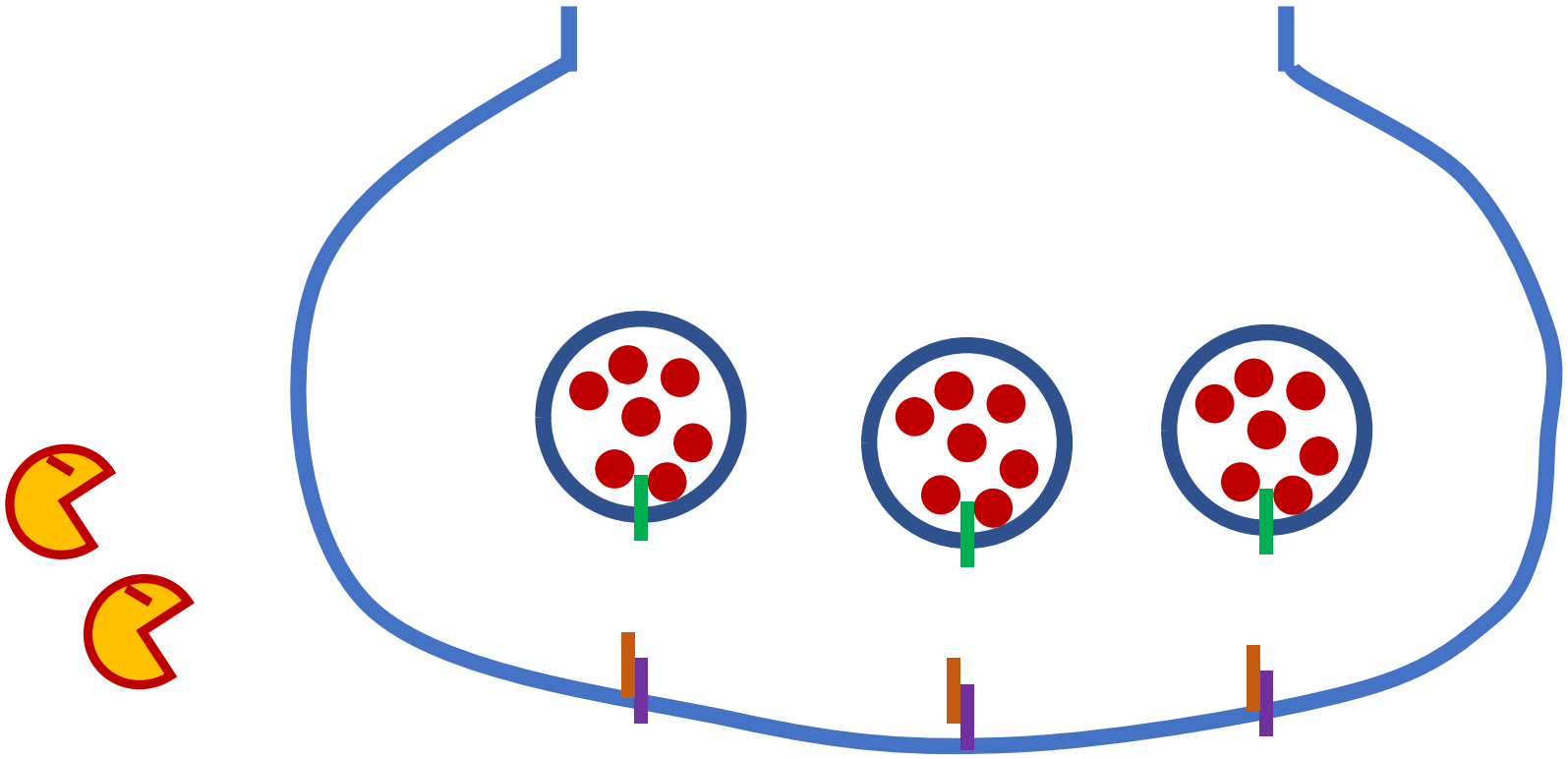
- A polypeptide consists of a toxic light chain (150 Da) and a non-toxic heavy chain (750Da).
- Toxin is heat labile.
- 7 serotypes exist- A, B, C, D, E, F, and G
- Intracellular target SNARE protein
  - **Synaptobrevin (B, D, F, G)**
  - **SNAP-25 (A, C, E)**
  - **Syntaxin (C)**



Pathophysiology of botulism



Pathophysiology of botulism

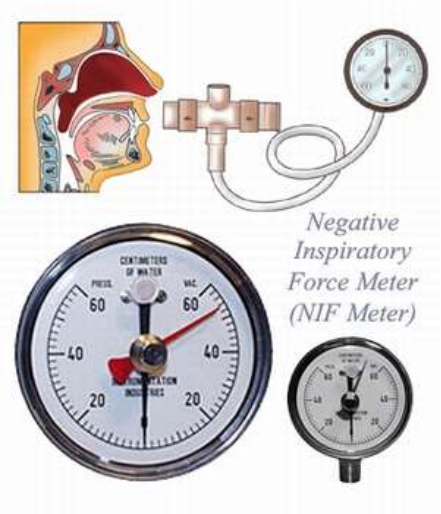


Clinical manifestation

- GI symptoms (food-borne, delayed onset 4-6hr)
  - Abdominal cramps, nausea, vomiting, and diarrhea
- Neurological symptoms (delayed onset 12hr to few days, slow recovery; weakness can persist for months)
- Bulbar palsy: diplopia, dysarthria, dysphonia, and dysphagia
- Ocular symptoms: dilated pupils, ptosis, diplopia
- Flaccid paralysis:
  - Descending generalized weakness and hypotonia,
  - Preserved or loss of deep tendon reflexes
  - Airway obstruction, and respiratory muscle paralysis

Management for botulism

- Observation on respiration
- Intubation & ventilation support



Antidote

Heptavalent Botulinum AntiToxin

HBAT

Equine Antibodies

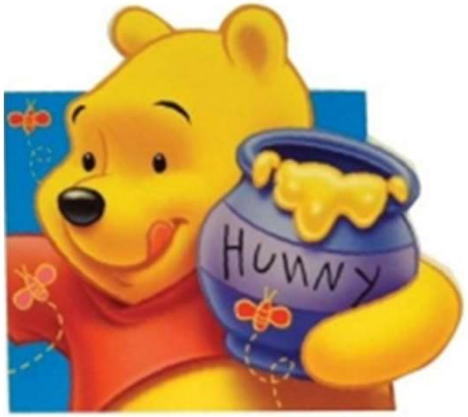
Antidote

Botulism Immune Globulin Intravenous (Human) (BIG-IV)

Baby BIG

Botulism: Etiology (% in US data)

- Food borne botulism (15%)
- Wound botulism (20%)
- Infant botulism (65%)
- Iartrogenic botulism (<1%)



Confirmation test

- http://nih.dmsc.moph.go.th/lab_nih/labnih58.pdf http://dmsc2.dmsc.moph.go.th/webroot/chonburi/fire_download/คู่มือการให้บริการ2560.pdf
- Culture for C. botulinum
- Mouse bioassay

- Immunoassay for toxin
- PCR for C. botulinum

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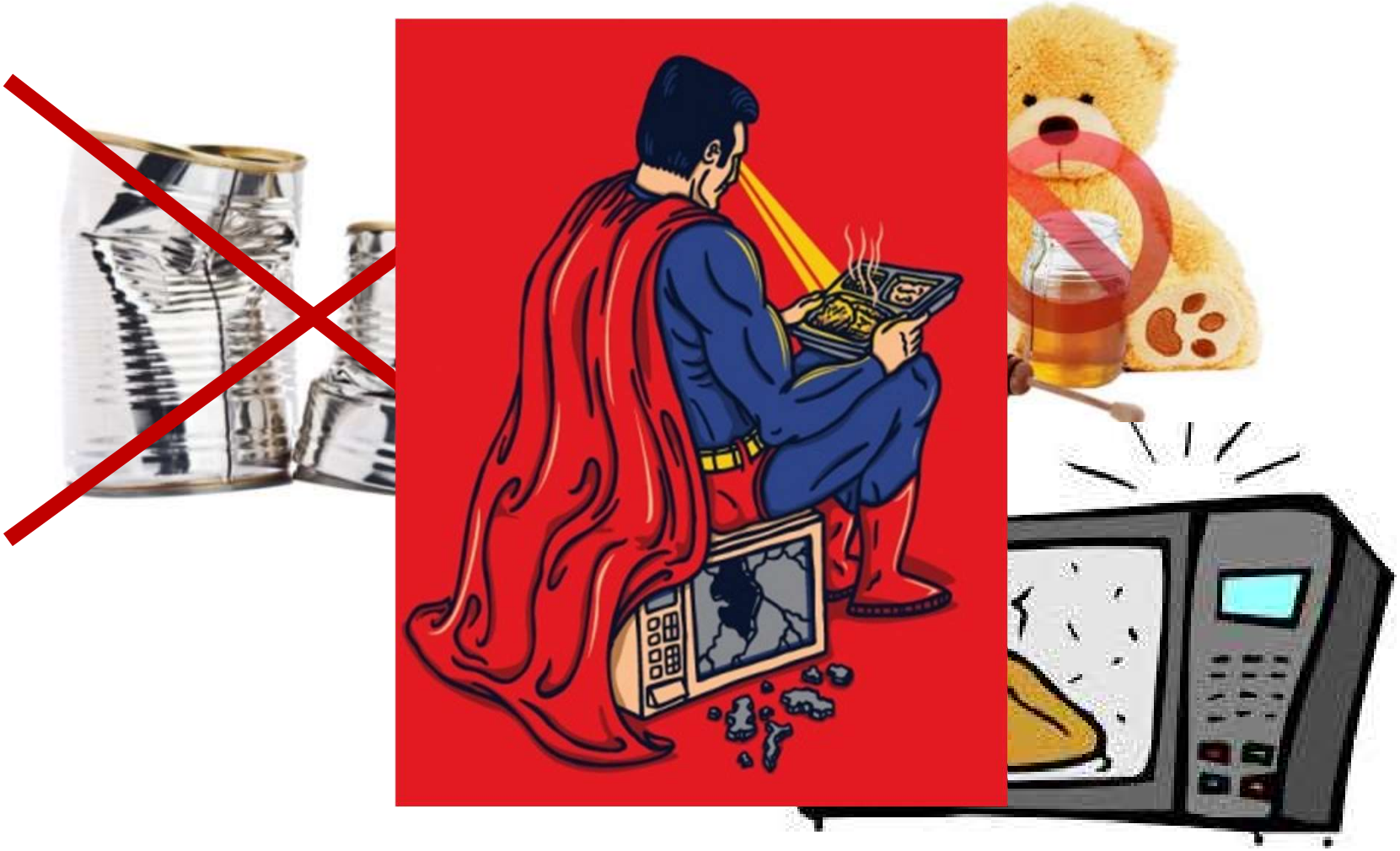
Prevention of food-borne botulism



Prevention of food-borne botulism

- Heating to destroy toxin:
  100°C for at least 10 minutes or
  80°C for at least 30 minutes

- Heating to destroy spore:
  120°C for at least 30 minutes

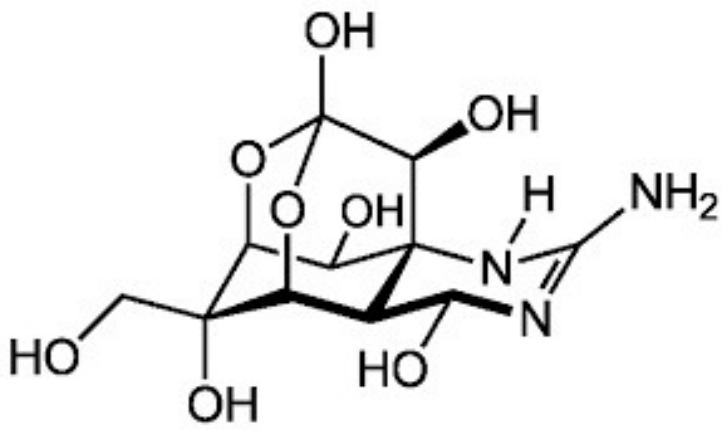
Botulinum Toxin

- Polypeptides; heat labile toxin
- From *C. botulinum*, Gram +ve bacilli with spore
- Spore is heat resistant
- Life threatening paralytic illness
- Onset can be lagged for hours to days
- Early recognition & give botulinum antitoxin
- Reheat your food
- No canned food jam or honey for infant

Tetrodotoxin

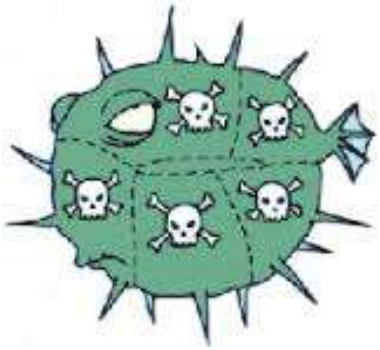
Tetrodotoxin

- Synthesized by bacteria in dinoflagellate
- Toxin is **HEAT-STABLE !!!**
- Peripheral neuron Na channel blockade



- Early onset (within 1 hour) and rapidly progress
- GI symptoms, numbness (peri-oral, tongue, distal limbs), then weakness
- **"Early onset of numbness BEFORE flaccid weakness; both start in distal area"**
- Duration of weakness: few days

Na channel blockade



- Tetrodotoxin:
  puffer fish,
  horseshoe crab,
  blue-ringed octopus bite

- Saxitoxin:
  paralytic shellfish

Horseshoe Crab

1. *Carcinoscorpius rotundicauda*
   Mangrove horseshoe crab
   Round tail
   Tetrodotoxin

2. Tachypleus gigas
   Giant king crab, Coastal horseshoe crab
   Triangular tail
   Safe

Puffer Fish

- Family Tetraodontia

Management of tetrodotoxin poisoning

- Observe on respiration
- Intubation and ventilation support

Confirmation test

- http://www.dmsc.moph.go.th/bkm/product_detail.php?id=19
- Immunochromatography assay for toxin
  Fast & easy to use (30 min)

- http://dmsc2.dmsc.moph.go.th/webroot/phitsanulok/web/food1.html
- LC-MS/MS
  Can report quantitative level

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Tetrodotoxin

- Heat stable toxin
- From bacteria
- Early onset of distal numbness follow by weakness
- Supportive management

Neurotoxic snake

Review snake bite

- Inland snake
  - Neurotoxic snake: cobra, king cobra, Malayan krait, banded krait
  - Hematotoxic snake: green pit viper, Malayan pit viper, Russell's viper
  - Non-toxic snake

- Sea snake: neuro-myotoxic snake

Neurotoxic snake bite

- Postsynaptic: block nicotinic R (nAChR)
- Severe local injury
  - งูจงอาง King cobra *Ophiophagus hanna*
  - งูเห่า Cobra *Naja kaouthai*

- Presynaptic (prolong effect): disrupt release of ACh from n terminal
- No local effect
  - งูทับสมิงคลา Malayan krait *Bungarus candidus*
  - งูสามเหลี่ยม Banded krait *Bungarus fasciatus*

Neurotoxic snake bite

- Antivenom Indication
  - Any motor weakness (even ptosis)
  - Known Malayan krait and Banded krait bite

- Dose of neurotoxic snake antivenom 10 vials
- No need for skin test

Neurotoxic snake bite

- Intubation criteria for neurotoxin:
  - Difficult swallowing -> prevent aspiration
  - Respiratory muscles weakness
  - Ptosis – palpebral fissure < 0.5 cm
  - Peak flow < 200 L/min

Wound care

- Dressing wound
- Elevate bitten area (reduce edema and local reaction)
- For cobra and king cobra – give antibiotics
  For krait give antibiotic if suspected infection
- Debridement as indicated
- Fasciotomy if suspected compartment syndrome

Sea snake

- Myotoxic (Neuro-myotoxic) snake bite

- Subfamily hydrophiinae, latcaudidae
  - Binding to postsynaptic nACh receptors at NMJ.
  - Muscle necrosis (phospholipase A2)

Sea snake

- Sea snake antivenom: **NOT** available in Thailand
- Mainly supportive care
  - Protect airway and assisted ventilation
  - Hydration, correct electrolyte abnormalities, and alkalinize urine
- Sea snake antivenom (Australia)
- Tiger snake antivenom (Australia)