Introduction to Clinical Toxicology

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Overviews

- Introduction of poison
- Evaluation of poisoned patients
  - Toxidromes/Toxicodynamics/Toxicokinetics
  - History/Laboratory/ECG/Imaging
- Initial management of poison patients
  - Supportive treatments
  - Antidotes
- Summary

What is poison?

Classification of poisons

- Antiquity
  - Animal poisons
    - Snake, spider, etc
  - Vegetable (plant) poisons
    - Cassava, Datura, etc
  - Mineral poisons
    - Lead, Arsentic, etc
  - Gases
    - Hydrogen sulfide/cyanide

Greek physician Dioscorides (40-80 A.D.) 迪奥科里斯

Poison

- Paracelcus (1493-1541)帕拉塞爾蘇斯: first begin the scientific approach to toxicology
- Introduce the dose-response concept to toxicology

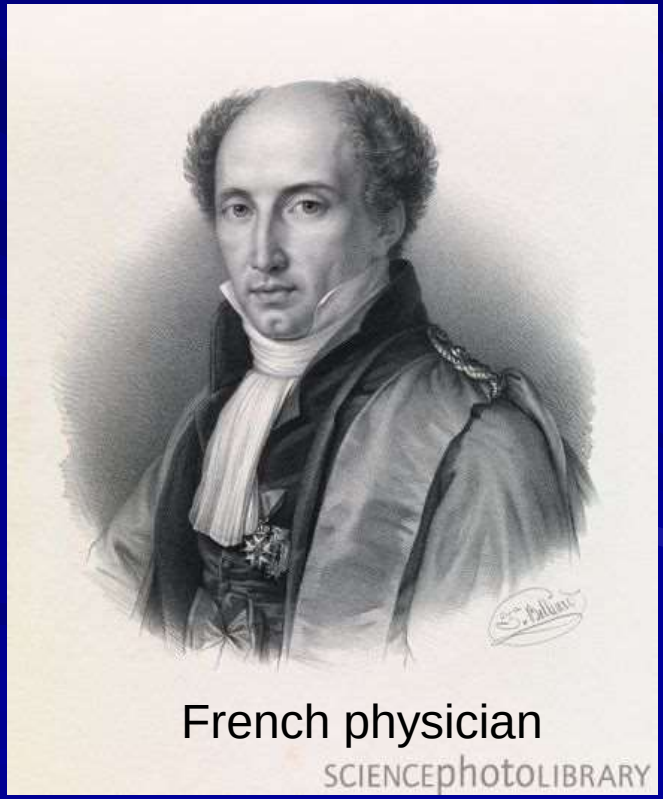
Swiss physician

- ” What is there that is not poison? All things are poison and nothing without poison. Solely, the dose determines that a thing is not a poison. “

---Third defense

Modern toxicology

- Bonaventure Orfila (1787-1853)文德奧爾菲拉: the father of modern toxicology
- Forensic medicine/chemical analysis
- Six groups of poisons
  - Acrids刺激
  - Astringents收斂
  - Corrosives侵蝕
  - Narcoticoacrids成癮
  - Septics腐敗
  - Stupefacients麻醉



Poisoning

- An event where a living organism is exposed to a chemical that adversely affects the functioning of that organism.
- Symptoms develop in close relation to the exposure.
- Absorption of a poison is necessary for systemic poisoning.

Initial evaluation of the patients with a suspected overdose or poisoning

Clinical history of toxic substance exposure

- Why: accidental vs. intentional
- Where: inside vs. outside (available poisons)
- What: inquiry EMS and friends
- When: how long since ingestion
- Initial presentation (pre-hospital): seizures, emesis, changing vital signs

Patients Should be Suspected to Have intoxication

- Unexplained illness in a previously health person
- A history of psychiatric disease (especially depression)
- Recent change in health, economic status, or social relationship
- Onset of illness while working with chemicals, or after ingestion of food, drink, or medications
- Onset of illness after arriving from a foreign country or after arrest for criminal activity

(Harrison's Internal Medicine 1998)

Toxic syndromes (Toxidromes)

- Vital signs + clinically apparent end-organ manifestations
  - CNS (mental status)
  - Eye (pupil size)
  - GI tract (peristasis)
  - Derma (dryness or diaphoresis)
  - Mucous membranes (moistness or dryness)
  - GU system (urine retention or incontinence)

Toxidromes

- Anticholinergic syndromes: (Hot, Dry, Red, Mad)
  - Antihistamine, Atropine, Anti-spasmodic agent
  - Herb drugs (Jimson weeds)
- Cholinergic syndromes: (SLUDGE)
  - Organophosphate, Carbamate,
  - Cholinergic crisis in myasthenia gravis
- Sympathomimmetic syndromes
  - Amphetamine, Cocaine
  - Cold tablets (Phenylpropranolamine. Ephedrine)
- Opioids
  - Morphine
- Serotonin syndrome
  - MAOI, SSRI, TCA

Case 1 scenario

- 20 yo male presents with agitation, slurred speech, and appears to be picking at invisible bugs. Physical exam reveals dilated pupils, dry mucous membranes, a flushed face, and dry armpits. Which toxidrome did this patient most likely have?

Anticholinergic Toxidrome

- Atropine, Antihistamines, TCAs, Chlorpromazine (Wintermin), Antiparkinsonism drugs
- Symptoms
  - **Mad** as a hatter **Blind** as a bat (Mydriasis)
  - **Hot** as a hare **Dry** as a bone
  - **Red** as a beet **Full** as a flask
  - **Tachy** like a pink flamingo
  - **Seizing** like a squirrel
- Same as Sympathetic BUT NO Sweating, slurred speech, ileus, urinary retention

Anticholinergic Treatment

- Tx- Supportive
- Physostigmine controversial
  - blocks metabolism of Ach leading to more post synaptic Ach
  - Contraindicated in TCA overdose! Cause brady, AVB, asystole, seizure
  - Watch for QRS widening
  - Used more for diagnostic purposes, 0.5-1 mg, up to 2mg

Case 2 scenario

56 yo male farmer presents to the ED with vomiting, drooling, lacrimation. Physical exam reveals miosis and the patients pants are soiled with urine and diarrhea. Which toxidrome did this patient most likely have?

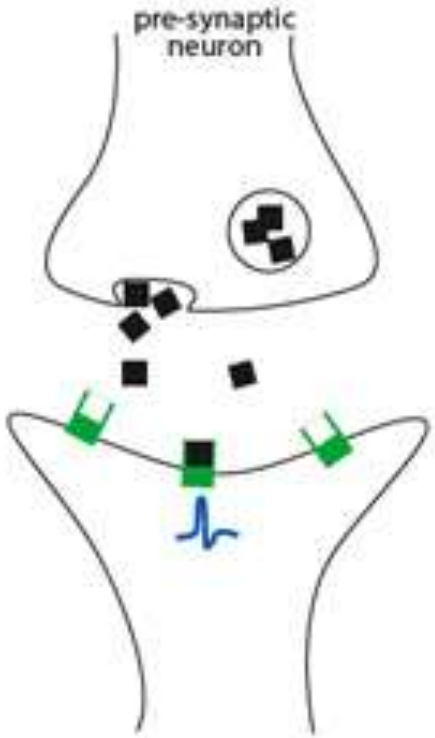
Cholinergic Toxidrome

Organophosphates, carbamates

- **SLUDGE**
  - **S**alivation
  - **L**acrimation
  - **U**rination
  - **D**efecation
  - **GI** upset
  - **E**mesis and Miosis

- **DUMBELS**
  - **D**iaphoresis
  - **U**rination
  - **M**iosis
  - **B**radycardia
  - **B**ronchorrhea
  - **B**ronchospasm
  - **E**mesis
  - **L**acrimation
  - **S**alivation
  - **S**eizure

Acetylcholine signaling at synapse



- Acetylcholine (ACh)
- ACh Receptor
- Signal transmission

ACh Esterase STOPS signaling process

- ACh
- ACh Receptor
- Signal transmission
- ACh Esterase

OP's inhibit ACh Esterase

- ACh
- ACh Receptor
- Signal transmission
- ACh Esterase
- Organophosphate pesticide (OP)

Cholinergic Toxidrome

- Treatment
  - Atropine: 2-5mg IV
    - Redosing 10-15 min
    - Only anti-muscarinic effect
    - Goal: decrease secretion
  - Pralidoxime (2 PAM)
    - Loading dose 30-50mg/kg, 約1- 2 g IV bolus
    - 8 -20 mg/kg/hr IV continuously
  - Benzos

Case 3 scenario

Police bring in a 23yo M who is agitated, combative, hallucinating, tachycardic, tachypnic, diaphoretic and has a Temp 101.4F. Which toxidrome did this patient most likely have?

Sympathomimetic Toxidrome

- Cocaine, Amphetamine, PCP, Xtasy, etc.
- Amped up
  - Agitated
  - Mydriasis
  - Tachycardia
  - Hyperthermia
  - Diaphoresis

Sympathomimetic Treatment

- Tx- Benzos, Benzos and more Benzos
- Beware of BB and “unopposed Alpha” stimulation
  - Paradoxical hypertension & coronary constriction
  - Vasodilator if needed
- Beware of complications: rhabdomyolysis, hyperthermia, MI and ICH/cerebral infarct

Opioid Toxidrome

- Morphine, Percocet, Heroin
- Depressed MS, Miosis, Hypoventilation
- Tx- naloxone or intubation
  - Start small (0.2 mg)

Opioid Withdrawal Toxidrome

- Symptoms
  - Mydriasis
  - Yawning
  - Lacrimation
  - N/V/D
  - Piloerection
- Not life threatening (if the patient has fever or AMS, think of different diagnosis)

Serotonin Syndrome

- Fluoxetine (Prozac), Paroxetine (Paxil), Sertraline (Zoloft), Citalopram
- Usually occurs w/ 2 or more drugs
- Triad
  - Autonomic instability
  - Muscle rigidity, myoclonus (lower limbs)
  - Altered mental status
- Tx- Benzos and consider cyproheptadine (1st generation antihistamine)

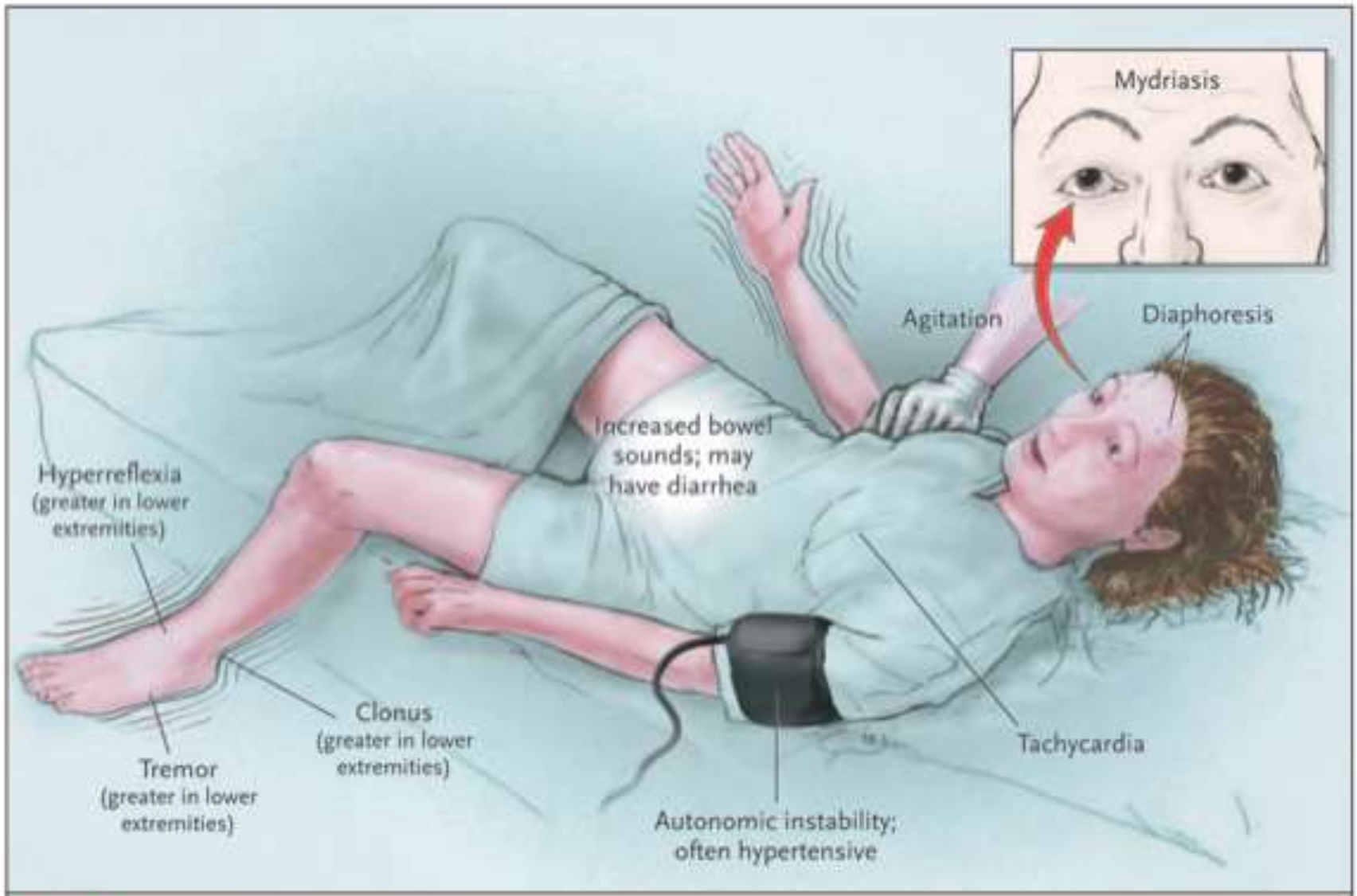


Figure 2. Findings in a Patient with Moderately Severe Serotonin Syndrome.

Hyperkinetic neuromuscular findings of tremor or clonus and hyperreflexia should lead the clinician to consider the diagnosis of the serotonin syndrome.

Principles of managing the acutely poisoned or overdose patients

Concepts of management

- Toxidromes
- Toxicodynamics

  What the poison does to the body

  Mechanism of toxicity
- Toxicokinetics

  What the body does to the poison

  Absorption, distribution, catabolism, elimination

Based on toxicokinetics

- **A**lter absorption (Decon.)
- **A**dminister antidote
- **B**asics
- **C**hange catabolism
- **D**istribute differently
- **E**nhance elimination

Alter absorption

- Irrigation (gastric lavage)
  - Aspiration pneumonia & Gut perforation risk
- Ipecac- NO
- Activated Charcoal
  - Dose (single/multiple), binding properties, antidotes, aspiration risk
- WBI- maybe

Administer antidote

Drug or Class	Antidote
Opiates	Naloxone
Benzodiazepines	Flumazenil
Acetaminophen	N-acetylcysteine
Organophosphates	Atropine, Pralidoxime
Iron	Deferoxime
Lead	DMSA
Methemoglobin	Methylene Blue
Ethylene glycol, Methanol	Fomepizole
Isoniazid (INH)	Pyridoxine (B_6)
Digoxin	Digibind®
Cyanide	Na-nitrite, Na-thiosulfate

Basics

- A, B, Cs
- Call poison control center
- ECG, ABG
- Blood Chemistry (Anion/Osm Gap if needed)
- Drugs screen, ASA and APAP levels

Though antidote is important, all poisoned patients will benefit from an organized, rapid clinical management plan.

Goldfrank's Toxicologic Emergencies 2011

Change catabolism

- Fomepizole
  - Competitive inhibitor of ADH
- Ethanol
  - Competitive substrate for ADH
- Sodium thiosulfate
  - Donate a sulfur moiety to form thiocyanate
- N-acetylcysteine (NAC)
  - Act as a sulfhydryl group donor (glutathione precursor)

Distribute differently

- Hyperbaric oxygen
  - Hasten the reversal of CO binding to HgB
- DigiFab
  - Have a high binding affinity for digoxin
- Deferoxamine
  - Bind free iron as a specific chelating agent
- Dimercaprol(BAL)
  - A dithol chelating agent for heavy metals
- Sodium nitrite/Amyl nitrite
  - Oxidize HgB to MetHb for binding free cyanide

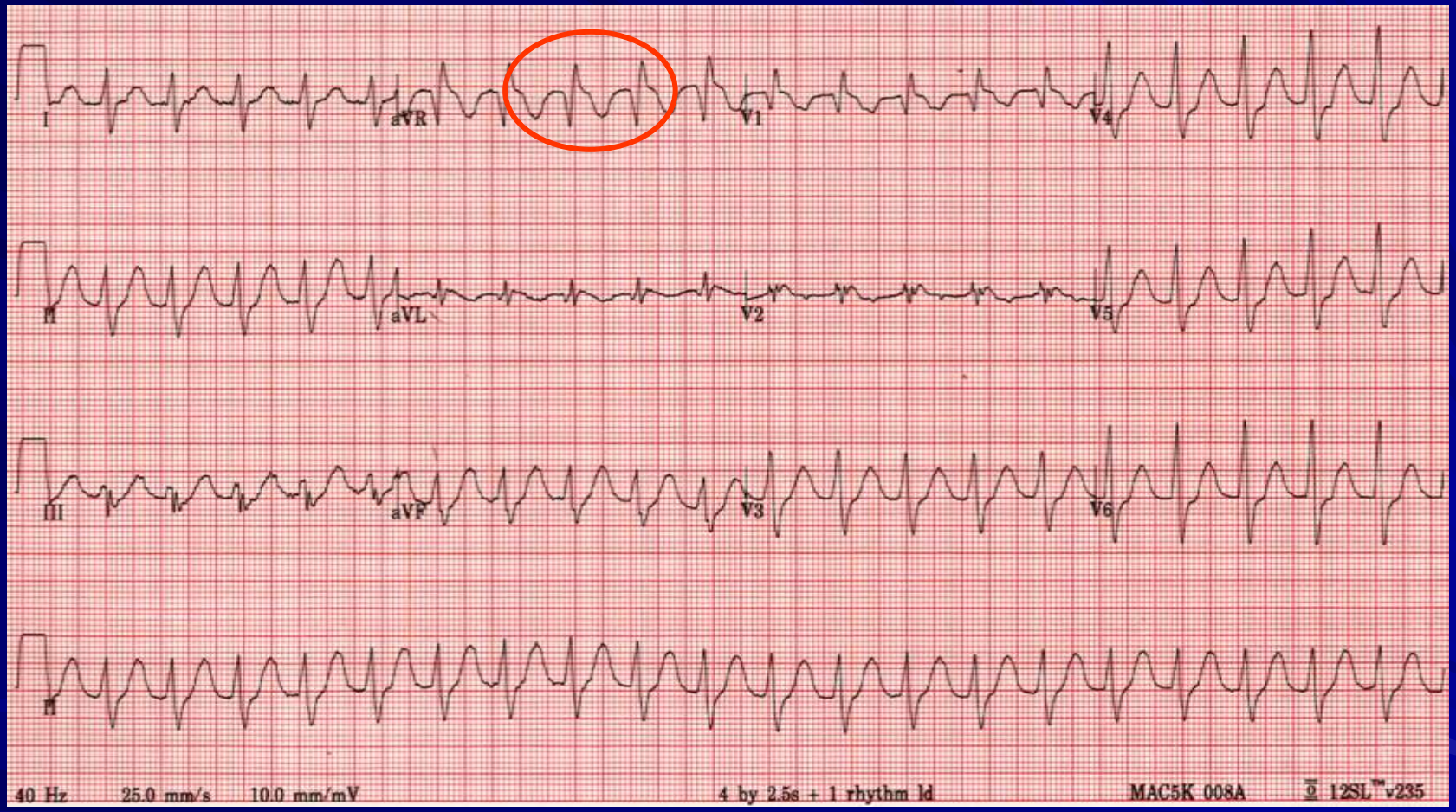
Enhance elimination

- Urinary Alkalinization
  - IV $NaHCO_3$ to achieve a urinary pH of 7.5 to 8.0
  - Phenobarbital, chlorpropamide, salicylate, methanol, 2-4-D (chlorophenoxy herbcide)
- Hemodialysis/Hemoperfusion
  - Small volume of distribution
  - Low molecular weight/ Low protein bound
  - Salicylate, methanol, ethylene glycol, lithium, theophylline

Lab Evaluation

- Three gaps
  - Anion gap
  - Osmolal gap
  - Oxygen gap
- Toxicological screening
  - APAP
  - Salicylate
  - Basic drug screen
- ECG
- ABG

ECG



Any abnormal findings?

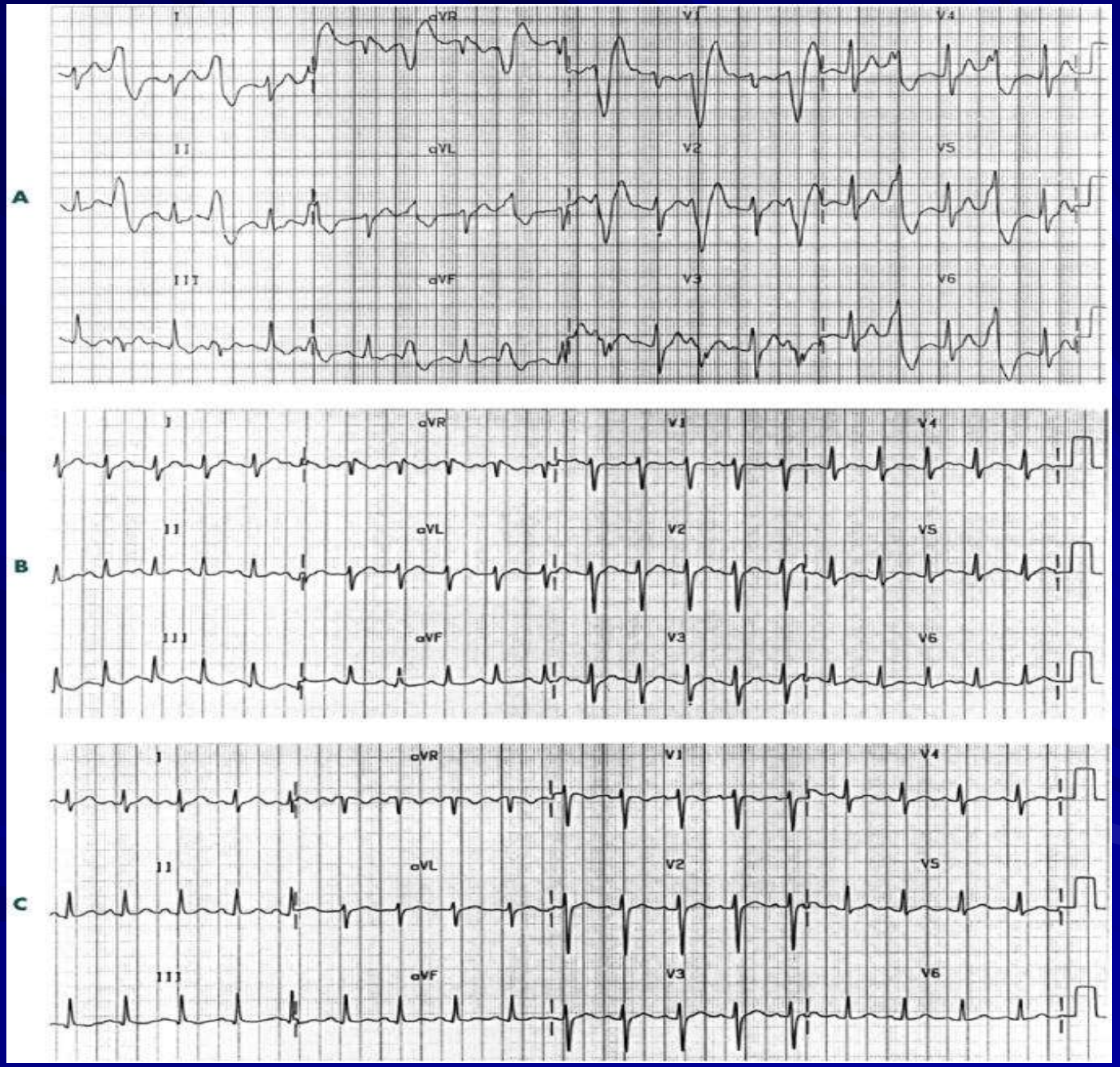
TCA

Amitriptyline, Desipramine, Doxepin

- Mechanism:
  - Na+ channel blockade (Wide QRS)
  - Anticholinergic Sx (AMS, Sz, etc)
  - Peripheral Alpha blockade (Hypotension)
  - GABA Inhibition (Lowers Sz threshold)
  - K+ channel blockade (Long QT)
- 1A+3C
- EKG: Wide QRS, Long QT, Prom. Terminal R wave in aVR

TCA
Amitriptyline, Desipramine, Doxepin

- Treatment
  - Na+ channel blockade
    - Na Bicarb
    - Hypertonic Saline
  - IVF and vasopressors
  - Intralipid
  - Sz - benzos


A
I
aVR
V1
V4
II
aVL
V2
V5
III
aVF
V3
V6
B
I
aVR
V1
V4
II
aVL
V2
V5
III
aVF
V3
V6
C
I
aVR
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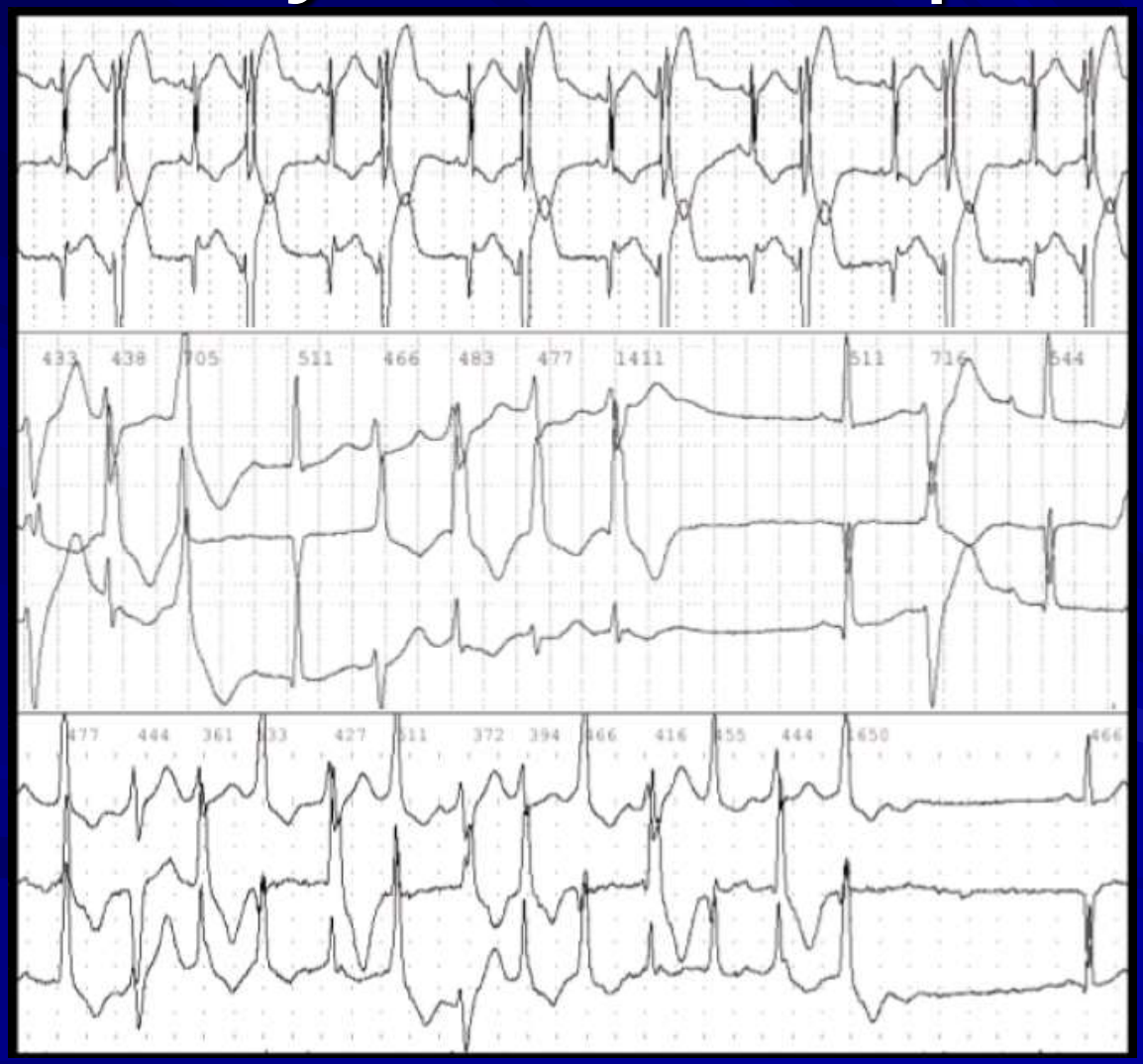
V5
III
aVF
V3
V6

What kind of drug overdose is mostly like the culprit?



Digoxin

- Digoxin, Fox Glove, Oleander
- Mechanism
  - Poisons the Na-K-ATPase Pump
  - Increased vagal tone
  - Increased intracellular Ca+
- S/S:
  - Blocks, QRS prolong, ventricular escape
  - Brady (slow a-fib)
  - Tachy (VPC, VT, Vf)
  - Hyper-K

Digitalis purpurea
毛地黃

Nerium indicum
夾竹桃

Cerbera manghas
海檬果

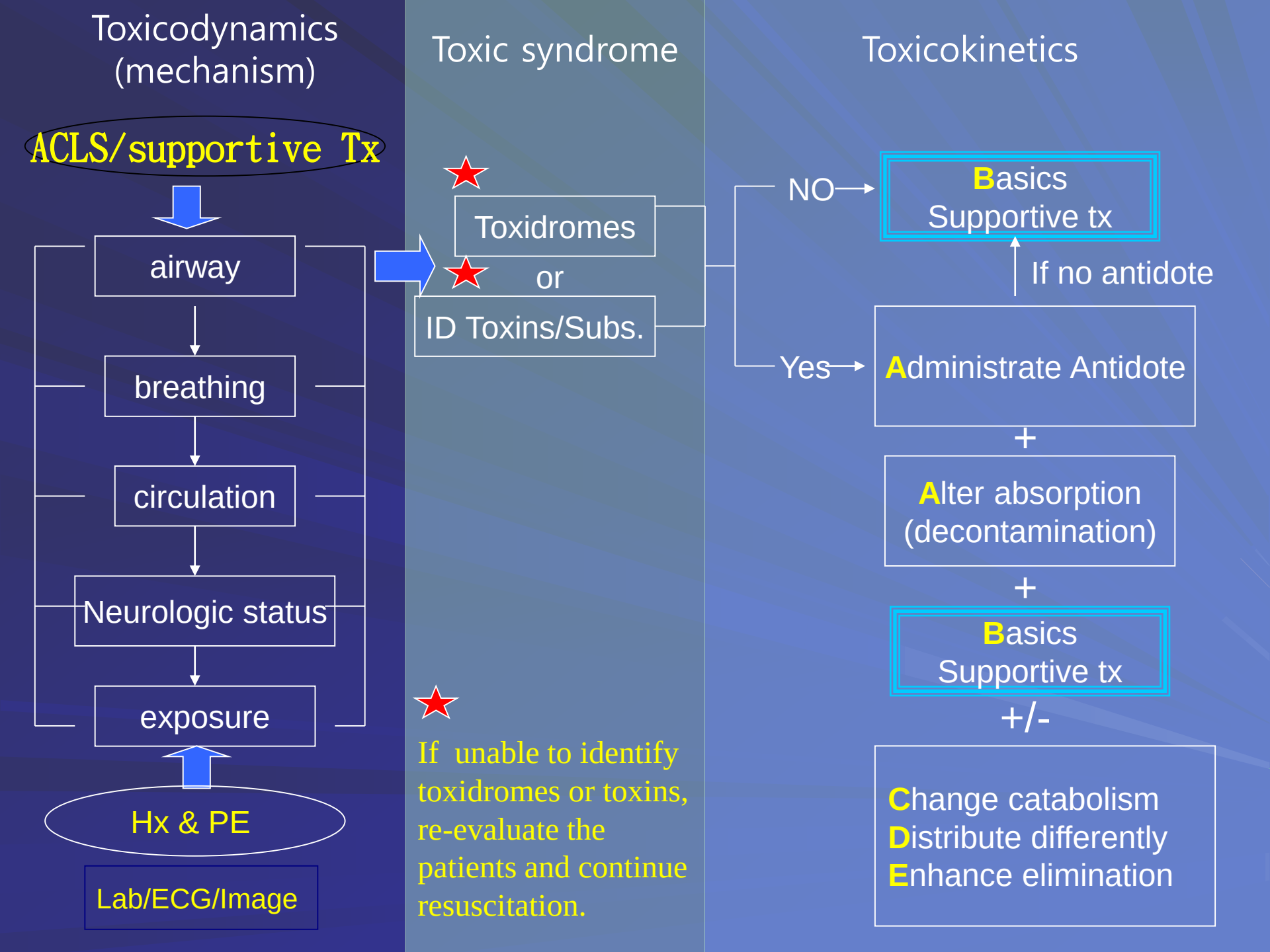
Digoxin

- Labs
  - Digoxin level (> 2 ng/mL)
  - Serum K+ 5.0 –5.5 BAD!
- Treatment
  - Digibind
    - Acute – 10 vials
    - Chronic – 1-2 vials
  - Beware of Ca for Hyper-K?
    - Worsen ventricular arrhythmia

Consideration of other causes

- Ingestion of multiple agents is common
- Some drug combinations are dangerous
- One drug may mask the effects of another
- An intracerebral bleeding may present much like a poisoning
- Metabolic causes for coma should be sought

Summary


Toxicodynamics (mechanism)
Toxic syndrome
Toxicokinetics
ACLS/supportive Tx
airway
breathing
circulation
Neurologic status
exposure
Hx & PE
Lab/ECG/Image
Toxidromes
or
ID Toxins/Subs.
If unable to identify toxidromes or toxins, re-evaluate the patients and continue resuscitation.
NO
Basics
Supportive tx
If no antidote
Yes
Administrate Antidote
+
Alter absorption
(decontamination)
+
Basics
Supportive tx
+/-
Change catabolism
Distribute differently
Enhance elimination

Importance of supportive care

- Many clinicians find it difficult to overcome the normal desire to want to do something to reduce GI absorption or enhance elimination of an ingested toxin

(Gastrointestinal decontamination after poisoning. Crit Care Clinics 13(4):709-725)

- The point (baseline of these unproved methods) is we should avoid complications due to these procedures

- Supportive care remains the mainstay of poison management
- The use of antidotes should be individualized to the toxic substance and physiological condition of the patient

Any questions?

Thank you!!