THE ED ANTIDOTE SHELF – PART I

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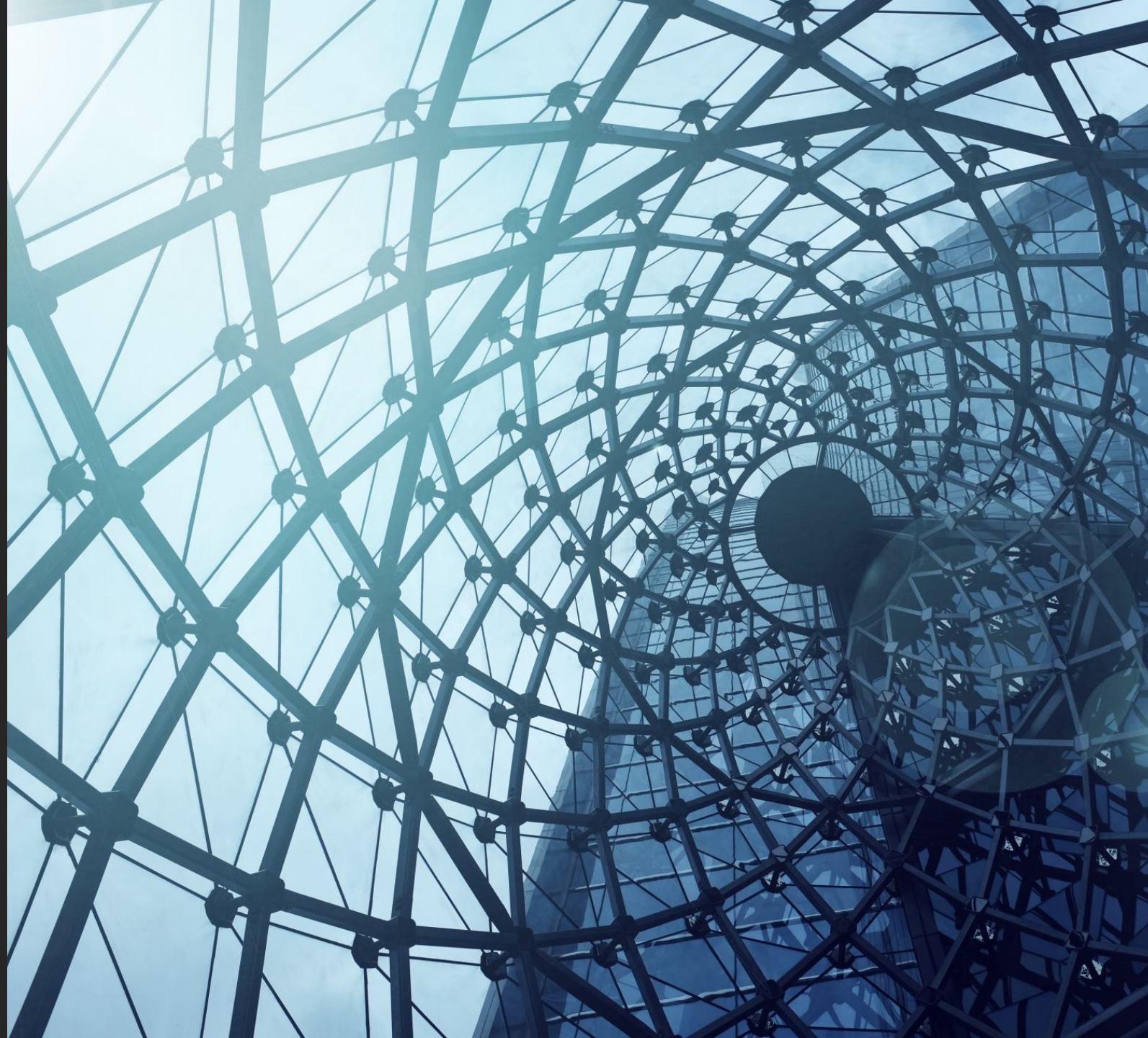


“The Best Physician Is Also a Philosopher”

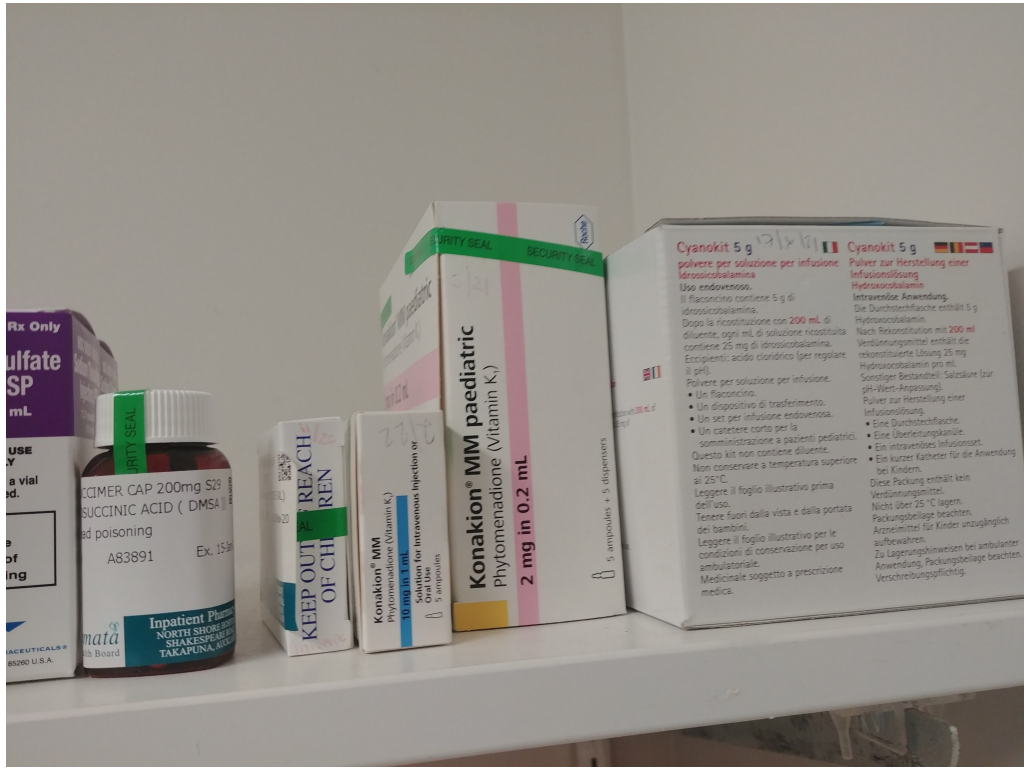
Galen of Pergamon- 120 AD

OUR ANTIDOTE SHELF

OUR ANTIDOTE SHELF - CONTENTS

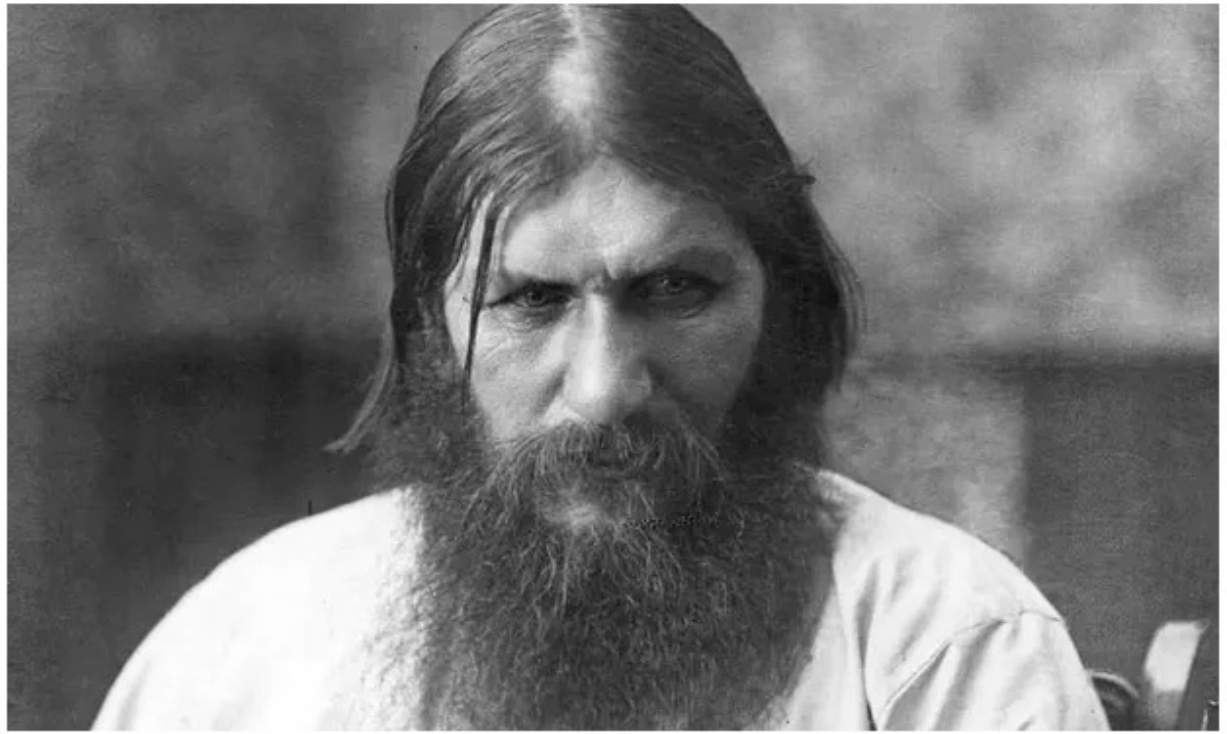
- N- Acetylcysteine
- Atropine sulfate
- Calcium gluconate
- Carbosorp X
- Desferroxamine mesylate
- Dimercaperol BAL
- Dehydrated alcohol
- Flumazenil
- Glucagon
- Intralipid
- Klean Prep
- Neostigmine
- Pralidoxime PAM
- Protamine sulfate
- Sodium Nitrite
- Sodium Thiosulfate
- Vitamin K
- Cyanokit
- DMSA
- Naloxone

CYANIDE TOXICITY



Poisoned, shot and beaten: why cyanide alone may have failed to kill Rasputin

Theories around the death of Grigori Rasputin still abound 100 years after the event. We examine the scientific credibility of some of the claims



▲ Grigori Yefimovich Rasputin, a mystic and spiritual healer born in Pokrovskoe in Siberia, wielded huge influence over the Russian royal family, particularly Alexandra, the Tsarina. Photograph: Laski Diffusion/Getty Images

LOST SPLENDOR – PRINCE YUSUPOV'S MEMOIRE

According to Yusupov, when Rasputin arrived at the palace he was taken down to the cellar where he was given cake and wine. Upstairs, a gramophone played Yankee Doodle Dandy to fool the monk in to believing there was a party in full swing.

Yusupov and his accomplices had planned things carefully. The cakes offered to Rasputin had been laced with enough potassium cyanide to slay a monastery full of monks. But Rasputin just kept eating them. Incredulous at the monk's survival, Prince Yusupov poured madeira into a cyanide-laced wine glass and handed it to Rasputin. Instead of collapsing into unconsciousness within seconds, as would be expected from a massive dose of cyanide, Rasputin continued to sip the wine like a connoisseur. A second lethal glass disappeared into the monk's mouth with little apparent effect other than some difficulty swallowing. Asked if he was feeling unwell he replied "Yes, my head is heavy and I've a burning sensation in my stomach." A third glass of tainted wine only seemed to revive him. Having ingested their whole stock of cyanide, the group of assassins were somewhat at a loss as to what to do next.

So they shot him.

CANADA

Woman revived, treated for cyanide poisoning after early morning fire in south Ottawa

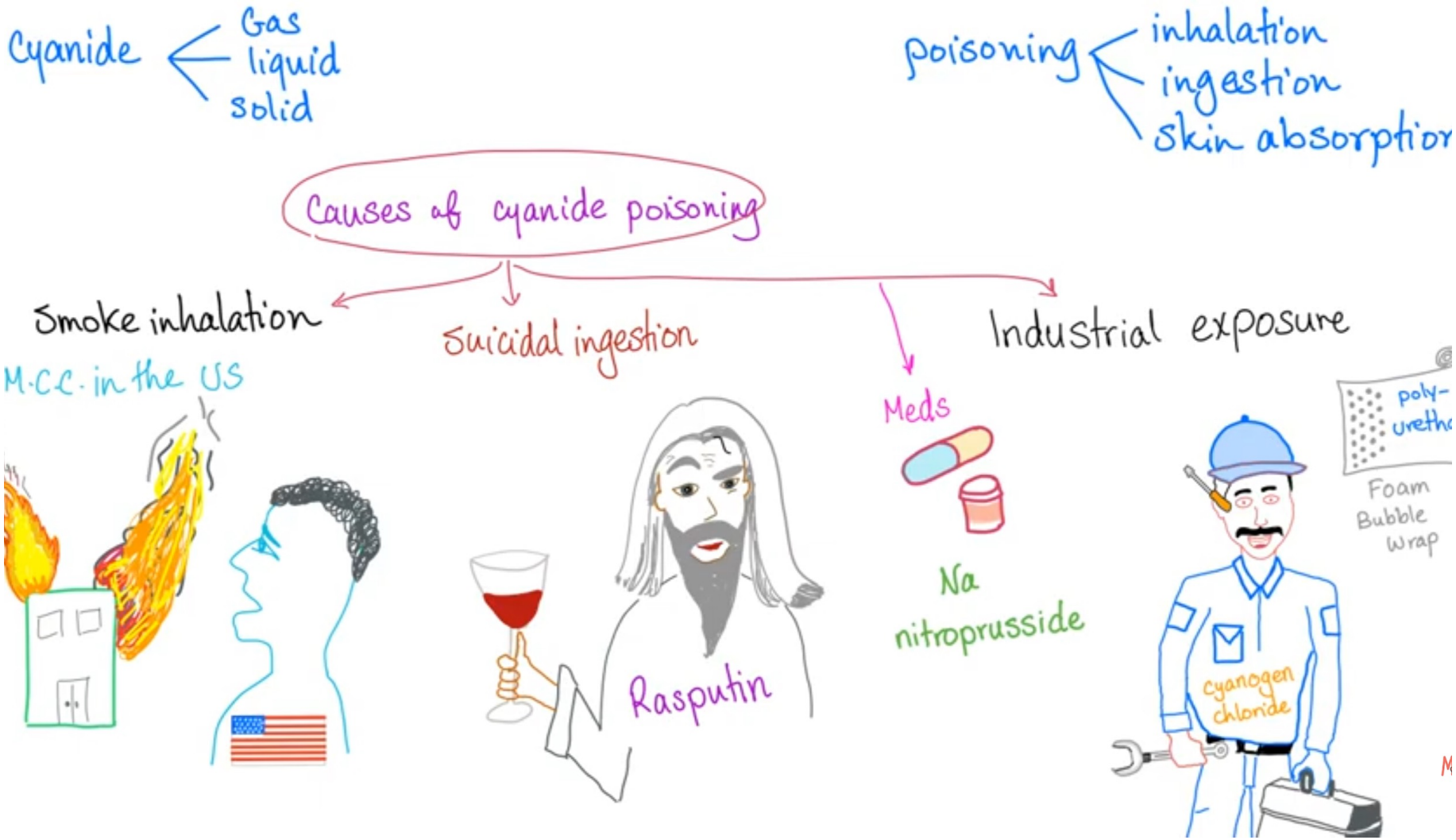
By Beatrice Britneff · Global News
Posted November 5, 2019 10:47 am

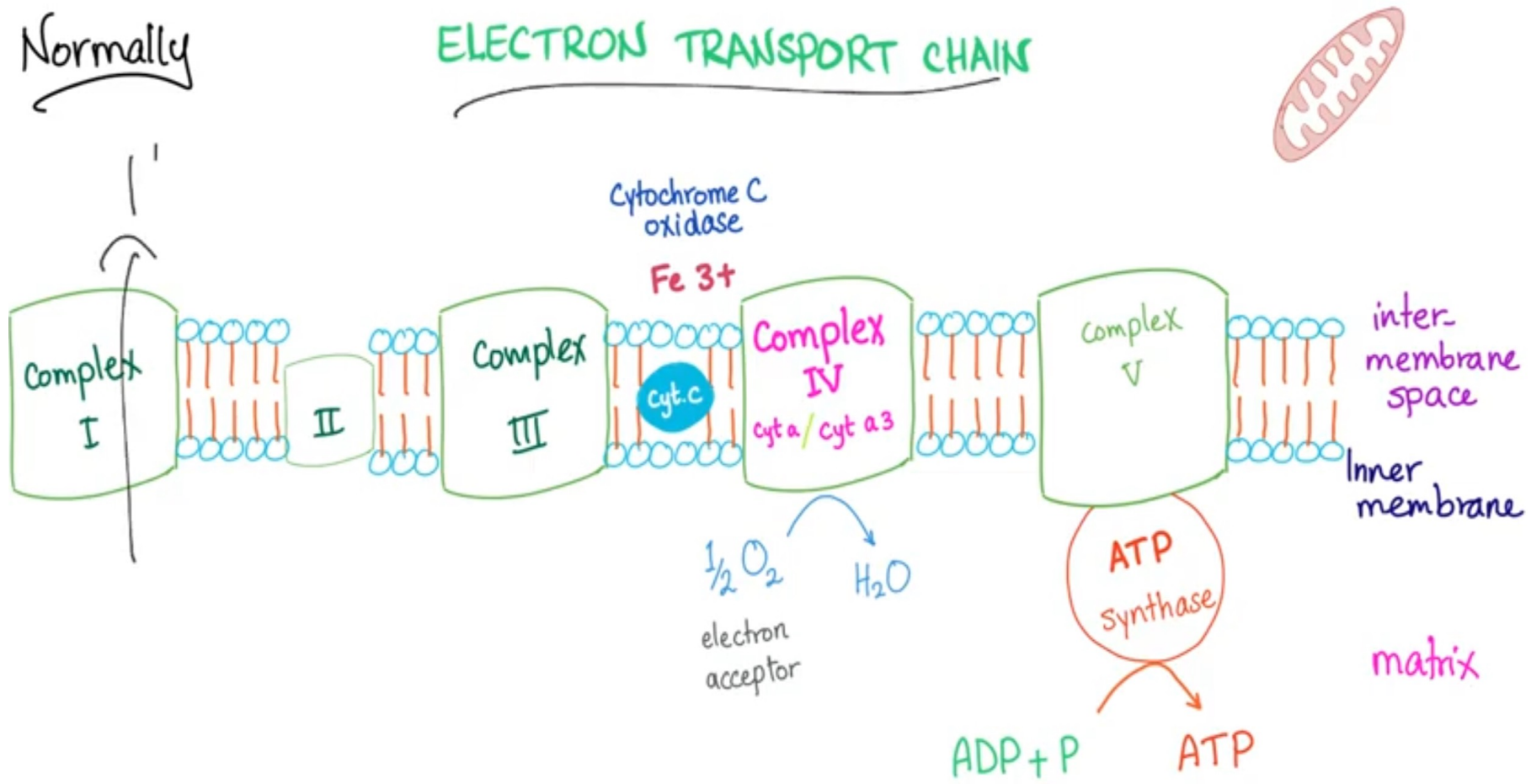
Ottawa paramedics file photo. Ottawa Paramedic Service / Twitter

FOOD SOURCES, MEDS

- https://www.youtube.com/watch?v=N3eGA9hKjRc

OUR ANTIDOTE SHELF


Cyanide
Gas
liquid
solid
poisoning
inhalation
ingestion
skin absorption
Causes of cyanide poisoning
Smoke inhalation
M.C.C. in the US
Suicidal ingestion
Rasputin
Industrial exposure
Meds
Na nitroprusside
poly-
uretha
Foam
Bubble
Wrap
cyanogen chloride


Normally
ELECTRON TRANSPORT CHAIN
Cytochrome C oxidase
Fe 3+
Complex I
II
Complex III
cyt.c
Complex IV
cyt a / cyt a3
complex V
inter membrane space
Inner membrane
matrix
1/2 O2
H2O
electron acceptor
ATP Synthase
ADP + P
ATP

Cyanide loves binding to Fe^{3+}

Therefore,

Cyanide will either bind to Fe^{3+} in the Met Hb

Or

will bind to Fe^{3+} in the Cytochrome C oxidase

cyanide → binds to Fe^{3+} in cytochrome oxidase

↓

inhibition of complex IV
(cyt a/a3)

↓

no ATP formation

When  cannot utilize O_2

⇓

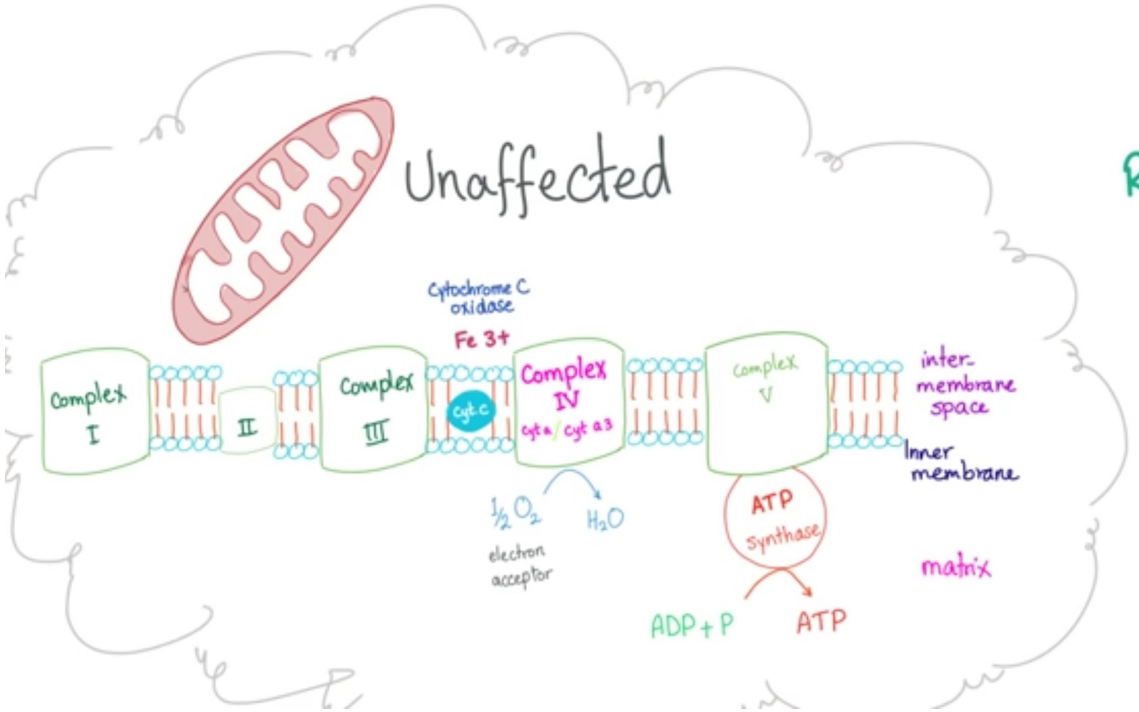
Anaerobic glycolysis

⇓

lactic acidosis => HAGMA

Cyanide poisoning

In the presence of Met Hb



CN^- + Met Hb

↓

Cyanomethemoglobin

Liver Rhodanase — Na thiosulfate

↓

Thiocyanate

Cyanide → binds to Fe^{3+} in cytochrome oxidase

↓

inhibition of Complex IV (cyt a/a3)

↓

no ATP formation

The  & are the most affected

no ATP formation → When  cannot utilize O_2

⇓

Anaerobic glycolysis

⇓

lactic acidosis ⇒ HAGMA

no conc. gradient for O_2 to flow from Hb to tissue → ⇓⇓ O_2 diffusion from Hb to tissue → TISSUE HYPOXIA

↓

⇑⇑ venous O_2 content ($\uparrow\uparrow P_vO_2$) → $P_aO_2 = P_vO_2$

Clinically

Symptoms

weakness (no ATP)

(Tissue hypoxia)

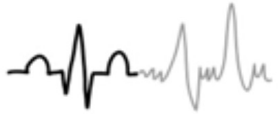
- Headache
- vertigo
- Dizziness
- seizure
- Coma

abd. pain

chest pain

S.O.B

Signs



arrhythmia

↓↓ HR

↓↓ B.P.

CHERRY-RED SKIN ($\uparrow\uparrow P_vO_2$)

CARDIOVASCULAR COLLAPSE

↑↑ R.R.

dx

ABG & VBG (venous)

P_aO_2: nl P_vO_2: ↑↑

$P_aO_2 = P_vO_2$

↓↓ A-V O_2 difference "< 10%"

HAGMA

↓ pH

↓ HCO_3^-

↑ anion gap "> 12"

blood labs

↑↑ blood lactate level "> 10 mmol/L"

↑↑ plasma cyanide conc.

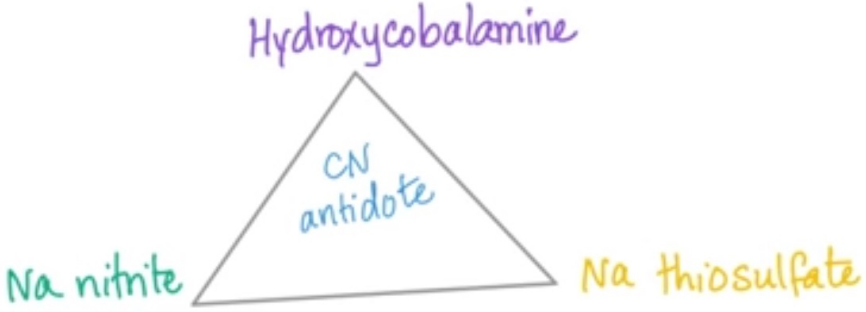
EKG: non-specific "Sinus tachycardia" Ischemic changes

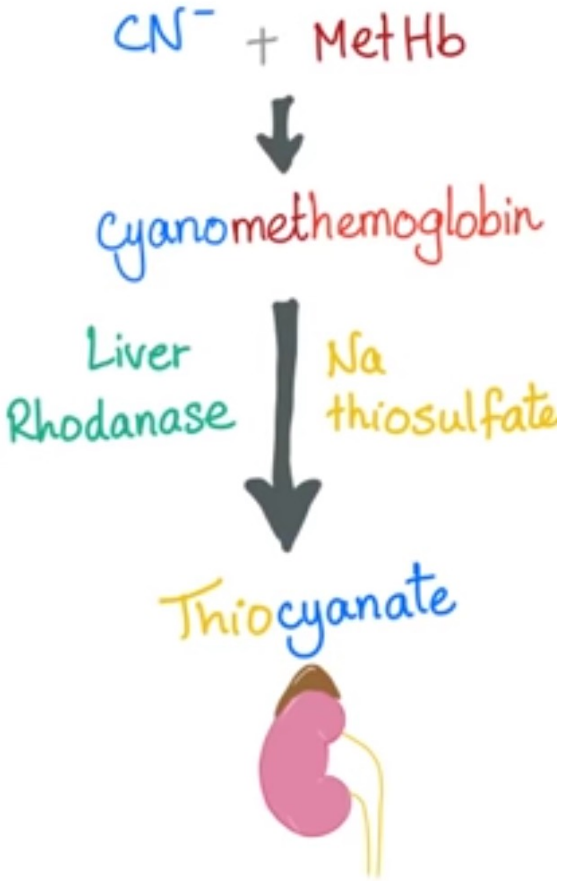
Carboxy-Hb conc.: to rule out CO poisoning

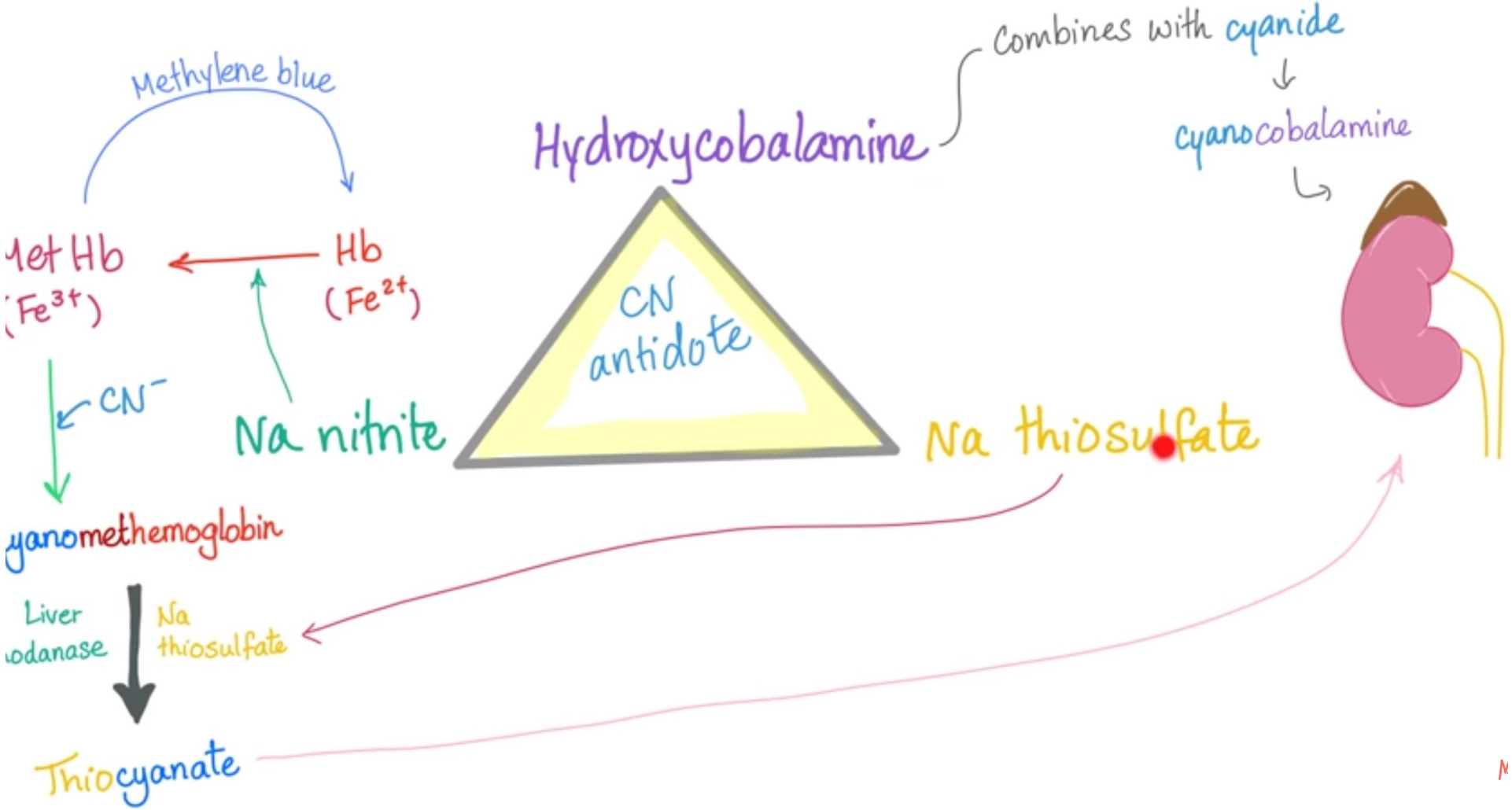
MetHb level: to monitor therapy.

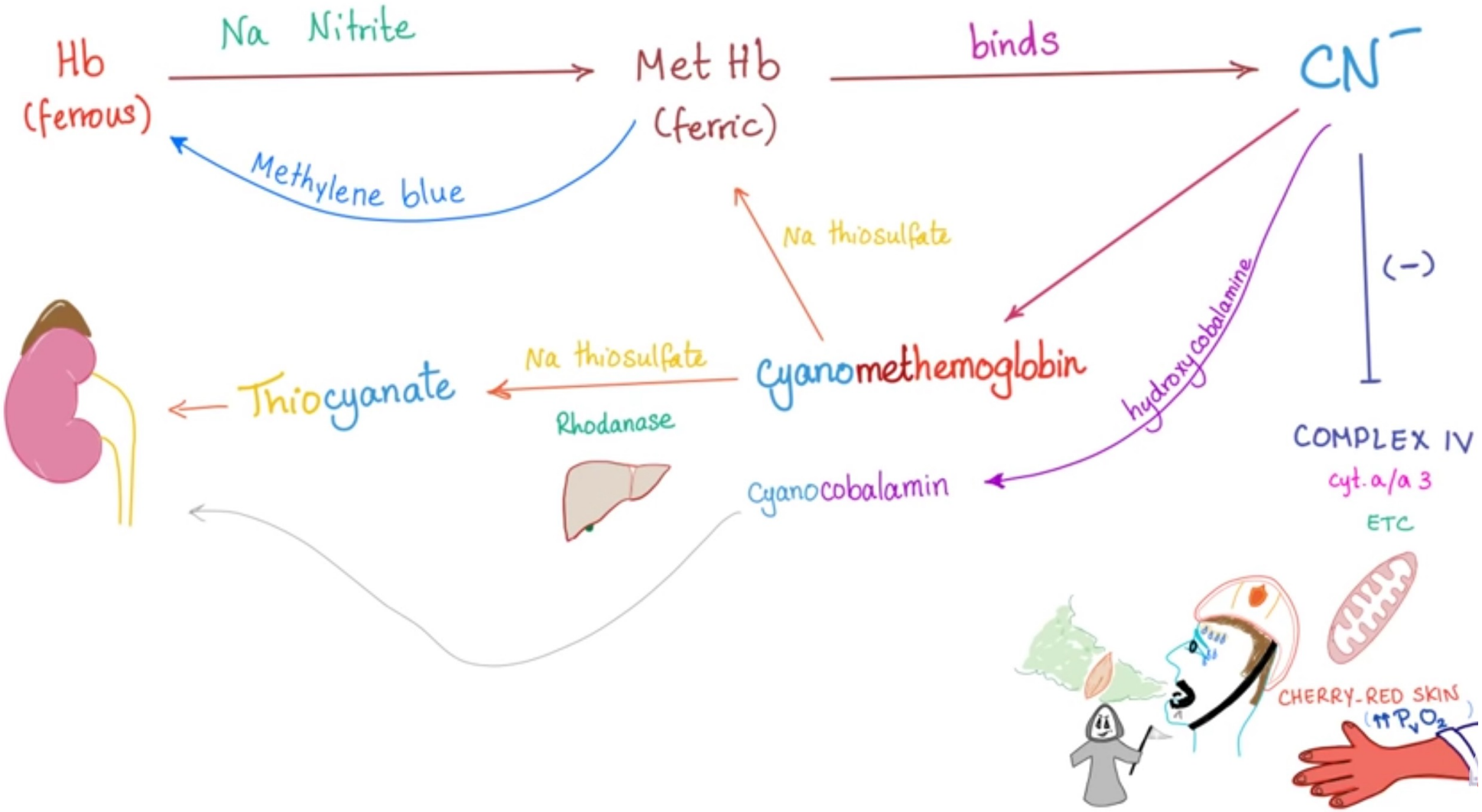
MANAGEMENT

- ABCs
- IV, O2, Monitor
- REMOVE CLOTHES
- Do not wait for labs
- Have a high suspicion
  - Worrisome history with
  - Cherry red skin
  - Dizziness/obtundation
  - High venous pO2
  - High lactic acid
  - GIVE CYANIDE ANTIDOE






Methylene blue
Met Hb
(Fe3+)
Hb
(Fe2+)
CN⁻
Na nitrite
yanomethemoglobin
Liver
odanase
Na
thiosulfate
Thiocyanate
Hydroxycobalamine
Combines with cyanide
cyanocobalamine
CN
antidote
Na thiosulfate


Hb
(ferrous)
Na Nitrite
Met Hb
(ferric)
binds
CN⁻
Methylene blue
Na thiosulfate
(−)
hydroxy cobalamine
Na thiosulfate
Thiocyanate
Cyanomethemoglobin
Rhodanase
COMPLEX IV
cyt. a/a 3
ETC
Cyanocobalamin
CHERRY-RED SKIN
(P_vO_2)

* While treating acute cyanide poisoning → DO NOT give methylene blue
(you need the MetHb)

* DO NOT let the MetHb level rise too much while treating CN^- poisoning
Methemoglobinemia is a disease as well.

* Na nitropnusside leads to cyanide poisoning, whereas
Na Nitrite & Na thiosulfate treats cyanide poisoning.

* Na nitropnusside & cyanide & Na nitrate & Na Nitrite → Hypotension

* In cyanide poisoning, it's difficult to distinguish between retinal arteries & veins
under fundoscopic exam $P_aO_2 = P_vO_2$

CYANOKIT V SODIUM NITRITE/SODIUM THIOSULFATE

- Activated hydroxycobalamine review:
  - does not induce methemoglobinemia
  - rapid onset of action, French trials show decreased mortality esp when administered by EMS
  - equal mortality reduction but ease of use with less hypotension and no need to monitor methemoglobin levels
  - pig studies show significant benefit of hydroxycobalamine w thiosulfate v sodium nitrite with thiosulfate
  - Cons:
    - Hypertension
    - Needs separate IV line (adult starting dose 5g, with additional doses of 2.5g as needed to reverse symptoms)
    - can interfere with common spectrophotometric tests and tests for carboyxhemoglobin, methemoglobin and oxyhemoglobin.
    - Average wholesale price is US $274.56 for sodium nitrite/thiosulfate combination and US $812.50 for two 2.5g vials of hydroxocobalamin

PHILOSOPHY OF PHYSICIANS

- Do we really NEED Sodium Nitrite on our antidote shelf?

OUR ANTIDOTE SHELF

“MARITAL STRIFE”

- A 40-year-old female with no significant past medical history presented to our tertiary hospital emergency department (ED) via ambulance with vague symptoms that included a headache and abdominal pain. She was accompanied by her two sons. Upon arrival, her nursing assessment documented a Glasgow Coma Scale (GCS) score of 15, vital signs (VS) of: heart rate 110 beats/minute, respiratory rate 18 breaths/minute, blood pressure 110/79mmHg, temperature 36.4 C, oxygenation saturation 91% on room air. She reported feeling well the evening prior to presentation. She denied any infective symptoms and her history had no suggestion of trauma. Within the hour of her arrival, her GCS score began to decrease, and she became unresponsive. Re-assessment noted no significant change in her VS, finger-stick blood glucose of 9.3mmol/L, pupils that were equal and reactive and no focal neurology or seizure activity. Further collateral history from her two children revealed a recent marital argument and no background of alcohol or recreational drug use.A venous blood gas (VBG) was obtained and analysed in the ED on a point of care (POC) analyser. Results were notable for a pH of 7.035 anion gap (calculated) of 31.8 and lactate of >31mmol/L. A full blood count showed a white blood cell count of 14.1x109/L but was otherwise unremarkable. Her basic metabolic panel revealed normal electrolytes, renal function and a bicarbonate of <8mmol/L. Her liver function tests were normal. Her ethanol (ETOH) and paracetamol levels were negative. An electrocardiogram showed a narrow complex sinus rhythm with normal QRS and QT intervals.
- Prophylactic antibiotics were administered and due to a GCS score of 4 and severe metabolic derangement, she was intubated and hyperventilated. A CT scan of her brain showed no acute intracranial abnormality. She was admitted to the intensive care unit
- When further laboratory investigations were obtained in the ICU to monitor her progress, it was noted that the main laboratory (Roche Cobas c502) lactate was significantly lower (12mmol/L) than that measured on the POC blood gas machines (Radiometer ABL 800 flex) in ED and the ICU (>31mmol/L).

The New York Times

Czechs See Peril in a Bootleg Bottle

A bartender in Prague on Friday covered up bottles of drinks containing more than 20 percent alcohol, in compliance with a recent government ban. David W. Cerny/Reuters

SEP 17, 2012 NY TIMES

- “The Czech Republic has banned the sale of liquor containing 20 percent or higher alcohol content after at least 20 people were killed and dozens of others were seriously injured from consuming methanol-tainted spirits.”
- “According to Czech News Agency, Vladimr Lipina, a 51-year-old car Czech factory worker from the industrial town of Havirov and one of those affected, bought a bottle of rum from a street kiosk on his way to a soccer game two weeks ago. He said he had a few shots but thought that the drink tasted strange. Four days after his pregame celebration, Mr. Lipina became blind. “I woke up with a terrible headache and stomachache, but I thought I would just get over it,” Mr. Lipina was quoted as saying. Doctors are not optimistic he will ever see again.”
- “The toxic spirits, including vodka and rum, were mostly purchased at stores and kiosks in the depressed region of northern Moravia. In several cases, whole families have fallen ill.
- The police on Wednesday found the body of a 28-year-old woman, the mother of an 8-year-old boy, at her home in Komorni Lhotka, a small northeastern village; her 60-year-old father was taken to a hospital in critical condition. Tests showed that they had been poisoned with methanol, although it is not clear where they had bought the tainted spirits.”

CZECH METHANOL MASS POISONING

- 121 cases presented over the course of one week
- 51 deaths and "many" with permanent ocular and neuro sequelae
- Rationed Fomepizole for the "very sick" and eventually ran out
- Used Fomepizole and Ethanol as antidotes – subsequent epidemiologic studies and retrospective analysis published
- Made a movie 2018

HTTPS://WWW.CLAWHAMMERSUPPLY.COM/BLOGS/MOONSHINE-STILL-BLOG/HOW-TO-MAKE-MOONSHINE


GL
Great Life With M
GL
GREAT LIFE WITH MY CAR
4 Liters
RADIATOR
COOLANT
U.S.A FORMULA
No Need To Dilute
Ready To Use


MADE IN THE USA
PATENTED FORMULA
ALL METAL PROTECTION
PEAK
ANTIFREEZE & COOLANT
FREEZE-UP -84 °F
MAXIMUM PROTECTION
BOIL-OVER +276 °F
WARNING: HARMFUL OR FATAL IF SWALLOWED OR INHALED. CONTAINS ETHYLENE GLYCOL.
One U.S. Gal. (3.78L)


NEO
ANTIFREEZE

TOXIC ALCOHOL POISONING

- Methanol
- windshield-wiper fluid and de-icing products, and may also be found in gas-line antifreeze, paint removers, shoe dyes and embalming fluid
- metabolised by alcohol dehydrogenase (ADH) to **formaldehyde**, which is further metabolised by aldehyde dehydrogenase (ALDH) to **formic acid**
- **Ocular** effects include blurry vision, reduced visual acuity, photophobia and the classic “snowstorm” vision. Permanent blindness may occur due to optic nerve atrophy
- Reported **neurological** effects include Parkinsonism, transverse myelitis and basal ganglia haemorrhages
- ARDS

- Ethylene Glycol
- radiator antifreeze, as well as degreasing agents, foam stabilizers and metal cleaners.
- Ethylene glycol is metabolised by ADH to **glycoaldehyde**, then by ALDH to **glycolic acid**, which is further metabolised to **glycoxylic acid** and finally **oxalic acid**
- **Neurological** effects include coma, seizures, meningism, muscle spasms, external ocular paralysis and delayed onset (5-20 days) of cranial nerve deficits
- Oxalic acid combines with serum calcium to form calcium oxalate, which leads to **hypocalcaemia** and **QTc prolongation**, with risk of ventricular arrhythmias
- **Renal toxicity** is produced when calcium oxalate crystals precipitate in the renal tubules, causing flank pain, oliguria and **acute renal failure**

METHANOL NEUROLOGIC SEQUELAE

Brain imaging (CT/MRI) in methanol intoxication may demonstrate **bilateral putamen necrosis, basal ganglia** haemorrhages and necrosis of the caudate nucleus with atrophy of the optic chiasma and lesions in the occipital cortex and subcortical white matter

LAB INVESTIGATIONS

- Recommended baseline investigations include:
  - Urea, electrolytes and creatinine
  - Serum osmolarity
  - Ethanol level + toxic alcohol panel
  - Arterial or venous blood gases
  - Urinalysis + microscopy for crystals
- An osmolar gap of >~ 10 mOsm in the setting of high anion gap metabolic acidosis (anion gap > 12) is suggestive of toxic alcohol ingestion
- Overtime, the initially elevated osmolar gap decreases as the toxic alcohol is metabolized and the anion gap w the formation of ketones/aldehydes and organic acids

- A spuriously elevated lactate may occur with ethylene glycol toxicity due to the structural similarity between glycolic acid and lactate
- How do we calculate the osmolar gap?
- What is the definitive treatment for toxic alcohol poisoning?
- What are some adjuncts to help expedite metabolism?

HOW DO WE CALCULATE THE OSMOLAR GAP?

HOW DO WE CALCULATE THE OSMOLAR GAP?

OG = measured serum osmolality − calculated osmolality

Calculated osmolality = 2 x Na + Glucose + Urea + ethanol (all values in mmol/L)

In non-SI laboratory units: Calculated osmolality = 2 x [Na mmol/L] + [glucose mg/dL] / 18 + [BUN mg/dL] / 2.8 + [Ethanol/3.7]

WHAT IS THE DEFINITIVE TREATMENT FOR TOXIC ALCOHOL POISONING?

WHAT IS THE DEFINITIVE TREATMENT FOR TOXIC ALCOHOL POISONING?

- **Dialysis**
- The indications for haemodialysis in methanol / ethylene glycol poisoning are:
  - Metabolic acidosis (pH < 7.25)
  - Visual abnormalities
  - Renal failure
  - Electrolyte abnormalities not responsive to conventional treatment
  - Haemodynamic instability refractory to ICU treatment
  - Serum concentration > 50mg/dL
  - Haemodialysis may not be needed if fomepizole is started early in ethylene glycol poisoning and there is no evidence of acidaemia or renal dysfunction.
  - Methanol is eliminated too slowly for antidotal treatment alone to be effective.

WHAT ARE SOME ADJUNCTS TO HELP EXPEDITE METABOLISM?

WHAT ARE SOME ADJUNCTS TO HELP EXPEDITE METABOLISM?

- Metabolic acidosis with an arterial pH < 7.3 should be treated with a sodium bicarbonate infusion to keep the pH between 7.35 and 7.45.
- In ethylene glycol toxicity, pyridoxine (100mg IV Q6H) and thiamine (100mg IV Q6H) increase the metabolism of glycolic and glycoxlic acid to the less toxic metabolites glycine and alpha-hydroxy-beta-ketoadipate.
- In methanol toxicity, folic acid (50mg IV Q4-6H) or folinic acid (1-2mg/kg IV Q4-6H) increases the breakdown of formic acid to carbon dioxide and water.

ANTIDOTAL THERAPY

- The indications to commence antidotal therapy are:
  - Serum concentration of methanol / ethylene glycol > 20 mg/dL
  - Confirmed or suspected methanol / ethylene glycol ingestion and two of the following:
    - Osmolar gap > 10 mOsm
    - Arterial pH < 7.3
    - Bicarbonate < 20 mmol/L
    - Presence of urinary oxalate crystals

DEHYDROGENATED ALCOHOL INFUSION

DOSAGE AND ADMINISTRATION

Adults – usual dose

☒ Direct IV injection	MUST NOT be used.
☒ Intermittent IV infusion	Not recommended.
☑ **Continuous IV infusion**	*Refer to TOXINZ or local protocols.*

Ethanol concentration	**Ethanol 5% w/v**	**Ethanol 10% w/v**
Loading dose (over 30 minutes) [12]		
	12 to 18 mL/kg	6 to 9 mL/kg
Maintenance dose [12]		
Non-alcoholic adult	1.8 to 2.4 mL/kg/hour	0.9 to 1.2 mL/kg/hour
Alcoholic adult	3.6 to 4.8 mL/kg/hour	1.8 to 2.4 mL/kg/hour
Child	3.6 mL/kg/hour	1.8 mL/kg/hour

Adjust loading dose if patient has already consumed ethanol.
Adjust maintenance rate according to blood ethanol concentration which must be maintained at 22 to 33 mmol/L (100 to 150 mg/dL).

☒ IM injection	MUST NOT be used.
☒ Subcutaneous injection	MUST NOT be used.

DEHYDROGENATED ALCOHOL INFUSION

MONITORING/OBSERVATION/CAUTION

- Monitor ethanol blood levels every 1 to 2 hours until 100 to 150 mg/dL are reached and then 2- to 4-hourly thereafter, adjusting infusion rate to maintain blood ethanol within this range [6,7].
- Monitor for CNS and respiratory depression [6].
- Continue ethanol administration until methanol levels cannot be detected and metabolic acidosis has been corrected, or ethylene glycol levels cannot be detected or are less than 2.4 mmol/L (15 mg/dL) with a normalised arterial pH [12]. Likely to be a few days [6].
- Monitor blood glucose levels every 20 to 60 minutes during ethanol administration hypoglycaemia may occur [12].
- Note: nasogastric administration is just as effective as the IV route [7].

FOMEPIZOLE

- Fomepizole (15mg/kg loading dose then 10mg/kg Q12H)
- Side effects – nausea, mild skin rash, dizziness
- Cost

AN ECONOMIC ANALYSIS: IS FOMEPIZOLE REALLY MORE EXPENSIVE THAN ETHANOL FOR THE TREATMENT OF ETHYLENE GLYCOL POISONING? SHIEW ET AL. CLINICAL TOXICOLOGY 2005.

- This study aims to compare the real costs of these two antidotes in the management of EG poisoning. Costs were based on treating a patient at a teaching hospital in central London (UK). These include the costs of ethanol, a critical care bed and 2 hourly ethanol assays for a patient treated with ethanol vs. the costs of fomepizole and a general medical (GM) ward bed for a patient treated with fomepizole.
- Thus a 3 day course of fomepizole for a 70 kg adult on a GM ward would cost $7673 vs. 3 days ethanol therapy on ICU costing $10367.
- Two recent case examples: A 2 year old child weighing 14 kg who ingested methanol was treated with 390 mg of fomepizole over 50 hours on a GM ward, the total cost was $1469. Ethanol therapy on PICU would have cost $7092.
- A 27 year old female weighing 65 kg with EG poisoning was treated with IV ethanol on ICU for 44 hours, costing $7092. Fomepizole therapy on a GM ward would have cost $4937.
- Despite the higher drug cost of fomepizole vs. ethanol, the additional expenses associated with ethanol therapy mean that fomepizole is often cheaper, particularly in pediatric patients due to the lower total doses of fomepizole.
- The overall costs of both therapies should be considered and not just the upfront drug costs. Additionally, fomepizole is well tolerated, easy to administer and has predictable kinetics. Clinical toxicologists need to reconsider which of these two agents should be the antidote of choice for EG and methanol poisoning.

PHILOSOPHY OF PHYSICIANS

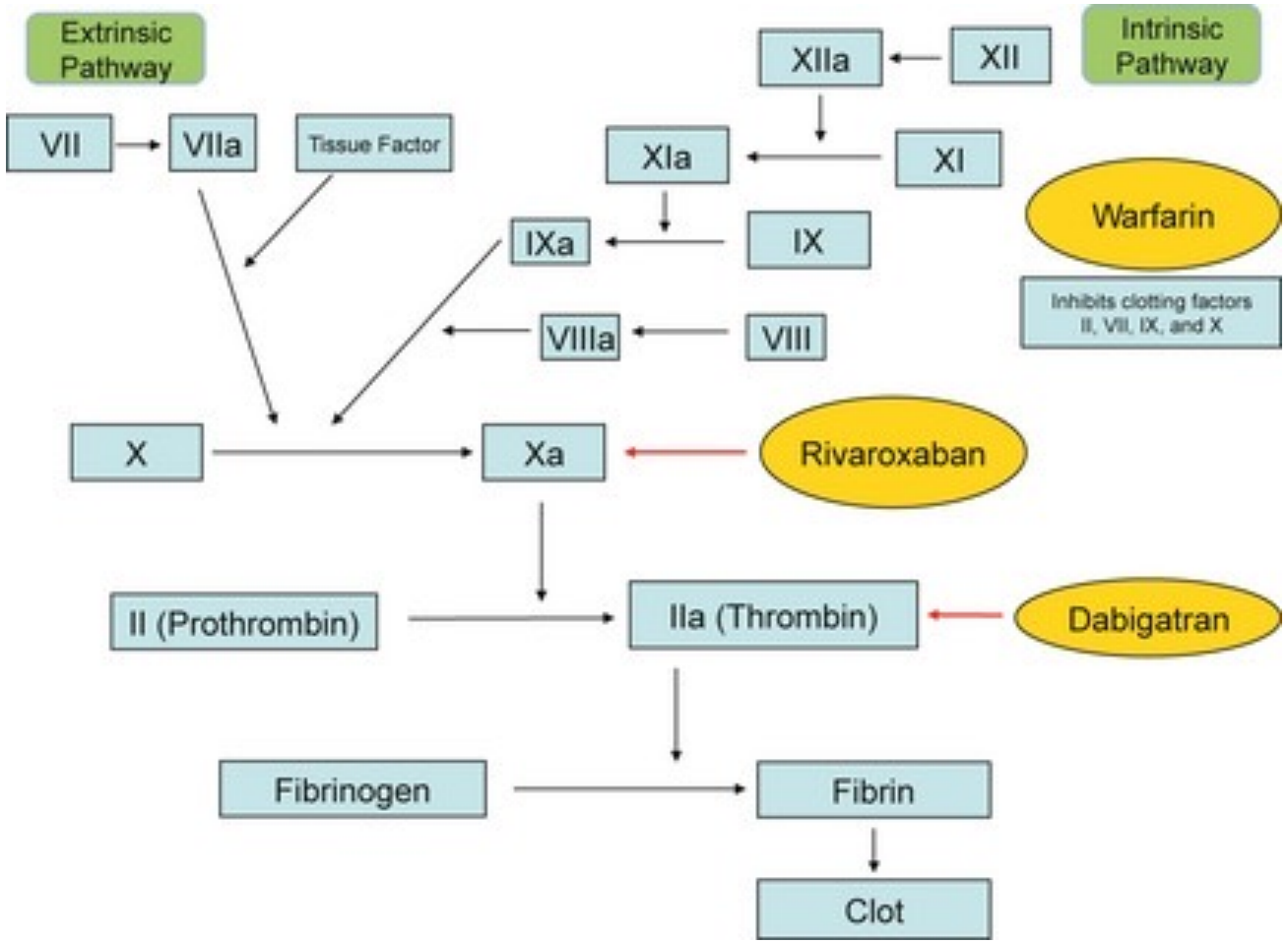
- Is it worthwhile for healthcare systems to shell out money for Fomepizole therapy

CHAPTER II OF OUR CASE EARLIER

- The discovery of apparent difference in reported lactic acid values prompted urine microscopy, which confirmed the presence of oxalate crystals. The findings of a serum ‘lactate gap’ and urinary crystals suggested a diagnosis of EG poisoning, which was later confirmed with a positive glycolic acid spot test followed by a quantified EG level of 3473mg/L, after treatment had begun. A laboratory serum osmolality was not obtained.
- Treatment was initiated with an ETOH IV infusion, thiamine, pyridoxine and sustained low efficiency dialysis (SLED) along with standard ICU care. Over the next three days, her condition improved significantly with a reducing lactate, normalisation of serum blood levels, improving conscious level and correction of polyuria. She was extubated on day three of her ICU admission, and she was able to confirm ingestion of EG, in the form of anti-freeze, as a self-harm attempt. She was seen by Psychiatry during her admission and was assessed to be stable for discharge home on day seven of admission.

OUR ANTIDOTE SHELF

ANTICOAGULANT REVERSAL



ANTICOAGULANT REVERSAL – IN CASE OF LIFE THREATENING BLEED

- **Unfractionated heparin**: Protamine 1 mg IV for every 100 units of heparin administered in the previous 2–3 h (up to 50 mg in a single dose) $50
- **Enoxaparin**: Dosed within 8 h: Protamine 1 mg IV per 1 mg enoxaparin (up to 50 mg in a single dose) Dosed within 8–12 h: Protamine 0.5 mg IV per 1 mg enoxaparin (up to 50 mg in a single dose) (partially effective)
- **Dabigatran**: (only give if aPTT is prolonged) Idarucizumab (Praxibind) 5 g IV (in two 2.5 g/50 mL vials) consider hemodialysis or idarucizumab redosing for refractory bleeding after initial administration if patient has renal insufficiency and persistent bleeding (long half life 17 hrs w renal excretion) - $4200 for both vials; 4 factor PCC can be backup
- **Warfarin**: Vitamin K 10 mg IV, plus 3 or 4 factor PCC (Prothrombin Complex Concentrate/KCentra) (FFP is out)– INR based or fixed dosing regimens available. $5080 per dose - INR -
  - **2-3.9**: 25 units/kg (2500 max)
  - **4-5.9**: 35 units/kg (3500 max)
  - **>6**: 50 units/kg (5000 max)
- **Factor Xa inhibitors (rivaroxaban, apixaban)** – Andexanet alfa, recombinant modified human Factor Xa. Cost $25000/dose, half life 5 hours. (some studies suggest that 4 factor PCC can be backup)

OUR ANTIDOTE SHELF

“The Best Physician Is Also a Philosopher”

Galen of Pergamon- 120 AD

BONUS QUESTION – TRUE OR FALSE?

- Cyanide toxicity decreases the PaO2?

REFERENCES

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