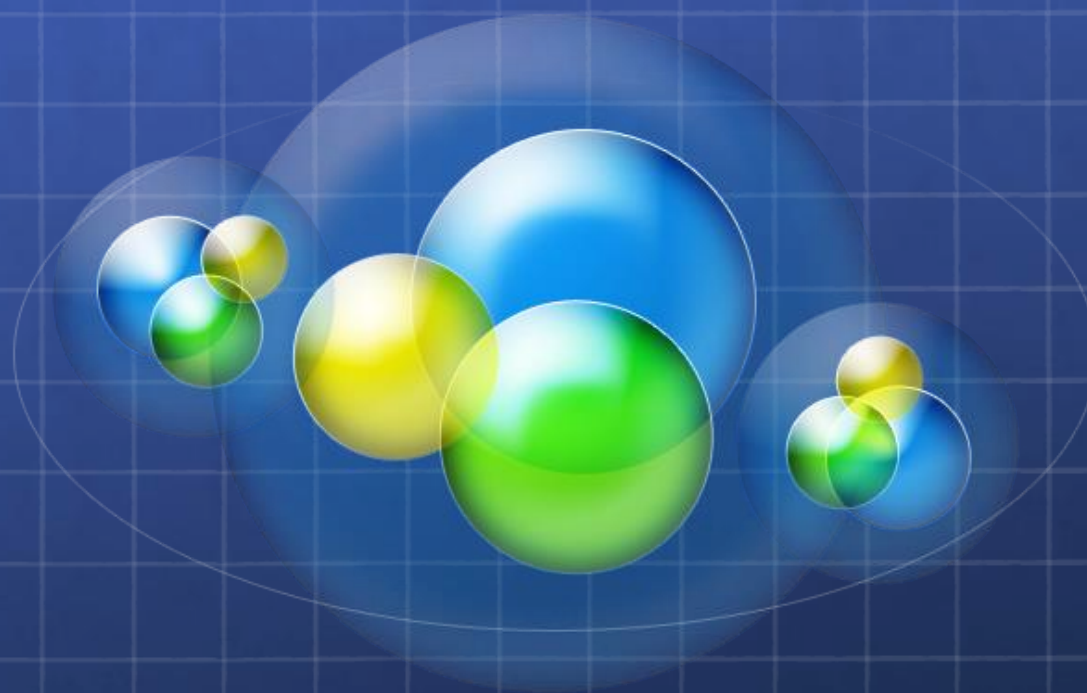


# Welcome!

**This activity has been planned and implemented in accordance with the accreditation requirements and policies of the Accreditation Council for Continuing Medical Education (ACCME) through the joint providership of Legacy Health and Oregon Emergency Medical Services for Children.**

**Legacy Health designates this live activity for a maximum of 1.0 AMA PRA Category 1 Credit(s)<sup>™</sup>. Physicians should claim only the credit commensurate with the extent of their participation in the activity.**

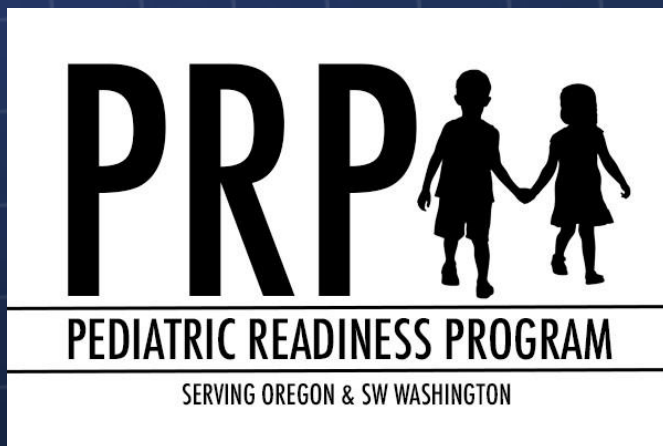


# Blue, Bluer, Bluest

**B. Zane Horowitz, M.D., FACMT**  
**Oregon-Alaska Poison Center**

# Pediatric toxicology




## Methemoglobinemia: blue, bluer & bluest




B. Zane Horowitz, M.D.  
Associate Medical Director  
Oregon-Alaska Poison Center

February 10, 2022

# Objectives

-  Describe risks of methemoglobinemia in both toddlers and teenagers
-  Identify diagnostic tests and threshold to treat
-  Identify contraindications to use of methylene blue

# CME Disclosure

-  None of the planners and faculty for this educational activity have relevant financial relationship(s) to disclose with ineligible companies whose primary business is producing, marketing, selling, re-selling, or distributing healthcare products used by or on patients.



# BLUE:

## I can't believe its not Toothpaste

- 🌐 A mother presents panic stricken complaining her daughter is blue. The mother reports that her 3-year-old had attempted to brush her teeth with teething gel about 2 hours prior to admission.
- 🌐 Initially the patient looked fine but now she appears blue-gray.

# Items that come in a tube

- 🌐 **High Fluoride Toothpaste**
- 🌐 **Steroid creams**
- 🌐 **Anti-fungal creams**
- 🌐 **Spermicides**
- 🌐 **Liniments (Methyl Salicylate)**
- 🌐 **Teething Gels**

# Brand names sometimes don't help





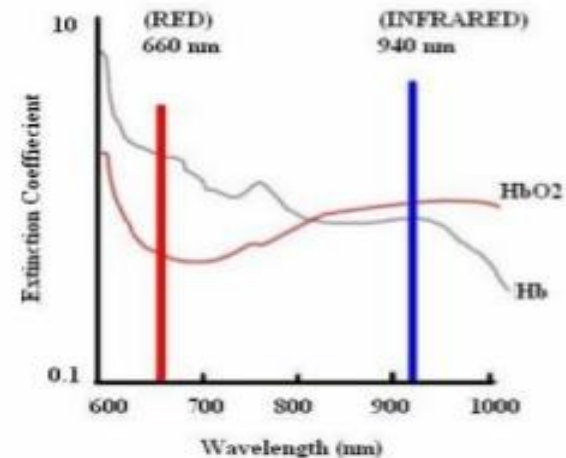
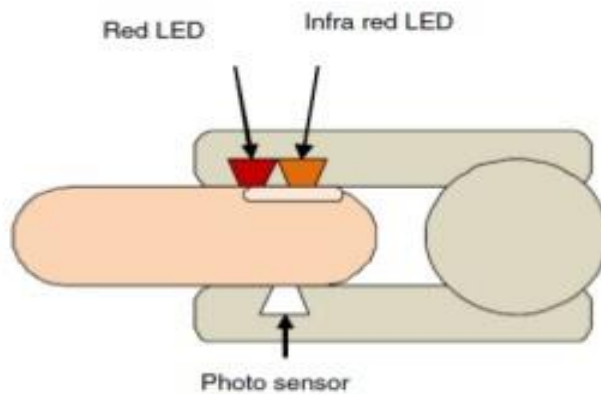
# Physical Exam

- 🌐 **Gen: Ashen gray, awake looking around room**
- 🌐 **Pulse oximetry 85%, doesn't improve with O2**
- 🌐 **VS: BP 90/50, P 130, RR 38, T 37**
- 🌐 **Lungs CTA, Heart RR no murmur**
- 🌐 **Skin: grey-blue**
- 🌐 **Neuro: awake, no focal deficit**



# Pulse Oximeter

## How does Pulse Oximeter work (part A)?



- HbO<sub>2</sub> is oxyhemoglobin which is the main carrier of blood oxygen.
- Hb is hemoglobin deprived of oxygen.

Wavelength [nm]	Extinction coefficient [ $l \cdot \text{mmol}^{-1} \cdot \text{cm}^{-1}$ ]	
	Hb	HbO <sub>2</sub>
660	0.81	0.08
940	0.18	0.29

# New Pulse OX

Measures by 7  
wavelengths:

- 🌐 Oxy Hgb
- 🌐 CO Hgb
- 🌐 Met Hgb



▶▶▶▶ boots are available in different colors!



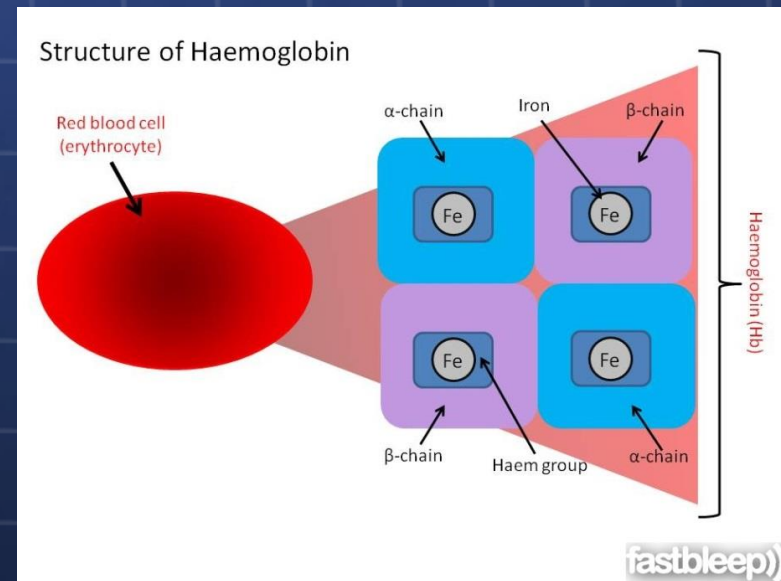
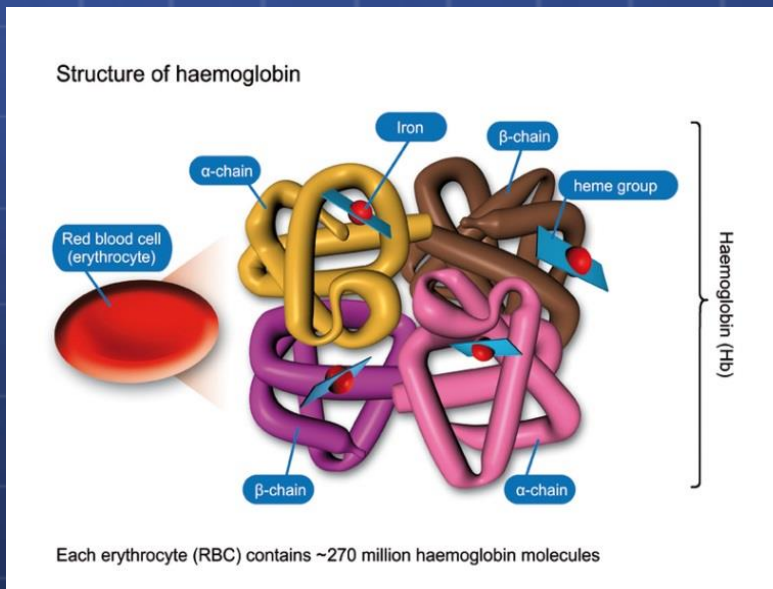


# Cyanosis

- 🌐 How many grams of deoxyhemoglobin does it take to cause cyanosis?
  - 🌐 Total Hgb is 15 gm/dl
- 🌐 5 grams/dl of deoxyhemoglobin
- 🌐 1.5 grams/dl of methemoglobin

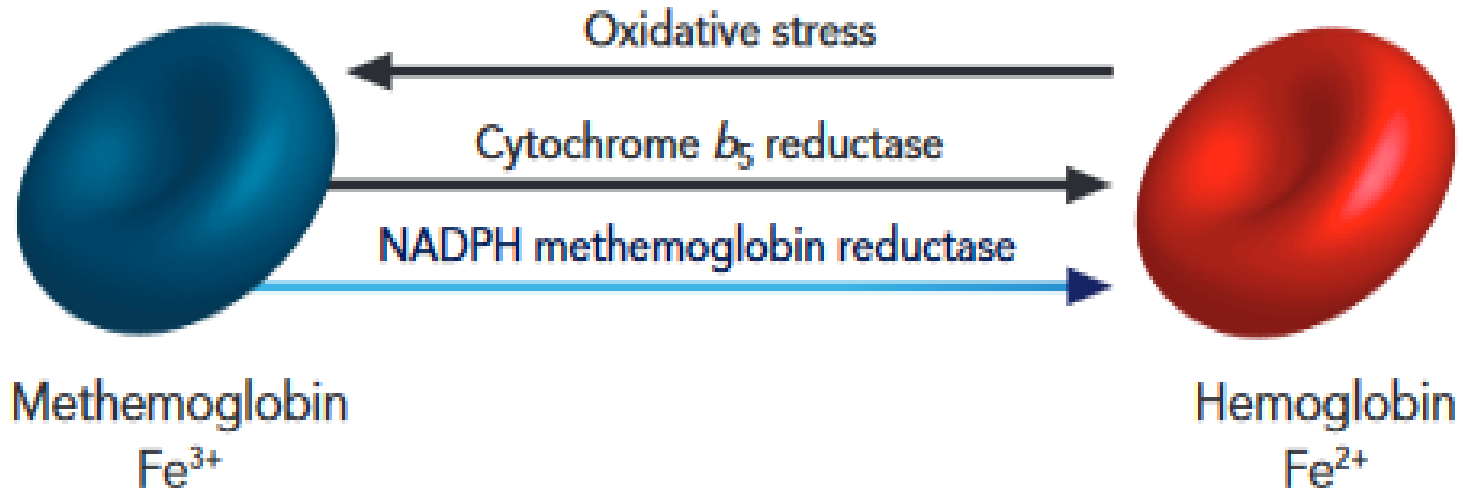


# Iron Binding Site in Hemoglobin



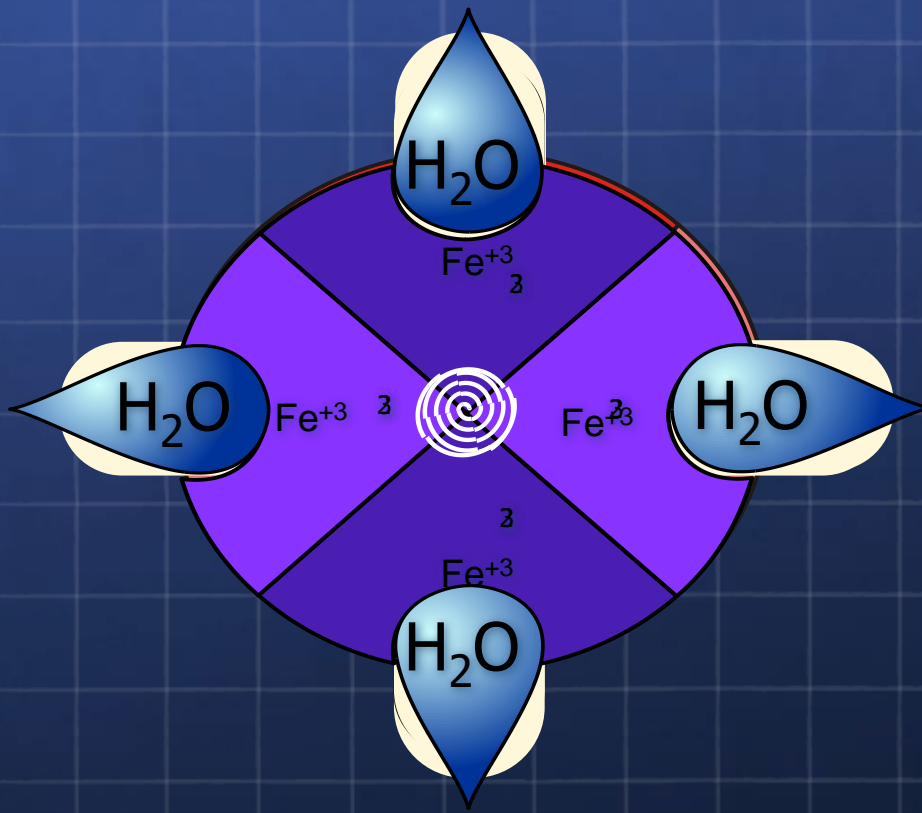
# From Red to Blue

## Methemoglobinemia Mechanism<sup>\*1</sup>



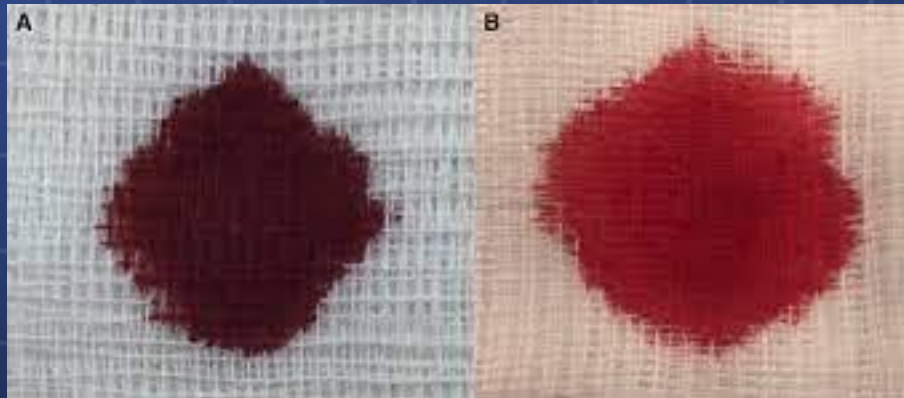
# Hemoglobin

## Methemoglobin



- Hemoglobin's ferrous iron ( $\text{Fe}^{+2}$ ) is oxidized to ferric iron ( $\text{Fe}^{+3}$ ) by nitrites.
- Oxygen ( $\text{O}_2$ ) cannot bind to methemoglobin's  $\text{Fe}^{+3}$ . Water ( $\text{H}_2\text{O}$ ) binds in oxygen's place.
- Methemoglobin cannot transport  $\text{O}_2$ .

# Just put blood on gauze



**Texts always say Chocolate Brown Blood  
but in reality looks dark burgundy colored**

# Chocolate Brown Blood



**FIGURE 1.** Normal arterial blood versus methemoglobinemia. Arterial whole blood with 1% methemoglobin (left) versus arterial whole blood with 72% methemoglobin (right)



# Pharmaceutical causes

## Local anesthetics \*

- Benzocaine

- Prilocaine

\* Lidocaine – but would have toxicity from lidocaine way before Methemoglobin occurs



## Antimicrobials

- Dapsone

- Chloroquine

- Primaquine

- Sulfonamides

- Trimethoprim

## Analgesics

- Phenazopyridine (Pyridium)

- Phenacetin

- Metoclopramide (Reglan)

- MethHGB. & SulfHGB

# Local Anesthetics

● Benzocaine: most commonly implicated (despite metered-dose spray)

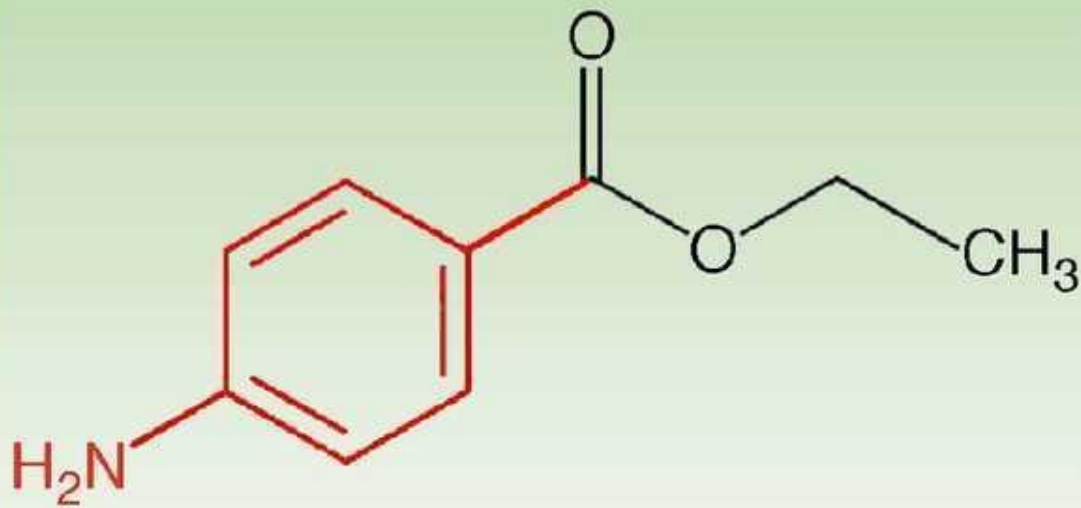
● Benzocaine is metabolized to: phenyl hydroxylamine and nitrobenzene (Both are potent oxidizers)



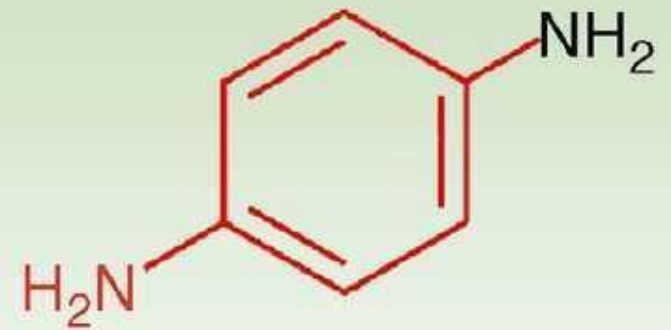
● Prilocaine is metabolized to ortho-toluidine another oxidizer

● EMLA (contains: prilocaine, tetracaine & lidocaine)





Benzocaine



Paraphenylenediamine

Actas Dermosifiliogr. 2013;104:156-8

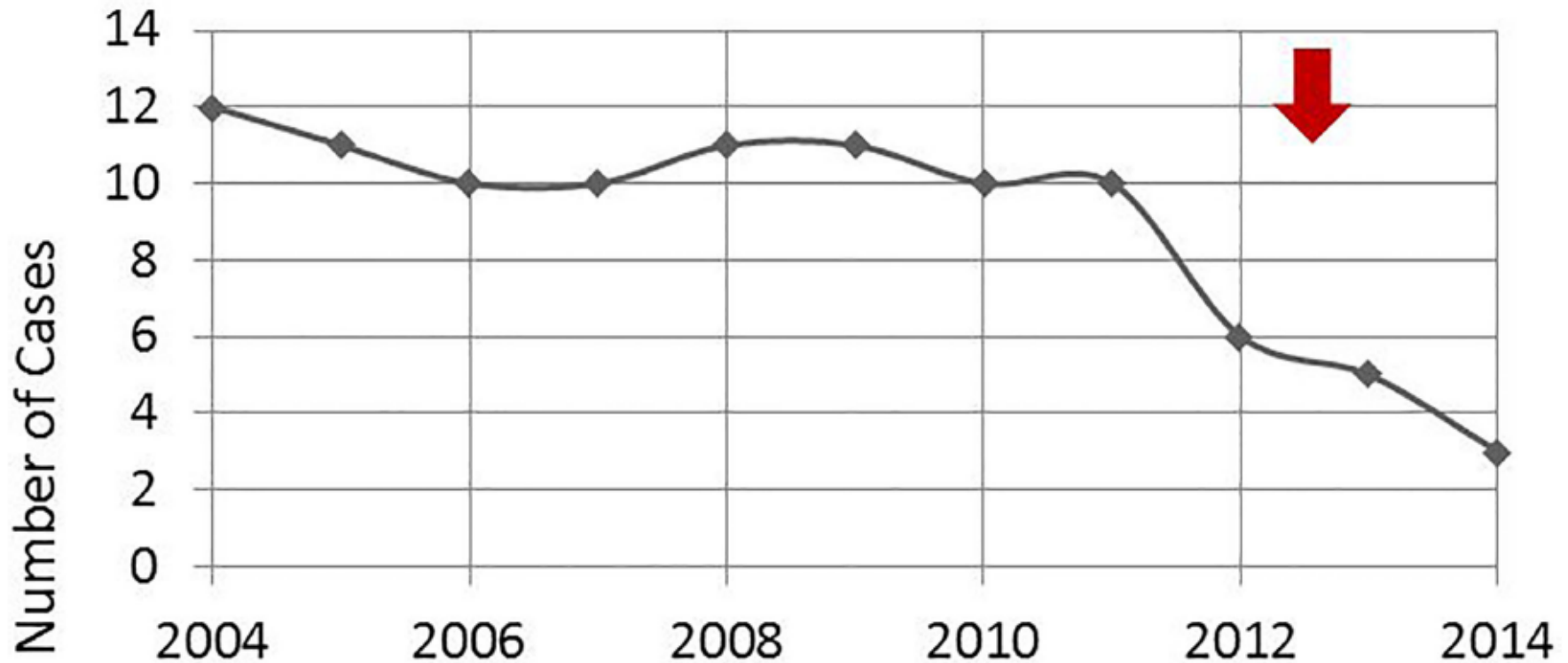
HENNA

# Pediatric Exposures to Topical Benzocaine Preparations Reported to a Statewide Poison Control System


RED ARROW is YEAR of  
FDA WARNING


Pediatric Exposures to Topical Benzocaine Preparations

*Vohra et al.*



# Methemoglobinemia: clinical features

 Symptoms related to reduced oxygen carrying capacity and delivery to tissues

 Cyanosis related to color of oxidized Hgb, not to hypoxia

 O<sub>2</sub> sat of “85%”

Methemoglobin Level (%)	Signs and Symptoms
3-15	Possibly none Pulse oximeter reads low SaO <sub>2</sub> Slate gray cutaneous coloration
15-20	Cyanosis Chocolate brown blood
20-50	Dyspnea Headache Fatigue, weakness Dizziness, syncope
50-70	Tachypnea Metabolic acidosis Dysrhythmias CNS depression, coma Seizures
>70	Grave hypoxic symptoms Death



# Treatment:

# Methylene Blue

## Indications

- Methemoglobinemia  $> 30\%$
- SX due to methemoglobinemia at lower levels:
  - dyspnea, syncope, chest pain
  - EKG changes

## Dosing

- 1-2 mg/kg IV  
(0.1 ml/kg of 1% solution)



# Methemoglobinemia: treatment



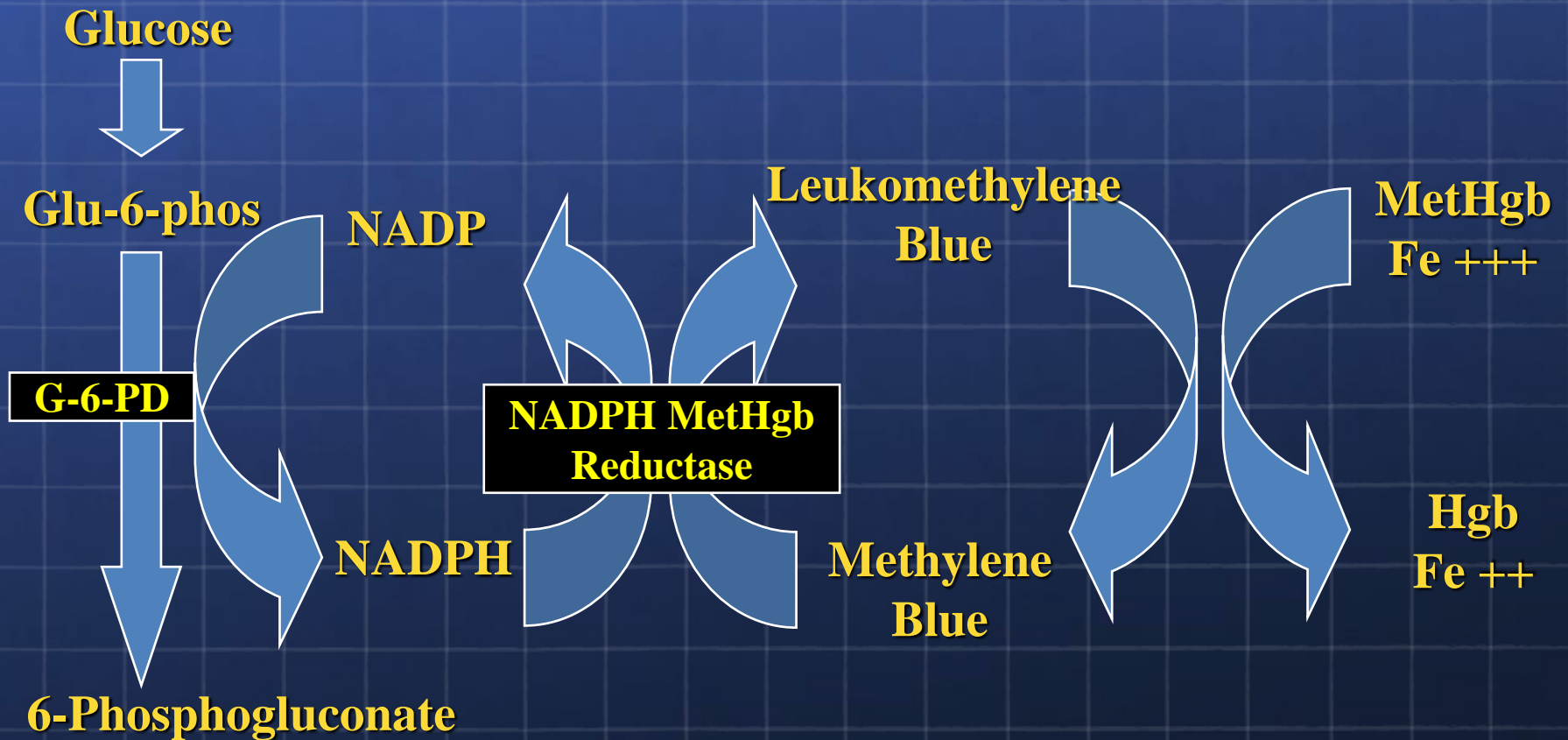
## Methylene blue

Reduced to leukomethylene blue by:  
NADPH and NADPH methgb reductase

G6PD is essential for generation of NADPH  
and therefore is essential for methylene blue  
to function

Leucomethylene blue Increases the  
conversion of Methgb to Hgb

# Methylene Blue



# Methylene blue

- Contraindications (relative):

- G6PD deficiency
- Renal failure

- Adverse effects:

- GI upset, headache, dizziness
- Methemoglobin induction
  - Excessive doses ( > 7 mg/kg) – direct oxidation of Hgb causes Methgb
- Hemolysis
  - Really excessive doses (> 15 mg/kg) – particularly in neonates



# Methylene Blue: Treatment Failure

Differential diagnosis of failure of methylene blue to work

- G-6-PD deficiency
- Congenital Methemoglobinemia
- Hemoglobin M
- Sulfhemoglobinemia



# Methemoglobinemia: Diagnosis

## Clinical TRIAD:

- Cyanotic appearance, sometimes out of proportion to symptoms
- “chocolate brown” blood
- Pulse oximetry 85%
- Laboratory Dx: co-oximetry
  - ABG analyzer
  - False positives : Sulfhgb



**FIGURE 1.** Normal arterial blood versus methemoglobinemia. Arterial whole blood with 1% methemoglobin (left) versus arterial whole blood with 72% methemoglobin (right)

# Bluer: Mono Mistake

- 🌐 16 yo male has abd pain for 2 weeks with Nausea.
- 🌐 Sent to ED for CT scan > right side abd mass.
- 🌐 Suspected Burkitt's Lymphoma.
- 🌐 WBC = 7.6 Uric acid 11.1 mg/dl Cr 1.6 mg/dl
- 🌐 STARTED on RASBURICASE for prevention of tumor lysis syndrome and hyperuricemia.

# Rasburicase

Recombinant urate oxidase enzyme

- 🌐 Sometimes started on clinical suspicion alone in patients with elevated uric acid.
- 🌐 Tumor lysis syndrome is its main indication:
  - 🌐 Release of nucleic acids, potassium, phosphorus with extensive tumor cell necrosis
  - 🌐 LAB criteria: Urate  $> 8$ ; Phosphorus  $> 4.5$ ; K  $> 6$
- 🌐 Prevents AKI by creating allantoin instead of urate crystals.

Tumor cell lysis



Release of DNA



Hyperkalemia

Purines

Phosphorous

Hypocalcemia

Allopurinol

Hypoxanthine/Xanthine

Ca-Phos Precipitation

Ca X Phos Product ~60

Xanthine Oxidase

Uric Acid

(low urinary excretion)

Urate nephropathy

(low urine pH)

Ca-Phos nephropathy

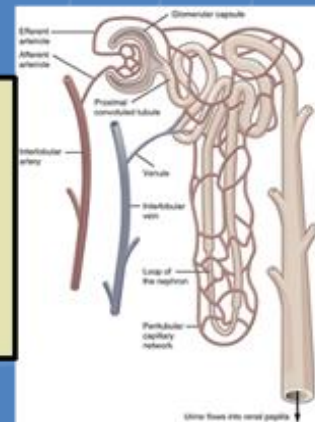
(high urine pH)

Rasburicase

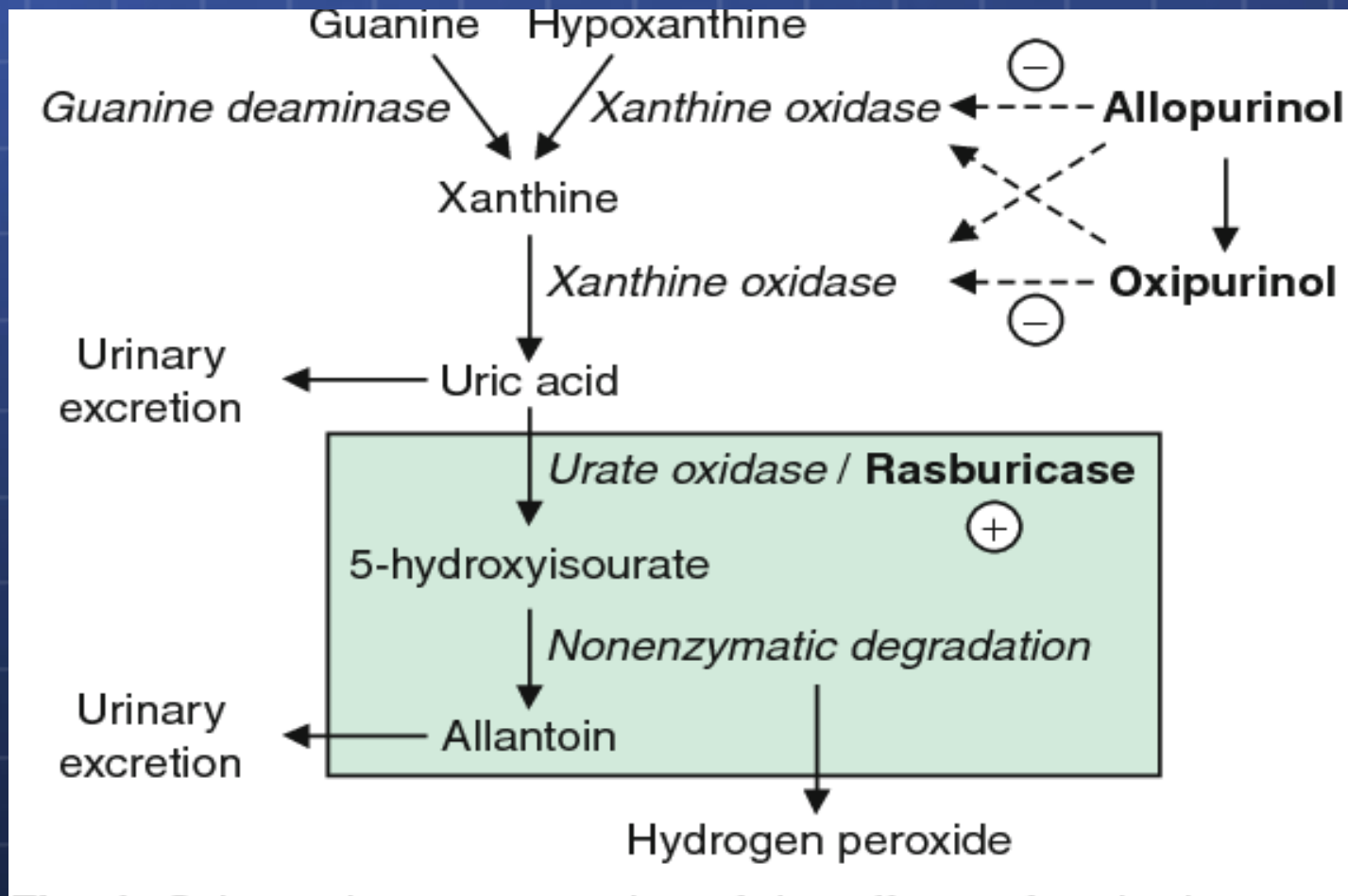
Uricase

Allantoin

(High urinary excretion)



# Rasburicase: Mechanism of Action



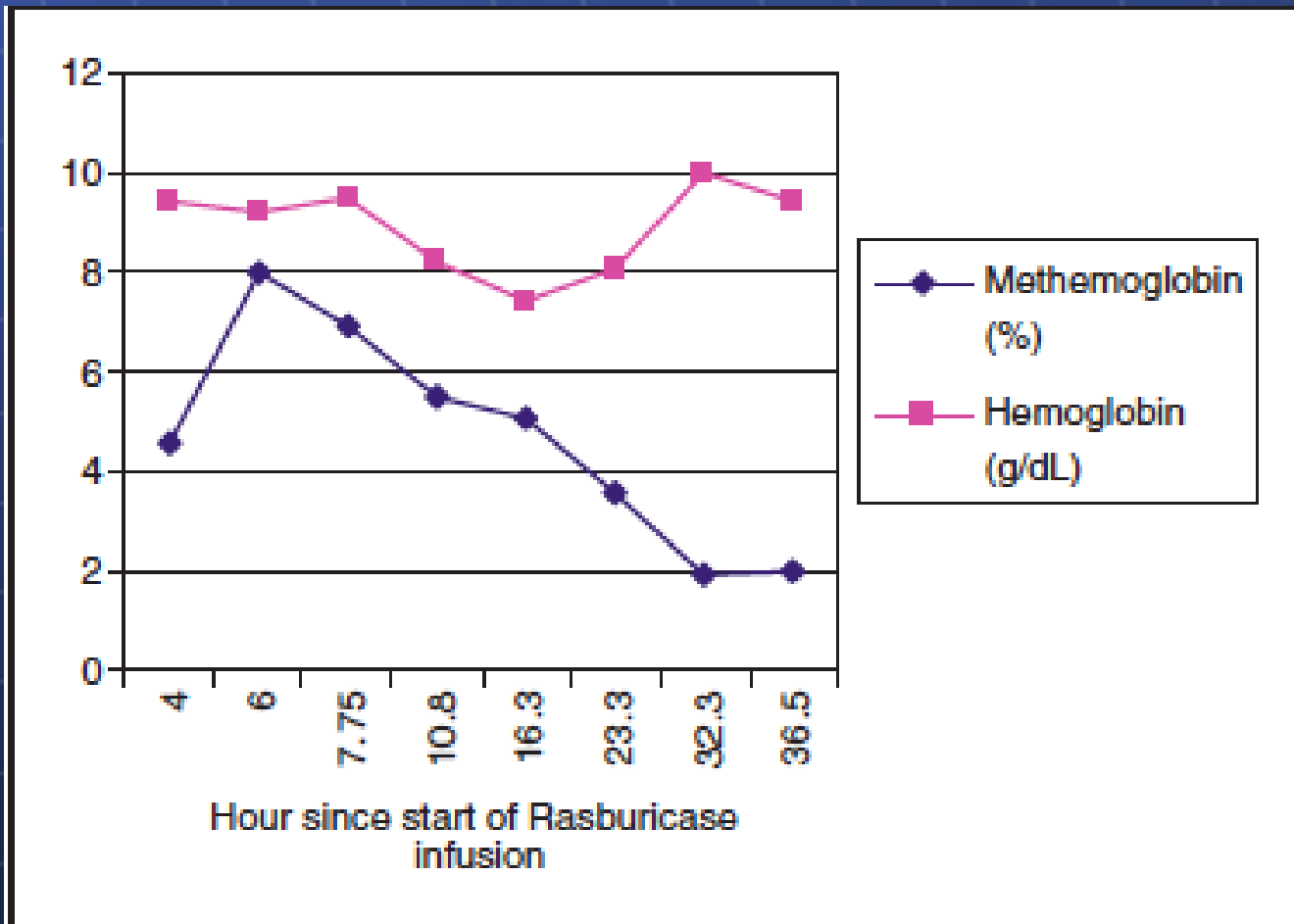
Allantoin is water soluble and thus reduces risk of AKI



# Tumor Lysis Syndrome Treatment

- 🌐 GIVEN 14 mg IV RASBURICASE
- 🌐 24 hours later: looked grey, Sats 87%
- 🌐 Otherwise alert and normal VS
- 🌐 Placed on 15 liter NRB mask O<sub>2</sub> > No change

# Methemoglobin

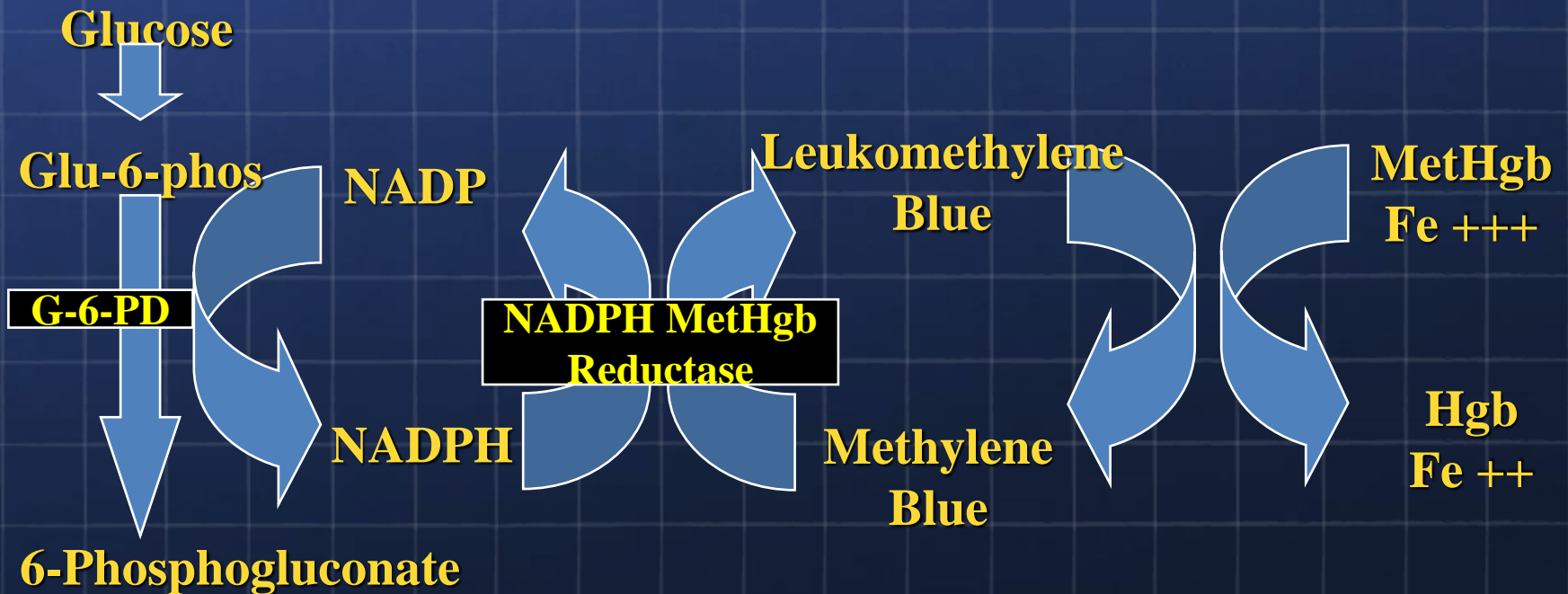


# Would you Use Methylene BLUE?



# Genomics

- RASBURICASE induces METHGB in predominantly G6PD deficient patients.
- Methylene Blue won't work if leukomethylene Blue can't be generated.



# OPTIONS ?

## 1. Watch and Wait

- Methemoglobin level is below threshold to Rx (typical cases in literature less than 20% Methgb).
- Don't be "persuaded" by sat monitor.

## 2. Vitamin C

- Might stimulate alternative pathway.
- Low toxicity; occ case reports.

## 3. Transfuse RBCs

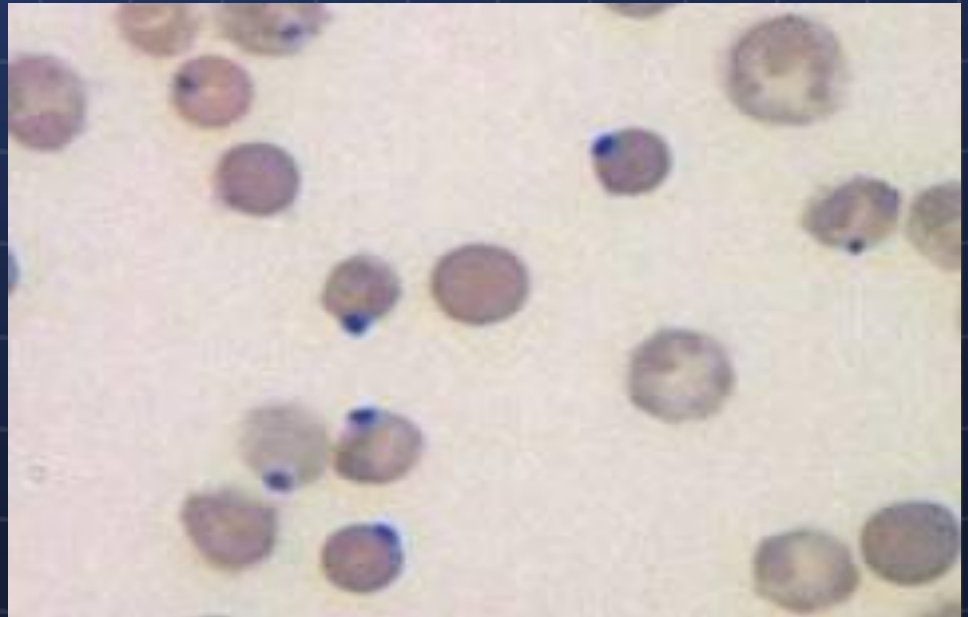
- Would reserve for severe case or hemolysis.



# Oxidant Stress

- 🌐 Methemoglobinemia and Hemolysis are 2 ends of the spectrum of OXIDANT STRESS.
- 🌐 Heinz body\* Hemolytic anemia may occur with any drug induced methemoglobinemia.

\* Denatured HGB

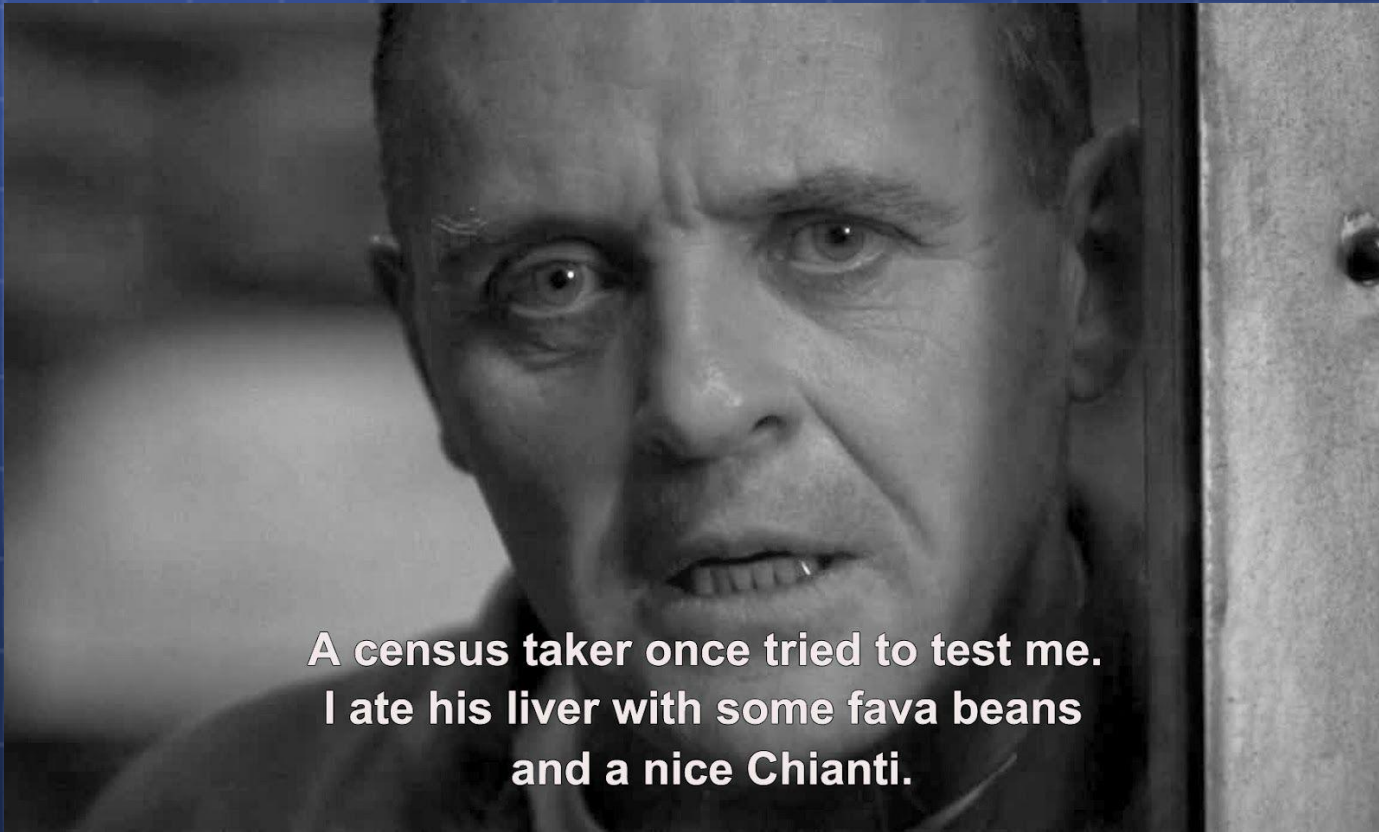


# What Should have been Done?

## BLACK BOX WARNING:

- Screen high risk patients for G6PD activity BEFORE starting RASBURICASE.
- DO NOT administer if known to be G6PD deficient.
- Stop RASBURICASE if methemoglobinemia occurs.

# Fava Bean G6PD



A census taker once tried to test me.  
I ate his liver with some fava beans  
and a nice Chianti.

# G6PD Deficiency

- 🌐 *G6PD* gene located on chromosome Xq28.
- 🌐 Males are hemizygous for one *G6PD* allele, making them more susceptible to this X-linked disorder.
- 🌐 Females randomly inactivate one X chromosome during development, resulting in a mosaic expression of either X chromosome.
- 🌐 400 million people worldwide; prevalence of 5%.
- 🌐 Protects against malaria, higher prevalence (> 25%) in countries where malaria once was.

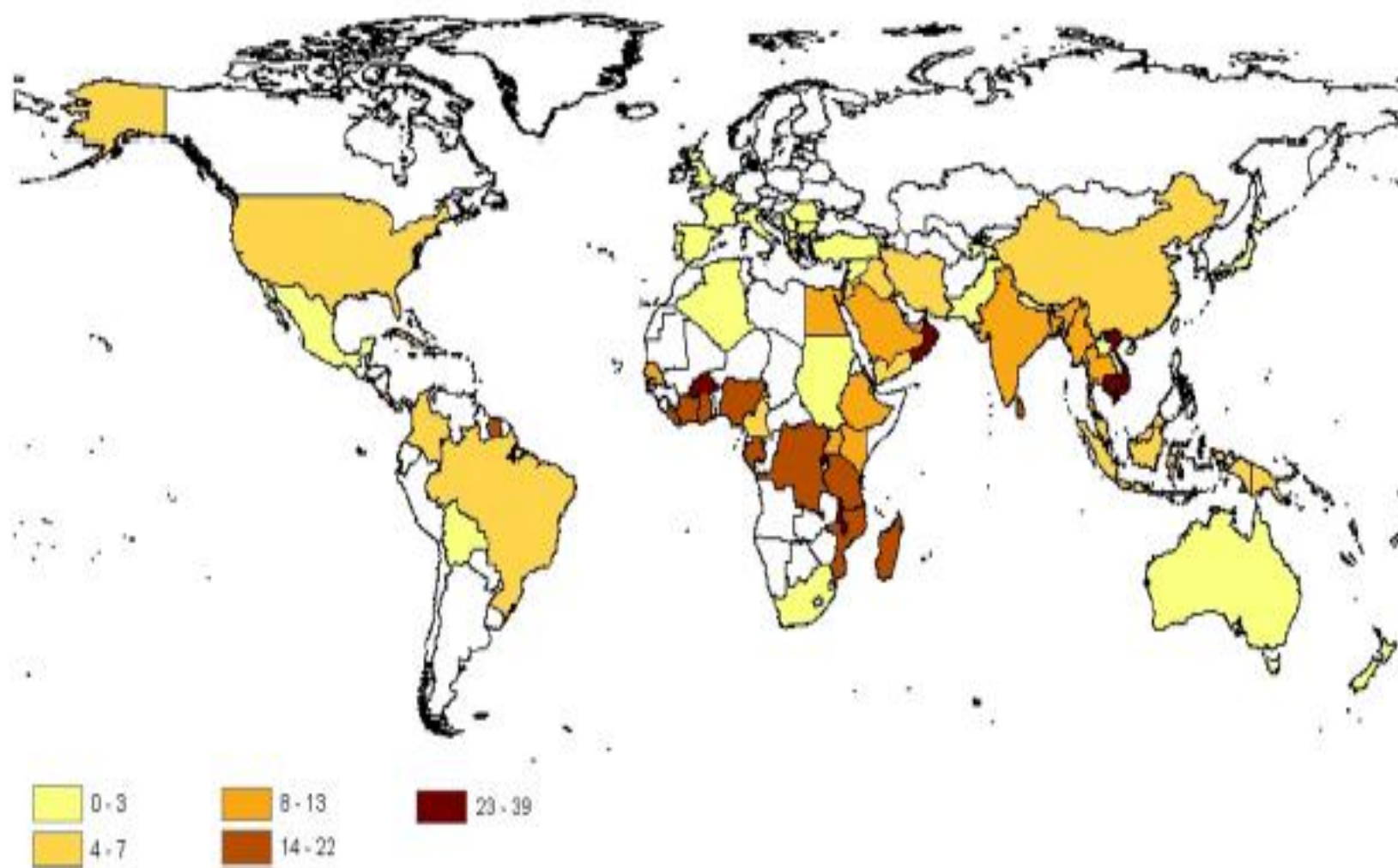
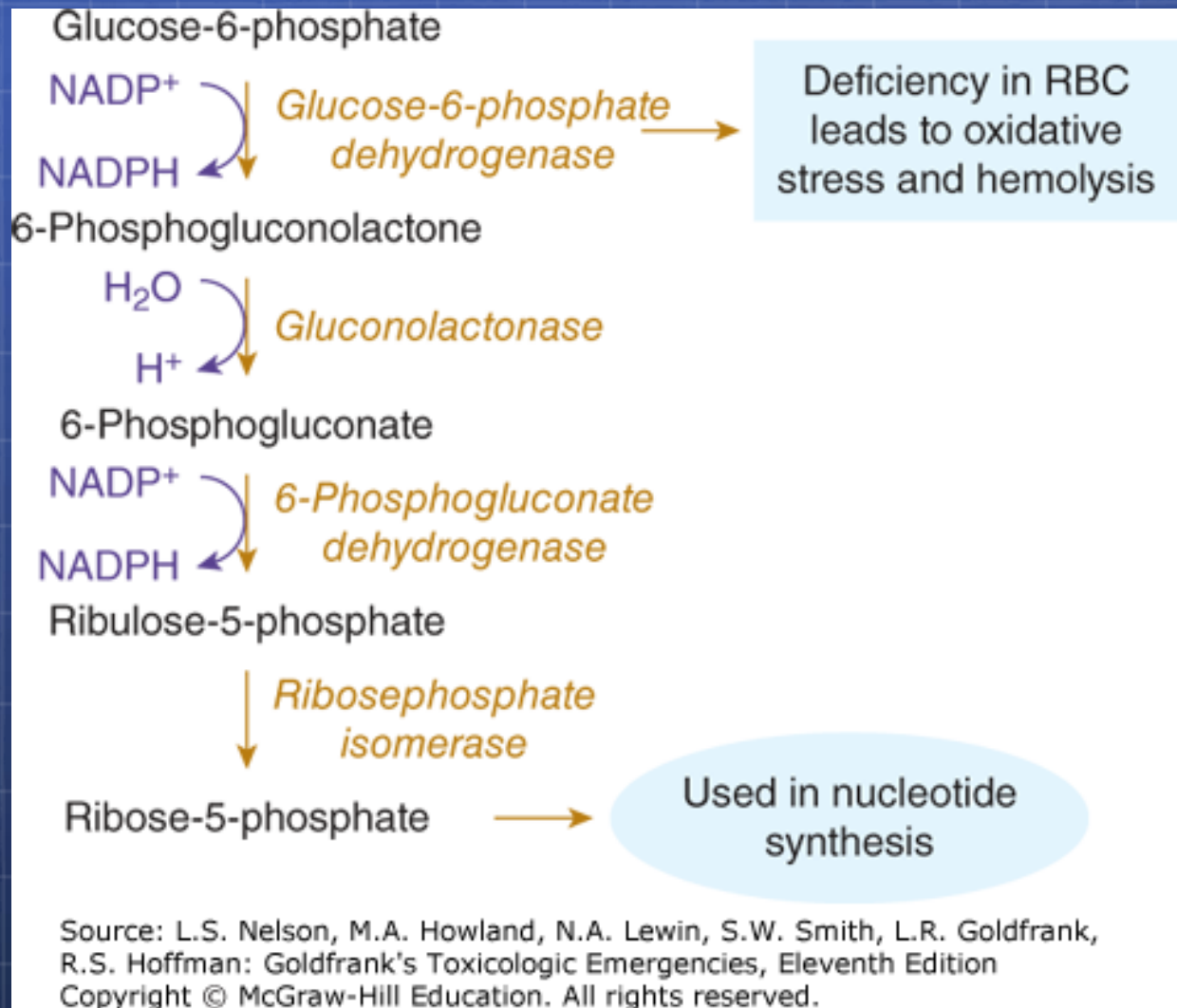


Fig. 1. Crude average G6PD prevalence as a percentage across countries from included studies.





The oxidation reactions of the hexose monophosphate shunt are an important source of **nicotinamide adenine dinucleotide phosphate (NADPH)** for reductive biosynthesis and for protection of cells against oxidative stress.

Deficiency of glucose-6-phosphate dehydrogenase, the first enzyme in the pathway, may result in red blood cell (RBC) hemolysis during oxidative stress.

# Outcome

- 🌐 **BIOPSY showed the mass to be lymph nodes from MONONUCLEOSIS.**
- 🌐 **Methemoglobin resolved (Pt actually given packed RBCS – but not clear he needed it).**
- 🌐 **Uric acid dropped to 0.5 mg/dl.**
- 🌐 **SHOULD BE CONSIDERED G6PD Deficient but wait 3 to 6 months to test.**

**Table 3.** Reported cases of rasburicase-induced methemoglobinemia and hemolytic anemia.

Source	Age/ Gender	Race	Dx	Peak MethHb (%)	Uric acid (mg/dL)	Rasburicase dose
Pui et al. [2]	12 M	AA	ALL	15.6	Unk	100 U/kg
Bosly et al. [3]	Pediatric	Unk	None	Unk	Unk	0.2 mg/kg
Browning et al. [4]	50 M	AA	None	9.8	14.6	0.21 mg/kg
Kizer et al. [5]	Adult	Unk	Mycosis fungoides	14.9	13.6	0.2 mg/kg
Kizer et al. [5]	Adult	Unk	DLBCL	21.5	14.0	0.2 mg/kg
Bhat et al. [6]	12 M	Laotian	T-ALL	10.1	22.1	0.2 mg/kg
Borinstein et al. [7]	14 M	Cambodian	Burkitt's lymphoma	12.6	10.8	0.2 mg/kg
Bauters et al. [8]	6 M	Caucasian	ALL	17.3	Unk	0.2 mg/kg
Ng et al. [9]	16 M	AA	Burkitt's lymphoma	8.0	11.1	0.2 mg/kg
Bucklin et al. [10]	62 M	AA	CLL/SLL	19.3	12.5	0.04 mg/kg 2
Cheah et al. [11]	46 M	Mauritian- Chinese	CLL	7.2	Unk	0.07 mg/kg
Sonbol et al. [12]	52 M	AA	Multiple myeloma	12.9	16.1	6 mg
Roberts et al. [13]	43 F	AA	Metastatic colon cancer	6.3	11.6	6 mg
Roberts et al. [13]	70 F	AA	Multiple myeloma	13.0	16.0	6 mg
Bontant et al. [14]	5 M	Congolese	ALL	20.0	3.6	0.2 mg/kg
Our case	56 M	AA	CML	9.5	11.8	0.03 mg/kg

# BLUEST:

## Teenage Sodium Nitrite Case

- 17-year-old female in a suicide attempt took 1 tablespoonful of sodium nitrite used for food preservation.
- Friend called 911 within minutes.



# Clinical Course

- Upon EMS arrival, the patient was not responding to commands, with her head and upper extremities held in flexion.
- Pupils were 4mm bilaterally.
- Foam was coming from her mouth.
- There was perioral cyanosis.
- Lung sounds were clear.
- Initial VS: HR 69. BP 82/33 RR 15 sat 74%
- EndtidalCO<sub>2</sub> (EtCO<sub>2</sub>) of 19mmHg.



# Timeline of events

TABLE 2. A timeline of events presented in this case report

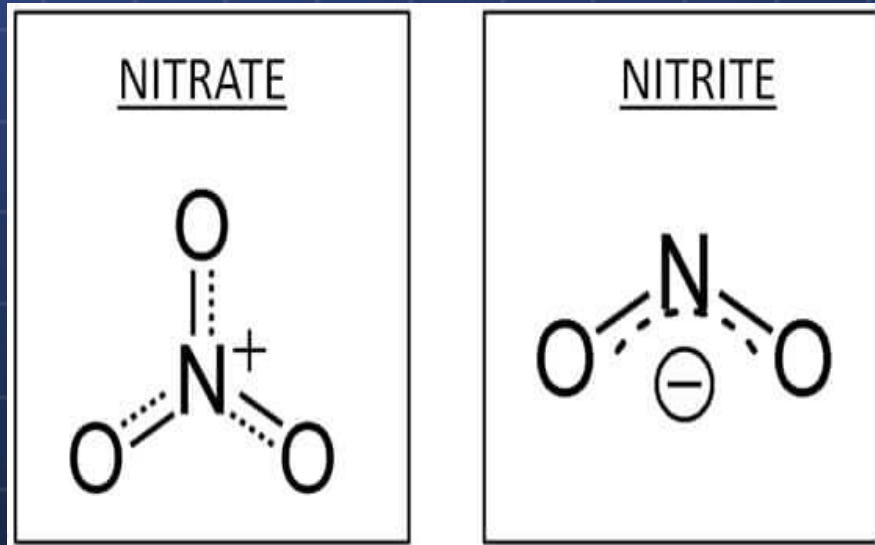
Time	Event
15:16	911 call
15:23	EMS arrival to patient
15:24	Poison control center contacted
15:37	Endotracheal intubation performed
15:46	Transportation initiated
15:52	Push dose epinephrine administered
15:54	Pulses lost and CPR initiated
16:07	Transfer of care to emergency department
16:20	Methylene blue dose #1
16:39	Methylene blue dose #2
16:57	Methylene blue dose #3
17:14	Termination of resuscitation

Also transfused 2 U RBCs

# Chemical Causes

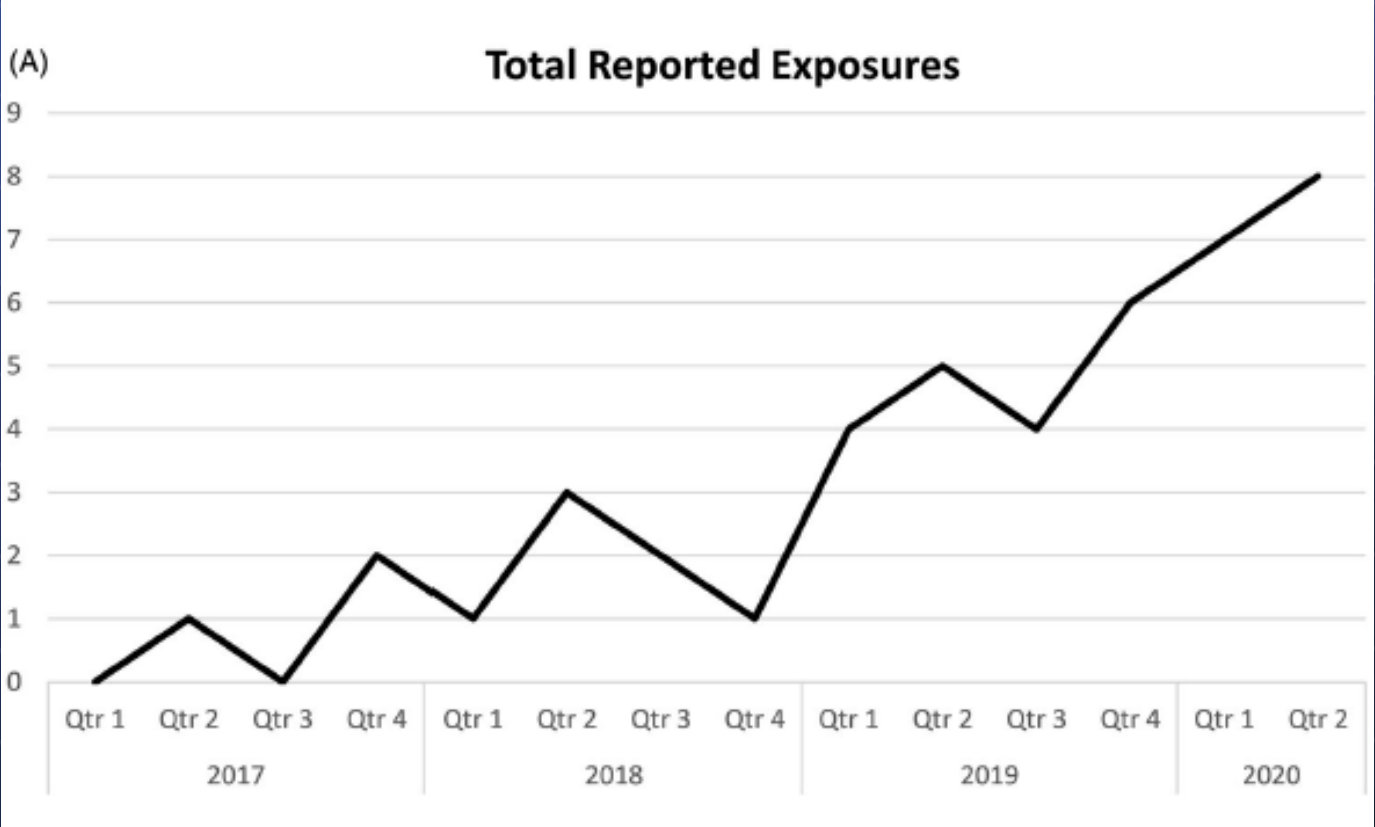
## 🌐 Nitrites and nitrates

- 🌐 Amyl nitrite
- 🌐 Butyl nitrite
- 🌐 Sodium nitrite



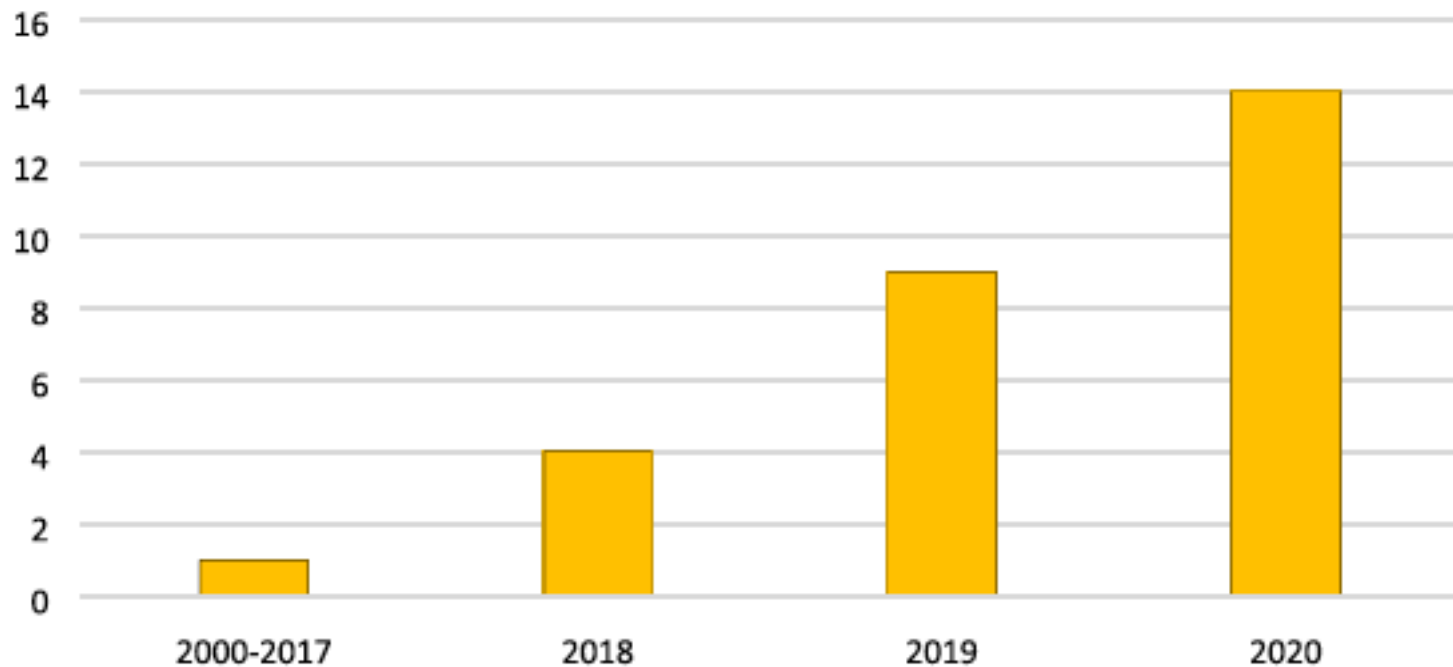
# Rising incidence and high mortality in intentional sodium nitrite exposures reported to US poison centers

Sean D. McCann<sup>a,b</sup> , Marit S. Tweet<sup>b,c</sup> and Michael S. Wahl<sup>b,d,e</sup>



# Canada Trend

Number of Methemoglobinemia deaths by year



# NY Times Expose

## Where the Despairing Log On, and Learn Ways to Die

 By Megan Twohey and Gabriel J.X. Dance

Dec. 9, 2021

It has the trappings of popular social media, a young audience and explicit content on suicide that other sites don't allow. It is linked to a long line of lives cut short.

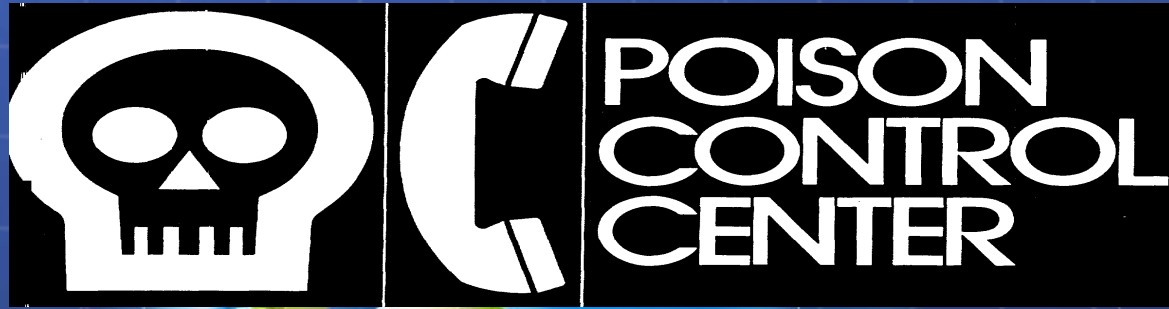


# What to do in severe cases?

- 🌐 Notify Poison Center so receiving Hospital can get Methylene Blue to the ER for pt's arrival.
- 🌐 Repeat each dose of Methylene Blue every 5 min.
- 🌐 RBC transfusion, and if needed exchange transfusion.
- 🌐 Continue CPR/ACLS for longer times.

# References

- 🌐 SEVERE METHEMOGLOBINEMIA LINKED TO GEL-TYPE TOPICAL BENZOCAINE USE: A CASE REPORT, Chung NY, J Emerg Med, 2010, 38 (5); 601–606.
- 🌐 METHEMOGLOBINEMIA INDUCED BY RASBURICASE IN A PEDIATRIC PATIENT: A CASE REPORT AND LITERATURE REVIEW, Ng JS, J Onco Pharm Practice, 2011; 428-431.
- 🌐 FATAL SODIUM NITRITE POISONING: KEY CONSIDERATIONS FOR PREHOSPITAL PROVIDERS, Neth MR, Prehospital Emerg Care, 2021, 25:6, 844-850.



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## NADH (nicotinamide adenine dinucleotide)

NADH - is a coenzyme that carries electrons from one reaction to another. It starts out as (NAD<sup>+</sup>), it accepts electrons from other molecules, and becomes reduced to NADH (NAD with a H (hydrogen ion + 2 electrons))

