Blues Review: The Unusual Blue Patient

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Learning Objectives

- Recognize/Distinguish various disease conditions associated with blue skin color
- Define/describe laboratory findings associated with blue skin color
- Compare normal and abnormal hemoglobin synthesis and other pathophysiological findings in Methemoglobinemia
- Describe/recognize drugs which are common causes of acquired Methemoglobinemia and Argyria

The Usual Blues –hypoxemia

- Low level of oxygen in the blood, esp the arterial blood
- Leads to hypoxia –low level of oxygen in the tissues
- Heart or Lung related
- Anemia with Hemoglobin level 3-5 gm/dL –will show cyanosis

Cyanosis -a bluish discoloration of the skin resulting from poor circulation or inadequate oxygenation of the blood

Central
- Congenital heart disease
- Bronchospasm; hypoventilation
- Intrapulmonary fistulas; shunts
- High altitude
- Methemoglobinemia/ Sulphemoglobinemia

Peripheral
- Low cardiac output
- Arterial or venous obstruction
- Cold temperatures

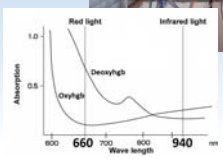
with 5 g/dL of deoxygenated hemoglobin

Normal ABG values

Measurement	Normal Arterial values	Clinical Significance
pH	7.35-7.45	Indicates acid base balance
pCO_2	35-45 mm Hg	Indicates adequacy of alveolar ventilation; represents respiratory component of acid-base balance
HCO_3^-	22-26 mEq/L	Bicarbonate level; indicates metabolic component of acid-base balance
PaO_2	80-100 mm Hg	Partial pressure of Oxygen; represents Oxygen dissolved in plasma
SaO_2	96-98%	Saturation of hemoglobin with Oxygen

Pulse Oximetry



- Non-invasive method for monitoring a patient's oxygen saturation. (SpO_2) - (like the SaO_2 in ABG but indirectly measured)
- Two wavelengths –one red and one infrared through a transluscent part of the body to a photodetector
- Measure the changing absorbance at each wavelength in pulsing arterial blood
- Pulse oximetry becomes unreliable when saturations fall below 70-80%.
- Caution!

4 unusual Blue medical conditions

- Pseudochromhydrosis
- Drug induced
- Argyria
- Methemoglobinemia

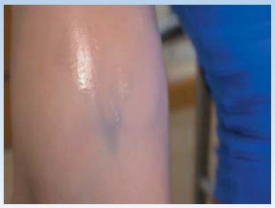
1.The blue girl

- A 17 year old female is sitting at lunch with her friends. "your face is turning blue." She does not feel unwell but is alarmed. She goes home and sees it on her neck and the back of here hand. She had been wearing a new pair of jeans without washing them first.
- She takes a shower and the blue is gone. It must've been the jeans.
- Two weeks later, she is in gym class and the instructor calls her over; asks if she if feeling alright because her face looks blue. She can also see the pale blue discoloration on her arms and chest. She is taken to the ER by a teacher.
- She is seen right away and put on oxygen for her cyanosis.

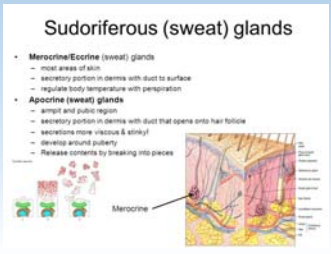
In the hospital

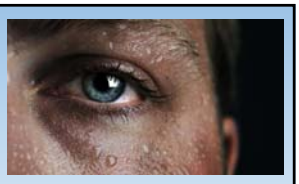
- She gets lots tubes of blood drawn, EKG, CT, ultrasound. All negative. She is sent home.
- This happens again and again
- Heart and lungs normal
- ABGs normal
- Skin biopsy is normal
- Blue color remains
- Consulted Rheumatology – Full workup was negative

Maybe it's ON the skin; not IN the skin


Sweat





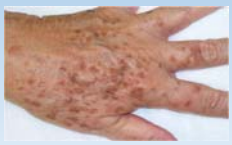

Colored Sweat

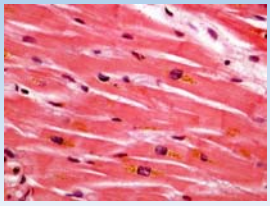
- Apocrine chromohidrosis
- Eccrine chromohidrosis
- Pseudochromohidrosis

Apocrine Chromhidrosis

- "Colored sweat"
- Rare
- perspire a pigmented sweat from apocrine glands –facial, axillary, areolar,
- Lipofuscin, made from the breakdown products of blood –"wear and tear" pigment – is responsible
- Varying Oxidation –different colors –yellow, green, blue, black
- Treatment – only temporary- Topical capsaicin, Botox injection – decreases amount of sweat –helps
- Never cured

Lipofuscin





Eccrine Chromhidrosis

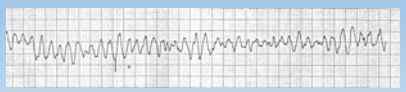
- RARE
- water soluble pigments are excreted via the eccrine glands
- Ingestion of certain antimalarial drugs and dyes or hyperbilirubinemia
- Mostly on palms and soles

Pseudochromhidrosis

- Sweat produced is clear, but interacts with something on the skin – bacteria, dyes, drugs that causes it to turn blue
- The Blue Girl
- Corynebacterium, Serratia, Bacillus, Piedra, Malassezia fufur
- Treatment – Systemic and Topical Antibiotics;- erythromycin (Corynebacterium); Cipro, cefacpene. Sulfa/trimethoprim (serratia)
- Hibiclens wash

2. Drug induced hyperpigmentation
Amiodarone

Amiodarone



- Used to treat arrhythmias, atrial fibrillation, ventricular tachycardia and fibrillation
- Class III antiarrhythmic; prolongs myocardial cell-action potential duration and refractory period, and causes noncompetitive antagonism of α- and β-adrenoceptors
- Advise to avoid prolonged sunlight exposure and to use sun-barrier cream or protective clothing.

3. Argyria/Argyrosis

Medical uses of silver

- Antimicrobial/bacteriostatic properties – 4 mechanisms:
  - Cell membrane binding
  - Electron transport chain inhibitor
  - DNA/RNA replication
  - Inhibitor of protein functional precursors
- When exposed to aqueous environment, elemental silver becomes oxidized and forms silver cations
- The cation is responsible for the desired antimicrobial activity (and undesired toxicicity)
- Used for treatment of Gonorrhea and Syphilis (before penicillin) and "nervous disorders"

ARGYROL

http://www.argyrol.com/agprotein.phtml

Opthalmia Neonatorum

- Common cause of blindness in newborns –infection via passage through the birth canal
- Gonorrhea/syphilis
- Silver nitrate drops/ointment used in newborn's eyes to prevent blindness (even after antibiotics were in wide use)

20th century Treatment

- Found in many drug preparations
- Eye drops in new born eyes
- Allergy medicines
- Skin treatments
- Anti smoking lozenges

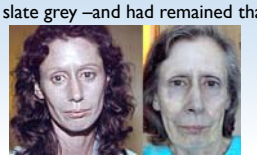
Argyria

- Prolonged contact with silver –ingested, topical, dental, industrial exposure
- Very little info on how much is too much – varies
- Skin turns light grey to dark blue. PERMANENT
- Concern raised in the 1930's about safety issues –but mostly ignored

Rosemary Jacobs

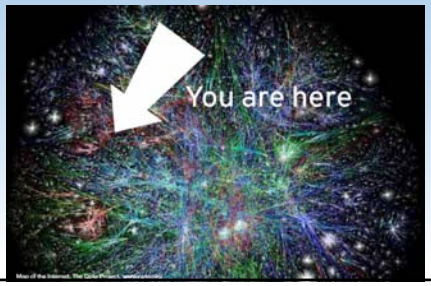
- Allergy drops
- 1953 -11 year old girl was given allergy drops by her physician for intermittent use.
- The drops were made at the local pharmacy
- 3-4 years later –her skin was slate grey –and had remained that way for the rest of her life

http://rosehttp://rosemaryjacobs.com/msp.html



1990's New wave of colloidal silver promotion on the internet

- Rosemary Jacobs influential voice in the fight against silver in medications
- FDA declares that colloidal silver can not be included in an over the counter drugs in 1999



What happens?

- Silver is no longer marketed as a drug; but as a dietary supplement – NOT regulated by the FDA!!!
- Internet claims that it is effective against over 600 diseases including AIDS, cancer, arthritis, leprosy, anthrax, acne…..

Medical uses of silver today

- Silver containing compounds are standard in burn wound care and becoming common in other wounds
- films, foams, alginates, salts, hydrogel, creams, etc.
- SSD, Silver sulfadiazine
- Elemental silver –Silver atoms Ag^0 lose an electron and become positively charged Ag^+ when comes in contact with liquid
- Multiple sites of antimicrobial action, resistance does not develop
- Local coloration but not systemic

International Consensus Statement

- http://www.woundsinternational.com/
- Wounds International, 2012
- "Appropriate Use of Silver Dressing in Wounds" Expert Working Group Consensus
- The major roles for antimicrobial dressings such as silver dressings in the management of wounds are to:
  - reduce bioburden in acute or chronic wounds that are infected or are being prevented from healing by microorganisms
  - act as an antimicrobial barrier for acute or chronic wounds at high risk of infection or re-infection
- Many RCT showing effectiveness-various wound types and dressings

BOX 5: When not to use silver dressings

- In the absence of signs of localised (overt or covert), spreading or systemic infection
- Clean surgical wounds at low risk of infection, eg donor sites, closed surgical wounds
- Chronic wounds healing as expected according to comorbidities and age
- Small acute wounds at low risk of infection
- Patients who are sensitive to silver or any of the dressing components
- Wounds being treated with enzymatic debridement
- During pregnancy or lactation
- When contraindicated by the manufacturer, for example, some manufacturers recommend that their silver dressings are not used during magnetic resonance imaging (MRI), or on/near body sites undergoing radiotherapy

But also,

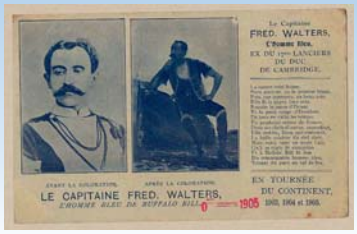
- https://timothytrespas.wordpress.com/2015/05/03/a-colloidal-silver-guide/
- *Human beings, in record numbers, are becoming Victims of secret human experimentation, mind control, gangstalking, remote neural connectivity w/Artificial Intelligence, covert drugging w/LSD, Microwave Directed Energy Weapon torture, Morgellons Nano-machines infection, and worse. Media will not report on: Mind Control & Murder: Millenial HOLOCAUST by the NEW World Order. Illuminated darkness…!*

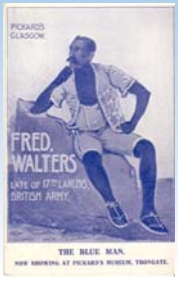
Some other (in)famous people with Argyria…

Paul Karason "Papa Smurf"

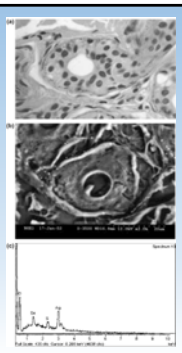
Stan Jones

Captain Fred Walters



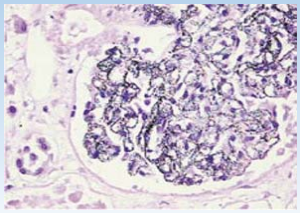


Silver deposition & Scanning EM of granules

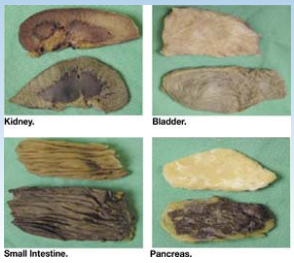


Clinical and Experimental Dermatology, 28, 254–256

Silver deposition in glomerulus

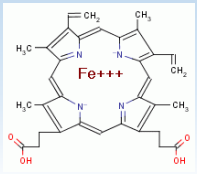


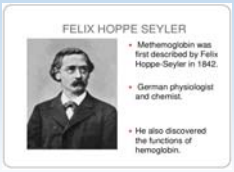
Silver deposits - Autopsy



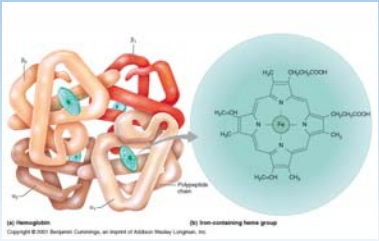
4. Methemoglobinemia

- The presence of increased Methemoglobin in the blood >1%





Hemoglobin

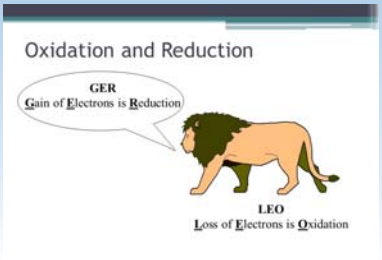


Hemoglobin - 4 heme groups with each containing iron in ferrous state (Fe2+)

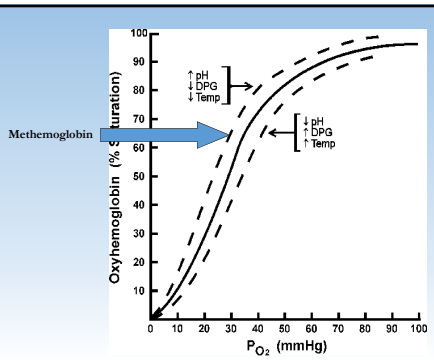
Background

- It is this ferrous state (Fe^{2+}) that allows O_2 to be transported and delivered to the tissues.
- With 4 heme groups having an iron in the ferrous state, one O_2 molecule may be carried on each heme
- Methemoglobin is an altered state of hemoglobin in which the ferrous (Fe^{2+}) irons of heme are oxidized to the ferric (Fe^{3+}) state
- The ferric hemes of methemoglobin are unable to bind and carry oxygen, resulting in functional anemia
- In addition, the oxygen affinity of any accompanying ferrous hemes in the hemoglobin tetramere is increased
- As a result, the oxygen dissociation curve is left shifted, and oxygen delivery to the tissues is impaired

Reminder…..



Oxidized hemoglobin



Pathophysiology

- RBC are continuously subjected to oxidative stressors that result in the formation of methemoglobin spontaneously in normal individuals at a rate of 0.5-3% of the available hemoglobin per day
- Reduction of methemoglobin maintains a steady state level of methemoglobin of about 1% of total hemoglobin

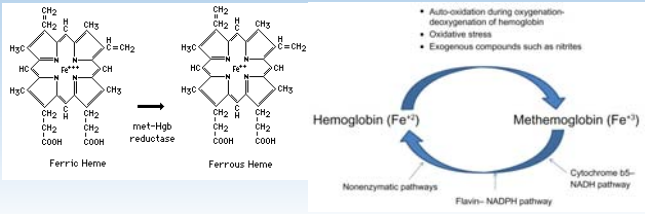
Pathophysiology

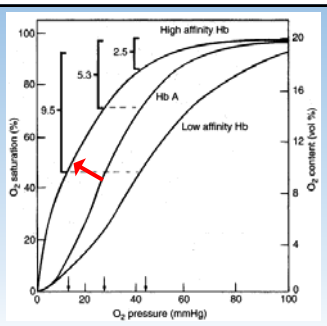
- The most physiologically important pathway for reducing methemoglobin back to hemoglobin is the NADH-dependent reaction catalyzed by methemoglobin reductase enzyme [cytochrome b5 reductase (b5R)], this accounts for 95% of the reducing activity
- Less important alternative pathway in Methemoglobin reduction is by an enzyme utilizing NADPH pathway
- Glutathione and ascorbic acid are slow-acting pathways that play minor roles in the direct reduction of methemoglobin

Pathophysiology

- Positively charged MetHb has high affinity for negative anions (cyanide, fluoride, chloride)
- Neutral Hb has high affinity for neutral ligands (CO, O_2, CO_2)
- thus MHb is not particularly good at transporting oxygen (functional anemia)

Methemoglobin - MetHb





•Leftward shift of Hb-Oxygen dissociation curve

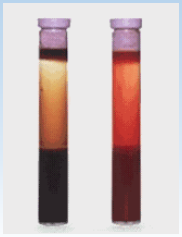
•Impaired oxygen delivery to tissues

Symptoms vs Met Hb concentration

Met Hb conc.	%Met Hb	Symptoms
<1.5 g/dL	<10	None
1.5-3.0 g/dL	10-20	Cyanotic skin
3.0-4.5 g/dL	20-30	Anxiety, lightheadedness, headache, tachycardia
4.5-7.5 g/dL	30-50	Fatigue, confusion, dizziness, tachypnea, tachycardia
7.5-10.5 g/dL	50-70	Coma, seizures, arrhythmias, acidosis
>10.5 g/dL	>70	death

5 g/dL of deoxygenated hemoglobin

Appearance of blood



- Chocolate-brown arterial blood
- does not become red with exposure to oxygen
- filter paper test
  - place drop of blood on filter paper - MHb will not turn red
- Potassium cyanide test
  - MHb turns red when CN added, sulfhemoglobin does not

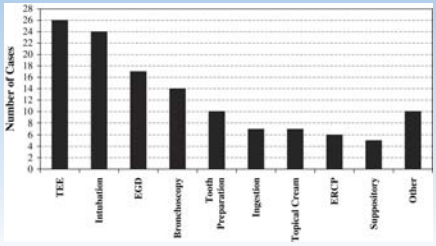
Most common Met Hb– acquired/toxic

- Excessive production of methemoglobin
- Any oxidant is a potential cause –prescribed drugs, recreational drugs, OD
- POTENTIALLY FATAL
- More frequent in premature infants and infants younger than 4 months
- Infant formula made with well water – nitrate
- Met Hb common in septic infants with gastroenteritis and acidosis
- Exact mechanism poorly understood
  - altered flora, RTA, low Cl, UTI, protein intolerance ….
- Infants <6 months
  - NADH-dependent reductase deficiency
  - Presence of Fetal Hb - infant Hb more prone to oxidative stress

Select Drugs documented to contribute to Methemoglobinemia	
Benzocaine, Cetacaine, Prilocaine (the 'caines')	Anesthetic – endotracheal intubation, transesophageal echocardiography, bronchoscopy, topical for hemorrhoids and dental/teething preps.
Celecoxib	Arthritic Pain
Dapsone	Prophylaxis for pneumocystis carinii in patients with human immunodeficiency virus (HIV). Also dermatologic applications.
EMLA Creams	Eutectic Mixture of Local Anesthetics.
Flutamide	Prostate Cancer
Nitrates	Food additives, well water, by-product of fertilizer run-off and incorporation into foods. Preservative
Nitric Oxide	Pulmonary vasodilatation
Nitroglycerin	Cardiac vasodilatation
Sodium Nitroprusside	Intravenous Antihypertansive, Vasodilator
Sodium Nitrate	Preservative salt used in meat and fish
Sulfonamides	Broad spectrum antibiotics

Benzocaine

Number of cases of methemoglobinemia associated with each benzocaine exposure type



European Heart Journal – Cardiovascular Imaging Volume 17, Issue 11, 1 Jan 2016

Methemoglobin and sepsis

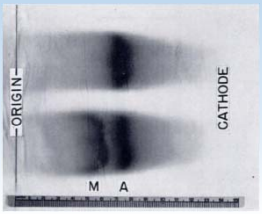
- Met Hb increases in sepsis
- Nitric Oxide (oxidizes Hb)
- Marker?

Three hereditary causes

1. Methemoglobinemia due to an altered form of hemoglobin (ie, Hb M) – change in amino acid ~ 7 variants
   - Autosomal Dominant
2. Methemoglobinemia due to an enzyme deficiency
   - deficiency of NADH cytochrome b5 reductase, which is encoded by the *CYB5R3* gene (also called NADH diaphorase)
   - Autosomal recessive
   - Heterozygotes – 50% enzyme activity and no cyanosis
   - Homozygotes –Cyanosis if Met Hb > 1.5%
   - Two types
3. Deficiency of NADPH-flavin reductase can also cause methemoglobinemia

1. Congenital Methemoglobinemia – Hemoglobin M

- Hemoglobin M
  - rare autosomal dominant disorder
  - stabilize heme iron in ferric (3+) state
  - death in homozygotes
  - lifelong cyanosis in heterozygotes



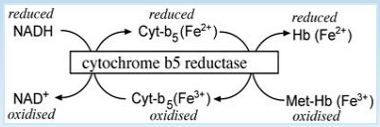
2. Two types of enzyme deficiency–(deficiency of NADH cytochrome b5 reductase)

- Type I – This is the most common variant, and the enzyme deficiency is limited to the erythrocytes causing cyanosis; cyanosis usually, but not always, develops during infancy
- Type II – Widespread deficiency of the enzyme occurs in various tissues, including erythrocytes, liver, fibroblasts, and brain; it is associated with severe CNS symptoms, including encephalopathy, microcephaly, hypertonia, athetosis, opisthotonos, strabismus, mental retardation, and growth retardation; cyanosis is evident at an early age

3. NADPH-MHb reductase deficiency

- NADPH-MHb reductase deficiency
  - exceedingly rare
  - Does not cause MHb
    - Enzyme only reduces MHb in presence of exogenous catalyzing agent (ie: methylene blue)
  - Patient would not respond to therapeutic methylene blue

NADH-dependent cytochrome b5 - metHb reductase system



The "Blue Fugates" of Kentucky

History

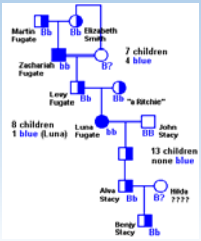
- Martin Fugate settled in Kentucky in the early 1820's – French Huguenot
- Married a local woman, Elizabeth Smith
- Both carried the recessive "blue" gene
- They had 7 children, 4 were blue
- Appalachian area –rural and isolated –intermarriages occurred and the chances for a double recessive inheritance increased
- As Kentucky became more populated, fewer blue children born
- Last blue child, Ben Stacy, from the Fugate family –born in 1975

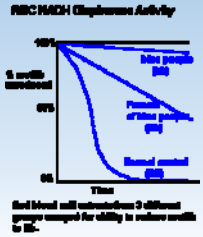
Medical sleuths -1960's

- Ruth Pendergrass, nurse in AHA clinic in Hazard, Ky.
- Madison Cawein, hematologist from the University of Ky. in Lexington
- Went to the hollows to try to find blue people
- One day, brother and sister, Patrick & Rachel Ritchie walked into the clinic
- "They were bluer'n hell"
- Examined; & interviewed no heart disease; they had blue relatives who lived into their 80's and 90's
- Inherited Methemoglobinemia

Daily Mail Feb 23, 2012

Fugate pedigree with genotypes





•Congenital NADH-diaphorase deficiency

The Blue Men of Lurgan, Ireland

- Brothers with a blue appearance
- treated by Dr. James Deeny in 1942 with ascorbic acid and sodium bicarbonate- Thought it was heart disease; other doctors skeptical
- Dr Henry Barcroft identified increased level of methemoglobin in the brothers; Dr. Quentin Gibson identified the enzyme deficiency pathway and a treatment
- "familial idiopathic methaemoglobinaemia"
- In 2002, analysed DNA from the surviving brother & 2 siblings – mutations in the cytb5r gene; siblings heterozygote
- >30 mutations

Other "blue people" - hereditary

- Huguenot descendents – Kentucky, Ireland, and Finland
- Native Americans –Navajo; Alaskan Eskimos; and natives of Yakusk, Siberia (might have common ancestry)
- Sporadic reports worldwide
- Recent report – patients with Hemoglobin E, rare variant found in SE Asia, also have high levels of Methemoglobin –not due to enzyme deficency

Comparison of Methemoglobinemia

Acquired/Toxin
- Recent onset cyanosis
- Unresponsive to 100% oxygen
- No cardiopulmonary pathology

TREATMENT
- STOP the offending agent once it's been identified
- Treatments –depend on Met Hb level

Hereditary/Congenital
- Long standing symptoms
- Symptoms in siblings, but not in parents

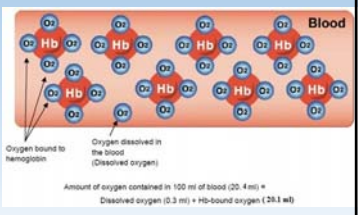
TREATMENT
- May treat to reduce blue color; no real danger –psychological

Diagnosis

- Arterial Blood Gas paired with oxygen saturation by co-pulse oximetry
- Measuring Methemoglobin
- Measuring enzyme levels
- Molecular testing –sequencing- for enzyme

ABGs

Normal Values	
pH	7.35-7.45
CO_2	35-45
pO_2	80-100
HCO_3	22-26
O_2 Sat.	95-100%



Clue to methemoglobinemia

- ABG and standard pulse oximetry (a "saturation gap" or difference between the oxygen saturation results of ABG alone (calculated) vs. standard pulse oximetry will be present in methemoglobinemia),
- ABG with co-oximetry, or multiple wavelength pulse oximetry (also called continuous pulse co-oximetry) can differentiate

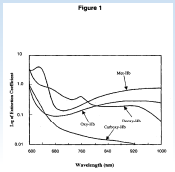
- Pulse oximetry
  - Not accurate in MHb!!
  - Only measures 2 wavelengths: 660 & 940nm
  - 100% MHb will read 85% saturation

The three most important measures of oxygen in blood are:

- 1. SaO2. It's a percentage that shows how saturated your arterial blood (hemoglobin) is with oxygen. It's obtained from an ABG with co-oximeter, so it's very accurate. Normal is 95-98%, although 90% or better is usually considered acceptable. It determines fractional oxygen saturation.
- 2. PaO2. It's the partial pressure of arterial oxygen. It's obtained from an ABG, and is an accurate measure of dissolved oxygen in arterial blood. A normal range is 80-100 mm Hg, although 60 or better is usually considered acceptable.
- 3. SpO2. It's similar to SaO2, although it's estimated by pulse oximetry. A normal value is 95-98%, although 90% or better is usually considered acceptable. It determines functional oxygen saturation.

Co-pulse oximetry

- Measurement of greater numbers of wavelengths enables the instrument to distinguish between deoxy and oxyhemoglobin, and carboxyhemoglobin and methemoglobin
- Co-oximetry
  - Measures four wavelengths
  - Maximal absorption peak at 630-631 nm (little interference from oxyhemoglobin)



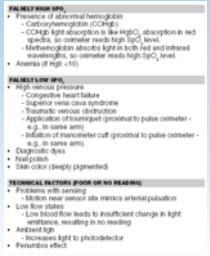
CO-OXIMETRY VS. PULSE OXIMETRY

CHARACTERISTIC	CO-OXIMETER	PULSE OXIMETER
Number of wavelengths of light	4	2
Technique	In vitro; arterial blood sample inserted into the machine	Noninvasive: digit or earlobe, where a pulse can be sensed easily by a portable machine
Measures	$\%O_2Hb$ (SaO_2); % unbound Hb; %COHb; %MetHb; Hb content	$\%O_2Hb$ ($SpO2$); % unbound Hb
Advantages	Highly accurate; can distinguish COHb from O_2Hb	Painless; allows for continuous monitoring; easily portable; relatively inexpensive; SpO_2 not affected by fetal Hb
Major disadvantages	Requires arterial sample; expensive to purchase, maintain, and operate; not available for most outpatients; fetal Hb interferes with SaO_2 reading	Doesn't differentiate COHb from O_2Hb; may give false sense of security in setting of progressive hypercapnia with supplemental O_2; correlation of SpO_2 with SaO_2 varies among machines; can be misused by caregivers unfamiliar with basic principles

More facts…..

HOW SOME FACTORS INFLUENCE PULSE OXIMETRY READING OF OXYGEN SATURATION

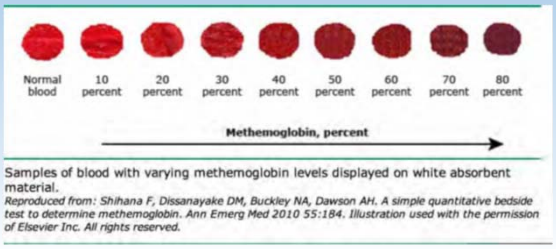
FACTOR	SaO_2 READING IS
Carboxyhemoglobin	Higher than true SaO_2
Methemoglobin	Higher than true SaO_2
Dark nail polish	Slightly lower than true SaO_2
Methylene blue	Much lower than true SaO_2
Fetal hemoglobin	No significant effect
Jaundice	No significant effect
Skin pigmentation	Variable
Decreased perfusion	Variable
Vasoconstriction	Variable
Cardiac arrhythmias	Variable
Hypothermia, shivering	Variable



Cofirmatory testing –Evelyn Malloy method

- Sodium Cyanide binds to positively charged methemoglobin eliminating the peak at 630-35 nm in direct proportion to methemoglobin concentration. bin
- The resulting change in optical density is directly proportional to the concentration of Met Hb.
- Next, add ferricyanide to convert to cyanmethemoglobin for measuring total Hemoglobin concentration
- Met Hb expressed as percentage of totl Hb

Chart



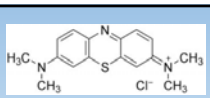
Samples of blood with varying methemoglobin levels displayed on white absorbent material.

Reproduced from: Shihana F, Dissanayake DM, Buckley NA, Dawson AH. A simple quantitative bedside test to determine methemoglobin. Ann Emerg Med 2010 55:184. Illustration used with the permission of Elsevier Inc. All rights reserved.

Treatment -Methylene Blue

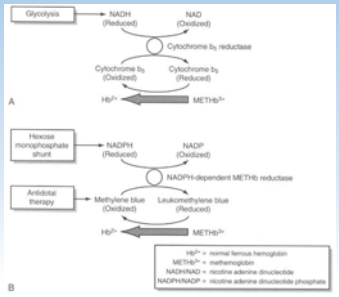
- Specific antidote for MHb
- 1-2 mg/kg over 5 minutes
- Repeat doses to maximum 7mg/kg

Methylene Blue



- Methylene blue is oxidized into leukomethyene blue by accepting an electron from NADPH in the presence of NADPH Reductase
- Leukomethylene blue then acts as an electron acceptor for methemoglobin resulting in its conversion back to hemoglobin
- Large doses of methylene blue are to be avoided –too much Methylene blue not being oxidized - causes hemolysis
- May paradoxically cause methemoglobinemia in patients with G6PD deficiency

A. The NADH-dependent cytochrome b5 methemoglobin reductase system (endogenous).
B, The NADPH-dependent methemoglobin reductase system (therapeutic).



Source: Ford: Clinical Toxicology

- Methemoglobinemia from Hemoglobin M –does not respond to methylene blue or ascorbic acid
- Dextrose should be given-
  - major source of NADH is from catabolism of sugar through glycolysis
  - Necessary to form NADPH through the hexose monophosphate shunt which is necessary for methylene blue to effective
- Patients with anemia or cardiorespiratory problems should be treated at lower levels of Met Hb

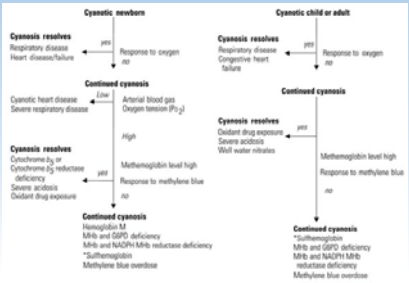
Methylene Blue – Caution!

- G6PD Deficiency:
  - Enzyme used in formation of NADPH
  - Insufficient NADPH produced to reduce methylene blue (oxidizing agent) to leukomethylene blue (reducing agent)
  - Relative buildup of methylene blue (oxidizing agent)
  - Can get paradoxical methemoglobinemia and methylene blue induced hemolysis

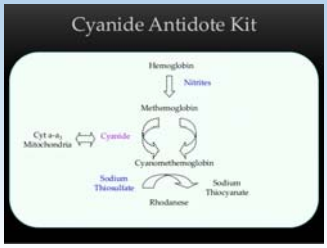
Other treatments

- Ascorbic acid –non enzymatic Met Hb reduction
- Exchange transfusion
- Hyperbaric oxygen treatment
- N-acetylcysteine, cimetidine, ketoconazole – experimental therapies

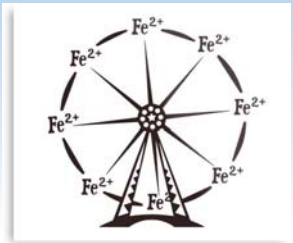
Clinical decision making in methemoglobinemia



Therapeutic Methemoglobinemia



End



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