Anemia in Indigenous or Remote Communities

MSERS Feb 17, 2022
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Faculty/Presenter Disclosure

- Dr. Benjamin Thomson, Associate Professor, Queen's University

- Relationships with commercial interests:
  Grants/Research Support:
  → Old: CIP, POEM (Western University), Innovation Research Grant, CTAQ (Queen's University), CIHR (CONNECT, ACHIEVE), PDOPPS trial funding

  → Current: None

- Committees: Ontario Renal Network Peritoneal Dialysis Focus Group

- Speaking fees: Baxter Canada

Mitigating Potential Bias

- No mitigation has been required. Content in this talk does not relate to either research grant topics, funding guidelines or funding organization objectives.

Learning Objectives

- Describe the epidemiology of anemia in Canadian Indigenous Communities
- Explain how Socioeconomic factors modify patterns anemia in Indigenous communities in Canada
- Describe the differential diagnosis of anemia
- Describe risk factors for iron deficiency, B12 deficiency anemia
- Identify when to refer to specialist (internal medicine or hematology)
- Review cases of Anemia, Identify Management plan

Case 1: Judy Shisheesh

- 58 year old woman
- 3 months of progressive shortness of breath
- **Profile:** Hypertension, Hysterectomy (for menorrhagia) age 41, Cholecystectomy (age 39)
- **Medications:** Amlodipine 5 mg PO daily
- **Social History:** She is married, with 5 children. She lives with her husband, 4 of her children, 3 of her grandchildren and mother in a home in Attawapiskat. Lifelong nonsmoker and consumes minimal alcohol.
  Administrator at diamond mine, then at band office
- **Investigations:** CBC, Lytes, Creatinine, LFTs normal, except
  Hemoglobin 80 g/L

- She is treated with oral iron for 3 months. You believe she is adherent to therapy

- Her hemoglobin after 3 months of oral iron is 76 g/L

1. **What should the diagnostic workup have included on her first visit?**
2. **How might her social history be relevant to the diagnosis of anemia?**

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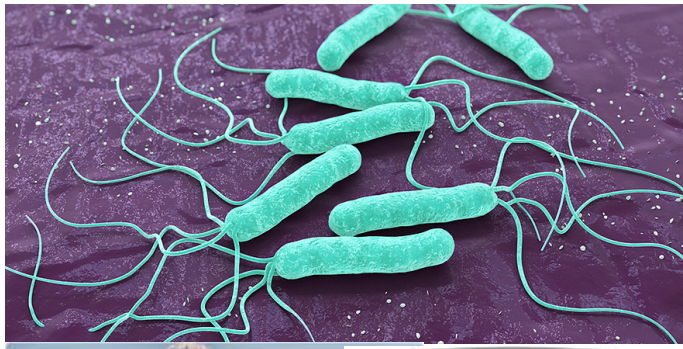
Epidemiology of Anemia in Indigenous Persons



Definition in anemia definition based on sex, age, altitude and pregnancy status
No adjustments in "normal" Hemoglobin in Canada based on race

Prevalence of anemia 29% to 60% (depending on study and population)
Infant anemia is also higher in Indigenous communities (> 50% in some communities).

Reasons for higher rates of anemia in Indigenous communities may include:
→ Use of cow's milk or evaporated milk (low in iron) rather than infant formula
→ Low food security
→ Higher rates of Helicobacter pylori infection (related to low water quality and sanitation)
→ Intestinal infections are likely cause in some communities due to water sanitation
→ Early pregnancy and multiple children may be a factor in some communities
→ Boil water advisories- higher rates Cholera/Diarrhea/Giardia/Salmonella/E.Coli infection

→ Other causes of anemia related to low food security and socioeconomic factors

Khambalia et al, 2011; Hodgins et al, 1998; Christofides et al, 2005; Willows and Gray-Donald, 2002; Willows and Gray-Donald, 2003; Willows and Gray-Donald, 2004

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Neskantga First Nation

Cat Lake First Nation Reserve

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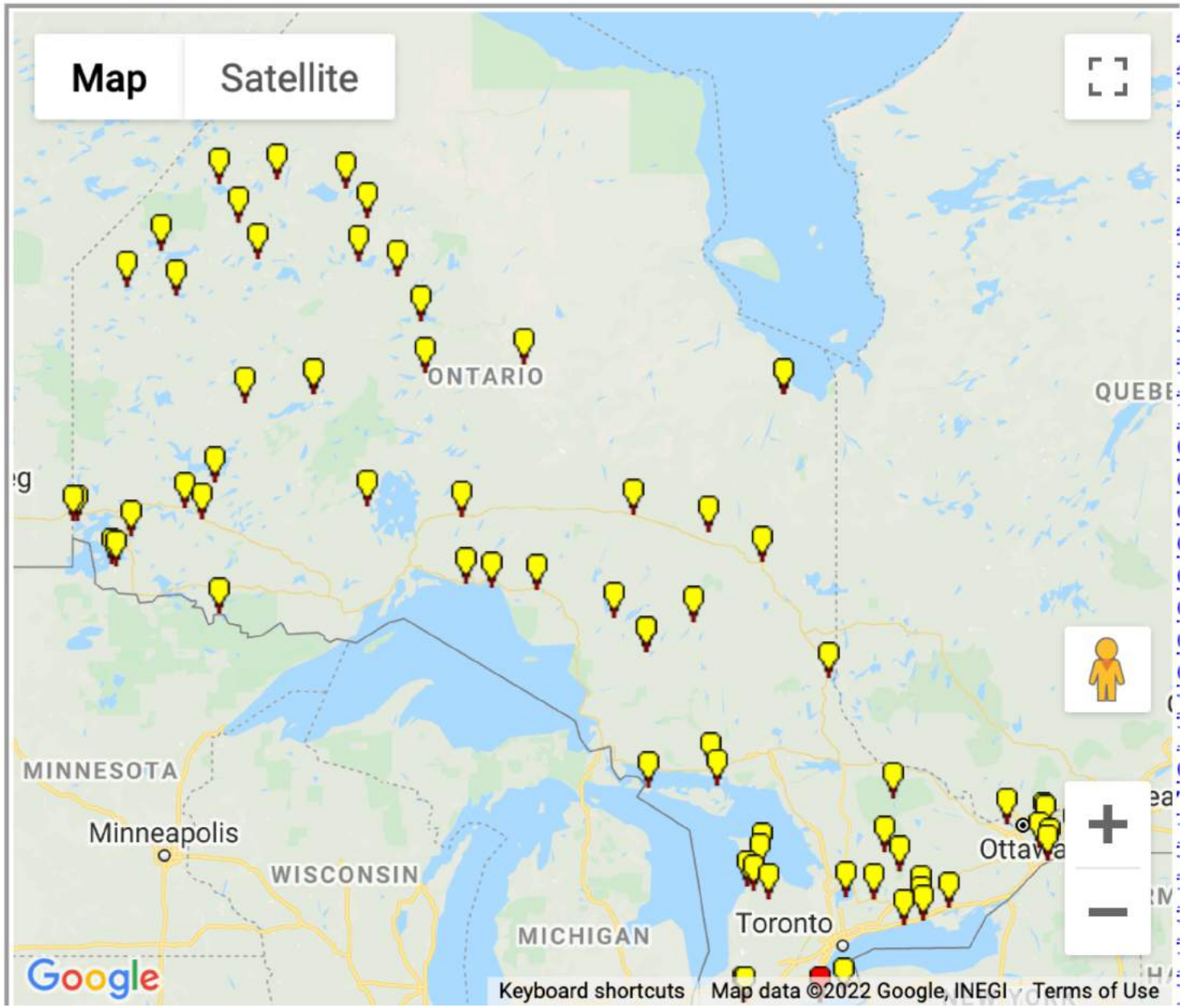


As of January 22, 2022

→ 72 communities in Ontario boil water advisories

→ 37 of these are indigenous communities

→ Of the 37 in Indigenous communities:

- → 18 are more than 2 years long
- → 8 are more than 10 years long

→ Of the 9 Ontario boil water advisories > 10 years, 8 are in Indigenous communities

→ Of the 24 Ontario boil water advisories > 2 years, 18 are in Indigenous communities

Center for Disease Control: Boil Water Advisory

Handwashing: ”use tap water and soap.” “scrub hands with soap and water for 20 seconds.”

Bathing and Showering: “Be careful not to swallow any water when bathing or showering.”
”Use caution when bathing babies and young children…consider…sponge bath.”

Brushing teeth: “Brush teeth with boiled or bottled water. Do not use tap water.”

Washing dishes: “Use disposable plates, cups and utensils…”
“Dishwashers are safe if…water reaches 66 degrees celcius”
“Sanitize all baby bottles.”
”Wash and rinse dishes as you normally would using hot water…then
…in a separate basin, add 1 teaspoon of unscented household liquid bleach for each gallon of warm water…
…soak the rinsed dishes in the water for at least one minute…
…let the dishes air dry completely before using again.”

Cleaning: “Clean washable toys and surfaces with bottled water, boiled water or water…with bleach.”

Center for Disease Control: Boil Water Advisory

Failure to be adherent may lead to:

- → Chronic diarrhea
- → Giardia
- → E.Coli
- → Salmonella
- → Viruses

Chronic diarrhea, Giardia commonly lead to:

- → malabsorption
- → abdominal cramping, decreased oral intake

This environment specifically increases risk of anemia

Diagnosis and Workup of Anemia: Two methods

APPROACH 1: Uses Reticulocyte Count (if not available, look at RDW)

→ Hematocrit = % volume of blood made up of rbc
→ When Hct low, bone marrow should release more early rbc precursors (reticulocytes) into peripheral blood.
→ This process is disrupted if rbc precusors lack factors required for production

RPI aka "Retic index" = (Re

Hematocrit	Matur
≥ 40%	1.0
30-30.9%	1.5
20-29.9%	2.0
<20%	2.5

PROBLEM:
Reticulocyte Count not available in most communities!

Maturation factor ~ days for a reticulocyte to become RBC once released into blood from marrow
RPI usually ranges 0 to 5

ORDER: Reticulocyte count, CBC (includes hematocrit)

Diagnosis and Workup of Anemia: Two methods

APPROACH 1: Uses Reticulocyte Count (if not available, look at RDW)

→ Reticulocytes are large cells (MCV > 100)
→ When there are two populations of rbc of very different size, RDW is increased
→ RDW = Rbc Distribution Width = Variance in the size of rbc

→ When RDW increased, it indicated two populations of sizes of cells:
(i) Reticulocytosis (high MCV with normal MCV)
(ii) Mixed deficiency eg. Iron (low MCV) and B12 (high MCV)
(iii) Iron deficiency (low MCV) with thyroid/liver disease or pregnancy (high MCV)

Diagnosis and Workup of Anemia: Two methods

APPROACH 2

Hemoglobin < 120 g/L non-pregnant female or < 130 g/L male

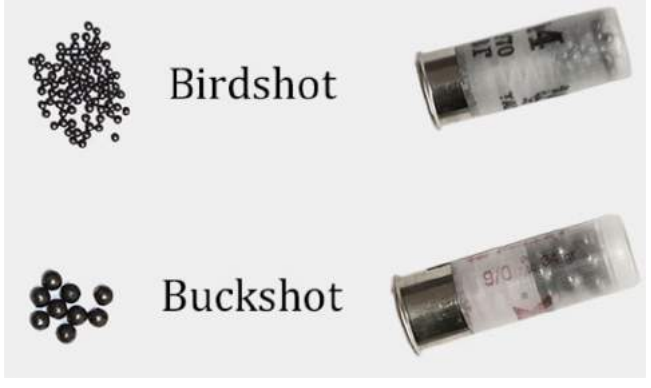
↓

On CBC report, find MCV (mean cell volume)

Microcytic Anemia (< 80 um3)

Iron deficiency
Anemia of chronic disease
Lead Poisoning

Thalassemias
Sideroblastic anemia



Macrocytic anemia (>96 um3)

Treble and Thompson, 2002

Diagnosis and Workup of Anemia: Two methods

APPROACH 2

Hemoglobin < 120 g/L non-pregnant female or < 130 g/L male

↓

On CBC report, find MCV (mean cell volume)

↓

Microcytic Anemia (< 80 um3)
Iron deficiency
Anemia of chronic disease
Lead Poisoning

Thalassemias
Sideroblastic anemia

Normocytic Anemia (80-96 um3)
Early iron deficiency anemia
Anemia of chronic disease

Combined deficiencies (eg. Iron + B12)
Hemolysis or bleeding
Primary marrow failure

Macrocytic anemia (>96 um3)
Hemolysis or bleeding
B12 or folate deficiency
Liver disease
Chronic alcohol intake
Thyroid disease
Pregnancy

Diagnosis and Workup of Anemia: Two methods

APPROACH 2

Hemoglobin < 120 g/L non-pregnant female or < 130 g/L male

↓

On CBC report, find MCV (mean cell volume)

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Microcytic Anemia (< 80 um3)
Iron deficiency
Anemia of chronic disease
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Thalassemias
Sideroblastic anemia

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Combined deficiencies (eg. Iron + B12)
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Macrocytic anemia (>96 um3)
Hemolysis or bleeding
B12 or folate deficiency
Liver disease
Chronic alcohol intake
Thyroid disease
Pregnancy

So much overlap- how do I tell these apart?

A few helpful tricks to diagnosis: Iron deficiency anemia

→ Iron binds to a protein in blood called transferrin
→ When iron levels are low, liver produces more transferrin in an attempt to catch up
→ TIBC (total iron binding capacity) reflects the total amount of transferrin
→ Transferrin saturation reflects the amount of transferrin bound to iron

→ When there is chronic inflammation, this decreases transferrin production by liver

→ Ferritin is an intracellular protein that stores iron, and thus indirect marker of total amount of iron stored in body
→ Ferritin is increases significantly with anoxia, infection, cancer, inflammation- "acute phase reactant"

	Iron deficiency anemia	Anemia chronic disease	Sideroblastic anemia
Serum Ferritin (20-250 ng/mL)*	***Low***	***Normal or up***	Up
Serum Iron (10.7-30.4 mmol/L)	Low	Normal or down	Normal or up
TIBC (43.0-80.6 mmol/L)	***High***	***Down***	Normal
Transferrin saturation (20-50%)	Low	Normal or down	Normal or up

* For adult males. For adult females = 10-120 ng/mL
→ Lead poisoning and iron deficiency appear similar.

More on Iron Deficiency Anemia to come….

A few helpful tricks to diagnosis

→ Take a full history of diet, bowel habits, occult bleeding, past medical/surgical history, medications
→ All women of child-bearing age should have pregnancy test

FOR ALL ANEMIA:

1. Child bearing female? Pregnancy test
2. Reticulocyte count (calculate RPI)
3. If MCV Low (Microcytic): Serum Iron/Ferritin/TIBC/Transferrin saturation +/- Lead level
4. If MCV Normal (normocytic): Serum Iron/Ferritin/TIBC/Transferrin saturation/TSH/B12/Folate/
   For hemolysis: Total Bilirubin/Haptoglobin/Lactate dehydrogenase/Reticulocyte count
   For bleeding: As above for hemolysis
5. If MCV High (Macrocytic): TSH/Pregnancy test/B12/Folate/Hemolysis and bleeding workup

   Blood smear for all cases- not commonly available

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Back to our case : Judy Shisheesh

- 58 year old woman, 3 months of progressive shortness of breath
- **Social History:** She is married, with 5 children. She lives with her husband, 4 of her children, 3 of her grandchildren and mother in a home in Attawapiskat. Lifelong nonsmoker and consumes minimal alcohol. Administrator at mine, then at band office
- **Investigations:** CBC, Lytes, Creatinine, LFTs normal, except Hemoglobin 79 g/L (MCV 97 um3)
- She is treated with oral iron for 3 months. You believe she is adherent to therapy
- Her hemoglobin after 3 months of oral iron is 76 g/L

1. **What should the diagnostic workup have included on her first visit?**

Reticulocyte count
Not child bearing age (and past hysterectomy) so pregnancy test not required
Based on the MCV of 97: Serum Iron/Ferritin/TIBC/Transferrin saturation/TSH/B12/Folate/Creatinine/ Total Bilirubin/Haptoglobin/LDH/Reticulocyte count

Our case : Judy Shisheesh

Reticulocytes:	5.3%	
PRI	2.0	
Hemoglobin:	80	Normal 135-180
MCV	97	Normal 80-97 fL
Ferritin	18	Normal 27-220
Iron	7	Normal 11-18 g/dL
TIBC	90	Normal 43-81 mmol/L
Transferrin satn	10%	Normal 20-45%

TSH/B12/Folate/Bilirubin/Haptoglobin/LDH/Creatinine normal

3 months before this, Hb was 146 (normal)

→ The iron studies suggest iron deficiency

"She lives with her husband, 4 of her children, 3 of her grandchildren and mother in a home in Attawapiskat."

You prescribe ferrous gluconate 300 mg PO bid and she returns 3 months later

Our case : Judy Shisheesh

Reticulocytes:	5.3%	
PRI	2.0	
Hemoglobin:	67	Normal 135-180
MCV	95	Normal 80-97 fL
Ferritin	15	Normal 27-220
Iron	5	Normal 11-18 g/dL
TIBC	91	Normal 43-81 mmol/L
Transferrin satn	9%	Normal 20-45%

TSH/B12/Folate/Bilirubin/Haptoglobin/LDH/Creatinine normal

→ Still iron deficient
→ PRI still neither up nor down
→ Skin lesions are still present

Oral iron has not corrected her anemia (it's worse!)

Case 2: John Peters

→ 37 year old man
→ Presents with numbness and tingling in fingers and toes, decreased energy
→ **PROFILE:** Schizophrenia, Depression, Hypertension, Remote history chronic alcoholism. He was admitted to Psychiatry ward 2018 after schizophrenia and depression episode with psychosis.
→ **MEDICATIONS:** Olanzapine 2.5 mg PO bid, Amlodipine 5 mg PO daily
→ **SOCIAL HISTORY:** Lives alone in his brother's shed. He has 3 siblings and mother still alive- minimal contact. Currently unemployed. No current alcohol use, smokes 1 ppd.
→ **INVESTIGATIONS**

TSH/Liver tests/CBC/Creatinine/Electrolytes/Calcium/Phosphate all normal except:

Hemoglobin	75	(normal 135-170 g/L)
MCV	95	(normal 80-97 fL)

He has not had blood work since 2018. At that time, Hemoglobin was 129 g/L.

→ **EXAM:** BP 129/67, hr 70 bpm. He has "cracks" at side of mouth and fingernails appear spoon shaped. His speech is slow and he is behaving oddly.

What else would you like to order?

Case 2: John Peters

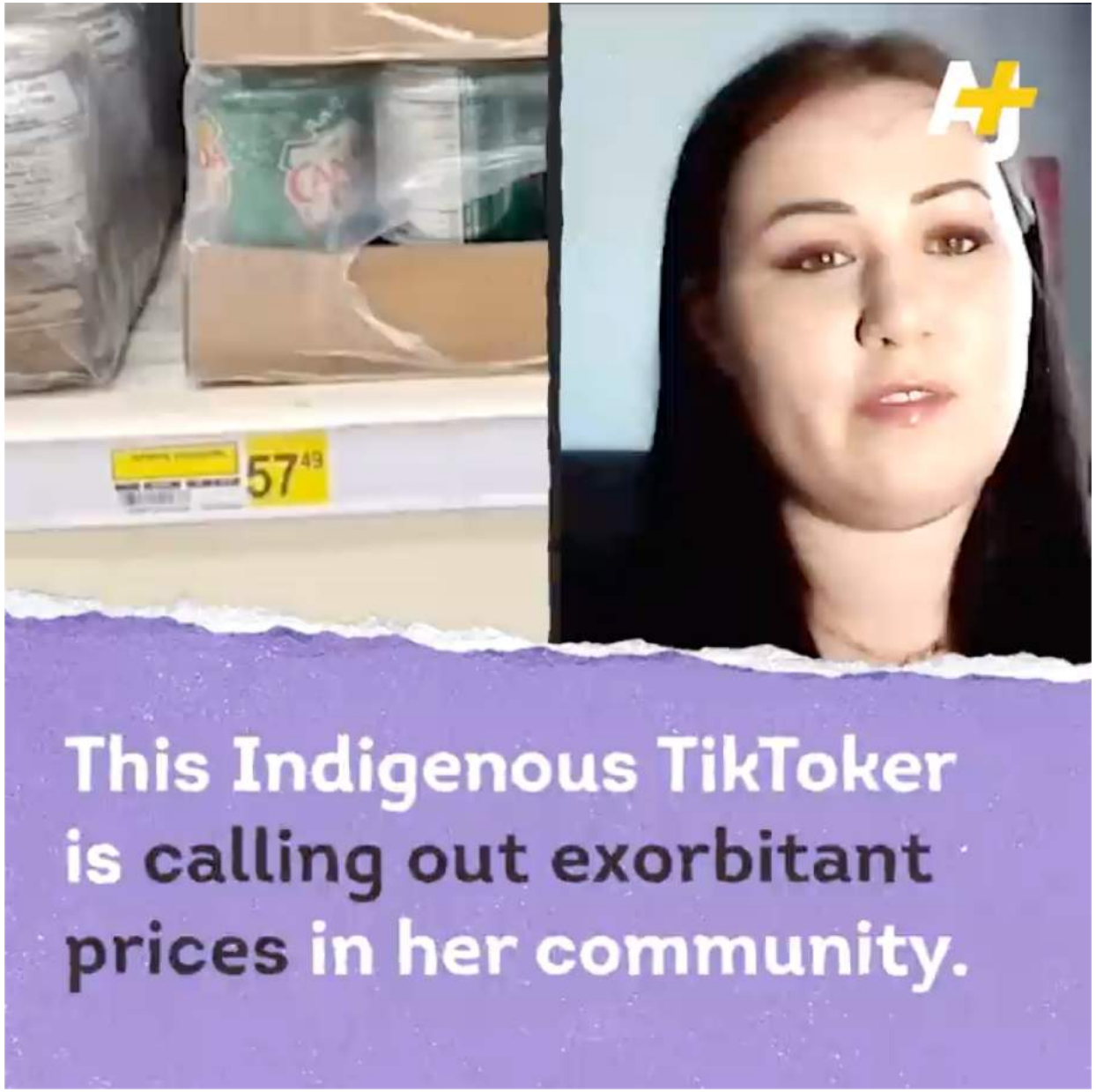
What else would you like to order?

PRI (retic index)	0.5 (low)
Hb	75 (low)
MCV	95 (normal)
Serum iron	Low
Ferritin	Low
TIBC	High
Transferrin Sat	Low
TSH	Normal
B12	Low
Folate	Normal
Bilirubin	Normal
Haptoglobin	Normal
LDH	Normal

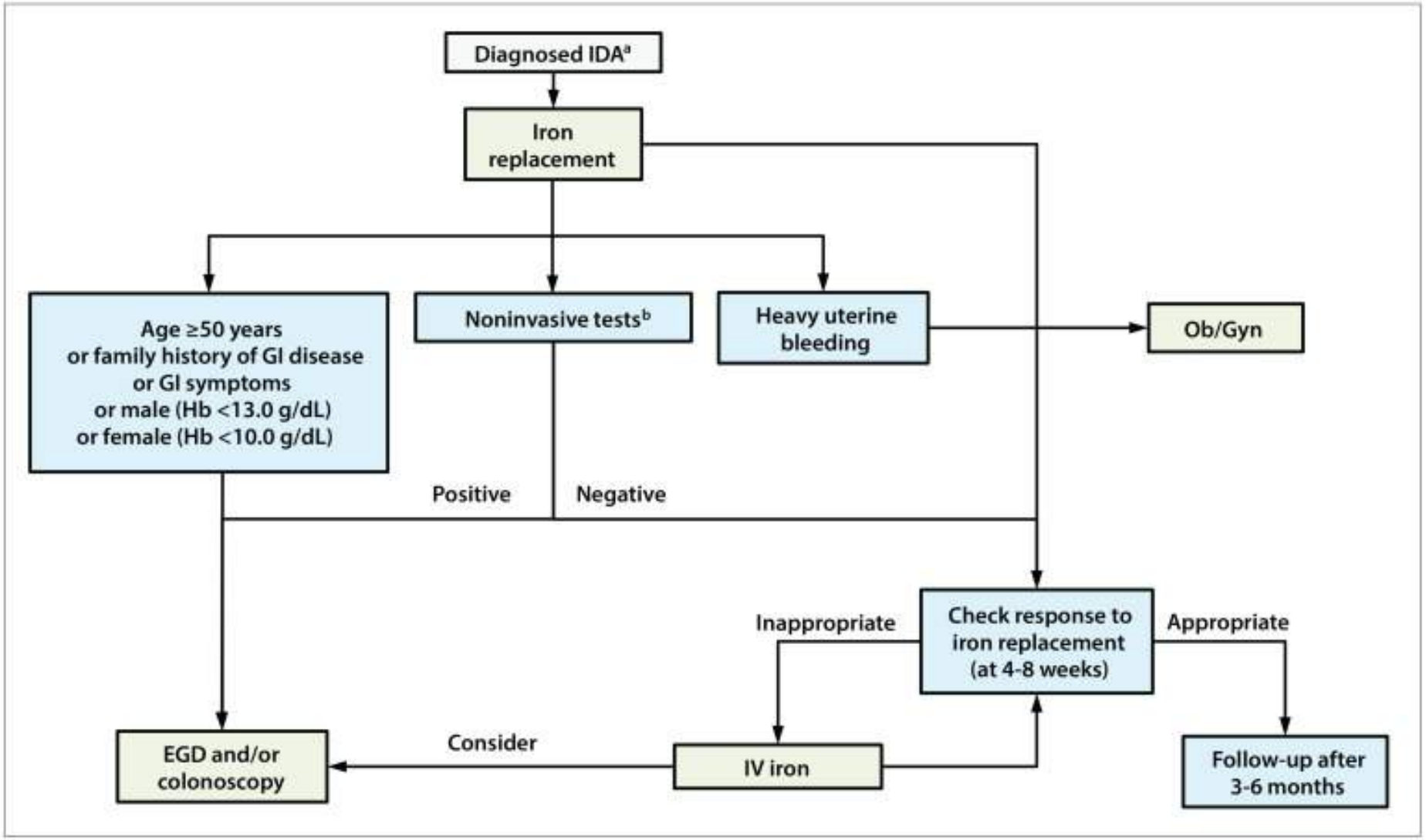
→ His low PRI suggests there is a problem with production of red blood cells (marrow)
→ His iron studies are consistent with iron deficiency – this should produce low or low normal MCV, but high normal here
→ B12 deficiency also present

Case 2: John Peters

What else would you like to order?



Management of iron deficiency anemia



Management of iron deficiency anemia

1. Which oral iron formulations are available?
2. When should I consider using IV iron?
3. What are the advantages of oral versus IV iron?
4. Are there alternatives to oral or IV iron to supplement diet?
5. What iron is best in pregnancy?
6. What medications interact with oral iron?

Management of iron deficiency anemia

Options for Oral Iron

Ferrous fumarate 300 mg PO (up to tid)
Ferrous gluconate 240/324/325 mg (up to tid)
Ferrous sulfate (liquid or tablet) (up to tid)

→ Giving with Vitamin C (200 mg per 30 mg iron) may increase absorption of iron (evidence for benefit limited)
→ Giving before bedtime may improve tolerability of oral iron
→ Giving more than once daily has not been proven to improve outcomes, but increases side effects
→ Gastrointestinal side effects expected in ~1/3 patients on oral iron: May be worse with ferrous fumarate

Disadvantages of Oral Iron

Limited daily absorption
Dose-dependent GI side effects
Uptake impaired in disease states (eg. Celiac, IBD)
Multiple drug interactions

Advantages of Oral (vs IV) Iron

Cheap
Avoids need for IV

Management of iron deficiency anemia

Iron Fish	Ferrous Gluconate (PO)	Ferrous Fumarate (PO)	Ferrous Sulfate (PO)	Iron Sucrose (IV)	Sodium Ferric Gluconate (IV)
PRESCRIBED AS					
Place in boiling water	300/324 mg	210/305/322 mg	220/300/324 mg	100/200/300 mg	62.5/125 mg
ELEMENTAL IRON EQUIVALENT					
6 to 8 mg/L	35-37 mg Floradix	66/101/107 mg Palafer	43/60/65 mg Ferodan/Ferrotrate.	100/200/300 mg Venofer	62.5/125 mg Ferrlecit

The use of iron skillets/pans also adds Iron to food, but quantity is uncertain

→ RDA Age 2-11 (13.7-15.1 mg/day), Age 12-19 (16.3 mg/day),
19.3-20.5 mg/day (men), 17.0-18.9 mg/day (women), 27 mg/day (pregnancy women)

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Management of iron deficiency anemia

Interactions to consider with oral iron:

→ Impaired absorpation with PPI/H2RA

→ Take at least 2 hours away from:
- → Levothyroxine
- → Antibiotics (Ciprofloxacin, Penicillin, tetracycline)
- → Calcium (in dairy, antacids, Tums, etc)
- → Coffee or black tea
- → Sinemet (parkinsons disease)
- → Cardiac medications (Minoxidil, Digoxin, Lasix)
- → Immunosuppresants (Cyclosporine, Methotrexate)
- → Seizure medications (Oxazepam, Phenytoin)

In Pregnancy, daily iron supplementation is recommended (W.H.O):

→ Dietary iron intake is inadequate in most pregnant mothers

→ Alternative day supplementation has comparable maternal and fetal outcomes with reduced side effects, with increased risk of maternal anemia at birth

→ Side effects for oral tablets are dose dependent

→ Two oral iron formulations *may* have fewer side effects in pregnancy:

1. Ferrous Bisglycinate (Ferrochel) versus ferrous ascorbate
   eg. “Mild Iron”, “EasyIron”, “CanPrev Iron”: 18-28 mg elemental iron per dose
2. Ferric iron polymaltose complex (Maltofer) compared to ferrous sulfate
   eg. 370 mg (contain 100 mg elemental iron)

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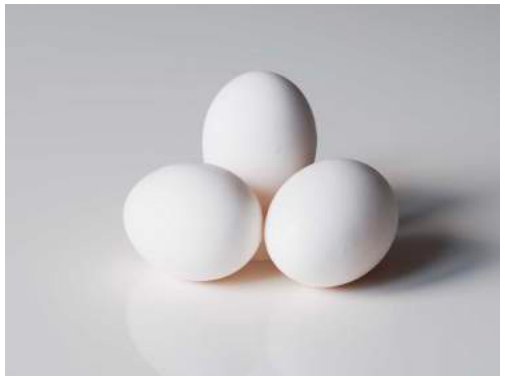
B12 deficiency

Vitamin B12 is typically found in animal origin products:

→ Fish, meat, poultry, eggs, dairy products.

→ Fortified cereals



Risk factors for Vitamin B12 deficiency are:

→ Decreased absorption: (i) Pernicious anemia (lack of intrinsic factor to bind to B12 for absorption)
(ii) Surgery of stomach (removes part of stomach that produces intrinsic factor
(iii) Prolonged severe gastritis (chronic alcoholism, Helicobacter pylori)

→ Decreased intake: (i) Dietary deficiency
* more common in chronic alcoholism
* Vegans
* Infants of vegans

Case 3: Paul Nakogee

→ 69 year old man
→ Presents with decreased energy over 6 months, with reduced appetite
→ **PROFILE:** Diabetes mellitus type 2, Hypertension, Dyslipidemia, Chronic alcoholism, Alcoholic liver disease, Recurrent diabetic foot infections, Coronary artery disease (MI 2013)
→ **MEDICATIONS:** ASA 81 mg PO daily, Metoprolol 25 mg PO bid, Ramipril 2.5 mg PO daily
Metformin 1000 mg PO bid, Gliclazide 30 mg PO daily, Insulin glargine 30 U SC qhs,
Atorvastatin 40 mg PO daily
→ **SOCIAL HISTORY:** He is retired- previously worked as miner, then in band office until age 65.
Ex-smoker (quit 2013), Quit drinking alcohol 2020,
Married, lives with wife in home. All his 5 children live off the reserve

Hemoglobin	78 Low (MCV 85 fL)
Creatinine	185 umol/L (high)

Electrolytes, calcium, phosphate, albumin, liver tests, thyroid all normal.

What else would you like to order?

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Thank you!

PRI (retic index)	0.8 (low)	rdw normal
Hb	78 (low)	
MCV	85 (normal)	
Iron	normal	
Ferritin	100 (normal)	
Transferrin satn	25% (normal)	
TIBC	Normal	
Creatinine	185 umol/L (was 90 umol/L in 2020)	

TSH/B12/Folate/Liver tests/Bilirubin/Haptoglobin/LDH all normal

→ The low PRI suggests the bone marrow is unable to produce enough rbc.
→ Iron, B12, folate are normal. Unlikely the low PRI is due to nutritional deficiency
→ PRI low from bone marrow failure or hormone issue (lack of EPO from kidney disease?)

→ Should be referred to nephrologist and hematologist.

→ Diagnosis turned out to be multiple myeloma leading to marrow failure, and kidney disease (causing EPO deficiency).

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"…obligated to consider more than a diseased organ, more even than the whole man- he must view the man in his world."

Dr. Harvey Cushing

Thank you!