Anemia Therapeutics
PHAR 451

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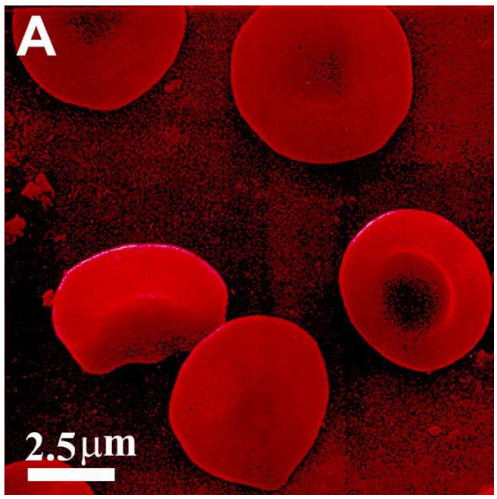


Things to think about

- Anemia is primarily defined by having a low _____ or _____.
- Anemias are classified mainly based on RBC _____, indicated by _____ in the lab profile.

Objectives

following the session and upon personal reflection and study, students will be able to

1. identify drug related-causes of anemia.
2. diagnose, then design and monitor a pharmacotherapeutic plan for management of anemia due to deficiencies of:

Fe **Folate** **B12**

Case 1

- 43 y/o F
- CC: tiredness, fatigue
- PMH: menometrorrhagia with chronic blood loss, GERD
- Medications on profile:
  - rabeprazole 20 mg daily.
- Labs:
  - Hgb 80↓, MCV 75↓, RDW 16↑, ferritin 20↓, TIBC 100 µmol/L↑, serum Fe 10 µmol/L, % saturation 10↓, RBC folate N, B12 N.

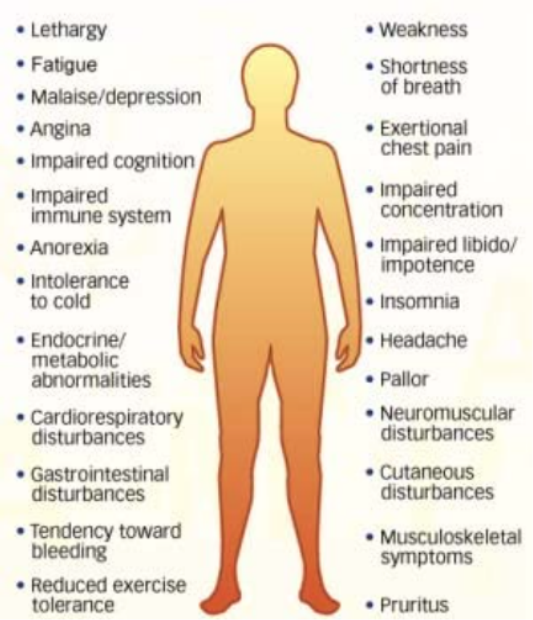
- What's going on here?

- Why?
- How should it be managed?

Why Anemia Matters

- S & Sx of anemia
- CHF
- CV events
- Atrial fibrillation
- Falls
  - 22% ↑ fall risk for every 10 g/L ↓ in HgB in hospitalized adults [J Am Med Dir Assoc 2006; 7: 287-293]
- Mortality

- COMMON SYMPTOMS
  - GENERAL– fatigue, dizziness
    - Insufficient O2 for body processes
  - SKIN – pale, cool, yellow
    - Vasoconstricted
    - Retain blood for vital organs
  - RESPIRATION- elevated
    - Shortness of breath
    - No hemoglobin for O2
  - HEART RATE – increased
    - Compensate/maintain O2 to organs
    - Can lead to chest pain, heart failure, heart attack



Why Anemia Matters

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Drug-Related Causes of Anemia

- **RBC synthesis inhibition**
  - e.g., many myelosupressive drugs
- **Vitamin/Mineral absorption/metabolism interference**
  - Iron: Al/Mg antacids, quinolones, tetracyclines, PPIs/ H2RAs
  - B12: PPIs, metformin
  - Folate: methotrexate, trimethoprim, PHT, EtOH
- **Hemolysis**
  - β-lactams, HCTZ, rifampin, quinidine, sulfonamides, acetaminophen, insulin, NSAIDs, isoniazid

Iron Deficiency Anemia

Lab Profile

Parameter	Finding
HgB	↓
MCV	↓
RDW	↑ / --
Ferritin	↓
TIBC/transferrin	↑
Serum Fe	-- / ↓
"% saturation" / "transferrin index" / "transferrin saturation"	↓

Iron Deficiency Anemia: Therapy

- Transfusion?
- Replace deficiency: 150-200 mg/d
  - PO therapy almost always preferred to parenteral
  - Maintenance: 1-2 mg/kg/d supplement if needed
- Address the underlying cause

Iron Deficiency Anemia: Therapy

- Fe Dosing Tips
  - Absorbed from duodenum and proximal jejunum, so expensive enteric coated or sustained release capsules, which release iron further down in the GI tract are not useful
  - Do not give with food with food because phosphates, phytates, and tannates in food bind Fe and ↓ absorption
  - Give 2 hours before or 4 hours after antacids
  - Think about PPIs, H2RAs [Am J Gastroenterol. 2009 Mar;104 Suppl 2:S5-9.]
  - Nausea/dyspepsia/vomiting (10-20%): ↓ dose, split doses, take with food.
  - Constipation: increase fluids, add docusate/fibre, reduce Fe dose
  - Adding ascorbic acid? [Int J Vitam Nutr Res. 2004 Nov;74(6):403-19]
- Pregnancy: 30mg/d supplement beginning at first prenatal visit

Nagaraju *et al. BMC Nephrology* 2013, **14**:64
http://www.biomedcentral.com/1471-2369/14/64

BMC Nephrology

RESEARCH ARTICLE Open Access

Heme iron polypeptide for the treatment of iron deficiency anemia in non-dialysis chronic kidney disease patients: a randomized controlled trial

Shankar P Nagaraju[1], Adam Cohn[2], Ayub Akbari[3], Janet L Davis[4] and Deborah L Zimmerman[3*]

Conclusion: HIP is similar in efficacy to IV iron sucrose in maintaining hemoglobin in ND-CKD patients with no differences in adverse events over 6 months. It is unclear if the greater ferritin values in the IV iron sucrose group are clinically significant.

Nephrol Dial Transplant (2012) 27: 4146–4153
doi: 10.1093/ndt/gfs372
Advance Access publication 7 September 2012

A randomized controlled trial of oral heme iron polypeptide versus oral iron supplementation for the treatment of anaemia in peritoneal dialysis patients: HEMATOCRIT trial

Katherine A. Barraclough[1], Fiona Brown[2], Carmel M. Hawley[1,3], Diana Leary[1], Euan Noble[1], Scott B. Campbell[1], Nicole M. Isbel[1], David W. Mudge[1], Carolyn L. van Eps[1] and David W. Johnson[1,3]

[1]Department of Nephrology, University of Queensland at Princess Alexandra Hospital, Brisbane, Australia, [2]Department of Nephrology, Monash Medical Centre, Melbourne, Australia and [3]Australasian Kidney Trials Network, School of Medicine, University of Queensland, Brisbane, Australia

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Conclusions. HIP showed no clear safety or efficacy benefit in PD patients compared with conventional oral iron supplements. The reduction in serum ferritin levels and high costs associated with HIP therapy suggest that this agent is unlikely to have a significant role in iron supplementation in PD patients.

HEMATOCRIT trial. Nephrol Dial Transplant 2012;27:4146–53.

CMRO
Current Medical Research & Opinion Vol. 29, No. 4, 2013, 291–303
0300-7995
doi:10.1185/03007995.2012.761599
Article RT-0323.R1/761599

Review

Tolerability of different oral iron supplements: a systematic review

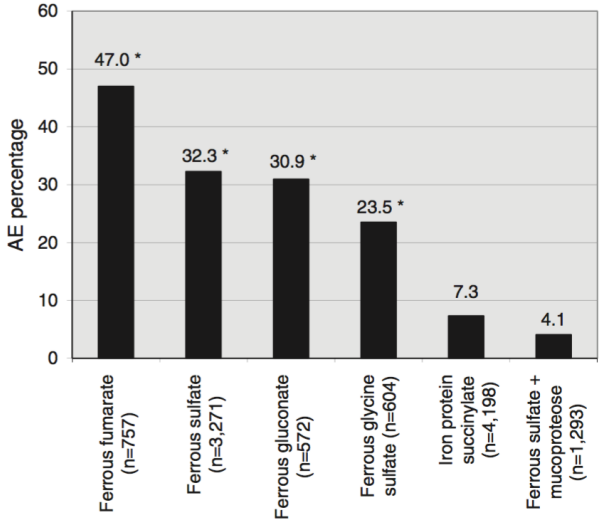

Figure 3. Overall tolerability. Tolerability of the iron supplements studied. The "*n*" shows the sample size of each iron supplement in which frequency has been calculated. *$p < 0.001$ compared to the iron supplement of reference (ferrous sulfate plus mucoproteose).

Cancelo-Hidalgo MJ, et al. Curr Med Res Opin 2013;29:291–303.

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Review

Tolerability of different oral iron supplements: a systematic review

Table 3. Relative risk of any type of adverse effect.
Studies with any dose and those using exclusively doses of 80–120 mg/day.

Oral iron supplement	All doses		80–120 mg/day	
	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value
Ferrous sulfate + mucoproteose	1 (reference value)	–	1 (reference value)	–
Iron protein succinylate	1.85 (0.85–4.05)	0.126	2.73 (0.79–9.49)	0.119
Ferrous glycine sulfate	7.19 (3.00–17.24)	<0.001	8.15 (1.92–34.57)	0.006
Ferrous gluconate	10.48 (4.44–24.74)	<0.001	15.42 (3.03–78.52)	0.002
Ferrous sulfate	11.15 (5.29–23.54)	<0.001	14.27 (4.11–49.57)	<0.001
Ferrous fumarate	20.77 (9.21–46.84)	<0.001	34.26 (9.10–129.07)	<0.001

Cancelo-Hidalgo MJ, et al. Curr Med Res Opin 2013;29:291–303.

Iron Deficiency Anemia: Therapy

- Parenteral Iron
  - When?
    - Non-response or intolerance to PO Fe
    - Severe Fe deficiency and hospitalized
    - Severe ongoing bleeding
    - TPN
    - Some dialysis patients on EPO

Table 4. Iron Preparations for Intravenous Use.*

Formulation	Dose per Infusion	
	Standard	Maximum per Single Infusion
Ferric gluconate (Ferlecit)	125 mg/10–60 min	250 mg/60 min
Iron sucrose (Venofer)	100–400 mg/2–90 min	300 mg/2 hr
Low-molecular-weight iron dextran (INFeD)†	100 mg/2 min	1000 mg/1–4 hr)
Ferumoxytol (Feraheme)†	510 mg/>1 min	510–1020 mg/15–60 min
Ferric carboxymaltose (Ferinject)†	750–1000 mg/15–30 min	750–1000 mg/15–30 min
Iron isomaltoside (Monofer)†‡	20 mg/kg of body weight/15 min	20 mg/kg of body weight/15 min

* Data are adapted from Powers and Buchanan[13] and Auerbach and Ballard[66]
† Drugs that can be administered as a total dose in a single infusion.
‡ Iron isomaltoside is licensed for use only in Europe.

Camaschella C. New England Journal of Medicine 2015;372:1832–43.

Iron Deficiency Anemia: Monitoring

- HgB and retics 1-2 weeks after starting PO Fe
- HgB ~monthly until normalized
- Duration of therapy:
  - Stop Fe when HgB normal
  - Continue Fe x 6 mos after normal HgB
  - Continue Fe indefinitely if underlying cause irreversible

Case 2

- **ID/CC:** 52 y/o Caucasian M, brought to ED in an inebriated state by EHS who found him lying in the street.
- **HPI:** ??
- **PMH:** ??
- **MPTA:** ??
- **O/E:** BP 100/70; HR 110 bpm; RR 28; 37 C. Lethargic but arousable. Pale and cachectic with jaundiced conjunctiva and skin. PERL. Lungs clear. Abdomen distended, shifting dulness indicating ascites. Liver enlarged. 2+ bilateral edema of his legs and feet. No focal neurologic defects.
- **Labs:** HgB 90↓; MCV 121 ↑; RDW ↑; WBC 15; Serum folate 0.5↓; RBC folate 50 ng/mL↓. FOB (-).

Folate Deficiency Anemia

Lab Profile

Parameter	Finding
HgB	↓
MCV	↑
RDW	↑
Ferritin	--
TIBC/transferrin	--
Serum Fe	--
"% saturation" / "transferrin index" / "transferrin saturation"	--

SERUM FOLATE and/or RBC Folate ↓

Folate Deficiency Anemia: Causes

- Diet: overcooked foods, lack of vegetables
- Drugs
- Alcoholism
- Malabsorption
  - IBD
  - Sprue (a.k.a. celiac disease)
  - short bowel

Folate Deficiency Anemia: Therapy

- Transfusion?
- Folate
  - Give folic acid (RDI = 100 mcg/d)
    - 1 - 5 mg PO daily x 1-4 months, or until HgB normalized
    - Correct underlying cause (eg, dietary deficiency) or continue supplementing
    - Folate-rich foods: anything green, OJ, cereals, flour, milk, bananas, strawberries
  - Never initiate folate without knowing the B12 level!
    - May correct the anemia, but won't prevent the irreversible neurologic complications of B12 deficiency

Folate Deficiency Anemia: Monitoring

- HgB & Retics 1-2 weeks after starting folate
  - Monthly thereafter until HgB plateaus
- q2 monthly after stopping folate, until HgB stable

Case 3

- 16 y/o M admitted to hospital
- CC: tiredness, breathlessness, weakness x 5 weeks
- PMH: nil.
- MPTA: nil.
- O/E: Pale, unwell. HR 120 bpm; BP 130/70; RR 20;
- Labs:
  - Hgb 58↓, MCV 116↑, RDW 12, Ferritin (N), Tsat 24%, folate (N), B12 <80 mmol/L↓. WBC 4.2. FOB (-).

B12 Deficiency Anemia

Lab Profile

Parameter	Finding
HgB	↓
MCV	↑
RDW	↑
Ferritin	--
TIBC/transferrin	--
Serum Fe	--
"% saturation" / "transferrin index" / "transferrin saturation"	--

SERUM B12 ↓, Schilling's test +, anti-IF antibody +

B12 Deficiency Anemia: Causes

- Diet: strict vegan, alcoholism
- Drugs
- Malabsorption
  - **Gastritis (chronic atrophic)**
  - Pancreatic insufficiency
  - IBD
  - short bowel
  - pernicious anemia
  - H.pylori [Arch Intern Med. 2000;160:1349-1353]
- Consequences:
  - Neurologic: spinal degeneration --> leg neuropathy --> weakness, spaticity, paraplegia
  - Neuropsych: memory loss, irritability, dementia

B12 Deficiency Anemia: Drug-Induced

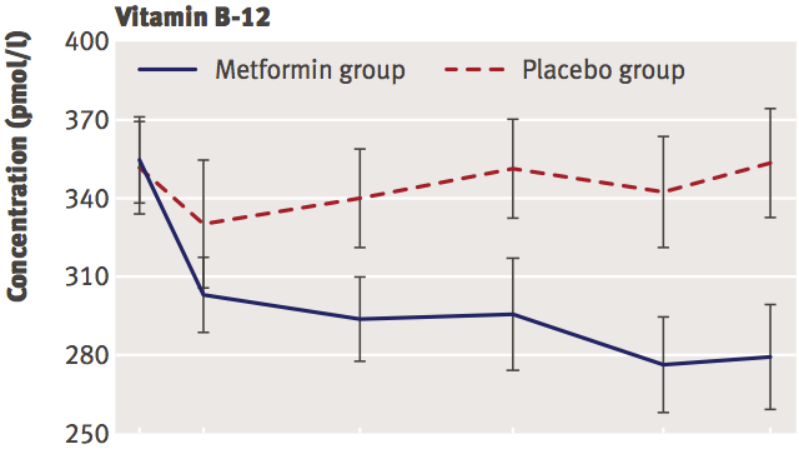
- Metformin
  - Case-control, N=155 cases, Chinese.

Risk Factor	Adjusted OR (95% CI)	*P* Value
Age (per 10-y increment)	1.60 (1.24-2.04)	<.001
Vegetarian	10.9 (1.09-109.00)	.04
Use of histamine H_2-receptor antagonist or proton pump inhibitor	1.33 (0.63-2.79)	.45
Daily dose of metformin (per 1-g increment)	3.75 (2.63-5.35)	<.001
Use of metformin for more than 3 y	2.39 (1.46-3.91)	.001

Arch Intern Med. 2006;166:1975-9

B12 Deficiency Anemia: Drug-Induced

- Metformin
  - RCT. N=390 patients with DM2 receiving insulin.
  - Metformin 850mg tid vs. placebo x 4.3 years



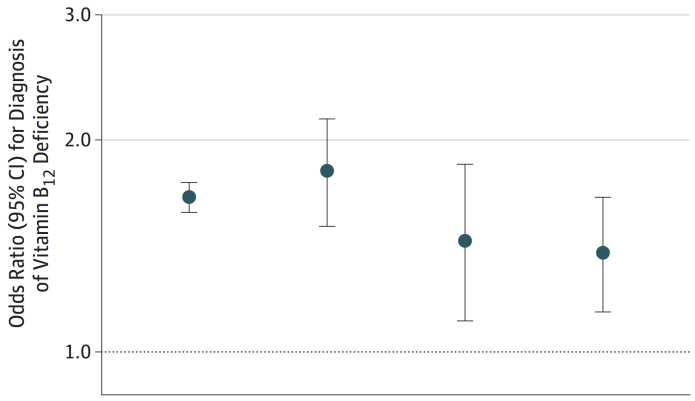
B12 deficiency (<150 pmol/L):

9.9% vs. 2.7%
NNH x 4.3y=14

de Jager et al. BMJ 2010;340:c2181

B12 Deficiency Anemia: Drug-Induced

Figure. Association Between a 2 or More Years' Supply of Proton Pump Inhibitors (PPIs) and a Diagnosis of Vitamin B_{12} Deficiency, Stratified by Time Since Most Recent Prescription



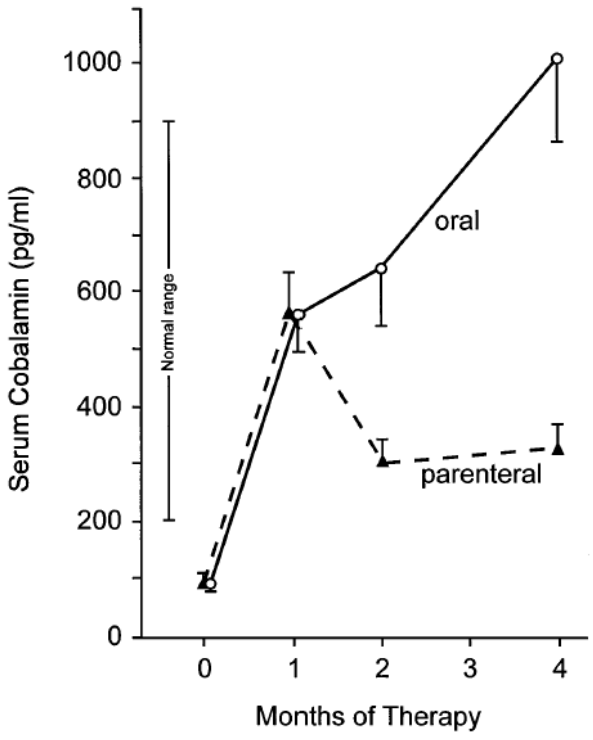
Patients, No.				
Cases	2697	190	79	154
Controls	11458	668	363	721

Lam JR, et al. JAMA 2013;310:2435–42.

B12 Deficiency Anemia: Therapy

- Transfusion?
- B12 (cyanocobalamin)
  - RDI = 3 mcg/d
  - IM: B12 1mg daily x 7 days, 1mg weekly x 4 weeks, then 1mg monthly
  - PO: 2mg daily
    - immediately or after initial parenteral replacement

Myth?: B12 replacement must be done parenterally



Kuzminski et al. Blood 1998;92:1191-8

Myth?: B12 replacement must be done parenterally

Table 5. Responses After 4 Months of Therapy With Oral or Parenteral Cyanocobalamin

	Oral	Parenteral	
MCV decreased ≥5 fL	9/18	8/15	
Hematocrit increased ≥5%	5/18	2/15	
Marked improvement or clearing of paresthesias, ataxia, or memory loss	4/18	4/15	
Serum methylmalonic acid decreased to <3 SD above the mean in normal controls	17/18	12/14*	
Serum total homocysteine decreased to <3 SD above the mean in normal controls	16/18†	13/15	
Serum cobalamin >300 pg/mL at 4 mo	18/18	7/14§	P<0.001
Serum cobalamin >200 pg/mL at 4 mo	18/18	10/14‖	P<0.001

Kuzminski et al. Blood 1998;92:1191-8
Butler et al. Family Practice 2006;279-85

Myth?: B12 replacement must be done parenterally

If you're going to go oral...

2000 mcg vitamin B12 PO daily indefinitely
[Kuzminski et al.]

or

1000 mcg vitamin B12 PO daily x 10 days, then weekly x 4 weeks, then monthly indefinitely
[Bolaman et al.]

Butler et al. Family Practice 2006;279-85

B12 Deficiency Anemia: Monitoring

- HgB & Retics 1-2 weeks after starting B12
  - Monthly thereafter until HgB plateaus
- In PA, once on a stable regimen and stable HgB, only infrequent monitoring required (eg, HgB q6 monthly)
- q2 monthly after stopping B12, until HgB stable

Anemia: Therapeutic Quick Hits

- What's This?
  - HgB 95 ↓
  - MCV ↑
  - RDW ↑
  - ferritin N
  - serum Fe N
  - TIBC/transferrin N
  - % sat N
  - folate ↓
  - B12 N
  - retics ↓

Anemia: Therapeutic Quick Hits

- What's This?
  - HgB 89 ↓
  - MCV ↓
  - RDW ↑
  - ferritin - not measured
  - serum Fe N
  - TIBC/transferrin ↑
  - % sat ↓
  - folate N
  - B12 N
  - retics ↓

Anemia: Therapeutic Quick Hits

- What's This?
  - HgB 70 ↓
  - MCV ↑
  - RDW ↑
  - ferritin N
  - serum Fe N
  - TIBC/transferrin N
  - % sat N
  - folate N
  - B12 N
  - retics ↑

Anemia: Therapeutic Quick Hits

- What's This?
  - HgB 101 ↓
  - MCV ↓
  - RDW N
  - ferritin ↑
  - serum Fe ↓
  - TIBC/transferrin N
  - % sat N
  - folate N
  - B12 N
  - retics ↓