Anemia: Not the New Normal

Kentucky Medical Association

August, 2023

Carolyn D. Burns, MD

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Relevant Financial Relationship(s):

Co-founder Collaborative Clinical Consulting, LLC

President, Society for the Advancement of Patient Blood Management

PBM consultant services provided to Accumen, Octapharma, Hemosonics

Advisory Board member, Werfen

Invited speaker for Zuellig Pharma, WellSky

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Purpose:

To Present the State of the Science Related to Anemia as a Silent Pandemic, its Diagnosis, Treatment, & Patient Impact.

Objectives:

- Set the stage: the urgent need for PBM, the Global Definition, and the concept of Blood Health.
- Review the etiologies of anemia, the vast symptoms associated with anemia and outcomes in anemic patients.
- Highlight the adverse outcomes of transfusion.
- Focus on non-transfusion alternatives, particularly re: iron deficiency

Desired Outcomes:

- At the end of this lecture, the audience will be able to apply the concepts learned into daily practice.

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PATIENT BLOOD MANAGEMENT:
Why the urgency?

Anemia is present in 1 in every 4 people.

- Worldwide, there are over 2 billion people affected by anemia.
- The most common etiology is iron deficiency.
- The WHO has identified anemia as a global health priority.
- An estimated 600 hundred million people have acute and/or chronic blood loss; congenital and/or acquired bleeding disorders contribute to the burden of anemia.
- Anemia and coagulopathy are each independently associated with increased morbidity, mortality and readmissions.

https://www.who.int/publications/i/item/9789240035744

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Patient Blood Management

The Global Definition

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"Patient Blood Management is a patient-centered, systematic, evidence-based approach to improve patient outcomes by managing and preserving the patient's own blood, while promoting patient safety and empowerment."

Shander A et al. Anesth Analg 2022; 135: 476-488.

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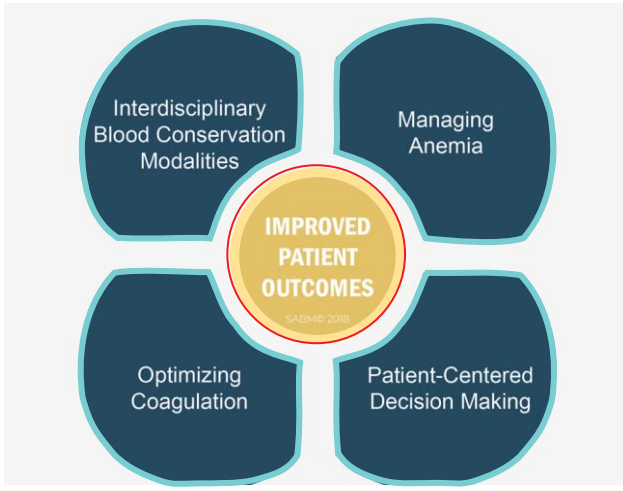

In both medical and surgical patients:

- Identify, evaluate, and treat anemia.
- Identify and rapidly address coagulation/hemostasis issues.
- Use all effective blood conservation methods.
- Carefully monitor patients.
- Thoroughly inform and educate healthcare providers, patients, and their caregivers; involve all parties in care plans and treatment decisions.
- Maintain continuity of care throughout all patient experiences.

Shander A et al. Anesth Analg 2020; 131: 74-85

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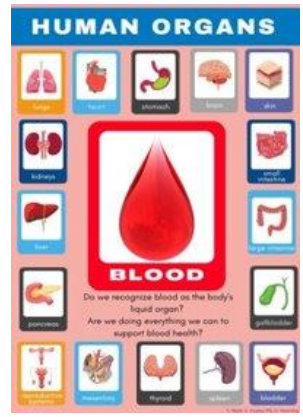
Blood as an Organ

An organ is a biological system [which works] together to perform one or more functions. Each organ has a specialized role in [the]…body and is made up of distinct tissues.



Functions far beyond mere gas exchange

- Ion homeostasis
- Vasodilatation
- System metabolism
- Detoxification
- Immune-modulation
- Cross-talk with other cells

Nemkov T et al. Expert Review of Proteomics 2018; 15: 855-864

Insufficiencies/failure of blood i.e., Blood Health, must be addressed, not just replaced.

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Anemia is a Silent Pandemic

Anemia is a sign, not a single disease, and often is multifactorial.

Anemia is a common complication of many diseases:

- 30-60% in patients with rheumatoid arthritis
- 30-80% in patients with inflammatory bowel disease
- 30-50% in patients with congestive heart failure
- 20-40% in diabetics w/o renal failure
- 40-60% in patients with chronic kidney disease

There is a strong association with abnormal iron absorption and metabolism.

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Consequences of Anemia

Patients with anemia are:*

2X more likely to develop hospital-acquired infections

3X more likely to die

4X more likely to develop AKI

5X more likely to receive transfusions

Have an odds ratio for 30-d readmission rates of 1.74/2.76/and 3.47 for mild, moderate, or severe anemia respectively**

Disability secondary to anemia is greater than asthma, diabetes and CV disease combined.

*Fowler AJ et al. Brit J Surg 2015; 102: 1314-24
**Koch C et al. J Patient Safety 2014; www.journalpatientsafety.com

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Anemia & Outcomes: Maternal-Fetal Health

Increased Risk for Mothers

- Cesarean delivery
- Preterm delivery
- Perinatal bleeding
- Transfusion
- Placental abruption
- Poor wound healing
- Postpartum depression

Increased Risk for Infants

- LBW/SGA
- Poor feeding
- Poor motor skills
- Poorer cognitive & social-emotional development

Anemia impacts 40% of pregnant women and up to 40% of children ≤5 yrs.

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Juul SE et al. Neonatology,2019; 115:269-274

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Anemia & Outcomes: Atrial Fibrillation

5-10% yearly growth in diagnosis

Anemia is associated with new-onset Afib

Patients with anemia and Afib have increased incidence of other cardiac events and mortality

Hanna-Rivero N. et al. BMC Cardiovascular Disorders 2022; 22: 204

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Anemia in Inflammatory Bowel Disease

1763 IBD patients; 54% with anemia
Those with anemia had increased:

- Hospitalizations
- LOS
- ED visits
- Overall healthcare costs

TABLE 1. Mean Direct Cost in Patients With Inflammatory Bowel Disease and Mild and Severe Anemia[3]

Cost category	Mild (mean cost [$], SD)	Severe (mean cost [$], SD)	P
Clinic cost	532.66 (820.53)	929.92 (1408.09)	.0115
Emergency department cost	262.18 (617.68)	575.57 (1057.18)	<.0001
Pharmacy cost	10,549.39 (26,149.74)	11,768.77 (29,252.23)	.0009
Admission cost	897.06 (1874.50)	4600.46 (8188.20)	<.0001
Total cost	18,384.42 (33,083.72)	25,741.77 (26,063.58)	.0003

Patel J. Am J Manag Care 2021; 27(suppl 11): S219-S223

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Hospitalized Patients

More than 1/3rd of patients NOT anemic on admission develop anemia during their EOC.

Anemia whether pre-admission, during admission or post-discharge, should… be treated.

…allogeneic blood cannot provide more than a temporary relief - at a potentially hefty price.

Krishnasivam D et al. Transfus 2018; 58: 2522-2528
Shander A, Goodnough LT. Ann Intern Med 2019; 170: 125-126

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SOCIETY FOR THE ADVANCEMENT OF PATIENT BLOOD MANAGEMENT

There is a common misconception that transfusion should be the default management strategy for anemia, that it is low risk, high benefit, despite robust clinical evidence to the contrary.

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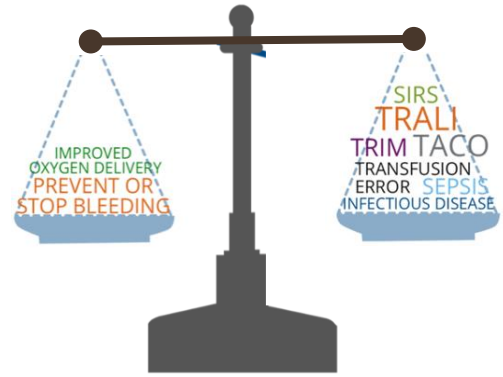
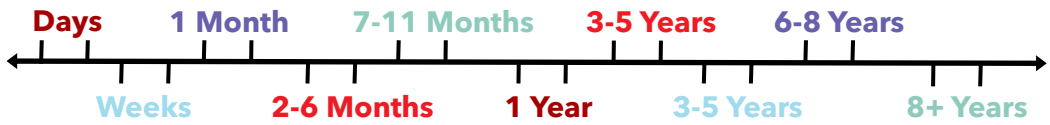
Transfusion: Benefits versus risks

- Delayed hemolytic reactions
- Post-transfusion purpura
- Transfusion-associated graft vs. host disease
- Transfusion-related iron overload





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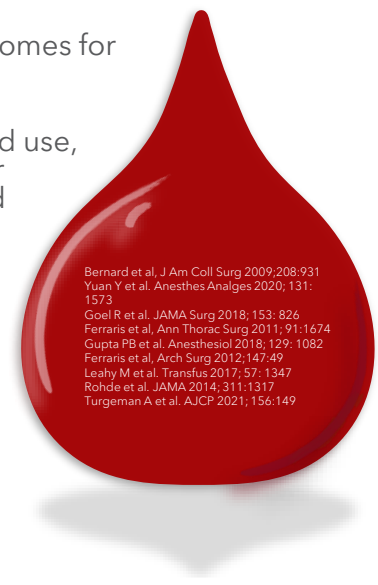
RBC Transfusion & Outcomes

- Liberal use of transfusion does not provide better outcomes for patients.
- A dose-response can be seen with peri-operative blood use, increasing the risk for wound infections, LOS, ventilator dependence, pneumonia, thromboembolic events and mortality.
- Increases in serious infections are seen in transfused medical patients.
- Evidence shows RBC transfusions do not necessarily improve O2 delivery or tissue perfusion.



Bernard et al, J Am Coll Surg 2009;208:931
Yuan Y et al. Anesthes Analges 2020; 131: 1573
Goel R et al. JAMA Surg 2018; 153: 826
Ferraris et al, Ann Thorac Surg 2011; 91:1674
Gupta PB et al. Anesthesiol 2018; 129: 1082
Ferraris et al, Arch Surg 2012;147:49
Leahy M et al. Transfus 2017; 57: 1347
Rohde et al. JAMA 2014; 311:1317
Turgeman A et al. AJCP 2021; 156:149

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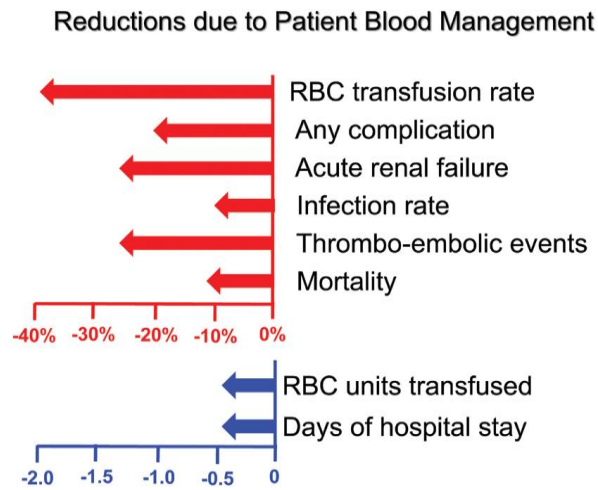
Patient Blood Management

Implementing Patient Blood Management results in reduced erythrocyte transfusions, major postoperative complications including mortality, and hospital length of stay.

Spahn D et al. Anesthesiology 2020; 133:212-222 (with permission)



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THE DIAGNOSIS OF ANEMIA

How do we evaluate?
What are the therapeutic options?

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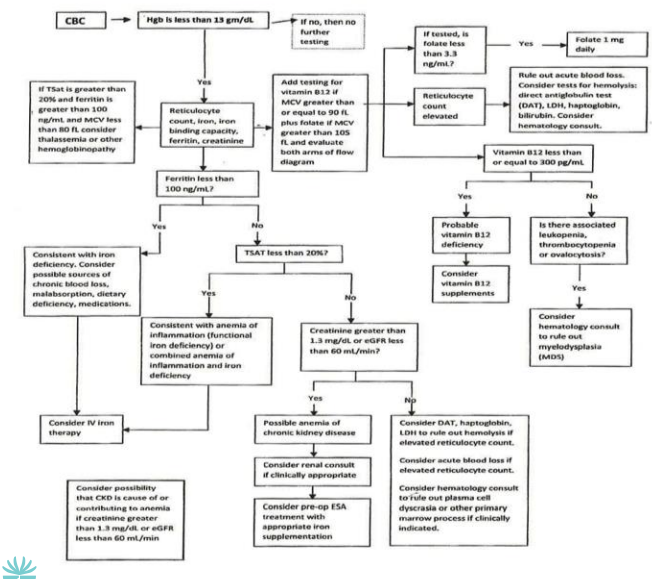
Appendix 1. Anemia Diagnosis and Laboratory Management Flow Sheet



Reticulocyte Hemoglobin Equivalent (Ret-He)

What is the Etiology?

Ask the "why"

Three things could be happening…the patient is

- not making RBCs.
- destroying RBCs.
- losing RBCs.

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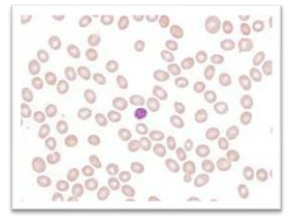
Iron Deficiency: THE most common etiology

- Signs and symptoms are non-specific.
- Symptoms vary based on severity and physiologic compensatory mechanisms.
- Critical/nadir Hgb level is not clear.



Weakness, fatigue, pallor	Headache
Irritability	Exercise intolerance
Cognitive dysfunction	Pica, especially for ice (pagophagia)
Poor feeding	Restless leg syndrome
Impaired myocardial function	Impaired immune function

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Iron Deficiency: Enteric Vs. Parenteral Iron

Enteric iron

- Lower cost, but slower response
- 30-40% of patients have gastrointestinal intolerance
- Poor absorption in many patients even if tolerated
- H2-blockers, PPI's, atrophic gastritis, intestinal malabsorption
- Consider every other day dosing

If there is inflammation:

- Enteric iron absorption is significantly impaired
- Release of storage iron is significantly impaired
- Erythropoietic cells become functionally iron deficient

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When Treating with IV Iron (CAVEATS)

- Avoid IV Fe in patients with acute bacteremia
- Add 1 mg oral folate daily; consider B12
- Add 500 mg Vitamin C X2 qd
- Consider Vitamin D

Optimize/Treat inflammatory comorbidities!

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Safety of IV Iron

Most common reactions include allergic (flushing, pruritis, urticaria, rash) and hypotension

Hypotension usually associated with rapid infusion

Few serious adverse drug events

Over-all AE rate reported as 3.8 per million doses

Risk of RBC transfusion:

- TACO = 1:100 transfused patients
- TRALI = 1: 5,000 transfused units
- AHR (ABO) = 1: 38-70K transfusions

https://pubmed.ncbi.nlm.gov

Avni T et al. Mayo Clin Proc 2015; 90:12
Dave C et al. Annals Intern Med 2022; 175: 656

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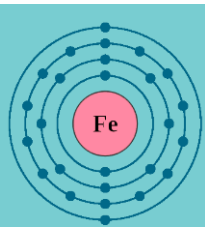
Estimated Treatment Costs

An Australian study found Rx of decreased Fe with or without overt anemia saved ~ $3,700.00 per patient.
Trentino K et al. Anesthesia 2021; 76: 357

Average annual per-patient costs for anemia patients is 54% higher than matched non-anemic patients.
Nissenson AR J Manag Care Pharm 2005; 11: 565: 74



Iron sucrose vs. RBCs =

$688.00/1 g dose vs. $761.00/unit RBC (X4 for 250mg/unit RBC) = ~$3000.00

Auron M & Kumar A. Amer Coll Physicians ACP Hospitalist, March 2012

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RX OF ANEMIA: Outcomes In Patients

"The great thing in the world is not so much where we stand, as in what direction we are moving."
Oliver Wendell Holmes

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Preoperative screening and intervention for mild anemia with low iron stores in elective hip and knee arthroplasty[1]

- Prospective comparative cohort study, before & after launch of program
- 1814 patients pre-intervention, 1622 post-intervention
- Anemia screening algorithm utilized for testing, consultation, & treatment

Pre-operative anemia screening and management…was associated with reduced RBC transfusion, readmission, critical care admission, LOS, and costs.

[1] Pujol-Nicolas A et al. Transfus 2017; 57: 3049-3057

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IV Iron in **Post-operative** Anemia

Intravenous ferric carboxymaltose vs. standard care in the management of post-operative anaemia: a prospective open-label, randomised controlled trial[1]

- Elective surgical patients with documented IDA, received 1000 mg FCM vs. no treatment
- Primary outcomes = change in Hgb, Fe stores, # transfusions
- Secondary outcomes = LOS, infections, safety of FCM, QUALY score @ 4 wks and 12 wks post discharge
- FCM group saw increased Hgb, return of Fe stores, decreased LOS, decreased txn

Post-operative IV iron is feasible, practical and could be incorporated into post-op anemia management as part of PBM strategies.

[1] Khalafallah A et al. Lancet Haematology 2016; e415-425

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CHF, Anemia, & Iron Therapy

- THE FAIR-HF TRIAL[1]
- The CONFIRM-HF Study[2]

Treatment of Fe-deficiency in patients with CHF is effective, has a solid safety profile and provides better QOL with or without associated anemia.

- AFFIRM-AHF[3]
- IRONMAN[4]

IV Fe decreases hospital admissions and shows a trend toward lower overall cardiovascular death.

[1] Filippatos et al Europ J Heart Fail 2013; 15: 1267
[2] Ponikowski P et al. Europ Heart J 2015; 36: 657
[3] Ponikowski P et al. Eur J Heart Failure 2019; 21: 1651
[4] Kalra PR et al. Lancet 2022; doi: 10.1016/S0140-67361(22)02083-9

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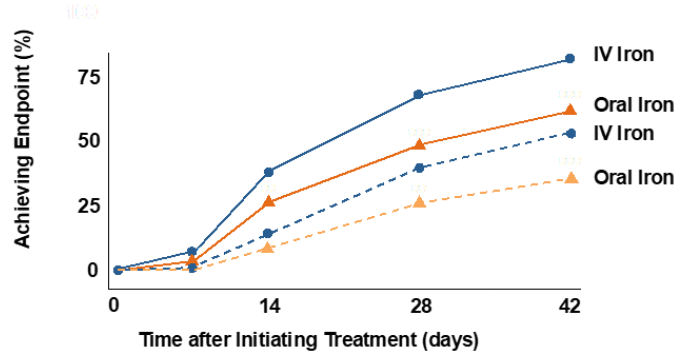
IV Iron Improves Anemia in Women with Menorrhagia

Proportion of patients achieving an Hgb increase of more than 2.0 g/dL or 3.0 g/dL according to treatment assignment; significant between-group differences.

Proportion of 477 Patients Achieving an Hgb Increase of 2 g/dL or 3 g/dL after Ferric Carboxymaltose



Van Wyck DB, et al. Transfusion. 2009;49:2719-2728

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Treatment of Fe Deficiency in Women with AUB

Multiple studies highlight the improved quality of life with Fe replacement

- 12 months of treatment with Fe replacement:
  - Increased energy, physical function, social function
  - Decreased anxiety and depression

Peurpaa P et al. Acta Obstetr Gynecol Scand 2014; 93: 654

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IV FE in IBD

TABLE 4. Changes in QoL, Disease Activity Scores, and CRP Before and After Iron Therapy

	Baseline SIBDQ (n = 336)	Posttreatment SIBDQ (n = 337)	Baseline Disease Activity (n = 335)	Posttreatment Disease Activity (n = 336)	Baseline CRP (n = 317)	Posttreatment CRP (n = 285)
CD	$_{36}48_{58}$	$_{41}54_{61}$	$_{3}6_{10}$ (HBI)	$_{1}4_{7}$ (HBI)	$_{1.8}5.8_{18.5}$	$_{1.0}3.9_{12.55}$
UC	$_{34}46_{59}$	$_{44}58_{64}$	$_{2}4.5_{10}$ (SCCAI)	$_{0}2_{6}$ (SCCAI)	$_{1.6}4.4_{11.1}$	$_{0.6}1.7_{8.6}$
Combined	$_{36}48_{58}$	$_{42}55_{62}$	~	~	$_{1.7}5.7_{15.9}$	$_{0.9}3.1_{12.0}$

$_{A}B_{C}$ represents the lower quartile A, the median B, and the upper quartile C. Differences between baseline and posttreatment SIBDQ scores are significant with $P < 0.001$ for CD, UC, and combined. Disease activity measured with HBI for patients with CD and SCCAI for patients with UC. Baseline and posttreatment disease activity scores trended toward improvement with $P = 0.051$ for HBI change and $P = 0.085$ for SCCAI change. CRP change was significant for combined and CD ($P < 0.005$), but not UC ($P = 0.55$).
n, number of patients where relevant data were available via chart review.

Coe CL et al. Crohn's & Colitis 360 2020; 2: 1-6.

SIBDQ = Short Inflammatory Bowel Disease Questionnaire
HBI = Harvey-Bradshaw Index
SCCAI = Simple Clinical Colitis Activity Index

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Outcomes with IV Iron Rx in CKD

- FIND-CKD: NDD-CKD RX with oral or IV Fe decreased need for ESA and transfusion
- DRIVE/DRIVE 2: DD-CKD Rx with IV Fe increased Hgb, decreased ESA dose
- PIVOTAL Trial: IV Fe in DD-CKD increased Hgb more rapidly, decreased need for ESA and decreased occurrence of MI, stroke and death

Macdougall IC et al. Nephrol Dialysis and Transplantation 2014; 29: 2075
Coyne DW et al. J Am Soc Nephrol 2007; 18: 975
Kapoian T et al. J Am Soc Nephrol 2008; 19: 372
Macdougall IC et al. N Engl J Med 2019; 380: 447

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Prevention of Hospital-Acquired Anemia from Excessive Phlebotomy

- Mean phlebotomy losses = 40-370 cc/day
- 100 cc phlebotomy loss decreases Hct ~ 2.0%

The most common reason for phlebotomy is sunrise.

Dr. Aryeh Shander

- Small volume tubes
- POC testing
- Reduce or eliminate standing orders for daily labs; lab "schedules"
- Focus on daily phlebotomy volumes
- Reinfusion sets to avoid discard
- Better TATs to avoid over-ordering
- Decrease duplicate testing
- COMMUNICATION with the lab

Seeber P & Shander A Basics of Patient Blood Management, 1st edition Blackwell Publishing 2007
Thavendiranathan P et al. J Gen Intern Med 2005; 20: 520-524

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BENEFITS OF ANEMIA MANAGEMENT

Anemia may be indicative of an underlying/undiagnosed malignancy or severe illness

Helps identify treatable co-morbidities

Reduces morbidity, mortality & readmission

Improves outcomes in medical & surgical patients

Can avoid transfusion and the associated risks/poorer outcomes

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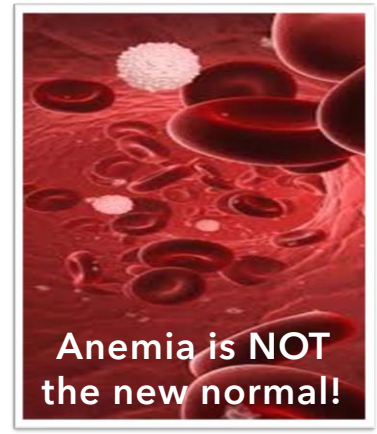
Blood is an Organ:

Disease(s) of the hematopoietic system, Blood Health, cannot be ignored and should be an integral part of patient-centered/patient-engaged care.

Inattention to Blood Health may represent the world's single biggest and costly failure to deliver care.

Hofmann, A., et al. Anesthesia Analgesia 2022; 135:511-523.



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"There is no doubt that our own blood is still the best thing to have in our veins."

WHO Policy Brief, 2021

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WORLD
ANEMIA
AWARENESS

World Anemia Awareness Day *February 13*

worldanemiaawareness.com

OfficialWorldAnemiaAwareness

HumanTouchMedia Foundation, 2023

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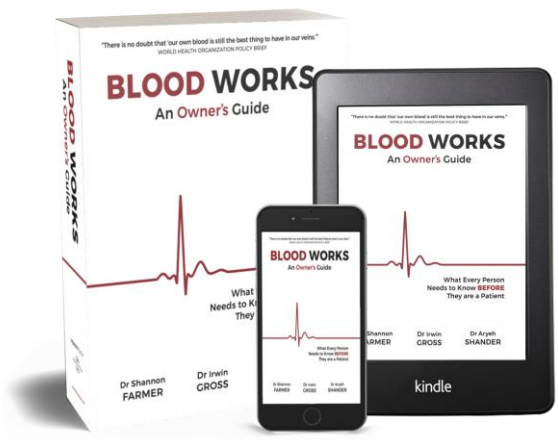

SCAN HERE

BloodWorksBook.com

Promo Code: SABM

HumanTouchMedia Foundation, 2023

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QUESTIONS/DISCUSSION

The treatment of a disease may be entirely impersonal;
the care of a patient must be completely personal.
Francis W Peabody (1927) JAMA 2015; 313:1868

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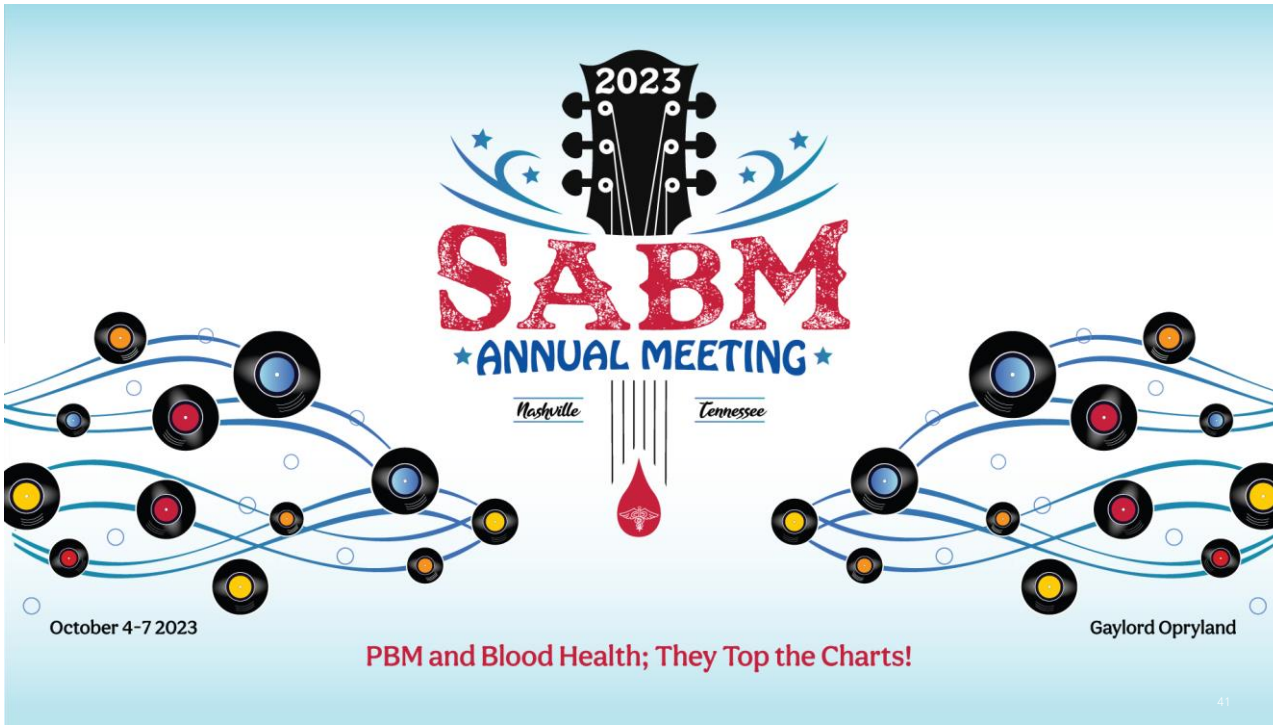

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Anemia Management Publications

- Munoz M et al. Anesthesia 2019; 73:1418-1431 (Post-op)
- Shander A et al. Ann Surg 2022; ahead of print; doi: 10.1097/SLA.0000000000005721 (Peri-surgical)
- Munoz M et al. Transfusion Med 2018; 28: 22-39 (Pregnancy and postpartum)
- Mansour D et al. Adv Ther 2021; 38: 201-225 (AUB)
- Corwin H et al. Ann Thorac Surg 2022; 113: 16-23 (CVS)
- Corsi F et al. J Clin Anesth 2023; doi: 10.1016/j.cliane.2022.111009 (CVS)
- Houry M et al. Anaesthes Crit Care Pain Med 2023; doi: 10.1016/j.accpm.2022.101171 (CVS)
- Guinn N et al. Anesth Analg 2022; 135: 532-544 (ERAS-CS)
- Tibi P et al. Ann Thorac Surg 2021; 112: 981-1004 (STS/SABM/AmSect/SCA)
- Jimenez KM and Gasche C. Acta Haematol 2019; 142: 30-36 (IBD)
- Busti F et al. Pharmaceuticals 2018; 11: 94 (CAA)

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						Iron Isomaltoside 1000–the generic name initially approved in the European Union and other markets
FDA Approved Indication	Iron deficiency in patients whom oral administration is unsatisfactory or impossible.	Venofer is an iron replacement product indicated for the treatment of iron deficiency anemia in adult patients with chronic kidney disease (CKD).	Iron deficiency anemia in adult patients and in pediatric patients age 6 years and older with chronic kidney disease receiving hemodialysis who are receiving supplemental epoetin therapy.	Iron deficiency anemia in adult patients with chronic kidney disease (CKD).	Iron deficiency anemia in adult patients who have intolerance to oral iron or have had unsatisfactory response to oral iron; or who have non-dialysis dependent chronic kidney disease.	Iron deficiency anemia in adult patients who have intolerance to oral iron or have had unsatisfactory response to oral iron; who have non-hemodialysis dependent chronic kidney disease.
Black Box Warning	Yes. Anaphylactic-type reactions, including fatalities, have followed the parenteral administration of iron dextran injection.	No	No	No	No	No
Route of Administration	IV injection IV infusion IM injection (not recommended)	IV injection IV infusion	IV injection IV infusion	IV infusion	IV injection IV infusion	IV injection IV infusion
Maximum FDA Approved Single Dose	100 mg	400 mg	125 mg	510 mg	750 mg	1000 mg
Dosing	Doses less than or equal to 300 mg, slow IV push at a rate not to exceed 50 mg/minute; or diluted in 100-250 ml normal saline. For administration of a 1000mg total dose infusion, the total calculated dose should be diluted in 500 ml (range of 250 to 1000 ml) of normal saline. After a test infusion, the solution may be infused over 1 or more hours.	Adult Patients with CKD on dialysis Administer Venofer 100 mg undiluted as a slow intravenous injection over 2 to 5 minutes, or as an infusion of 100 mg diluted in a maximum of 100 mL of 0.9% NaCl over a period of at least 15 minutes, per consecutive hemodialysis session. Venofer should be administered early during the dialysis session. 2.2 Adult Patients CKD not on dialysis Administer Venofer 200 mg undiluted as a slow IV injection undiluted over 2 to 5 minutes on 5 different occasions over a 14-day period. There is limited experience with administration of an infusion of 500 mg of Venofer, diluted in a maximum of 250 mL of 0.9% NaCl, over a period of 3.5 to 4 hours on day 1 and day 14. 2.3 Adult Patients with CKD receiving peritoneal dialysis Administer Venofer in 3 divided doses, given by slow intravenous infusion, within a 28-day period: 2 infusions each of 300 mg over 1.5 hours 14 days apart followed by one 400 mg infusion over 2.5 hours 14 days later. Dilute Venofer in a maximum of 250 mL of 0.9% NaCl	Adult Dosage and Administration The recommended dosage of Ferrlecit for the repletion treatment of iron deficiency in hemodialysis patients is 10 mL of Ferrlecit (125 mg of elemental iron). Ferrlecit may be diluted in 100 mL of 0.9% sodium chloride administered by intravenous infusion over 1 hour per dialysis session. Ferrlecit may also be administered undiluted as a slow intravenous injection (at a rate of up to 12.5 mg/min) per dialysis session. For repletion treatment most patients may require a cumulative dose of 1000 mg of elemental iron administered over 8 dialysis sessions. Ferrlecit has been administered at sequential dialysis.	The recommended dose of Feraheme is an initial 510 mg intravenous injection followed by a second 510 mg intravenous injection 3 to 8 days later. Administer Feraheme as an undiluted intravenous injection delivered at a rate of up to 1 mL/sec (30 mg/sec). The recommended Feraheme dose may be readministered to patients with persistent or recurrent iron deficiency anemia.	Up to 750 mg can be delivered in a single dose. Give 2 doses separated by at least 7 days for a total cumulative dose of up to 1500 mg per course1 Administer intravenously by Infusion over at least 15 minutes; Slow push injection at the rate of approximately 100 mg (2 mL) per minute over at least 7.5 minutes; For patients weighing less than 50 kg (110 lb), give each dose as 15 mg/kg body weight. When administered via infusion, dilute up to 750 mg of iron in no more than 250 mL of sterile 0.9% sodium chloride injection, USP, such that the concentration of the infusion is not <2 mg of iron per mL and administer over at least 15 minutes. When administering as a slow intravenous push, give at the rate of approximately 100 mg (2 mL) per minute. A total dose infusion of 1000mg in 250mL NS over 15 minutes has been successfully administered in clinical trials.	For patients weighing 50 kg or more: Administer 1,000 mg of Monoferric as an intravenous infusion. For patients weighing less than 50 kg: Administer Monoferric as 20 mg/kg actual body weight as an intravenous infusion. Repeat Monoferric treatment if iron deficiency anemia reoccurs. Withdraw the appropriate volume of Monoferric and dilute in 100 mL to 500 mL of 0.9% Sodium Chloride Injection, USP. Final diluted concentration should be more than 1 mg iron/mL. Administer the prepared solution via intravenous infusion over at least 20 minutes.

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	Iron Dextran	Iron Sucrose	Ferric Gluconate	Ferumoxytol	Ferric Carboxymaltose	Ferric Derisomaltose
Pediatric Indication	Yes. > 4 months of age	No	Yes. >6 years of age	No	No	No
Pediatric Dosing	Greater than 10 Kg: Administer 100 mg iron dextran IV per day until total calculated dose is given. 5-10 Kg: Administer 50 mg iron dextran IV per day until the total calculated dose is given. Infants greater than 4 months but less than 5 Kg: Administer 25 mg iron dextran IV per day until the total calculated dose is given.	Pediatric Use Safety and effectiveness of Venofer in pediatric patients have not been established.	The recommended pediatric dosage of Ferrlecit for the repletion treatment of iron deficiency in hemodialysis patients is 0.12 mL/kg Ferrlecit (1.5 mg/kg of elemental iron) diluted in 25 mL 0.9% sodium chloride and administered by intravenous infusion over 1 hour per dialysis session. The maximum dosage should not exceed 125 mg per dose.	N/A	N/A	N/A
Lactating Women	Traces of unmetabolized iron dextran are excreted in human milk.	It is not known whether iron sucrose is excreted in human milk.	It is not known whether Ferrlecit is excreted in human milk. Benzyl alcohol present in maternal serum is likely to cross into human milk and may be orally absorbed by a nursing infant. Caution should be exercised when Ferrlecit is administered to a nursing woman [see Use in Specific Populations].	It is not known whether ferumoxytol is present in human milk.	The available published data on the use of ferric carboxymaltose in lactating women demonstrate that iron is present in breast milk. However, the data do not inform the full potential exposure of iron for the breastfed infant. Among the breastfed infants, there were no adverse events reported that were considered related to ferric carboxymaltose exposure through breastmilk.	The available data on the use of Monoferric in lactating women demonstrate that iron is present in breastmilk. However, the data do not inform the potential exposure of iron for the breastfed child or the effects on milk production.

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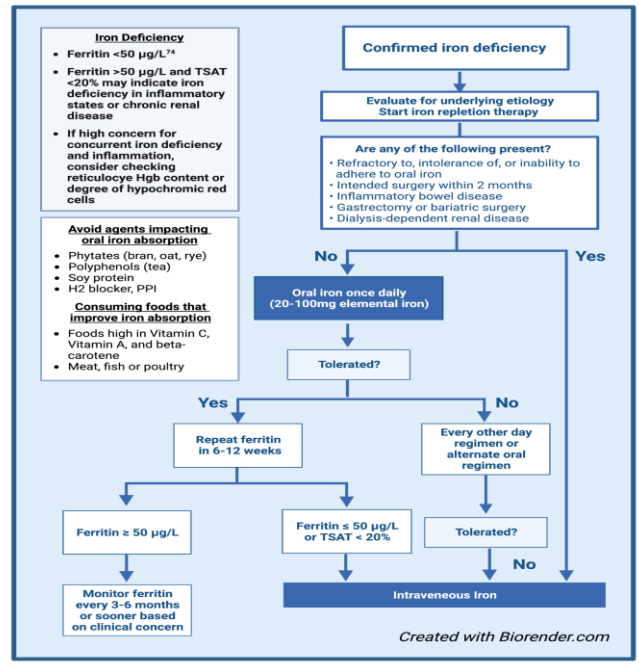
Proposed algorithm for treating iron deficiency



Lo J et al. Eur J Haematol 2022; doi: 10.1111/ejh.13892 (with permission)

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Iron Dose Requirement (The Ganzoni Formula)

Total iron deficit = 80 X 2 X 2.4 + 500 = 884 mg

- Most often amount administered = 500-1000 mg

Formula total iron deficit (mg) = Weight X (Target Hgb – Actual Hgb) x 2.4 + Iron stores (500 mg)

Example: 70 yo ♂ wt. = 80 kg has measured Hgb = 9, desired target Hgb = 11

WHEN TREATING WITH IV IRON (CAVEATS)

- Avoid IV Fe in patients with acute bacteremia
- Add 1 mg oral folate daily; consider B12
- Add 500 mg Vitamin C X2 qd
- Consider Vitamin D

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Comments Regarding ESAs

- ESA reduces perioperative transfusions. Consider in multiple patient scenarios including patients where blood is not an option.
- Use lowest dose and shortest administration period needed to avoid AEs.
- Consider thromboprophylaxis in patients at higher risk for thrombosis.
- Management in CA-associated anemia: Hgb < 10 g/dL and on chemotherapy without curative intent.
- Beware of Hgb levels above 11 g/dL; hyperviscosity.
- **Replete Fe stores!!**

Cho BC et al. Anesth Analg 2019; 128: 981; Spahn D et al. Lancet 2019; 393: 2201; Bohlius J et al. Blood Adv 2019; 3: 1197

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Some Logistics…

- Pre-printed order sets/treatment algorithms makes it easier and more efficient to manage patients
  - Include most common diagnoses with check boxes; ensure accurate documentation of medical necessity
  - Include most common treatment regimens and doses
- Reimbursement for use of ESAs and/or intravenous iron may be restricted by CMS coverage determinations (National and/or Local).
- There may be a difference between medically appropriate use, the coverage determination, and the "labeled" indications for the medication.
- ESA will NOT be covered if the patient's ferritin is < 100 ng/ml or transferrin saturation (TSat) is < 20%
- Be sure your patients are iron replete before treating with an ESA.

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POTENTIAL TREATMENTS FOR ANEMIA

Hypoxia-inducible factor (HIF) has a distinct role in erythropoiesis in patients with CKD

- HIF-prolyl hydroxylase inhibitors e.g., roxadustat, vadadustat
- Oral medications in trials for DD-CKD and NDD-CKD patients
- Effective, but there remains need for safety assessment

Terminal differentiation erythropoietic agents

- Luspatercept for MDS, CKD, β-thalassemia
- Imelestat for MDS

New agents for SSD

- L-glutamine, voxelotor, crizanlizumab

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Potential Treatments for Anemia

Is there a role for anti-hepcidin drugs?

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- Hepcidin is a key regulatory hepatic peptide involved in control of intestinal Fe absorption and distribution of Fe stores.
- An increase in hepcidin causes a decrease in intestinal absorption and decreased release for erythropoiesis.
- Increased levels of hepcidin have been noted in the critically ill and cause the development of the functional Fe deficiency seen in these patients.
- Hepcidin antagonist clinical trials include:
  - 1. Inhibitor NOX-H94, a mirror image RNA oligonucleotide
  - 2. LY2787106, a humanized Ab
  - 3. PRS-080, protein which binds hepcidin

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