An Oncologists Approach to Anemia in Adults
(There are not many updates)

Christie Hilton DO
POMA Winter Symposium 2019
Nemicolin Woodlands

#POMAD8
#ChoosePOMA

8

Disclosures

- None

#POMAD8
#ChoosePOMA

9

Objectives

- Define anemia
- Review the classification of anemia by MCV
- Review a standard approach to evaluation of anemia.
- Discuss transfusion Guidelines
- Pearls for when to order additional "special" tests

#POMAD8
#ChoosePOMA

10

Anemia Defined

- Anemia is the manifestation of a problem – not the problem
- Anemia describes the condition of having less than "normal" amount of blood cells / reduction in hemoglobin or hematocrit
  - We must remember that **2.5-5% of "normal" adults** will have values below the "normal range" (*)
- Etiology:
  - **Blood loss**
    - Bleeding, Trauma
  - **Inadequate production**
    - Bone marrow disorders, Not enough ingredients to make blood cells (iron, etc.), Thalassemia
  - **Destruction of Cells**
    - Hemolysis for any cause, Mechanical destruction

(*)Blood. 2006; 107:1747-1750 #POMAD8 #ChoosePOMA

11

The definition of anemia: what *is* the lower limit of normal of the blood hemoglobin concentration?
Blood. 2006; 107:1747-1750

Anemia defined:

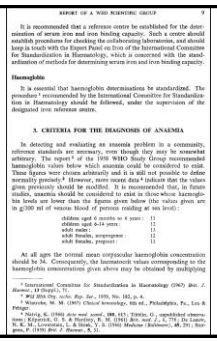
1968 WHO criteria used in epidemiologic studies – never intended to be a guideline standard

- Men: Hemoglobin < 13 g/dL
- Women: Hemoglobin < 12 g/dL

Report of a WHO Scientific Group. WHO Tech Rep Ser. **1968**;405:1-40
Ernest Beutler and Jill Waalen. **Blood. 2006; 107:1747-1750** #POMAD8 #ChoosePOMA

12

A reproduction of the page of the WHO report that has been used as a standard for anemia in epidemiologic studies.



REPORT OF A WHO SCIENTIFIC GROUP 9

It is recommended that a reference centre be established for the determination of serum iron and iron binding capacity. Such a centre should establish procedures for checking the collaborating laboratories, and should keep in touch with the Expert Panel on Iron of the International Committee for Standardization in Haematology, which is concerned with the standardization of methods for determining serum iron and iron binding capacity.

Haemoglobin

It is essential that haemoglobin determinations be standardized. The procedure[1] recommended by the International Committee for Standardization in Haematology should be followed, under the supervision of the designated iron reference centre.

3. CRITERIA FOR THE DIAGNOSIS OF ANAEMIA

In detecting and evaluating an anaemia problem in a community, reference standards are necessary, even though they may be somewhat arbitrary. The report[2] of the 1958 WHO Study Group recommended haemoglobin values below which anaemia could be considered to exist. These figures were chosen arbitrarily and it is still not possible to define normality precisely.[3] However, more recent data[4] indicate that the values given previously should be modified. It is recommended that, in future studies, anaemia should be considered to exist in those whose haemoglobin levels are lower than the figures given below (the values given are in g/100 ml of venous blood of persons residing at sea level):

children aged 6 months to 6 years:	11
children aged 6–14 years:	12
male adults:	13
adult females, nonpregnant:	12
adult females, pregnant:	11

At all ages the normal mean corpuscular haemoglobin concentration should be 34. Consequently, the haematocrit values corresponding to the haemoglobin concentrations given above may be obtained by multiplying

[1] International Committee for Standardization in Haematology (1967) *Brit. J. Haemat.*, **13** (Suppl.), 71.
[2] *WHO Bull. Org. mond. Santé, Bur. Sér.*, 1959, No. 183, p. 4.
[3] Wintrobe, M. M. (1967) *Clinical hematology*, 6th ed., Philadelphia, Pa., Lea & Febiger.
[4] Hässig, K. (1966) *Acta med. scand.*, **180**, 451; Zittoun, C., unpublished observations; Kilpatrick, D. S. & Hershey, N. M. (1941) *Brit. med. J.*, **1**, 778; De Leeuw, N. K. M., Lowenstein, L. & Hsieh, Y. S. (1966) *Medicine (Baltimore)*, **45**, 291; Stargens, P. (1959) *Brit. J. Haemat.*, **5**, 51.

blood

Ernest Beutler, and Jill Waalen
Blood 2006;107:1747-1750

#POMAD8
#ChoosePOMA

13

The definition of anemia: what *is* the lower limit of normal of the blood hemoglobin concentration?
Blood. 2006; 107:1747-1750

Anemia defined:

1968 WHO criteria used in epidemiologic studies – never intended to be a guideline standard

- Men: Hemoglobin < 13 g/dL
- Women: Hemoglobin < 12 g/dL

These values do not account for:

- Age, race, altitude, smoking, or other patient factors (kidney disease, chronic illness, relative hypoxia/smoking, thalassemia etc...)

Report of a WHO Scientific Group. WHO Tech Rep Ser. **1968**;405:1-40
Ernest Beutler and Jill Waalen. **Blood. 2006; 107:1747-1750**
#POMAD8
#ChoosePOMA

14

The definition of anemia: what *is* the lower limit of normal of the blood hemoglobin concentration?
Blood. 2006; 107:1747-1750

Anemia defined:

1968 WHO criteria used in epidemiologic studies – never intended to be a guideline s

- Men: He
- Women:

These valu

- Age, race illness, relative hypoxia/smoking, thalassemia etc...)

The WHO reported hemoglobin values have been used as standards for defining anemia.

"The casual treatment of the lower level of normal, given in whole numbers without decimal points" in the document which deals with nutritional anemia, "clearly suggests that the authors never intended for these values to become a hallowed international standard."

Ernest Beutler and Jill Waalen. **Blood. 2006; 107:1747-1750**

Report of a WHO Scientific Group. WHO Tech Rep Ser. **1968**;405:1-40
Ernest Beutler and Jill Waalen. **Blood. 2006; 107:1747-1750**
#POMAD8
#ChoosePOMA

15

Anemia History

- Is there a recent history of:
  - Loss of appetite
  - Weight loss
  - Fever
  - Night sweats
  - Symptoms that suggest malignancy or infection

#POMAD8
#ChoosePOMA

16

Anemia History

- Is there a recent history of: loss of appetite, weight loss, fever, and/or night sweats →Malignancy or Infection
- Clinical blood loss?
  - Hematemesis, hemoptysis, melena, hematochezia, hematuria, postmenopausal vaginal bleeding, heavy menses

#POMAD8
#ChoosePOMA

17

Anemia History

- Is there a recent history of: loss of appetite, weight loss, fever, and/or night sweats →Malignancy or Infection
- Clinical blood loss?
  - Hematemesis, hemoptysis, melena, hematochezia, hematuria, postmenopausal vaginal bleeding, heavy menses
- Medical history associated with anemia
  - Known celiac or symptoms to make you suspect celiac disease
  - History of Gastric bypass or bowel resection.
  - Chronic diarrhea to suggest malabsorption
  - History of anemia / transfusion history
  - Peptic Ulcer Disease
  - AVMs

#POMAD8
#ChoosePOMA

18

Anemia History

- Is there a recent history of: loss of appetite, weight loss, fever, and/or night sweats →Malignancy or Infection
- Clinical blood loss?
- Medical history associated with anemia
- Acute, subacute, chronic / transfusion history

#POMAD8
#ChoosePOMA

19

Anemia History

- Is there a recent history of: loss of appetite, weight loss, fever, and/or night sweats →Malignancy or Infection
- Clinical blood loss?
- Medical history associated with anemia
- Acute, subacute, chronic / transfusion history
- Family history and Ethnicity
  - Thalassemia and other hemoglobinopathies are particularly common in patients from the Mediterranean, Middle East, sub-Saharan Africa, and Southeast Asia

#POMAD8
#ChoosePOMA

20

Anemia: Approach to the CBC with differential

- **Is the platelet count in normal range?**
  - Thrombocytopenia with anemia
    - Consider
      - Aplastic anemia
      - Hypersplenism
      - Cancer with marrow involvement/Hematologic Malignancy
      - Sepsis
      - B12/folate/Copper deficiency
  - Thrombocytosis with anemia
    - Consider
      - Myeloproliferative neoplasm
      - Iron Deficiency
      - Infection
      - Inflammatory discorders

#POMAD8
#ChoosePOMA

21

Anemia: Approach to the CBC with differential

- **Is the platelet count in normal range?**
- **Is the white blood cell count in normal range? Does the differential look funny?**

#POMAD8
#ChoosePOMA

22

Anemia: Approach to the CBC with differential

- **Is the platelet count in normal range?**
- **Is the white blood cell count in normal range? Does the differential look funny?**

- **Mean corpuscular volume (MCV)**
  - < 80 = microcytic
  - Between 80-95 (up to 100) = normocytic
  - > 95 (or 100) = macrocytic

#POMAD8
#ChoosePOMA

23

Anemia: Approach to the CBC with differential

- **Is the platelet count in normal range?**
- **Is the white blood cell count in normal range? Does the differential look funny?**

- **Mean corpuscular volume (MCV)**
  - < 80 = microcytic
  - Between 80-95 (up to 100) = normocytic
  - > 95 (or 100) = macrocytic
- **Red cell distribution width**
  - Measures degree of variation among size of RBCs.
  - Above 14.5% suggests wide range of RBC sizes.

#POMAD8
#ChoosePOMA

24

Anemia: Approach to the CBC with differential

- **Is the platelet count in normal range?**
- **Is the white blood cell count in normal range? Does the differential look funny?**

- **Mean corpuscular volume (MCV)**
  - < 80 = microcytic
  - Between 80-95 (up to 100) = normocytic
  - > 95 (or 100) = macrocytic
- **Red cell distribution width**
  - Measures degree of variation among size of RBCs.
  - Above 14.5% suggests wide range of RBC sizes.
- **Reticulocyte count:** Measures percentage of reticulocytes (immature RBCs) in peripheral blood.
  - **High** in acute blood loss, hemolysis, exogenous erythropoietin (EPO), iron or B12 repletion.
  - **Low** in bone marrow disorders, lack of ingredients to make blood, low EPO, and conditions that impair erythropoiesis.
  - **Corrected reticulocyte count** OR **reticulocyte index**
    - above 2% suggests appropriate bone marrow response.
    - under 2%, then BM response insufficient for degree of anemia.

#POMAD8
#ChoosePOMA

25

Anemia: Approach to the CBC with differential

- **Is the white blood cell count in normal range? Does the differential look funny?**
- **Is the platelet count in normal range?**
- **Mean corpuscular volum**
  - < 80 = microcytic
  - Between 80-95 (up to 100
  - > 95 (or 100) is macrocytic
- **Red cell distribution widt**
  - Measures degree of variat
  - Above 14.5% suggests wic
- **Reticulocyte count:** Measures percentage of reticulocytes (immature RBCs) in peripheral blood.
  - **High** in acute blood loss, hemolysis, exogenous erythropoietin (EPO), iron or B12 repletion.
  - **Low** in bone marrow disorders, lack of ingredients to make blood, low EPO, and conditions that impair erythropoiesis.
  - **Corrected reticulocyte count** OR **reticulocyte index**
    - above 2% suggests appropriate bone marrow response.
    - under 2%, then BM response insufficient for degree of anemia.

Corrected reticulocyte count = reticulocyte count x (patient Hct/goal Hct).

Reticulocyte index = accounts for increased RBC survival in patients who are anemic. Correction factor applied based on degree of anemia.

#POMAD8
#ChoosePOMA

26

Calculator: Reticulocyte Production Index (RPI) in adults

RPI = (Hct / 45) * Retic / Maturation

Input:

Hct %
Retic %

Results:

RPI %
Decimal precision 1
Reset form

Notes

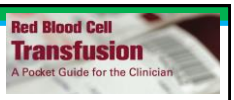
- The **Maturation** term represents the maturation time of red blood cells (in days) at various levels of anemia.
- **Maturation** = 1.0 for **Hct** >=40%.
- **Maturation** = 1.5 for **Hct** 30 to 39.9%.
- **Maturation** = 2.0 for **Hct** 20 to 29.9%.
- **Maturation** = 2.5 for **Hct** <20%.
- An **RPI** >3 shows a normal marrow response to anemia. An **RPI** <2 is an inadequate response to anemia.
- With a normal H&H, an **RPI** of 1 is normal.

Hutchinson RE, Davey FR. Hematopoiesis. In: Henry JB, ed. *Clinical Diagnosis and Management by Laboratory Methods 19th edition*. WB Saunders 1996.

#POMAD8
#ChoosePOMA

27

Anemia: When to transfuse



- Treatment of symptomatic anemia
- Prophylaxis in life-threatening anemia
- Restoration of oxygen-carrying capacity in case of hemorrhage
- Exchange transfusion

JAMA. 2016;316(19):2025-2035
Hematology.org (pocketguides)

#POMAD8
#ChoosePOMA

29

Transfusion Guidelines

One unit of PRBC will raise the hemoglobin of an average-size adult by ~1 g/dL (HCT ~3%)

Transfusion trigger depends on institution where you practice

- Less than 8g/dL for patients
  - Undergoing cardiovascular surgery
  - Orthopedic patients
  - GI bleed patients
- Less than 7g/dL for patients with chronic anemia
- In acute blood loss - transfuse independent of Hgb level if 30% of blood volume lost (trauma)
- Depends on symptoms/scenario
- Perioperative transfusion threshold - varies

JAMA. 2016;316(19):2025-2035
Hematology.org (pocketguides)

#POMAD8
#ChoosePOMA

30

Anemia : Transfusion Trigger

Clinical Situation	Potential Transfusion Threshold	Strength of Recommendation	Quality of Supporting Evidence
Adult Inpatients, Hemodynamically Stable	Hgb** ≤ 7 gm/dL	Strong	Moderate
ICU Patients, Hemodynamically Stable (adult or pediatric)	Hgb ≤ 7 gm/dL	Strong	High
Postoperative Orthopedic or Cardiac Surgery Patients	Hgb ≤ 8 gm/dL§ or for symptoms†	Strong	Moderate
Cardiovascular Disease	Hgb ≤ 8 gm/dL‡ or for symptoms†	Strong	Moderate
Acute Coronary Syndrome	AABB does not recommend for or against a liberal or restrictive RBC transfusion strategy	Uncertain	Very Low
All Patients	Guided by symptoms as well as by Hgb level	Weak	Low

"Cannot be generalized to the preoperative setting, where expected surgical blood loss must be taken into account in transfusion decision making."

† Chest pain, orthostatic hypotension or tachycardia unresponsive to fluids, or congestive heart failure.
‡There remains some uncertainty regarding the risk of perioperative myocardial infarction with a restrictive transfusion strategy.

JAMA. 2016;316(19):2025-2035
Hematology.org (pocketguides)

#POMAD8
#ChoosePOMA

31

Anemia- To transfuse or not to transfuse
Notable Data on Transfusion Thresholds

The New England
Journal of Medicine

VOLUME 340 FEBRUARY 11, 1999 NUMBER 6

A MULTICENTER, RANDOMIZED, CONTROLLED CLINICAL TRIAL
OF TRANSFUSION REQUIREMENTS IN CRITICAL CARE

PAUL C. HÉBERT, M.D., GEORGE WELLS, PH.D., MORRIS A. BLAJCHMAN, M.D., JOHN MARSHALL, M.D., CLAUDIO MARTIN, M.D., GIUSEPPE PAGLIARELLO, M.D., MARTIN TWEEDDALE, M.D., PH.D., IRWIN SCHWEITZER, M.SC., ELIZABETH YETISIR, M.SC., AND THE TRANSFUSION REQUIREMENTS IN CRITICAL CARE INVESTIGATORS FOR THE CANADIAN CRITICAL CARE TRIALS GROUP*

NEJM 1999;340:409-17

#POMAD8
#ChoosePOMA

32

A MULTICENTER, RANDOMIZED, CONTROLLED CLINICAL TRIAL OF TRANSFUSION REQUIREMENTS IN CRITICAL CARE
NEJM 1999;340:409-17

Background

- To determine whether a restrictive strategy of red-cell transfusion and a liberal strategy produced equivalent results in critically ill patients by comparing the rates of death from all causes at 30 days and the severity of organ dysfunction.

Methods

- 838 critically ill patients with:
  - euvolemia after initial treatment

  And
  - hemoglobin concentrations of less than 9.0 g/dL within 72 hours after admission to the ICU.
- Randomly assigned to "restrictive strategy" (418 patients) or "liberal strategy" (420 patients)

- Restrictive = PRBCs transfused for Hgb < 7.0 (maintained Hgb of 7.0 to 9.0)
- Liberal = PRBCs transfused for Hgb < 10.0 (maintained at 10.0 – 12.0)

#POMAD8
NEJM 1999;340:409-17 #ChoosePOMA

33

Results

30-day mortality was similar in the two groups (18.7% vs. 23.3%, P= 0.11)

Subset analysis:

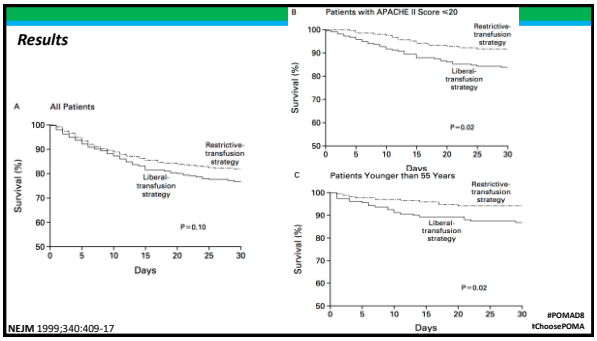
- 30 day mortality rate was significantly lower in:
  - Restrictive group patients who were "less acutely ill
    - Acute Physiology and Chronic Health Evaluation II (APACHE II) score of «20
      - 8.7% in the restrictive-strategy group and 16.1% in the liberal-strategy group, P=0.03
  - Patients < 55 years of age (5.7% and 13%, P=0.02)

  - but not among patients with clinically significant cardiac disease (20.5 percent and 22.9 percent, respectively; P=0.69).
  - The mortality rate during hospitalization was significantly lower in the restrictive-strategy group (22.2 percent vs. 28.1 per- cent, P=0.05).

#POMAD8
NEJM 1999;340:409-17 #ChoosePOMA

34

Results



NEJM 1999;340:409-17

#POMAD8
#ChoosePOMA

35

Results

TABLE 3. COMPLICATIONS THAT OCCURRED DURING THE PATIENTS' STAYS IN THE INTENSIVE CARE UNIT.

COMPLICATION*	RESTRICTIVE-TRANSFUSION STRATEGY (N=418)	LIBERAL-TRANSFUSION STRATEGY (N=420)	ABSOLUTE DIFFERENCE BETWEEN GROUPS	95% CONFIDENCE INTERVAL†	P VALUE
	no. (%)		percent		
Cardiac	55 (13.2)	88 (21.0)	7.8	2.7 to 12.9	<0.01
Myocardial infarction	3 (0.7)	12 (2.9)	2.1	—	0.02
Pulmonary edema	22 (5.3)	45 (10.7)	5.5	1.8 to 9.1	<0.01
Angina	5 (1.2)	9 (2.1)	0.9	—	0.28
Cardiac arrest	29 (6.9)	33 (7.9)	0.9	−2.6 to 4.5	0.60
Pulmonary	106 (25.4)	122 (29.0)	3.7	−2.3 to 9.7	0.22
ARDS	32 (7.7)	48 (11.4)	3.8	−0.2 to 7.8	0.06
Pneumonia	87 (20.8)	86 (20.5)	−0.3	−5.8 to 5.1	0.92
Infectious	42 (10.0)	50 (11.9)	1.9	−2.4 to 6.1	0.38
Bacteremia	30 (7.2)	40 (9.5)	2.3	−1.4 to 6.1	0.22
Catheter-related sepsis	21 (5.0)	17 (4.0)	−1.0	−2.8 to 1.8	0.50
Septic shock	41 (9.8)	29 (6.9)	−2.9	−6.7 to 0.8	0.13
Hematologic‡	10 (2.4)	10 (2.4)	0	−2.1 to 2.1	1.00
Gastrointestinal§	13 (3.1)	19 (4.5)	1.4	−1.2 to 4.0	0.28
Neurologic¶	25 (6.0)	33 (7.9)	1.9	−1.6 to 5.3	0.28
Shock‖	67 (16.0)	55 (13.1)	−2.9	−7.7 to 1.8	0.23
Any complication	205 (49.0)	228 (54.3)	5.2	−1.5 to 12.0	0.12

NEJM 1999;340:409-17

#POMAD8
#ChoosePOMA

36

The APACHE II Severity of Disease Classification System

Physiologic Variable	+4	+3	+2	+1	0	+1	+2	+3	+4
Temperature - rectal (°C)	≥41	39-40.9		38.5-38.9	36-38.4	34-35.9	32-33.9	30-31.9	≤29.9
Mean Arterial Pressure (mm Hg)	≥160	130-159	110-129		70-109		50-69		≤49
Heart Rate	≥180	140-179	110-139		70-109		55-69	40-54	≤39
Respiratory Rate (nonventilated or ventilated)	≥50	35-49		25-34	12-24	10-11	6-9		≤5
Oxygenation (mm Hg) a. $FiO_2 \geq 0.5$ record $A-aDO_2$ b. $FiO_2 < 0.5$ use PaO_2	a. ≥500	350-499	200-349		<200				
	b.				> 70	61-70		55-60	<55
Arterial pH	≥7.7	7.6-7.69		7.5-7.59	7.33-7.49		7.25-7.32	7.15-7.24	<7.15
Serum Sodium (mmol/l)	≥180	160-179	155-159	150-154	130-149		120-129	111-119	≤110
Serum Potassium (mmol/l)	≥7	6-6.9		5.5-5.9	3.5-5.4	3-3.4	2.5-2.9		<2.5
Serum Creatinine (mg/dl, Double point score for acute renal failure)	≥3.5	2-3.4	1.5-1.9		0.6-1.4		<0.6		
Hematocrit (%)	≥60		50-59.9	46-49.9	30-45.9		20-29.9		<20
White Blood Count (in 1000 mm³)	≥40		20-39.9	15-19.9	3-14.9		1-2.9		<1
Glasgow Coma Scale (GCS)	Score = 15 minus actual GCS								
Serum HCO_3 (venous, mmol/l, use if no ABGs)	≥52	41-51.9		32-40.9	22-31.9		18-21.9	15-17.9	<15
A = Total Acute Physiology Score APS	Sum of the 12 individual variable points								
B = Age Points	C = Chronic Health Points								
≤44 years 0 points 45-54 years 2 points 55-64 years 3 points 65-74 years 5 points ≥75 years 6 points	If the patient has a history of severe organ system insufficiency or is immunocompromised assign points as follows: a. For nonoperative or emergency postoperative patients – 5 points b. For elective postoperative patients – 2 points								
APACHE II Score = Sum of A (APS points) + B (Age points) + C (Chronic Health points)									

Crit Care Med 1985;13(10):818-829.

#POMAD8
#ChoosePOMA

37

Authors Conclusions

"A restrictive strategy of red-cell transfusion is at least as effective as and possibly superior to a liberal transfusion strategy in critically ill patients, with the possible exception of patients with acute myocardial infarction and unstable angina. "

NEJM 1999;340:409-17

#POMAD8
#ChoosePOMA

38

Anaesthesia 2019, 74 (Suppl. 1), 49–57 doi:10.1111/anae.14466

Review Article

Optimisation of pre-operative anaemia in patients before elective major surgery – why, who, when and how?

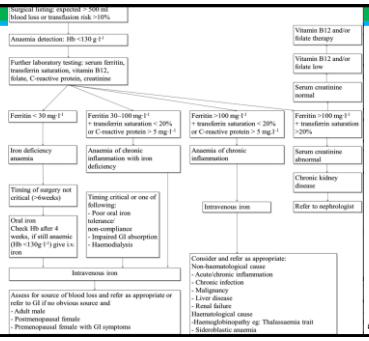
K. E. Munting[1] and A. A. Klein[2]

- Review article that looks at optimizing pre-operative anemia in surgical patients who are planned to have a surgery where more than 500mL blood loss is expected.
- This is a European article (not from US institutions.)

#POMAD8
#ChoosePOMA

40

- Their proposed management algorithm.



#POMAD8
#ChoosePOMA

41

Why limit transfusions?

Choosingwisely.org
Hematology.org
ASH University

#POMAD8
#ChoosePOMA

42

Why limit transfusions?
- Limited blood supply

#POMAD8
#ChoosePOMA

43

Why limit transfusions?
- Limited blood supply
- Adverse reactions
  - **Cardiac overload / TACO**
  - **Lung injury / TRALI**

#POMAD8
#ChoosePOMA

44

Why limit transfusions?
- Limited blood supply
- Adverse reactions
  - **Cardiac overload / TACO**
  - **Lung injury / TRALI**

Transfusion-associated circulatory overload (TACO)
- Approximately 1% of transfusions.
- New onset or exacerbation of acute respiratory distress (dyspnea, orthopnea, count) 3-6 hours after transfusion.
- May be associated with:
  - elevated BNP, elevated central venous pressure, left heart failure, positive fluid balance, pulmonary edema
- Risk factors:
  - cardiac or renal dysfunction, female gender, age > 60 years, severe anemia with volume expansion, positive fluid balance, transfusion of multiple products.
- Mortality rate 1.4-8.3%.

Management includes stopping transfusion and other fluids, sit patient up, supplemental oxygen, diuretic therapy.

#POMAD8
#ChoosePOMA

45

Why limit transfusions?

- Limited blood supply
- Adverse reactions
  - **Cardiac overload / TACO**
  - **Lung injury / TRALI**

Transfusion-related acute lung injury (TRALI)

- Development of symptoms within 6 hours of transfusion
  - Hypoxemia
  - Hypotension
  - Bilateral pulmonary edema
  - Transient leucopenia
  - Fever.
- 10-20% fatal.
- Treatment = Supportive care.

#POMAD8
#ChoosePOMA

46

Why limit transfusions?

- Limited blood supply
- Adverse reactions
  - **Cardiac overload**
  - **Lung injury**
  - **Infections**
- Cost
  - $200 to $300
  - There are added costs for:
    - Type of product
    - Storage and processing
    - Hospital / infusion center
    - Equipment fees

#POMAD8
#ChoosePOMA

47

"Who gets what product?"

Leukocyte Reduction

- Decrease risk of recurrent febrile, nonhemolytic transfusion reactions
- Decrease risk of cytomegalovirus transmission
- Decrease risk of HLA-alloimmunization

Most commonly achieved with filtration.

Washed

- Decrease risk of anaphylaxis in IgA-deficient patient with anti-IgA antibodies
- Decrease allergic reactions in patients with history of reactions to blood product transfusion

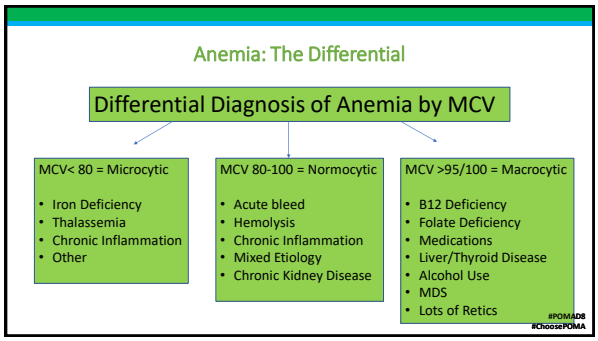
Irradiated

- Prevention of TA-GVHD
- Donor categories
  - Product donated by family member
  - Product from HLA-selected donor
  - Products from directed donors whose relationship to recipient's family has not been established
- Acute leukemia: HLA-matched or family-donated products
- Allogeneic stem cell transplant recipient
- History of treatment with purine analogues and related drugs
  - Fludarabine
  - Cladribine
  - Pentostatin
  - Clofarabine
  - Bendamustine
  - Nelarabine
  - History of treatment with alemtuzumab (anti-CD52)
- Aplastic anemia on rabbit antithymocyte globulin

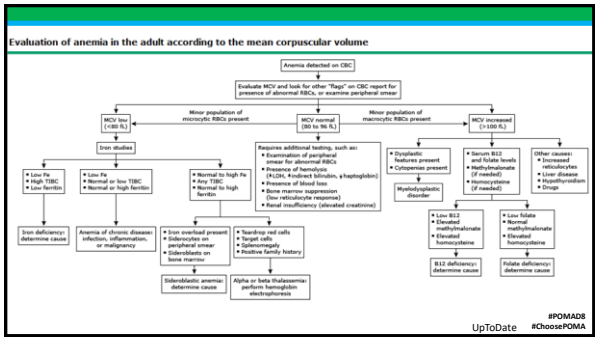
JAMA. 2016;316(19):2025-2035 and Hematology.org (pocketguides)

#POMAD8
#ChoosePOMA

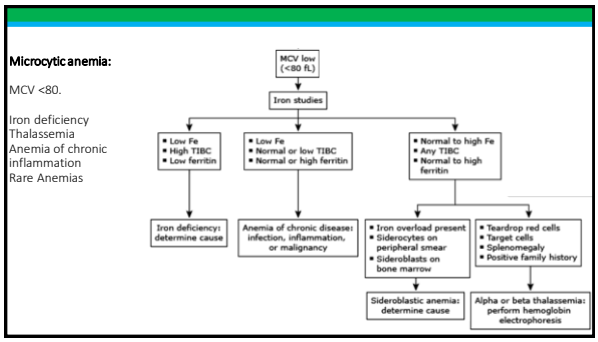
48


Anemia: The Differential
Differential Diagnosis of Anemia by MCV
MCV< 80 = Microcytic
• Iron Deficiency
• Thalassemia
• Chronic Inflammation
• Other
MCV 80-100 = Normocytic
• Acute bleed
• Hemolysis
• Chronic Inflammation
• Mixed Etiology
• Chronic Kidney Disease
MCV >95/100 = Macrocytic
• B12 Deficiency
• Folate Deficiency
• Medications
• Liver/Thyroid Disease
• Alcohol Use
• MDS
• Lots of Retics
#POMAD8
#ChoosePOMA

49


Evaluation of anemia in the adult according to the mean corpuscular volume
Anemia detected on CBC
Evaluate MCV and look for other "flags" on CBC report for presence of abnormal RBCs, or examine peripheral smear
MCV low (<80 fL)
Minor population of microcytic RBCs present
MCV normal (80 to 96 fL)
Minor population of macrocytic RBCs present
MCV increased (>100 fL)
Iron studies
Low Fe
High TIBC
Low ferritin
Low Fe
Normal or low TIBC
Normal or high ferritin
Normal to high Fe
Any TIBC
Normal to high ferritin
Requires additional testing, such as:
Examination of peripheral smear for abnormal RBCs
Presence of hemolysis (ALDH, ↑indirect bilirubin, ↓haptoglobin)
Presence of blood loss
Bone marrow suppression (low reticulocyte response)
Renal insufficiency (elevated creatinine)
Dysplastic features present
Cytopenias present
Myelodysplastic disorder
Serum B12 and folate levels
Methylmalonate (if needed)
Homocysteine (if needed)
Other causes:
Increased reticulocytes
Liver disease
Hypothyroidism
Drugs
Low B12
Elevated methylmalonate
Elevated homocysteine
Low folate
Normal methylmalonate
Elevated homocysteine
Iron deficiency: determine cause
Anemia of chronic disease: infection, inflammation, or malignancy
Iron overload present
Siderocytes on peripheral smear
Sideroblasts on bone marrow
Teardrop red cells
Target cells
Splenomegaly
Positive family history
B12 deficiency: determine cause
Folate deficiency: determine cause
Sideroblastic anemia: determine cause
Alpha or beta thalassemia: perform hemoglobin electrophoresis
UpToDate
#POMAD8
#ChoosePOMA

50


Microcytic anemia:
MCV <80.
Iron deficiency
Thalassemia
Anemia of chronic inflammation
Rare Anemias
MCV low (<80 fL)
Iron studies
Low Fe
High TIBC
Low ferritin
Low Fe
Normal or low TIBC
Normal or high ferritin
Normal to high Fe
Any TIBC
Normal to high ferritin
Iron deficiency: determine cause
Anemia of chronic disease: infection, inflammation, or malignancy
Iron overload present
Siderocytes on peripheral smear
Sideroblasts on bone marrow
Teardrop red cells
Target cells
Splenomegaly
Positive family history
Sideroblastic anemia: determine cause
Alpha or beta thalassemia: perform hemoglobin electrophoresis

51

Microcytic Anemia

Iron deficiency anemia

- Ferritin <20 suggests iron deficiency
- Ferritin > 100 unlikely iron deficient (some authors say 800)
- Bone Marrow staining for iron is the gold standard for diagnosis

- **Soluble transferrin receptor is NOT sensitive to inflammation therefore**
  - **High sTfR level suggests iron deficiency even if ferritin elevated.**

#POMAD8
#ChoosePOMA

52

Alternate Day Oral Iron Dosing in Iron Deficiency Anemia
Blood 2018 132:4891

Background

- Practice guidelines for Iron deficiency anemia (IDA) suggest taking ferrous iron in divided doses.
- Recent studies suggest that **split daily dosing may increase serum hepcidin** which reduces iron bioavailability.
- Adherence to oral iron supplementation can also be a barrier to treatment.
- In practice iron dosing varies significantly with unclear evidence of benefit from a particular dosing regimen.

#POMAD8
#ChoosePOMA

53

Alternate Day Oral Iron Dosing in Iron Deficiency Anemia
Blood 2018 132:4891

Methods

- Retrospective study
- Evaluating outcomes of different schedules of oral iron supplement In 146 patients with iron deficiency anemia (Hb <12.2 and/or ferritin of < 30 ng/mL) treated between June 2017-June 2018.
  - Patients with multifactorial anemia were excluded.
- Descriptive statistics and Chi-square were used for analysis.
- Four oral iron schedules were used
  1. Every other day(QOD) 60% (88/146)
  2. Daily (QD)15% (22/146)
  3. Twice daily (BID) 12%(18/146)
  4. Three times a day (TID) 12% (18/146).

#POMAD8
#ChoosePOMA

54

Alternate Day Oral Iron Dosing in Iron Deficiency Anemia
Blood 2018 132:4891

- Mean age was 66.8 ± 1.3
- Women constituted 70% of the cohort (M/F 44/102)
- Mean Hb was 11.59 ± 0.12
- Median ferritin was 22 ng/ml

#POMAD8
#ChoosePOMA

55

Alternate Day Oral Iron Dosing in Iron Deficiency Anemia
Blood 2018 132:4891

Results:

- After one month of OIS a mean increase in Hb was (0.44 mg/dl + 0.04)
- GI toxicity occurred in 10.2% (15/146)
- Therapy discontinuation in 4.8% (7/146)
- IV iron was required in 9.6 % (14/146) of all cases.
- Among patients without GI toxicity 65% (85/131) were on QOD vs other schedules (X^2 11.7 p=0.008), 63% (87/139) were compliant on QOD (X^2 9.05 p=0.029).
- Salvage IV iron was not required in 64% (84/132) of QOD patients (X^2 22.7 p=<0.001).
- One month post therapy, patients on QOD schedule had ≥1 g/dl improvement in 38% (10/26) (X^2 9.18 p= 0.027) and increase of >0.5g/dl in 68% (69/102) of cases (X^2 9.63 p= 0.022).

#POMAD8
#ChoosePOMA

56

Alternate Day Oral Iron Dosing in Iron Deficiency Anemia
Blood 2018 132:4891

Results:

- After one month of OIS a mean increase in Hb was (0.44 mg/dl + 0.04)
- GI toxicity occurred in 10.2% (15/146)
- Therapy discontinuation in 4.8% (7/146)
- IV iron was required in 9.6 % (14/146) of all cases.
- Among patients without GI toxicity 65% (85/131) were on QOD vs other schedules (X^2 11.7 p=0.008), 63% (87/139) were compliant on QOD (X^2 9.05 p=0.029).
- Salvage IV iron was not required in 64% (84/132) of QOD patients (X^2 22.7 p=<0.001).
- One month post therapy, patients on QOD schedule had ≥1 g/dl improvement in 38% (10/26) (X^2 9.18 p= 0.027) and increase of >0.5g/dl in 68% (69/102) of cases (X^2 9.63 p= 0.022).
- **Conclusion: "Alternate day iron dosing may optimize iron absorption and is possibly a better tolerated regimen. Larger prospective studies need to confirm these findings"**

#POMAD8
#ChoosePOMA

57

Microcytic Anemia

Iron deficiency anemia

- Causes
  - Bleeding (overt and occult)
  - Low Iron Supply
    - Malabsorption
      - Gastric bypass
      - Celiac Sprue
      - Inflammatory bowel disease
      - Parasites
      - Etc.
    - Achlorhydria
    - Poor nutrition
  - Rare causes
    - Chronic hemolysis with PNH

Copper Deficiency

- Excess zinc ingestion
  - Cold remedies/lozenges
  - Denture cream

Thalassemia

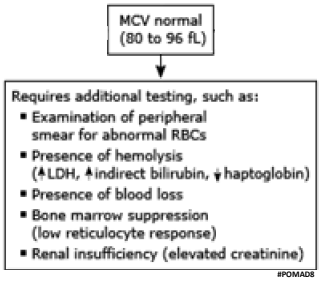
- Diagnose with hemoglobin electrophoresis followed by alpha gene mutation analysis if needed

#POMAD8
#ChoosePOMA

58

Normocytic anemia

- MCV 80-100.
- Acute bleeding
- Anemia of CKD
- Anemia of chronic inflammation
- Mixed microcytic and macrocytic
- If no acute bleeding
  - Check reticulocyte count.
  - Consider checking serum EPO level.
    - If low they might respond to an erythropoietin stimulating agent



#POMAD8
#ChoosePOMA

59

Normocytic Anemia

Anemia of Chronic Inflammation:

- High ferritin
- Low TIBC
- Normal serum iron
- Normal or slightly high transferrin saturation (serum iron divided by TIBC).
- These patients **rarely respond to oral iron therapy**.
  - **Increased Hepcidin** (upregulated by IL6) leads to **decreased iron absorption from the GI tract** (due to decreased ferroportin)

#POMAD8
#ChoosePOMA

60

Normocytic Anemia

Anemia of Chronic Inflammation:

- High ferritin
- Low TIBC

Treatment:
Treat the underlying cause

- Normal serum iron
- Normal or slightly high transferrin saturation (serum iron divided by TIBC).
- These patients **rarely respond to oral iron therapy**.
  - **Increased Hepcidin** (upregulated by IL6) leads to **decreased iron absorption from the GI tract** (due to decreased ferroportin)

#POMAD8
#ChoosePOMA

61

Anemia of Chronic Disease (ACD) / Anemia of Inflammation

- Normocytic or Microcytic
- Hemoglobin usually not below 8 g/dL
- Resolves with treatment of underlying disease
- Can be caused by many disorders (to name a few)
  - Rheumatologic illnesses: Lupus, RA, Vasculitis
  - Infections: HIV, TB, Endocarditis
  - Malignancy

Iron Studies	Serum Iron	TIBC	Transferrin sat	Ferritin
Iron Deficiency	Decreased	increased	Decreased	Decreased
ACD	Decreased	Decreased or N	Decreased or N	Increased or N

#POMAD8
#ChoosePOMA

62

Serum transferrin receptor concentration

- Transferrin receptors are expressed on the surfaces of all cells depending on their need for iron.
- When functional iron depletion occurs more transferrin receptors appear on cell surfaces and the concentration of the extracellular domain (serum transferrin receptor or STfR) in the plasma increases.
- The magnitude of the increase is proportional to the size of the functional iron deficit.

Encyclopedia of Food Sciences and Nutrition (Second Edition)
2003, Pages 215-220

#POMAD8
#ChoosePOMA

63

Normocytic Anemia

Anemia of Chronic Inflammation:

- High ferritin
- Low TIBC
- Normal serum iron
- Normal or slightly high transferrin saturation (serum iron divided by TIBC).
- These patients **rarely respond to oral iron therapy**.
  - **Increased Hepcidin** (upregulated by IL6) leads to **decreased iron absorption from the GI tract** (due to decreased ferroportin)

Anemia of Chronic Kidney Disease

- Hypoproliferative, normocytic (usually), and normochromic
- Etiology =
  - decreased renal erythropoietin synthesis +/-
  - decrease RBC half life +/-
  - absolute or functional iron deficiency

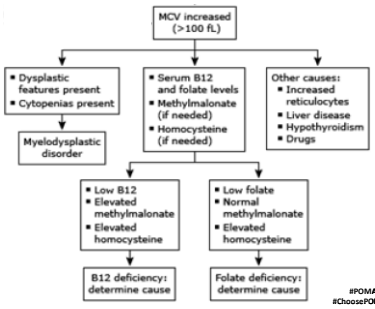
#POMAD8
#ChoosePOMA

64

Macrocytic anemia
MCV >95-100

Consider:

- Alcohol use
- Liver disease
- Medications
  - Methotrexate
  - Azathioprine
  - Hydroxyurea
- B12, folate
- TSH
- Reticulocytosis
- If no answer, then refer for BM biopsy.



#POMAD8
#ChoosePOMA

65

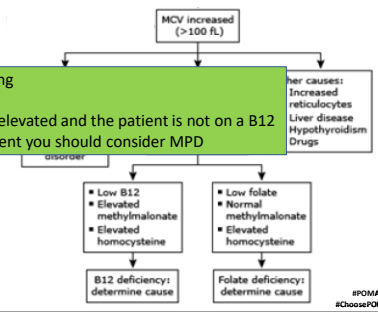
Macrocytic anemia

Consider:

- Alcohol use
- Liver disease
- Medications
  - Methotrexate
  - Azathioprine
  - Hydroxyurea
- B12, folate
- TSH
- Reticulocytosis
- If no answer, then refer for BM biopsy.

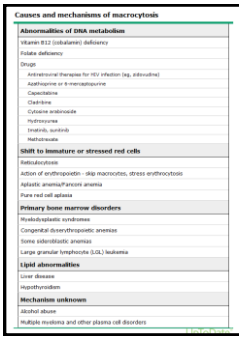
Interesting

If B12 is elevated and the patient is not on a B12 supplement you should consider MPD



#POMAD8
#ChoosePOMA

66



Causes and mechanisms of macrocytosis
Abnormalities of DNA metabolism
Vitamin B12 (cobalamin) deficiency
Folate deficiency
Drugs
Antiretroviral therapies for HIV infection (eg, zidovudine)
Azathioprine or 6-mercaptopurine
Capecitabine
Cladribine
Cytosine arabinoside
Hydroxyurea
Imatinib, sunitinib
Methotrexate
Shift to immature or stressed red cells
Reticulocytosis
Action of erythropoietin - skip macrocytes, stress erythrocytosis
Aplastic anemia/Fanconi anemia
Pure red cell aplasia
Primary bone marrow disorders
Myelodysplastic syndromes
Congenital dyserythropoietic anemias
Some sideroblastic anemias
Large granular lymphocyte (LGL) leukemia
Lipid abnormalities
Liver disease
Hypothyroidism
Mechanism unknown
Alcohol abuse
Multiple myeloma and other plasma cell disorders

MCV >115
- consider artifact when cold agglutinins are present
- RBCs clump and are read by the machine as one large red cell instead of a clump of cells.
- Warming the specimen prior to repeat count should return the MCV to normal

UpToDate

#POMAD8
#ChoosePOMA

67

Erythropoietin

- Erythropoietin is a hormone produced in the kidney by cells that sense oxygenation
- Erythropoietin stimulates RBC production by binding to the RBC precursor cell surface where it promotes survival and proliferation
- Reticulocytes survive in the circulation for one day then become mature red blood cells.
- The bone marrow must produce approximately 50,000 reticulocytes/microL of whole blood each day in order to achieve a stable RBC mass.
- Reticulocyte production increases with high levels of EPO.
  - Can increase production fivefold in adults and seven to eightfold in children in response to EPO if marrow is normal and proper nutrients present

#POMAD8
#ChoosePOMA

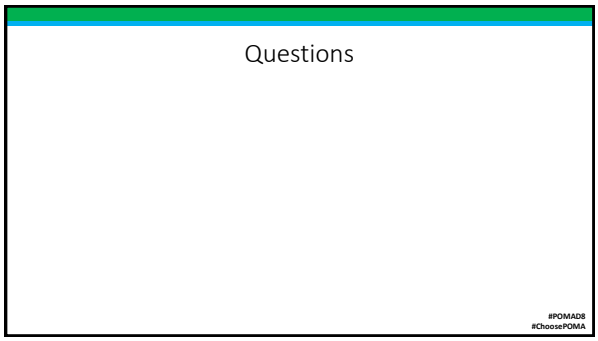
68

Erythropoiesis-stimulating agents
Epogen/Procrit/Aranesp

- Correct iron deficiency prior to use
  - Goal iron saturation > 20%.
  - Goal ferritin >100
- ESAs are known to promote thrombosis if hemoglobin is permitted to be >12 g/dL.
- Not used in patients receiving chemotherapy for curative intent as studies showed decreased survival in patients receiving ESAs.
  - Possibly cancer cells can have epo receptors and binding with ESAs may act as a growth factor

#POMAD8
#ChoosePOMA

69



70