

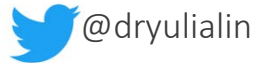
Patient Blood Management: Treating Anemia

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Disclosures

- Research: Canadian Blood Services, Octapharma
- Consulting: Choosing wisely Canada

Objectives

1. Advocate for the importance of patient blood management
2. Diagnose and treat iron deficiency anemia
3. Decide which patients should receive preoperative erythropoietin

Patient Blood Management

- PBM is a patient-centered and organized approach in which the entire health care team coordinates efforts to improve results by managing and preserving a patient's own blood.

Pre-op

Treat anemia

During surgery

Minimize blood
loss

Post-op

Appropriate use
of blood

Patient Blood Management

- PBM is a patient-centered and organized approach in which the entire health care team coordinates efforts to improve results by managing and preserving a patient's own blood.

Antenatal

Treat anemia

Peridelivery

Minimize blood
loss

Postpartum

Appropriate use
of blood

Why is treating preoperative anemia so important?

#1 Preoperative anemia is associated with increased mortality

2018 PBM Consensus Conference

OR 2.09 (95%CI, 1.48-2.95)

2014 Europe N= 39,309 pts

OR 1.99 (95%CI, 1.67-2.37)

2011 US NSQIP N= 227, 425 pts

OR 1.42 (95% CI, 1.31-1.54)

#2 Preoperative anemia is potentially modifiable

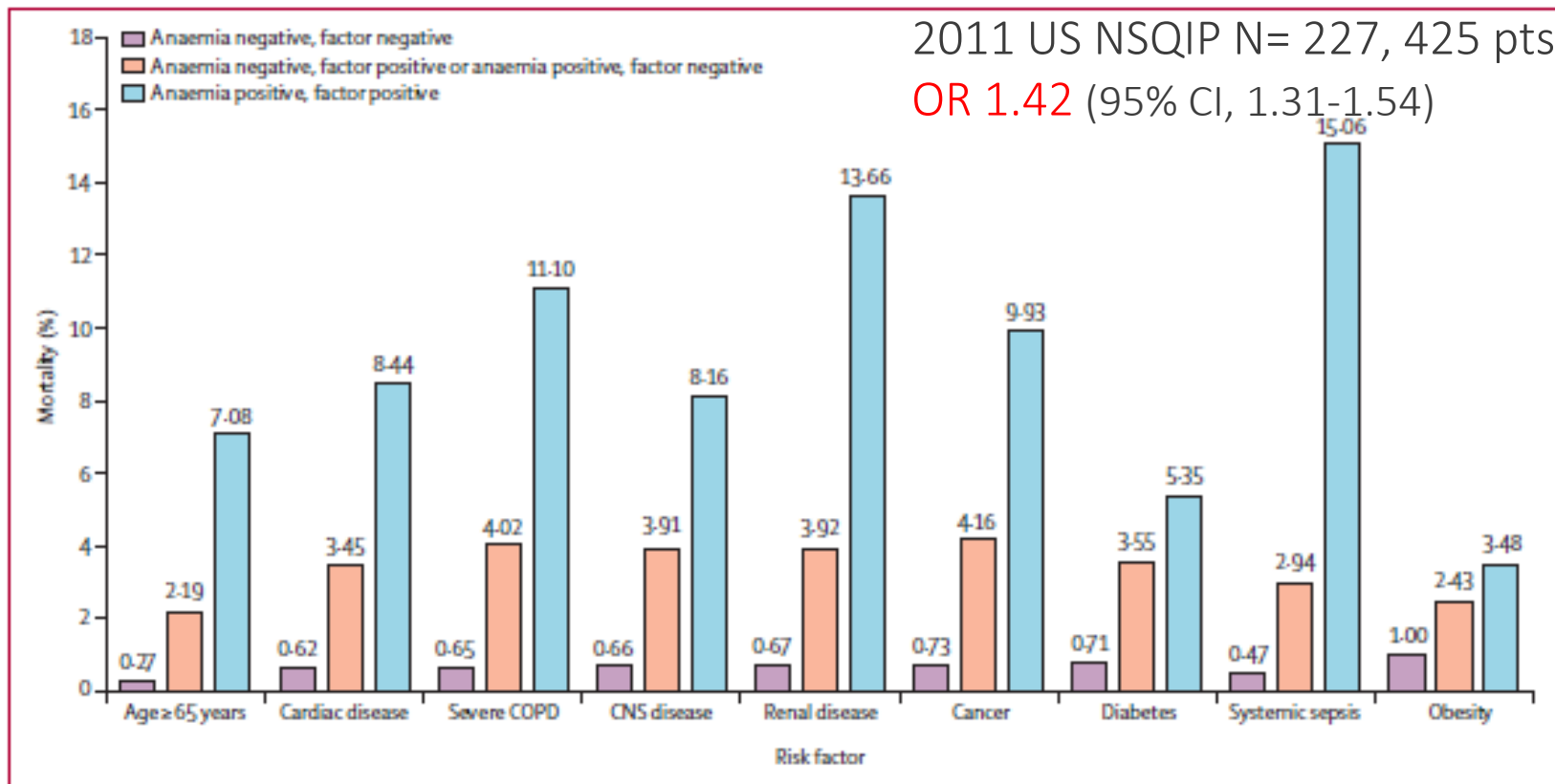
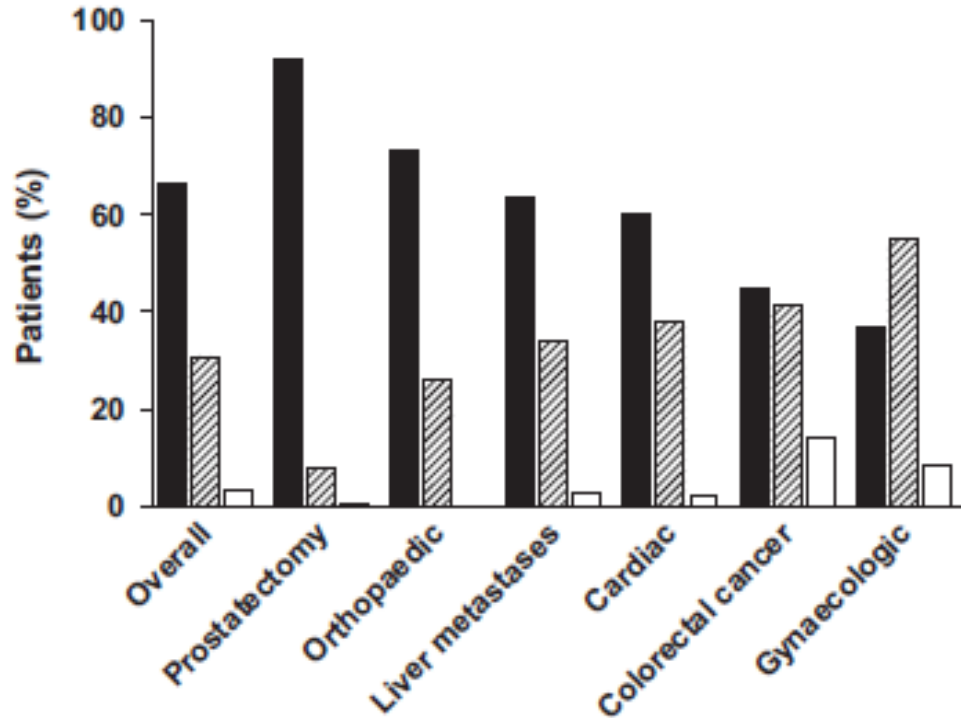


Figure 1: 30-day mortality, by anaemia and risk factor status
COPD=chronic obstructive pulmonary disease.

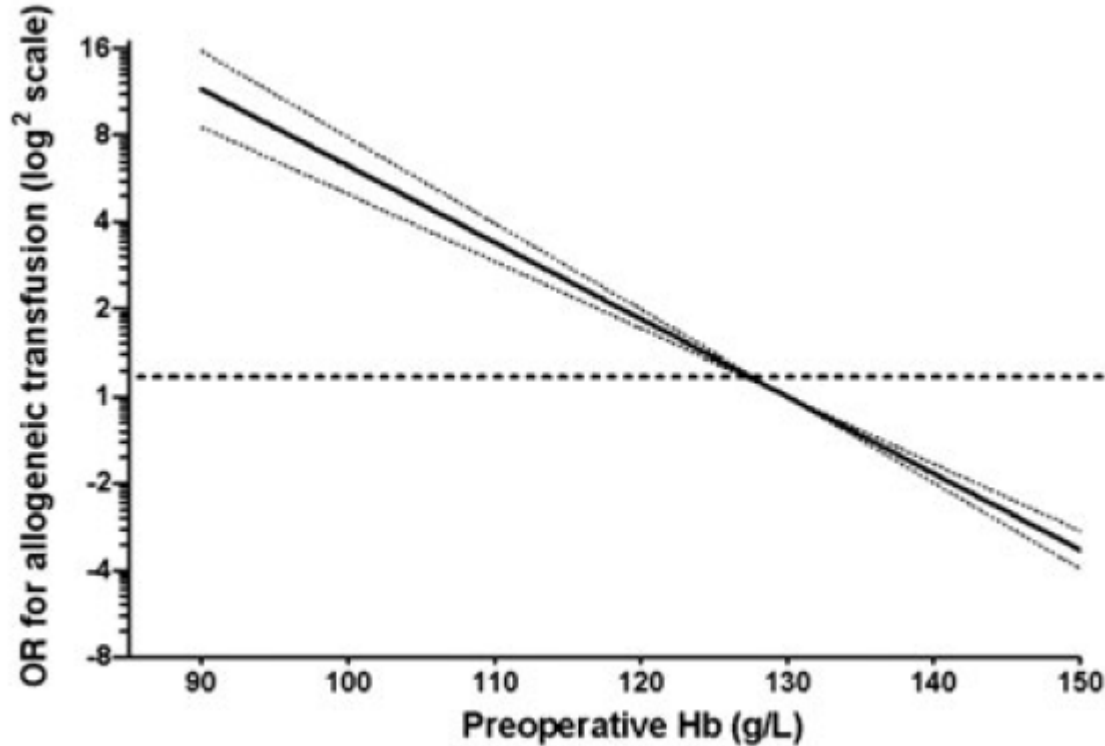
#3 Preoperative anemia is common (25-40%)!

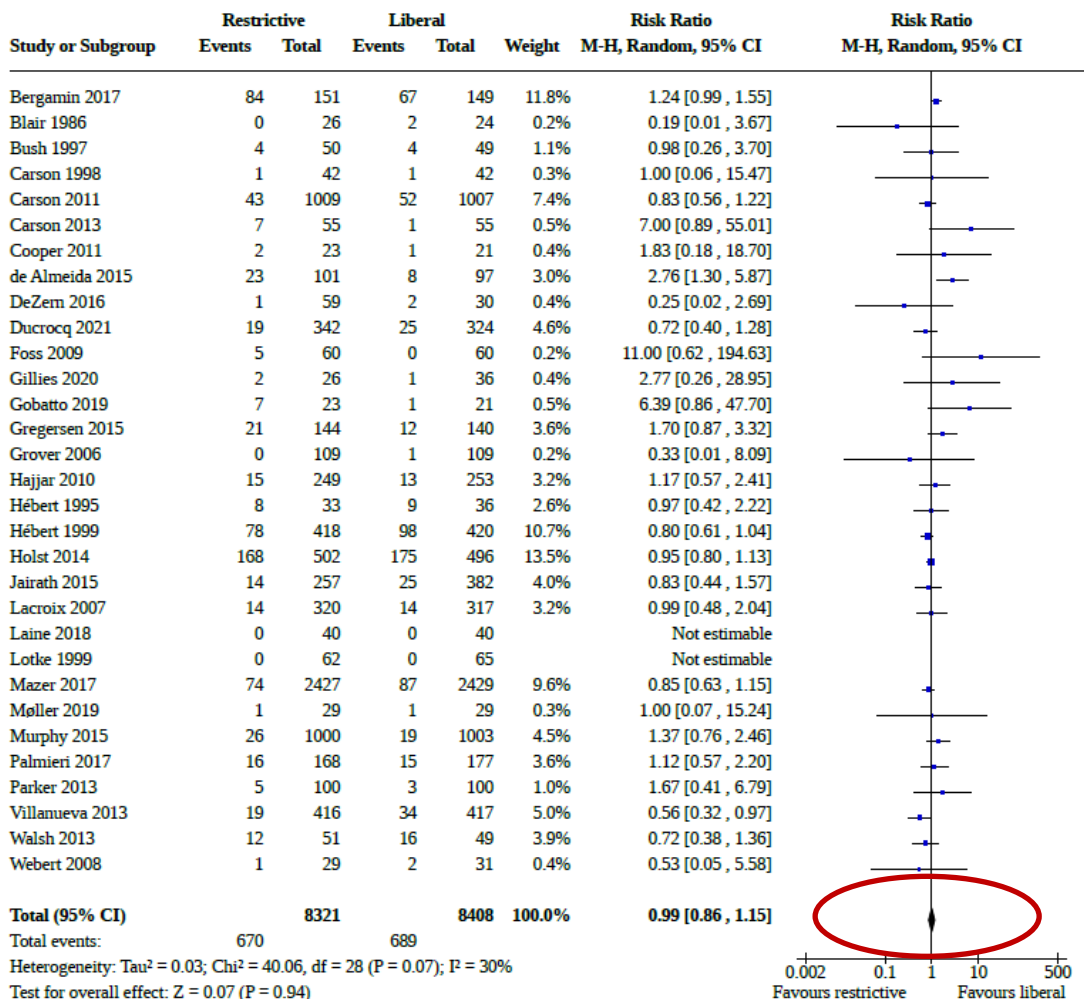


Anemia in 36% (1/3)

N = 3342 pts

#4 Pre-op anemia associated with ↑ transfusion





31 trials
 16,729 pts
 30 day mortality
 OR 0.99
 (0.86, 1.15)

*Comparing hb thresholds not transfusion vs. no transfusion

Advocate for PBM because...

1. Preoperative anemia is bad
2. Preoperative anemia is modifiable
3. Preoperative anemia is common
4. Transfusion does not correct effect & has risks
5. The donor supply is a precious resource

What are strategies to treat anemia and preserve the patient's own blood?

Poll Question

- Which of the following interventions have you prescribed before?
 - Autologous blood
 - Oral iron
 - Intravenous iron
 - Epoetin alfa or darbepoetin

Quick point:
Autologous blood donation
is to be considered only in rare
circumstances!

What is Autologous Donation?

- Patient donates own blood before surgery with sufficient time to allow patient to make up loss
- Goal: to provide additional RBC units for surgery (↑ red cell mass)



Pitfalls of Autologous Donation

- Takes at least 4 wks to re-generate autologous blood
- Preop Hb was **11 g/L lower** in autologous group (systematic review 14 RCTs)
- More expensive due to 50% wastage rate
 - 1 allogeneic unit costs \$422 (CBS 2018-19)

Summary – Autologous Blood

- Preop autologous blood donation **NOT recommended**
- Exceptions
 - Patients with very rare blood type not easily met by donor base (e.g. unusual or multiple antibodies)
 - Contact the transfusion service in these cases!

Objective #2:
Diagnose and Treat
Iron Deficiency Anemia (early)




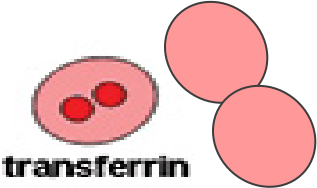
What is Preop Anemia?

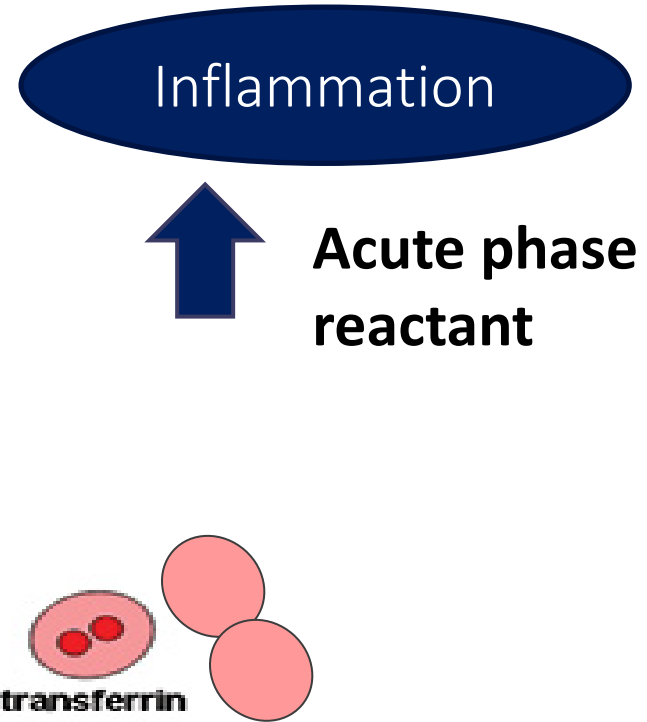
- ~~WHO: Hb < 130 g/L males; Hb < 120 g/L females~~
- **NEW:** Hb < 130 g/L used for all (high blood loss surgery)
 - Both sexes lose same amount of blood
 - Lower Hb in females may simply reflect iron deficiency
 - Accepting lower preop Hb for females ↑transfusion risk
 - NSQIP data: risk increases as hemoglobin levels < 130 g/L with no sex differential

Detection

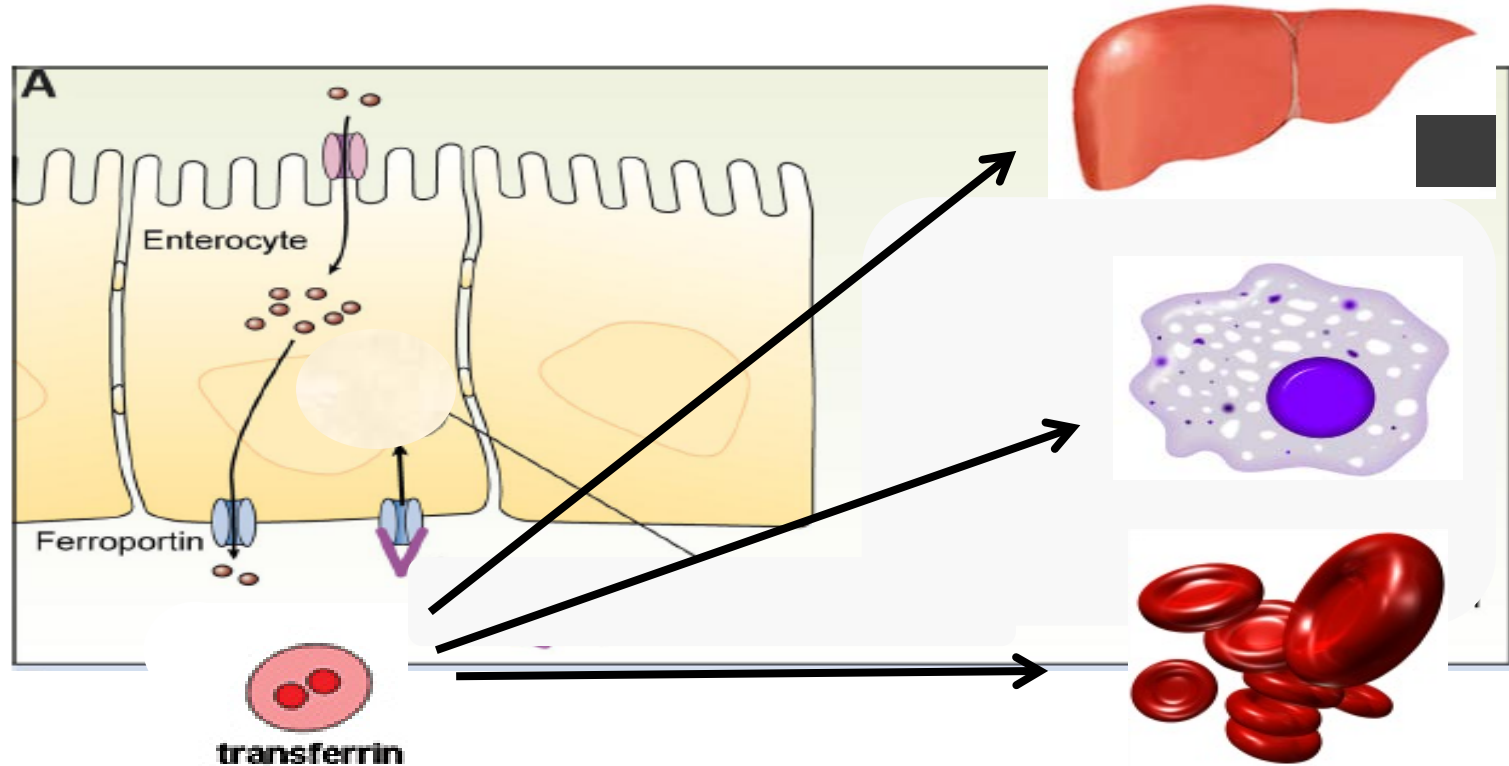
- Who should be screened?
 - All high blood loss surgery (> 500 mL): ortho, cardiac, cancer
 - All high risk for severe anemia: colorectal, gyne
- When?
 - 4-8 weeks before surgery
- How?
 - CBC, ferritin, TSAT, B12, creatinine
 - Focus on iron deficiency anemia (common & treatable)

How to diagnose IDA?

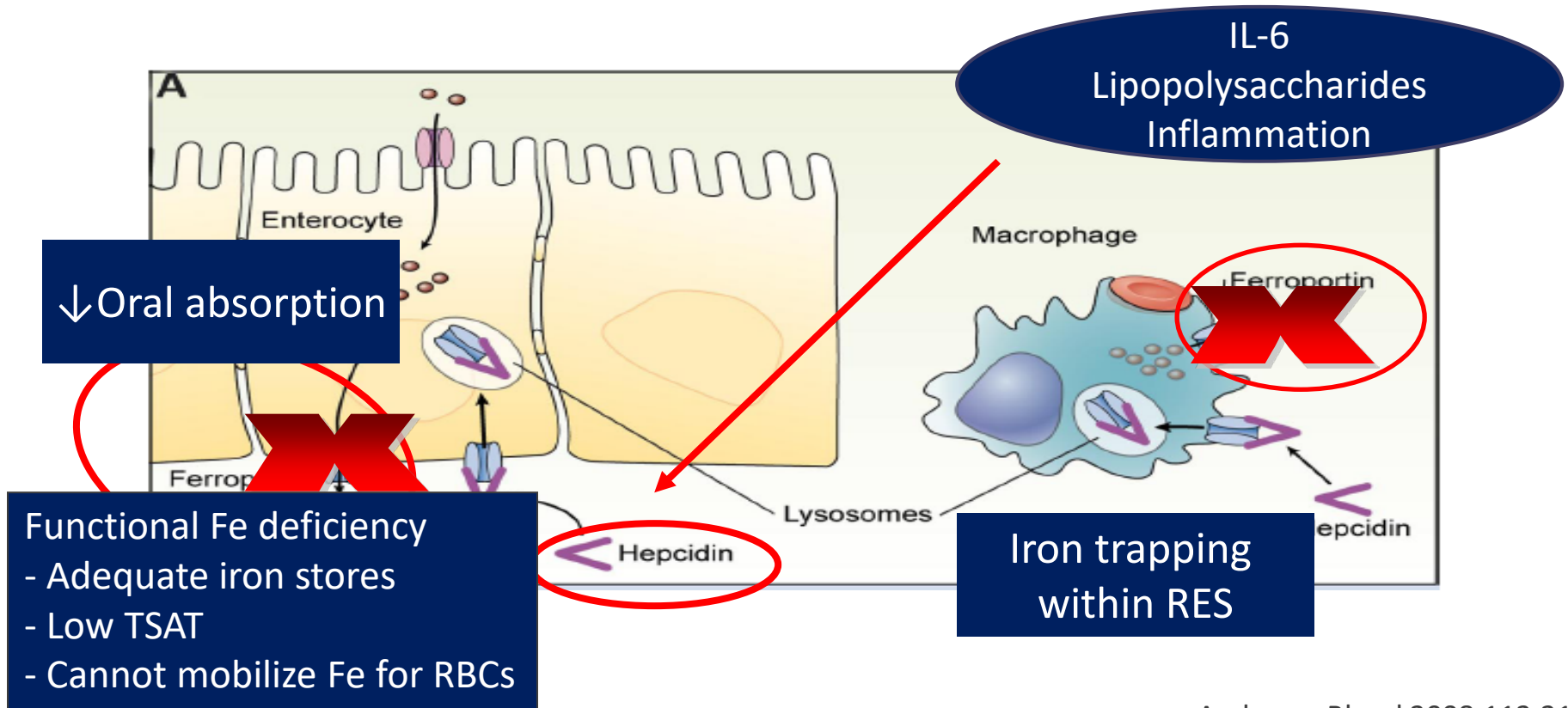
- Ferritin 
 - Reflection of iron stores
 - Ferritin < 30 ug/L = Iron deficiency
- Serum Fe 
- Transferrin (TIBC) 
 - Transport protein of Fe
- Transferrin saturation 
 - Serum Fe / TIBC



Iron Pathway



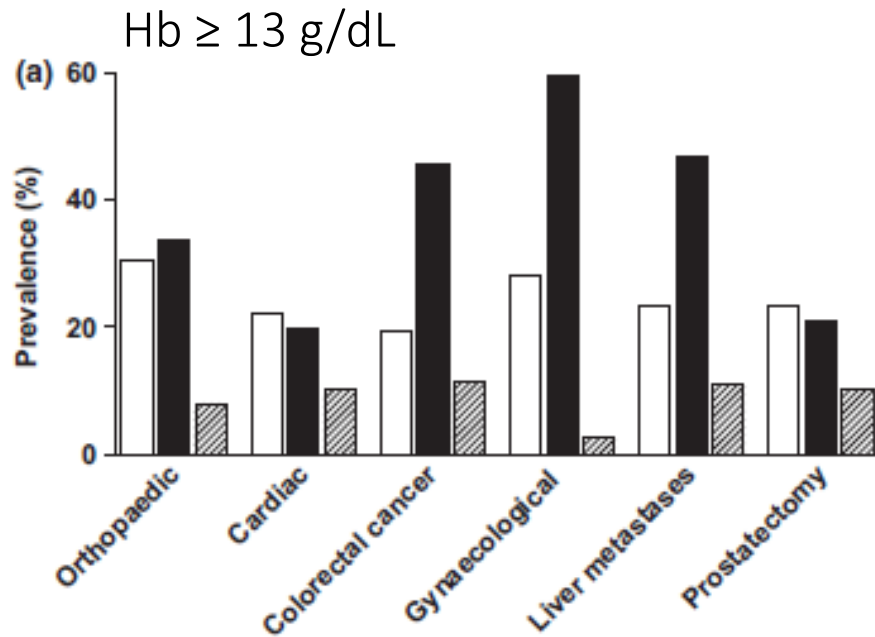
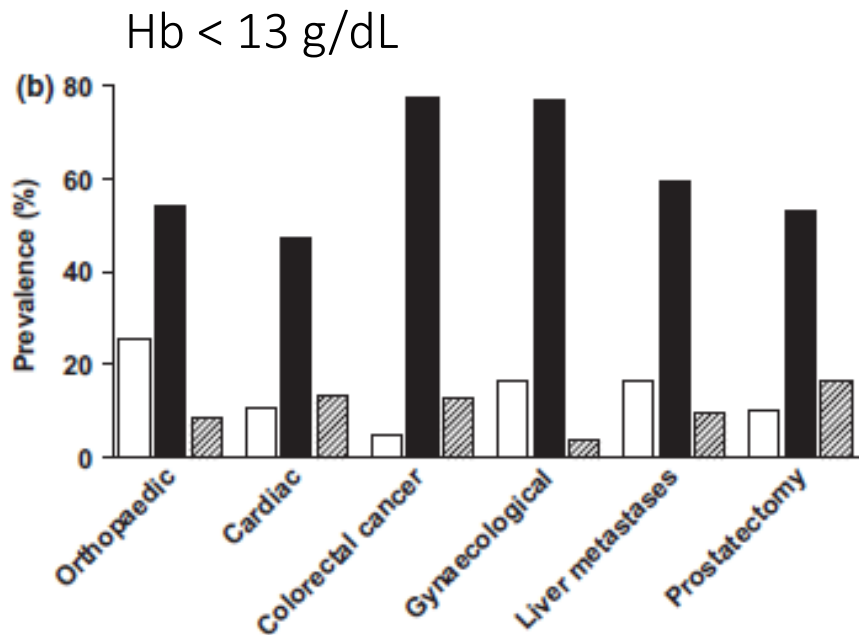
Anemia of Chronic Disease – Hepcidin



Defining iron deficiency anemia

Absolute Iron Deficiency: Ferritin < 30 mcg/L; or
Ferritin < 100 + TSAT < 20% ± CRP > 5 mg/L

Low iron stores: Ferritin 30-100 mcg/L + TSAT > 20%



Low iron stores
 Absolute ID
 Iron sequestration

Anemia in 36% (1/3)

Table 1. Causes of iron-deficiency anemia in the preoperative setting

Causes of preoperative iron-deficiency anemia

Too much iron OUT

Increased loss

- Blood loss, eg, gastrointestinal, gynecological bleeding
- Blood donation

Increased requirements

- Rapid growth in infants and children
- Pregnancy
- Use of ESAs

Too little iron IN

Decreased iron intake

- Iron-poor diet
- Vegetarian or vegan

Decreased absorption

- Celiac disease
 - Gastrectomy, gastric bypass, gut resection
 - *Helicobacter pylori*
 - Inflammatory bowel disease
 - Drugs: antacids, proton pump inhibitors
 - Foods: calcium, tannins (tea, coffee), phytates
-



GI lesions in IDA:
Colon 5-10%
Upper GI 1-5%

Oral Iron

Guidelines
recommend oral
iron if at least 6-8
weeks preop

- Preoperative

- Small studies: no difference (RCT) to small \uparrow Hb, \downarrow transfusion rate (observational)
- Greater benefit if given for
 - Longer course (> 14 days vs. < 14 days)
 - Patients with anemia (vs. no anemia)

- ~~• Postoperative: no benefit~~

Oral Iron Salts



	Dose mg	Elemental mg	Cost
Ferrous gluconate (ODB)	300	35	\$0.07
Ferrous sulfate	300	60	\$0.13
Ferrous fumarate (ODB)	300	100	\$0.18

- Give once a day on an empty stomach
- Absorption only 10% of elemental Fe
- GI side effects: epigastric pain, heartburn, nausea, vomiting, constipation or diarrhea

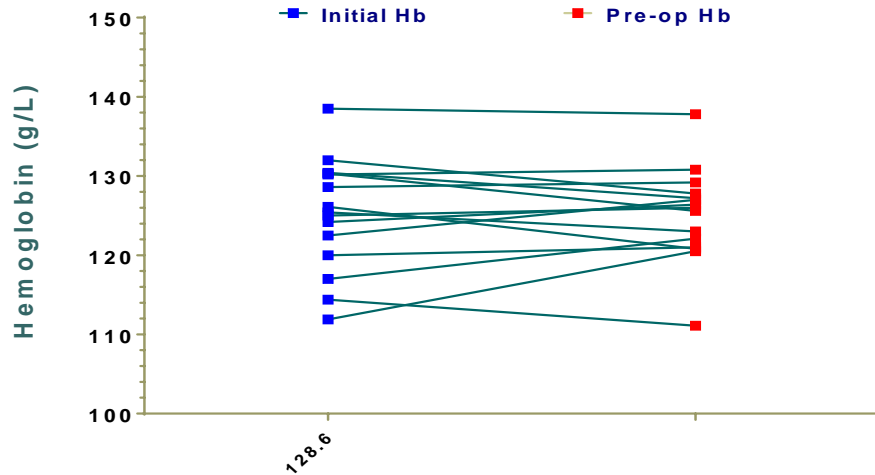
Oral Iron



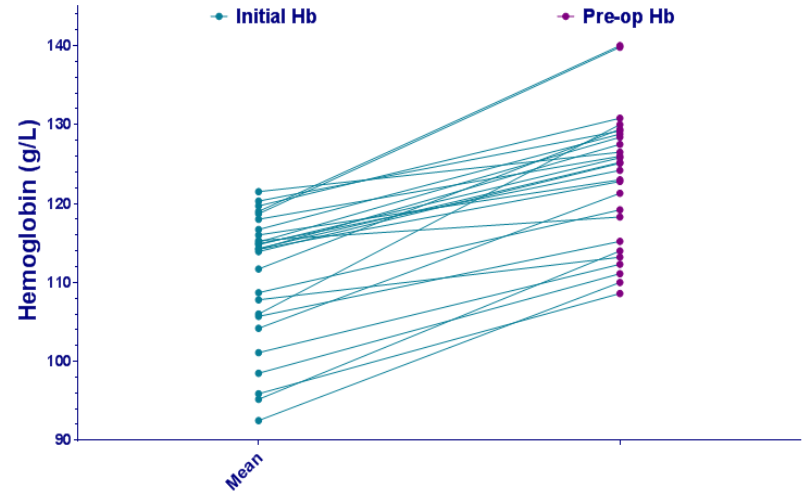
	Dose mg	Elemental mg	Cost
Polysaccharide (Triferexx)	150	150	\$0.71
Polysaccharide (Feramax)	150	150	\$0.95
Polysaccharide (Odan)	150	150	\$0.72
Heme iron (Proferrin)	398	11	\$1.03
Heme iron (Optifer alpha)		11	\$0.86

- Fewer side effects
- No evidence that more effective than oral iron salts

Oral iron only



IV iron only



2017 ONTraC data: Hb change 1 g/L vs. 13 g/L ($p < 0.0001$)
Lead time < 3 weeks in ~50%

Oral vs. IV iron

- Oral iron: response in 3-4 weeks; 5-10g/L per week
- Indications for IV iron
 - Oral iron not tolerated or effective (absorption or active bleeding)
 - Moderate/severe anemia, e.g. Hb < 100 g/L
 - Short time to surgery < 6-8 weeks

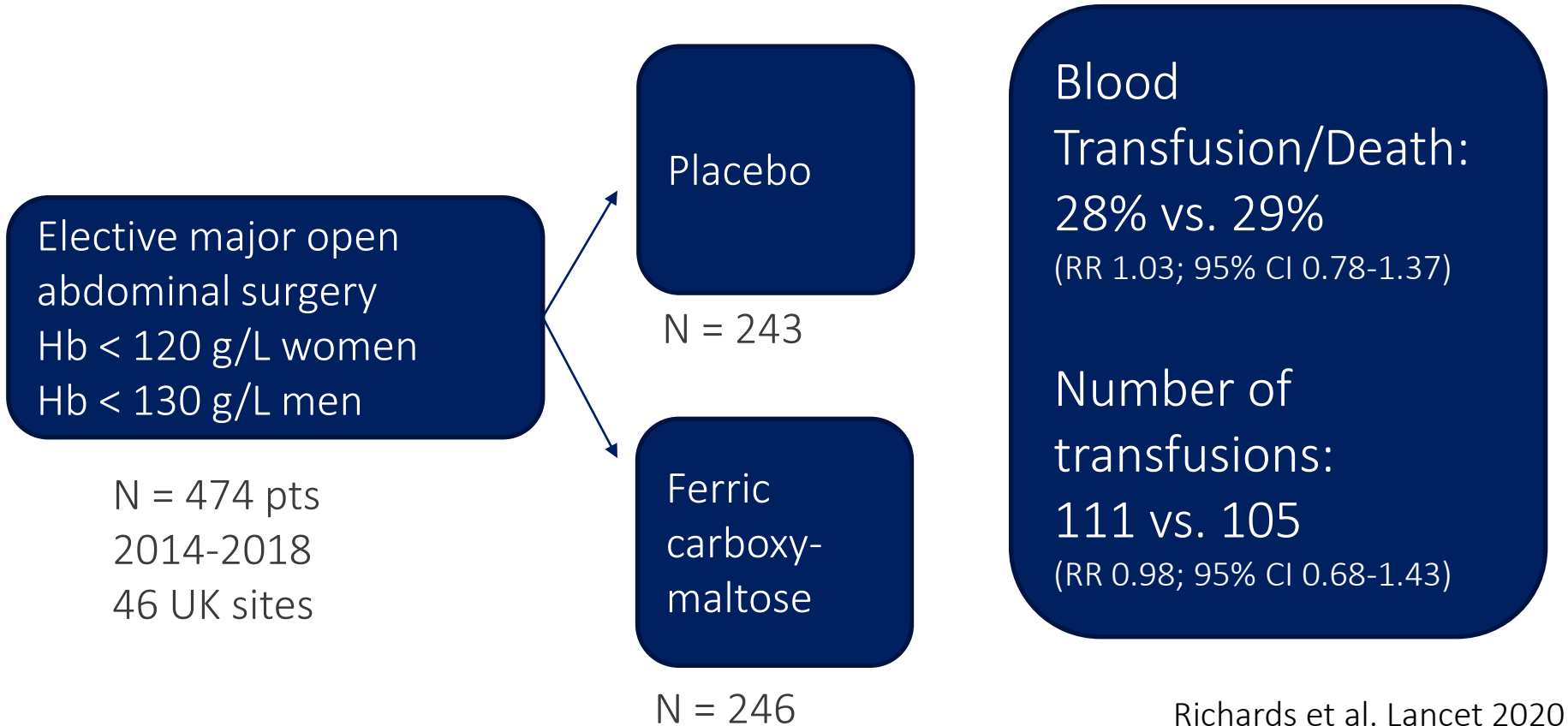
RCT: IV Iron in Abdo Surgery

- 72 pts for major abdominal surgery
 - Average Hb 107 g/L; Ferritin < 300, TSAT < 25% (mean ferritin 19-37)
- Randomized to IV iron or usual care
 - Ferric carboxymaltose 15mg/kg up to 1000mg preop + postoperative 0.5 mg per mL blood loss
 - Usual care: nothing
 - Only 3 patients prescribed oral iron in entire cohort
 - IV iron: 1 pt preop and 4 pts post-op

RCT: IV Iron in Abdo Surgery

- Terminated early due to poor outcomes in usual care group! (target 268 pts)
 - ↑ Hb increment 8 g/L vs. 1 g/L pre-op (p=0.01)
 - ↓ transfusion 12.5% vs. 31.3% (p<0.0003)
 - ↓ length of stay 7.0 vs 9.7 days (p=0.026)
 - ↑ Hb at 4 wks 122 g/L vs. 111 g/L (p<0.001)
- *“Usual care failed the majority of participating patients, leaving them untreated with a treatable condition”*

PREVENTT Trial



PREVENTT Trial

- Mean baseline Hb 111 g/L with Hb above 100 g/L in 83%
- No baseline iron criteria; 5% had IBD; 29% had iron deficiency
- Intervention:
 - Median 15 days preop; Hb ↑ 5 g/L preop
 - Anemia corrected 21% vs. 10%
 - No specific transfusion protocol
- No difference in subgroups (Hb <> 100; ferritin <>100)
- No difference in postop complications, LOS, QOL
- Decreased risk of readmission to hospital in IV iron group*

PREVENTT Trial

- Secondary analysis
 - Hb increase with preop IV iron
 - Absolute iron deficiency +8.9 g/L
 - Functional iron deficiency +2.8 g/L
 - No iron deficiency – minimal difference
 - No difference in outcomes: transfusion or death, postop complications or length of stay
 - Low MCV group had reduced death or transfusion and fewer units of blood following iv iron compared to placebo
- Absolute iron deficiency: should investigate and treat
- However, questions delay of surgery to optimize (depends on degree of anemia)

Latest systematic review...

- Evidence to date for Preoperative treatment
 - Iron supplementation increases Hb but may not result in reduced # of pts transfused (N=700 pts)
 - Iron \pm ESAs increases Hb and probably results in reduced # of pts transfused (N=1500 pts)

Intravenous iron	iron sucrose	ferric gluconate	iron isomaltoside
Name	Venofer	Ferrlecit	Monoferric
Indication	IDA in CKD	IDA in HD epo	IDA no oral iron cannot be used
Max single dose	300mg	125 mg	1500 mg
Test dose	No	No	No
Infusion time @ SBK	2 hours	1 hour	30 min (500mg) 60 min (1000mg)
Costs @ SBK	\$29.01 per 100mg	\$45.52 per 100mg	\$47.48 per 100mg
Life threatening ADE	0.6 per 10 ⁶	0.9 per 10 ⁶	comparable

Munoz et al. Blood Transfus 2012;10:8-22; Chertow et al. Nephrol Dial Transpl 2006;21:378-82; Wang et al. JAMA 2015;314:2062-68

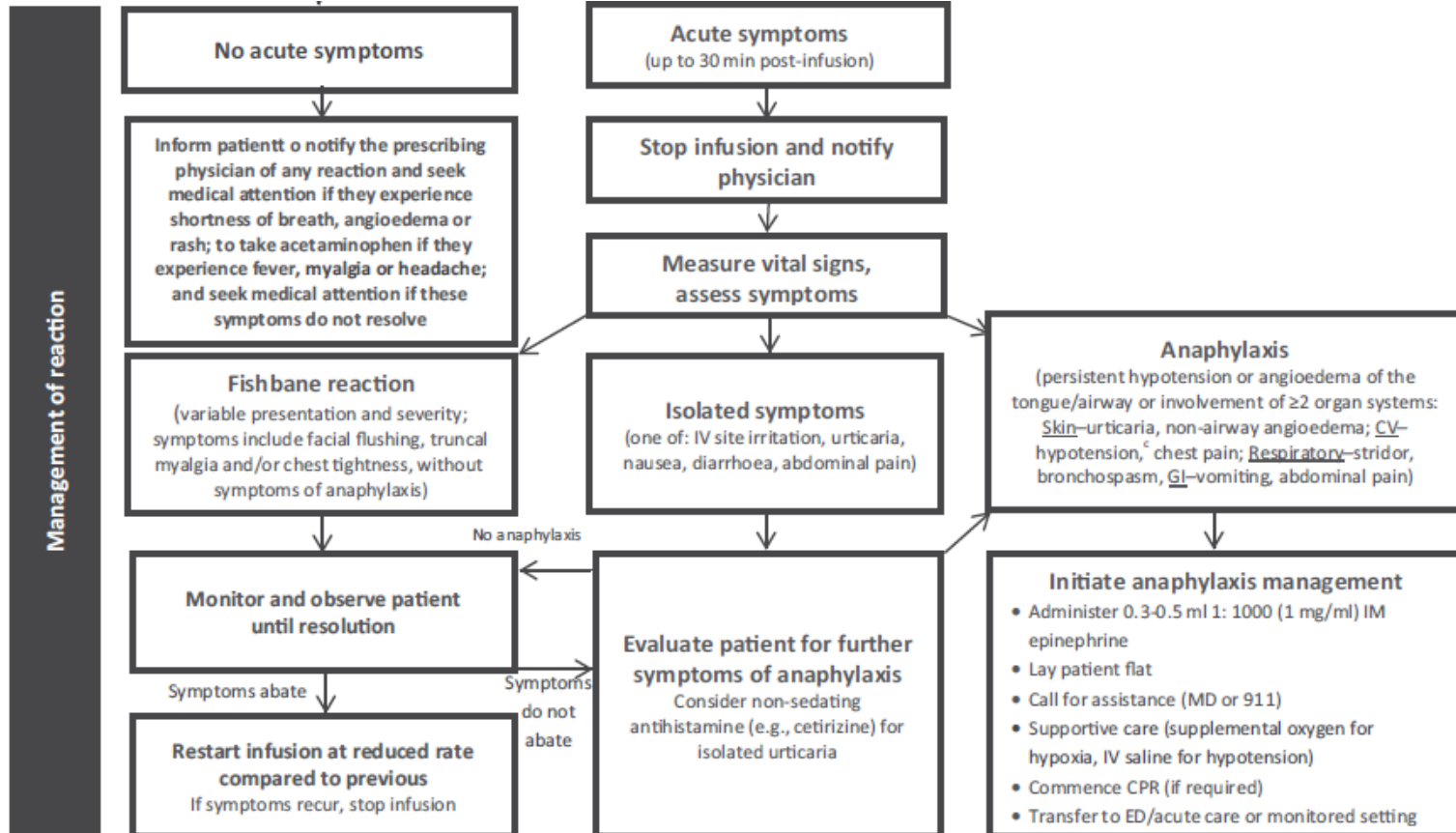
How to give it

- What dose?
 - Ganzoni formula
 - Dose = [wt (kg) x (target - initial Hb g/dL) x 2.4] + 500mg
 - In practice, 1000 - 1500 mg

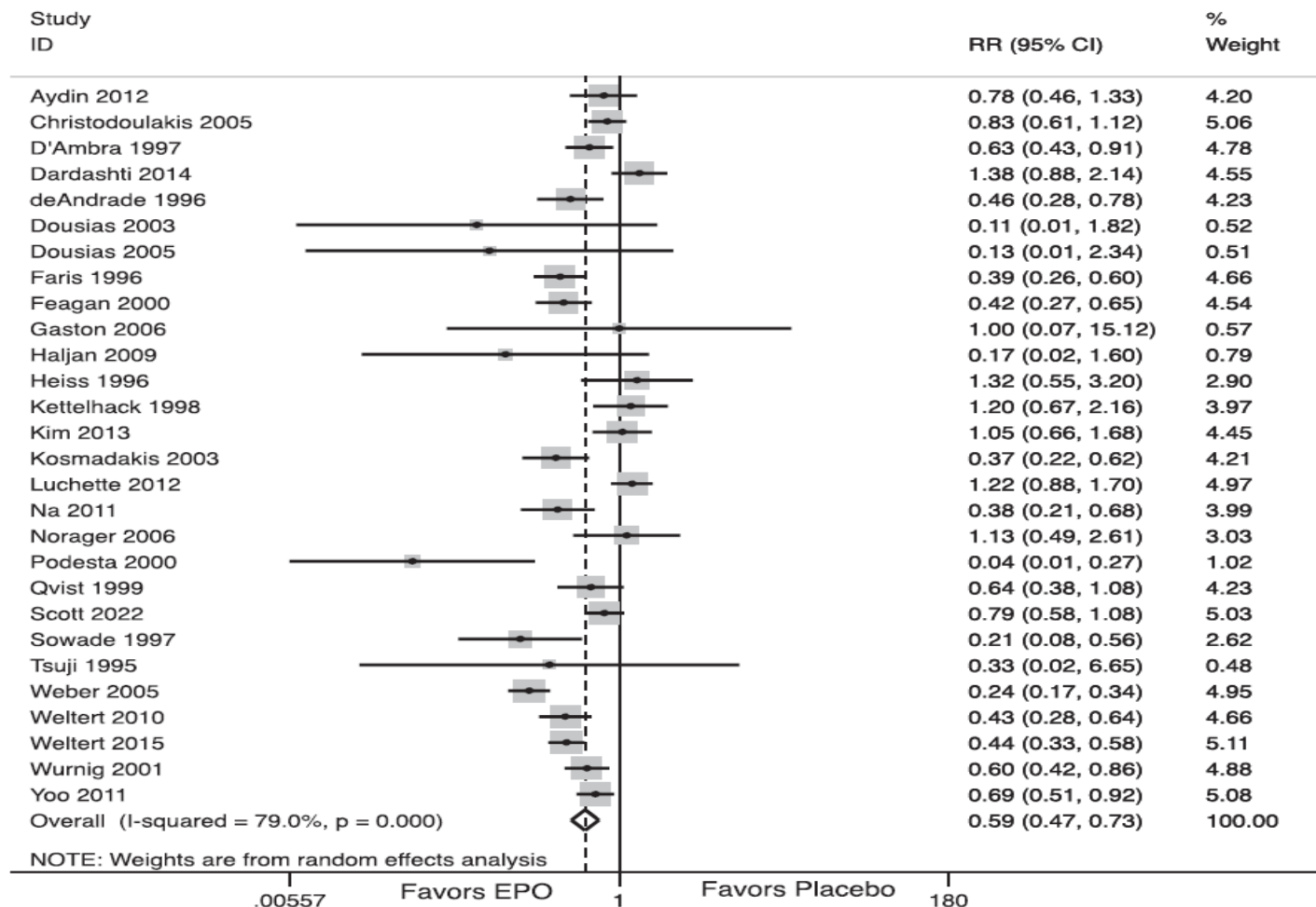
How to give it

- Side effects
 - Serious allergic reactions are rare but include anaphylaxis
 - Fishbane reactions: flushing, chest tightness (encourage hydration before coming to appt)
 - Hypotension 1-2%, metallic taste, headache, muscle cramps, arthralgias
- Contraindications:
 - Active infection, previous allergy to IV iron

Hypersensitivity reactions



Objective #3:
Consider the role of
Erythropoiesis-stimulating agents



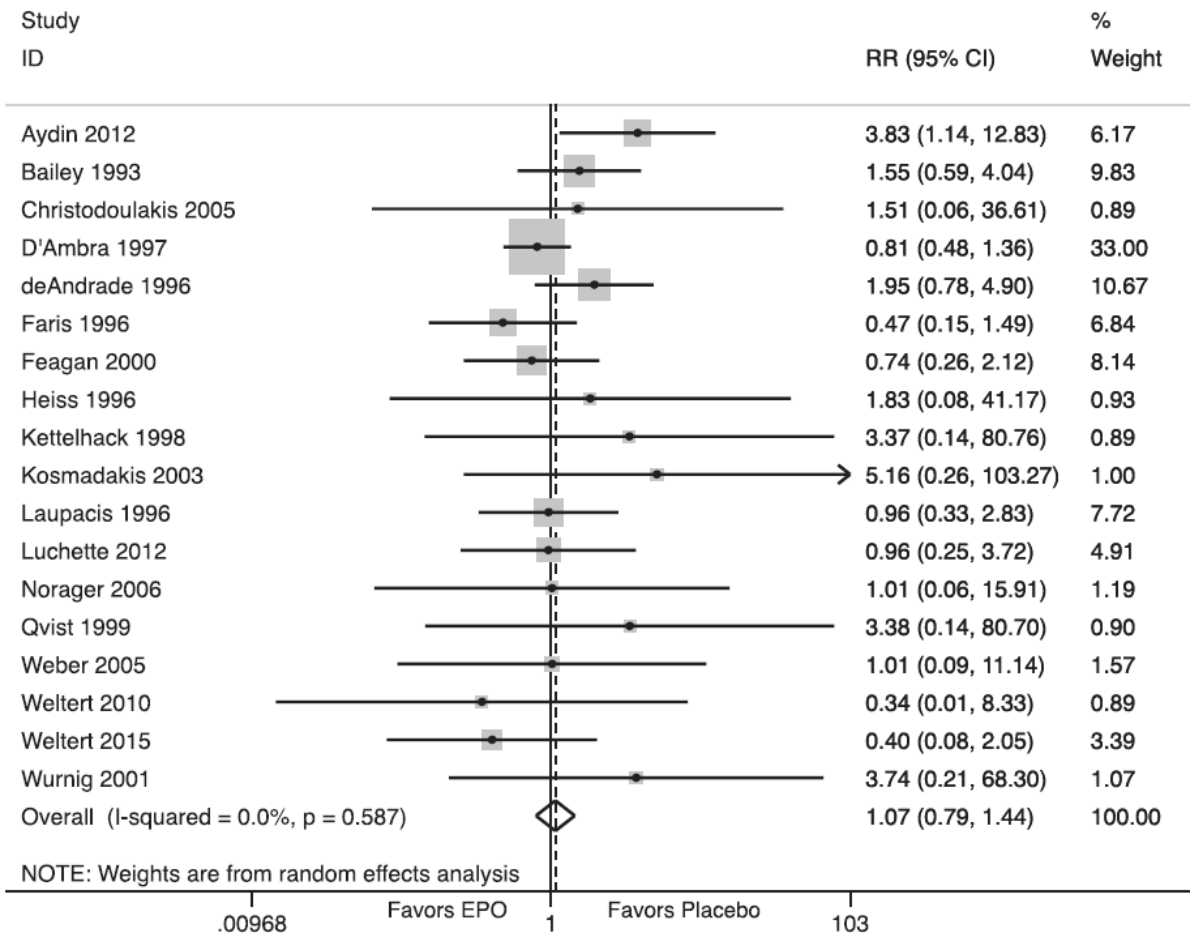
Preop EPO in
Surgical Pts
32 trials
4,750 pts

Decreased
transfusion
OR 0.59
(0.47, 0.73)

Figure 2. The weighted (pooled) estimate for the effect of preoperative erythropoietin (EPO) administration on incidence of whole hospitalization allogeneic transfusions (risk ratio [RR], 0.59; 95% CI, 0.47–0.73; $P < .001$) compared to placebo administration.

Concerns about ESA

- Chronic kidney disease
 - CHOIR: Epo to ↑ Hb to 135 g/L (vs. 113 g/L) associated with ↑ arterial TE events
 - CREATE: Epo to ↑ Hb to 130-150 g/L (vs. 105-115 g/L) – no difference
 - TREAT: Darbepoietin to ↑ Hb to 130 g/L (vs. placebo) – no difference in composite outcome, but ↑ stroke in darbepoietin group
 - ESA used for > 16 months



Preop EPO in
Surgical Pts
not associated
with ↑ TE events

Overall rate 4.1%
2° outcome
Uncertainty (wide
95% CI)

Figure 3. The weighted (pooled) estimate for effect of preoperative erythropoietin (EPO) administration on incidence of thromboembolic events (risk ratio [RR], 1.02; 95% CI, 0.78–1.33; $P = .68$) compared to placebo administration.

ESA in Cancer

- Mortality effect RR 0.97 – 1.17 (2 SR ↑, 3 SR no difference)
 - Controversial: How? VTE related? Poor responders to ESAs = worse prognosis? Seen in trials that targeted high Hb > 120 g/L
- Concern about tumour progression
 - Not clear how as tumours have low/undetectable EpoR
 - Theories unproven: angiogenesis, ↑tissue oxygenation → tumour growth, contribution to chemo resistance
- ↑ venous TE RR 1.48-1.67 (5 SR)
- Most studies in cancer used ESA > 8 weeks

The role of ESAs

Guidelines: role of preop ESAs less clear

1. High blood loss surgery (> 10% transfusion)
 - cardiac, orthopedic, major abdominal surgery

When to use Epo?

CanJSurg

For patients with anemia who have no evidence of IDA or IDA refractory to iron supplementation, referral to a hematologist should be considered for treatment with erythropoietin and intravenous iron infusions.

Strong

High

10. In patients with inadequate response to IV iron or when iron sequestration or inflammation limits the bioavailability of iron, an ESA should be considered on a case-by-case basis.

NAC

11. In patients with anemia and evidence of inflammation or renal failure where an ESA is indicated, it should be combined with IV iron.

Figure 2. Leading pathophysiological mechanisms contributing to hypoferremia and AI in CKD, IBDs, autoimmune diseases, cancer, chronic lung diseases, CHF, infectious diseases, and ICUs.

Anemia of inflammation



The role of ESAs


Guidelines: role of preop ESAs less clear

1. High blood loss surgery (> 10% transfusion)
 - cardiac, orthopedic, major abdominal surgery
2. Patients with anemia: Hb < 120-130 g/L
 - Religious objections to blood transfusion
 - Multiple alloantibodies → difficult to find blood

Even if there is not much time...

- Ultra-short anemia treatment
 - 484 pts elective cardiac surgery, anemia, ferritin < 100
 - Day before surgery: iv iron 20mg/kg, epo 40,000 units, B12, folic acid (vs. placebo)
 - ↓RBC units in 7d (median 0 vs. 1; OR 0.7 (95% CI 0.50-0.98))
 - Despite ↓RBC transfusion, higher Hb at 7 days
 - No difference in clinical outcomes, TE, safety

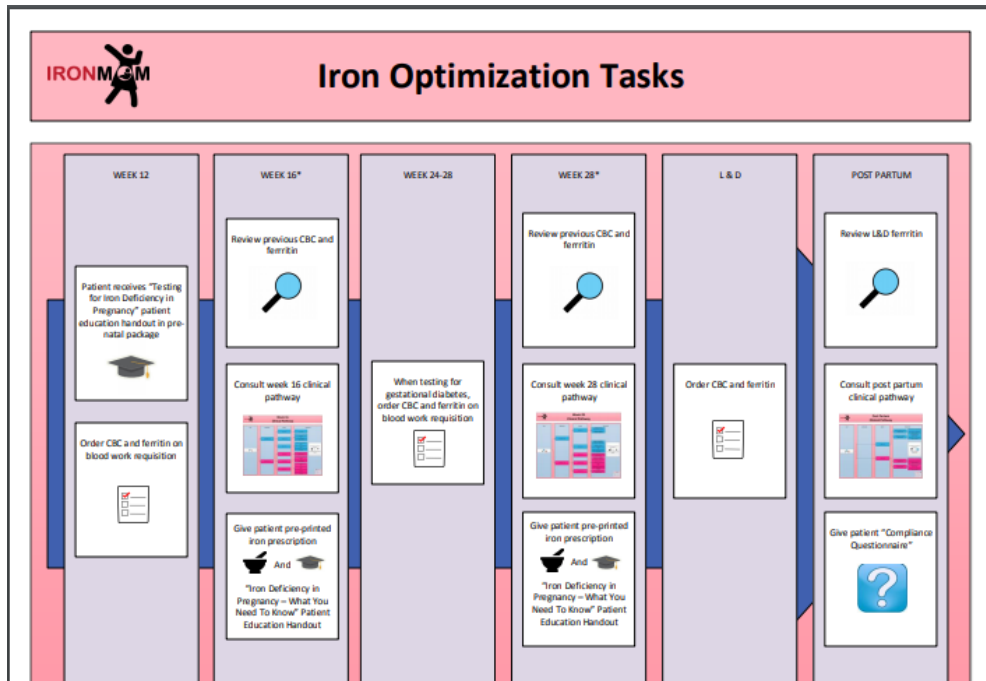
Practical Aspects

- Requires adequate lead time (3-4 weeks)
- Dose: 40,000 units s.c. q weekly x 2-4 doses  short term use
- Side effects: flu like symptoms with bone/muscle pain, hypertension (typically with longer term use)
- Iron supplementation
- Cost effectiveness uncertain
- Postop DVT prophylaxis

Obstetrics - Screen for Anemia

- ACOG
 - All pregnant women should be screened for anemia
 - Treat with iron if iron deficient
- BCH
 - Full blood count at booking (1st trimester) and at 28 wks
 - Anemic women with no other obvious cause: diagnostic trial of oral iron with CBC repeat at 2-3 wks

QI Project – IRON MOM Canada

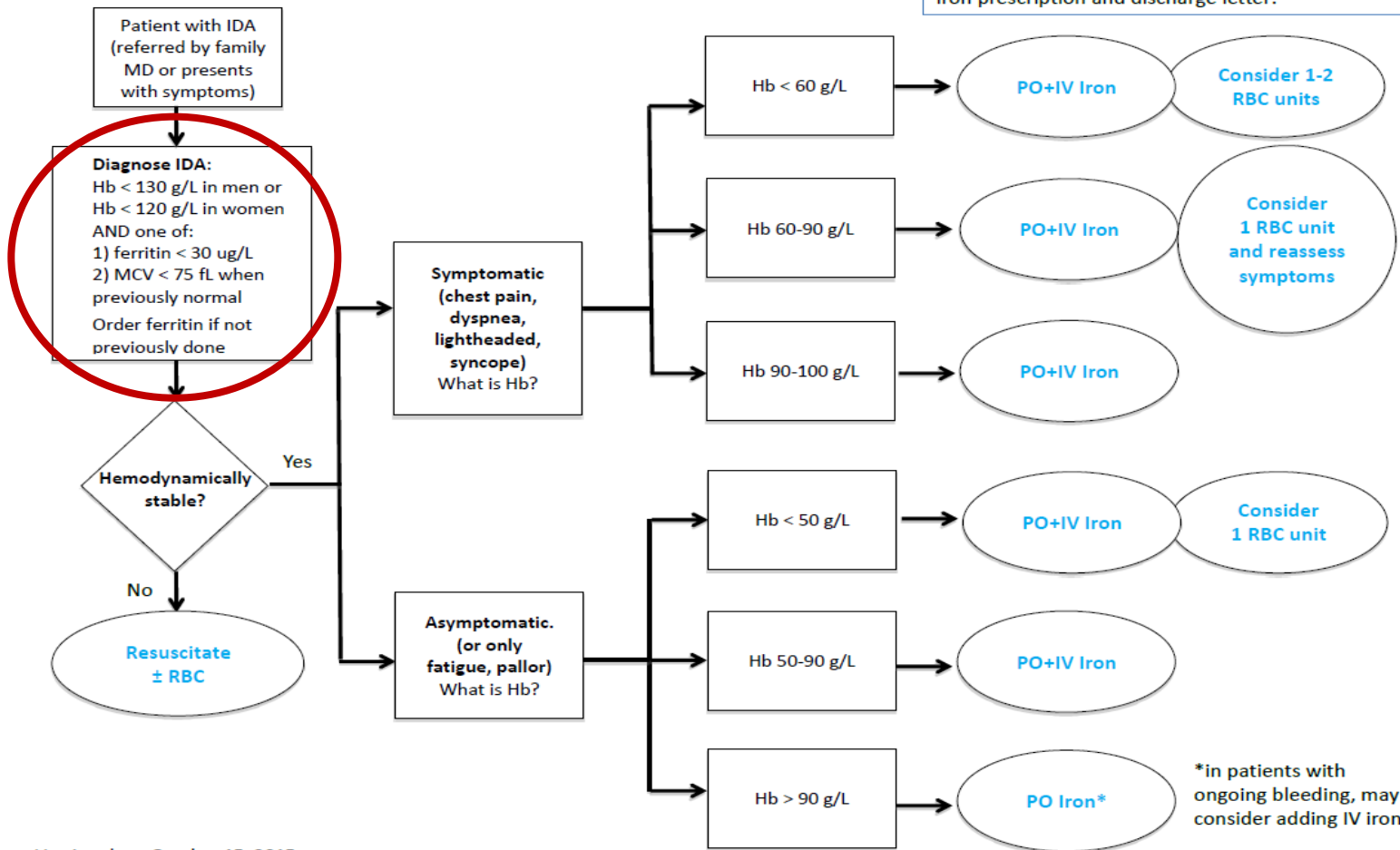


Outcomes:

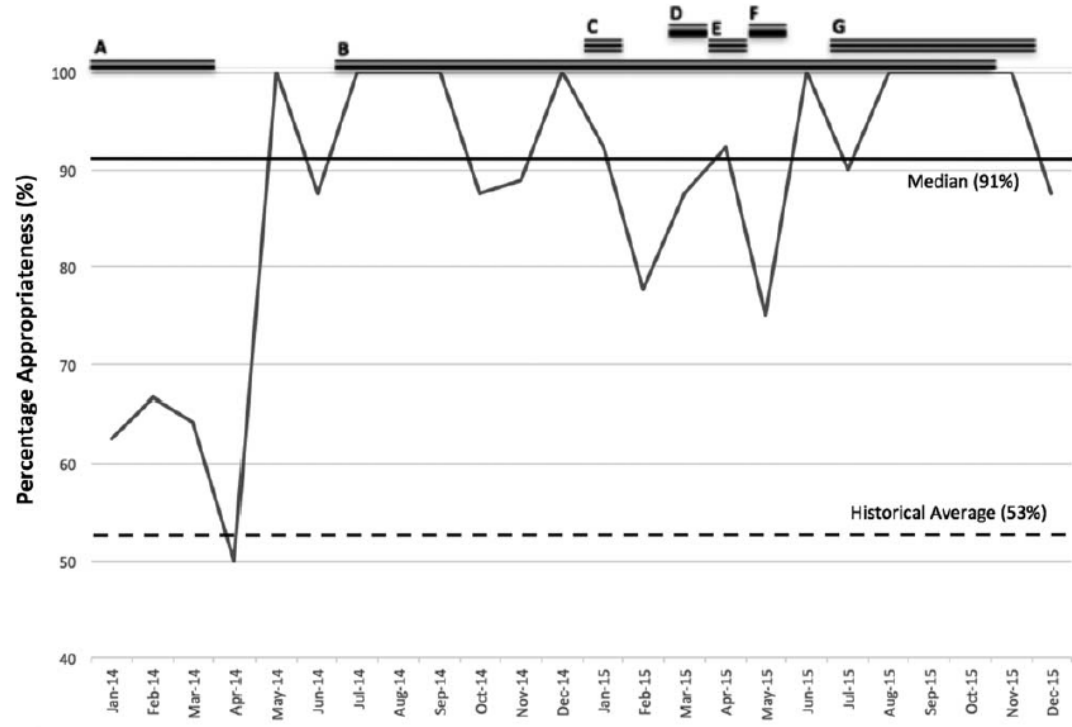
- ↑ ferritin tests
- ↓ anemia at delivery (13.5% to 10.6%, $p>0.001$)
- ↓ transfusions (1.2% vs. 0.8%, $p=0.049$)

Guideline for Iron Deficiency Anemia Management in the ED

Note: Please refer to WebER for patient pamphlet, IV iron orders (written consent not required), oral iron prescription and discharge letter.



Emergency Dept - Appropriate transfusion for IDA



- A. IV iron avail. in ED
- B. IV iron guideline
- C. Stakeholder feedback
- D. Grand rounds
- E. Access to TM MD
- F. Podcast release
- G. ED IDA toolkit

Summary – Treat anemia

- Preoperative anemia & transfusion are associated with bad perioperative outcomes
- Look for treatable anemia (Do CBC EARLY!)
- Look for iron deficiency anemia (common)
 - Ferritin < 30 ug/L; Ferritin < 100 ug/L + TSAT<20%
 - Make sure the underlying cause is identified in IDA
- Consider preop erythropoietin in high blood loss surgery especially in pts with religious objections or rare blood needs