

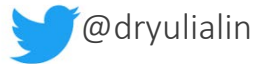
Patient Blood Management: Treating Anemia

Yulia Lin, MD, FRCPC, CTBS

Division Head, Transfusion Medicine, Sunnybrook HSC

Associate Professor, Dept of Laboratory Medicine and Pathobiology, University of Toronto

Transfusion Camp Day 4, March 26, 2021



Disclosures

- No conflicts of interest

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 an evidence-based, multidisciplinary approach to optimizing care of patients who might need transfusion

Pre-op

Treat anemia

During surgery

Minimize blood
loss

Post-op

Appropriate use
of blood

Patient Blood Management

- PBM is an evidence-based, multidisciplinary approach to optimizing care of patients who might need transfusion

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

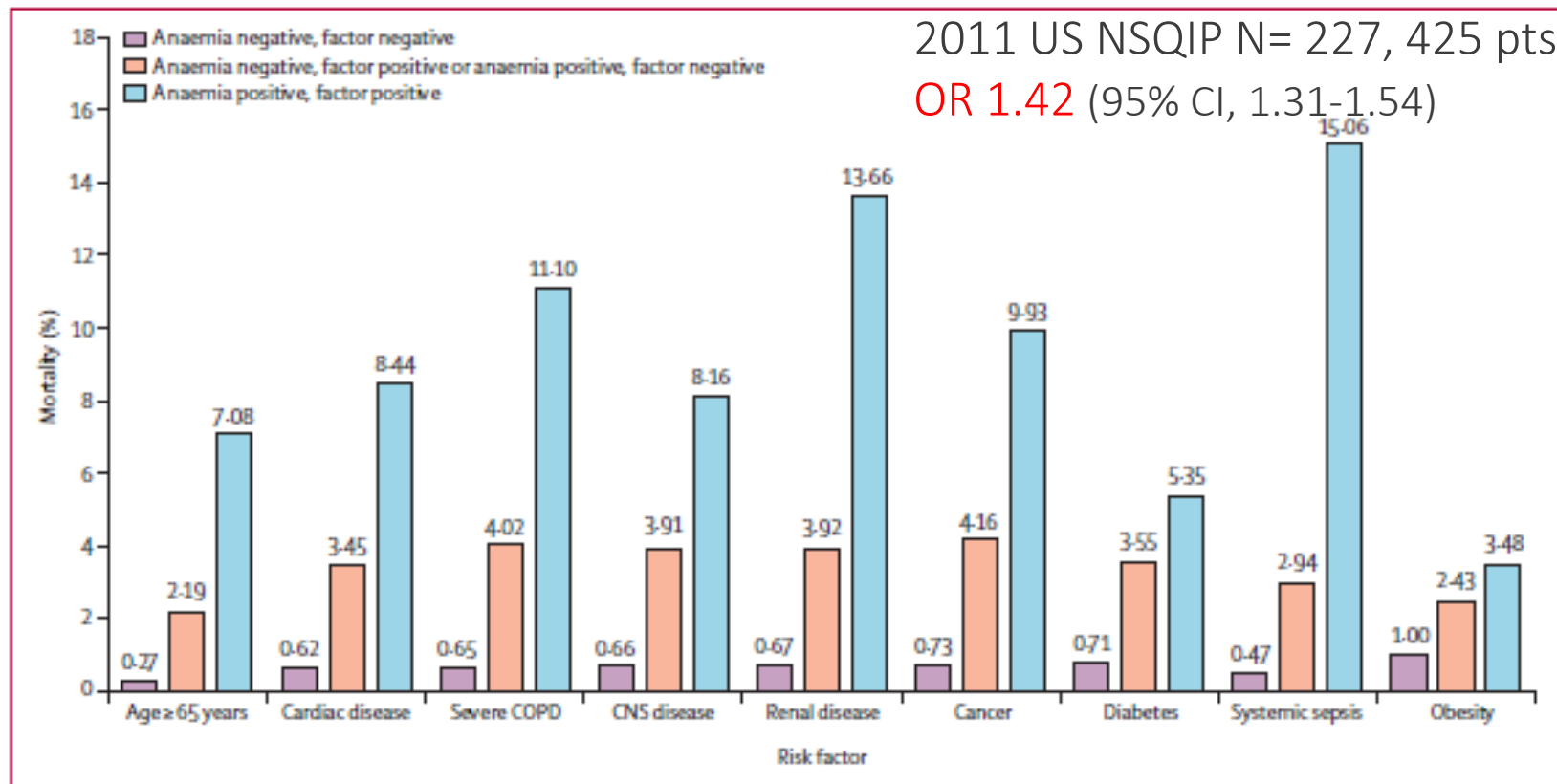
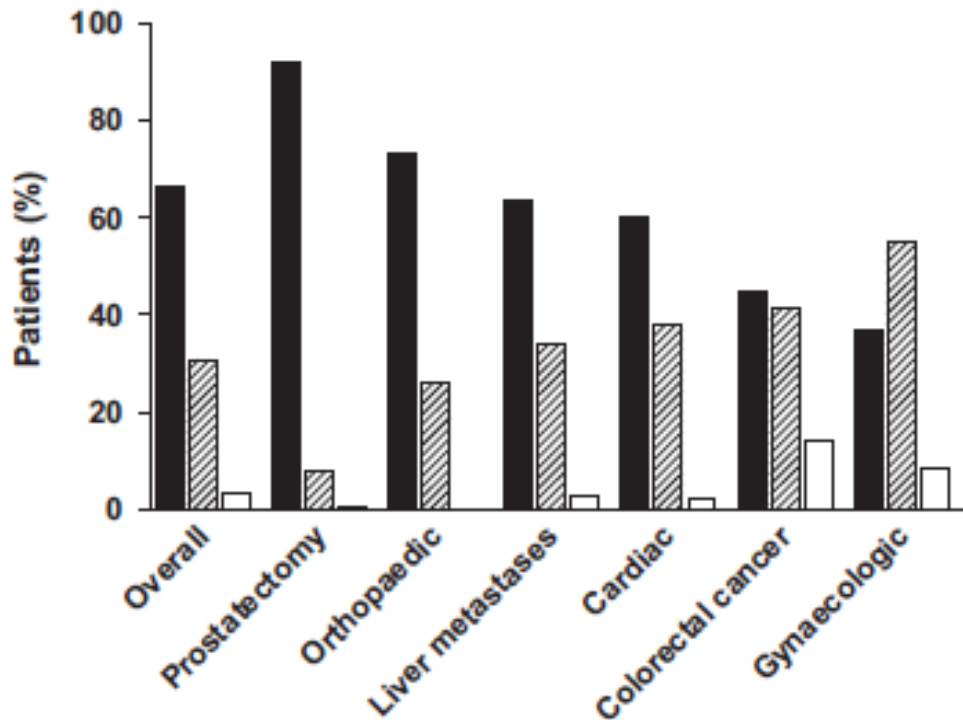


Figure 1: 30-day mortality, by anaemia and risk factor status
COPD=chronic obstructive pulmonary disease.

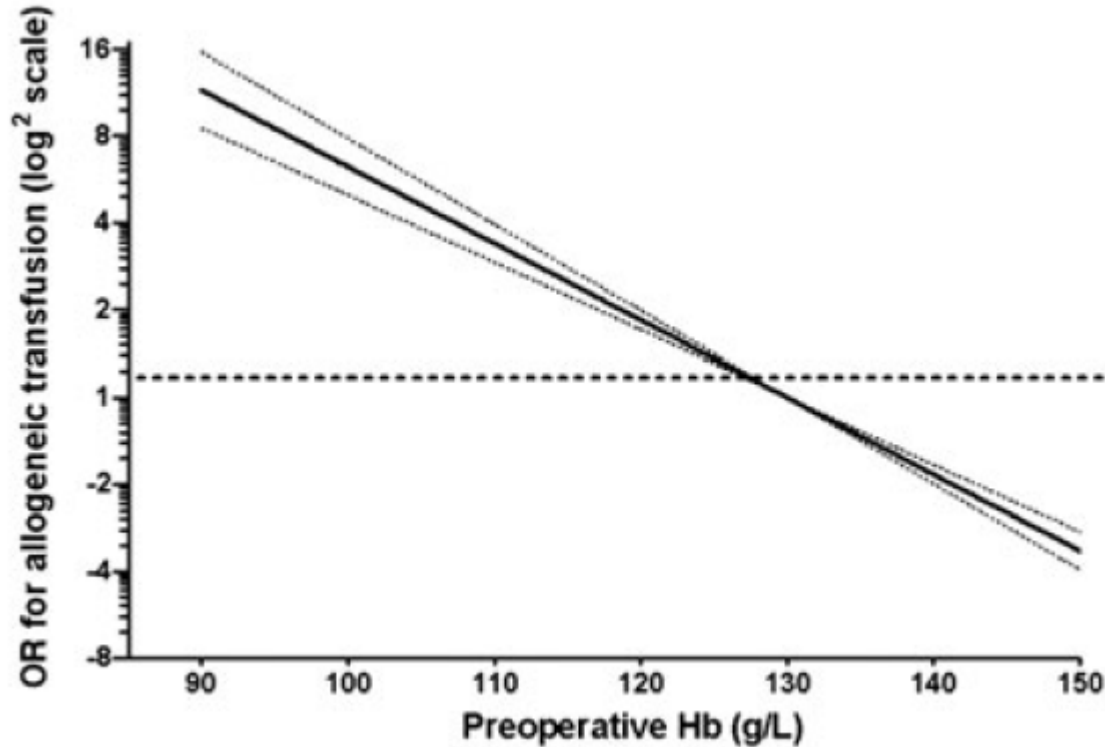
#3 Preoperative anemia is common (25-40%)!



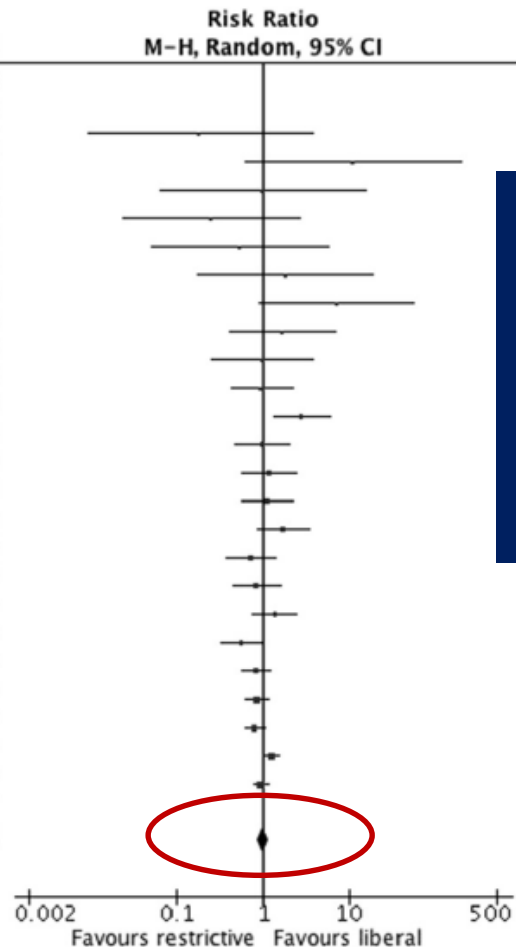
Anemia in 36% (1/3)

N = 3342 pts

#4 Pre-op anemia associated with ↑ transfusion



Study or Subgroup	Restrictive		Liberal		Weight	Risk Ratio	
	Events	Total	Events	Total		M-H, Random, 95% CI	M-H, Random, 95% CI
Laine 2017	0	40	0	40		Not estimable	
Lotke 1999	0	62	0	65		Not estimable	
Blair 1986	0	26	2	24	0.2%	0.19 [0.01, 3.67]	
Foss 2009	5	60	0	60	0.3%	11.00 [0.62, 194.63]	
Carson 1998	1	42	1	42	0.3%	1.00 [0.06, 15.47]	
DeZern 2016	1	59	2	30	0.4%	0.25 [0.02, 2.69]	
Webert 2008	1	29	2	31	0.4%	0.53 [0.05, 5.58]	
Cooper 2011	2	23	1	21	0.4%	1.83 [0.18, 18.70]	
Carson 2013	7	55	1	55	0.5%	7.00 [0.89, 55.01]	
Parker 2013	5	100	3	100	1.1%	1.67 [0.41, 6.79]	
Bush 1997	4	50	4	49	1.2%	0.98 [0.26, 3.70]	
Hébert 1995	8	33	9	36	2.7%	0.97 [0.42, 2.22]	
de Almeida 2015	23	101	8	97	3.2%	2.76 [1.30, 5.87]	
Lacroix 2007	14	320	14	317	3.4%	0.99 [0.48, 2.04]	
Hajjar 2010	15	249	13	253	3.4%	1.17 [0.57, 2.41]	
Palmieri 2017	16	168	15	177	3.8%	1.12 [0.57, 2.20]	
Gregersen 2015	21	144	12	140	3.9%	1.70 [0.87, 3.32]	
Walsh 2013	12	51	16	49	4.2%	0.72 [0.38, 1.36]	
Jairath 2015	14	257	25	382	4.2%	0.83 [0.44, 1.57]	
Murphy 2015	26	1000	19	1003	4.7%	1.37 [0.76, 2.46]	
Villanueva 2013	19	416	34	417	5.3%	0.56 [0.32, 0.97]	
Carson 2011	43	1009	52	1007	7.9%	0.83 [0.56, 1.22]	
Mazer 2017	74	2427	87	2429	10.2%	0.85 [0.63, 1.15]	
Hébert 1999	78	418	98	420	11.4%	0.80 [0.61, 1.04]	
Bergamin 2017	84	151	67	149	12.6%	1.24 [0.99, 1.55]	
Holst 2014	168	502	175	496	14.4%	0.95 [0.80, 1.13]	
Total (95% CI)		7792		7889	100.0%	1.00 [0.86, 1.16]	
Total events	641		660				
Heterogeneity: Tau ² = 0.03; Chi ² = 34.44, df = 23 (P = 0.06); I ² = 33%							
Test for overall effect: Z = 0.02 (P = 0.99)							



26 trials
15,681 pts
30 day mortality
OR 1.00
(0.86, 1.16)

*Comparing hb thresholds not transfusion vs. no transfusion

NSQIP Studies of Perioperative Transfusion

Study	Surgery type	# pts	Outcome	Assoc w/ transfusion
Halabi 2010	Colorectal cancer resection	27 120	30-day mortality	OR 1.78
O’Keeffe 2010	Lower extremity revascularization	8 799	30-day mortality	OR 1.92
de la Fuente 2011	Pancreatico-duodenectomy	6 293	30-day mortality	OR 1.91
Tzeng 2013	Hepatectomy in elderly	7 621	30-day mortality	OR 2.37
Pugeley 2013	Lumbar discectomy	4 310	Any complication	OR 1.54
Fischer 2014	Breast reconstruction	16 063	Major surgical complications	OR 2.9
Hart 2015	Total knee arthroplasty	13 662	30-day mortality	OR 2.7
Prescott 2015	Gynecologic cancer surgery	8 519	30-day mortality	OR 3.38

Courtesy of J. Pendergrast, Transfusion Camp Day 4. March 2018.

Advocate for PBM because...

1. Preoperative anemia is bad
2. Preoperative anemia is modifiable
3. Preoperative anemia is common
4. Transfusion is a bad outcome
5. The donor supply is a precious resource

What are strategies to treat anemia and prevent transfusion?

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)

Current state in 2021

- 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)




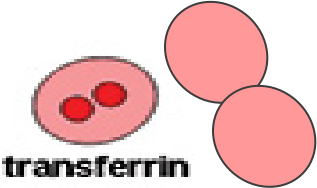
What is Preop Anemia?

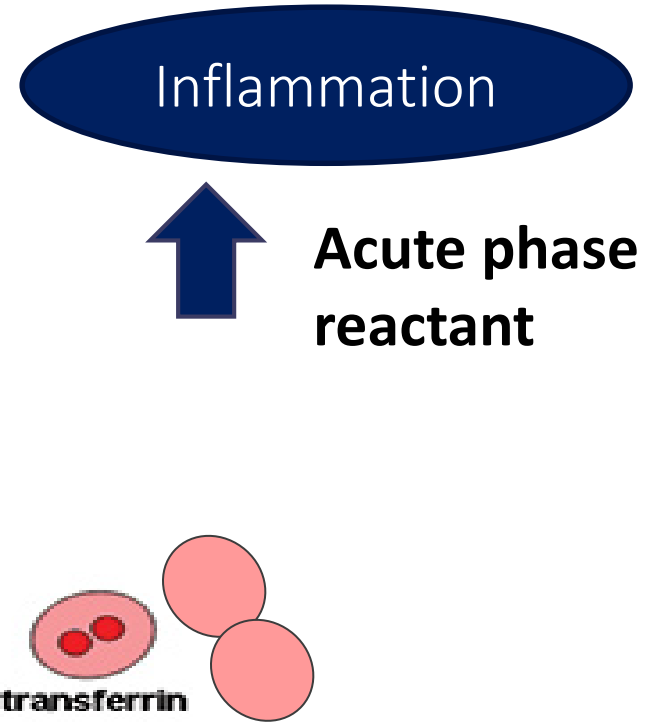
- WHO: Hb < 130 g/L males; Hb < 120 g/L females
- **NEW:** Hb < 130 g/L used for all (high blood loss surgery)
 - Both sexes lose same amount of blood
 - Women have lower circulating blood volume
 - Accepting lower preop Hb for women ↑transfusion risk
 - NSQIP data: risk increases as hemoglobin levels < 130 g/L with no sex differential

Detection

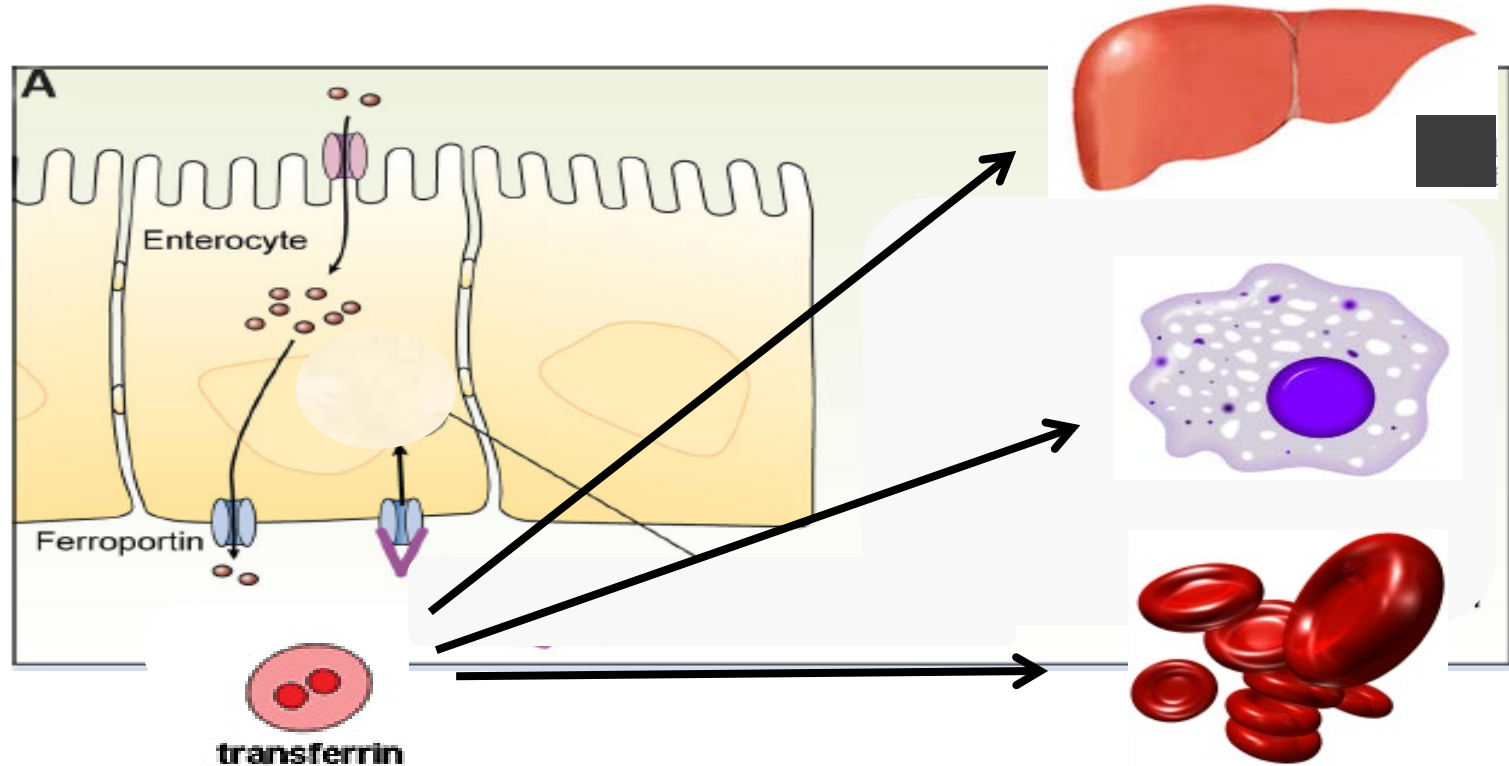
- Who should be screened?
 - All high blood loss surgery (> 500 mL): ortho, cardiac, cancer
 - All high risk for severe anemia: colorectal, gyne
- When?
 - 4-8 weeks before surgery
- How?
 - CBC, ferritin, TSAT, B12, creatinine
 - Focus on iron deficiency anemia (common & treatable)

How to diagnose IDA?

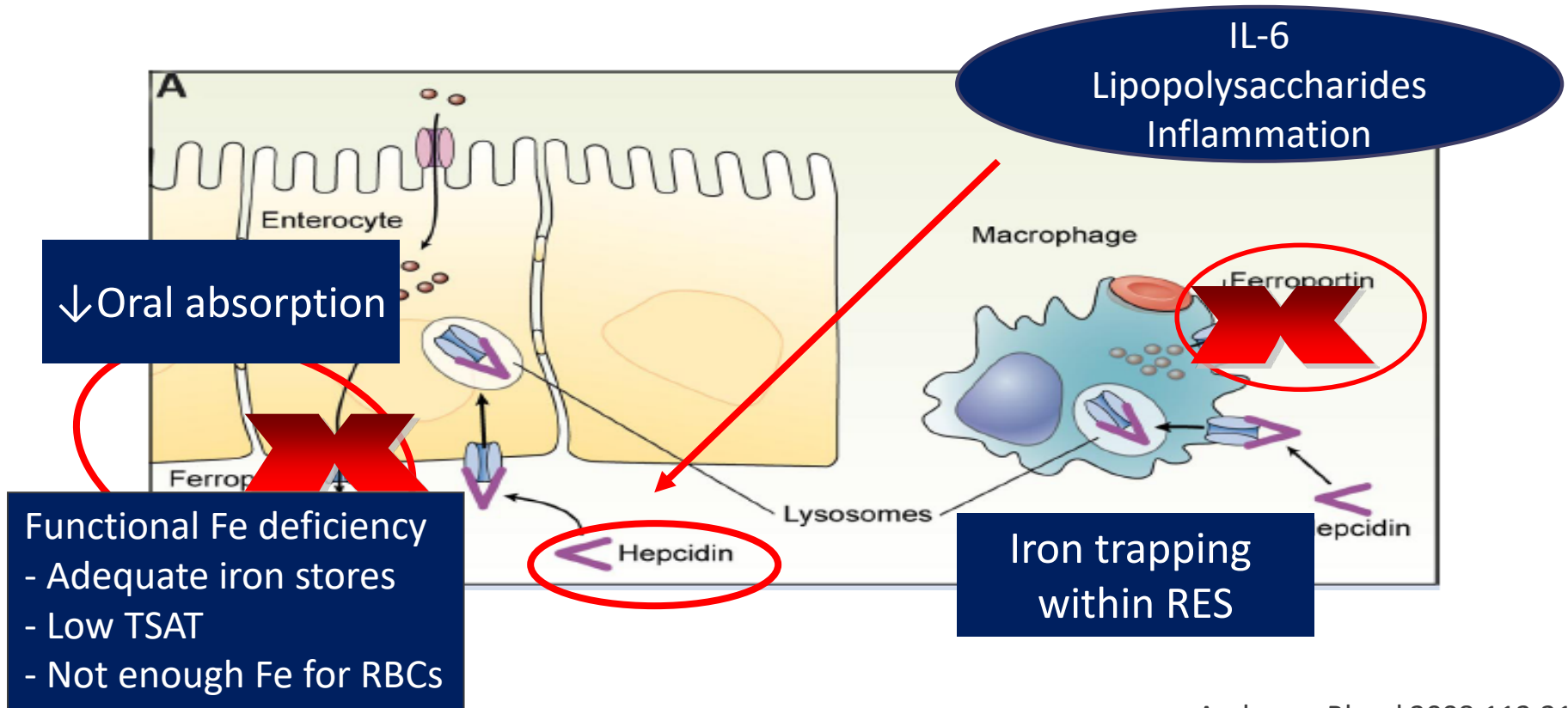
- Ferritin 
 - Reflection of iron stores
 - Ferritin < 30 ug/L = Iron deficiency
- Serum Fe 
- Transferrin (TIBC) 
 - Transport protein of Fe
- Transferrin saturation 
 - Serum Fe / TIBC



Iron Pathway



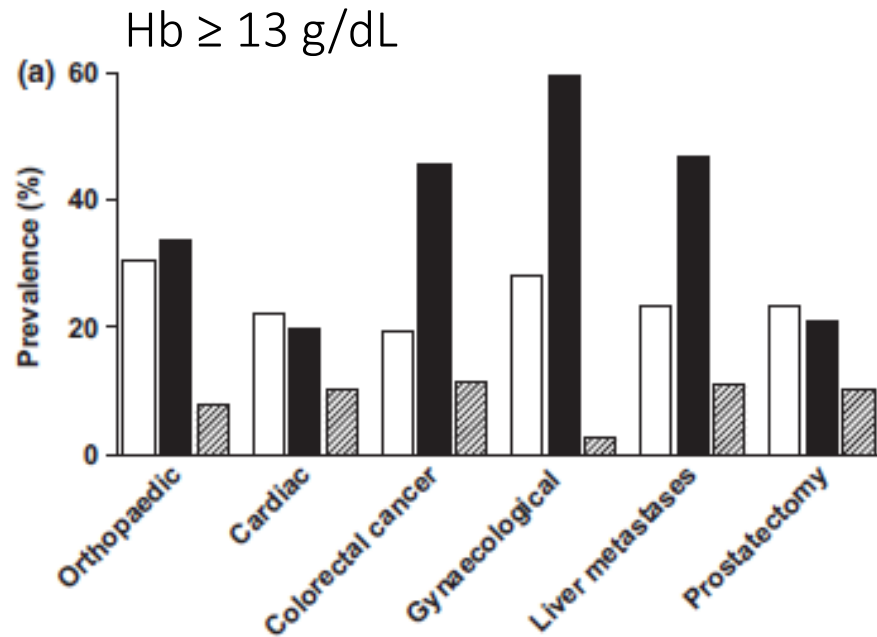
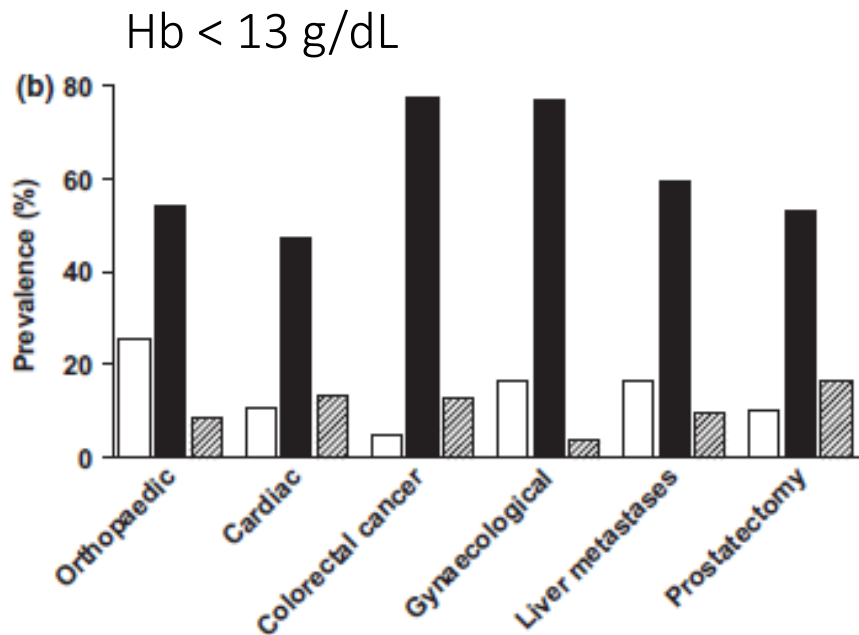
Anemia of Chronic Disease – Hepcidin



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%

Case:
Vegan x 10 yrs
OGD, C-scope N
Chronic anemia
HTN → Kidney

Oral Iron

- 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	\$0.13
Ferrous sulfate	300	60	\$0.03
Ferrous fumarate (ODB)	300	100	\$0.13-0.43

- Inexpensive (over the counter)
- Take on an empty stomach
- Absorption only 10% of elemental Fe
- GI side effects: epigastric pain, heartburn, nausea, vomiting, constipation or diarrhea

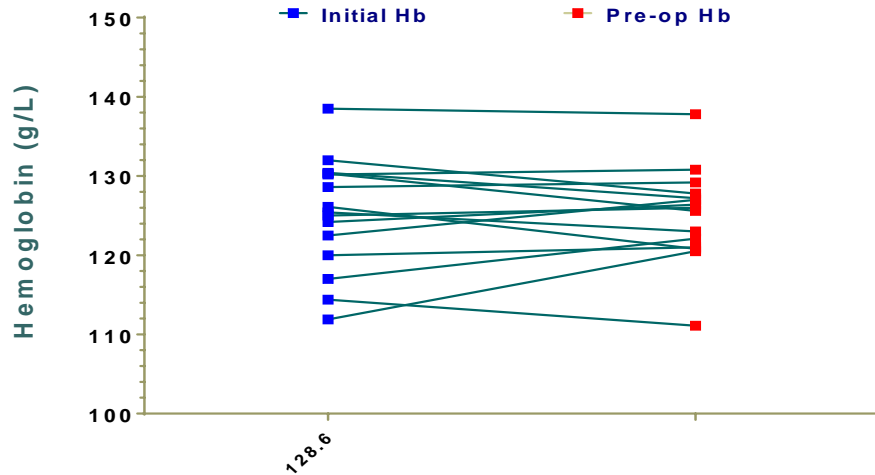
Oral Iron



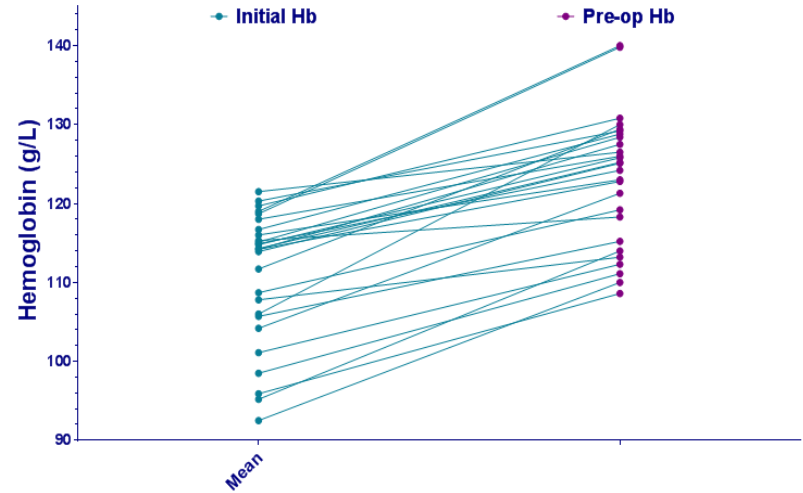
	Dose mg	Elemental mg	Cost
Polysaccharide (Triferex)	150	150	\$0.71
Polysaccharide (Feramax)	150	150	\$0.92
Heme iron (Proferrin)	398	11	\$1.03

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

Oral iron only



IV iron only



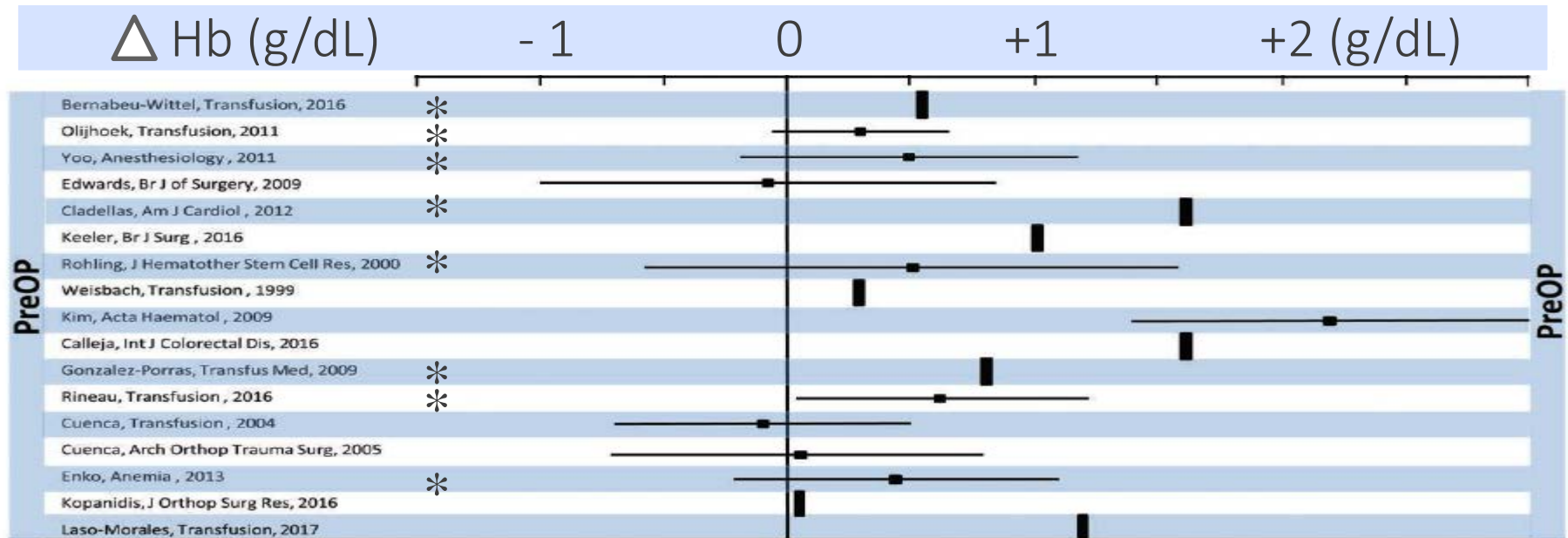
2017 ONTraC data: Hb change 1 g/L vs. 13 g/L ($p < 0.0001$)
Lead time < 3 weeks in ~50%

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
 - Short time to surgery < 4-6 weeks
 - Severe anemia, e.g. Hb < 100 g/L
 - Active bleeding

Preoperative IV iron

- ↑ Hb in 11 of 17 studies (+/- ESA*)
- ↓ transfusion in 8 of 13 studies



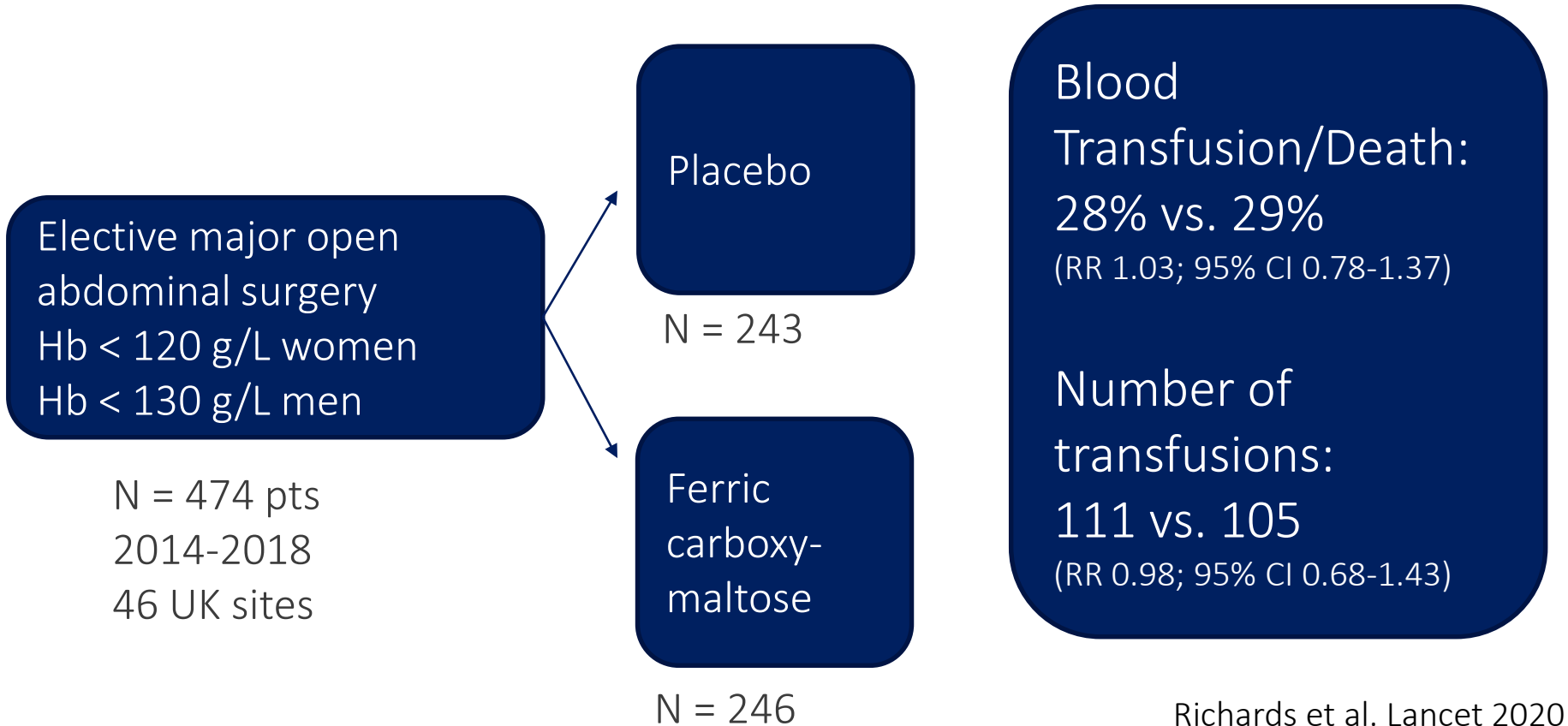
RCT: IV Iron in Abdo Surgery

- 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

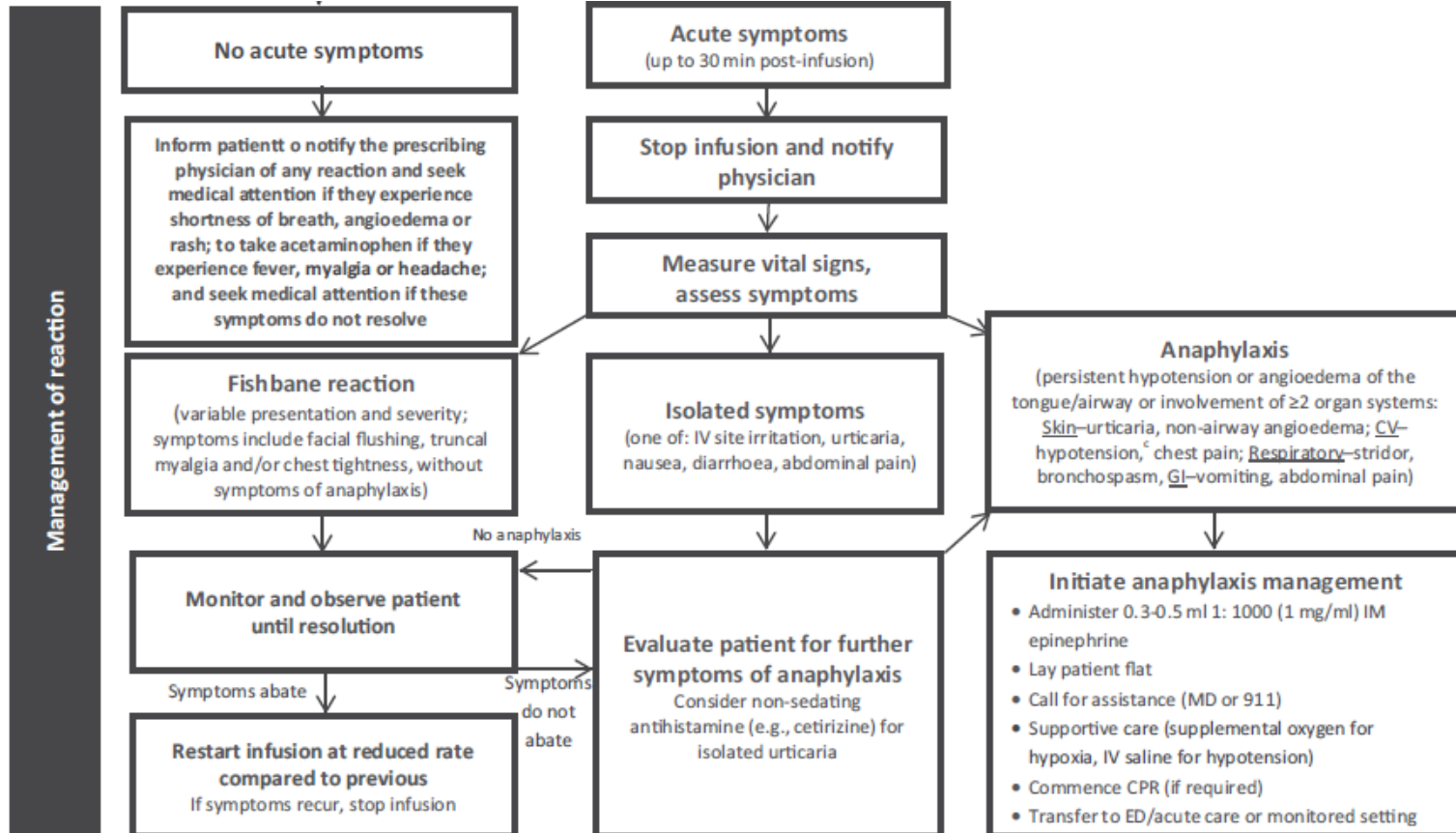
- Mean baseline Hb 111 g/L with Hb above 100 g/L in 83%
- No baseline iron criteria; 5% had IBD; 29% had iron deficiency
- Intervention:
 - Median 15 days preop; Hb ↑ 5 g/L preop
 - Anemia corrected 21% vs. 10%
 - No specific transfusion protocol
- No difference in subgroups (Hb <> 100; ferritin <>100)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

Intravenous iron	iron sucrose	ferric gluconate	iron isomaltoside
Name	Venofer	Ferrlcit	Monoferic
Indication	IDA in CKD	IDA in HD epo	IDA no oral iron cannot be used
MW (kDa)	43	289-440	150
Max single dose	300mg	125 mg	1500 mg
Test dose	No	No	No
Infusion time	2 hours	1 hour	60 minutes (1000mg)
Cost (ONT wholesale)	\$39.56 (100mg)	\$44.50 (100mg)	\$48.60 (100mg)
Life threatening ADE	0.6 per 10 ⁶	0.9 per 10 ⁶	comparable

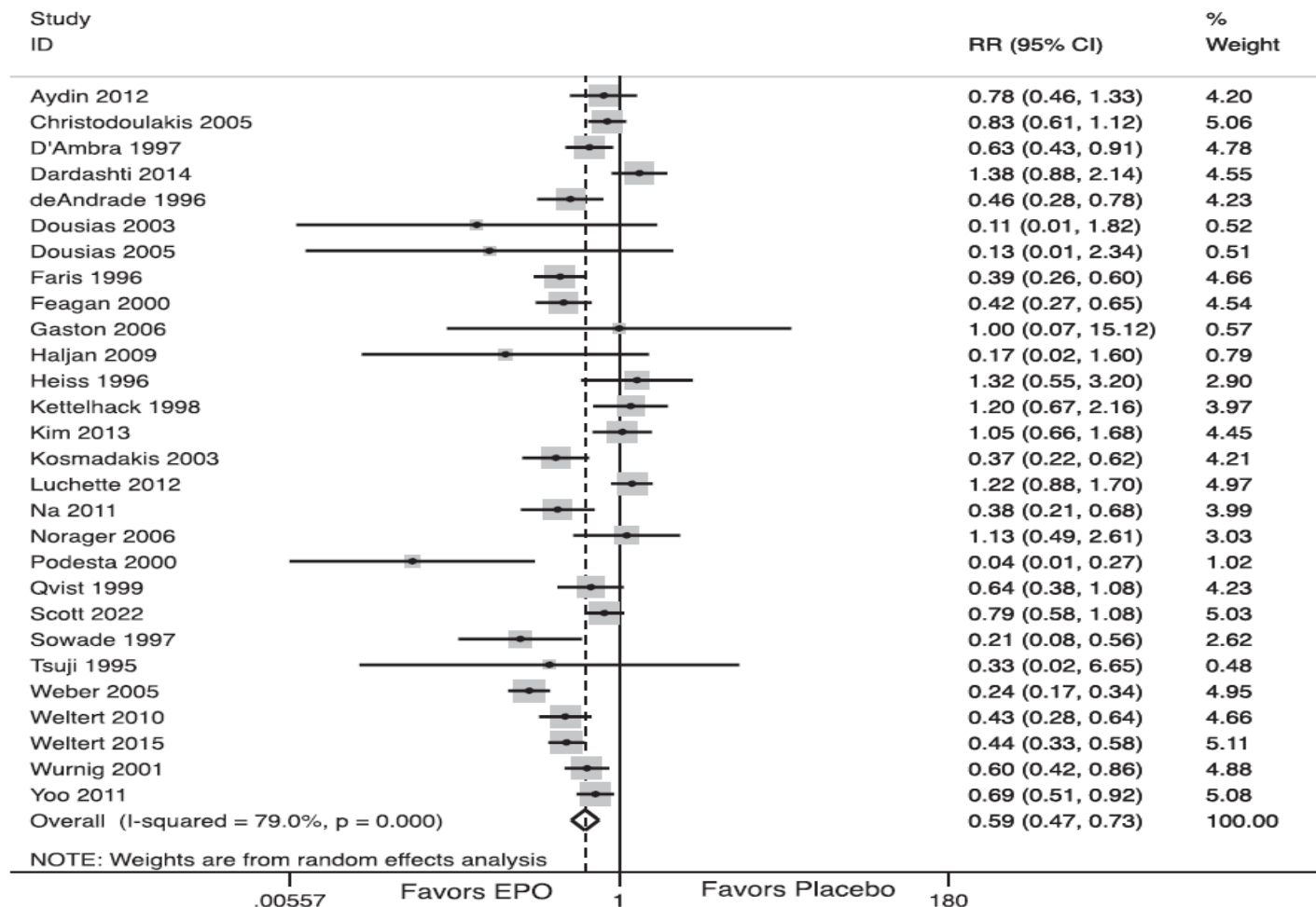
How to give it

- What dose?
 - Ganzoni formula
 - Dose = [wt (kg) x (target - initial Hb g/dL) x 2.4] + 500mg
 - In practice, 1000 - 1500 mg
- Adverse effects: rare anaphylactic (24 per 100,000 US data), hypotension, muscle cramps, arthralgias, back pain, headache

Hypersensitivity reactions



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



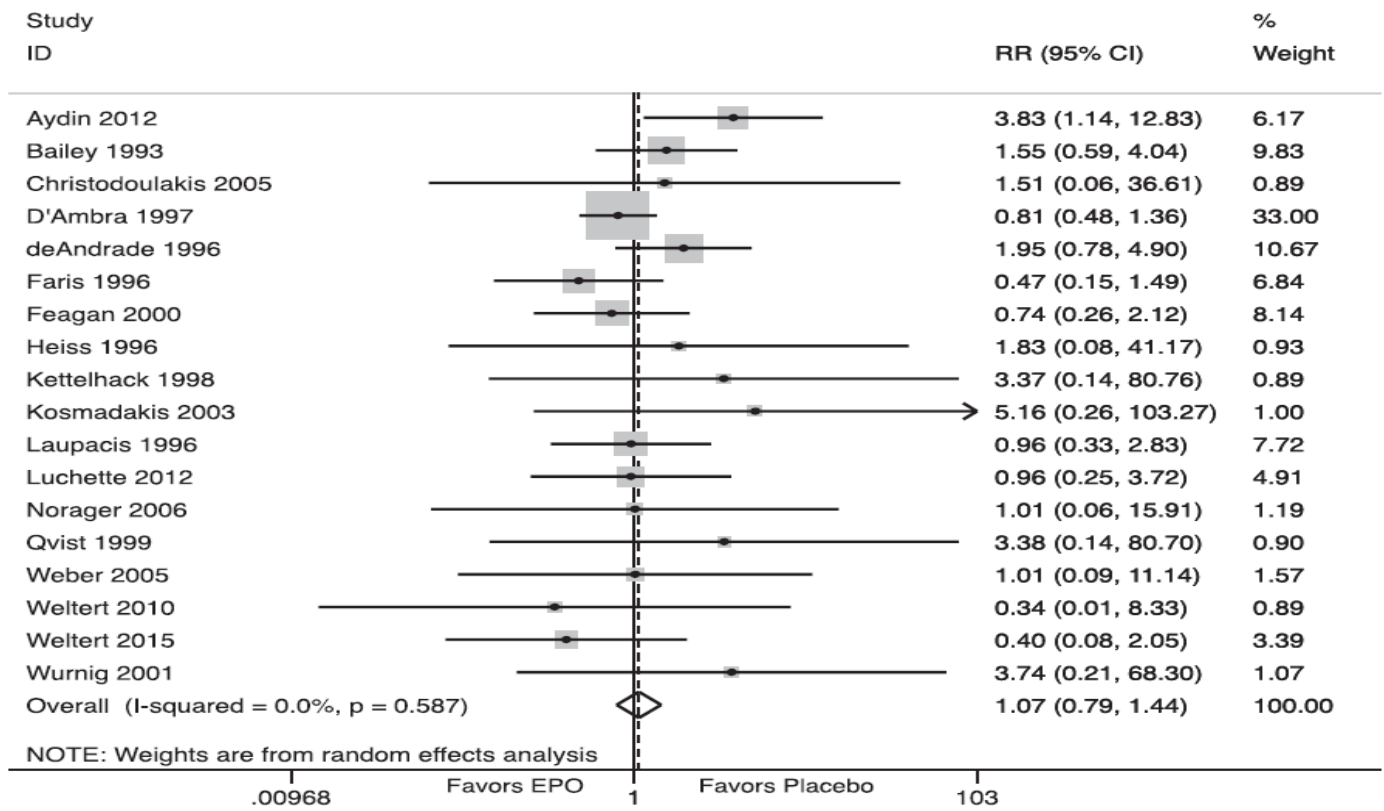
Preop EPO in
Surgical Pts
32 trials
4,750 pts

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

No increase in thrombosis

OR 1.07 (0.79, 1.44)

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.

Concerns about ESA

- Cancer
 - Concern about tumour progression
 - Not clear how as tumours have low/undetectable EpoR
 - Restricted to certain tumour types (e.g. H&N XRT)
 - Controversial whether there is \uparrow mortality RR 0.97 – 1.17 (2 SR \uparrow , 3 SR no difference)
 - How? VTE related? Poor responders to ESAs?
 - ESA use > 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
2. Patients with anemia: Hb < 12-13 g/dL
 - 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))
 - No difference in clinical outcomes, TE, safety

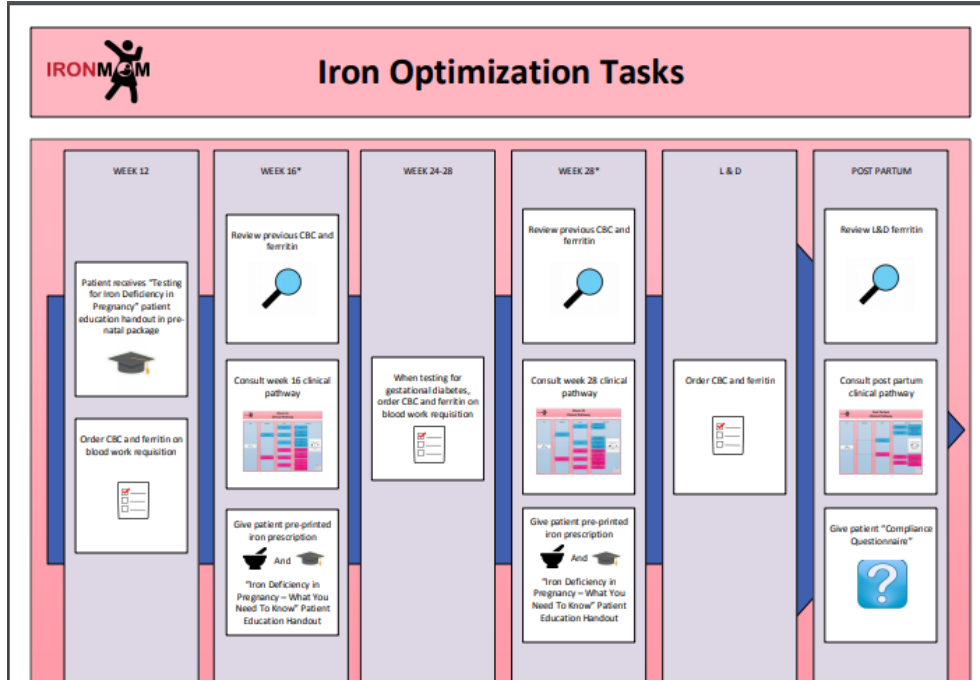
Practical Aspects

- 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

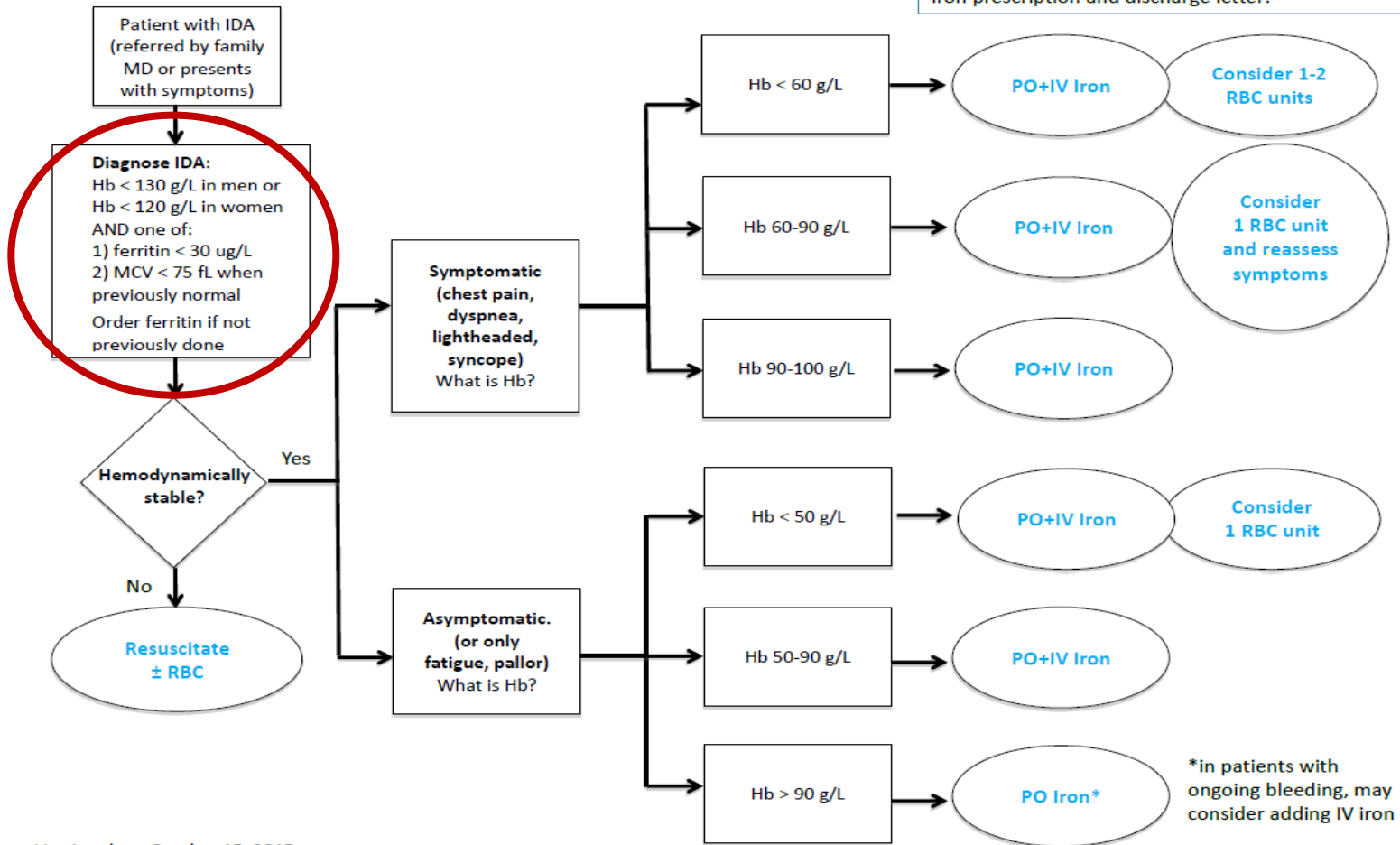


Outcomes:

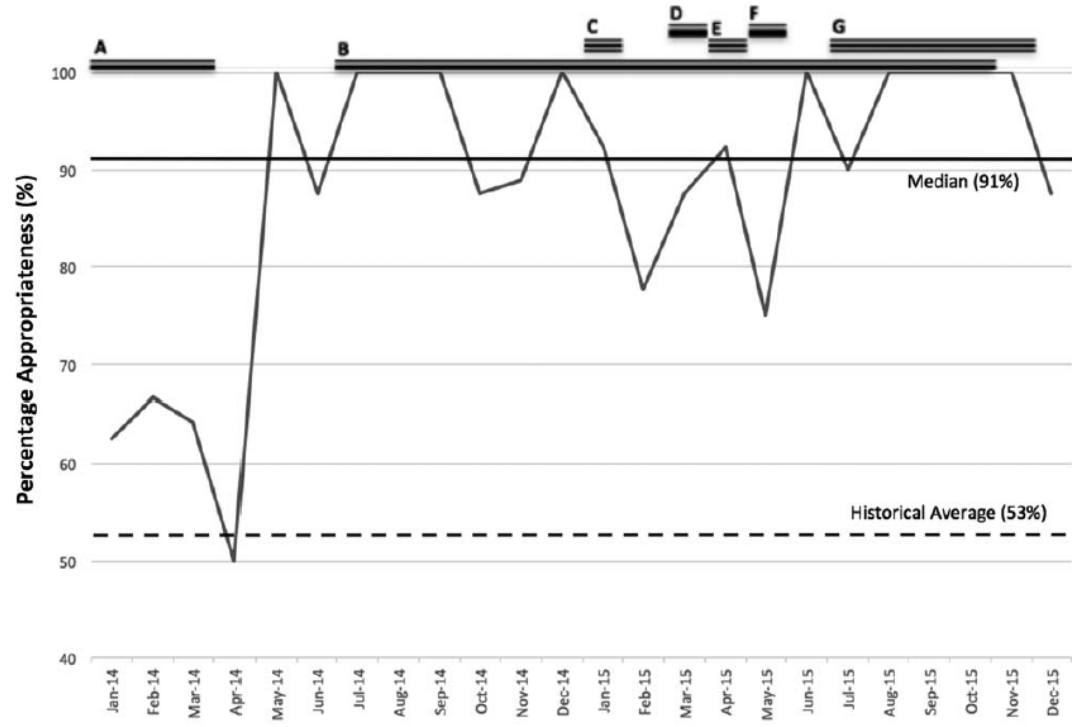
- ↑ ferritin tests
- ↓ anemia at delivery (13.5% to 10.6%, $p>0.001$)
- ↓ transfusions (1.2% vs. 0.8%, $p=0.049$)

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

Preoperative Anemia Pathway

