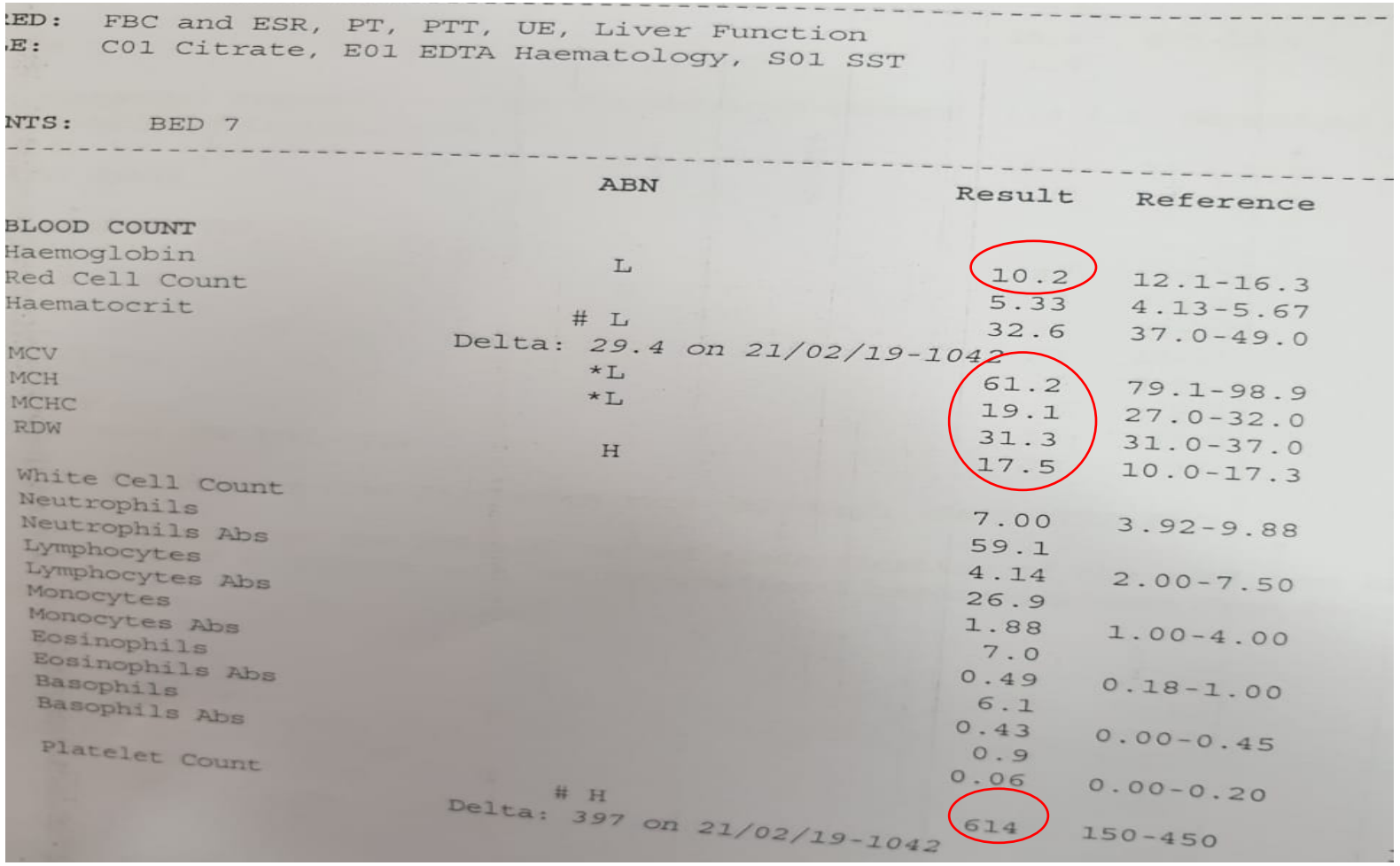
Patient Blood Management

Anthony Beeton

Case study 1



ED: FBC and ESR, PT, PTT, UE, Liver Function
E: C01 Citrate, E01 EDTA Haematology, S01 SST

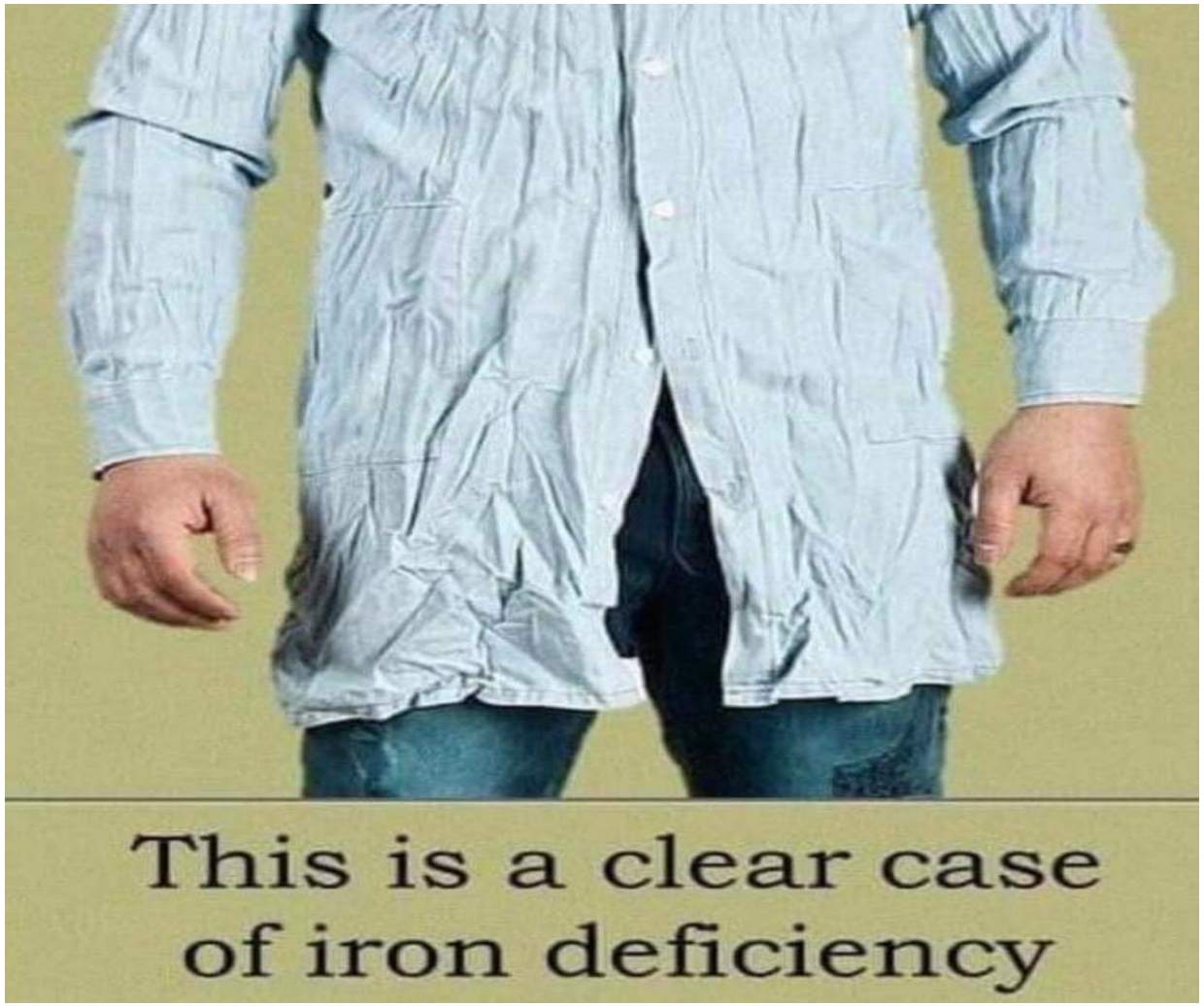
NTS: BED 7

	ABN	Result	Reference
BLOOD COUNT			
Haemoglobin	L	10.2	12.1-16.3
Red Cell Count		5.33	4.13-5.67
Haematocrit	# L	32.6	37.0-49.0
	Delta: 29.4 on 21/02/19-1042		
MCV	*L	61.2	79.1-98.9
MCH	*L	19.1	27.0-32.0
MCHC		31.3	31.0-37.0
RDW	H	17.5	10.0-17.3
White Cell Count		7.00	3.92-9.88
Neutrophils		59.1	
Neutrophils Abs		4.14	2.00-7.50
Lymphocytes		26.9	
Lymphocytes Abs		1.88	1.00-4.00
Monocytes		7.0	
Monocytes Abs		0.49	0.18-1.00
Eosinophils		6.1	
Eosinophils Abs		0.43	0.00-0.45
Basophils		0.9	
Basophils Abs		0.06	0.00-0.20
Platelet Count	# H	614	150-450
	Delta: 397 on 21/02/19-1042		

B thalassaemia minor

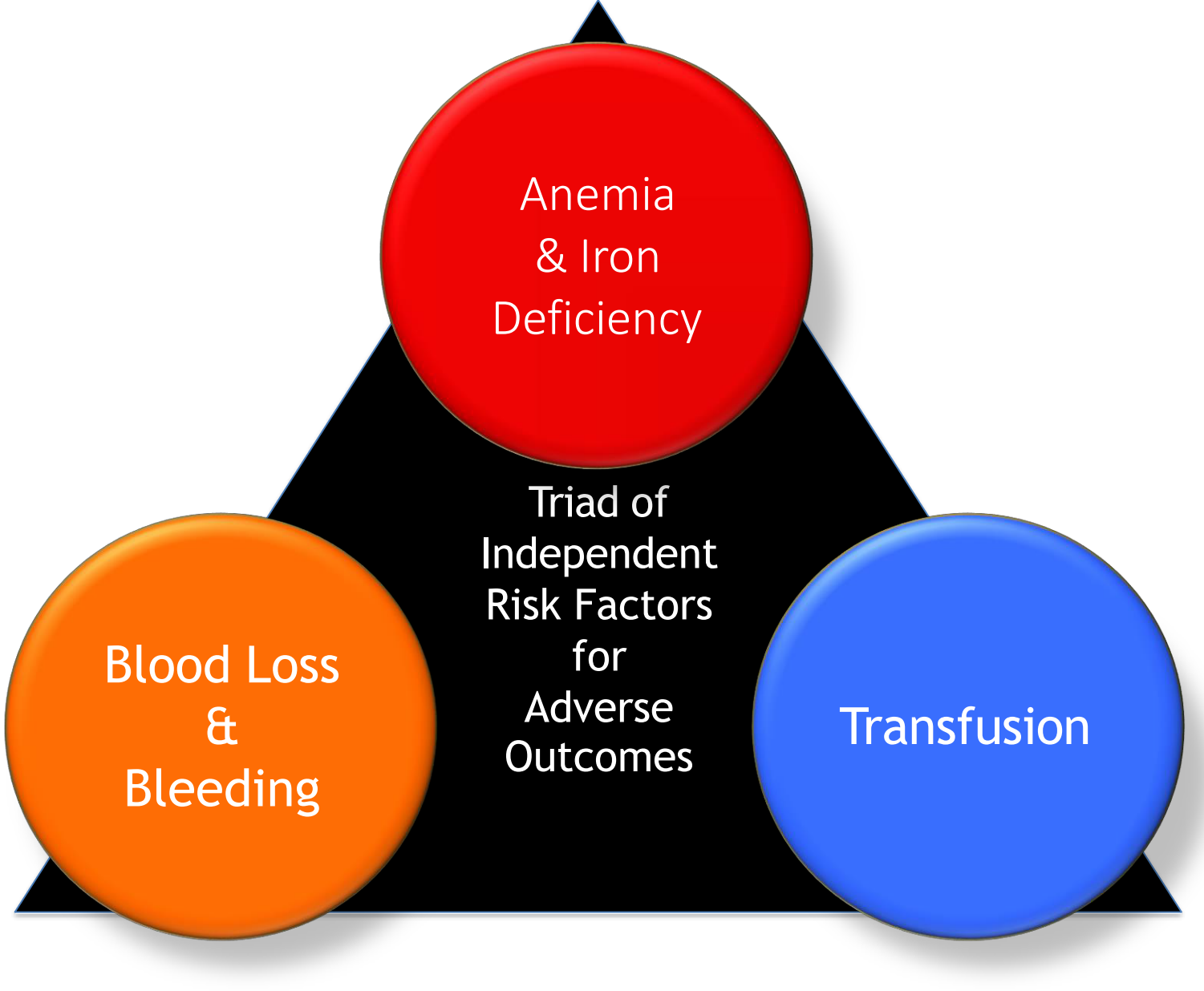
Iron studies

- Serum iron 37 µg/dl (40 – 150)
- Ferritin 12 ng/ml (>40)
- T_{SAT} 11% (> 25)

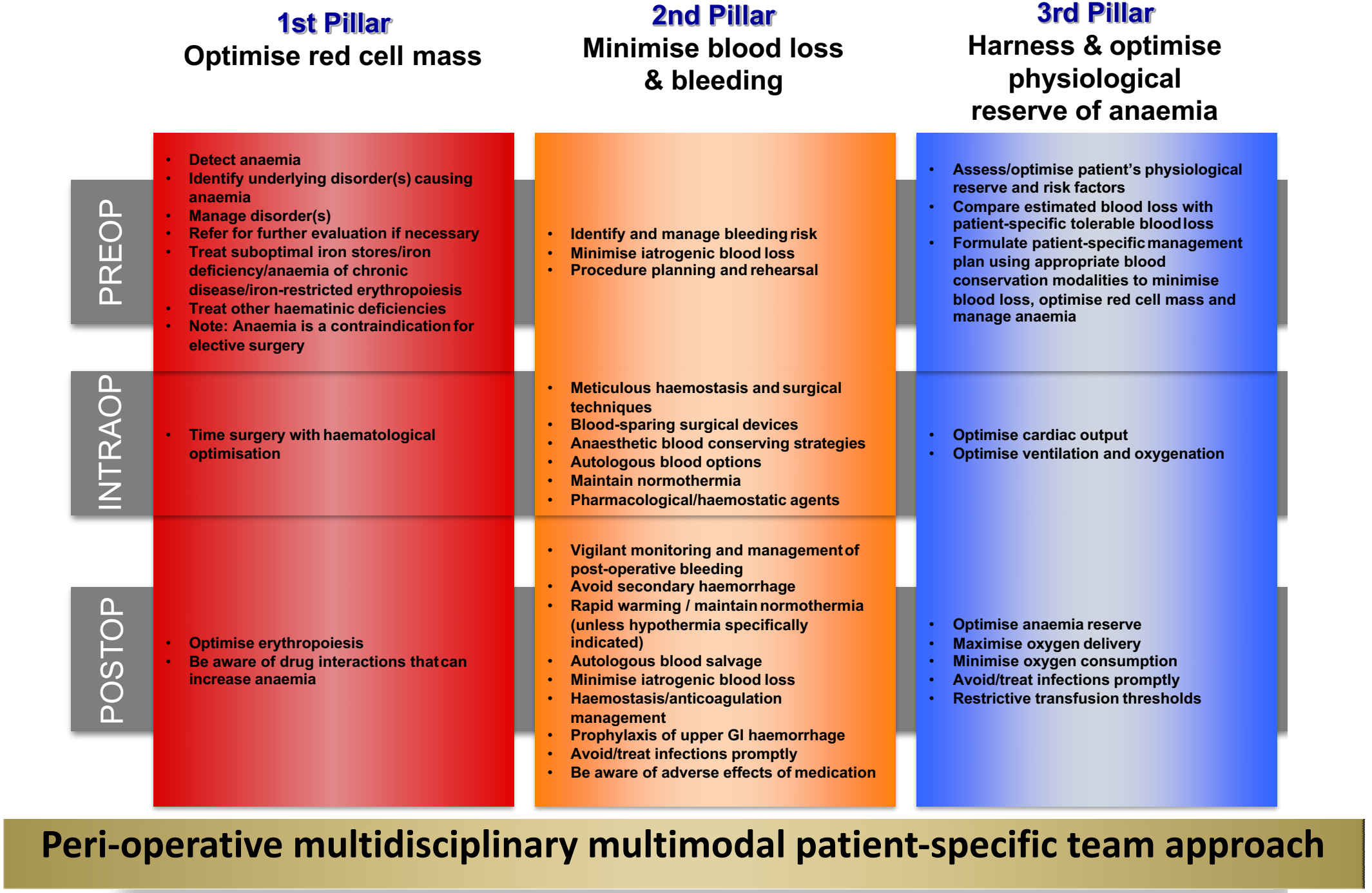

This is a clear case
of iron deficiency

Case study 1

- Assumed iron overloaded
- Proceeded to pancreaticoduodenectomy
- Blood loss 650 ml
- Transfused 3 units packed cells in peri-operative phase
- Physician declined iron replacement (“unsafe in ICU”)
- Discharged day 18 with Hb 8.9

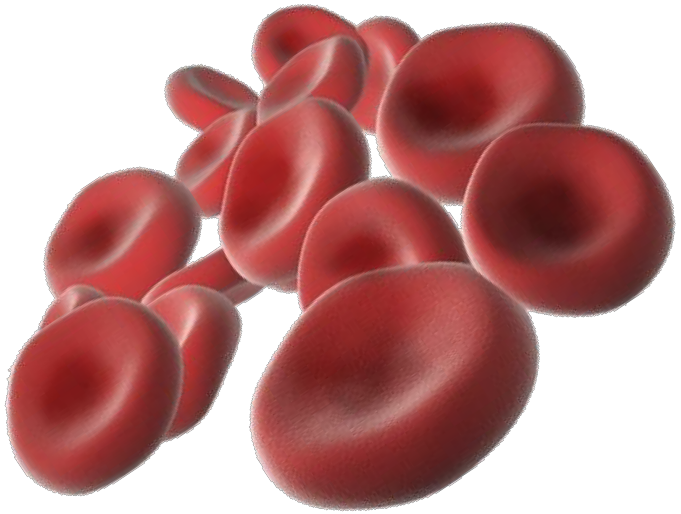


Farmer SL., Towler SC, Leahy MF, Hofmann A. Best Pract Res Clin Anaesthesiol, 2013. 27(1): p. 43-58.



Hofmann et al. Current Opinions in Anaesthesiology 2012

Anaemia

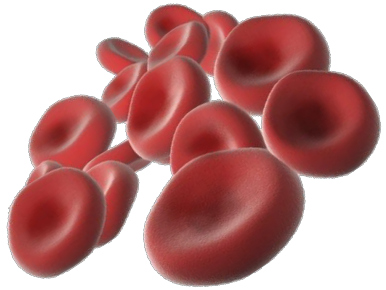


Global, regional, and national incidence, prevalence, and years lived with disability for 310 diseases and injuries, 1990–2015: a systematic analysis for the Global Burden of Disease Study 2015

*GBD 2015 Disease and Injury Incidence and Prevalence Collaborators**

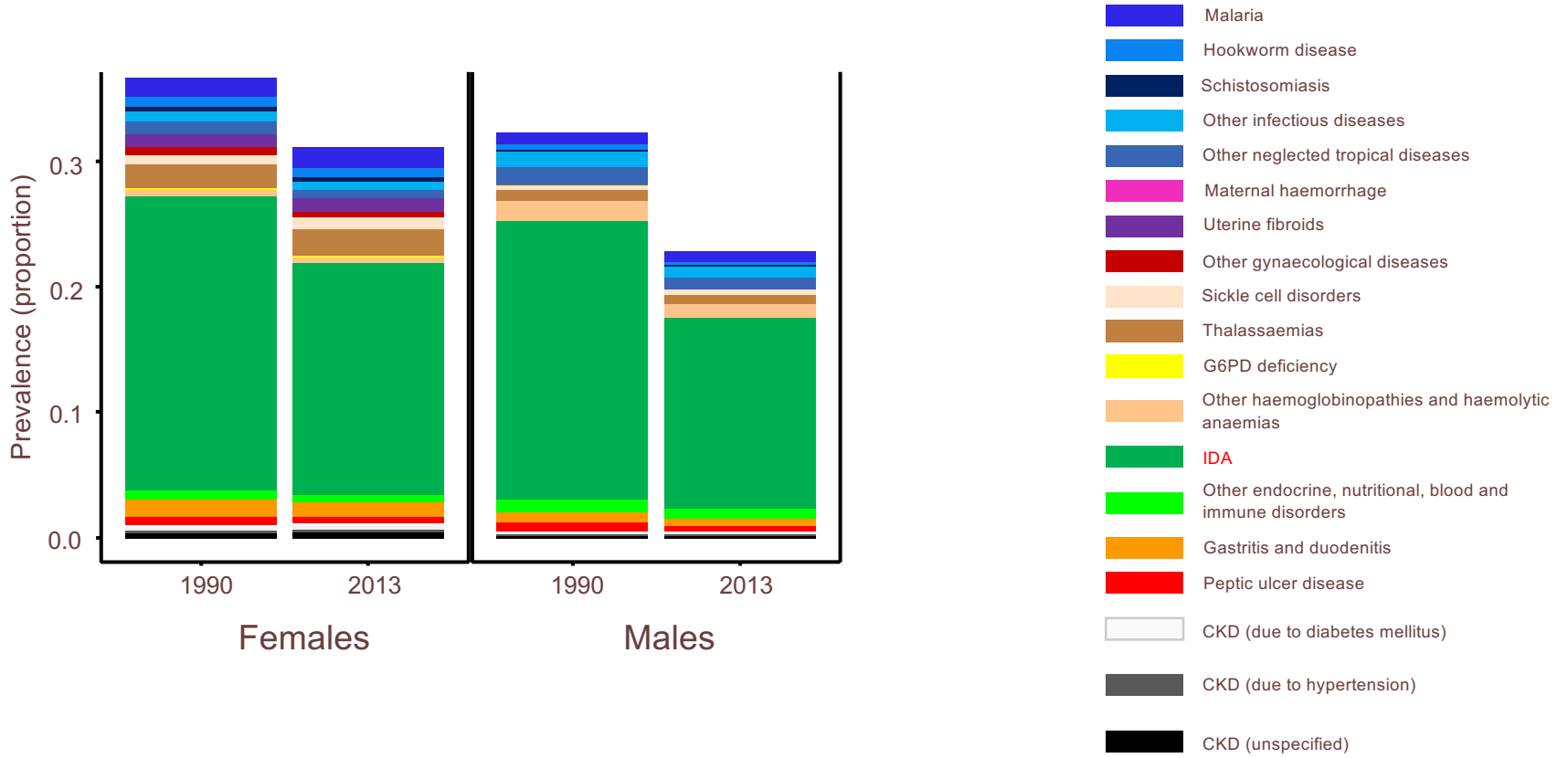
www.thelancet.com **Vol 388 October 8, 2016**

- The impairment that affected the greatest number of people in 2015 was **anaemia, with 2.36 billion (2.35–2.37 billion) individuals affected**
- The prevalence of **iron-deficiency anaemia** alone was **1.46 billion** (1.45-1.46 billion).



Prevalence of anaemia and IDA

ID is the global #1 cause of anaemia



GBD 2013 Mortality and Causes of Death Collaborators. *Lancet* 2015;385:117–71

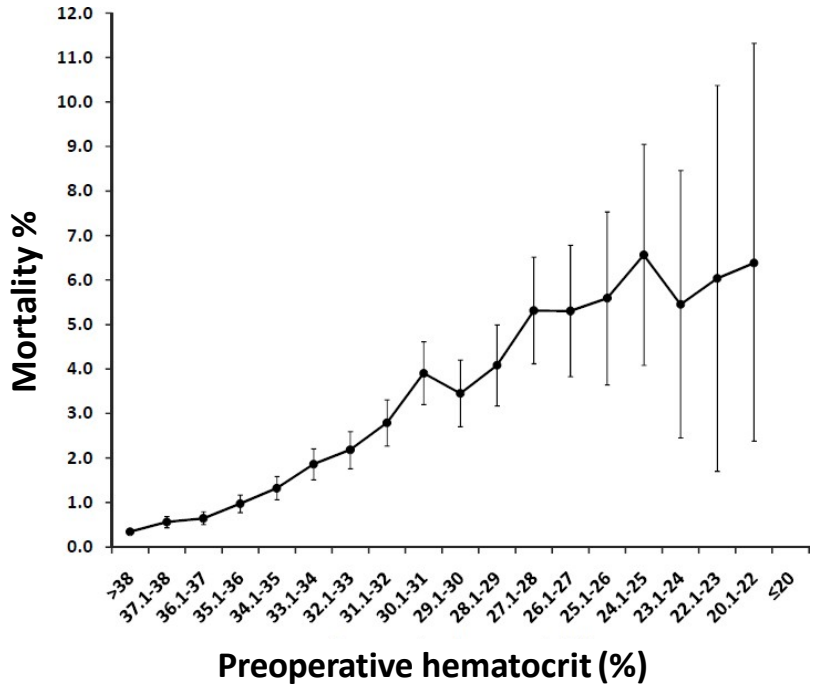
Systematic review

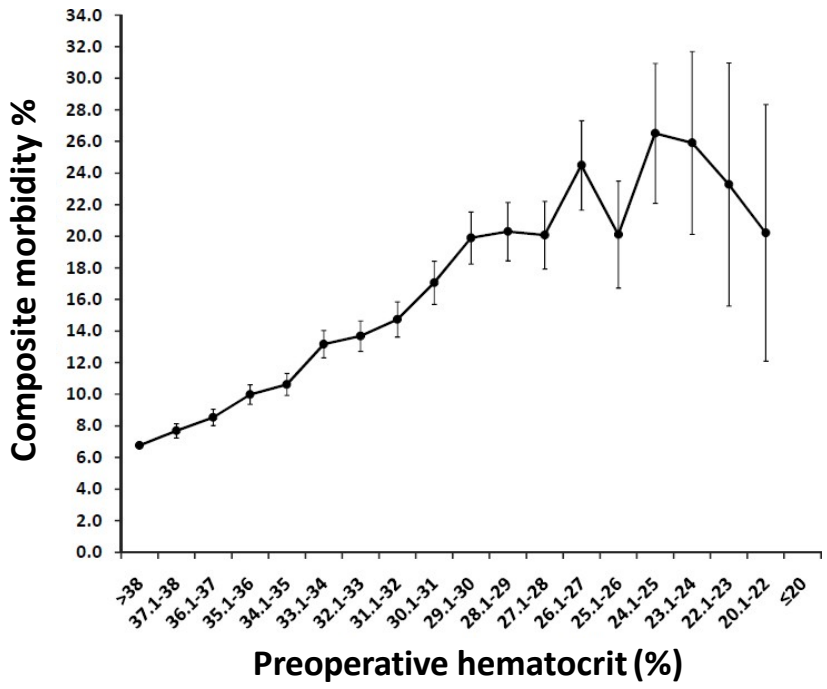
Meta-analysis of the association between preoperative anaemia and mortality after surgery

- **949 449 patients in 24 studies analyzed**
- **39% of patients were anaemic (WHO definition)**
- **Anaemia was associated with**
  - Perioperative mortality - OR 2.90 (2.30 – 3.68, $p < 0.001$)
  - Acute kidney injury - OR 3.75 (2.95 – 4.76, $p < 0.001$)
  - Infections - OR 1.93 (1.06 – 1.55, $p < 0.01$)
  - Stroke in cardiac surgery- OR 1.28 (1.17 – 3.18, $p < 0.001$)
  - RBC transfusion - OR 5.04 (4.12 – 6.17, $p < 0.001$)

Fowler A.J. et al. Br J Surg (2015) 102: 1314

Effect of Anaemia on Peri-operative Mortality and Composite Morbidity





Musallam, K.M., et al., Preoperative anaemia and postoperative outcomes in non-cardiac surgery: a retrospective cohort study. Lancet, 2011.

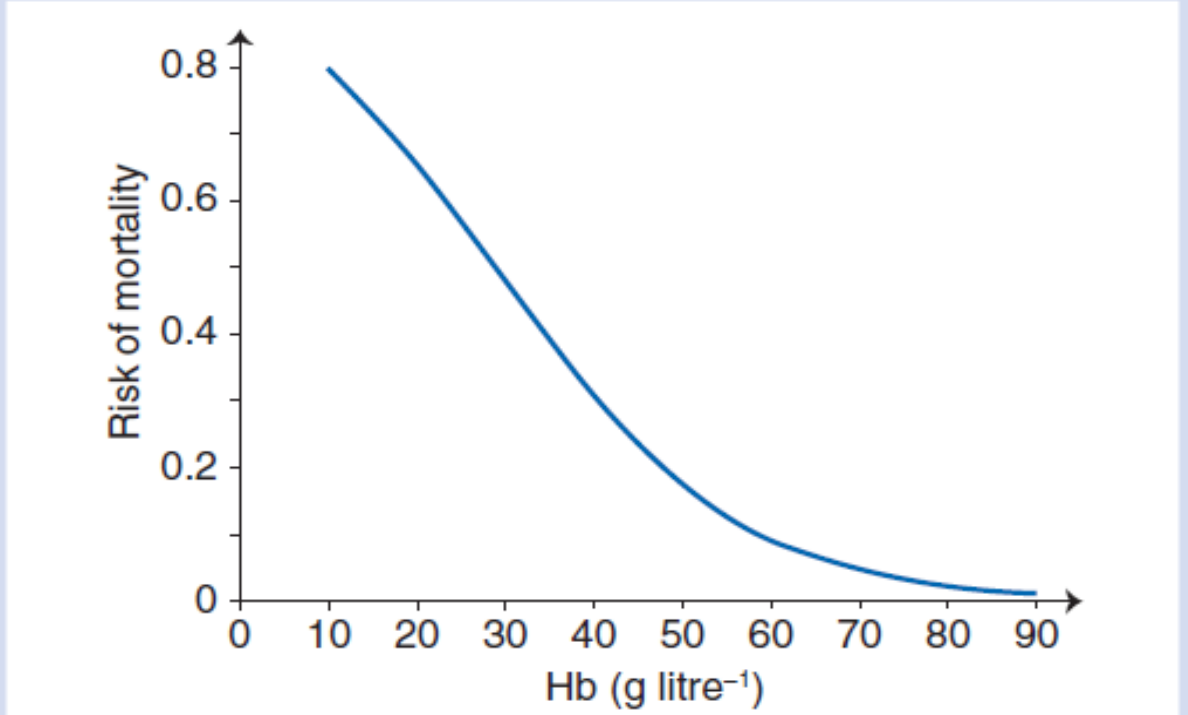
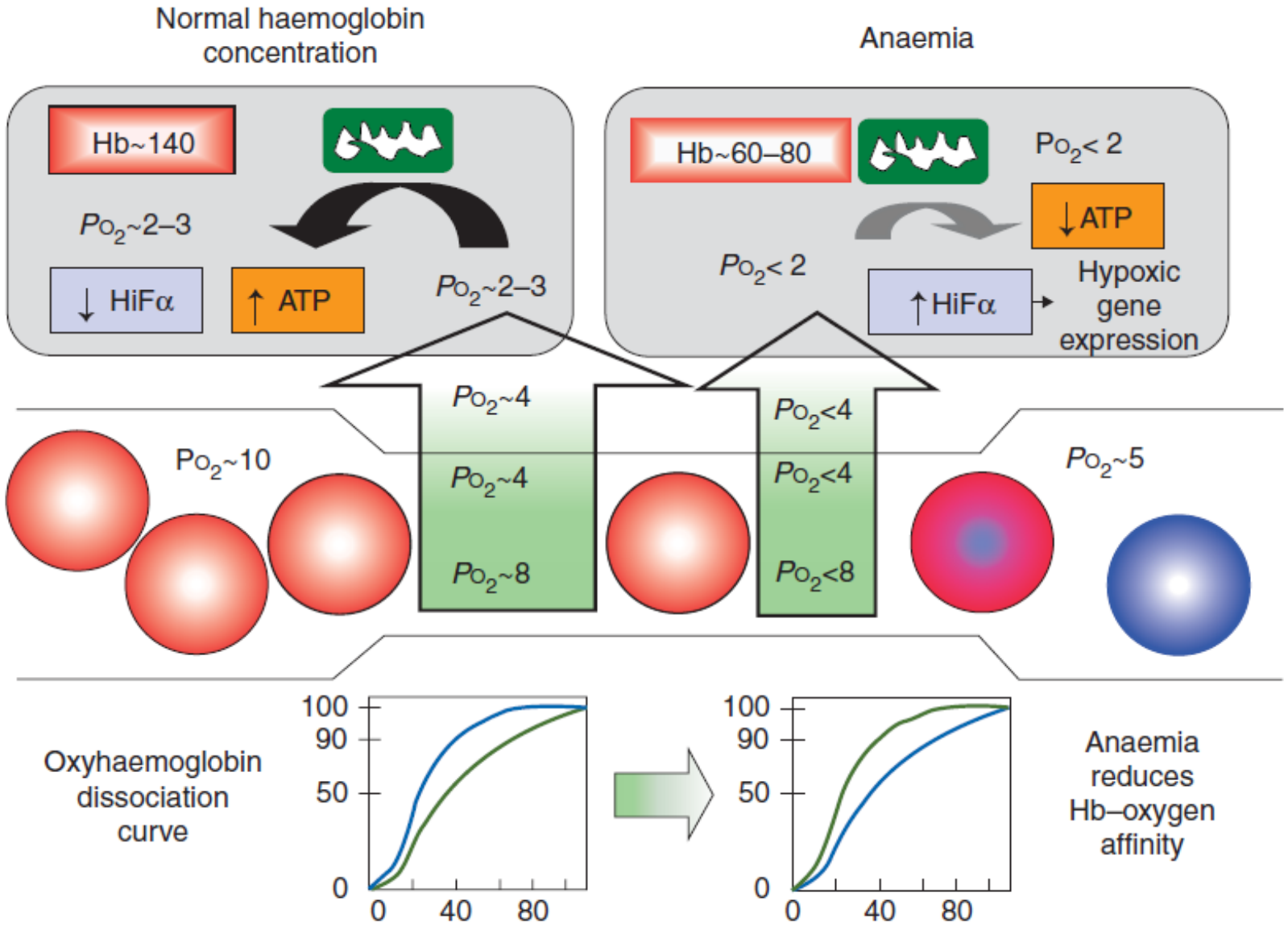


Fig 2 Estimated risk of death at various Hb concentrations. Data are based on a subset of patients (n=19) who could not be transfused, and had agreed to receive an Hb-based oxygen carrier because or in anticipation of severe anaemia, but did not receive the product for various reasons.[67] Risk of mortality for each Hb concentration was calculated using an equation obtained from running a logistic regression model with final status (dead/alive) as the dependent and Hb as the independent variables.


Normal haemoglobin concentration
Anaemia
Hb~140
Hb~60–80
Po_2~2–3
Po_2< 2
↓ HiFα
↑ ATP
↓ ATP
↑ HiFα
Hypoxic gene expression
Po_2~10
Po_2~4
Po_2~4
Po_2~8
Po_2<4
Po_2<4
Po_2<8
Po_2~5
Oxyhaemoglobin dissociation curve
100
90
50
0
0
40
80
Anaemia reduces Hb–oxygen affinity

Preoperative anaemia and clinical outcomes in the South African Surgical Outcomes Study

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[4] *Department of Anaesthesia and Perioperative Medicine, Groote Schuur Hospital, New Somerset Hospital and Faculty of Health Sciences, University of Cape Town, South Africa*
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[6] *Department of Anaesthesia, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa*
[7] *Department of Anaesthesia, Chris Hani Baragwanath Academic Hospital and Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa*
[8] *Perioperative Research Group, Department of Anaesthetics, Critical Care and Pain Management, School of Clinical Medicine, College of Health Sciences, Nelson R Mandela School of Medicine, University of KwaZulu-Natal, Durban, South Africa*
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Background. In high-income countries, preoperative anaemia has been associated with poor postoperative outcomes. To date, no large study has investigated this association in South Africa (SA). The demographics of SA surgical patients differ from those of surgical patients in the European and Northern American settings from which the preoperative anaemia data were derived. These associations between preoperati

Objectives y in SA adult non-cardia nd (*i*) critical care admis

Methods. We performed a secondary analysis of the South African Surgical Outcomes Study (SASOS), a large prospective observational study of patients undergoing inpatient non-cardiac, non-obstetric surgery at 50 hospitals across SA over a 1-week period. To determine whether pr e conducted a multivariat care identified in the origi

Results. T sociated with in-hospital mortality (odds ratio (OR) 1.657, 95% confidence interval (CI) 1.055 - 2.602; p=0.028) and admission to critical care (OR 1.487, 95% CI 1.081 - 2.046; p=0.015).

Conclusions. Almost 50% of patients undergoing surgery at government-funded hospitals in SA had preoperative anaemia, which was independe perative risk, with a clea urgery allow time for as r emergency surgery, perioperative clinicians in all specialties should educate themselves in the principles of patient blood management.

S Afr Med J 2018;108(10):839-846. DOI:10.7196/SAMJ.2018.v108i10.13148

Anaemia incidence ~ 50%

Mortality increased by 66%

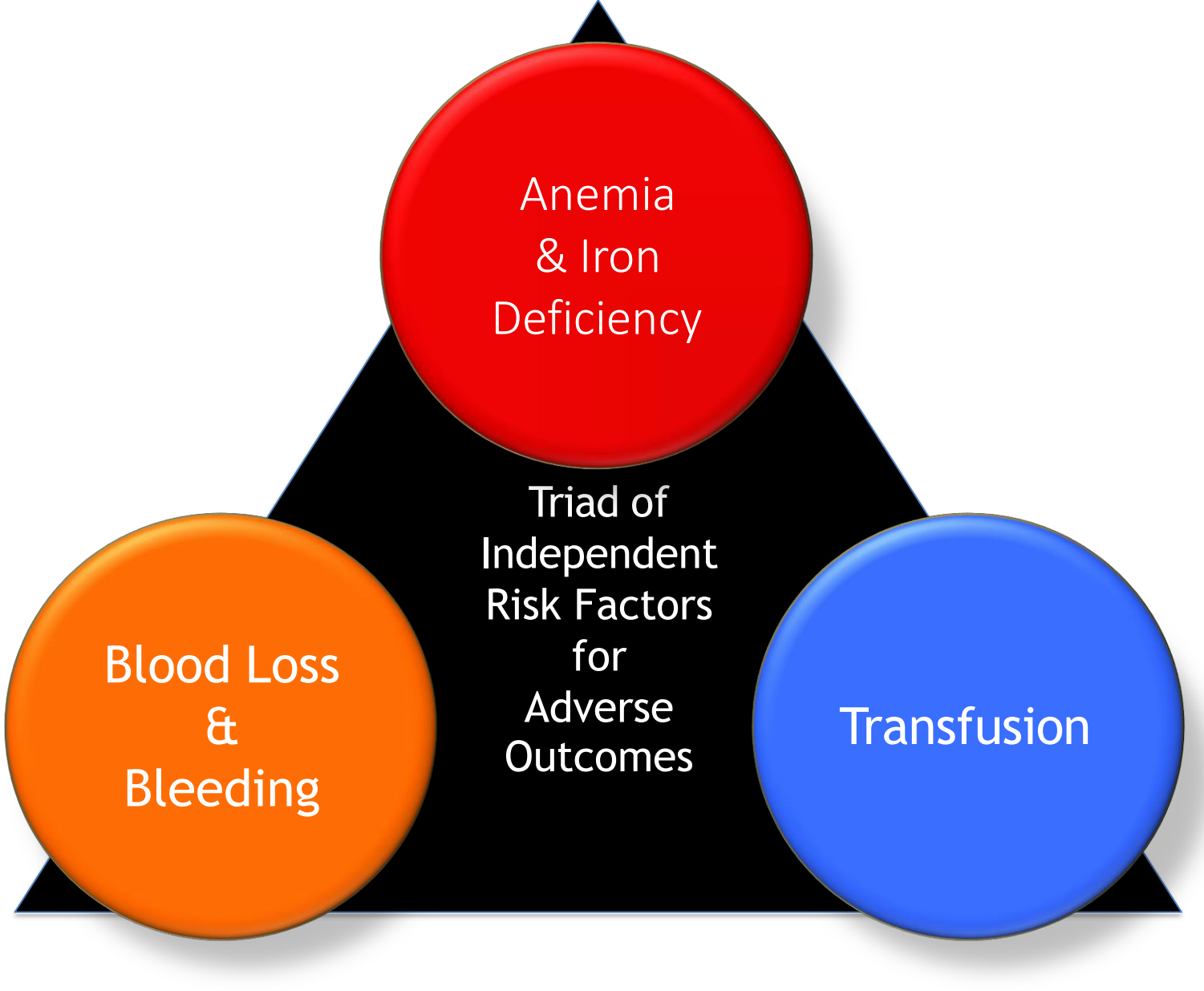
ICU stay increased by 50%

Targeted anemia surveillance and intervention should be a greater priority in high-risk populations, especially young children

50 % of anaemias are IDA

of other disease processes rather than as a target for intervention in and of itself. It is somewhat ironic, then, that etiology-specific

Kassebaum NJ et al. Blood, 2014;123: 615-24



Farmer SL., Towler SC, Leahy MF, Hofmann A. Best Pract Res Clin Anaesthesiol, 2013. 27(1): p. 43-58.

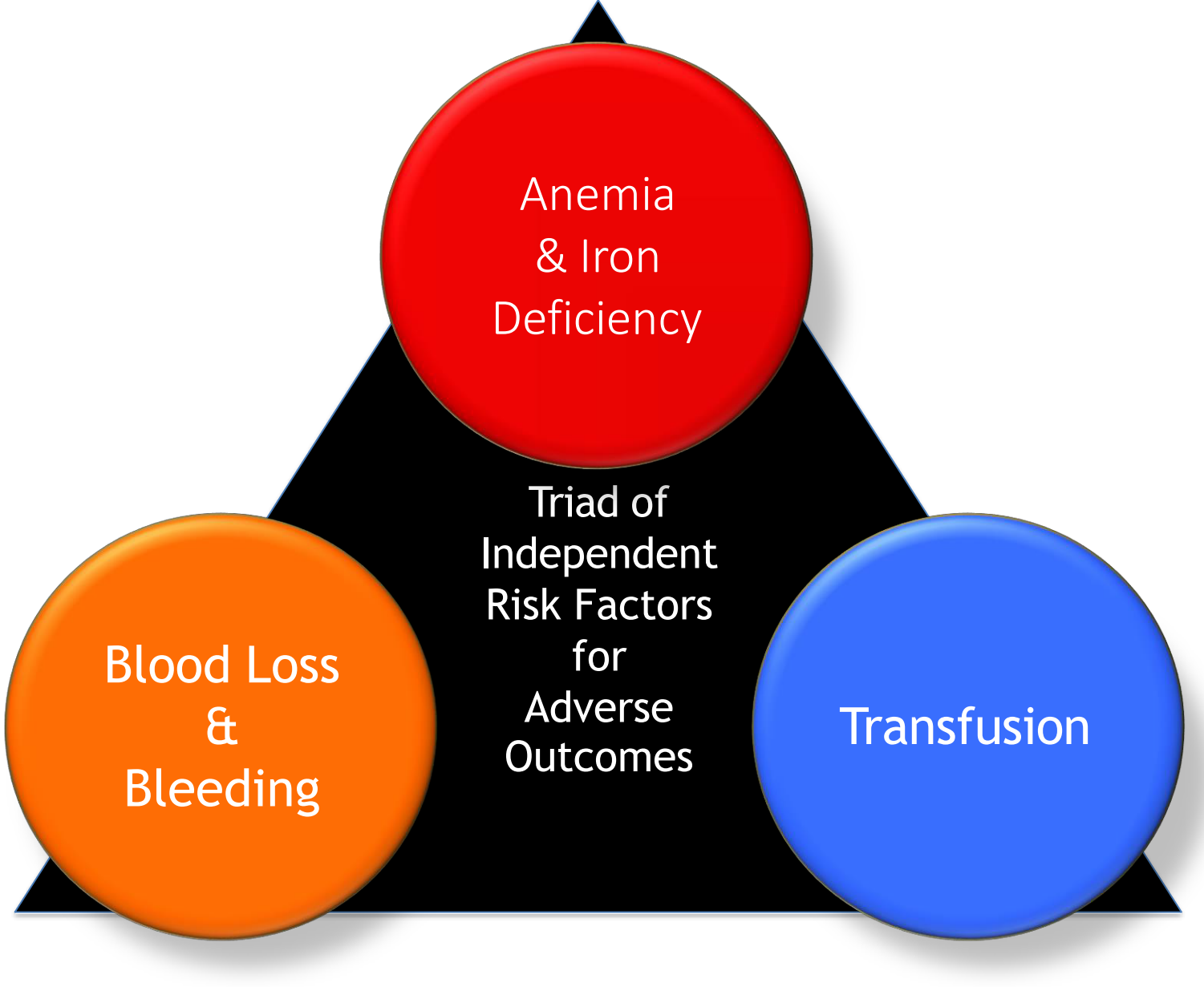
Major blood loss associated with increased

- Mortality (3-fold)
- Major morbidity (3-fold)
- ICU and hospital length of stay
- Likelihood of transfusion

Causes

- On average 75 – 90% local surgical interruption or vessel interruption
- 10–25% acquired or congenital coagulopathy

Shander A. *Surgery* 2007
Ranucci M et al. *Ann Thorac Surg* 2013;
96:478 Vivacqua et al *Ann Thorac Surg* 2011
Christensen et al *J Thorac Cardiovasc Surg*
2009 Spence et al *Am J Surg* 1990
Stokes, M.E., et al *BMC Health Serv Res*,
2011 Ye, X., et al *BMC Health Serv Res*,
2013 Alstrom, U., et al *Br J Anaesth*, 2012



Farmer SL, Towler SC, Leahy MF, Hofmann A. Best Pract Res Clin Anaesthesiol, 2013. 27(1): p. 43-58.

“[M]ore patients have died in any one year owing to transfusion immunomodulation’s side effects than died in the entire transfusion transmitted AIDS epidemic”

Blumberg, N. and J.M. Heal, Immunomodulation by blood transfusion: an evolving scientific and clinical challenge. Am J Med, 1996. 101(3): p. 299-308.

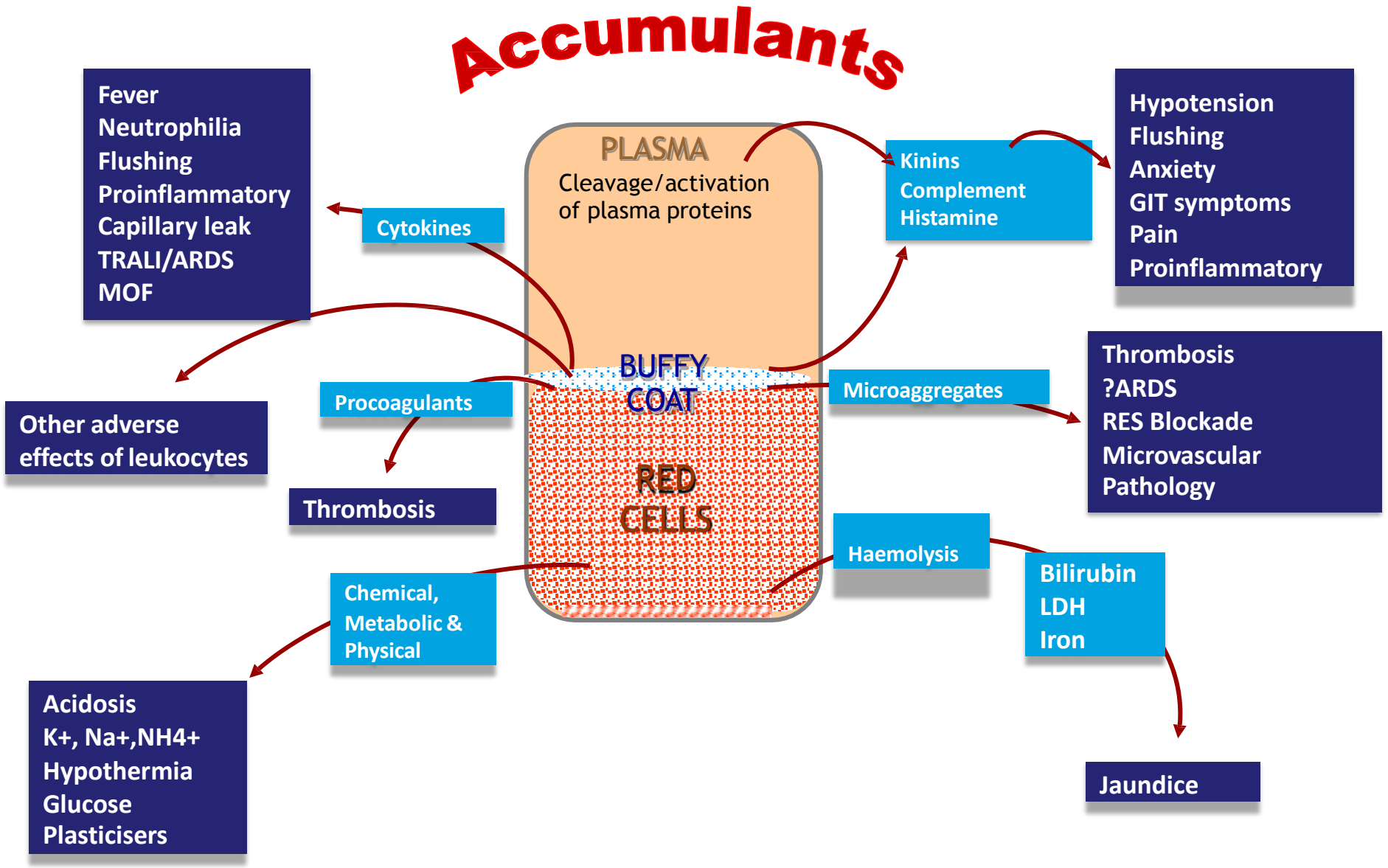
Ann Thorac Surg 2001;72:S1832–7

Blood Transfusion: The Silent Epidemic

Bruce D. Spiess, MD

Department of Anesthesiology, Virginia Commonwealth University/Medical College of Virginia, Richmond, Virginia

RED CELL STORAGE LESIONS



Acknowledgement: Prof. James Isbister

Transfusion and Apheresis Science 43 (2010) 69–78

Contents lists available at ScienceDirect

Transfusion and Apheresis Science

journal homepage: www.elsevier.com/locate/transci

Perfusion vs. oxygen delivery in transfusion with "fresh" and "old" red blood cells: The experimental evidence

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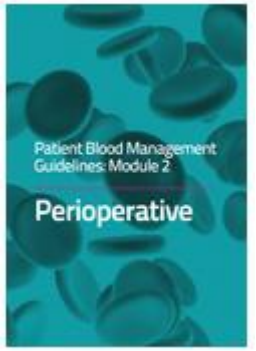
[a] Department of Bioengineering, University of California, San Diego, CA, United States
[b] Society for the Advancement of Blood Management, Milwaukee, WI, United States

Impairment of oxygen transport of stored RBCs was first reported when measurement of the corresponding oxygen dissociation curves showed an immediate and significant increase in the oxygen affinity during the initial week of storage at 4 °C. This resulted in a decrease of oxygen delivery during transfusion of stored RBCs by comparison to normal RBCs, the difference being proportional to the volume transfused and storage time [16].

Mortality Risk of Anaemia and Transfusion Clearly Adressed



3.2 Effect of anaemia on outcomes

Question 4 (Aetiological question) (GNQ1)

In patients undergoing surgery, is anaemia an independent risk factor for adverse outcomes?

Preoperative anaemia is independently associated with an increased risk of morbidity and mortality.

Preoperative anaemia is associated with increased hospital length of stay in non-cardiac surgery

3.3 Effect of red blood cell transfusion on outcomes

Question 5 (Interventional question) (GNQ2)

In patients undergoing surgery, what is the effect of RBC transfusion on patient outcomes?

RBC, red blood cell

In cardiac & non-cardiac surgery, RBC transfusion is independently associated with increased morbidity & mortality. This relationship is dose dependent.

In cardiac & non-cardiac surgery, RBC transfusion is associated with significantly longer stays in hospital and ICU


Patient Blood Management Guidelines: Module 6
Neonatal and Paediatrics

2018 Frankfurt Consensus Conference highlights

- Pillar 1
  - Recommendations based on weight of evidence & safety – efficacy profiles
  - Strong recommendation for detection & management of anaemia before major elective surgery
  - Conditional recommendation for iron supplementation in adult pre-operative patients with IDA
  - Route and iron formulation to be individualized
  - Conditional recommendation against routine EPO in anaemic pre-operative adult patients
  - Conditional recommendation for combination od IV iron and EPO in pre-operative adult orthopaedic patients with Hb < 13

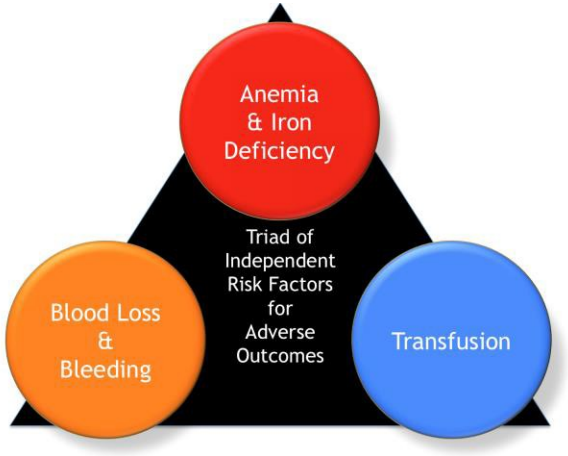
Mueller MM, van Remoortel H, Meybohm P et al. JAMA 2019; 32(10): 983 - 997

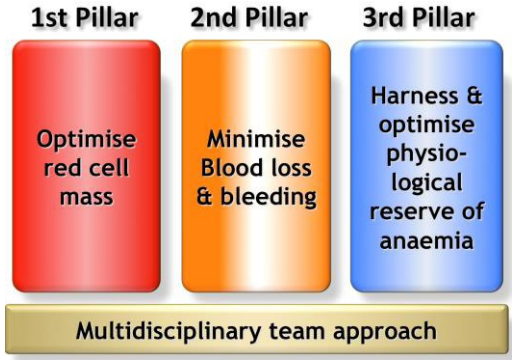
2018 Frankfurt Consensus Conference highlights

- Further consensus recommendations
  - Transfusion triggers in a variety of high risk, haemodynamically stable scenarios 7 – 8 g/dL
  - Abandonment of less restrictive transfusion targets
  - Worldwide implementation of PBM programmes

Mueller MM, van Remoortel H, Meybohm P et al. JAMA 2019; 32(10): 983 - 997

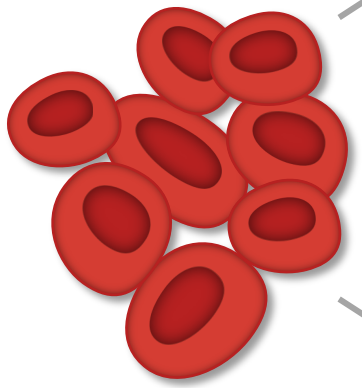
THE CHALLENGES | THE SOLUTION | THE EXPANSION





- **Anaemia, blood loss and transfusion are modifiable risk factors for adverse outcomes**
- **PBM addresses these risks:**
  - **Reduced mortality**
  - **Reduced morbidity**
  - **Reduced transfusions, thus leading to improved safety**
  - **Reduced LOS**
  - **Less cost**
- **PBM recommended as STANDARD OF CARE by the WHO, EC/EU, NBA, NHS, ESA, EBA, ACSQHC, SABM, IFPBM, AABB, ARC Blood Service and others**

The anaemia epidemic



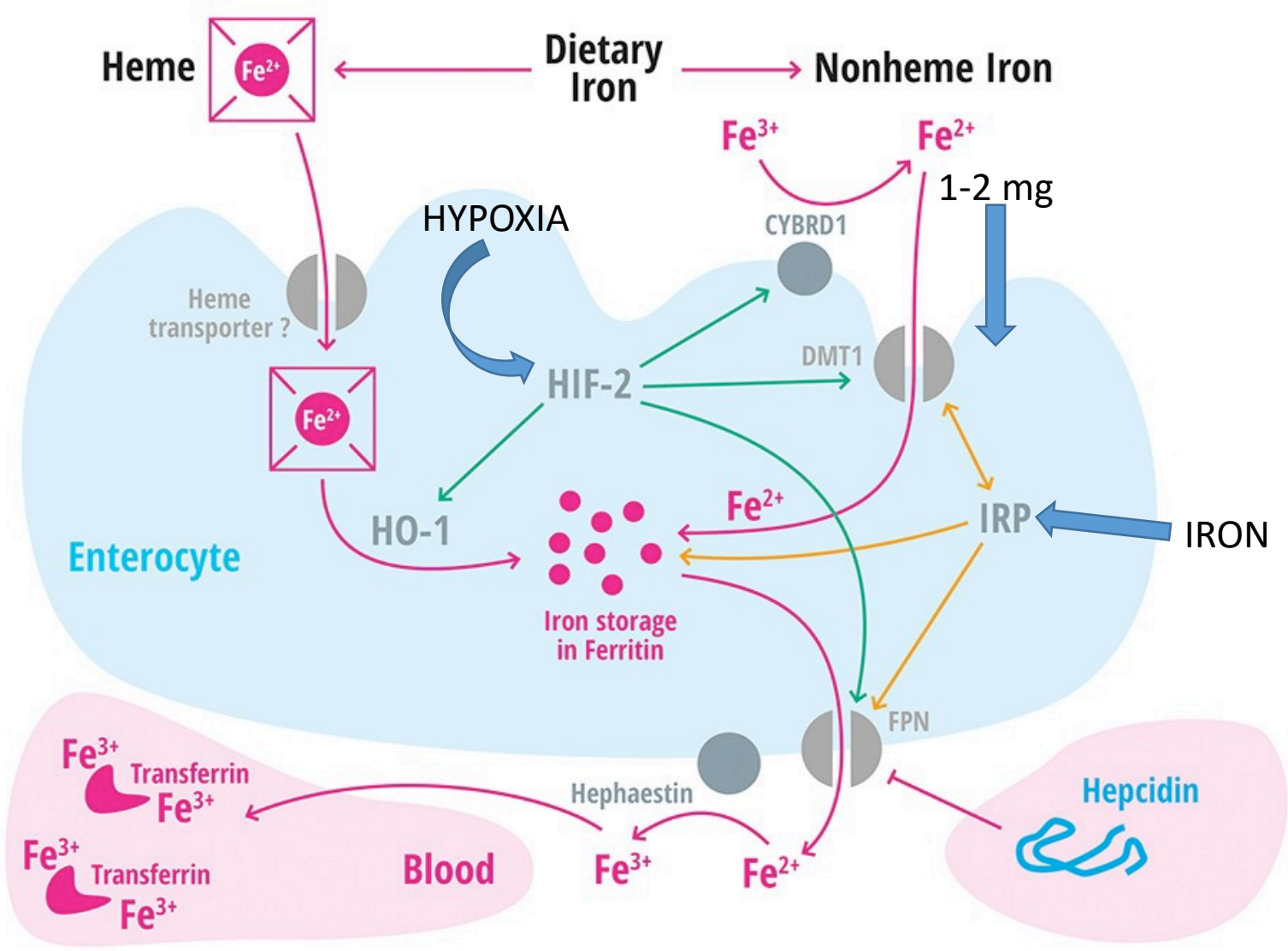
National/regional/ international strategies

Anaemia detection and diagnosis

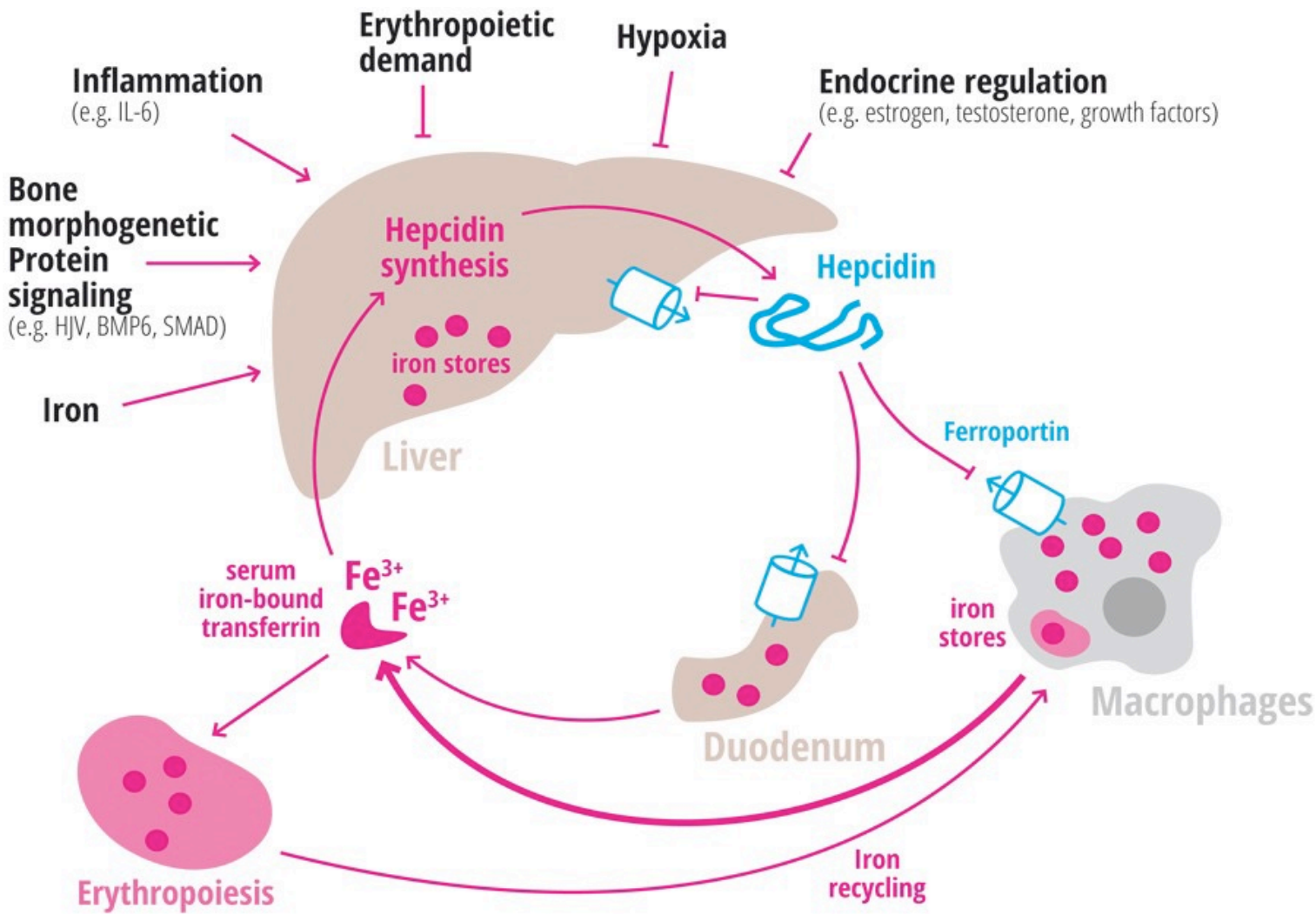
Anaemia management

Individual patient strategies

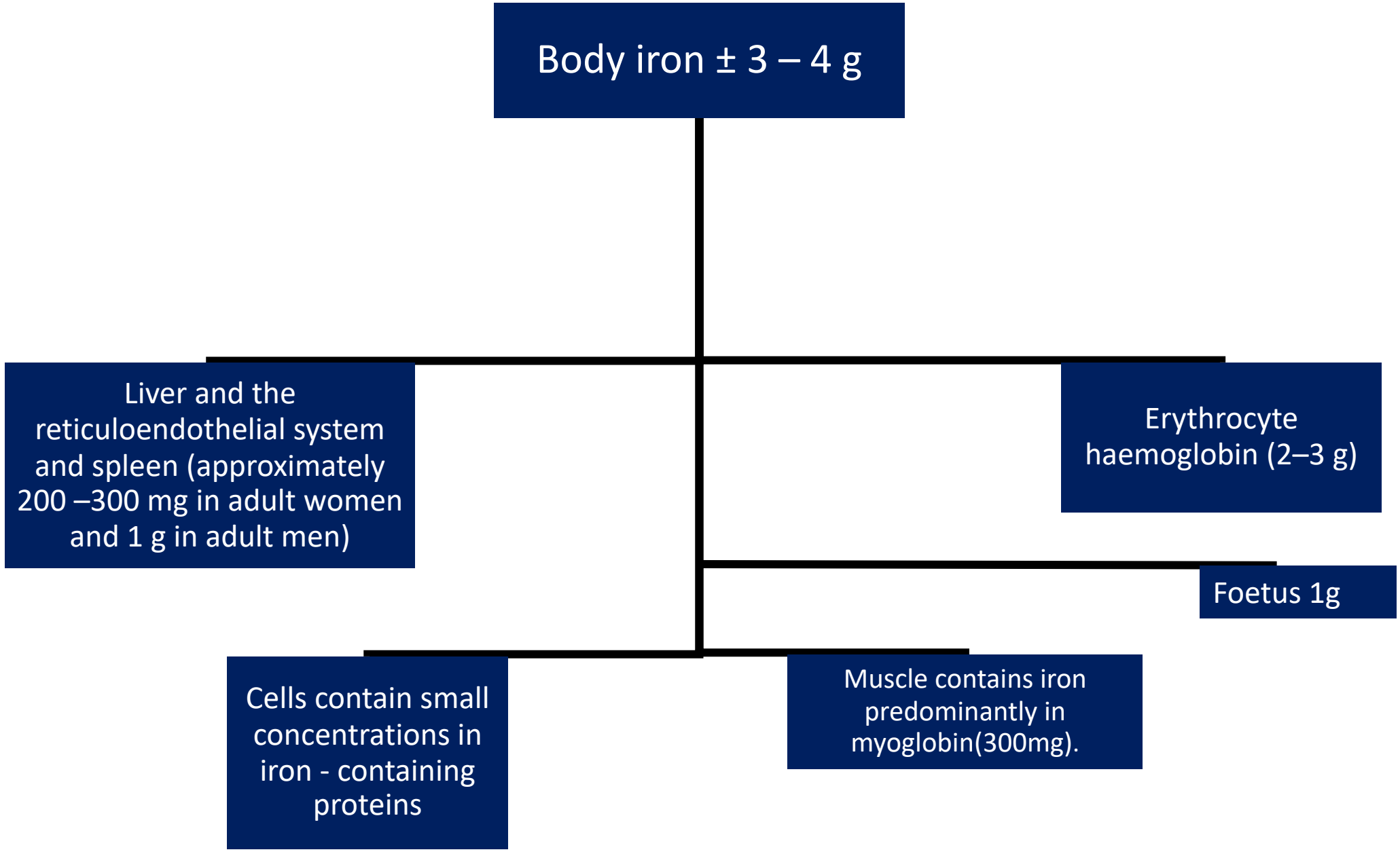
Screen your high-risk patient



von Drygalski, A Adamson J. Iron Metbolism in man. Journal of Parenteral and Enteral Nutrition 2013 (37) 599 – 606



von Drygalski, A Adamson J. Iron Metbolism in man. Journal of Parenteral and Enteral Nutrition 2013 (37) 599 – 606


Body iron ± 3 – 4 g
Liver and the reticuloendothelial system and spleen (approximately 200 –300 mg in adult women and 1 g in adult men)
Erythrocyte haemoglobin (2–3 g)
Foetus 1g
Cells contain small concentrations in iron - containing proteins
Muscle contains iron predominantly in myoglobin(300mg).

Iron deficiency

- Sequence of events
  - Inefficient energy metabolism in all cells especially muscle (FATIGUE)
    - “the 100 hungry enzymes”
  - Use of iron stores with normal haematopoiesis
  - Making smaller cells with normal Hb conc (microcytosis – MCV)
  - Making small cells with reduced Hb conc (hypochromia – MCHC)
  - Poor reticulocyte response

Munoz M, Gomez-Ramirez S, Besser M et al. Blood Transfus 2017; 15: 422 - 37

Misconceptions in iron deficiency

1. A normal ferritin excludes IDA
   - Wide range of normal ferritin values (~40 – 500 ng/ml)
     - < 30 ng/ml – **always** iron deficiency
   - Ferritin – acute phase reactant – released by liver in inflammatory states
   - Levels of 30 – 100 with evidence of inflammation (CRP) usually ID
     - Check t_{sat} – if < 20% = ID
   - Levels of > 100 with microcytosis / hypochromia
     - Defect of iron utilization
     - Usually need iron with erythropoietin (EPO)
   - Iron therapy at higher ferritin levels – CCF; CKD; cancer – all tend to have elevated hepcidin & intestinal absorption / storage release block

Munoz M, Gomez-Ramirez S, Besser M et al. Blood Transfus 2017; 15: 422 - 37

Misconceptions in iron deficiency

2. Non anaemic ID does not need intervention
   - Huge iron deficit before Hb falls
   - Fatigue & effort intolerance present before anaemia
   - Proven benefit for iron therapy
     - Athletes
     - Blood donors
     - Pregnant / menstruating women (ID - maternal / foetal adverse effects)
     - Cancer (decreased thrombosis)
     - CCF (energy; QOL; survival)
     - Peri-operatively (ID - infection / transfusion / fatigue)
     - Iron deficits 1 – 2 g – difficult to correct orally

Munoz M, Gomez-Ramirez S, Besser M et al. Blood Transfus 2017; 15: 422 - 37

Misconceptions in iron deficiency

3. Oral iron is always efficacious if tolerated
   - Deficits of > 1 g
   - Can absorb < 5mg/day – 200 days + to correct (Hb rises not > 1 mg/dl/month)

Useless peri-operatively

- PPI / antacids inhibit absorption
- Best approach for tolerability (greatest % absorption)
  - Low doses
  - Alternate days (oral iron increases hepcidin)
- The **only** indication is cost

Munoz M, Gomez-Ramirez S, Besser M et al. Blood Transfus 2017; 15: 422 - 37

Misconceptions in iron deficiency

4. IV iron should be reserved for severe anaemia
   - Critical anaemia requires blood transfusion until haemodynamics / ischaemia resolve
     - Hyperlactataemia
     - Diastolic or global hypotension with tachycardia
   - Must be followed by **IV iron** for maximum efficacy
   - IV superior to oral in every situation and cost is the only interfering variable
     - Well tolerated
     - Rapid, sustained effect after 1 – 2 doses
     - No Hb overshoot (unlike EPO)
     - Many safe formulations

Munoz M, Gomez-Ramirez S, Besser M et al. Blood Transfus 2017; 15: 422 - 37

Misconceptions in iron deficiency

5. IV iron has a high incidence of side effects
    - Severe anaphylaxis rare < 1:250 000 (15 – 20 times lower than RBC transfusion). Tryptase diagnostic
    - Fishbane reactions resembling allergy or myalgia / arthralgia more common and are generally self limiting without therapy – related to labile iron
        - Choice of agent – FCM lowest
        - Appropriate dilution
        - Speed of administration
    - Infusions must still be done in medically registered and resourced environments
    - Hypophosphataemia
    - Benefit far outweighs risk
    - Deaths associated with IV iron usually multifactorial (CCF; sepsis; cancer)

Munoz M, Gomez-Ramirez S, Besser M et al. Blood Transfus 2017; 15: 422 - 37

Table I - Characteristics of different intravenous iron formulations.

	Iron gluconate[6]	Iron sucrose[7]	LMWID[8]	Ferric carboxymaltose[9]	Iron isomaltoside 1000[10]	Ferumoxytol[11]
Brand name	***Ferrlecit®***	***Venofer®***	***Cosmofer® INFeD®***	***Ferinject® Injectafer®***	***Monofer® Monoferro®***	***FeraHeme® Rienso®***
Molecular weight (kDa)	289-440	30-60	165	150	150	750
Labile iron (% injected dose)[1]	3.3	3.5	2.0	0.6	1.0	0.8
Maximal single dose (mg)	125	200	20 mg/kg	20 mg/kg (max 1,000 mg)	20 mg/kg	510
Infusion time for 1,000 mg (min)[2]	720	300	180*	45	45	90
Product cost per 1,000 mg (€)[3]	-	112	103	192	192	162[4]
Administration cost per 1,000 mg (€)[5]	554	231	139	35	35	70
Total cost per 1,000 mg dose (€)	-	342	242	227	227	232

1) Jahn MR, *et al*. Eur J Pharm Biopharm 2011; **78**: 480-91.

Munoz M, Gomez-Ramirez S, Besser M et al. Blood Transfus 2017; 15: 422 - 37

Misconceptions in iron deficiency

6. IV iron increases the risk of infection / oxidative stress

- Bacteria thrive on elemental (free / labile) iron
  - Highest levels with transfusion
  - Moderate levels with chronic / repeated iron therapy
  - Short term iv iron risk ~ placebo
  - Any iron therapy contra-indicated in severe systemic sepsis – evidence free zone
  - Chronic iron therapy – advisable to use low doses (FCM < 400 mg/month)
  - Sepsis risk from ID or IDA is orders of magnitude higher than that from free serum iron
- Oxidative stress – similar concerns with chronic iron therapy
  - Use agents with lowest free iron concs and at lowest effective doses

Munoz M, Gomez-Ramirez S, Besser M et al. Blood Transfus 2017; 15: 422 - 37

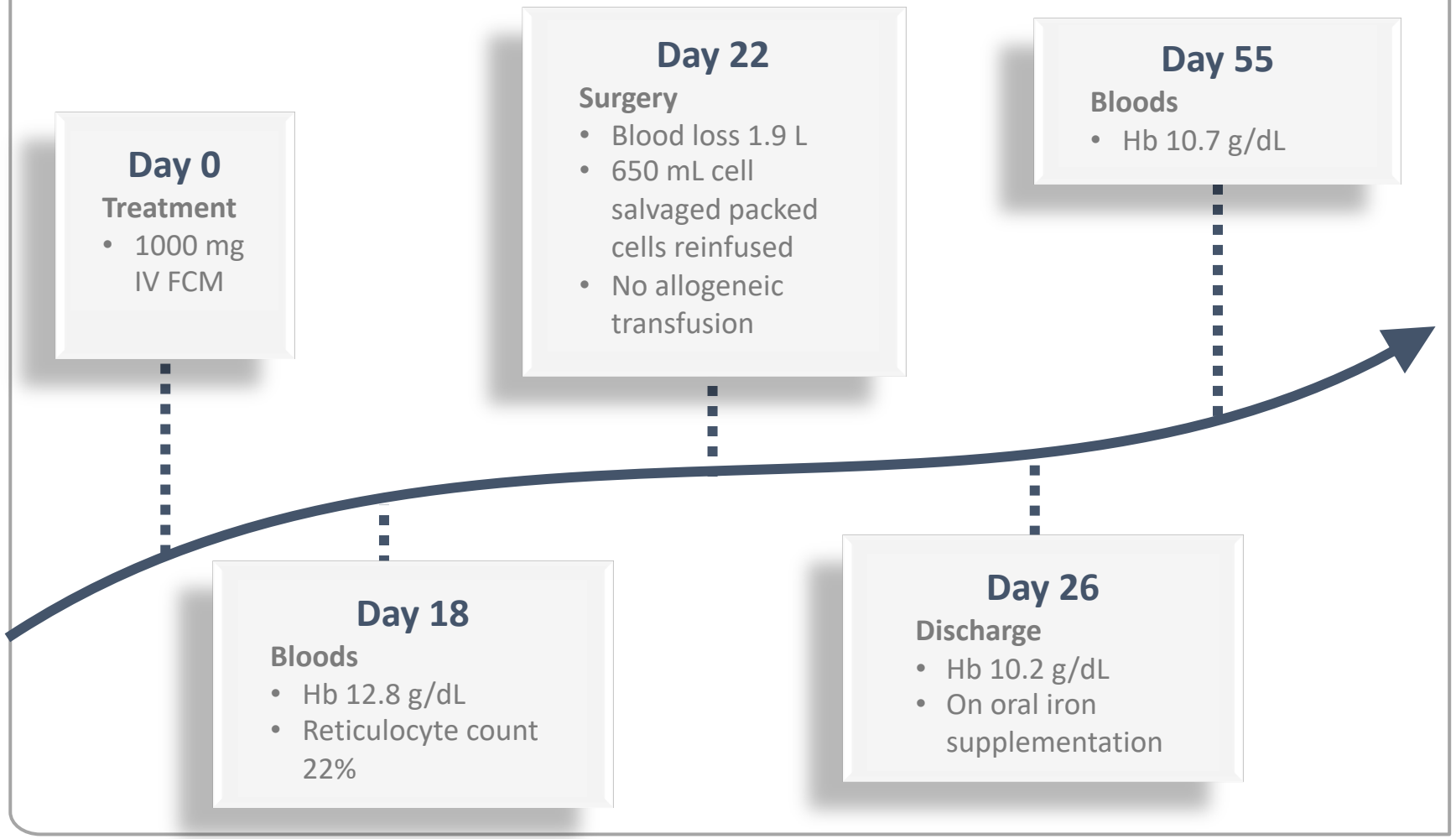
Peri-operative management of ID

- Assess iron status on initial presentation (early morning)
  - FBC & reticulocytes; CRP
  - Serum iron; ferritin; t_{sat}
- If overt ID / IDA / inflammation with ferritin < 100 ng/ml
  - IV FCM / isomaltoside 1000 mg single infusion or 500 mg x 2 (<50 kg)
    - Ideally > 3 weeks pre-op but any time better than no infusion
    - Reassess Hb; reticulocytes 3 weeks after iron infusion and if Hb not increased > 2 g/dl, repeat infusion +/- EPO
    - Reassess 3 weeks post-op in case further supplementation required

Case study 2

- 50 year old female (medical doctor), 56 kg
- Years of lower abdominal pain, distension, fatigue and peri-menopausal bleeding
- Huge retroperitoneal mass (? Sarcoma)
- Hb 9.9 g/dL
- Overtly iron deficient on iron studies
- Team and patient favoured brief delay in surgery for iron therapy

Case Notes


Day 0
Treatment
• 1000 mg IV FCM
Day 18
Bloods
• Hb 12.8 g/dL
• Reticulocyte count 22%
Day 22
Surgery
• Blood loss 1.9 L
• 650 mL cell salvaged packed cells reinfused
• No allogeneic transfusion
Day 26
Discharge
• Hb 10.2 g/dL
• On oral iron supplementation
Day 55
Bloods
• Hb 10.7 g/dL

1st Pillar
Optimise red cell mass

2nd Pillar
Minimise blood loss & bleeding

3rd Pillar
Harness & optimise physiological reserve of anaemia

PBM

- Saves lives and morbidity
- Saves money
- Reduces hospital stay
- Reduces transfusion
- Is the right thing to do from an individual patient and societal perspective

Peri-operative multidisciplinary multimodal patient-specific team approach

Hofmann et al. Current Opinions in Anaesthesiology 2012