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King's Lynn
NHS Foundation Trust

Anaemia, Optimisation and Iron Deficiency

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First the facts

Iron deficiency anaemia (IDA) has a prevalence of 5.8-13.1% among adult men and post-menopausal women in the developed world (World Health Organisation (WHO) 2006).

While menstrual blood loss is the commonest cause of IDA in pre-menopausal women, blood loss from the gastrointestinal (GI) tract is the commonest cause in adult men and post-menopausal women.

Iron deficiency affects more people than any other condition, constituting a public health condition of epidemic proportions. More subtle in its manifestations than, for example, protein-energy malnutrition, iron deficiency exacts its heaviest overall toll in terms of ill-health, premature death and lost earnings (WHO 2014).

Anaemia
Classified by the WHO as:

- Haemoglobin **<130g/**l in men over 15 years of age
- Haemoglobin **<120g/l** in non-pregnant women over 15 years of age
- Haemoglobin **<110g/l** in pregnant women

Iron Deficiency
Classified as:

- Reduced or low Mean Cell Haemoglobin
- Reduced or low Mean Corpuscular Volume (e.g. 96 2 years ago and currently 88)
- Ferritin <25чmg/l **without** coexistent disease
- Ferritin <100 чmg/l **with** coexistent disease
- Transferrin Saturation <20%
- Low serum Iron (see local laboratory reference range but usually < 10ng)

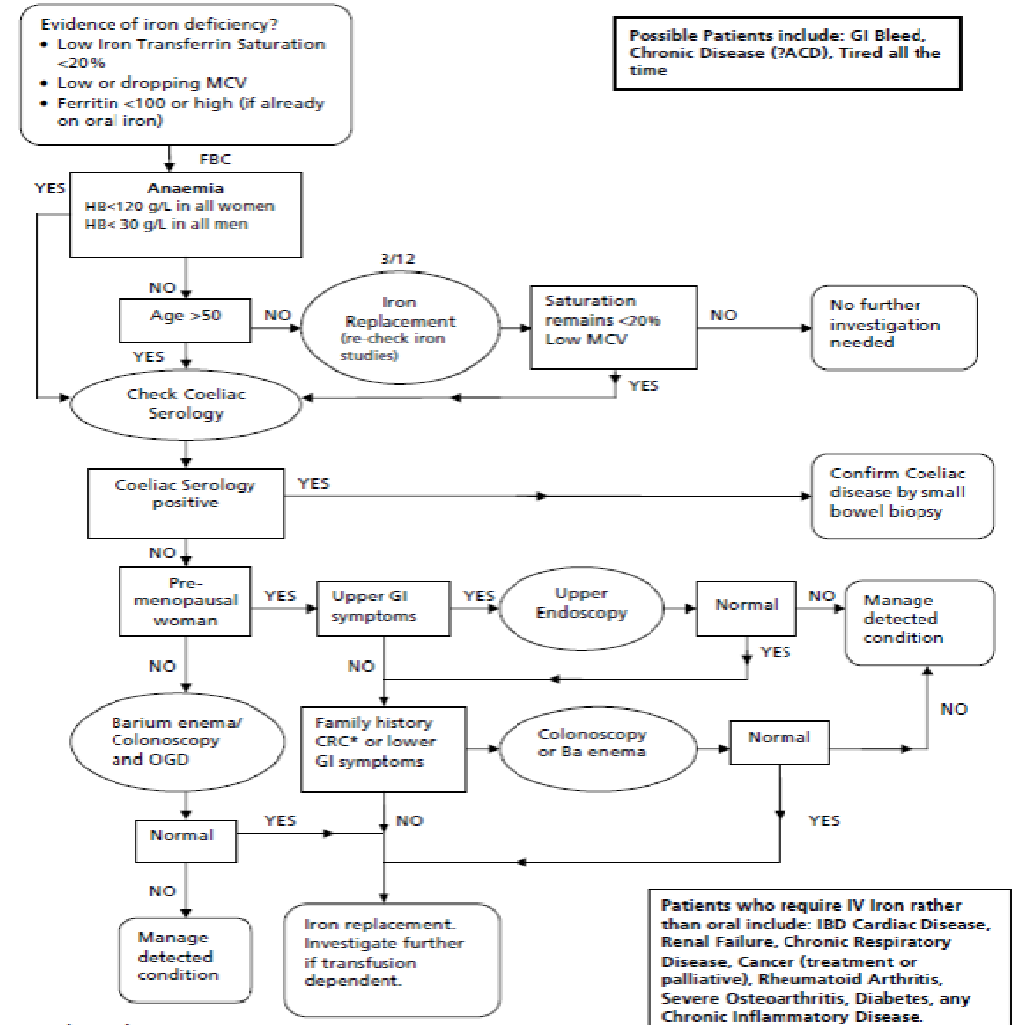
So the patient is anaemic

Making the Diagnosis

The principles are:

1. Confirm the diagnosis of iron deficiency iron deficiency anaemia or functional iron deficiency - do the blood tests.
2. Assess the person to determine the cause and severity of anaemia - take the history and examine the patient.
3. Refer for further investigation to the appropriate speciality (for example gastroenterology, surgery or gynaecology).
4. Treat adults with iron deficiency anaemia (**including** pregnant women) with the appropriate preparations.
5. Monitor response or delegate a monitoring plan, including re-referral, clearly to the General Practitioner.

Management of Iron Deficiency in Adults



*Colorectal Cancer

Based on BSG Guidelines in Gastroenerology

Causes of Iron Deficiency (1) Blood Loss

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- Acute
  - Childbirth
  - Trauma
  - Surgery
  - Gastrointestinal Acute Bleed
    - Ulceration/erosion
    - Rupture
  - Rupture
    - Spleen
    - Oesophageal Varices
    - Aneurysm
  - Increased red Cell or Platelet consumption in Sepsis
- Chronic
  - Menhorrhagia
  - Chronic GI loss
    - (eg Aspirin or NSAIDS)
    - Erosion from Ulcers
    - Diverticular Disease
    - Angioplasia
  - Chronic Kidney Disease and renal Dialysis
  - Haematuria
    - Ca Prostate
    - Kidney Disease
    - Self Catheterisation
  - Occult loss (eg from Tumour invasion)
  - Regular Blood donation
  - High Performance Sport (consumption from increased oxygen requirements)

Causes of Iron Deficiency (2)

- Growth and development

- Pregnancy
  - Fetus - 270mg
  - Placenta and cord - 90mg
  - Delivery - 150mg
  - Normal loss - 280mg
    (1mg per day)
  - >RCM - 450mg
  - Total -1240mg

BUT

  - No Menses + 240-480mg

Net requirement 700 – 1400mg
(2.5-5mg/d.)

Causes of Iron Deficiency (3)
Impaired Absorption/ Insufficient Iron Supply

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- Chronic Disease
  - Heart Failure
  - Chronic Kidney Disease
  - Respiratory Failure
  - Rheumatoid Arthritis
  - Osteoarthritis
  - Uncontrolled Diabetes
- Acute or Chronic Infections
  - Viruses
    - Hepatitis
    - HIV
  - Leprosy
  - Fungal Infection
    - Candida
    - Aspergillus
  - Parasitic
    - Malaria
- Inflammatory Bowel Disease
  - Crohn's
  - Ulcerative Colitis
  - Irritable Bowel Disease (severe)
- Achlorhydria (absent Gastric Acid)
  - Gastric Bypass/Resection
  - Helicobactor Pylori Infection
  - Hypothyroidism
  - Pernicious Anaemia
  - Stomach Cancer
- Poor dietary Intake
  - Vegetarian diet
  - Vegan Diet
  - Fussy diet!

Important to understanding

- Ferroportin
  - The channel that allows Iron out of the gut cells and into the circulation
  - Lack of Ferroportin means:
    - enterocytes cannot export iron absorbed from gut
    - storage iron cannot be released from reticuloendothelial cells
- Hepcidin
  - Discovered in 2000
  - A hormone released by the Liver to regulate systemic levels of Iron.
    - Inhibits absorption of Iron from the gut
    - Regulates the amount of iron recycled from Macrophages
    - Inhibits mobilisation of Iron within cells in Iron stores (stored as Ferritin)
  - Also released in response to inflammation and infection
- Transferrin
  - The transportation system for Iron to the cells

Inflammation inhibits erythropoiesis

- Monocytes are activated and produce a variety of cytokines-
- Tumour necrosis factor (TNF) and interleukin (IL)1 shorten red cell lifespan
- IL6 acts as a plasma expander causing haemodilution
- TNF and IL1 inhibit erythropoietin secretion from the kidney
- TNF and IL1 stimulate lymphocytes to produce interferon which inhibits erythroblast proliferation.
- IL6 causes release of Hepcidin which inhibits iron absorption from the gut and iron release from macrophages.
- All these effects produce inhibition of erythropoiesis and anaemia

Back to investigation……..
What do the results mean?

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SERUM FERRITIN

- **FERRITIN is the primary iron storage protein-** reflects **<u>storage</u>** iron in the hepatocytes and macrophages

- Serum ferritin below normal is 100% specific for iron deficiency anaemia although "normal range" varies with age and sex.

- BUT Ferritin is an acute phase protein so false elevation of ferritin can occur in various disease states :-

1. Inflammation – infection, cardiac disease, COPD, wear and tear, cancer even obesity.
2. Renal failure.
3. Liver damage and alcohol.
4. Hyperthyroidism.
5. Poorly controlled diabetes.
6. Rare congenital disorders.

TRANSFERRIN SATURATION (%TSat)

- **Transferrin is the main transporter protein for iron in plasma and %transferrin saturation** reflects balance between the available iron and iron demand

- In the setting of an iron deficient bone marrow, serum iron is low due to reduced stores, and transferrin saturation is reduced.

- In the setting of inflammation, iron is blocked in the macrophages as ferritin (due to effects of hepcidin via ferroportin) leading to reduced supply for transport to the bone marrow (bound to transferrin) Therefore demand exceeds supply (although stores are adequate) causing **functional iron deficiency** and so also characterised by reduced transferrin saturation (<20%)

Iron deficient erythropoiesis

- **There are 2 types of iron deficient erythropoiesis**
- True iron deficiency (low hepcidin state) characterised by ferritin <100, T sat %<20 %
- Functional iron deficiency (high hepcidin state) characterised by ferritin >100 but T sat %<20 %

Functional iron deficiency

- Functional iron deficiency rises when, despite adequate stores of iron in the reticuloendothelial system and in the liver, there is a limited supply of iron available for erythropoiesis
- Transferrin saturation <20% is a sensitive measure of iron deficient erythropoeisis in the presence of inflammation or cancer (or during treatment with erythropoietin) whereas ferritin is not
- 40% of patients with very high ferritins can have functional iron deficiency when assessed by transferrin saturation.

Parameters of iron metabolism disorders

	Haemoglobin (g/l)	Ferritin* (µg/l)	Transferrin saturation TSAT (%)	Soluble transferrin receptor sTfR (mg/l)	Mean cell volume of erythrocytes MCV (fl)	Mean reticulocyte haemoglobin CHr (pg)
Normal values	♀ 120 - 160 ♂ 130 - 170	♀ 30 - 150 ♂ 30 - 300	16 - 45	0.83 - 1.76**	80 - 96	28 - 35
Iron deficiency without anaemia	n	↓	↓	↑	n – ↓	n – ↓
with anaemia	↓	↓↓	↓↓	↑↑	↓	↓
Anaemia with chronic disease	↓	n – ↑↑	↓	n – ↑	n – ↓	↓
Iron overload (primary, e.g. haemochromatosis)	n	↑ – ↑↑	↑ – ↑↑	↓	n	n
Renal anaemia (without EPO administration)	↓	n – ↑	↓	n – ↑	n	↓
Haemolysis	n – ↓	n – ↑	n – ↑	↑	n – ↑	n

* As ferritin serum is an acute phase protein, CRP should also always be determined

** The reference values are dependent on the test, here Dade Behring, Marburg, Germany

Does Iron Deficiency Really Matter?

- Treatment is ……..
  - Better for the Patient
  - Better for the Budget
  - Better for the Clinicians

- No treatment
  - Increases mortality and morbidity
  - Increases bleeding
  - Increases infections
  - Increases insomnia
  - Decreases lactation
  - Decreases performance (Cognitive and Physical)
  - Decreases growth and development
  - Increases length of stay

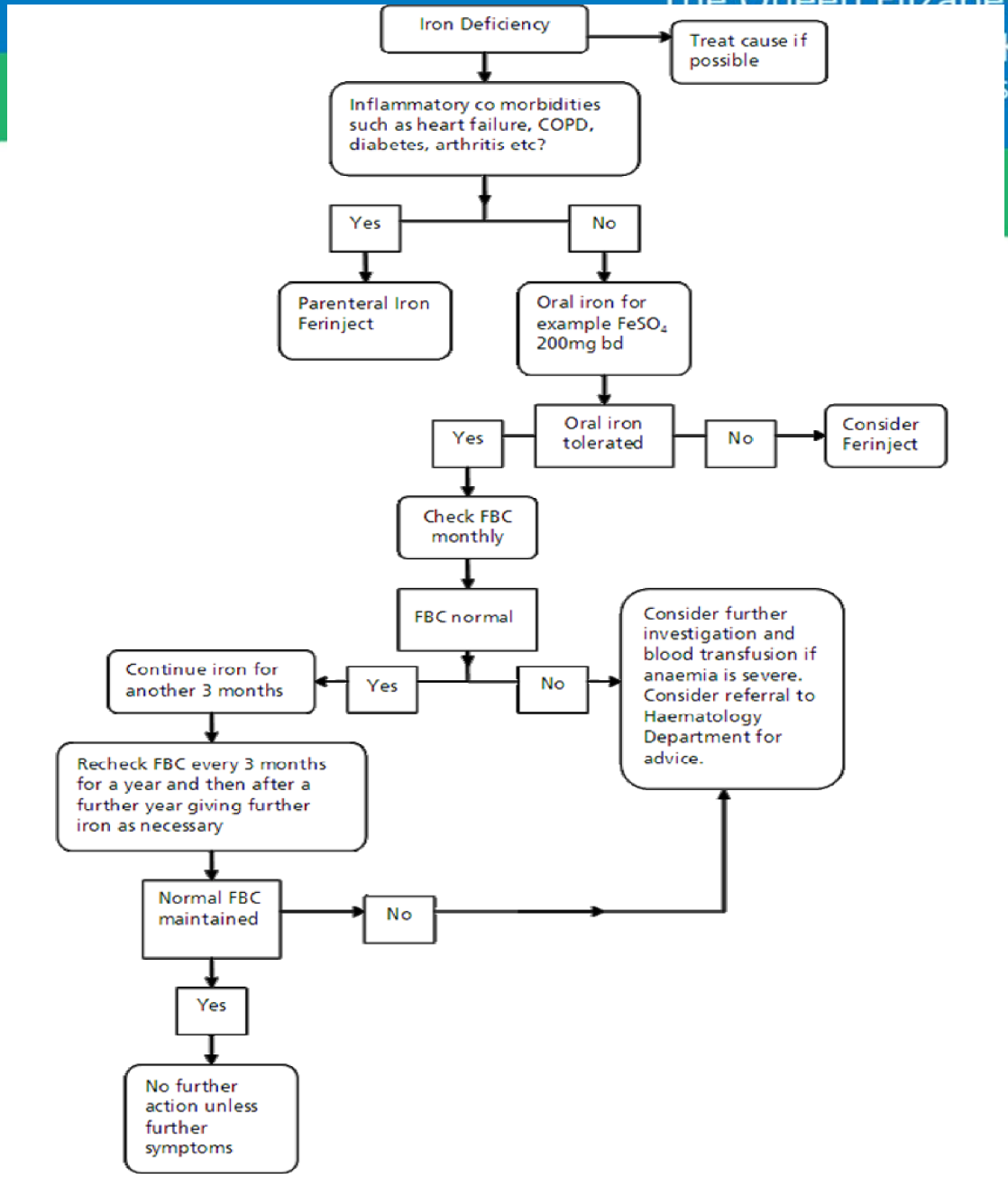
When do we use Oral Iron?

- Young
- Fit
- Previously well
- No Chronic Disease
- Especially no bowel disease
- Or Gastric diseases
- No infections
- Pregnant
- Children

Rationale for intravenous iron use in functional iron deficiency

- Intravenous iron delivers iron to the macrophages which in turn can deliver it to the bone marrow even though the anaemia of chronic disease block persists ie intravenous iron seems to overcome this block in some way which is as yet unknown.

- By contrast 1 unit of red cells although equivalent to 250mg of iron delivers iron which is not available for further erythropoiesis due to high hepcidin levels.


Iron Deficiency
Treat cause if possible
Inflammatory co morbidities such as heart failure, COPD, diabetes, arthritis etc?
Yes
No
Parenteral Iron Ferinject
Oral iron for example $FeSO_4$ 200mg bd
Yes
Oral iron tolerated
No
Consider Ferinject
Check FBC monthly
FBC normal
Continue iron for another 3 months
Yes
No
Consider further investigation and blood transfusion if anaemia is severe. Consider referral to Haematology Department for advice.
Recheck FBC every 3 months for a year and then after a further year giving further iron as necessary
Normal FBC maintained
No
Yes
No further action unless further symptoms

What should happen in an ideal world?

- Patients have a date for surgery and the names of the ward they will be admitted to and the Ward Manager.
- They have a couple of weeks notice before their Pre-assessment clinic appointment.
- They can park the car (we are rural. What buses?).
- They are seen at their appointment time.
- The blood results will already be available to the staff.
- If they need seeing then the Anaesthetist is the one that will gas them.
- They will have their fears assuaged and feel confident in the staff.
- A plan will be made for any further treatments or investigations that are required.
- These extras will happen either the same day or at a mutually convenient time.
- They will be admitted on the morning of surgery as stated and planned.
- Their surgery will go like a dream. They will be discharged in a few days as planned having had no complications
- They will write a letter to the local paper and the CEO praising their care and expressing their delight at feeling better.

The reality–ish

- Patients get 24 hours notice, there is nowhere to park and they are not sure where they are going.
- They are still not sure when they will have their op.
- No Anaesthetist is available
- They forgot to have their bloods done or they couldn't get an appointment at the surgery with the phlebotomist or nurse.
- The history taken appears quite different from the one in the referral letter. Nothing in the OP notes or letter from the surgeon
- There is no capacity to do extra ECGs, Chest x-rays and no blood results are available before they leave
- They have 3 further hospital visits for further investigations.
- They still don't know when they are scheduled for surgery
- Their surgery is cancelled until further notice.
- They still don't know anyone's name.

What is optimisation?

Getting the best from patients for patients

The whole package

- Bloods – correct what you can
- Stop drugs or make provision for not being able to stop
- Work as a team with other specialities as needed
- Agree who will do what and when
- Communicate with the patients
- Write a clear plan in the notes covering pre, intra and post op

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What is the difference between pre-assessment and preadmission?

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Enhanced Recovery After Surgery

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Enhanced Recovery Partnership Programme

Delivering enhanced recovery

Helping patients to get better sooner after surgery

First published 31 March 2010

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Optimising patients with anaemia prior to surgery

What should be done and why?		Where and when is best?
General health check including full blood count • If anaemic (haemoglobin in females below 12g/dL and males below 13g/dL) look for a cause. • If iron deficient, treat with oral iron and look for cause.	BEST PRACTICE	**GP surgery** • Optimise prior to referral. • Early detection of anaemia. • Time to treat iron deficiency or refer other anaemias.
Benefits of detecting anaemia prior to surgery • Earlier detection, more opportunity to treat anaemia and raise haemoglobin. • Higher haemoglobin at surgery, lack of symptoms of anaemia. Less likely to need blood transfusion. Own red cells physiologically better than transfused red cells.	EARLY + RESOURCES	**Pre-op clinic** • Optimise prior to surgery. • Treat iron deficiency. • Identify those who might need transfusion; counsel. • Specialist referral for cause of anaemia.
Cost of detecting anaemia prior to surgery • Detection of anaemia may lead to delay or cancellation of surgery to investigate and manage anaemia. • Investigation of anaemia may be costly and require specialist input. • Treatment of iron deficiency takes time (iv iron quicker than oral). • Detecting another illness causing anaemia may change priorities but patient remains symptomatic from joint disease.	TOO LATE	**Admission for surgery** • Anaemic patients likely to be transfused or cancelled. • Can still target blood.

Shander A et al. Br. J. Anaesth. 2012;bja.aes139

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A multimodal approach to PBM (or blood conservation).

	1st Pillar Optimise haemopoiesis	2nd Pillar Minimise blood loss and bleeding	3rd Pillar Harness and optimise tolerance of anaemia
Preoperative	• Screen for anaemia • Identify underlying disorder(s) causing anaemia • Manage underlying disorder(s) • Refer for further evaluation if necessary • Treat iron deficiency, anaemia of chronic disease, iron-restricted erythropoiesis • Note: anaemia is a contraindication for elective surgery	• Identify and manage bleeding risk (past/family history, current medications, etc) • Minimise iatrogenic blood loss • Procedure planning and rehearsal • Preoperative autologous blood donation (in selected cases or when patient choice)	• Assess/optimise patient's physiological reserve and risk factors • Compare estimated blood loss with patient-specific tolerable blood loss • Formulate patient-specific management plan using appropriate blood-conservation modalities to minimise blood loss, optimise red cell mass and manage anaemia • Restrictive evidence-based transfusion strategies
Intraoperative	• Timing surgery with haematological optimisation	• Meticulous haemostasis and surgical techniques • Blood-sparing surgical techniques • Anaesthetic blood-conserving strategies • Autologous blood options • Pharmacological/haemostatic agents	• Optimise cardiac output • Optimise ventilation and oxygenation • Restrictive evidence-based transfusion strategies
Postoperative	• Treat anaemia/iron deficiency • Stimulate erythropoiesis • Be aware of drug interactions that can cause/increase anaemia	• Vigilant monitoring and management of post-operative bleeding • Avoid secondary haemorrhage • Rapid warming – maintain normothermia (unless hypothermia specifically indicated) • Autologous blood salvage • Minimising iatrogenic blood loss • Haemostasis/anticoagulation management • Prophylaxis of upper gastrointestinal haemorrhage • Avoid/treat infections promptly • Be aware of adverse effects of medication	• Optimise tolerance of anaemia • Treat anaemia • Maximise oxygen delivery • Minimise oxygen consumption • Avoid/treat infections promptly • Restrictive, evidence-based transfusion strategies

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Enhanced Recovery After Surgery

NHS

Enhanced Recovery Partnership Programme

Delivering enhanced recovery

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Impact of potential improvements in length of stay assessed using 2008-09 HES data

Procedure group	Current mean LOS	Current median LOS	No. major providers	Total no. patients	Potential mean LOS (1)	Potential mean LOS (2)	Potential median LOS (3)	Potential bed days saved (4)
Colectomy	10.2	8	152	10,300	7.9	8.4	6	17,900
Excision of rectum	12.4	9	148	9,500	9.1	10.0	7	23,600
Primary hip replacement	6.3	5	157	55,100	5.1	5.6	4	58,900
Primary knee replacement	6.1	5	156	64,500	5.0	5.5	4	63,200
Bladder resection	16.5	14	56	1,200	12.5	13.7	11	4,000
Prostatectomy	4.7	4	71	3,000	3.1	3.6	2	3,800
Hysterectomy	4.3	4	153	36,500	3.1	3.5	3	34,800
								206,200

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Case study

- 48 year old female. Married no children.
- Works in HR – highly stressful job
- Psoriatic Arthritis for 10 years
- Probable IBD
- Continuously iron deficient
- Refusing Blood Components
- 'Homeopathic' doses of IV Iron (Venofer) from Rheumatologist
- Exhausted all the time – cannot walk up the road to the post office.
- Still at work
- Often had to beg Doctor for more Iron when feeling "dreadful"
- Referred to Anaemia clinic at patient request for maintenance

Anaemia Clinic

- Results post last course of Venofer (sub therapeutic dose)prior to Anaemia Clinic
  - Hb 101, WBC 10.2, Plts 525 , TSAT 16%, Iron 7.5, Ferr 525, CRP 28
- Seen in clinic one month later (after referral)
  - Hb 94, WBC 9.65, Plts 358, TSAT 5%, Iron 3.5, Ferr 358, CRP 25
  - Switched to Ferinject
  - Serum Sickness
- 1 month post Ferinject
  - Hb 87, WBC 9.0, Platelets 522 Iron 3.3, Ferritin 565, TSAT 9%, CRP 29
  - Switched back to Venofer at Patient's request
  - 7 x 200mg Venofer given over 3 weeks
  - Bowels opened average of 6 times per day
  - Exhausted, not sleeping, weepy and depressed. Still at work.

Cont....

- 4 weeks later
  - Hb 92, WCC 10.8, Platelets 499, Iron 5.3, Ferritin 712, TSAT 12%, CRP 13
  - Discussed with Gut Surgeon. Urgent appointment.
  - Sent off on Sick Leave
  - Need to increase Hb to >100g/l prior to surgery so that anastomosis/wounds will heal.
  - Prescribed further Venofer
  - Bowel working still causing concern
- 2 week later
  - Hb still 95
  - TSAT 14%
  - Arghhh!
  - Further Venofer
  - Add 300mg/kg Eprex (Epoetin Alpha) daily for 3 days
- 2 days prior to surgery Hb 122, TSAT 41%, CRP 11
- 2 days post op Hb 109, TSAT 40%
- 2 weeks post op Hb 131, TSAT 29%
- 2 months post op Hb 145, TSAT 25%, Back on Rheumatoid treatments including Methotrexate. Able to walk round the village with her husband and back at work.
- 1 year post op Hb 135 TSAT 25% back on all meds. Building stamina. Living.

What about Medical Patients?

- The evidence is mounting
  - Heart Failure
    - FAIR HF Trial. Anker S. et al *2009 NEJM* Patients had improved symptoms, functional capacity and quality of life
    - Now CONFIRM HF
  - Renal
    - NICE guidance suggests IV Iron use
  - Palliative Cancer Care
    - Fewer, shorter hospital visits
    - Fewer peaks and troughs in wellbeing
    - Increased physical and cognitive function
  - Obstetrics
    - Pavord et al BCSH Guidelines
  - BCSH guidelines on the investigation of functional iron deficiency

Where were we? What year?

'The mass of literature on the subject of Blood Transfusions accumulated during the past 25 years is so great, and most of it so readily available, that one shows lack of temerity at least to attempt a discussion of this subject before this audience. The transfusion of blood may be a life-saving procedure under certain circumstances. It may be a necessary supportive measure under others, but it is too often undertaken when the doctor can think of nothing else to do after all other therapy has failed. My objective today is to discuss briefly the common surgical and medical conditions for which transfusion of blood is indicated in which we can obtain good physiological results and to point out those conditions in which it is little more than a gesture done as it were to satisfy the urge to do something.'

NEJM

The New England
Journal of Medicine

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The Massachusetts Medical Society

SECTION OF MEDICINE

**Lower Section Room, Municipal Auditorium, Springfield,
Tuesday, June 9, 1936, 2 p. m.**

PRESIDING:
Dr. William D. Smith, Boston, Chairman.
Dr. Laurence B. Ellis, Boston, Secretary.

CHAIRMAN SMITH: Will the meeting please come to order.

The first duty of the Section is the selection of the Chairman and the Secretary for the coming year, and, in accordance with the usual custom, the Chair will appoint as the Nominating Committee to suggest names Dr. Dwight O'Hara, Chairman, Dr. George R. Minot and Dr. Chester M. Jones. They will report later and abide the pleasure of the Section.

I do not see Dr. Hamilton here. Apparently she is delayed, so we will pass on to the second paper. To those of us who have had our moments of indecision whether to transfuse or not to transfuse in some of our medical problems, Dr. Bock's paper should be of interest. His subject is "The Use and Abuse of Blood Transfusions."

THE USE AND ABUSE OF BLOOD TRANSFUSIONS*

BY ARLIE V. BOCK, M.D.†

THE mass of literature on the subject of blood transfusions accumulated during the past twenty-five years is so great and most of it so readily available that one shows lack of temerity at least to attempt a discussion of the subject before this audience. The transfusion of blood may be a life-saving procedure under certain circumstances, it may be a necessary supportive measure under others, but it is too often undertaken when the doctor can think of nothing else to do after all other therapy has failed. My objective today is to discuss briefly the common surgical and medical conditions for which transfusion of blood is indicated, in which we can expect good physiological results, and to point out those conditions in which it is little more than a gesture, done, as it were, to satisfy the urge to do something.

SURGICAL INDICATIONS

1. *Shock.* Many theories of the cause of primary and secondary shock have been offered by able investigators, most of them recently reviewed briefly by Blalock.[1] Because of the complexity of the events no theory yet proposed can be considered the final answer as to the etiology of shock. We know that if treatment of the condition is to be successful it must accomplish two things, restoration of diminished blood volume and elevation of low blood pressure. Blood volume may be reduced by gross hemorrhage or it may be reduced by blood lost in the periphery of the body, as suggested by Freeman,[2] or by extravasation of serum through damaged capillaries. If hemorrhage has occurred, transfusion of blood, together with such supportive measures as heat, is the immediate indication. No other therapy is so successful. In shock without much or any hemorrhage, 6 per cent gum acacia in normal saline may be just as effective as blood, and has the advantage of greater availability. Repeated transfusions of blood or infusions of acacia may be necessary but, are usually not, if no delay has occurred in the first instance. Acacia may be used as a supportive measure until transfusion can be arranged. Prolongation of the shock state results in tissue asphyxia, capillary damage, petechial hemorrhages, and rapid change in general to an irreversible state.

One of the common accompaniments of shock is dehydration, a state associated with loss of water, base, chloride and increase of nonprotein nitrogen. When such a state exists, transfusion alone is not adequate therapy but normal salt solution, often in large quantities, should be administered intravenously, or it may be given in eight-ounce quantities by rectum every half hour. When facilities permit, serum chloride

*Read at the Annual Meeting of the Massachusetts Medical Society, Section of Medicine, Springfield, June 9, 1936.

†Bock, Arlie V.—Physician, Massachusetts General Hospital. For record and address of author see "This Week's Issue," page 469.

With thanks to Aryer Shander

And where are we now?

'The anaemia, as I mentioned in a previous letter, is chronic anaemia which can not be corrected without blood transfusion. I leave it to you to organise that pre-operatively. I think once you have done that you will be safe to go ahead with surgery'.

GP to Ortho Consultant January 2013
Patient awaiting a Primary Hip Replacement