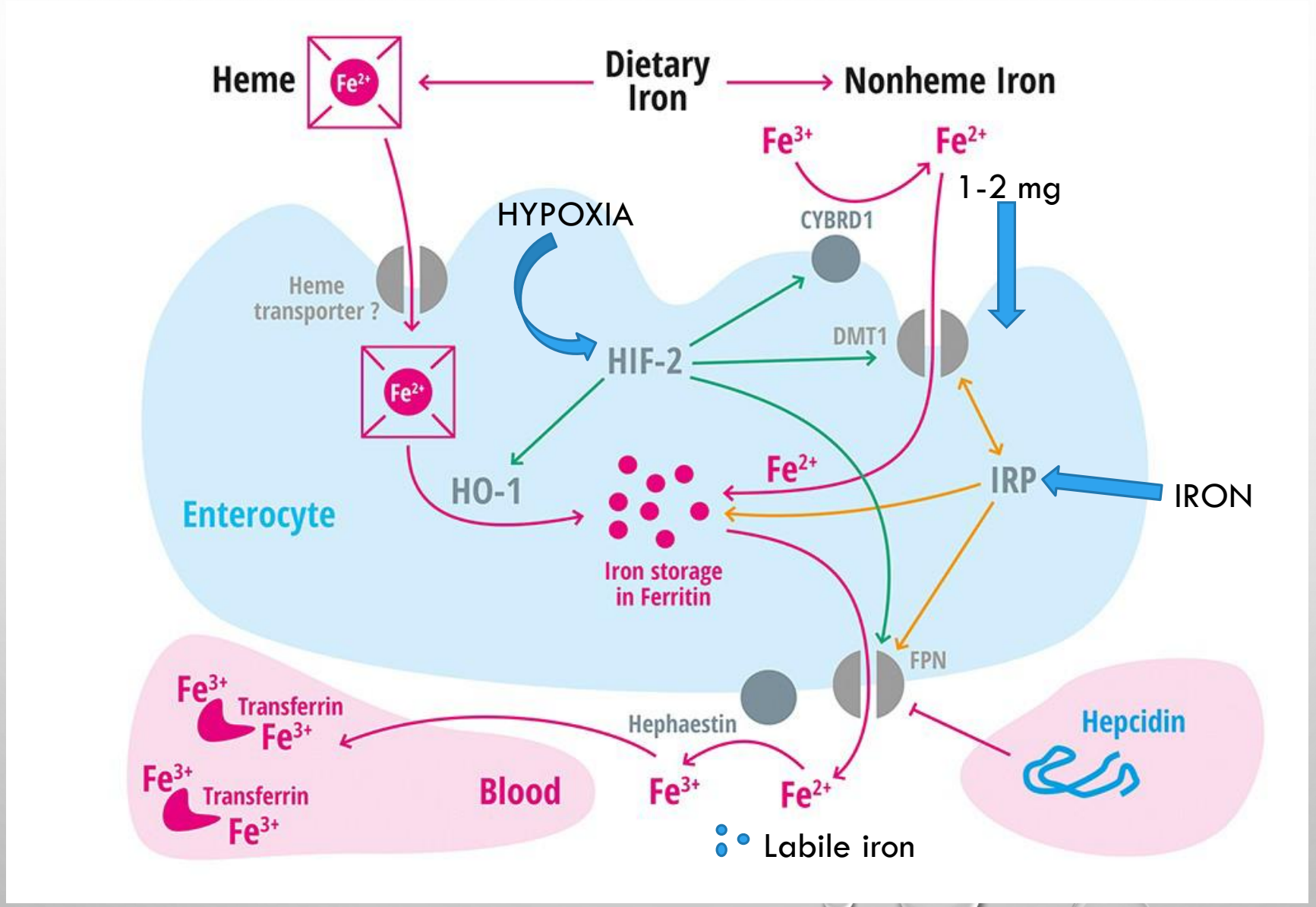
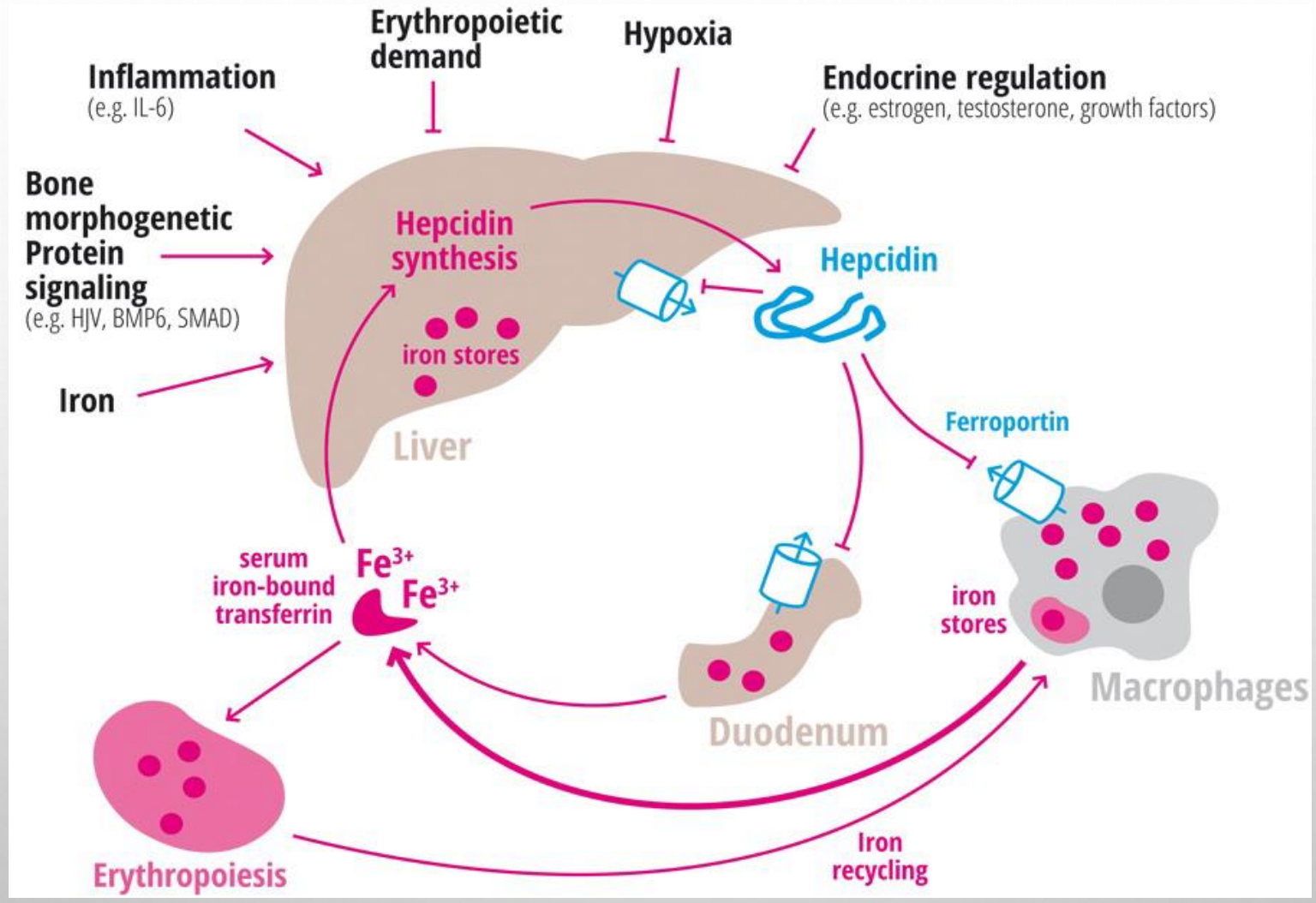
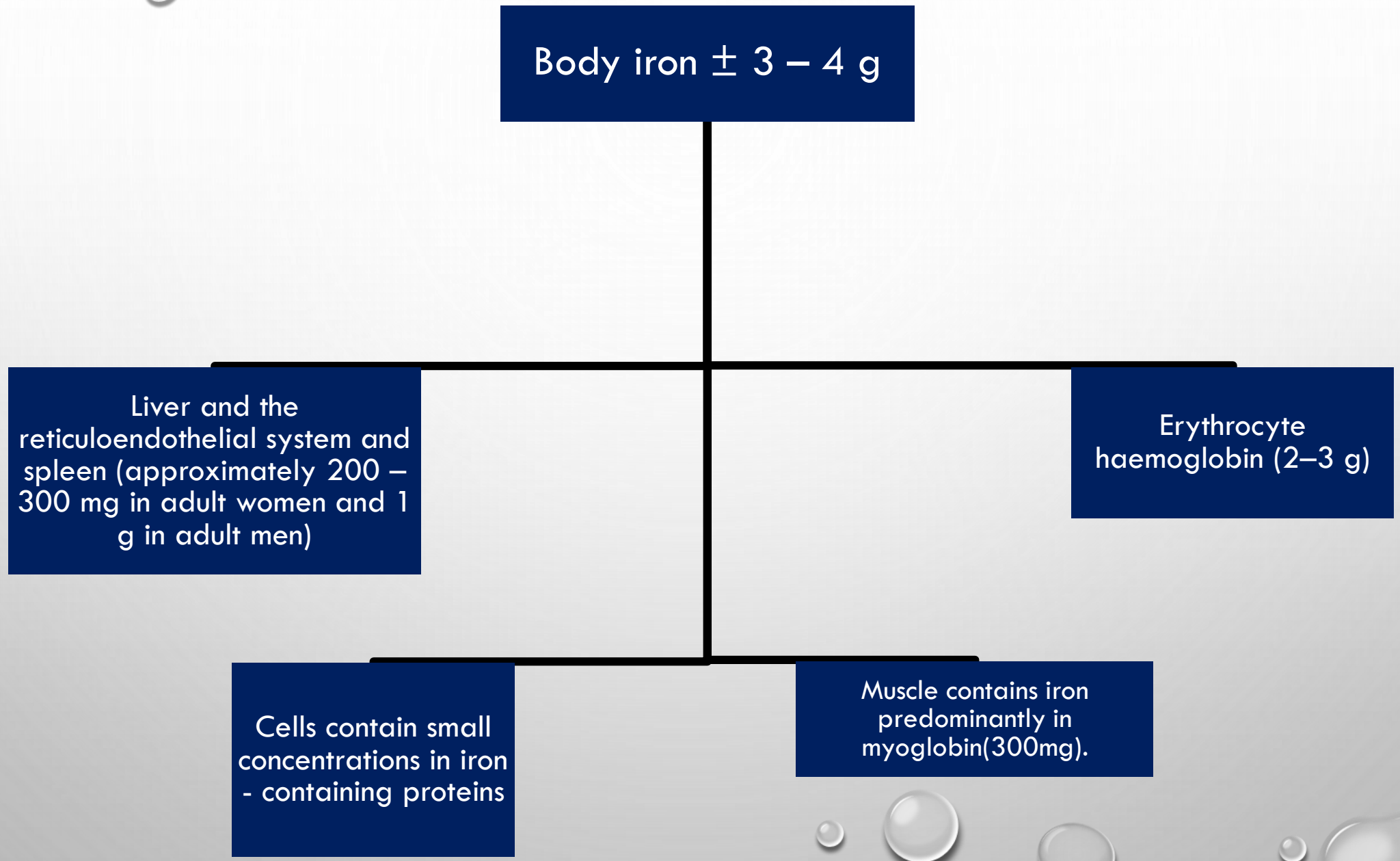
IRON DEFICIENCY / ANAEMIA

ANTHONY BEETON


Heme
Fe2+
Dietary Iron
Nonheme Iron
Fe3+
Fe2+
1-2 mg
HYPOXIA
CYBRD1
Heme transporter ?
DMT1
HIF-2
Fe2+
HO-1
Fe2+
IRP
IRON
Enterocyte
Iron storage in Ferritin
FPN
Hephaestin
Hepcidin
Fe3+ Transferrin Fe3+
Fe3+ Transferrin Fe3+
Blood
Fe3+
Fe2+
Labile iron


Erythropoietic demand
Hypoxia
Inflammation
(e.g. IL-6)
Endocrine regulation
(e.g. estrogen, testosterone, growth factors)
Bone morphogenetic Protein signaling
(e.g. HJV, BMP6, SMAD)
Hepcidin synthesis
Hepcidin
iron stores
Iron
Liver
Ferroportin
serum iron-bound transferrin
Fe^{3+}
Fe^{3+}
iron stores
Macrophages
Duodenum
Erythropoiesis
Iron recycling


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)
Cells contain small concentrations in iron - containing proteins
Muscle contains iron predominantly in myoglobin(300mg).

IRON PHYSIOLOGY

- TOXICITY
  - FREE IRON / LABILE IRON POOL
  - FERROUS (2+)
- “100 HUNGRY ENZYMES”
- FERRITIN – IRON STORE INDICATOR
- ANAEMIA A LATE PRESENTATION IN I.D.

IRON DEFICIENCY

- SEQUENCE OF EVENTS
  - USE OF IRON STORES WITH NORMAL HAEMATOPOIESIS
  - INEFFICIENT ENERGY METABOLISM IN ALL CELLS ESPECIALLY MUSCLE (FATIGUE)
  - MAKING SMALLER CELLS WITH NORMAL HB CONC (MICROCYTOSIS – MCV)
  - MAKING SMALL CELLS WITH REDUCED HB CONC (HYPOCHROMIA – MCHC)
  - MAKING FEWER CELLS

IRON PHYSIOLOGY TESTS

- INDIRECT – HB; MCV; MCHC; RETIC COUNT; RDW ETC. ETC.
- DIRECT
  - SERUM IRON
  - FERRITIN
  - TRANSFERRIN SATURATION (T_{SAT})

ANAEMIA

- 1/3 OF WORLD'S POPULATION (2.36 BILLION PEOPLE)
  - HIGHER IN AFRICA
  - SASOS 47.8% ANAEMIA
    - INDEPENDENT PREDICTOR OF DEATH & AKI
  - WOMAN OF CHILD BEARING AGE / CHILDREN
  - > 50% OF ANAEMIA IS IDA
  - ID CO-EXISTS WITH MANY OTHER ANAEMIAS
  - ANAEMIA ASSOCIATED WITH ADVERSE OUTCOMES – DEATH; ORGAN DYSFUNCTION & **TRANSFUSION**
- ID FAR COMMONER THAN IDA
- COMMONEST DISEASE IN THE WORLD
- ORAL IRON CHEAP BUT NOT RELIABLE AND SLOW TO WORK WITH MANY S/E S

TRANSFUSION

- ONLY FOR SYMPTOMATIC OXYGEN DELIVERY DEFICIT
  - NO LIFE SUSTAINING SUBSTITUTE AVAILABLE
- AROUND 1 – 1.5% OF SOUTH AFRICANS ARE DONORS
- BLOOD USAGE INVERSELY PROPORTIONAL TO UNDERSTANDING OF TRANSFUSION (PATHO)PHYSIOLOGY
- ~ 11.8% OF RED CELL TRANSFUSIONS INDICATED
- FIXES BLOOD TESTS NOT NECESSARILY PATIENTS

TRANSFUSION

- PATHOPHYSIOLOGY
  - VOLUME OVERLOAD
  - IMMUNOLOGICAL EFFECTS – TRAIL; TRIM
  - INFECTION – IMMUNOLOGICAL; FREE IRON / HAEM
  - STORAGE INJURY – CYTOKINES; PROCOAGULANTS; HAEM; FREE IRON
  - POOR OXYGEN DELIVERY
    - LEFT SHIFT IN OLD RBC
    - POOR MICROVASCULAR FLOW
    - POORER DO_2 AT HIGHER HB AFTER BANKED BLOOD TRANSFUSION

TYPICAL IDA PICTURE

- MICROCYTIC HYPOCHROMIC ANAEMIA
- FERRITIN < 30 NG/ML
- TRANSFERRIN SATURATION < 20%

ID - MISCONCEPTIONS

1. A NORMAL FERRITIN EXCLUDES IDA
   - WIDE RANGE OF NORMAL 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

ID - MISCONCEPTIONS

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 VIA NORMALIZATION OF PLATELET SYNTHESIS)
     - CCF (ENERGY; QOL; SURVIVAL)
     - PERI-OPERATIVELY (ID PREDISPOSES TO INFECTION / TRANSFUSION / FATIGUE)
     - IRON DEFICITS 1 – 2 G – DIFFICULT TO CORRECT ORALLY

ID - MISCONCEPTIONS

3. ORAL IRON IS ALWAYS EFFICACIOUS IF TOLERATED
   - DEFICITS OF > 1 G
   - CAN ABSORB < 5MG/DAY – 200 DAYS + TO CORRECT (HB RISES NOT > 0.7 MG/DL/MONTH)
   - NEED TO CONTINUE FOR 3 MONTHS AFTER CORRECTION OF IDA TO REPLENISH IRON RESERVES
   - > 70% INTOLERANCE AT DOSES > 100 MG/DAY
   - PPI / ANTACIDS INHIBIT ABSORPTION
   - BEST APPROACH FOR TOLERABILITY (GREATEST % ABSORPTION)
     - LOW DOSES
     - BD DOSES
     - ALTERNATE DAYS
   - THE **ONLY** INDICATION IS COST

ID - MISCONCEPTIONS

4. IV IRON SHOULD BE RESERVED FOR SEVERE ANAEMIA
   - CRITICAL ANAEMIA REQUIRES BLOOD TRANSFUSION UNTIL HAEMODYNAMICS / ISCHAEMIA RESOLVE
   - 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

ID - MISCONCEPTIONS

5. THERE IS NO NEED FOR FOLLOW UP AFTER IRON REPLETION
   - IV IRON
     - WELL-BEING IMPROVES AFTER 2 – 3 DAYS
     - RETICULOCYTE COUNT INCREASES IN A WEEK
     - HB RISES FROM 1 – 2 WEEKS AFTER INFUSION
     - MAXIMUM RESPONSE IN 4 – 6 WEEKS
   - SHOULD RE-ASSESS AFTER 6 – 8 WEEKS WHERE IV IRON NO LONGER CONFOUNDS TESTS
   - MUST REASSESS BECAUSE MOST UNDERLYING CAUSES CONTINUE (MALIGNANCY; GI INFLAMMATION AND BLEEDING; CKD; CCF)

ID - MISCONCEPTIONS

6. ALL IV IRONS ARE THE SAME
   - ALL CAN PRODUCE RAPID CORRECTION OF ID AND IDA
   - ORIGINATORS SHOWN TO BE SUPERIOR OVER SOME GENERICS
   - FCM HAS MOST EVIDENCE AND IS UNIQUELY INDICATED IN CCF
   - SIDE EFFECTS RELATED TO HIGH % LABILE IRON (E.G. IRON SUCROSE OR GLUCONATE AND IRON DEXTRANS) AND THE PRESENCE OF DEXTRAN
   - FCM / IRON ISOMALTOSIDE - MINIMAL S/E S AS LOW FREE IRON AND HIGH SUGAR BINDING
     - CAN BE ADMINISTERED FAST (15 – 30 MIN)
     - STILL MONITOR Q15MIN AND FOR 30 MIN AFTER CONCLUSION BUT LARGELY MYTHOLOGY

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

ID - MISCONCEPTIONS

7. IV IRON HAS A HIGH INCIDENCE OF SIDE EFFECTS
   - SEVERE ANAPHYLAXIS RARE < 1:250 000 (15 – 20 TIMES LOWER THAN RBC TRANSFUSION)
   - 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
   - TRYPTASE
   - INFUSIONS MUST STILL BE DONE IN MEDICALLY REGISTERED AND RESOURCED ENVIRONMENTS
   - BENEFIT FAR OUTWEIGHS RISK
   - DEATHS ASSOCIATED WITH IV IRON USUALLY MULTIFACTORIAL (CCF; SEPSIS; CANCER)
   - HYPOPHOSPHATAEMIA ASSOCIATED PREDOMINANTLY WITH FCM – RELATED TO DECREASED RENAL REABSORPTION AND INCREASED FIBROBLAST GF LEVELS. WORSE WITH VIT D DEFICIENCY. CLINICAL RELEVANCE?

ID - MISCONCEPTIONS

8. PREMEDICATIONS REDUCE INFUSION REACTIONS
   - ANTIHISTAMINE CAUSE FAR MORE S/E S THAN THEY PREVENT
     - SOMNOLENCE; HYPOTENSION; BRADYCARDIA ETC
   - CHECK TRYPTASE TO DETECT TRUE ALLERGY – FOR FUTURE REFERENCE
   - MULTI-ALLERGIC / ASTHMATIC PATIENTS MAY BENEFIT FROM A SHORT COURSE OF PERI-INFUSION STEROID

ID - MISCONCEPTIONS

9. 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

ID - MISCONCEPTIONS

10. IS ADJUVANT IRON NECESSARY IN PATIENTS ON EPO WITH NORMAL FERRITIN?
    - PATIENTS WITH INFLAMMATORY ANAEMIA / ANAEMIA OF CHRONIC DISORDERS / FUNCTIONAL IRON DEFICIENCY E.G. CKD MAY RESPOND TO EPO SINCE IT:
        - REDUCES HEPCIDIN
        - ENHANCES IRON ABSORPTION
    - EPO PRODUCES RAPID HAEMATOPOIESIS
        - IRON DEMANDS HIGH AND IV IRON IS MANDATORY OTHERWISE “APPARENT” EPO RESISTANCE
        - IRON ALSO REDUCES THROMBOCYTOSIS AND VTE
        - IDEALLY GIVE IV IRON (E.G. FCM 1000MG) BEFORE EPO

PERI-OPERATIVE MANAGEMENT OF ID / IDA

- ASSESS IRON STATUS ON INITIAL PRESENTATION
  - FBC & RETICULOCYTES
  - 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

- 50 YEAR OLD FEMALE MEDICAL DOCTOR
- LARGE RETROPERITONEAL TUMOUR
- PRESENTED WITH FATIGUE AND HB OF 9.7 (IRON DEFICIENT)
- SURGERY DEEMED URGENT BUT NOT EMERGENT
- IV FCM 1G GIVEN 18 DAYS BEFORE SCHEDULED SURGERY
- HB ON DAY OF SURGERY 13.9
- SURGERY WITH CELL SALVAGE
  - BLOOD LOSS 2200ML – 900 ML SALVAGED BLOOD RETURNED WITH HCT OF 46%. NO BANKED BLOOD
  - DISCHARGED HOME WITH HB 10.8

PATIENT BLOOD MANAGEMENT

- ANAEMIA MANAGEMENT IS A CORNERSTONE OF PBM
- THE TOXICITY OF IRON THERAPY IS LARGELY MYTHOLOGY
- THE BENEFIT OF TRANSFUSION FOR MANAGEMENT OF ANAEMIA IS ENTIRELY MYTHOLOGY
- PBM IS A NON-NEGOTIABLE INTERVENTION FOR BETTER PATIENT OUTCOMES AND OPTIMAL RESOURCE MANAGEMENT