A Tale of Two Syndromes

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WITS UPTO SPAED CONFERENCE

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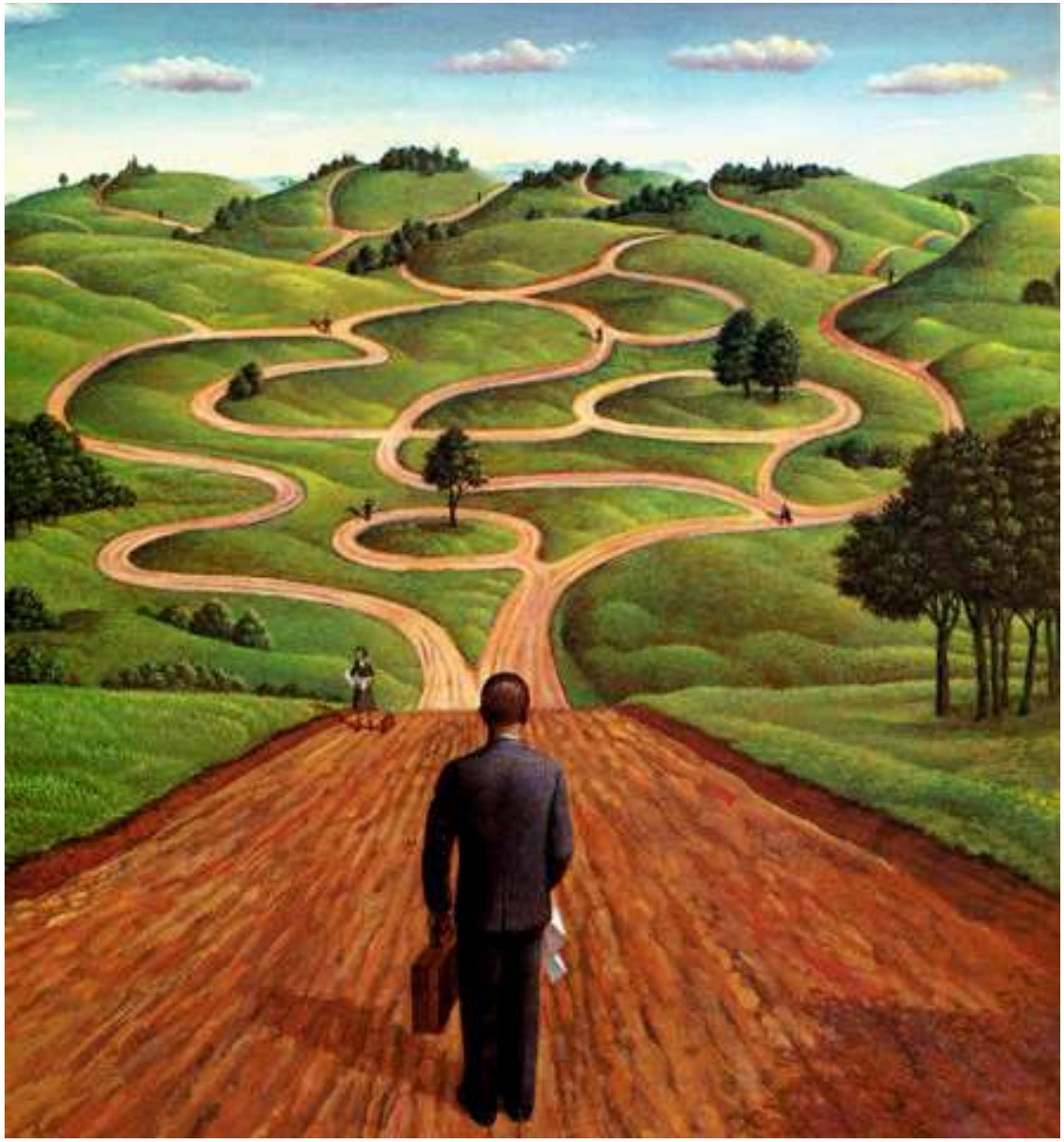
The journey…

- Illustrate **two important syndromes** affecting children
  - 1 common
  - 1 uncommon
  - Surprisingly linked
- Using cases demonstrate important take-home points



cancer.gov/publications/dictionaries/cancer-terms/def/syndrome

An official website of the United States government

NIH NATIONAL CANCER INSTITUTE

syndrome

(SIN-drome)

A set of symptoms or conditions that occur together and suggest the presence of a certain disease or an increased chance of developing the disease.

Case 1

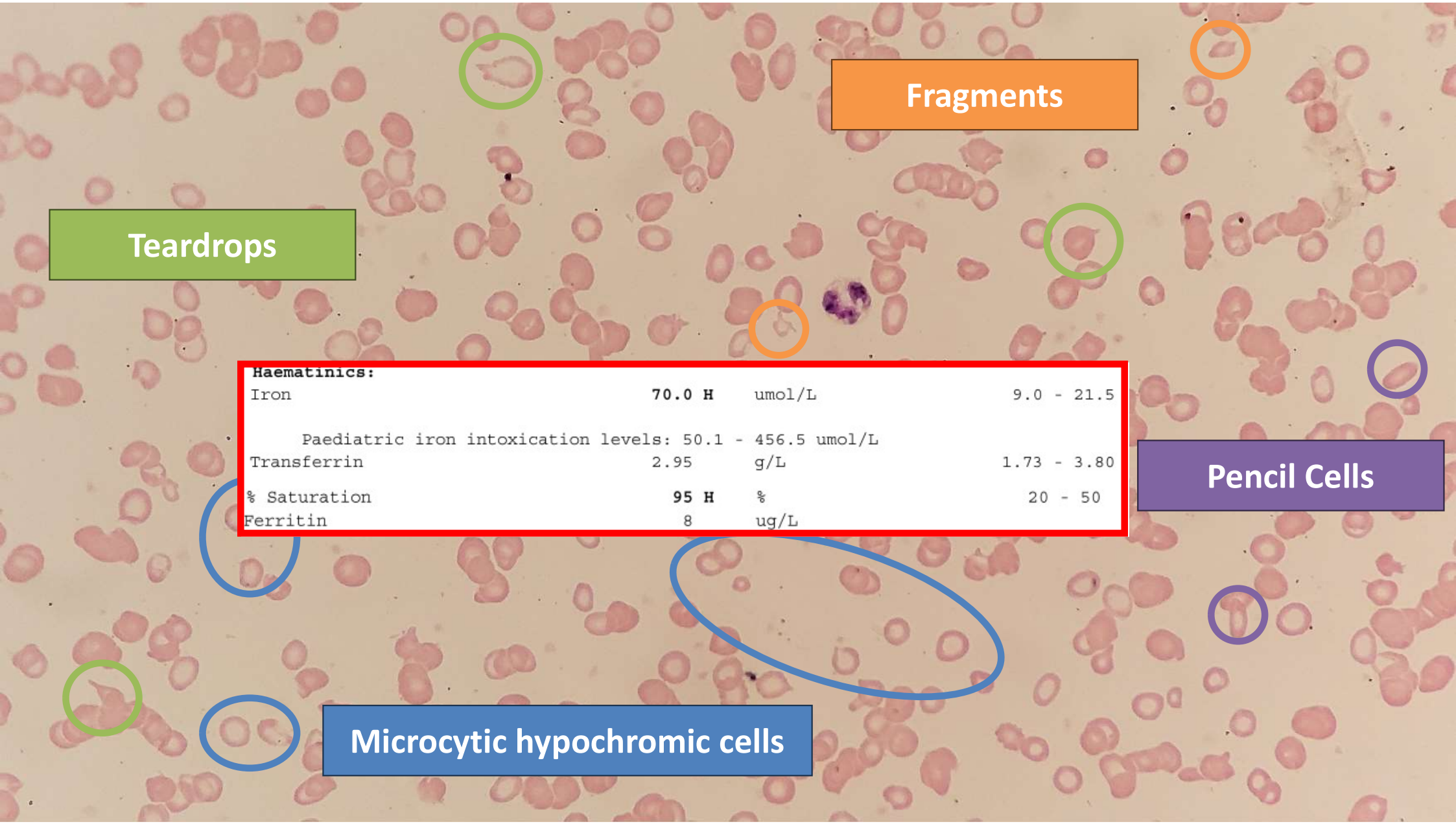
- **11-year-old male** presented with features of **symptomatic anaemia**

Date	20/10/22
WCC	7.39
RCC	2.09 L
HB	2.8 L
HCT	0.128 L
MCV	61.3 L
MCH	13.6 L
PLT	33 L

APPROACH TO A MICROCYTIC HYPOCHROMIC ANAEMIA

Date	20/10/22
WCC	7.39
RCC	2.09 L
HB	2.8 L
HCT	0.128 L
MCV	61.3 L
MCH	13.6 L
PLT	33 L

1. **I**ron deficiency
2. Iron deficiency
3. Iron deficiency
4. Iron deficiency
5. Iron deficiency
6. Iron deficiency
7. Iron deficiency
8. Iron deficiency
9. Iron deficiency
10. Iron deficiency
11. **A**naemia of chronic disease
12. **T**halassaemia trait
13. **S**ideroblastic anaemia (**L**ead)
14. Rare causes


Fragments
Teardrops
Haematinics:
Iron 70.0 H umol/L 9.0 - 21.5
Paediatric iron intoxication levels: 50.1 - 456.5 umol/L
Transferrin 2.95 g/L 1.73 - 3.80
% Saturation 95 H % 20 - 50
Ferritin 8 ug/L
Pencil Cells
Microcytic hypochromic cells

THE LANCET
Haematology

ARTICLES | VOLUME 10, ISSUE 9, E713-E734, SEPTEMBER 2023

Download Full Issue

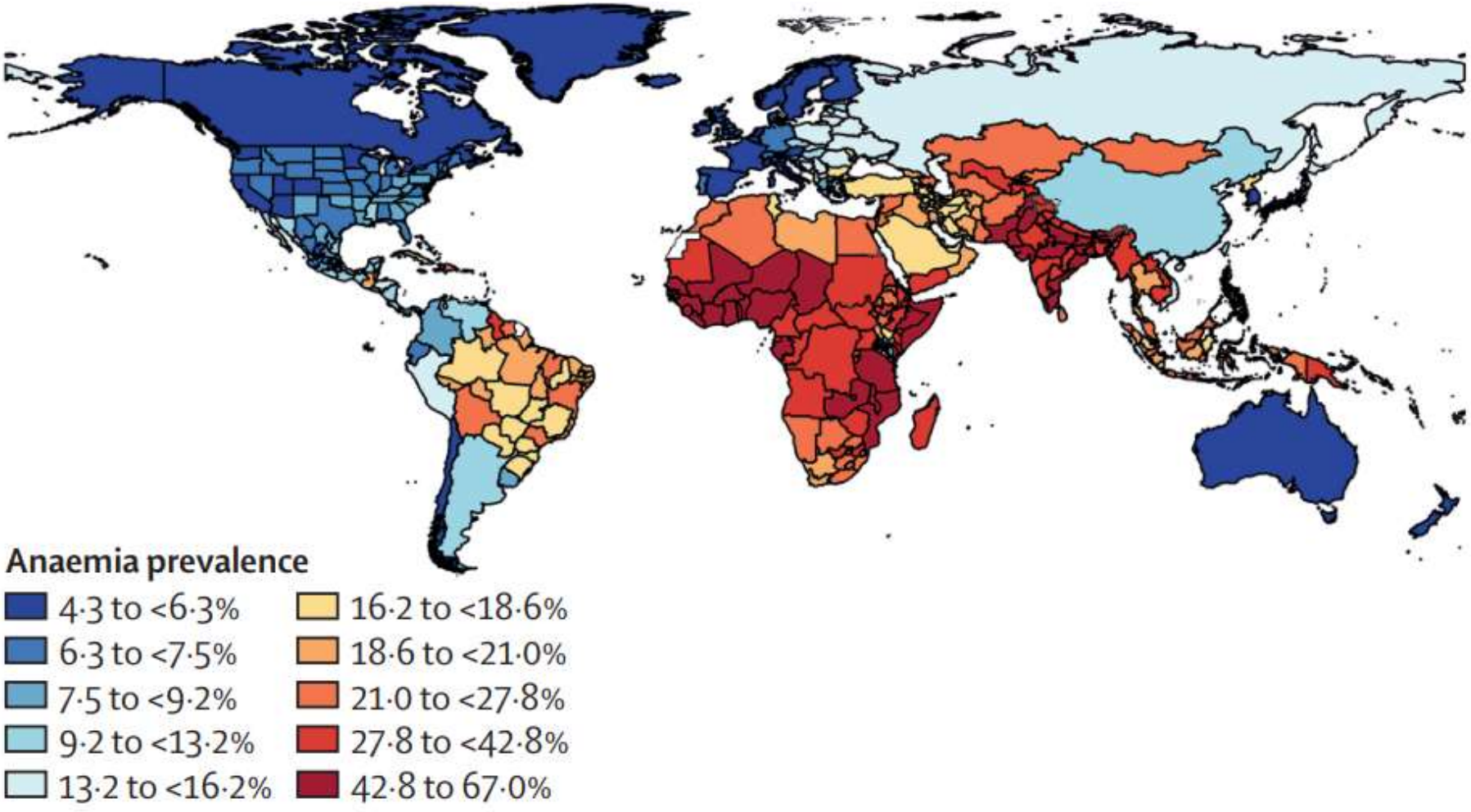
Prevalence, years lived with disability, and trends in anaemia burden by severity and cause, 1990–2021: findings from the Global Burden of Disease Study 2021

GBD 2021 Anaemia Collaborators † • Show footnotes

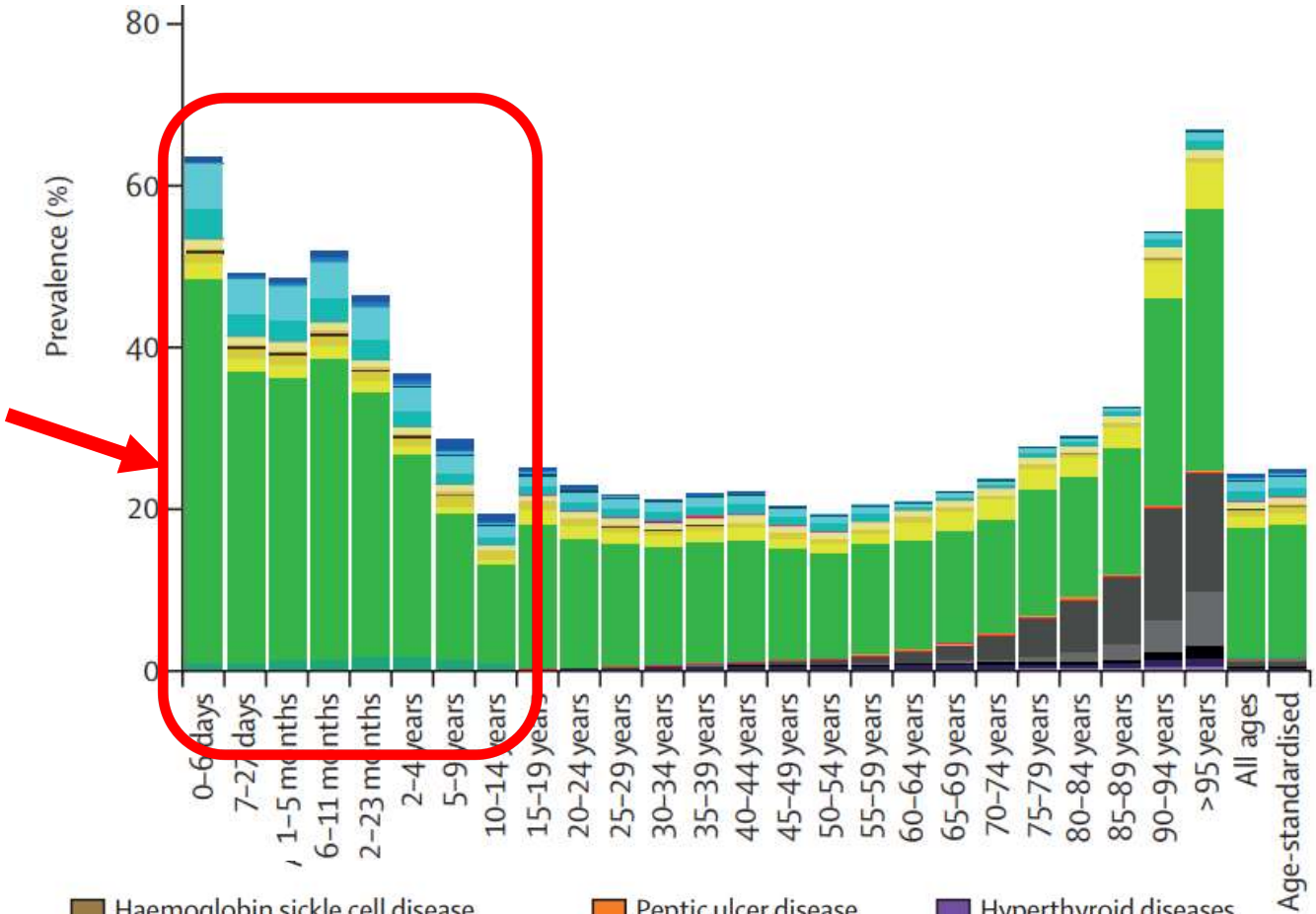
Open Access • Published: July 31, 2023 • DOI: https://doi.org/10.1016/S2352-3026(23)00160-6 •

Check for updates

Anaemia prevalence



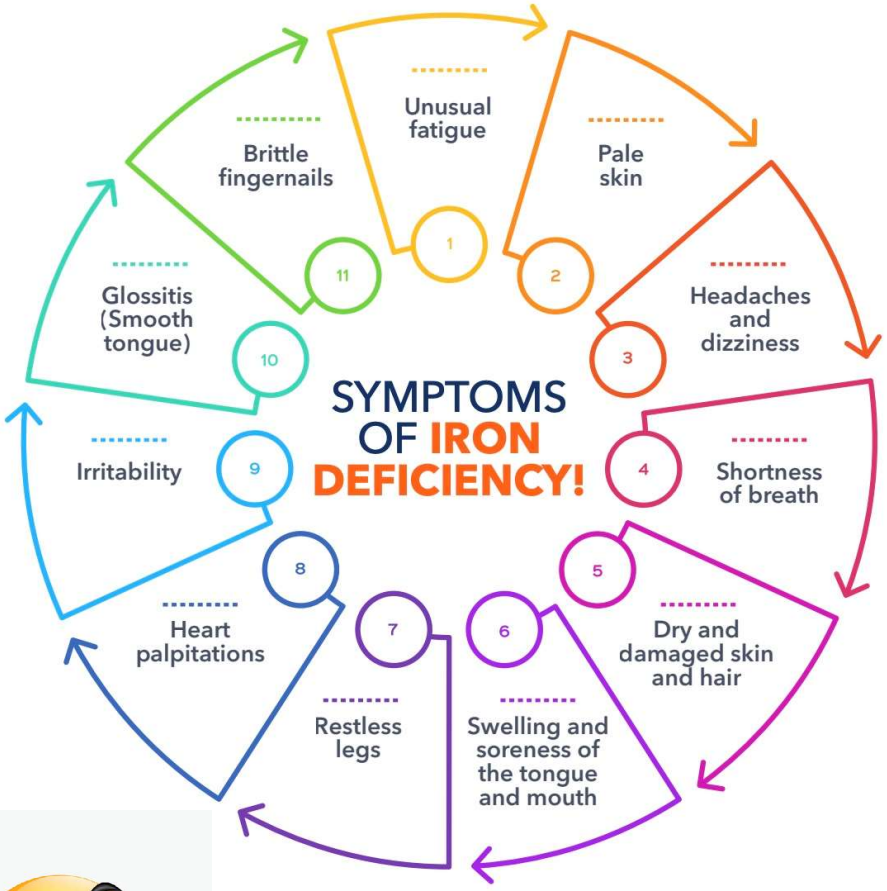
Age distribution



Causes

- *P falciparum* malaria
- *P vivax* malaria
- Clinical malaria
- Hookworm disease
- Schistosomiasis
- Other NTD
- Other infectious diseases
- HIV/AIDS
- Maternal haemorrhage
- Uterine fibroids
- Menstrual disorders
- β-thalassaemia major
- Haemoglobin E/β-thalassaemia
- Haemoglobin H
- β-thalassaemia trait
- Haemoglobin E trait
- Homozygous sickle cell disease and severe sickle cell disease
- Haemoglobin sickle cell disease
- Mild sickle cell disease/β-thalassaemia
- Sickle cell trait
- G6PD deficiency
- Hemizygous G6PD deficiency
- Other haemoglobinopathies
- Iron deficiency
- Vitamin A deficiency
- Gastritis and duodenitis
- Peptic ulcer disease
- Crohn's disease
- Ulcerative colitis
- Cirrhosis
- CKD stage 3
- CKD stage 4
- CKD stage 5 untreated
- CKD stage 5 on dialysis
- Hypothyroid diseases
- Hyperthyroid diseases
- Other endocrine

Manifestations of iron deficiency



Thrombocytopenia?

Iron containing proteins

Protein	Function
Haemoglobin	Oxygen transport
Myoglobin	Oxygen transport
Cytochromes	Electron transport. Respiration
Adrenodoxin	Electron transport. Oxidation/reduction
Ferredoxin	Electron transport. Oxidation/reduction.
Cyt P450 and b5	Drug detoxification
Ribonucleotide reductase	DNA synthesis
Proline hydroxylase	Collagen synthesis
Peroxidases	Decomposition of hydroperoxides
Catalase	Decomposition of hydronen peroxide
Lipoxygenase	HPETE and leukotriene synthesis
Cyclooxygenase	Prostaglandin and thromboxane synthesis
Aconitase	Tricarboxylic acid cycle
Succinate dehydrogenase	Tricarboxylic acid cycle
NADH dehydrogenase	Electron transport. Respiration
Xanthine oxidase	Conversion of xanthine to uric acid
Aldehyde oxidase	Metabolism of aldehydes
Transferrin	Iron transport in plasma
Lactoferrin	Iron binding in milk and other secretions
Ferritin	Iron storage
Haemosiderin	Iron storage
Hephaestin	Protein affecting iron metabolism
Ferroportin	Protein affecting iron metabolism
Hepcidin	Protein affecting iron metabolism

Adapted from reference [25].

THERAPY OPTIONS

BLOOD

- Only treats anaemia in the short-term
- Does not address the underlying iron deficiency until much later (recycling of red cells).
- High Cost R2 200 to R3 100
- RISKS of transfusion.

ORAL IRON

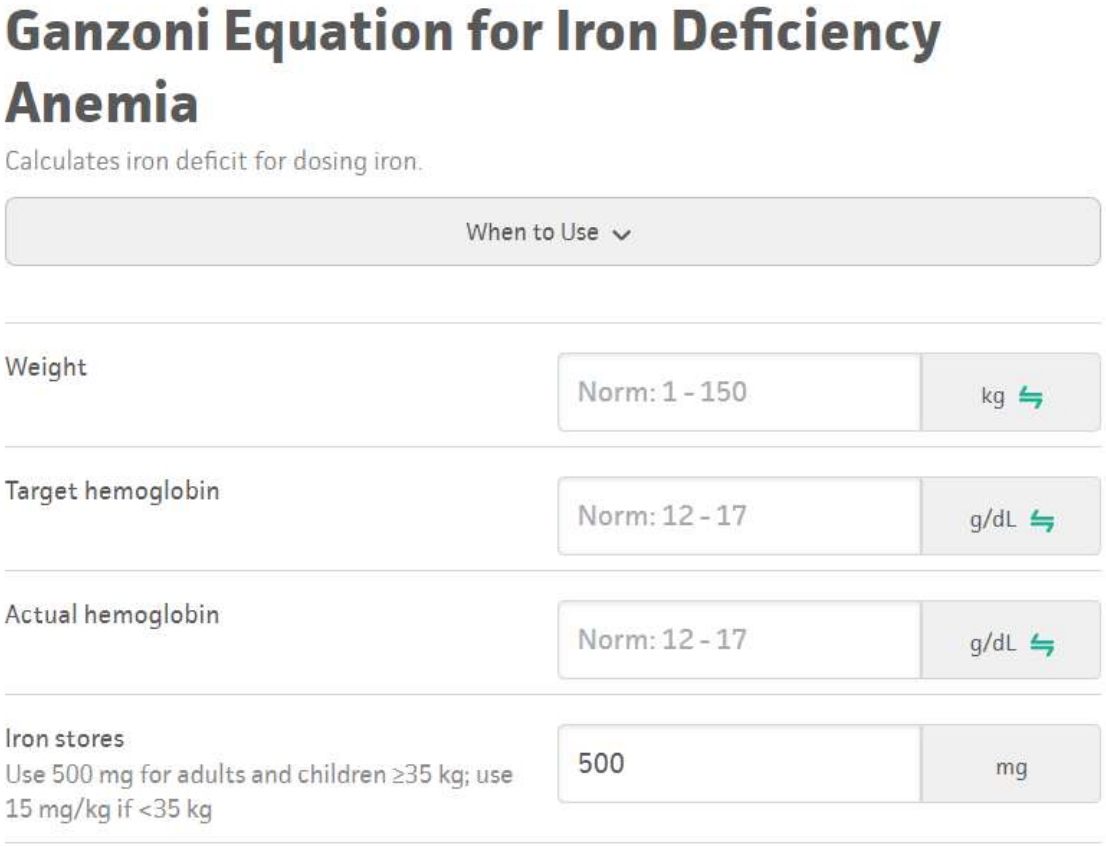
- Cheapest product which is widely available.
- Slowly replaces iron stores.
- If absorption issue, ineffective.
- Side effects and compliance can be an issue.

IV IRON

- Rapidly replaces iron stores and provides the bone marrow substrate needed to address the anaemia.
- Newer preparations have a good safety profile.
- Lower cost of therapy. ~R120 – R510 per dose of iron sucrose

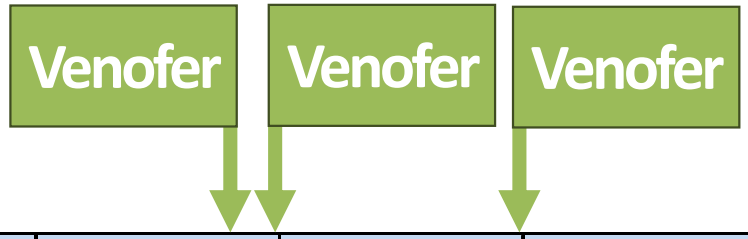
Intravenous Iron Sucrose Therapy

- Widely **available**
- Generally **safe** (low rates of anaphylaxis) - no test dose required
- Can be used to get to target haemoglobin or just start replacement
- **Dosing** (alternate days) of
  - 100mg in children
  - 200mg adolescents



$$Deficit = \boldsymbol{wt} \times (\boldsymbol{target\ Hb - actual\ Hb}) \times 2.4 + \boldsymbol{iron\ stores}$$

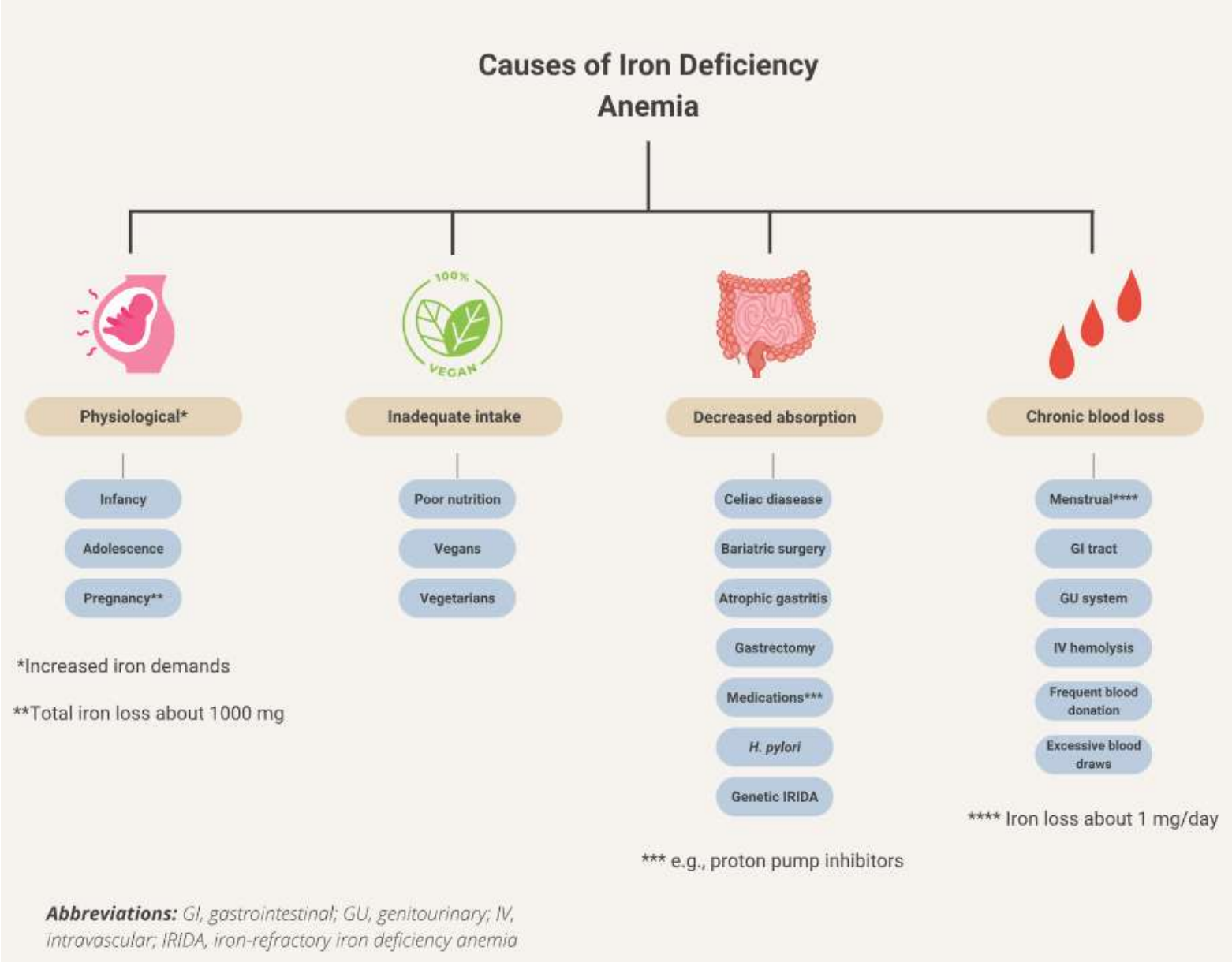
CASE 1: What did we do?



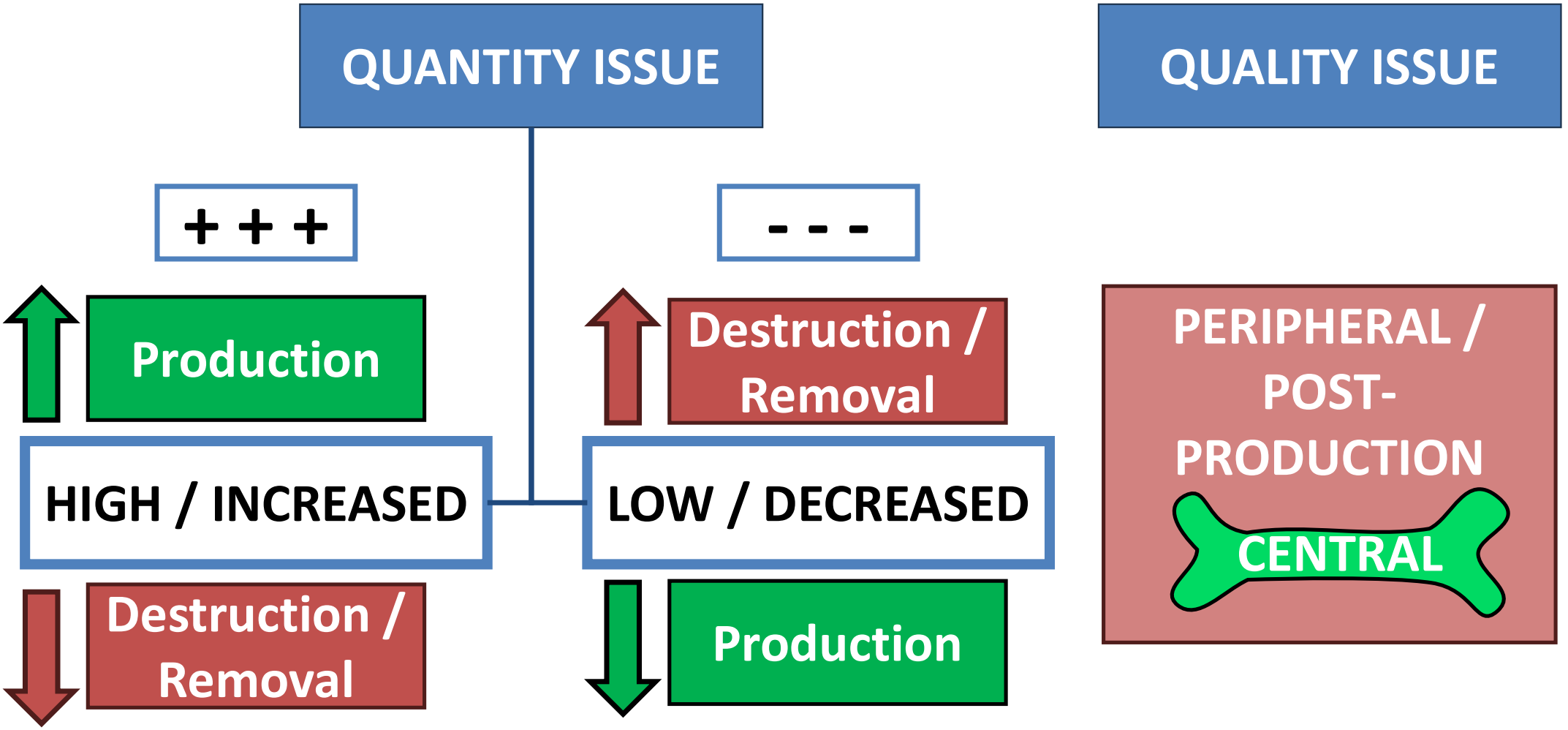
Date	20/10/22	24/10/22	26/10/22	22/05/23	31/07/23	06/11/23
WCC	7.39	38.97 H	22.74 H	7.58	5.95	4.55
RCC	2.09 L	2.76 L	3.23 L	5.63 H	4.96	5.01
HB	2.8 L	3.9 L	4.7 L	12.3	10.5	10.6
HCT	0.128 L	0.164 L	0.218 L	0.425	0.353	0.368
MCV	61.3 L	59.4 L	67.5 L	75.4 L	71.2 L	73.4 L
MCH	13.6 L	14.1 L	14.6 L	21.9 L	21.2 L	21.1 L
PLT	33 L	68 L	155 L	348	533 H	445 H

Why call iron deficiency a syndrome?

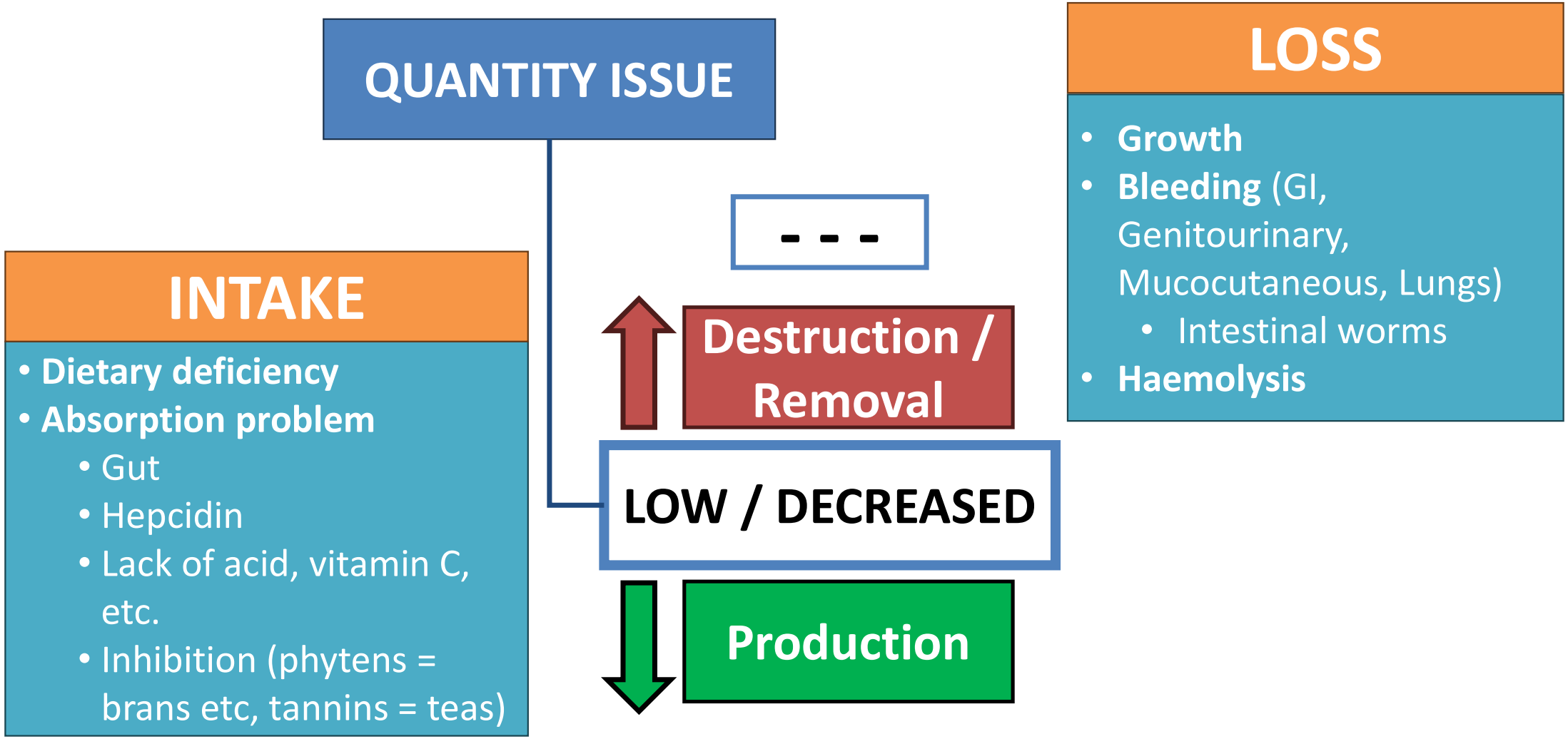
- You need to think of a cause



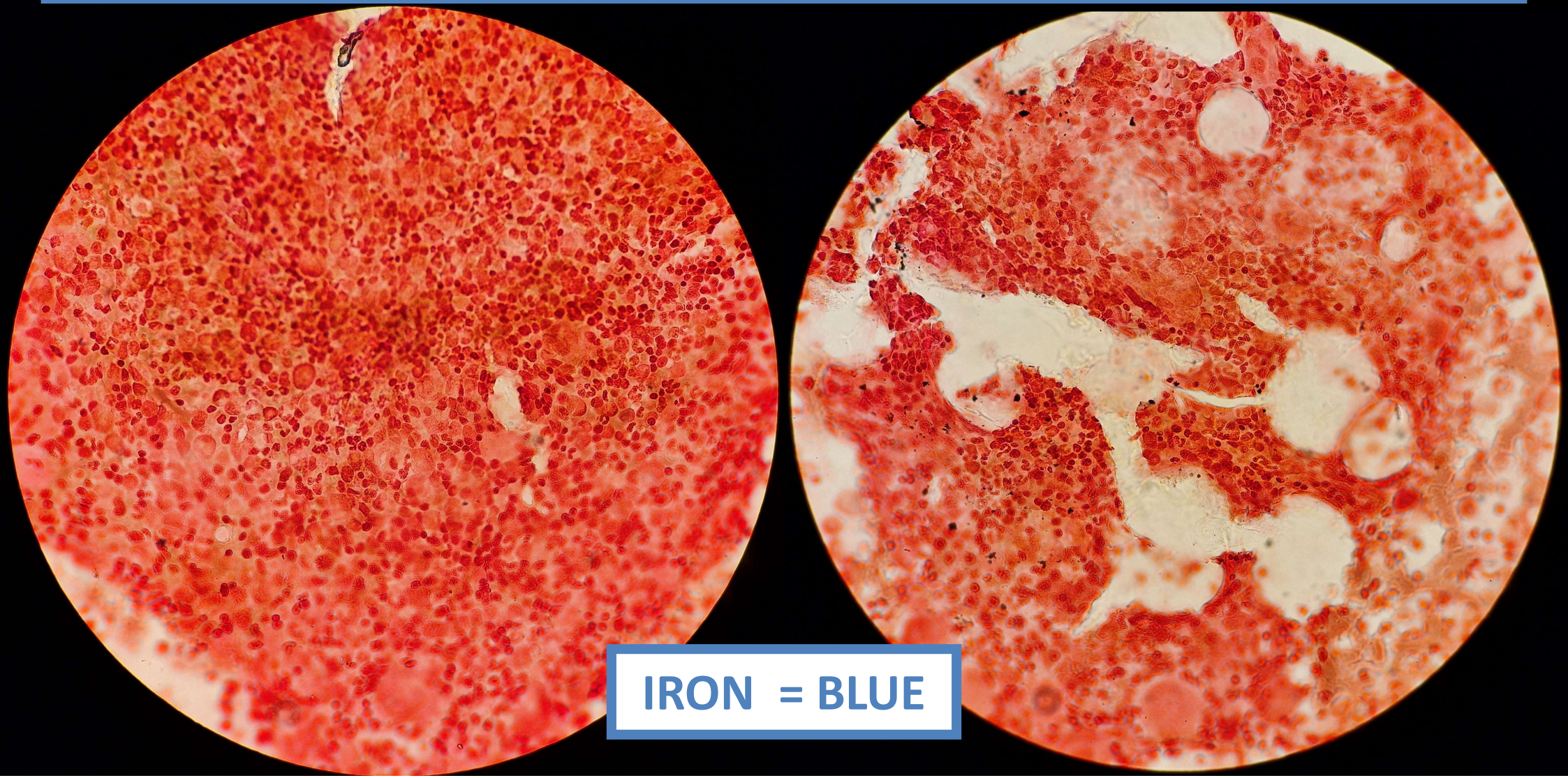
HAEMATOLOGY: GENERAL APPROACH

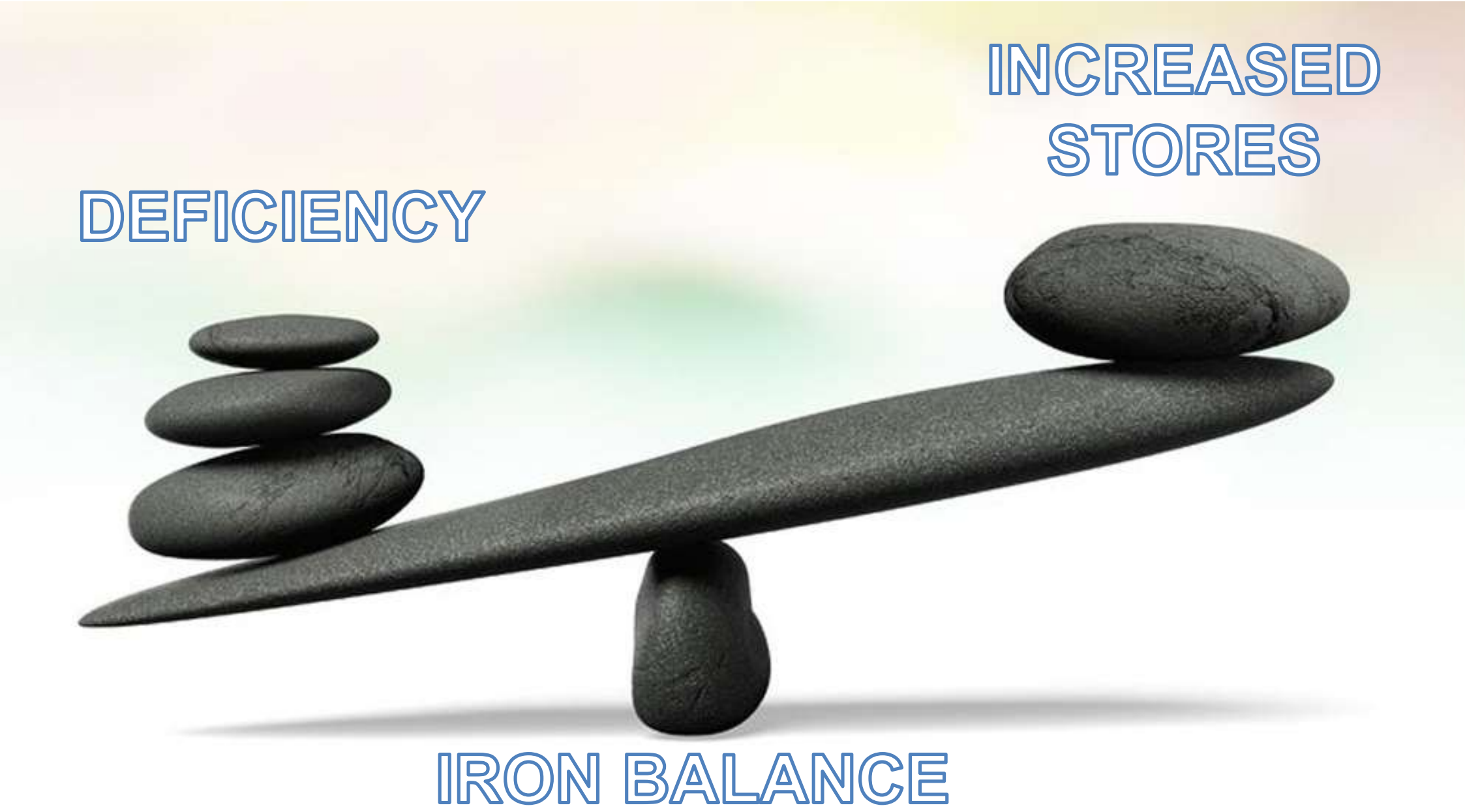


How does iron deficiency develop?



IRON STORES IN A CHILD WITH NO EVIDENCE OF IRON DEFICIENCY




INCREASED
STORES
DEFICIENCY
IRON BALANCE


E
1/4
1/2
3/4
F

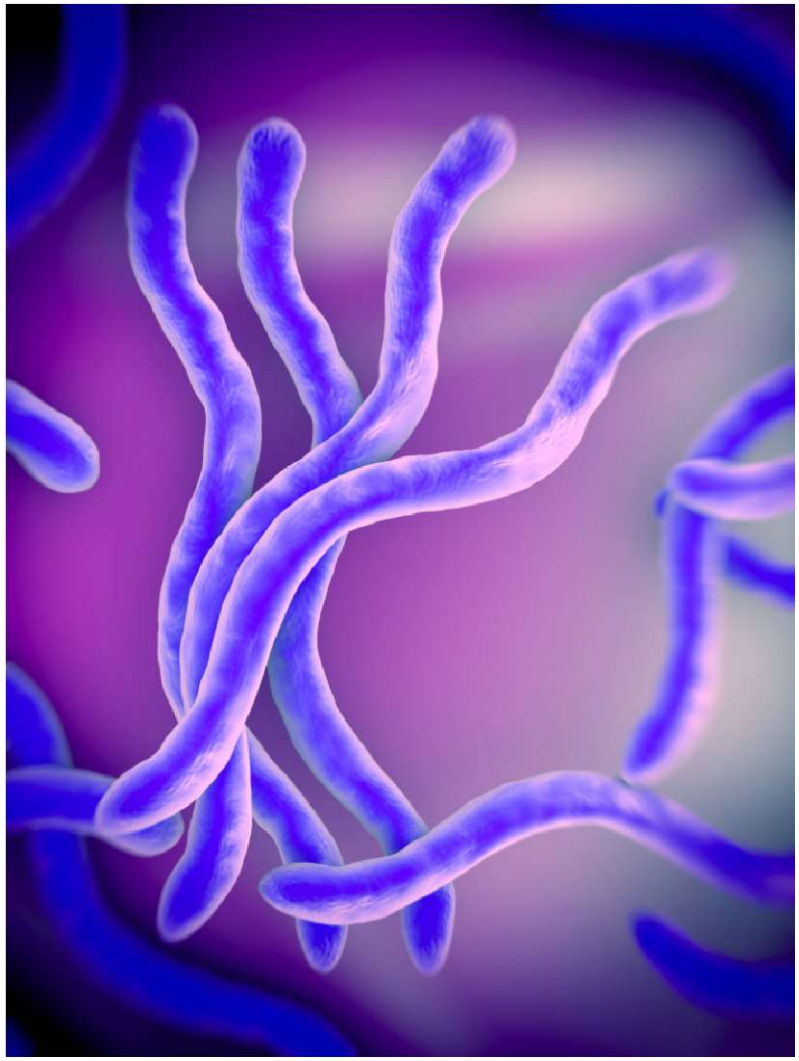

F
E
ODO/TRIP
DISP

Why call iron deficiency a syndrome?

- You need to think of a **cause**

IN CHILDREN:

- Tend towards **low iron levels**
- **Growing**
- **Small dietary deficit** will allow development
- **Intestinal parasites**
- **Malabsorption**
- **Bleeding** – rarer

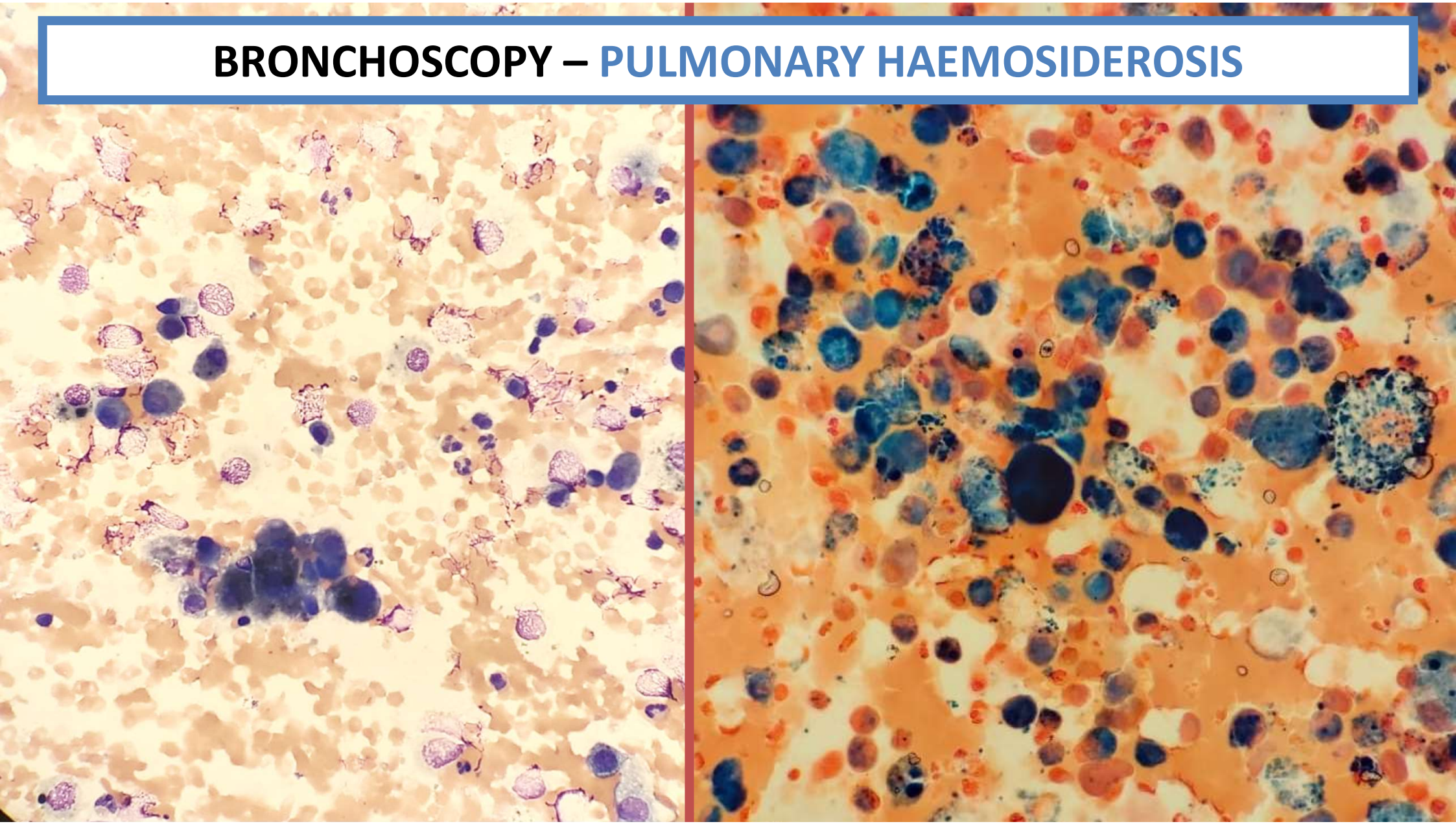


Finding/addressing the cause

- Detailed **history**
- Ensure **adequate intake**
- Consider **deworming**
- Consider **absorption** problem
- Then start thinking **blood loss**
  - **Haemolysis**
  - **GIT**
  - **Genitourinary**
  - **Pulmonary**

IF YOU DO NOT FIND AND ADDRESS THE CAUSE, YOU DO NOT SOLVE THE PROBLEM

BRONCHOSCOPY – PULMONARY HAEMOSIDEROSIS



Case 2

- **9-year-old female**
- Presented with **swelling of the right arm**
  - Spontaneously following bumping of it
- On examination she was found to be:
  - **Cyanosis**
  - **Plethora**
  - **Clubbing**

Undiagnosed Tetralogy of Fallot

Secondary Polycythaemia

Upper limb DVT

Results

Reference	Unit	FBC	
3.9 - 10	*x 10^9/L*	WCC	5.29
3.8 - 5.4	*x 10^12/L*	RCC	**?**
10 - 16	*g/dL*	HB	**20.6**
0.3 - 0.5	*L/L*	HCT	**0.694**
77 - 92	*fL*	MCV	82.1
26 - 32	*pg*	MCH	**?**
33 - 35	*g/dL*	MCHC	**?**
12 - 15	*%*	RDW	**?**
180 - 440	*x 10^9/L*	PLT	**80**

Fe studies	
Serum Fe	**6.4**
TF	2.23
% Sat	**11**
Ferritin	**17**

Management

- **Partial exchange** transfusion
  - Venesection with replacement of fluid volume given cardiac condition
- **Iron replacement**
- **Anticoagulation**
  - **Clexane** in hospital
  - Converted to **Rivaroxaban** for discharge

Cause of thrombosis?

ASH PUBLICATIONS

blood

102.IRON HOMEOSTASIS AND BIOLOGY | NOVEMBER 2, 2023

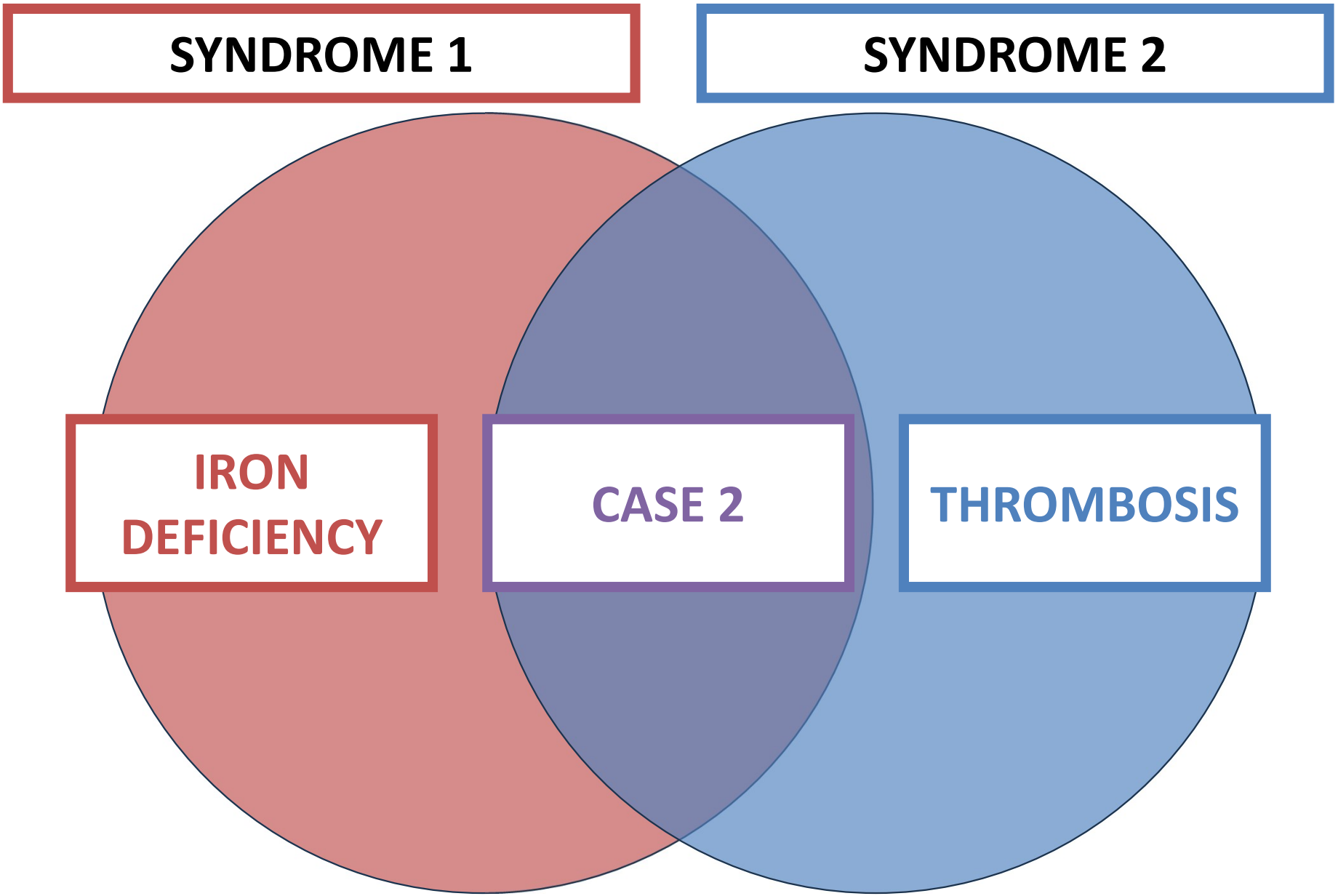
Association between Iron Deficiency Anemia and Thrombosis, a Population Based Study

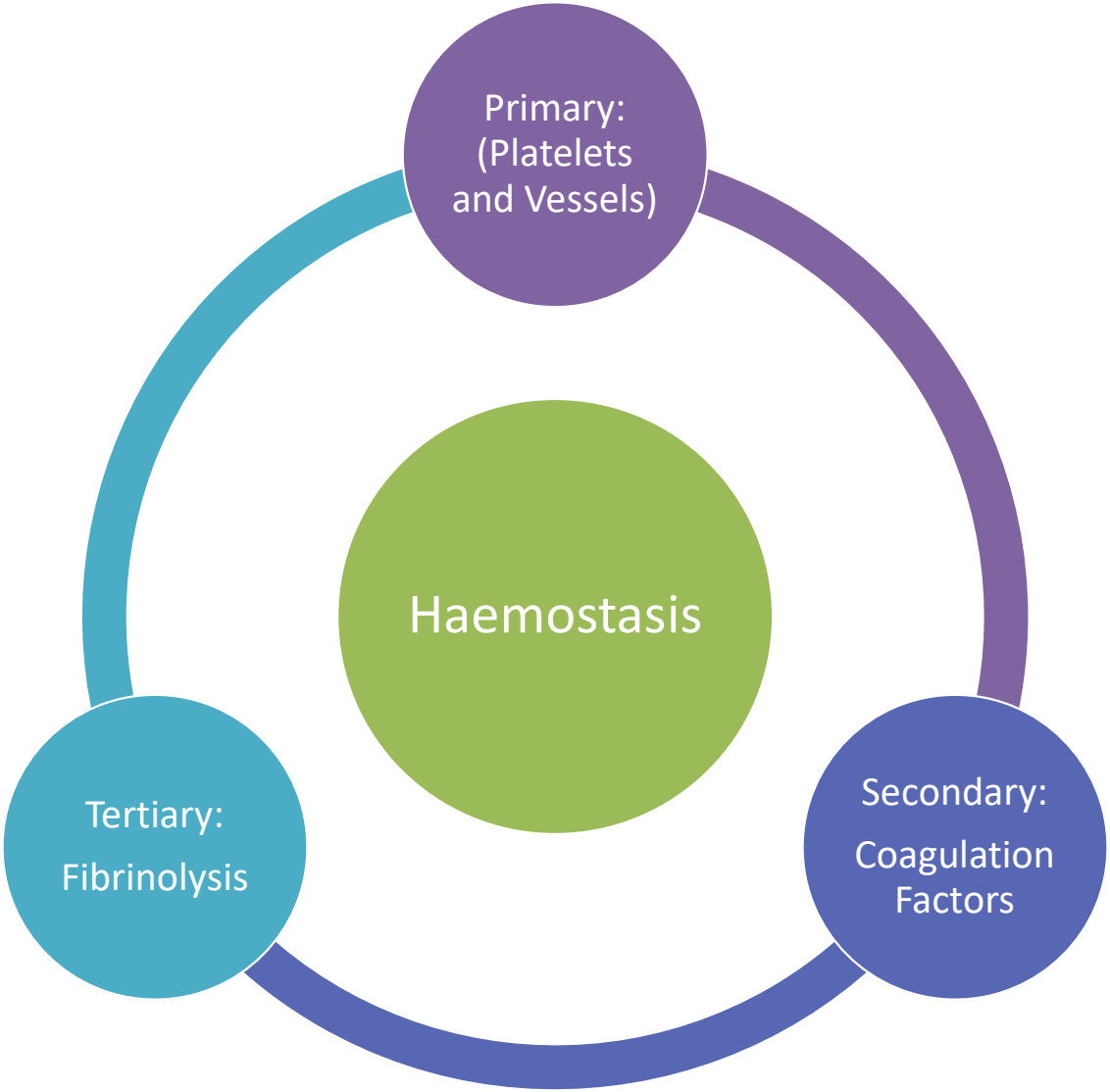
Eric Nathan Laber, Damian A Laber

Blood (2023) 142 (Supplement 1): 5232.

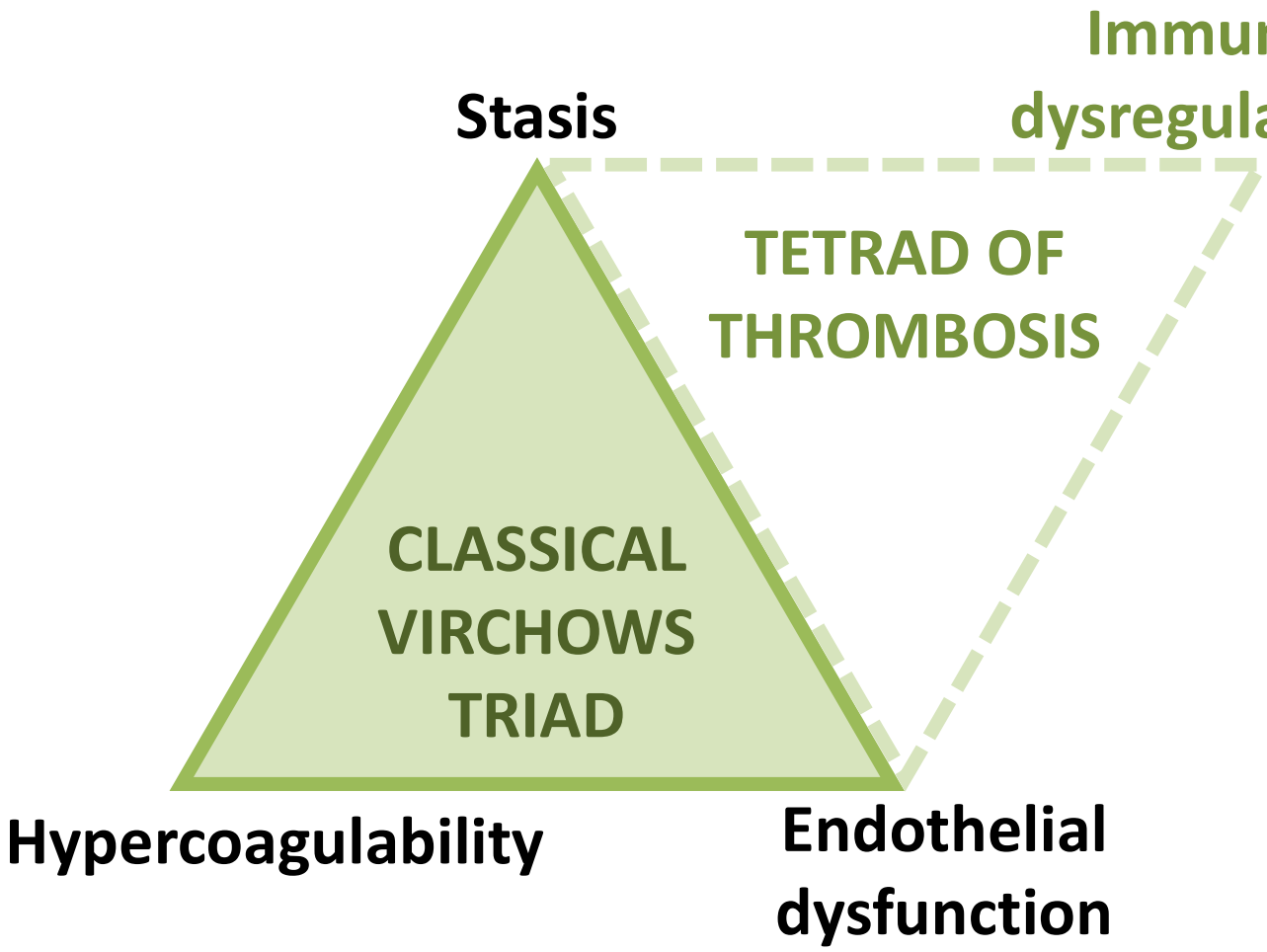
https://doi.org/10.1182/blood-2023-190934

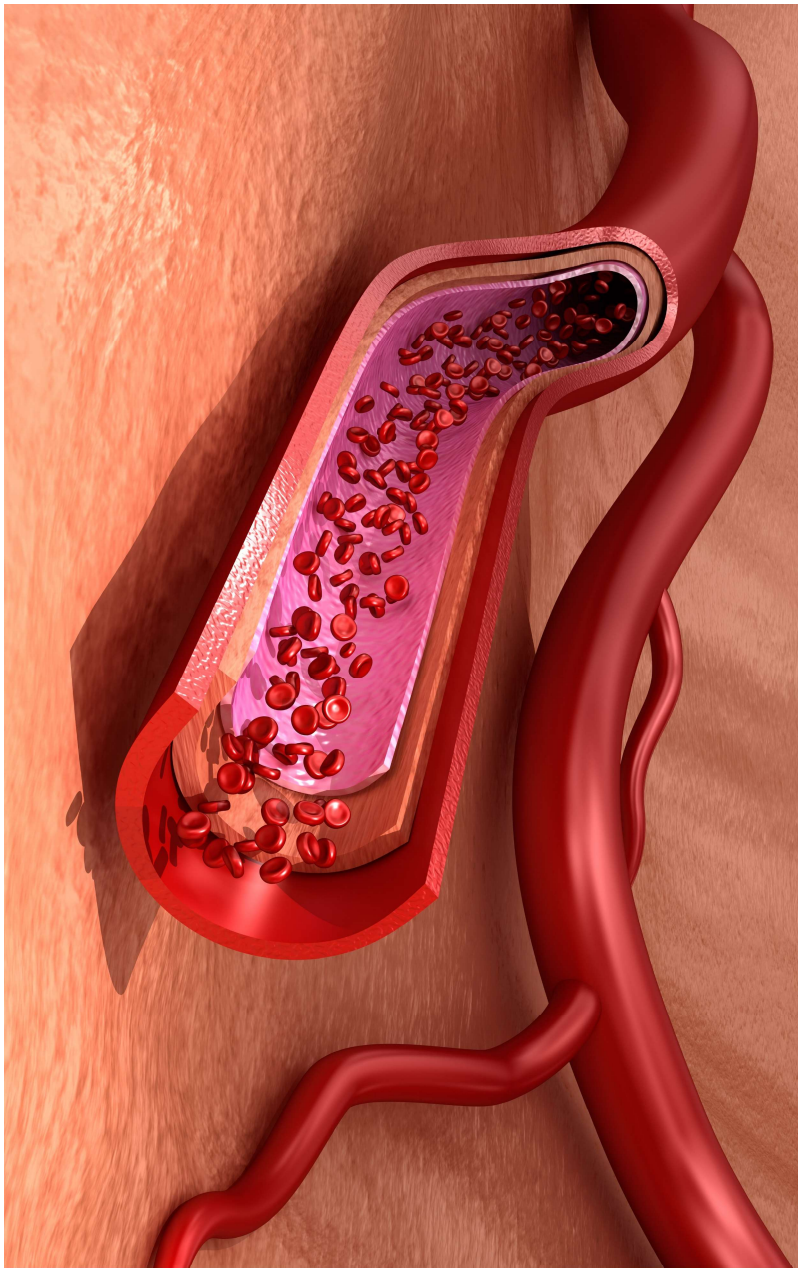
Conclusions: In this population based study, the incidence of thrombosis was 6-10 times greater in patients with IDA compared to no-IDA. Our data suggests that IDA is a risk factor for thrombosis in all patients. Prospective studies might be needed to confirm our findings. Finally, our data suggests that treatment of IDA might decrease the risk of thrombosis.


SYNDROME 1
SYNDROME 2
IRON DEFICIENCY
CASE 2
THROMBOSIS


Primary:
(Platelets
and Vessels)
Haemostasis
Secondary:
Coagulation
Factors
Tertiary:
Fibrinolysis

Thrombosis: Causes





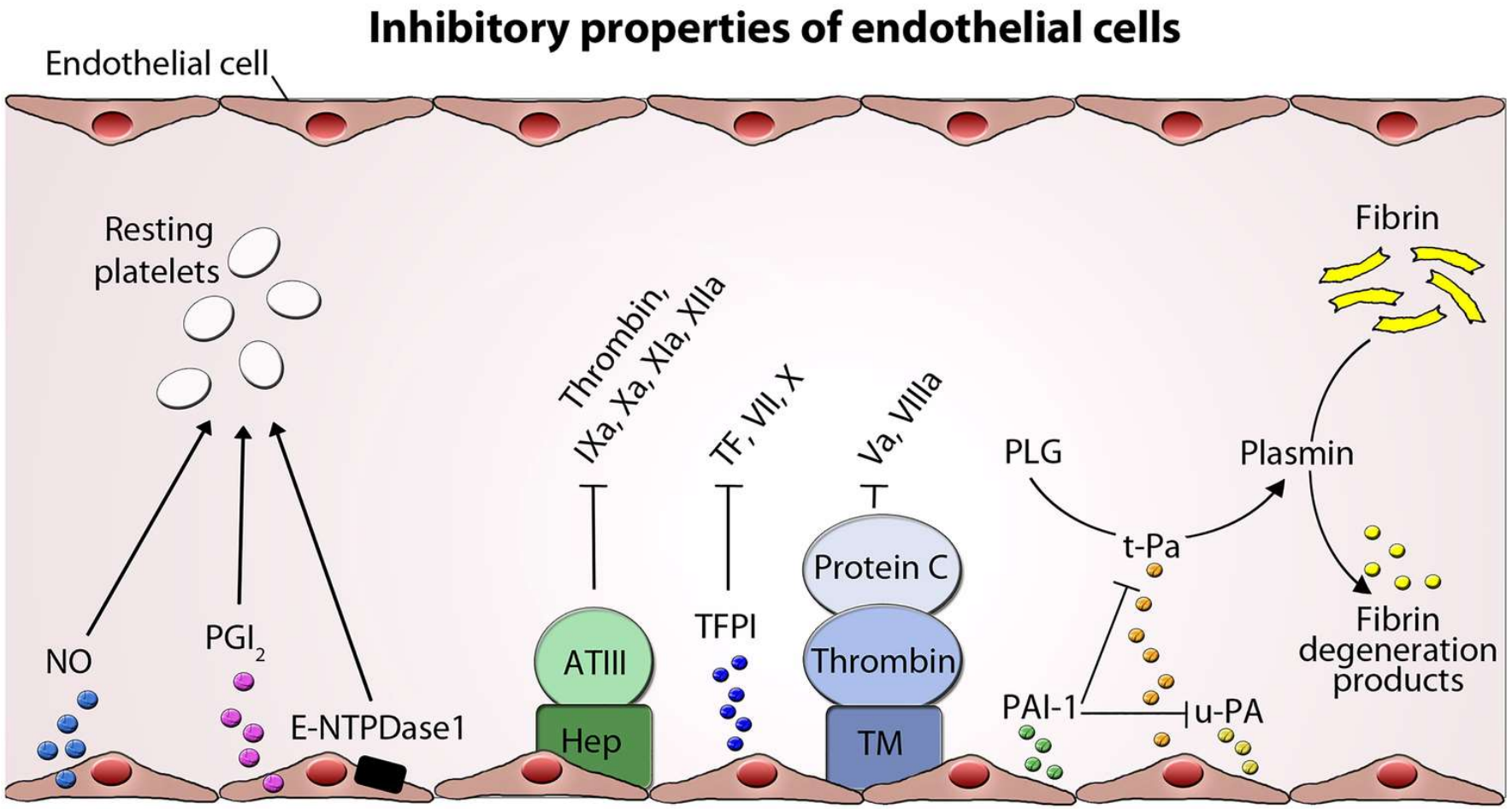
Paediatric Thrombosis

Home > Cell and Tissue Research > Article

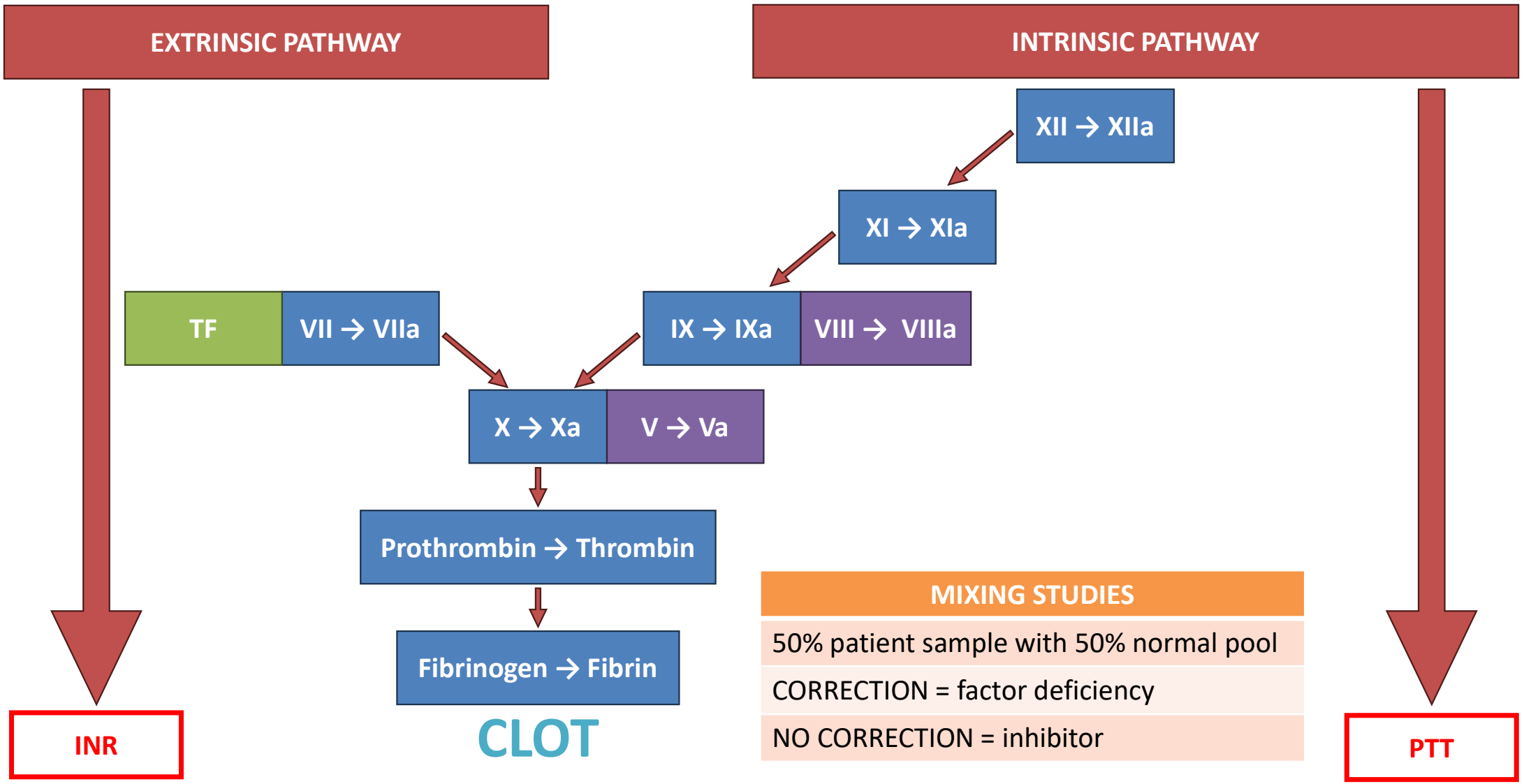
Endothelial cells and coagulation

Review | Open access | Published: 20 May 2021
Volume 387, pages 391–398, (2022) Cite this article

Katharina Neubauer & Barbara Zieger

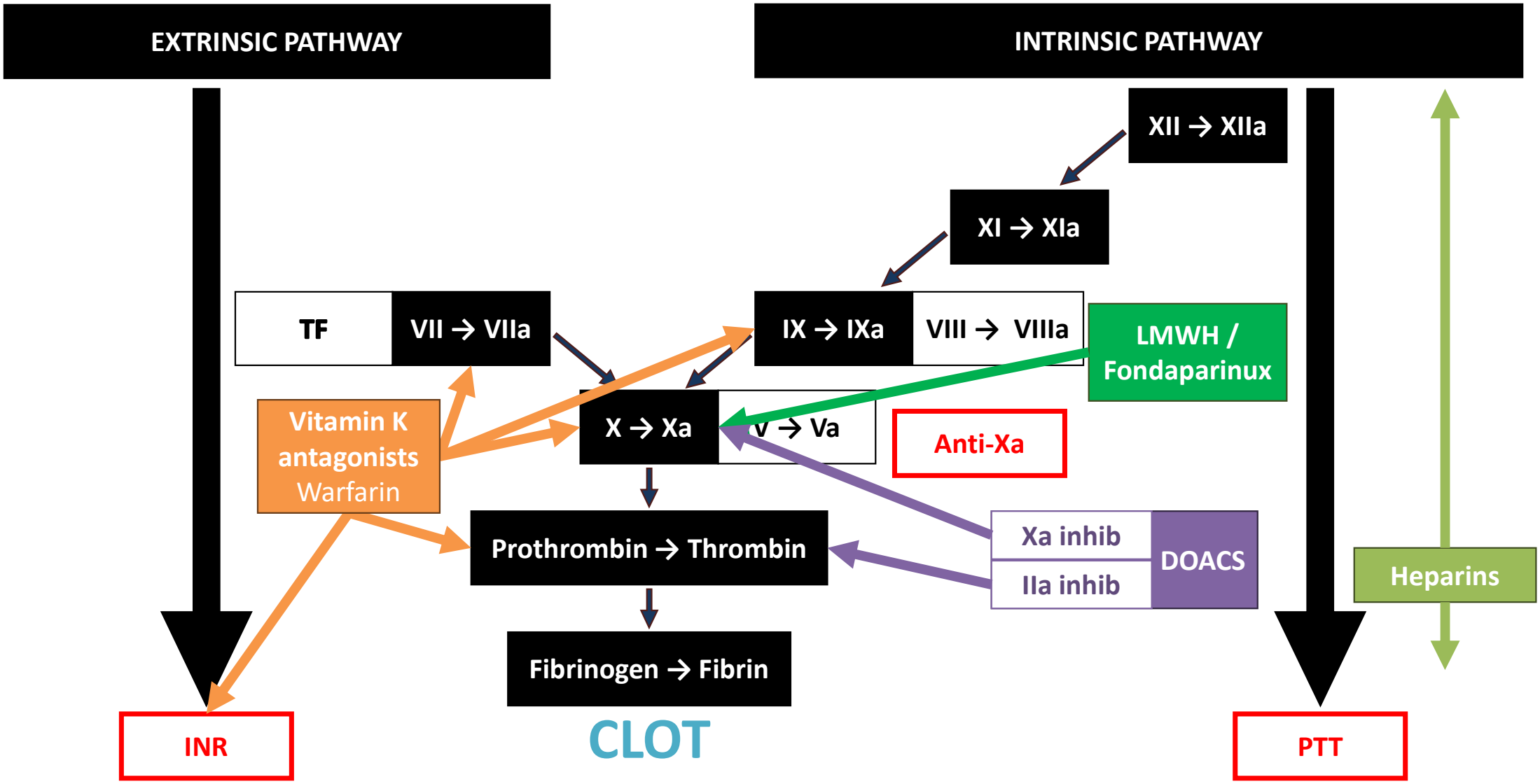


LABORATORY BASED COAGULATION CASCADE



MIXING STUDIES
50% patient sample with 50% normal pool
CORRECTION = factor deficiency
NO CORRECTION = inhibitor

ANTICOAGULANT DRUGS



Anti-Xa inhibitors

- Drugs:
  - **LMWH** (e.g. Enoxaparin) – subcutaneous injection
  - **Fondaparinux** – subcutaneous injection
  - **Rivaroxaban** – oral tablet
  - **Apixaban** – oral tablet
- Used in the **treatment** of **venous thromboembolism** and **stroke prevention** in non-valvular **atrial fibrillation**
- Used for **prophylaxis** for **venous thromboembolism** (i.e. prolonged hospital admission)
- **Effects** measured using **anti-Xa levels** – SPECIFIC for each drug
- Settings where **VKA** is still the drug of choice:
  - **Anti-phospholipid syndrome**
  - **Valvular Atrial Fibrillation**

HOW I TREAT | FEBRUARY 1, 2024

How I treat pediatric venous thromboembolism in the DOAC era

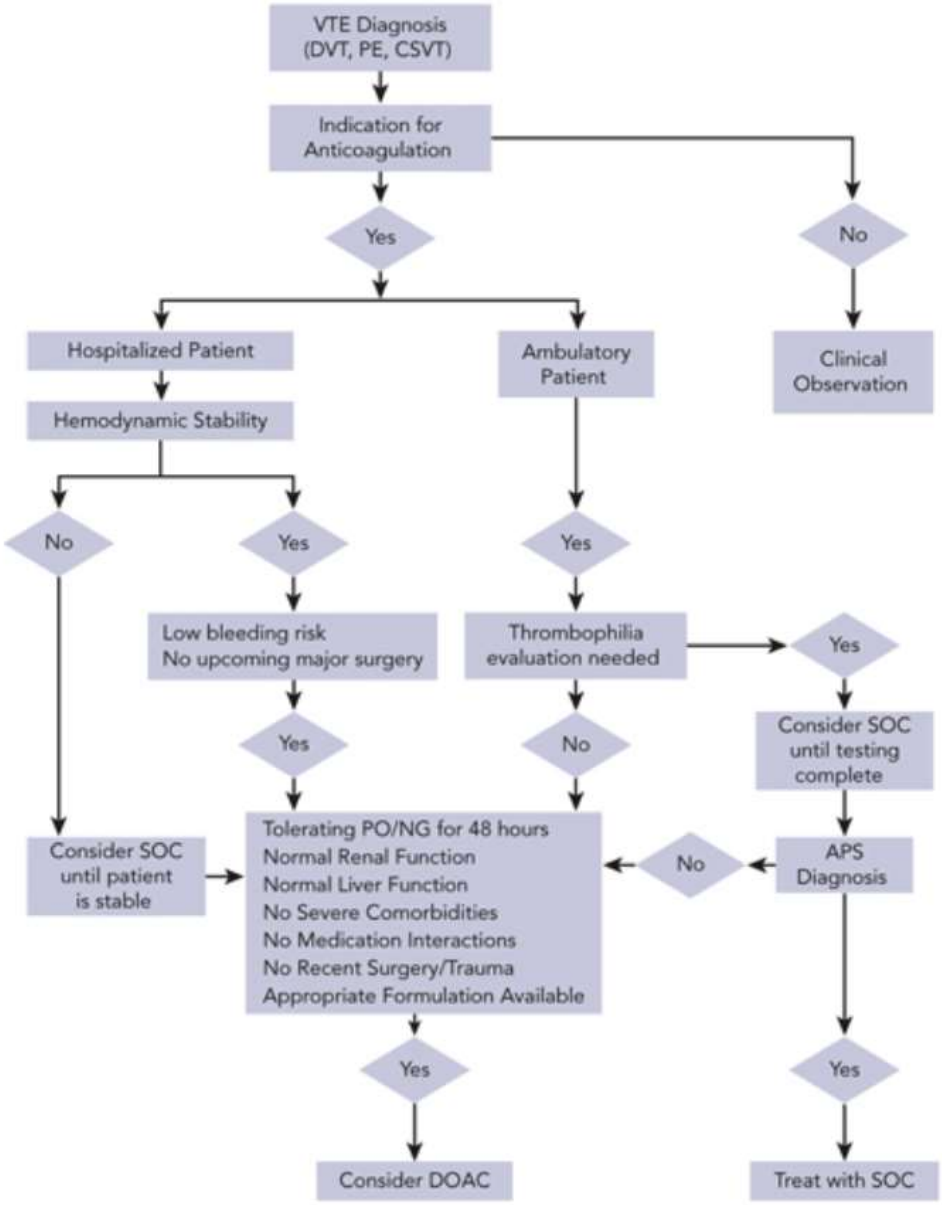
Clinical Trials & Observations

Rukhmi V. Bhat, Guy Young, Anjali A. Sharathkumar

Blood (2024) 143 (5): 389–403.

https://doi.org/10.1182/blood.2022018966

- Licenced overseas:
  - Rivaroxaban
  - Dabigatran



XARELTO® (rivaroxaban)
Medical Information

https://www.janssenscience.com/products/xarelto/medical-content/xarelto-dosing-and-administration-in-pediatric-patients

Recommended Dosage in Pediatric Patients Birth to Less than 18 Years for Treatment of and Reduction in Risk of Recurrent VTE[1,a,b]

Dosage Form	Body Weight	1 mg XARELTO = 1 mL Suspension			
		Dosage			Total Daily Dose[c]
		Once a Day[d]	2 Times a Day[d]	3 Times a Day[d]	
Oral suspension only	2.6 kg to 2.9 kg	-	-	0.8 mg	2.4 mg
	3 kg to 3.9 kg	-	-	0.9 mg	2.7 mg
	4 kg to 4.9 kg	-	-	1.4 mg	4.2 mg
	5 kg to 6.9 kg	-	-	1.6 mg	4.8 mg
	7 kg to 7.9 kg	-	-	1.8 mg	5.4 mg
	8 kg to 8.9 kg	-	-	2.4 mg	7.2 mg
	9 kg to 9.9 kg	-	-	2.8 mg	8.4 mg
	10 kg to 11.9 kg	-	-	3 mg	9 mg
	12 kg to 29.9 kg	-	5 mg	-	10 mg
Oral suspension or tablets	30 kg to 49.9 kg	15 mg	-	-	15 mg
	≥50 kg	20 mg	-	-	20 mg

[a]Initiate XARELTO treatment following at least 5 days of initial parenteral anticoagulation therapy.[b]Patients <6 months of age should meet the following criteria: at birth were at least 37 weeks of gestation, have had at least 10 days of oral feeding, and weigh ≥2.6 kg at the time of dosing.[c]All doses should be taken with feeding or with food since exposures match that of 20 mg daily dose in adults.[d]Once a day: approximately 24 hours apart; 2 times a day: approximately 12 hours apart; 3 times a day: approximately 8 hours apart.

Monitoring of DOACs?

JOURNAL ARTICLE

2021 European Heart Rhythm Association Practical Guide on the Use of Non-Vitamin K Antagonist Oral Anticoagulants in Patients with Atrial Fibrillation

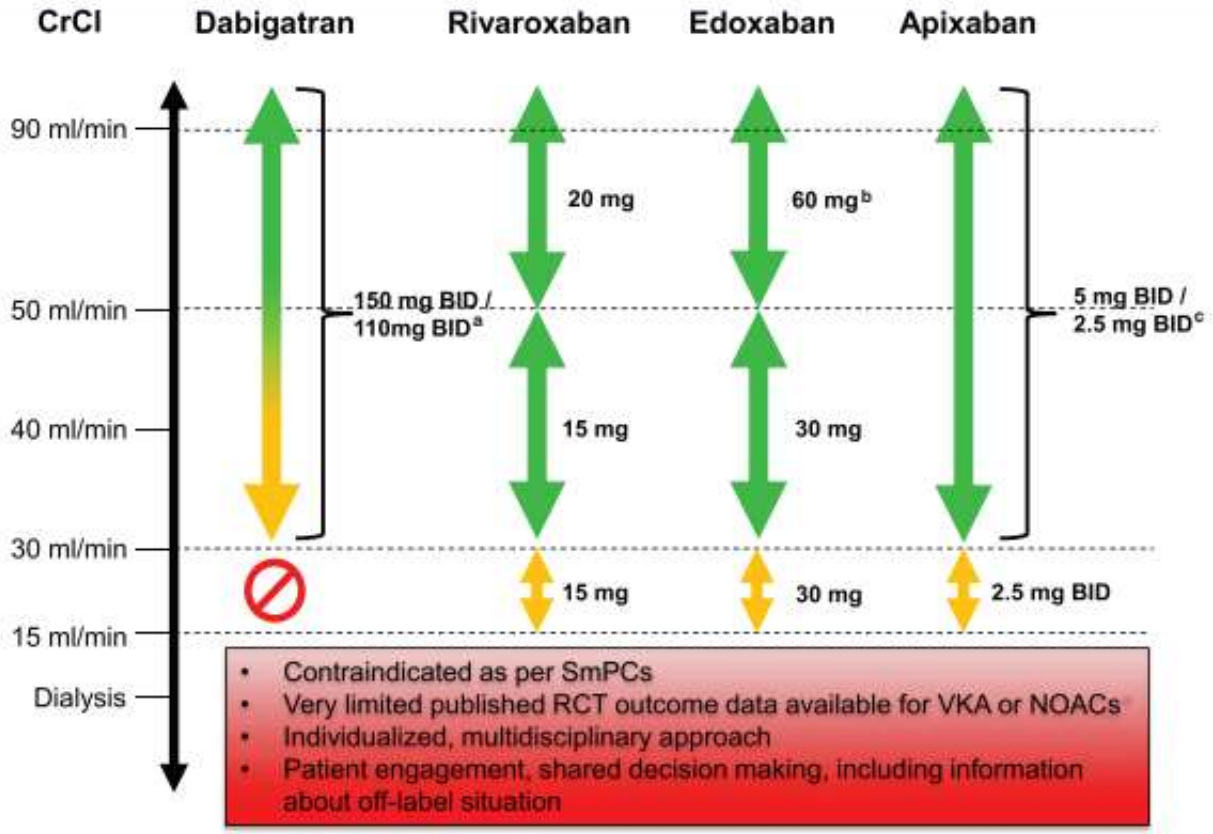
- Big selling point is the **lack of** need for **monitoring**
- However, **special populations require** monitoring such as paediatrics
- **Anti-Xa**
  - 6-monthly
  - Growth
  - Clinical change

Table 11 Plasma levels and coagulation assays in patients treated with NOACs for stroke prevention in AF

	Dabigatran[97,548,549]	Apixaban[550]	Edoxaban[98,100]	Rivaroxaban[519,520,551]
Expected plasma levels of NOACs in patients treated for AF*				
Peak levels	52–383	69–321	101–288	178–343
Trough levels	28–215	34–230	12–43	12–137
Expected impact of NOACs on routine coagulation tests[148,150,158,549,552–554]				
PT	(↑) peak (↑) if supratherapeutic[149]	(↑) at peak	↑ at therapeutic levels (if sensitive assay is used) Normal values do not exclude trough levels	↑ at therapeutic levels (if sensitive assay is used) Normal values do not exclude trough levels
aPTT	↑↑(↑) Normal values exclude supratherapeutic- but not therapeutic levels	(↑) at peak	(↑) at peak	(↑) at peak
ACT	↑(↑) Consistent with effect on aPTT	(↑)	(↑)	(↑)
TT	↑↑↑↑ Normal values exclude presence of Dabigatran	–	–	–

ACT, activated clotting time; AF, atrial fibrillation; aPTT, activated prothrombin time; NOAC, non-vitamin K antagonist oral anticoagulant; PT, prothrombin time.
*[ng/ml] 5–95% percentiles for FXa inhibitors and 10–90% percentiles (ng/ml) for Dabigatran).

DOACs and renal dys-function



JOURNAL ARTICLE

2021 European Heart Rhythm Association Practical Guide on the Use of Non-Vitamin K Antagonist Oral Anticoagulants in Patients with Atrial Fibrillation

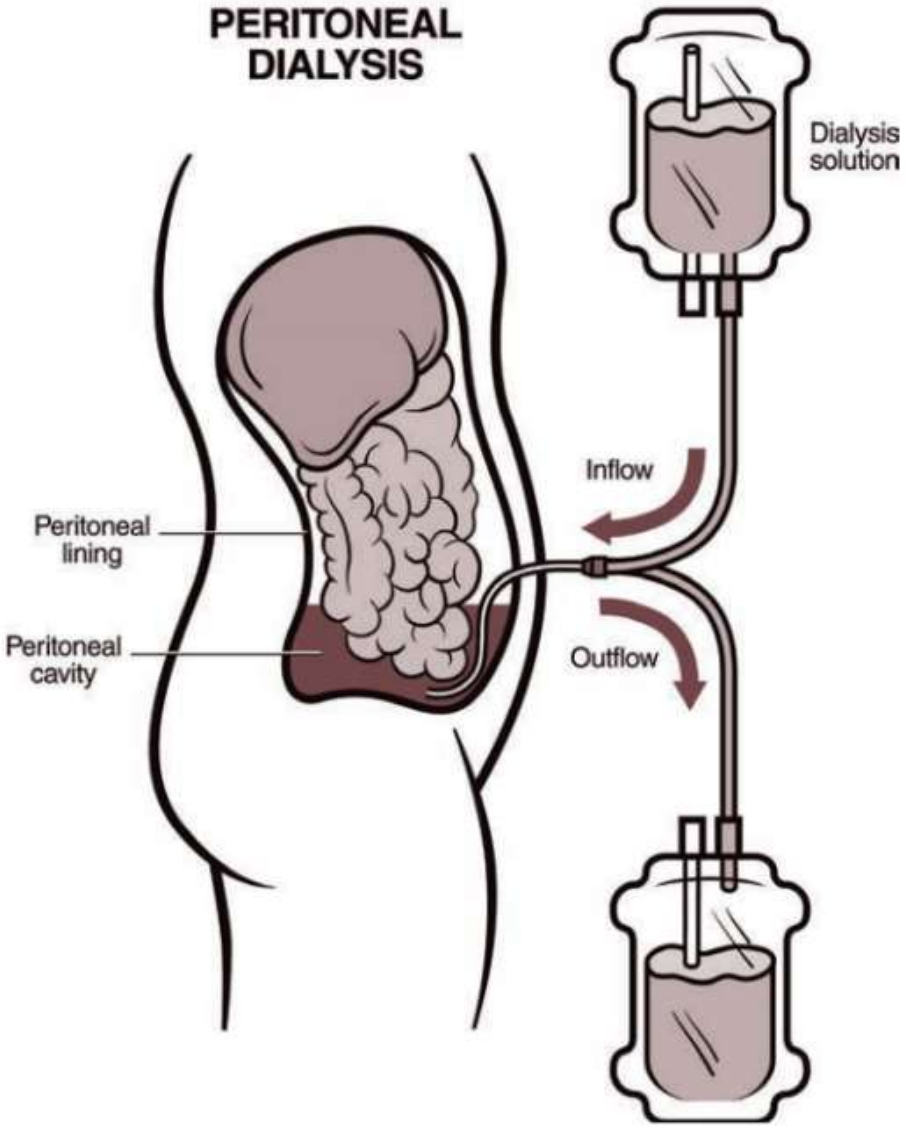
Figure 7 Use of NOACs according to renal function. [a]110 mg BID in patients at high risk of bleeding (per SmPc). [b]Other dose reduction criteria may apply (weight ≤ 60 kg, concomitant potent P-Gp inhibitor therapy). According to EMA, SmPc edoxaban should be used in 'high CrCl only after a careful evaluation of the individual thromboembolic and bleeding risk'.[473] See text for details. [c]2 × 2.5 mg only if at least two out of three fulfilled: age ≥80 years, body weight ≤60 kg, creatinine ≥1.5 mg/dL (133 µmol/L). Orange arrows indicate cautionary use; see text for details. BID, twice daily; CrCl, creatinine clearance; EMA, European Medicines Agency; NOAC, non-vitamin K antagonist oral anticoagulant; RCT, randomized clinical trial; VKA, vitamin K antagonist.

Bleeding with DOACs

- There is no available product to directly treat in South Africa
- **Andexanet alpfa**
  (R Hundereds of thousand a dose)
  - Recombinant Xa product
- Best option available – **Novoseven**
  - Recombinant VIIa
- **Prothrombin** complex
  - Haemosolvex

Case 3

- **10-year-old girl**
- Presented with **end-stage renal disease**
- Initially started on **haemodialysis** (femoral **Quinton line)**
- Then converted to **peritoneal dialysis** (line removed)
- 3-months later – represented with **DVT of the leg**



journal of thrombosis and haemostasis®

ORIGINAL ARTICLE | VOLUME 21, ISSUE 6, P1601-1609, JUNE 2023 Download Full Issue

Real-world use of apixaban for the treatment and prevention of thrombosis in children with cardiac disease

Christina VanderPluym • Paul Esteso • Ashish Ankola • ... Maria A. Cetatoiu • Kimberlee Gauvreau • Jesse J. Esch • Show all authors

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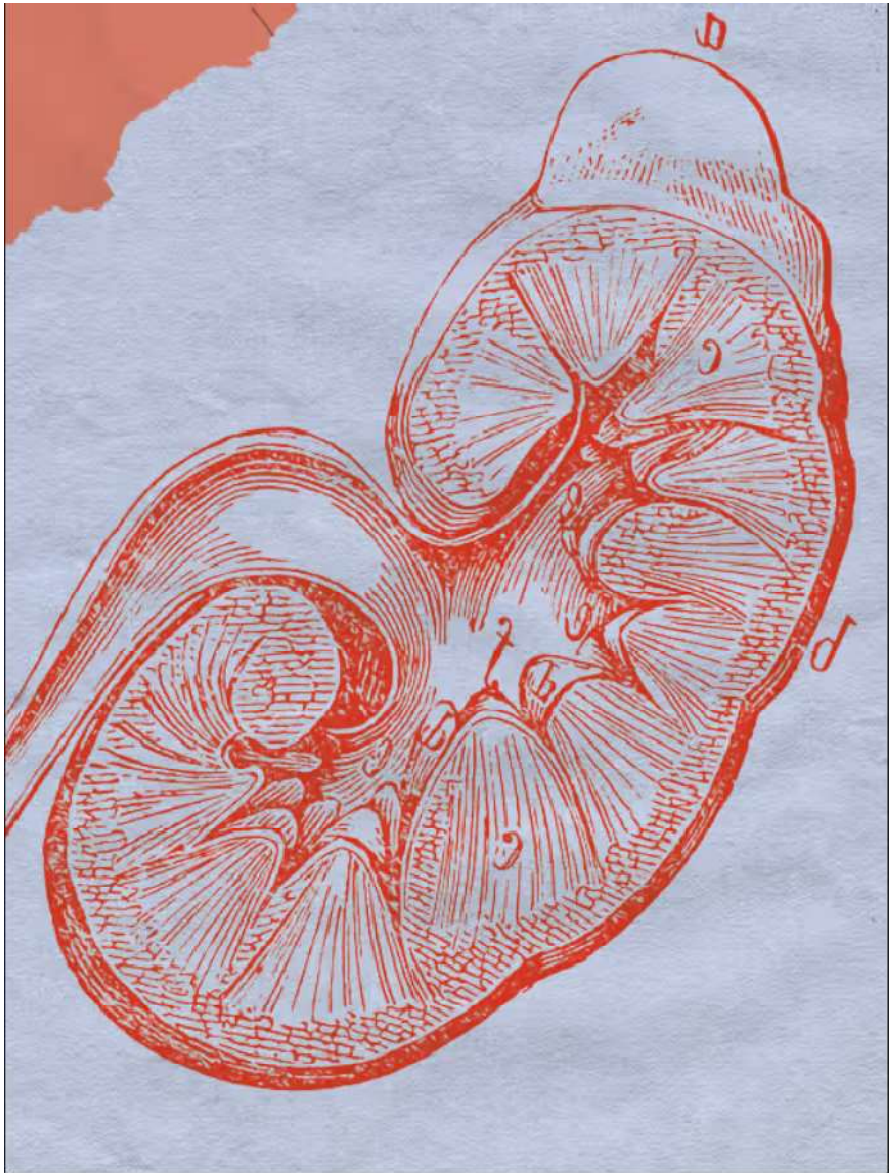
- Weight 4 to 9 kg: 0.625 mg twice daily
- Weight >9 to 18 kg: 1.25 mg twice daily
- Weight >18 to 29 kg: 2.5 mg twice daily
- Weight >29 to 35 kg: 3.75 mg twice daily
- Weight >35 kg: 5 mg twice daily, except in the following circumstances:
  - Treatment of acute pulmonary embolism (PE): 10 mg twice daily x 7 days, then 5 mg twice daily
  - Weight >100 kg and high-risk thrombosis indication: consider 7.5 mg twice daily starting dose

Progress

- Started on **Clexane at 1mg/kg/BD**
- **Struggled** with dosing
- **Decreased** to 0.5mg/kg/daily
- Trough levels were in therapeutic range
- **DOAC?**
- **Cannot use Rivaroxaban** due to renal clearance
- **Managed to get Apixaban** sponsored
- **Treated for 3 months** with Apixaban – good response



Summary

- Iron deficiency and thrombosis should be thought of as syndromes –
  - SEARCH for a cause
- Iron deficiency is COMMON
- Consider IV iron for certain cases, particularly severe cases
- Iron deficiency has complications
- DOACs are good drugs to consider for treating thrombosis