Iron Management in CKD/ESKD

A review on KDIGO 2025 CLINICAL PRACTICE GUIDELINE

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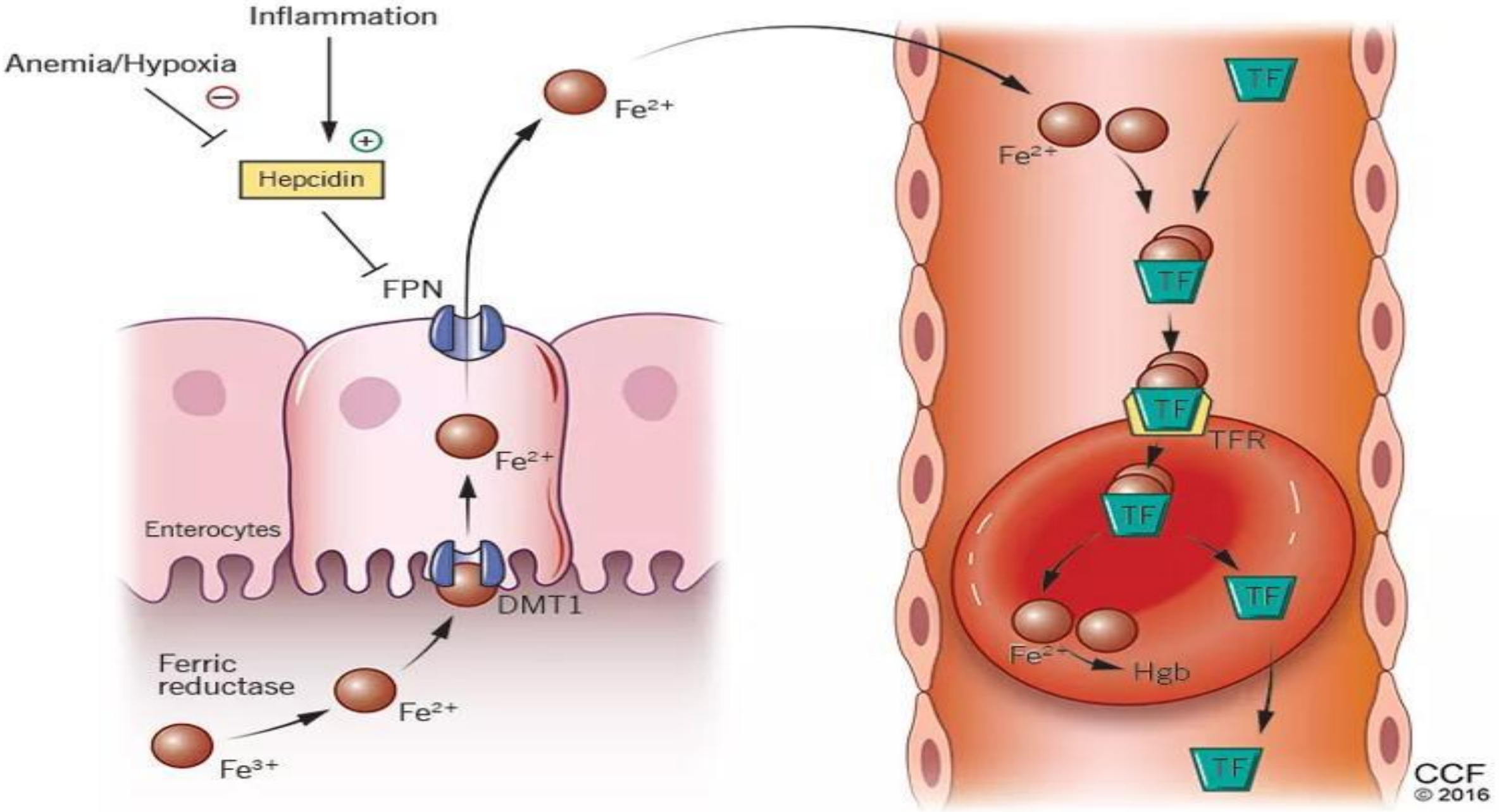
Inflammation
Anemia/Hypoxia
Hepcidin
FPN
Fe2+
Enterocytes
Fe2+
DMT1
Ferric reductase
Fe2+
Fe3+
Fe2+
TF
TF
TF
TFR
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Fe2+
Hgb
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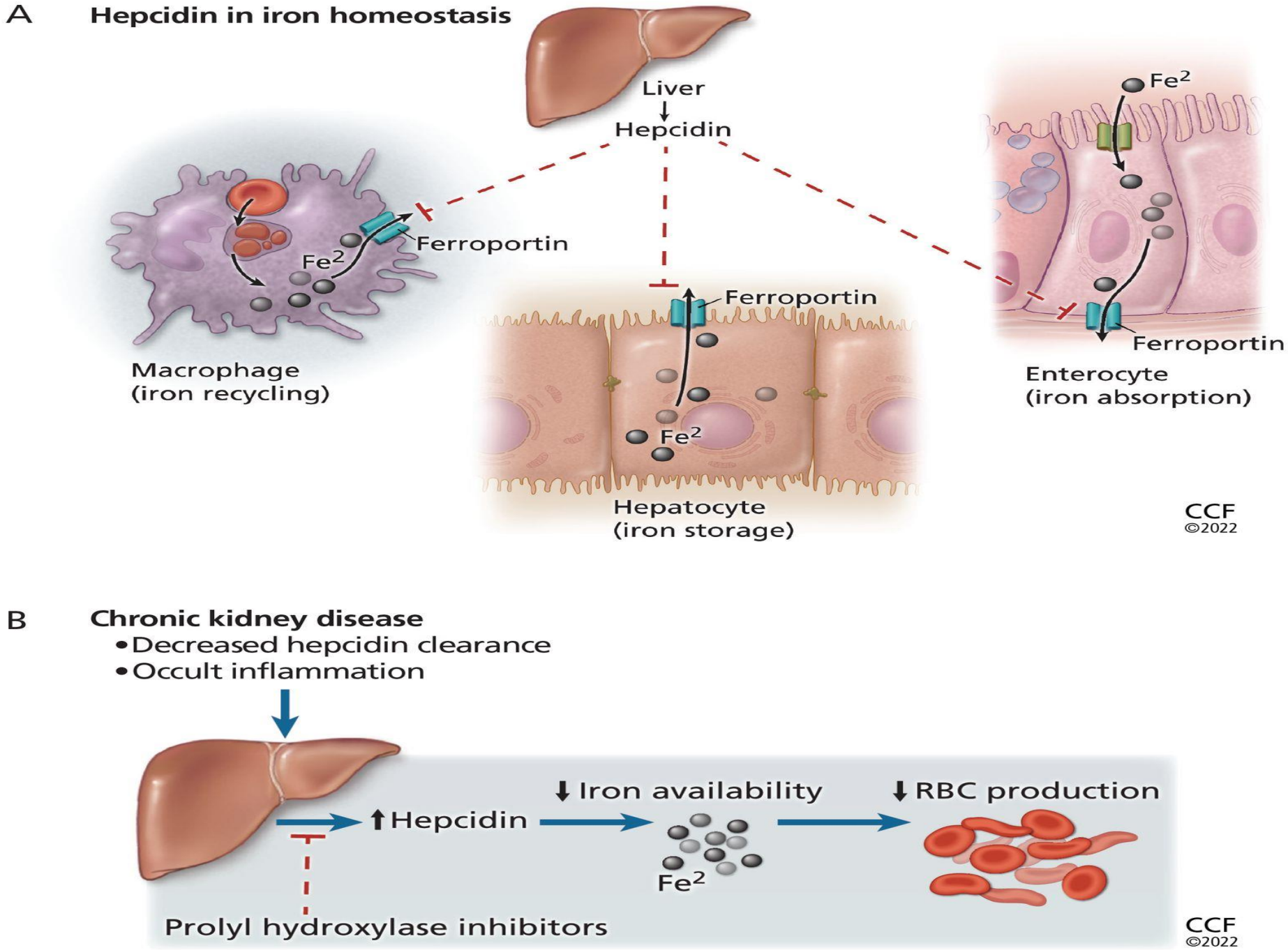
A
Hepcidin in iron homeostasis
Liver
Hepcidin
Fe2
Ferroportin
Macrophage
(iron recycling)
Ferroportin
Fe2
Hepatocyte
(iron storage)
Fe2
Ferroportin
Enterocyte
(iron absorption)
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B
Chronic kidney disease
• Decreased hepcidin clearance
• Occult inflammation
Hepcidin
Iron availability
RBC production
Fe2
Prolyl hydroxylase inhibitors
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KDIGO 2025 CLINICAL PRACTICE GUIDELINE FOR ANEMIA IN CHRONIC KIDNEY DISEASE (CKD)

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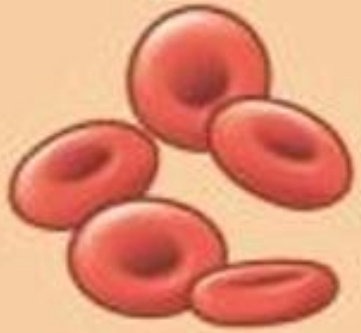
Definitions

Systemic iron deficiency

↓ferritin, ↓TSAT

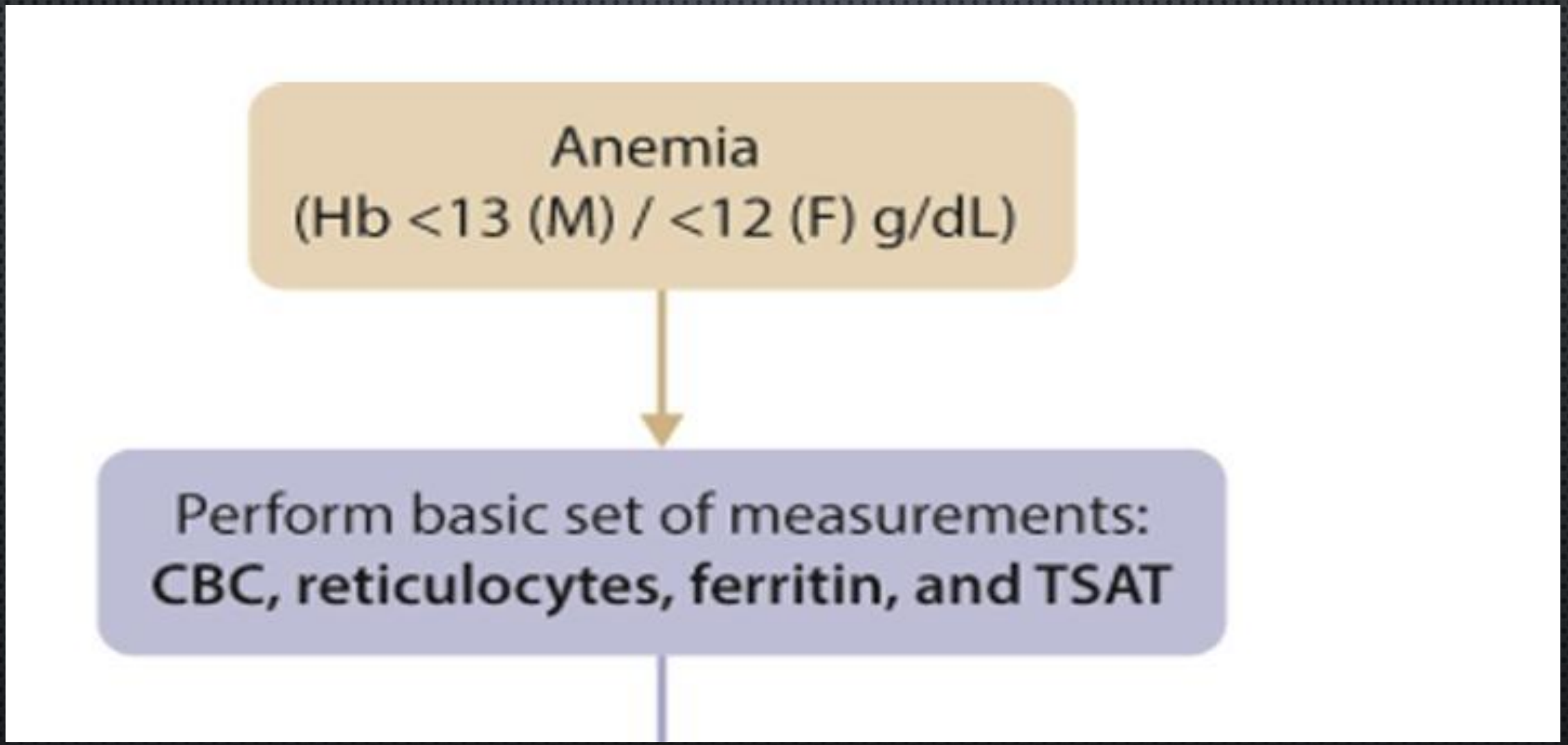
(e.g., ferritin <100 ng/l (µg/l) in CKD G1–G5, <200 ng/l (µg/l) in CKD G5HD, TSAT<20%)

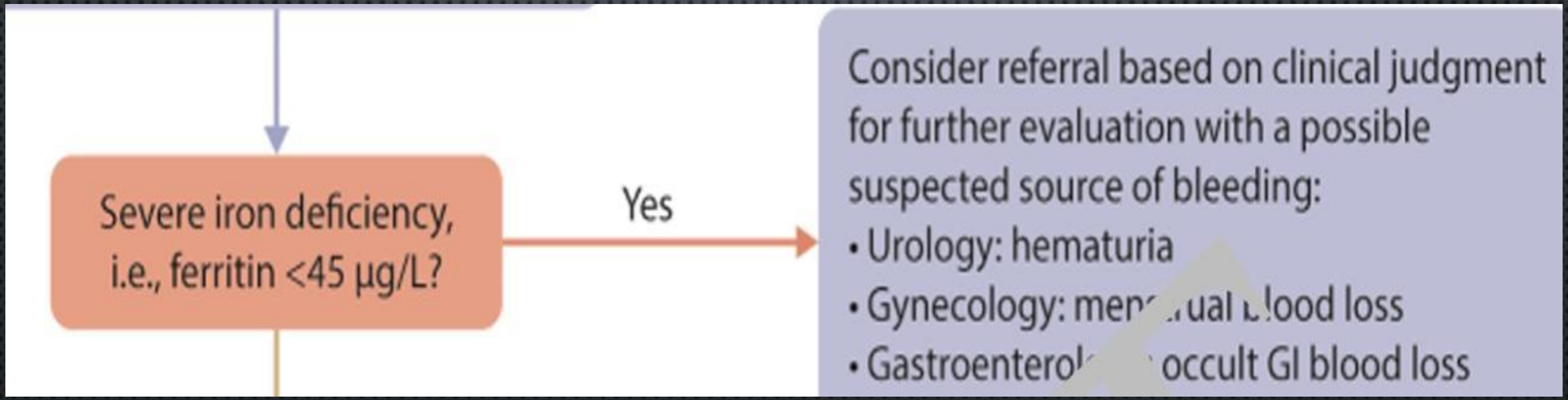


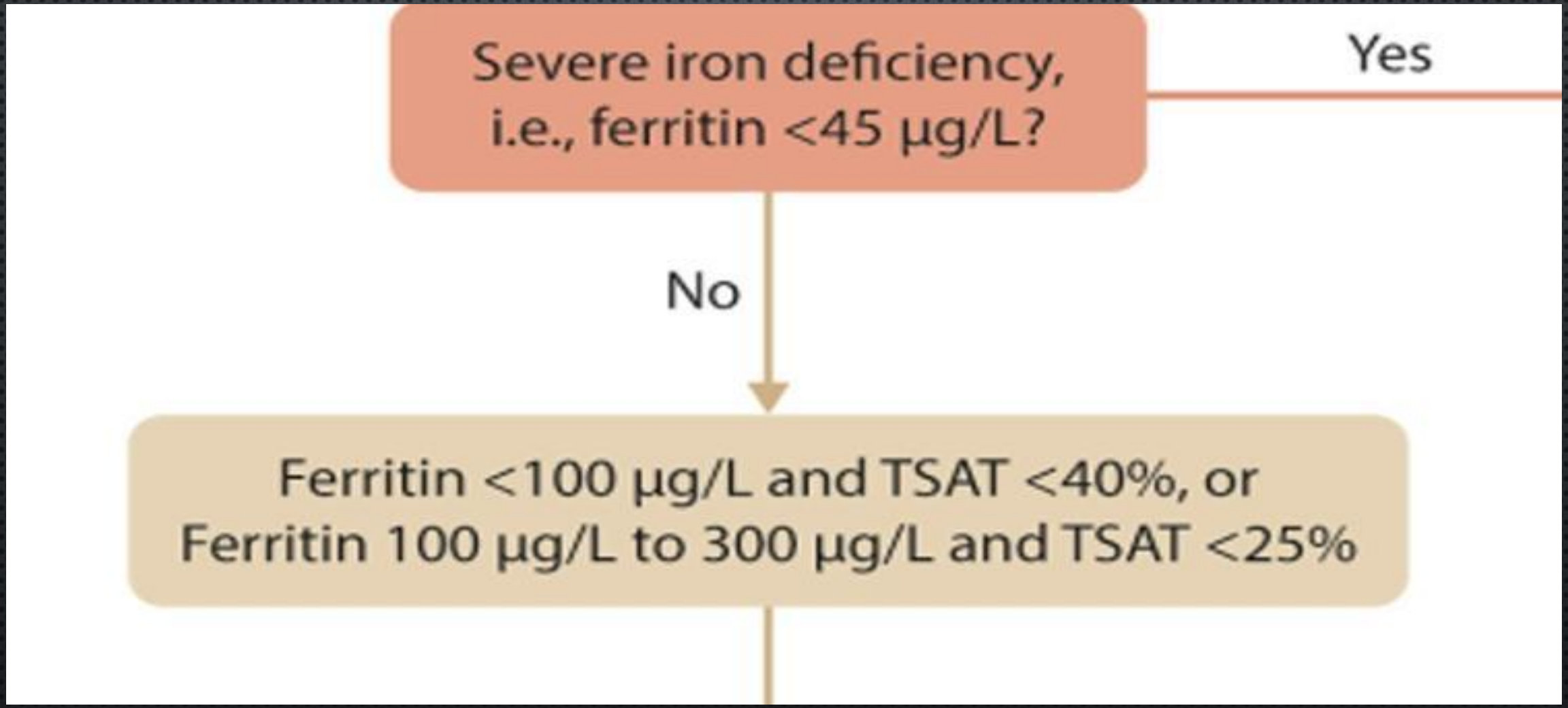
Iron-restricted erythropoiesis

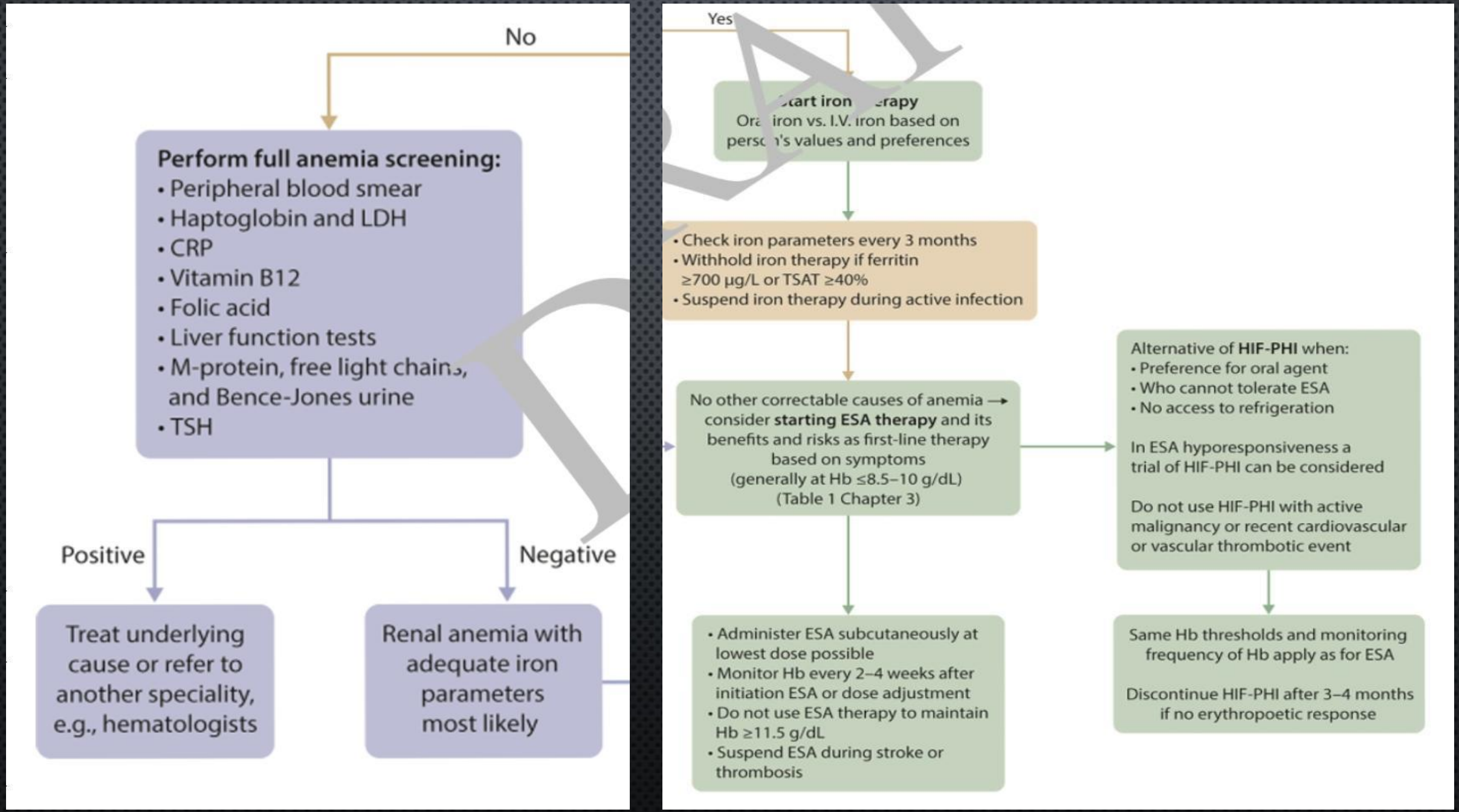
↑ferritin, ↓TSAT

(e.g., ferritin >100–200 ng/l (µg/l), TSAT<20%)


Anemia
(Hb <13 (M) / <12 (F) g/dL)
Perform basic set of measurements:
CBC, reticulocytes, ferritin, and TSAT


Severe iron deficiency, i.e., ferritin <45 µg/L?
Yes
Consider referral based on clinical judgment for further evaluation with a possible suspected source of bleeding:
• Urology: hematuria
• Gynecology: menstrual blood loss
• Gastroenterology: occult GI blood loss


Severe iron deficiency, i.e., ferritin <45 µg/L?
Yes
No
Ferritin <100 µg/L and TSAT <40%, or
Ferritin 100 µg/L to 300 µg/L and TSAT <25%


No
Perform full anemia screening:
• Peripheral blood smear
• Haptoglobin and LDH
• CRP
• Vitamin B12
• Folic acid
• Liver function tests
• M-protein, free light chains, and Bence-Jones urine
• TSH
Positive
Negative
Treat underlying cause or refer to another speciality, e.g., hematologists
Renal anemia with adequate iron parameters most likely
Yes
Start iron therapy
Oral iron vs. I.V. iron based on person's values and preferences
• Check iron parameters every 3 months
• Withhold iron therapy if ferritin ≥700 µg/L or TSAT ≥40%
• Suspend iron therapy during active infection
No other correctable causes of anemia → consider starting ESA therapy and its benefits and risks as first-line therapy based on symptoms (generally at Hb ≤8.5–10 g/dL) (Table 1 Chapter 3)
Alternative of HIF-PHI when:
• Preference for oral agent
• Who cannot tolerate ESA
• No access to refrigeration
In ESA hyporesponsiveness a trial of HIF-PHI can be considered
Do not use HIF-PHI with active malignancy or recent cardiovascular or vascular thrombotic event
• Administer ESA subcutaneously at lowest dose possible
• Monitor Hb every 2–4 weeks after initiation ESA or dose adjustment
• Do not use ESA therapy to maintain Hb ≥11.5 g/dL
• Suspend ESA during stroke or thrombosis
Same Hb thresholds and monitoring frequency of Hb apply as for ESA
Discontinue HIF-PHI after 3–4 months if no erythropoetic response

Practice Point 1.2.1: In people with CKD, test for anemia at referral, regularly during follow-up, and when anemia is suspected based on symptoms (Figure 5). Test for anemia with the following set: complete blood count (CBC), reticulocytes, ferritin, transferrin saturation (TSAT) (Figure 6).

Population	Frequency (at least)
CKD G3	Annually
CKD G4	Twice a year
CKD G5 or G5D	Every 3 months

Recommendation 2.1: In people with anemia and CKD treated with hemodialysis (CKD G5HD), we suggest initiating iron therapy if ferritin ≤500 ng/ml (≤500 µg/l) and TSAT ≤30% (*2D*).

Recommendation 2.2: In people with anemia and CKD G5HD in whom iron therapy is being initiated, we suggest using intravenous iron rather than oral iron (*2D*).

Practice Point 2.1: In people with CKD G5HD in whom iron therapy is being initiated, administer intravenous iron using a proactive approach to maintain stable iron status.

Recommendation 2.3: In people with anemia and CKD not receiving dialysis or treated with peritoneal dialysis (CKD G5PD), we suggest initiating iron if (*2D*):

- **ferritin <100 ng/ml (<100 µg/l) and transferrin saturation (TSAT) <40%, or**
- **ferritin ≥100 ng/ml (≥100 µg/l) and <300 ng/ml (<300 µg/l), and TSAT <25%.**

Recommendation 2.4: In people with anemia and CKD not receiving hemodialysis in whom iron is initiated, we suggest using either oral or intravenous iron based on the person's values and preferences (*2D*).

Practice Point 2.2: In people with CKD treated with iron, it is reasonable to withhold iron if ferritin ≥700 ng/ml (≥700 µg/l) or TSAT ≥40%.

Practice Point 2.3: In people with CKD treated with oral iron, the choice between different formulations and dosing schedules is guided by cost, individual patient preference, tolerability, and efficacy.

Practice Point 2.4: In people with CKD treated with intravenous iron, the choice between different formulations is guided by cost, individual preference, and recommended dosing schedules.

Practice Point 2.5: In people with CKD treated with iron, it is reasonable to test hemoglobin, ferritin, and TSAT every 3 months for those not receiving dialysis or CKD G5PD and every month for those with CKD G5HD.

Practice Point 2.6: In people with CKD treated with iron, certain circumstances may warrant more frequent iron testing as shown in Table 5.

Table 5 | Circumstances warranting more frequent iron testing

- Initiation of or increase in dose of ESAs or HIF-PHIs
- Episodes of known blood loss
- Recent hospitalization
- Important increase in ferritin or TSAT or overshooting target limit

ESA, erythropoietin-stimulating agents, HIF-PHI, hypoxia-inducible factor-prolyl hydroxylase inhibitors; TSAT, transferrin saturation

Practice Point 2.7: Switch from oral to intravenous iron if there is an insufficient effect of an optimal oral regimen after 1 to 3 months.

Practice Point 2.8: In people with CKD treated with iron, consider temporarily suspending iron therapy during systemic infection.

Practice Point 2.9: In people with CKD treated with intravenous iron, considerations pertaining to hypersensitivity reactions to intravenous iron include the following:

- **Intravenous iron should only be administered if there is capability to manage acute hypersensitivity and hypotensive reactions,**
- **Intravenous doses of iron should not exceed the maximum dose/administration for the compound (Table 4),**

- **Pretreatment with corticosteroids or antihistamines is not routinely necessary (type 1 histamine [H1]-channel blockers), and**
- **Test doses of intravenous iron are not usually required, because lack of response does not predict the risk of hypersensitivity.**

Table 1. Oral Therapies for Iron Repletion in CKD

Characteristic	Ferrous Sulfate	Ferrous Fumarate	Ferrous Gluconate	Ferric Citrate	Ferric Maltol	Sucrosomial Iron
Side effect						
Dyspepsia	++	++	++	+	+	+
Constipation	+	+	+	+	+	+
Available over the counter	Yes	Yes	Yes	No	No	Yes
Phosphate binder	No	No	No	Yes	No	No
Approximate minimum annual cost, USD	$10.80[a]	$237.60[a]	$37.60[a]	$8,294.40[b]	$7,200.00[b]	$720.00[b]

Based on information from Lexicomp.[63] Abbreviation: CKD, chronic kidney disease.
[a]Based on daily iron repletion dose.
[b]Based on recommended dose.

Table 2. Newer (Third-Generation) Intravenous Iron Formulations

Agent	Molecular Weight, Da	Maximum Weekly Dose	Minimum Infusion Time, min	[Fe], mg/mL	Black Box Warning	Severe Hypersensitivity	Hypophosphatemia
Ferumoxytol	731,000	510 mg	15	30	Yes	0.2%	0.4%
Ferric carboxymaltose	150,000	750 or 1,000 mg	15	50	No	1.6%	~40%
Ferric derisomaltose	150,000	1,000 mg or 20 mg/kg if <50 kg	15	100	No	0.3%	3.5%

No test dose is required for any of the 3 agents. Table based on information from Glaspy et al,[56] Balakrishnan et al,[64] and Lexicomp.[63]

Table 2 | Factors to consider when choosing between oral and intravenous iron

Oral iron	Intravenous iron
Slower increase in Hb, ferritin, TSAT	More rapid increase in Hb, ferritin, TSAT Delayed and reduced ESA use Possibly faster increase in QoL
Side effects • More frequent • Less severe Constipation and other gastrointestinal symptoms are frequent. If the patient suffers from these symptoms at baseline, then i.v. iron may be preferred	Side effects • Less frequent • More severe Hypotension and immediate hypersensitivity reactions are uncommon but can occur with any i.v. iron agent, especially in people with a history of drug allergies
Less expensive More convenient	More expensive Requires trained healthcare providers
Accessibility • Appealing to people who want to limit hospital visits. • Addresses mobility inequality for people with CKD	
Preserve veins for hemodialysis vascular access	Consider possible effect on preserving veins for hemodialysis vascular access
Inconsistent adherence	Assured administration
Avoid if intestinal absorption impaired	

Table 3 | Oral iron formulations, treatment regimen, and factors influencing the choice between different formulations

	Dose per tablet	Elemental iron per tablet	Starting dose	Considerations
Ferric citrate	1 g	210 mg	CKD not receiving dialysis: 1 tablet, 3 times daily	In CKD not receiving dialysis, it will help with phosphate-binding as a secondary effect
			CKD G5D: 2 tablets, 3 times daily	In CKD G5D, indicated as a phosphate binder with iron supplementation being an additional effect
Ferric maltol	30 mg	30 mg	1 tablet, 2 times daily	Taken between meals
Ferrous sulphate	325 mg	65 mg	1 tablet, 3 times daily	Taken between meals
Ferrous fumarate	325 mg	106 mg	1 tablet, 2 times daily	Gastrointestinal side effects, dark green stools
Ferrous gluconate	300 mg	35 mg	4–6 tablets, daily	Less gastrointestinal side effects and better bioavailability
Liposomal iron	30 mg	30 mg	1 tablet, daily	Less gastrointestinal side effects and better bioavailability
Heme iron polypeptide	12 mg	12 mg	1 tablet, 3–4 times daily	Less gastrointestinal side effects and better bioavailability

Table 4 | Intravenous iron formulations and treatment regimen

	Elemental iron concentration	Maximum single dose	Minimum infusion time for maximum dose	Minimum injection time	Considerations
Low-molecular weight iron dextran	50 mg/ml	20 mg/kg	15 min for 50 mg, 100 mg/min 4–6 hours	>60 min	Hypersensitivity lower than high-molecular weight dextran
Iron sucrose	20 mg/ml	200 mg	15 min	5 min	For people with CKD G1–G5 not receiving HD, requires multiple patient visits as 1000 mg cannot be given at a single sitting. (5 doses of 200 mg over 5 weeks)
Ferric gluconate	12.5 mg/ml	125 mg	60 min	10 min	Ferric gluconate in sucrose complex (250 mg 4 doses weekly)
Ferric carboxymaltose	50 mg/ml	750 mg (FDA) 1000 mg (EMA)	15 min	7.5 min (FDA) 15 min (EMA)	Full dose can be given in 1 or 2 sittings (750 mg 2 doses 1 week apart) May cause hypophosphatemia, especially in people with early CKD and kidney transplant recipients
Ferric derisomaltose / iron isomaltoside	100 mg/ml	1000 mg (FDA) 20 mg/kg (EMA)	20 min	250 mg/min (max. 500 mg) (EMA)	Full dose can be given in single sitting
Ferumoxytol	30 mg/ml	510 mg	15 min	15 min	Full dose can be given in single sitting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