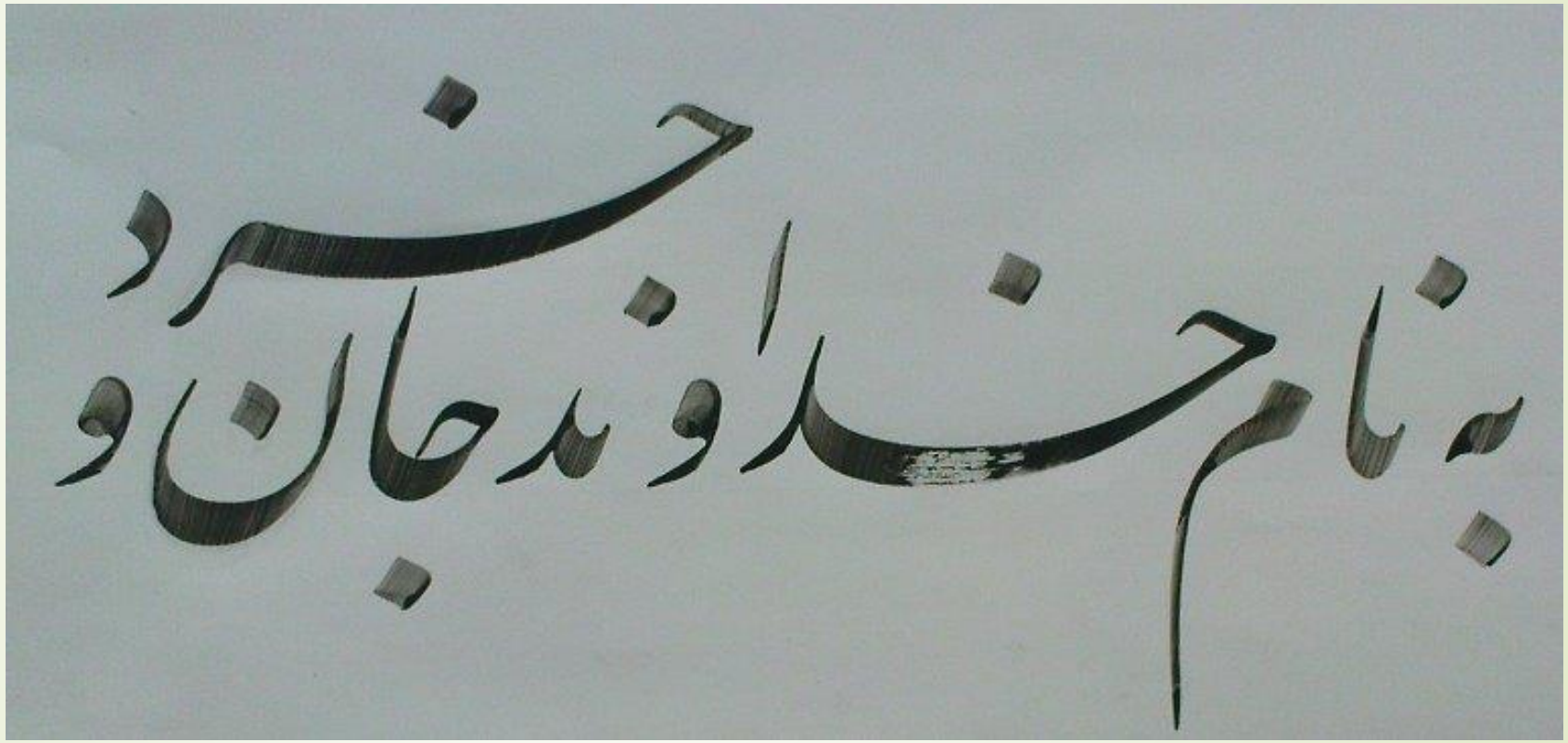

به نام خداوند جان و خرد

Refractory anemia in ESRD patient

Dr M.Zaare

Nephrologist

Assistant professor at Tabriz university of medical science

Definition of ESA hyporesponse

AJN
American Journal
of Nephrology

In-Depth Topic Review

Am J Nephrol 2021;52:450–466
DOI: 10.1159/000516901

Received: March 1, 2021
Accepted: April 26, 2021
Published online: July 19, 2021

Managing Anemia across the Stages of Kidney Disease in Those Hyporesponsive to Erythropoiesis-Stimulating Agents

Matthew R. Weir

Division of Nephrology, University of Maryland Medical Center, Baltimore, MD, USA

Table 1. Definitions of ESA hyporesponse

Source	Definition of ESA hyporesponse
NKF-KDOQI [21]	450 units/kg per week i.v. EPO or 300 units/kg per week s.c. EPO
KDIGO [11]	No increase in Hb concentration from baseline after the first month of ESA treatment on appropriate weight-based dosing
NICE best practices/The Renal Association [18]	Failure to reach the target Hb level despite s.c. epoetin dose >300 IU/kg/week (450 IU/kg/week i.v. epoetin) or darbepoetin dose >1.5 μg/kg/week
ERI [16]/EHRI [22]	Weight-adjusted weekly ESA dose divided by the Hb value >12.7–20.0 IU weekly/kg/Hb, g/dL

NKF-KDOQI, National Kidney Foundation-Kidney Disease Outcomes Quality Initiative; KDIGO, Kidney Disease Improving Global Outcomes; EHRI, ESA hyporesponsiveness index; EPO, erythropoietin; ESA, erythropoiesis-stimulating agent; Hb, hemoglobin; ERI, ESA response index.

Kidney Diseases

Review Article

Kidney Dis 2022;8:103–114
DOI: 10.1159/000521162

Received: October 13, 2021
Accepted: November 22, 2021
Published online: January 14, 2022

Erythropoietin-Stimulating Agent Hyporesponsiveness in Patients Living with Chronic Kidney Disease

Henry H.L. Wu[a, b] Rajkumar Chinnadurai[b, c]

[a]Department of Renal Medicine, Lancashire Teaching Hospitals NHS Foundation Trust, Preston, UK; [b]Faculty of Biology, Medicine and Health, The University of Manchester, Manchester, UK; [c]Department of Renal Medicine, Northern Care Alliance NHS Foundation Trust, Salford, UK

Table 1. Selected definitions of ESA hyporesponsiveness in patients living with CKD

Guideline	Definition of ESA resistance
ERBG 2004 [22]	Increase in erythropoietin dose ≥25% to maintain the same HgB level or < 1 mg/dL gain in HgB after 2–4 weeks
KDIGO 2012 [23]	Initial ESA resistance: No increase in Hgb concentration from baseline after the first month of ESA treatment on appropriate weight-based dosing
	Subsequent ESA resistance: If after treatment with stable doses of ESA, they require 2 increases in ESA doses up to 50% beyond the dose at which they had been stable in an effort to maintain a stable HgB concentration
KDOQI/NKF guidelines on anemia in CKD [24]	As per KDIGO 2012 (refer to KDOQI US commentary on KDIGO 2012 Clinical Practice Guideline for Anemia in CKD)
KHA-CARI 2013 [25]	As per KDIGO 2012
NICE 2021 [26] and BRA 2017 [27]	An aspirational HgB range is not achieved despite treatment with 300 IU/kg/week or more of subcutaneous epoetin or 450 IU/kg/week or more of intravenous epoetin or 1.5 µg/kg/week of darbepoetin Or There is a continued need for the administration of high doses of ESAs to maintain the aspirational HgB range

ERBG, European Best Practice Guidelines; KDOQI, Kidney Disease Outcomes Quality Initiative; NKF, National Kidney Foundation; KDIGO, Kidney Disease Improving Global Outcome; KHA-CARI, Kidney Health Australia-Caring for Australasians with Renal Impairment; NICE, National Institute of Clinical Excellence; BRA, British Renal Association; HgB, hemoglobin; CKD, chronic kidney disease; ESA, erythropoietin-stimulating agent.

Prevalence and Characteristics of ESA Hyporesponse

- vary widely depending on the characteristics of the population studied and the criteria used
- estimates of prevalence:
  - 12.5% when both Hb level and ESA dose were included
  - 30.3% when only change from baseline in Hb was considered

outecome

- associated with increased all cause mortality in patients with CKD
- associated with adverse outcomes in patients with anemia of diabetic kidney disease
- associated with adverse outcomes in patients with anemia in heart failure

Causes of decreased response to ESA therapy

1. Iron deficiency
2. Bleeding
3. Red blood cell life span
4. Inflammation and infection
5. Hyperparathyroidism
6. Vitamin D

7. Relative vitamin B12 deficiency
8. Aluminum intoxication
9. Concomitant Medications:
   - Angiotensin-converting enzyme (ACE) inhibitors
10. Pure red cell aplasia
11. Other hematologic disease

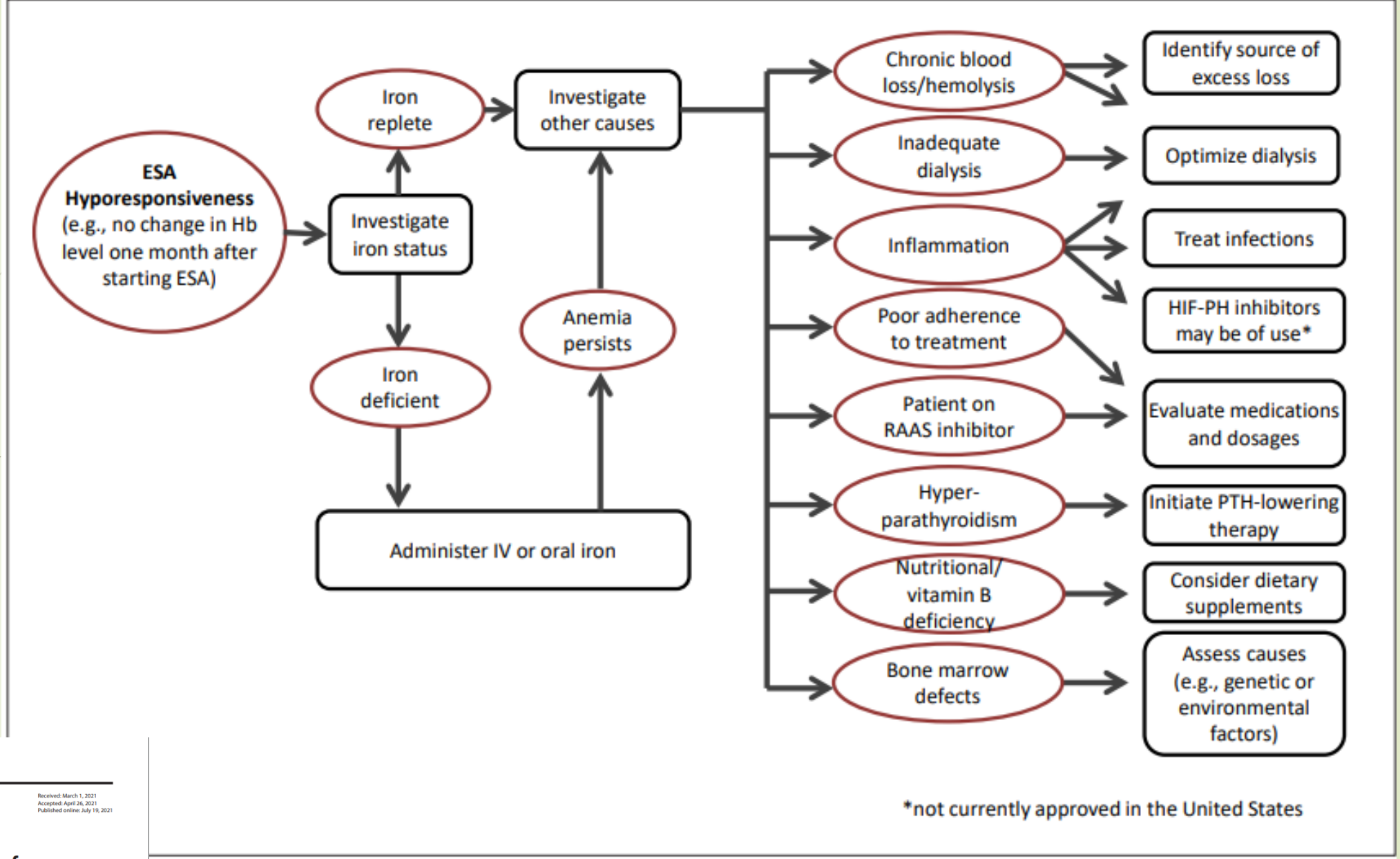


Fig. 1. Factors associated with ESA hyporesponse. ESA, erythropoiesis-stimulating agent; RAAS, renin-angiotensin-aldosterone system; HIF, hypoxia inducible factor; HIF-PH, HIF prolyl hydroxylase; PTH, parathyroid hormone.

AJN
American Journal
of Nephrology

In-Depth Topic Review

Am J Nephrol 2021;52:450–466
DOI: 10.1159/000516901

Received: March 1, 2021
Accepted: April 26, 2021
Published online: July 19, 2021

Managing Anemia across the Stages of Kidney Disease in Those Hyporesponsive to Erythropoiesis-Stimulating Agents

Matthew R. Weir

Division of Nephrology, University of Maryland Medical Center, Baltimore, MD, USA

Bleeding

- Occult bleeding:
  - fecal occult blood
- obvious bleeding:
  - undergoing surgery
  - menstruating women
  - accidents involving the vascular access

Red blood cell life span

- RBC lifespan: 20%–30% shorter
- correlation between degree of shortening of RBC lifespan and ESA resistance
- Treatment: no

Inflammation and infection

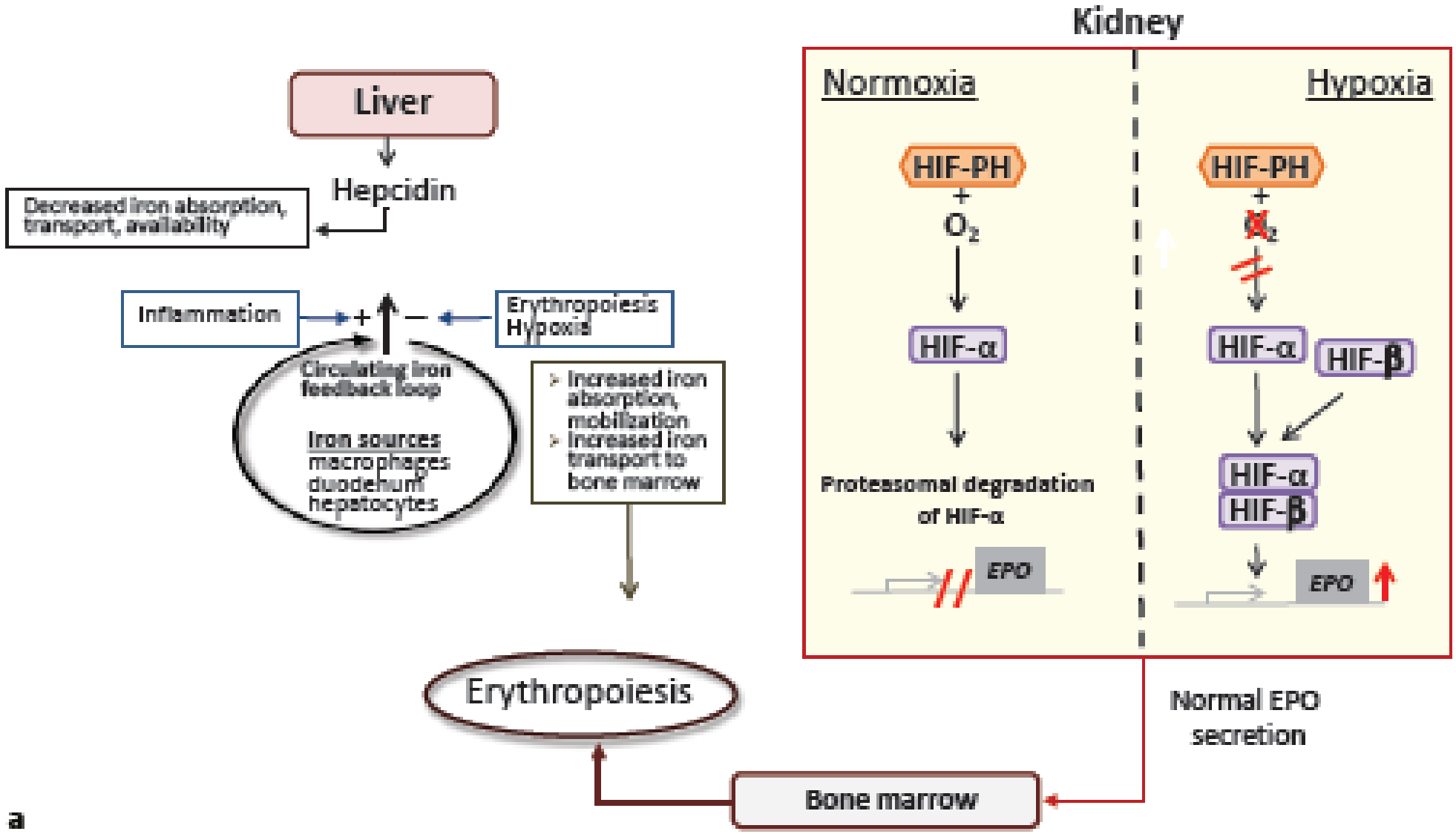
- infection→ inflammatory states →resistance to ESA therapy
- mechanism:
  - Cytokine release → down regulation of expression of erythropoietin receptors on erythrocyte precursors
  - Inflammation →IL-1β, TNF-a, and IL-6 → hepatocytes →increases production and secretion of hepcidin →diminishing intestinal iron absorption

- Marker: C-reactive protein (CRP)
  - Elevate in:
    - retained, nonfunctioning renal allograft
    - cytomegalovirus (CMV) infection
  - reduced in:
    - hepatitis C
- search for occult infection in patients with unexplained ESA resistance
- Infection: higher doses of ESA may be need
- positive correlation between hepcidin level and ESA dose
- Hyporesponsive patient to ESAs: IL-6 and C-reactive protein (CRP) levels are significantly higher

- The hypoxia-inducible factor (HIF) pathway plays a critical role in the normal physiologic response to hypoxia, including the upregulation of EPO
- In CKD, HIF is not activated
  - Mechanisem:
    - reduced oxygen delivery to the kidney& reduced kidney tissue oxygen consumption→ pseudonormoxic state → impairs production of endogenous EPO

Normally functioning kidney

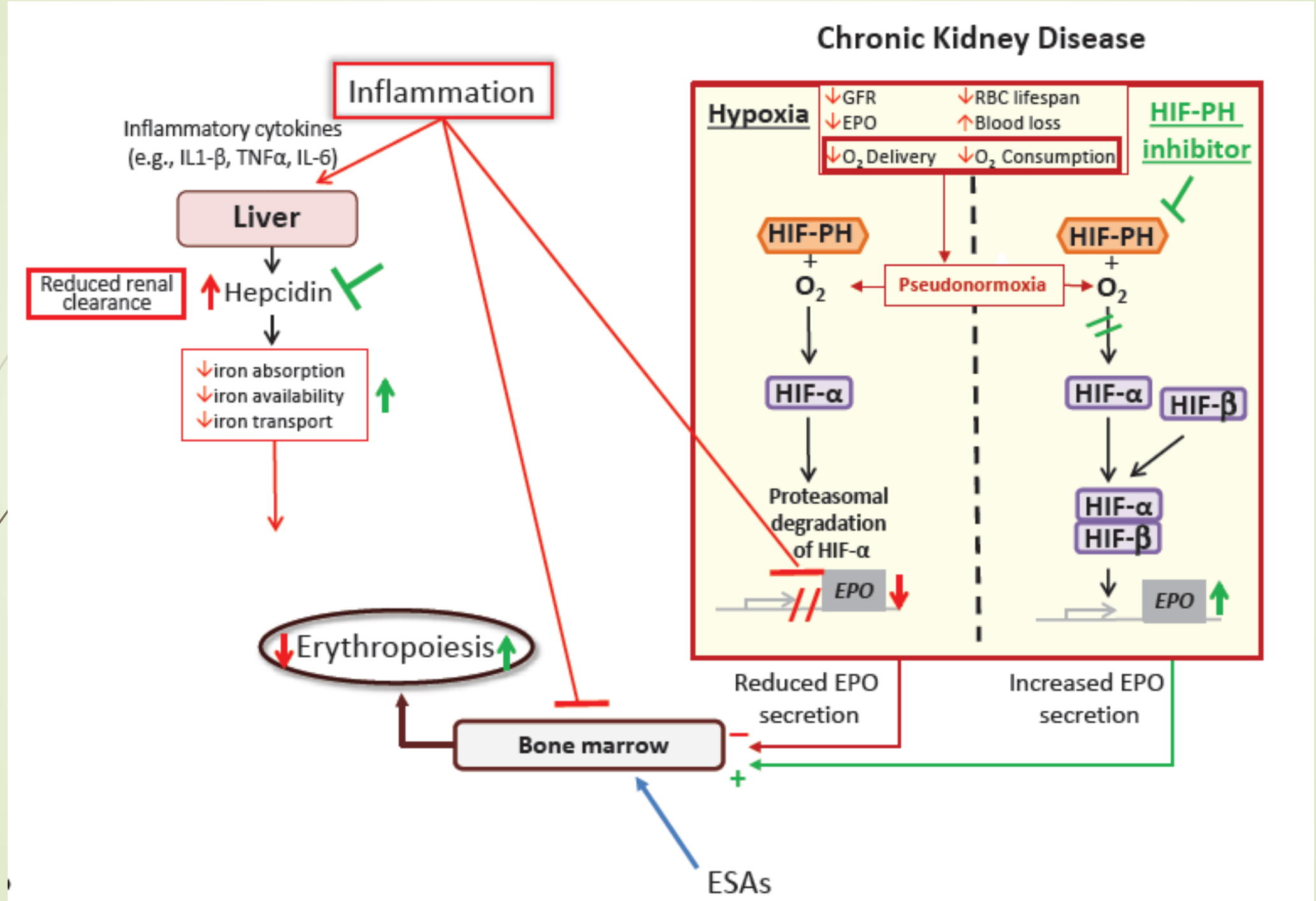
- Normal condition:
  - HIF-PHs sense and utilize oxygen (O2)→ degradation the HIF-a subunit of the HIF transcription factor → EPO is not expressed
  - minimal expression of Hepcidin by the liver
- Hypoxic condition:
  - inactive HIF-PHs → HIF-a subunit to dimerize with the HIF-β subunit → promote expression of EPO → erythropoiesis


Liver
Hepcidin
Decreased iron absorption, transport, availability
Inflammation
+
–
Erythropoiesis Hypoxia
Circulating iron feedback loop
Iron sources
macrophages
duodenum
hepatocytes
Increased iron absorption, mobilization
Increased iron transport to bone marrow
Erythropoiesis
Bone marrow
Kidney
Normoxia
Hypoxia
HIF-PH
+
O_2
HIF-α
Proteasomal degradation of HIF-α
EPO
HIF-PH
+
O_2
HIF-α
HIF-β
HIF-α
HIF-β
EPO
Normal EPO secretion
a

CKD patient

- reduced kidney oxygen delivery and consumption →normal oxygen gradient persists →prevents activation of the HIF pathway → prevents appropriate increases in EPO
- Inflammation:
  - suppress EPO transcription by inflammatory cytokines such as IL-1β and TNF-a
  - IL-1β, TNF-a, and IL-6 →stimulate production of hepcidin in the liver→ reduces the expression of the iron exporter FPN on the surface of many tissues, including macrophages and in the duodenum

- diminished kidney function→ reduces the clearance of hepcidin → accumulation of hepcidin→ restricting iron → reduces erythropoiesis
- HIF-PH inhibitors:
  - increase HIF-a → activate the HIF pathway →produce endogenous EPO
  - indirectly suppress hepcidin expression → restores FPN activity → allows mobilization of iron from internal stores


Chronic Kidney Disease
Inflammation
Inflammatory cytokines
(e.g., IL1-β, TNFα, IL-6)
Liver
Reduced renal clearance
Hepcidin
↓iron absorption
↓iron availability
↓iron transport
Erythropoiesis
Bone marrow
ESAs
Hypoxia
↓GFR
↓EPO
↓RBC lifespan
↑Blood loss
↓O2 Delivery
↓O2 Consumption
HIF-PH inhibitor
HIF-PH
+
O2
Pseudonormoxia
HIF-α
Proteasomal degradation of HIF-α
EPO
HIF-β
Reduced EPO secretion
Increased EPO secretion
−
+

- Inflammation → IL-1β and TNF-α → transcription factors NF-κB and GATA-2 →inhibit EPO transcription → impair EPO production

- diabetes mellitus and/or hypertension are associated with inflammation
- patients with DD-CKD who were hyporesponsive to ESAs had higher rates of hypertension and other cardiovascular diseases and higher rates of cardiovascular event-related hospitalizations

Hyperparathyroidism

- clear relationship between elevated iPTH levels and diminished ESA response
- There is an inverse correlation between PTH and Hb levels
- mechanism(s):
  - unclear
  - suppression of endogenous EPO production by PTH
  - inducing fibrosis in bone marrow
  - decreasing RBC survival or production
- after parathyroidectomy, responsiveness improves
- patients receiving PTH-lowering therapies and improved Hb levels

FGF 23

- In patients with DD-CKD increased risk of ESA hyporesponse in the lowest (5–440 pg/mL) and highest (8,621–76,000 pg/mL) quintiles

Vitamin D

- Hgb levels are lower in dialysis patients with low serum levels of 25-hydroxyvitamin D
- vitamin D: suppressor of hepcidin

Relative vitamin B12 deficiency

- Vitamin B12 and folic acid levels :checked when unexplained ESA resistance is present;
- Etiology:
  - taking proton-pump inhibitors
  - intensive, high-flux hemodialysis and hemodiafiltration
- hemodialysis patients with serum vitamin B12 levels of less than 300 pmol/L: A short course of three treatments of hydroxycobalamin 1,000 mcg per week was given.
- Treatment was repeated if B12 levels remained below 300 pmol/L.
- Hydroxycobalamin treatment reduced 50% in EPO requirement
- IV iron requirements were also reduced by half.
- Cyanocobalamin (a form of B12 commonly used in oral supplements) should not be given to ESKD patients because of cyanide accumulation

Aluminum intoxication

- Microcytic anemia associated with impaired iron utilization.
- intestinal aluminum absorption is significantly increased in patients with iron deficiency.
- Diagnosis:
  - serum aluminum level
  - deferoxamine stimulation test
  - bone biopsy

Concomitant Medications

1. Angiotensin-converting enzyme (ACE) inhibitors
   - reduce EPO production in patients with chronic renal failure or following renal transplant
   - RAAS inhibitor use should be carefully evaluated in patients hyporesponsive to ESAs
2. Pentoxifylline
3. Statins
   - In DD-CKD: ameliorate ESA hyporesponse
   - in predialysis, long-term statin therapy: associated with ESA hyporesponse
   - Hemodialysis: lower hsCRP levels and a lower ERI and required lower ESA doses

Pure red cell aplasia

- Presention:
  - Hgb declines rapidly as does the reticulocyte count
  - transfusion-dependent
  - bone marrow demonstrates absence of erythroid precursors
- etiology:
  - development of antierythropoietin antibodies that neutralize both therapeutic and endogenous erythropoietin

Table 2. Potential factors of ESA hyporesponsiveness and responding treatment

Risk factor	Responding treatment
Iron deficiency • Absolute • Functional	Iron supplementation, treat cause of blood loss. Address other factors, i.e., inflammation and uremia, which may have led to functional iron deficiency. IV iron required for functional iron deficiency
Inflammation and hepcidin accumulation	Address likely cause of inflammation, i.e., antibiotics for acute infection and steroid treatment for systemic inflammation. To lower serum hepcidin production and accumulation, rule out sources of infection from catheter and graft access
Uremia	Increased uremic clearance; adequate dialysis delivery – increased dialysis intensity and dialysate flow, e.g., convective HD; and improved membrane permeability
CKD-MBD • Vitamin D deficiency • Secondary hyperparathyroidism • Other CKD-MBD factors – elevated FGF-23, ALP	Vitamin D supplementation (native and activated), calcimimetics, low-phosphate diet, and phosphate binders. Consider parathyroidectomy if refractory to medical treatment
Non-iron malnutrition • Folic acid deficiency • Vitamin C deficiency • Copper deficiency • α-Lipoic acid deficiency • L-Carnitine deficiency • Other non-iron malnutrition factors – PEW, vitamin B_6 deficiency, vitamin B_{12} deficiency	Nutritional supplementation to address the cause of non-iron nutritional deficiency
Other factors of ESA hyporesponsiveness • Drug-induced factors – ACEi, ARB • Malignancy • Primary bone marrow and myelosuppressive disorders • Antibody-mediated pure red cell aplasia • Aluminum overload	Reduce dose or hold ACE inhibitor and ARBs Treat underlying oncological or hematological cause, and reduce its associated complications Anti-ESA treatment if indicated Supportive treatment for aluminum overload

CKD-MBD, chronic kidney disease-mineral bone disease; FGF-23: fibroblast growth factor-23; ALP, alkaline phosphatase; PEW, protein energy wasting; ACEi, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blocker; ESA, erythropoietin-stimulating agent; HD, hemodialysis.

Therapeutic Options and Strategies to Improve ESA Response

- Management of Infection
- Optimization of Dialysis
- Correction of Iron Deficiency

Targets for New Therapeutic Options

- Hypoxia-Inducible Factor
- *HIF-PH Inhibitors*
- Hepcidin Antagonists

Other hematologic disease

- hematologic diseases as nonuremic subjects:
  - hematologic malignancy
  - myelodysplastic syndromes
  - hemolysis

Hemolysis

- Chronic Hemolysis:
  - high-grade ESA resistance
  - increased serum lactic dehydrogenase (LDH)
  - increased serum unconjugated bilirubin
  - decrease in serum haptoglobin

Hemolysis- causes

TABLE 34.2 Causes of Hemolysis in Dialysis Patients

- Related to the hemodialysis procedure
  - Dialysis solution
    - Contaminants
      - Chloramine
      - Copper, zinc
      - Nitrates, nitrites
      - Overheated
      - Hypo-osmolar
  - Reuse of sterilants (formaldehyde)
  - Kinked or defective tubing—trauma to RBCs
  - Needle trauma to RBCs
  - Subclavian catheter (helmet cells, schistocytes)
- Malfunctioning cardiac valve prosthesis
- Insufficient dialysis
- Hypersplenism
- Associated diseases
  - Sickle cell anemia
  - Other hemoglobinopathies
  - Connective tissue diseases with vasculitis
- Drug-induced
- Hypophosphatemia

Hemolysis

- Severe hemolysis
  - hypotension, or hypertension
  - abdominal, chest, and/or back pain
  - shortness of breath
  - nausea, vomiting, or diarrhea
  - encephalopathy

Etiology

- Faulty or kinked blood line tubing
- Chloramine in the dialysis solution
- Hypotonic or overheated dialysis solution
- copper, zinc, or nitrate in the water supply
- formaldehyde not rinsed out of the dialyzer

Treatment

- Terminate dialysis: in acute, severe hemolysis
- Circulatory support
- Electrocardiogram:
  - hyperkalemic changes
  - acute cardiac ischemia
- hemoglobin, hematocrit, and serum chemistries, especially serum potassium

Refrenses

- Brooks DH. Handbook of dialysis. Nephrology Nursing Journal. 2015 May 1;42(3):295-6.
- Weir MR. Managing anemia across the stages of kidney disease in those hyporesponsive to erythropoiesis-stimulating agents. American Journal of Nephrology. 2021;52(6):450-66.
- Wu HH, Chinnadurai R. Erythropoietin-stimulating agent hyporesponsiveness in patients living with chronic kidney disease. Kidney Diseases. 2022;8(2):103-14.


© aartibhardwaj photographs