ESA HYPORESPONSIVENESS

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INTRODUCTION

- People with ESA hyporesponsiveness are at increased risk for cardiovascular events, kidney failure, and death.
- ESA hyporesponsiveness can be acute or chronic (>4 months).
- Its prevalence varies by geographical region ranging from 12.5% to 30.3% as reported in recent studies.
- The most common causes of ESA hyporesponsiveness are inflammation and iron deficiency.

Guideline	Definition of ESA resistance
ERBG 2004	Increase in erythropoietin dose ≥25% to maintain the same Hb level or < 1 mg/dL gain in Hb after 2–4 weeks
KDIGO 2012	Initial ESA resistance: No increase in Hb 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	As per KDIGO 2012 (refer to KDOQI US commentary on KDIGO 2012 Clinical Practice Guideline for Anemia in CKD)
NICE 2021 and BRA 2017	An aspirational Hb 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 Hb range

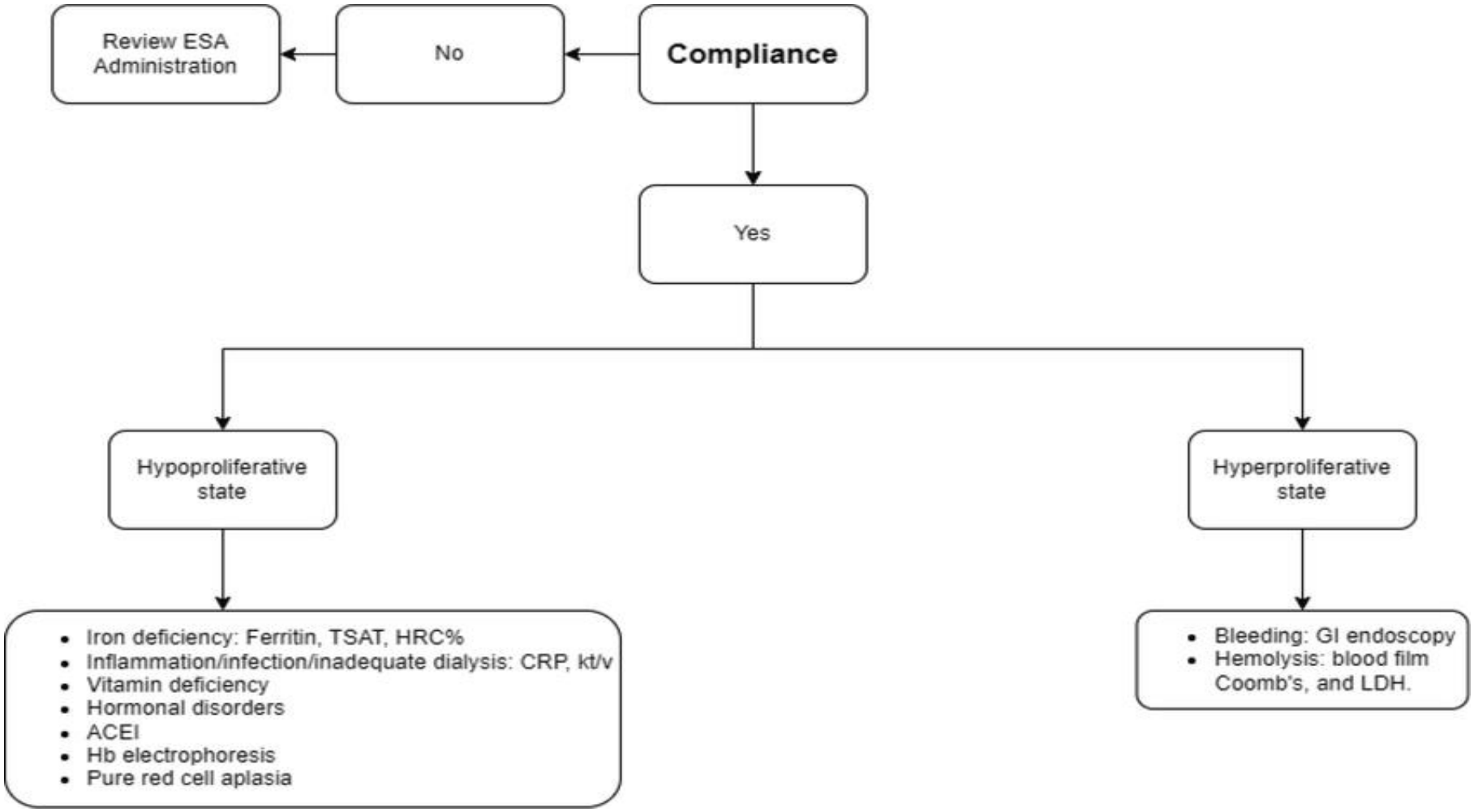
KDIGO 2025

- 3.7.1: In people with anemia and CKD G5D and CKD not receiving dialysis with initial or subsequent ESA hyporesponsiveness, identify and treat the underlying causes of ESA hyporesponsiveness, if possible.

- Practice Point 3.7.2: In people with CKD, anemia, and ESA hyporesponsiveness, if there is a desire to raise the Hb to avoid a transfusion or improve symptoms attributable to anemia, a trial of HIF-PHI may be considered after discussion of potential risks and benefits prior to treatment.

- Practice Point 3.7.4: In patients with CKD, anemia, and ESA hyporesponsiveness, if a desired erythropoietic response has not been achieved after 3–4 months of initiating a trial of HIF-PHI, discontinue treatment.

APPROACH TO ESA HYPORESPONSIVENESS



Tests	Finding and action
1. Check adherence	If poor, attempt to improve (if self-injection)
2. Reticulocyte count	If $>130{,}000/\mu l$, look for blood loss or hemolysis: endoscopy, colonoscopy, hemolysis screen
Serum vitamin B_{12}, folate	If low, replenish
Iron status	If low, replenish iron
Serum PTH	If elevated, manage hyperparathyroidism
Serum CRP	If elevated, check for and treat infection or inflammation
Underdialysis	If underdialyzed, improve dialysis efficiency
ACEi/ARB use	If yes, consider reducing dose or discontinuing drug
3. Bone marrow biopsy	Manage condition diagnosed e.g., dyscrasia, infiltration, fibrosis

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin-receptor blocker; CRP, C-reactive protein; PTH, parathyroid hormone.

HIF PHI in ESA hyporesponsiveness

- HIF-stabilizers suppresses hepcidin and other pro-inflammatory cytokine production.
- Regulating iron homeostasis: increase transferrin, transferrin receptor concentration, duodenal cytochrome B, divalent metal transporter-1, and ceruloplasmin levels.
- DREAM ND and DREAM D trials prove efficacy similar to EPO in increasing Hb levels and also positive reduction in hepcidin levels and LDL levels.
- Avoid drug in patients with proliferative diabetic retinopathy , ADPKD , suspected malignancy and having thrombotic events.
- Administer drug on empty stomach or 2 hours after food.
- No desired response after 3-4 months – discontinue HIF-PHI.