Emerging Evidence On Anemia

Evidence, Education, and Better Patient Outcomes

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19 Mantua Rd., Mt. Royal NJ 08061
info@SABM.org • info@ANEMIA.org.

Contributors

Michael Auerbach M.D.
Private Practice, Baltimore Maryland
Clinical Professor of Medicine
Georgetown University School of Medicine
Washington, DC

Irwin Gross M.D.
Senior Medical Director, Accumen, Inc.
San Diego, CA

Aryeh Shander M.D.
Chief, Department of Anesthesiology, Critical Care Medicine, Pain Management & Hyperbaric Medicine
Englewood Hospital & Medical Center
Englewood, NJ
Clinical Professor of Anesthesiology, Medicine and Surgery
Icahn School of Medicine
New York, NY

Emerging Evidence on Anemia, Transfusion, Intravenous Iron and Its Impact On Patient Outcomes

The Need for Updated Intravenous Iron Coverage

Is anemia really a problem?

What is the evidence? What are the barriers?

Anemia is a widely under-recognized condition that is:

- Epidemic
- Often accepted or ignored as a harmless problem
- Associated with poor medical and surgical outcomes
- An independent risk factor for morbidity and mortality

Anemia diagnosis and treatment is poorly understood by many practicing clinicians

- Common treatment modalities can be ineffective and even harmful
- There is lack of awareness of established science in various disease states

Current treatment is limited by:

- Physician knowledge of and comfort with new intravenous iron therapies
- Medicare Administrative Contractor's (MAC's) limitations on (Medicare) coverage

How can the problem be fixed?

1. Broaden clinical application of new evidence
2. Create universal inclusion criteria for coverage across all MAC's
3. Add qualifying diagnosis codes for coverage
4. Promote education and awareness of anemia

Recognizing the prevalence of anemia and need for improved management

Anemia is under-recognized as a condition

Epidemic

Anemia and iron deficiency are extremely common. It is estimated that greater than one third of adults over the age of 65 have unexplained anemia, defined as a hemoglobin less than 12 g/dL. Seventeen percent (17%) of adults over the age of 65 have been shown to have iron deficiency and of those with iron deficiency anemia, only 50% normalized their hemoglobin with oral iron therapy.

Iron deficiency in the hospitalized patient population, both functional and true iron deficiency, is also extremely common.

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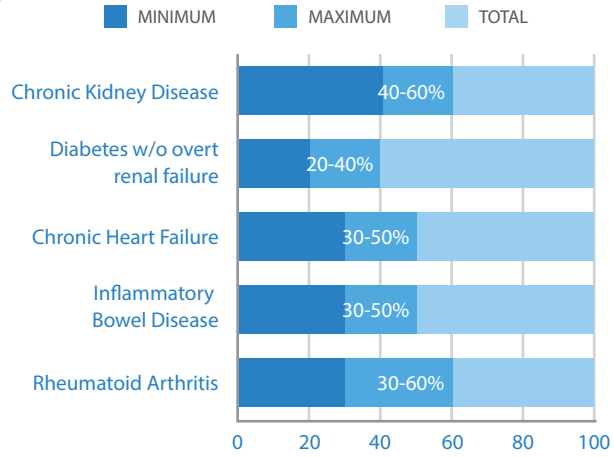
Prevalence of Iron Deficiency Anemia



Hospital acquired anemia is prevalent and has a significant impact on clinical outcomes with major health care implications.

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Hospital Acquired Anemia

10 hospitals, from 1/2009 – 08/2011
188,447 Hospitalizations
Endpoints: Mortality, Charges and LOS

	MILD	MODERATE	SEVERE
Definition	>11-12F > 11-13M	9.1 ≤ 11	≤ 9.0
HAA (74%)	29%	41%	30%
Mort RR	1.0	1.51	3.28
LOS	1.08	1.28	1.88
Charges	1.06	1.18	1.80

References for charts and graphs can be found on page 6

Often accepted or ignored as a harmless problem

Anemia has become a "normalized deviation" with a long tradition of acceptance as a harmless problem that can be ignored in most cases or easily corrected with transfusion.

Anemia: A Potent Multiplier of Mortality

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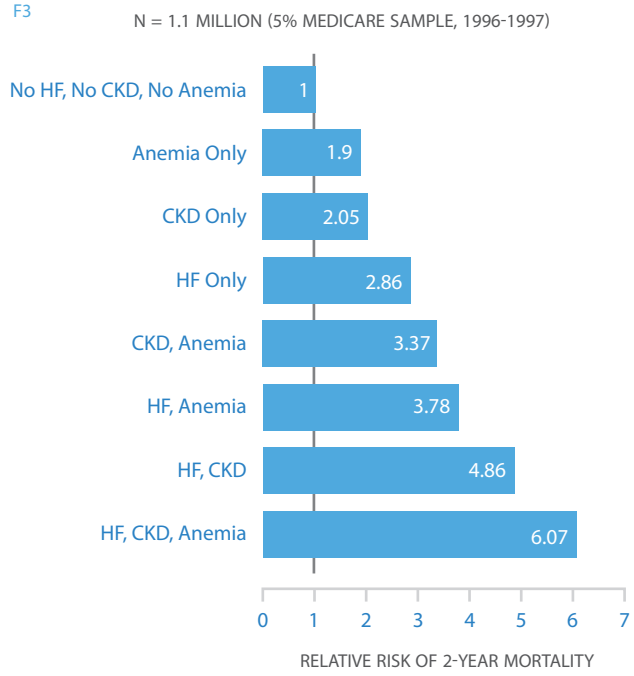

Associated with poor surgical outcomes

The association of preoperative anemia with postoperative mortality is a compelling reason to manage anemia in the perisurgical patient population.

Preoperative Anemia Is Associated With Postoperative Mortality

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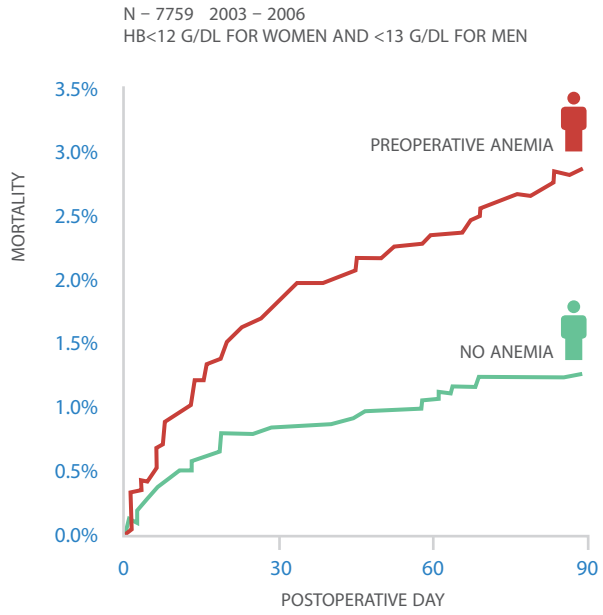

The impact of preoperative anemia on colon and rectal surgery outcomes in 23,000 patients selected from the National Surgical Quality Improvement Program (NSQIP) database was reported as shown in Figure 5.

Does Preoperative Anemia Adversely Affect Colorectal Surgery Outcomes?

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2005-2008 - NSQIP (251 HOSPITALS)
CO – MI, CVA, AKI, MORTALITY AND HLOS
N – 23,348 – 47.4 % ANEMIC
UNI, MULTI, LOGISTIC REGRESSION AND PROPENSITY SCORING

ANEMIA	HCT	N	CO-OR	HLOS
None	(>38%)	12,281	1.0	-
Mild	(30-37%)	9037	1.47	-
Moderate	(26-29%)	1726	1.87	1.2
Severe	(21-25%)	304	2.1	1.6

Anemia diagnosis and treatment is poorly understood by many practicing clinicians

Enteric iron therapy is ineffective and may be harmful

Side effects associated with oral iron are well known. These complications often lead to non-compliance with as many as 40 to 50% of patients unable to tolerate enteric iron therapy.

Costly For much of the medical community, transfusion as treatment for anemia remains the default position. Knowing that significant morbidity and mortality is independently associated with anemia, a new clinical paradigm is needed where anemia is managed regardless of the level of hemoglobin.

Transfusion as a treatment of anemia compounds the problem and increases costs. Activity based cost analysis shows that the cost of transfusion independent of complications associated with the transfusion range from $800 per unit to over $1200 per transfused unit. Anemia recognition, diagnosis and treatment will reduce the cost and complications of transfusion.

Lack of awareness of emerging science by Medicare administrative contractors

In patients treated with an erythropoietic stimulating agent (ESA), intravenous iron is much more efficacious than is enteric iron in ensuring an adequate response to the ESA at the lowest possible dose.

In a study published in the mid-1990s, the target hemoglobin level is achieved with significantly lower doses of erythropoietin when intravenous iron is used as opposed to enteric iron.

Maintenance Therapy With IV vs. Oral Iron in EPO-Treated Patients

F6

		BASELINE	2 MONTHS	4 MONTHS
HCT, % ACHIEVED	IV Iron	32.5 ±0.6	33.6 ±0.9*	34.4 ±0.7*
	PO Iron	31.8 ±0.3	32.1 ±0.3	31.8 ±0.4
EPO, U/RX REQUIRED	IV Iron	7100 ±571	3350 ±689*	4050 ±634*
	PO Iron	6750 ±419	7250 ±409	7563 ±378

PO IRON = 200-300 MG/D; IV IRON = 200 MG/WK.
*P<.05 COMPARED TO PO IRON GROUP.

The addition of IV iron to erythropoietin when treating patients with cancer-associated anemia results in a statistically significant increase in the percentage of patients who respond to treatment.

Addition of IV Iron to EPO Increases Hgb Response in Cancer-associated Anemia

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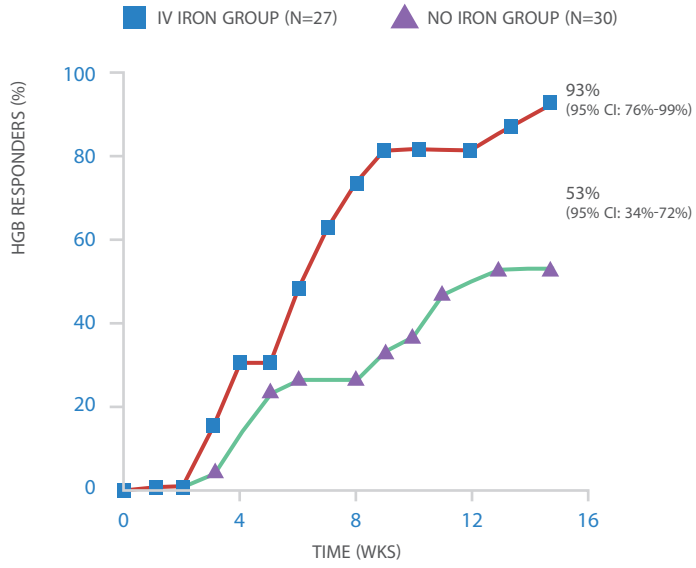

The superiority of intravenous iron over enteric iron is demonstrated in this study of intravenous iron in women with anemia secondary to menorrhagia.

IV Iron Improves Anemia in Women with Menorrhagia

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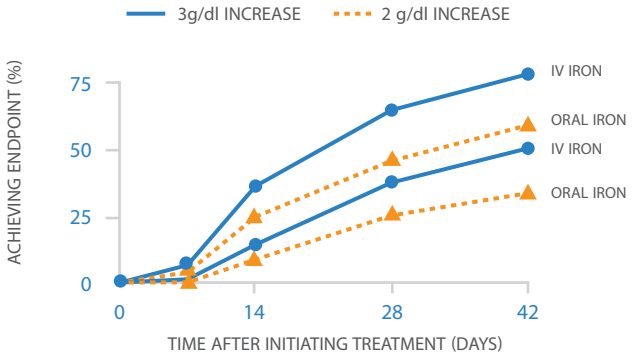
PROPORTION OF 477 PATIENTS ACHIEVING AN HGB INCREASE OF 2 G/DL OR 3 G/DL AFTER FERRIC CARBOXYMALTOSE



Proportion of patients achieving an Hgb increase of more than 2.0 g/dL or 3.0 g/dL according to treatment assignment; significant between-group differences.

A high percentage of patients with inflammatory bowel disease (IBD) have significant iron deficiency anemia. Moreover, there is a relative contraindication for enteric iron in patients with active IBD due to the potential for a direct toxic effect by enteric iron on the gastrointestinal mucosa. The superiority of an intravenous iron preparation, ferric carboxymaltose, over oral ferrous sulfate was demonstrated, with a higher percentage of patients achieving the target hemoglobin.

Ferric Carboxymaltose in IBD Patients

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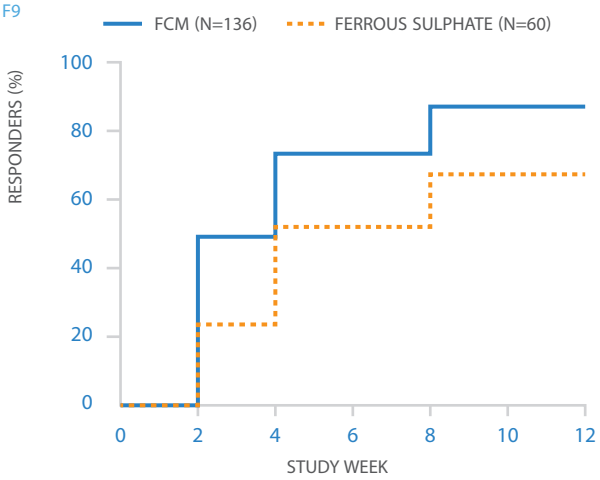


DOSING

Ferric carboxymaltose: The median calculated iron deficit was 1405.5 mg (range 937–2102 mg), requiring 1–3 administrations on an individual basis at 1 week intervals.

Ferrous sulfate: 2x100 mg/day for 12 weeks (total 16,800 mg). Non-inferiority of ferric carboxymaltose confirmed in primary endpoint.

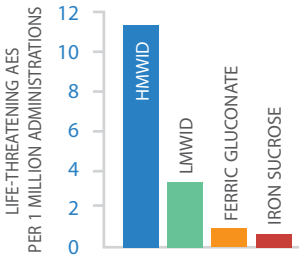
Factors that limit expanded evidence-based treatment of anemia with intravenous iron

Physician knowledge and comfort with new intravenous iron therapies

Adverse events (AE) with intravenous iron therapy vary with the type of preparation. (Fig. 10)

AEs and IV Iron Therapy

F10



FDA MedWatch reports (2001-2003) show HMWID was associated with a 3.4-fold increase in odds of life-threatening AEs

This analysis likely overestimates AEs with LMWID (all AEs reported by generic name only where attributed to LMWID)

In tens of thousands of patients in prospective studies SAEs with IV iron are vanishingly rare

MAC limitations on Medicare coverage

A number of the Medicare Administrative Contractors (MAC) limit reimbursement of intravenous iron through the use of medical policy articles.

Restriction 1: Requirement that patients first fail a trial of enteric iron due to either intolerance or lack of efficacy before intravenous iron will be covered.	Problem: Intravenous iron is known to have superior efficacy and is associated with fewer adverse events than is the use of enteric iron. This requirement imposes an unnecessary and ineffective treatment, increasing cost, risk and adverse events.
Restriction 2: If an ESA is co-administered on the same day as intravenous iron, both will not be reimbursed.	Problem: Studies demonstrate that in the chronic kidney disease patient population as well as the oncology patient population, co-administration of intravenous iron oftentimes results in the need for a lower dose of ESA in order to achieve the same target hemoglobin and a higher percentage of patients who respond to therapy. This is likely to be true in other patient populations as well.
Restriction 3: None of the Medicare administrative contractors recognize and provide coverage for iron deficiency that exists independent of anemia.	Problem: The medical policy article in some regions has not been updated to cover all intravenous iron preparations. In recent years, several new intravenous iron medications have become available and are FDA approved now in the United States. While intravenous iron is an effective therapy in the setting of iron deficiency in the absence of anemia, it will not be reimbursed unless the hemoglobin is in fact below threshold and the patient is anemic.

How can the problem be fixed?

1. Application of new and existing evidence

Because of the established risks associated with pre-operative anemia, a number of authors have published clinical pathways to the management of pre-operative anemia. (Fig. 11 at end of document)

2. Expand MAC Inclusion Criteria for Coverage

For these reasons, the *Society for Advancement of Blood Management*® is advocating for expanded inclusion criteria for **intravenous iron coverage** by:

☑ **1.** **Elimination** of the requirement of failure to respond to oral iron therapy.

☑ 2. Coverage for:

- both elective and non-elective surgery
- when an inflammatory process has been documented by either an elevated high sensitivity CRP or a transferrin saturation less than 20% concordant with an elevated ferritin level, intravenous iron will be covered
- patients with known inflammatory bowel disease or rheumatoid arthritis, regardless of disease activity
- patients with chronic kidney disease, stage three or higher, as demonstrated by a decrease in the GFR even if the ferritin is greater than 100 ng/ml and the transferrin saturation is greater than 20%
- patients with chronic heart failure and ferritin less than 100 ng/mL, or a transferrin saturation less than 20%, regardless of hemoglobin level, recognizing that published data show improved functional status in these patients regardless of hemoglobin level when treated with intravenous iron
- patients with iron deficiency without anemia if the transferrin saturation is less than 20% and the ferritin is less than 100 ng/mL

3. Add Diagnosis Codes that Support Coverage (Medical Necessity)

SABM is requesting diagnostic coverage:

- For transferrin saturation less than 20% in the setting of a patient with malignancy
- In patients with total iron deficit greater than 1 gram, if the ferritin is less than 100 ng/ml and the transferrin saturation less than 20%
- For iron deficiency as demonstrated by a decreased transferrin saturation and/or ferritin in pregnancy and within eight weeks after delivery
- Any patient being treated with an ESA
- If the transferrin saturation is less than 35% but above 20% and ferritin is below a safety threshold of 1200 ng/mL but above 100ng/mL, include coverage for iron administered on this same day as the erythropoietic stimulating agent
- For patients with obesity and patients who are a status post bariatric surgery.

The following additional, qualifying diagnoses are recommended:

- Functional iron deficiency
- Inflammatory states, unspecified, both acute and chronic
- Chronic heart failure
- Obesity
- Malignancy
- Dysfunctional uterine bleeding and related codes
- Pregnancy
- Bariatric surgery
- Iron deficiency as defined by a decrease in ferritin or transferrin saturation, even in patients who do not have anemia

4. Promote anemia education and awareness

Current medical literature shows the superiority of intravenous iron over enteric iron in the management of iron deficiency anemia and functional iron deficiency anemia, as well as iron sequestration states in a variety of patients. These patient populations include patients with:

- cancer, and chemotherapy-induced anemia
- acute and chronic inflammatory states, such as rheumatoid arthritis and inflammatory bowel disease
- chronic kidney disease and chronic heart failure
- hospital-acquired anemia
- bariatric surgery patients
- preoperative anemia regardless of the surgical procedure being performed
- hospital acquired and peri-operative anemia.

The requirement that patients first fail a course of enteric iron before intravenous iron can be used unnecessarily delays treatment, increases risk and increases cost and adverse events in patients who require treatment of their anemia.

Further, it is clear that there may be cost savings associated with the use of intravenous iron concomitantly with the use of erythropoietic stimulating agents, since studies demonstrate a higher percentage of patients who respond to ESAs when intravenous iron is given as well as the need for lower doses of ESAs to achieve the same hemoglobin target.

What YOU can do

1. **Contact** the Medical Director of your Medicare Administrative Contractor and request re-evaluation of the Medical policy Article if your MAC has a Medical Policy Article restricting the use of intravenous iron. Share this publication with the Medical Director when making the request.
2. **Share** your concerns about the Medical Policy Article restrictions with your congressional representation if your hospital has a legislative liaison with your congressional delegation. Emphasize that restricting the use of intravenous iron leads to higher costs and poorer clinical outcomes.
3. **Ask** your hospital's clinical and executive leadership to do #1 and #2 above. Go to SABM.org for a sample letter you can send.

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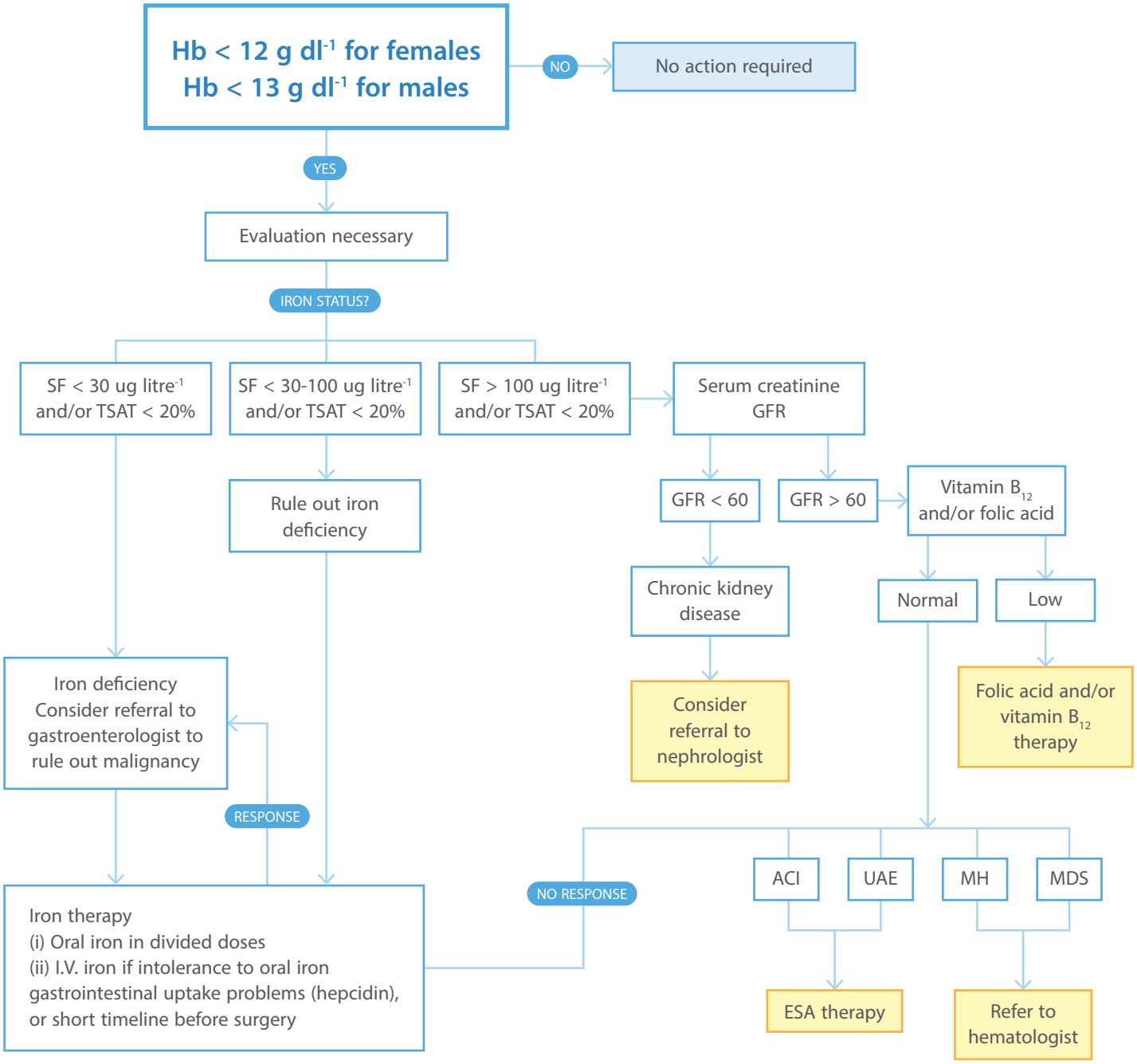

Hb Hemoglobin
SF Serum Ferritin
GFR Glomerular Filtration Rate
ACI Anemia of Inflammation

UAE Undifferentiated Anemia of the Elderly
MDS Myelodysplastic Syndrome
ESA Erythropoiesis Stimulating Agent
MH Malignant Hematology (e.g. chronic lymphocytic leukemia)