ANEMIA OF INFLAMMATION/ CHRONIC DISESAE IN CHILDREN

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CASE PRESENTATION

- An 8 Y old boy 15 kg , Single Child . Parents; no relation ship
- Fever , Cough since 5 days ago **and Pallor**
- History of Primary immune deficiency(PID / IEI) since 3 Y ago with diagnosis of; **Mendelian Suseptibilty to Mycocbacterial Disease ; MSMD** on **IFN Y& Antibiotic**
- **PE: Fever , Mild Splenomegaly ,No dyspnea**
- CXR : Right side infiltration
- **WBC; 4000 /ul PMN ; 60% L; %30 % M : 8% E: 2%**
  - **Hb: 8 gr/ dl MCV : 84 fl Platelet ; 170000/ ul**

❖ **What is the reason of Anemia ??**

CASE PRESENTATION
WHAT IS THE REASON OF ANEMIA ?

- Iron Deficiency Anemia(IDA)
- Anemia of Inflammation / Chronic disease
- Anemia duo to Underlying Disease (PID); Hematologic Presentation(anemia) in PID
- Hemolysis
- or ???? Combination of …..
- ……

ANEMIA OF CHRONIC DISORDERS IN CHILDREN

ANEMIA IN THE PEDIATRIC PATIENT. PATRICK G GALLAGHER BLOOD 2022

- **Anemia is not a specific disease entity per se but represents a heterogeneous group of pathologic conditions**
- Anemia ; Most common hematologic abnormality in infants & children.
- Globally, **Iron deficiency anemia** is the most common cause of anemia

Other important causes of anemia in Children;

- **Infections ,Hemoglobinopathies, & Other Inflammation/ chronic diseases**
- **Anemia of inflammation & iron-deficiency; the two most common anemias ,often coexisting disorders in developing countries with a high prevalence of nutritional deficiencies and infections**

APPROACH TO THE ANEMIC CHILD:

- Anemia :increased morbidity, including neurologic complications, increased risk of LBW, infection, and heart failure, & increased mortality

Diagnosis ;

- **History ,physical Examination ,Laboratory investigation**
- **Genetic testing(NGS,…) :Inherited anemias**

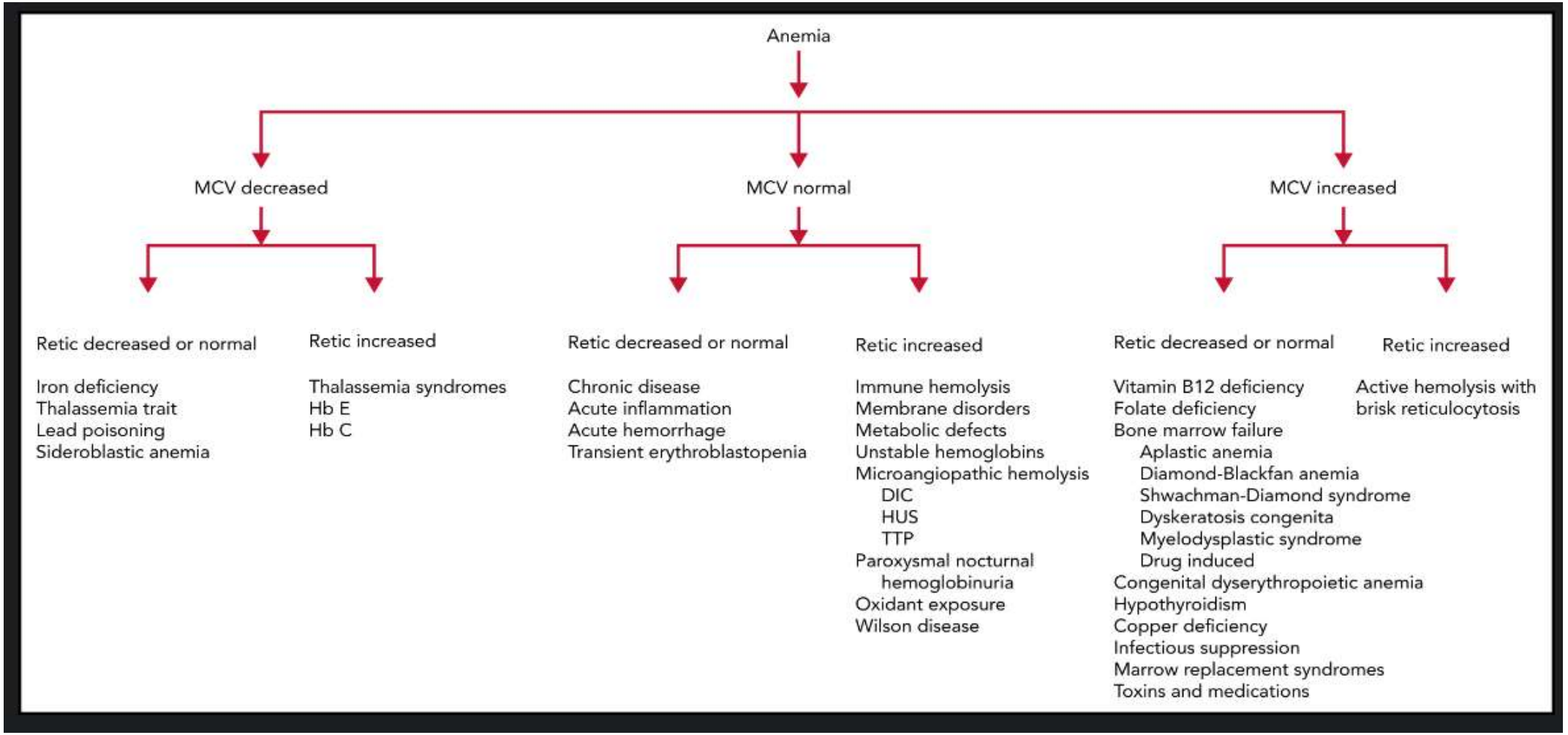
CLASSIFICATION OF ANEMIA

ANEMIA IN THE PEDIATRIC PATIENT.PATRICK G. GALLAGHER.BLOOD (2022) 140 (6): 571–593.

Anemia can be classified in many ways, such as;

- **Congenital or Acquired**
- **Hemolytic or Nonhemolytic**
- **Acute or Chronic**
- **MCV : Normocytic , Macrocytic , Microcytic**
  - **Anemia of Inflammation/ Chronic diseases**
  - **40% of all anemias worldwide ;AI or combined anemias , account for >1 billion affected individuals.**

AN APPROACH TO ANEMIA BASED ON MEAN CORPUSCULAR VOLUME AND RETICULOCYTE COUNT.



ANEMIA OF INFLAMMATION /CHRONIC DISEASE

wide variety of disorders:

- **Infection, Renal*** ,Rheumatologic & Autoimmune disease**
- **GI diseases ;Ulcerative colitis, Crohn's disease, & Celiac disease**
- **Heart failure, Chronic lung disease**
- **Obesity**

Malignancies ; Hodgkin's lymphoma and non-Hodgkin's lymphoma; and certain solid tumors,…

- **In HSCT ; GVHD**

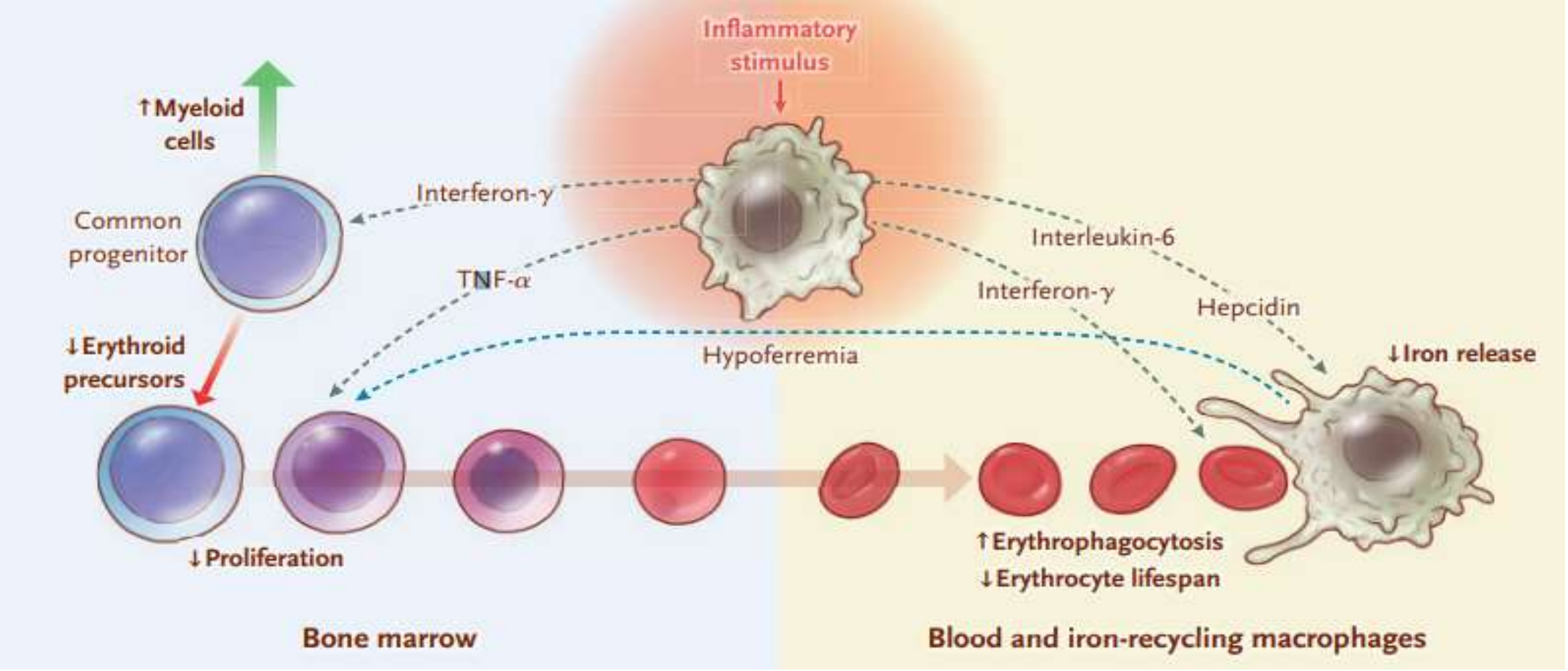
ANEMIA OF INFLAMMATION/ CHRONIC DISEASES

- **AI:** Is prevalent in patients with diseases that cause **prolonged immune activation** and **release of Cytokines ; Interferon-γ ,TNF-α, IL1 ,IL6 by inflammatory cells**

Cytokines restrict :

- **Erythropoiesis both directly and indirectly**
- **Shorten the Erythrocyte lifespan.**

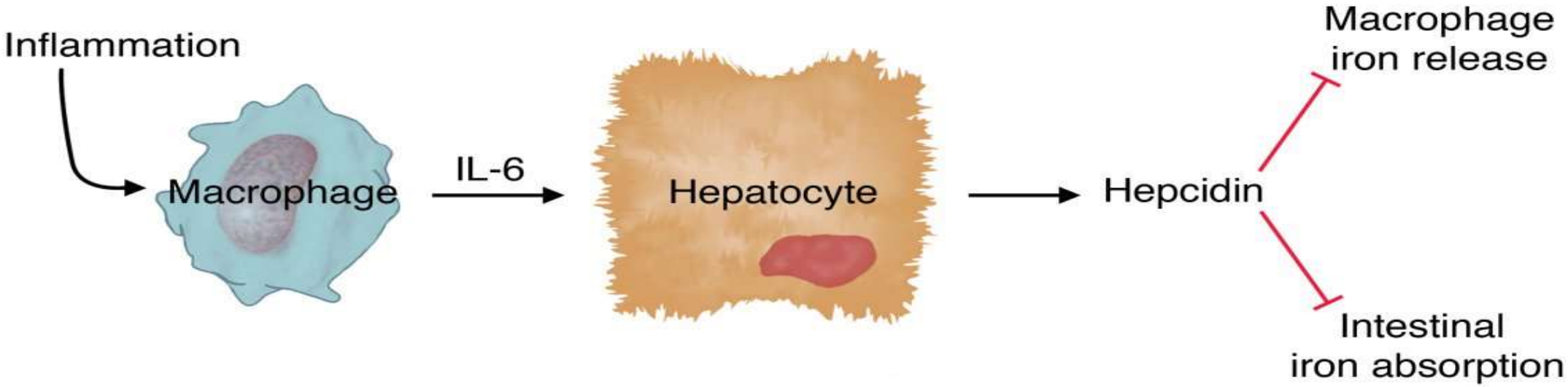
ROLE OF SYSTEMIC INFLAMMATION
IMPAIRED IRON METABOLISM
N ENGL J MED.2019



REGULATION OF HEPCIDIN PRODUCTION IN INFLAMMATION;

HEPCIDIN ;A KEY REGULATORY PROTEIN SYNTHESIZED BY HEPATOCYTES , ALSO EXPRESSED IN MONOCYTES AND MACROPHAGES

HEPCIDIN INHIBITS MACROPHAGE IRON RELEASE AND INTESTINAL IRON ABSORPTION, LEADING TO HYPOFERREMIA



ROLE OF SYSTEMIC INFLAMMATION. N ENGL J MED.2019

Several factors contribute to anemia of AI / Ch disease

High levels of Cytokines & Impaired Iron metabolism

- **Hematopoiesis toward myeloid-cell production rather than erythropoiesis (interferon-gamma)** inhibit erythroid-precursor proliferation **(TNF-α)**
- Activate macrophages for erythrophagocytosis and **thereby shorten the erythrocyte lifespan (Interferon-gamma)**
- **Inhibit** the release of recycled iron from macrophages ; **Hypoferremia inhibits erythroblast proliferation (interleukin-6 through hepcidin), causing hypoferremia**

ANEMIA OF INFLAMMATION /CHRONIC DISEASE

More reasons :

- **Mild Hemolysis**
- **Sampling**
- **Dialysis , Surgeries**
- **Inhibitors of Ep in circulation (Chronic renal disease …)**
- **Iron deficiency association(IDA) *******
- **Decreased B12, CARNITINE DEFICIENCY**
- **Hypersplenism…….**

ANEMIA OF INGFLAMMATION / CHRONIC DISEASE

ANEMIA (ANEMIA of CHRONIC INFLAMMATION)

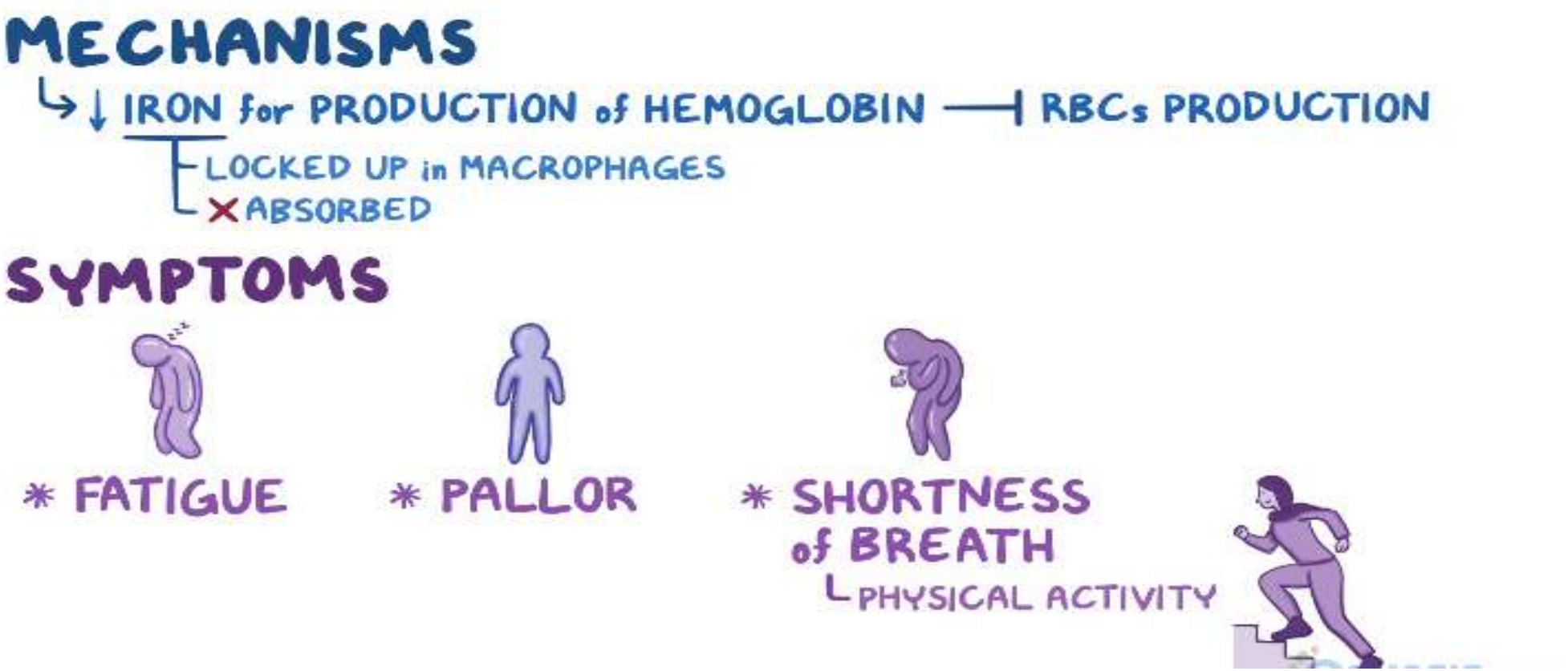
* ↓↓↓ (RBC) COUNT
* CHRONIC DISEASE STATES:
  - INFECTIONS
  - MALIGNANCY

  - DIABETES

  - AUTOIMMUNE DISORDERS

* CAUSE
  - CONTINUOUS INFLAMMATION → CHRONIC DISEASE
    ↳ IMPAIRS IRON METABOLISM → ↓ RBC PRODUCTION
* 2ND MOST COMMON TYPE of IRON DEFICIENCY ANEMIA

PRESENTATION OF ANEMIA IN INFLAMMATION / CHRONIC DISEASE



LABORATORY STUDIES FOR ANEMIA OF INFLAMMATION DIAGNOSIS

- **CBC , PBS**
- **CRP & ESR ; Inflammatory markers in Clinical work up for systemic inflammatory processes. (also may be leukocytosis)**
- **Anemia usually mild, Hb 10-12 gr dl. Some times 6-9 gr / dl**
- **Usually Normochromic, normocytic, occasionally Microcytic**

THE ANEMIA CHARACTERISTICS OF INFALAMTION/ CHRONIC DISEASE

- Iron studies (Iron , TIBC, Ferritin , …..)
- Evaluation of Iron deficiency anemia - IDA as a diagnostic challenge as inflammation alters markers of body iron status.

DIFFERENCES IN BIOMARKERS OF IRON DEFICIENCY AND ANEMIA OF INFLAMMATION

Biomarker*	Iron Deficiency	Anemia of Inflammation
Mean corpuscular volume	Low	Normal
Mean corpuscular hemoglobin	Low	Normal
Reticulocyte hemoglobin content	Low	Normal
Percentage of hypochromic erythrocytes	High	Low
Serum transferrin	High	Low
Serum transferrin receptor	High	Normal
Serum ferritin	Low	High
Serum hepcidin	Low	High

LABORATORY TESTS TO DIFFERENTIATE ANEMIA OF CHRONIC DISEASE FROM IRON-DEFICIENCY ANEMIA.

Variable (serum levels)	Anemia of inflammation	Iron-deficiency anemia	Anemia of inflammation and iron-deficiency anemia
Iron	Reduced	Reduced	Reduced
Transferrin	Reduced to normal	Increased	Reduced
Transferrin saturation	Normal to mildly reduced	Reduced	Reduced
Ferritin	Normal to increased	Reduced	Reduced to normal
sTfR	Normal	Increased	Increased
sTfR index	Normal	Increased	Increased
Signs of inflammation	Present	Absent	Present

Abbreviation: *sTfR*, Soluble transferrin receptor.

DIAGNOSIS OF ANEMIA IN INFLAMMATION / CHRONIC DISEASE

BMA & BMB? : NORMAL CELLULARITY , MARROW HEMOSIDERIN MAY BE INCREASED

* COMPLETE BLOOD COUNT ⟶ MILDLY ↓ HEMOGLOBIN ~ 10-12 g/dL
  - ANEMIA ~  NORMOCYTIC ⟶  MICROCYTIC

* IRON STUDIES

LOW	NORMAL-LOW	NORMAL-INCREASED
~ SERUM IRON ~ TRANSFERRIN SATURATION	~ SERUM IRON TRANSFERRIN ~ TOTAL IRON BINDING CAPACITY	~ SERUM FERRITIN

* HEPCIDIN ↑
  - ASSAYS
    - ~ ✗ WIDELY AVAILABLE

* BONE MARROW EXAMINATION ⟶ MACROPHAGES
  - ✗ ROUTINELY PERFORMED
  - ↑ IRON STORES & ERYTHROID PRECURSOR

- **THERAPEUTIC OPTIONS FOR THE TREATMENT OF ANEMIA OF CHRONIC DISEASE.**
  TREATMENT :UNDERLYING CONDITION, SOME PATIENTS: ERYTHROPOIETIN-STIMULATING AGENTS & IN SEVERE CASES REQUIRE TRANSFUSION.

Treatment	Anemia of chronic disease	Anemia of chronic disease with true iron deficiency
Treatment of underlying disease	Yes	Yes
Transfusions[a]	Yes	Yes
Iron supplementation	No[b]	Yes
Erythropoietin agents	Yes	Yes, in patients who do not have a response to iron therapy

TREATMENT OF ANEMIA IN INFLAMMATION / CHRONIC DISEASE

TREATMENT

* CORRECTING UNDERLYING PROBLEM or DISEASE PROCESS

INFECTION	TUMOR	DIABETES
~ ANTIBIOTICS	~ SURGICAL REMOVAL	~ IMPROVED BLOOD GLUCOSE CONTROL

* INTRAVENOUS IRON THERAPY
  - ~ HEMOGLOBIN (< 7g/dL)
    - ↳ TRANSFUSION w/ PACKED RBCs
    - ↳ ERYTHROPOETIC AGENTS
      - EPOETIN ALFA
      - DARBEPOETIN ALFA

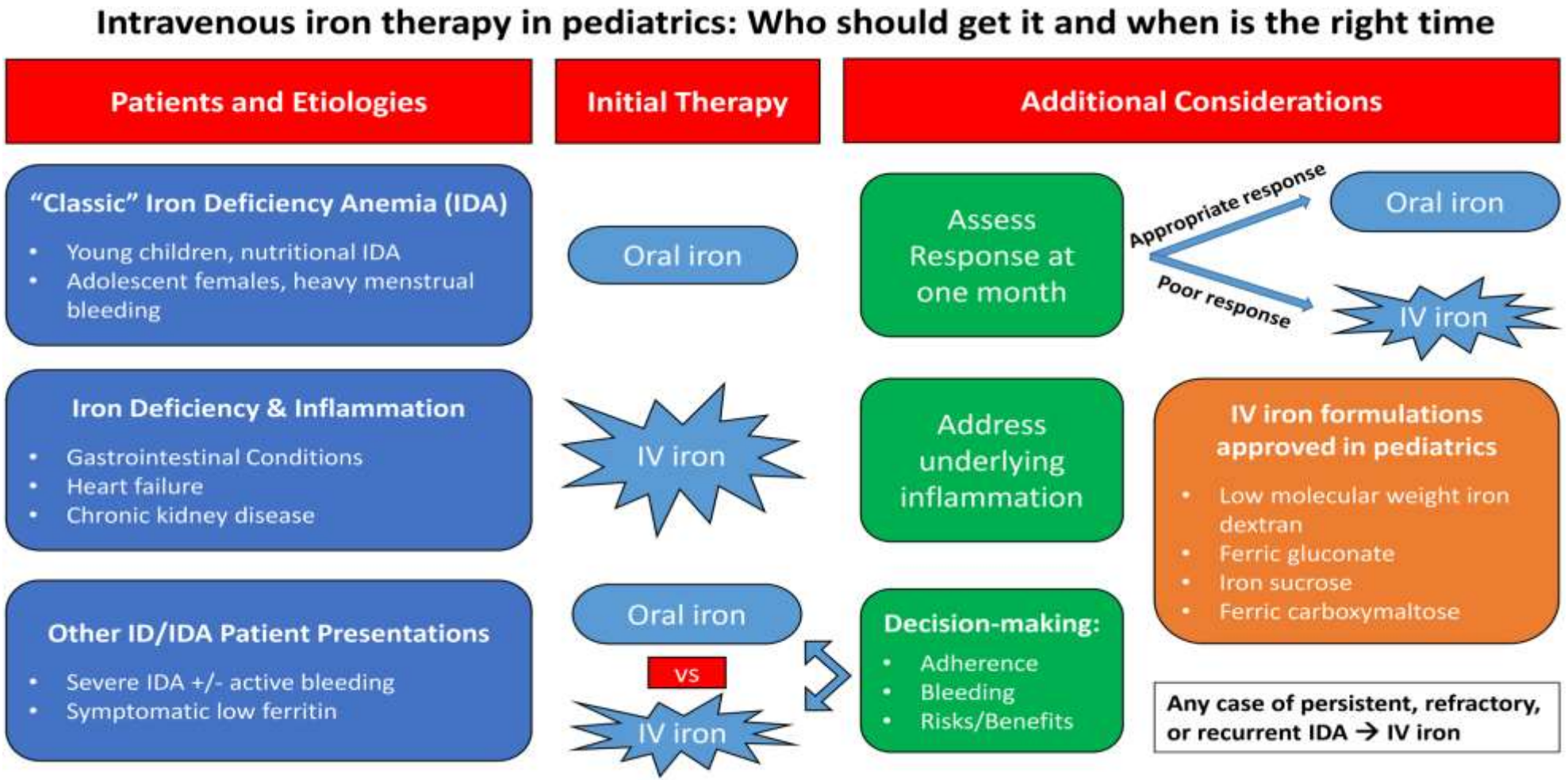
EPO AGENTS:
STIMULATES RED CELL PRODUCTION , DIFF AND SURVIVAL

- **Epoetin alfa -Epogen : 2-3/week**
  - **P;(8 mo-17 Y). 50-400 u/kg SC/IV 2-3 times weekly**
  - Initiate when HB level <10 g/dL, if Hb level approaches or exceeds 11 g/dL, reduce or interrupt
  - **Darbepoetin alpha (DA); Once - Twice /week**
  - **≥1 month:**
  - Initiate treatment when the Hb level is <10 g/dL, If HB level approaches or exceeds 12 g/dL, reduce or interrupt the dose
  - Starting dose ; **(<18 yr) ; 0.45 mcg/kg SC or IV/ q week**

EPO STIMULATETORS

SIDE EFFECTS ? HIGH BLOOD PRESSURE -FEVER - DIZZINESS,NAUSEA,PAIN AT THE SITE OF THE INJECTION.

IV IRON THERAPY IN PEDIATRICS, WHO SHOULD GET IT AND WHEN IS THE RIGHT TIME



IV IRON THERAPY IN PEDIATRICS, WHO SHOULD GET IT AND WHEN IS THE RIGHT TIME

Iron sucrose

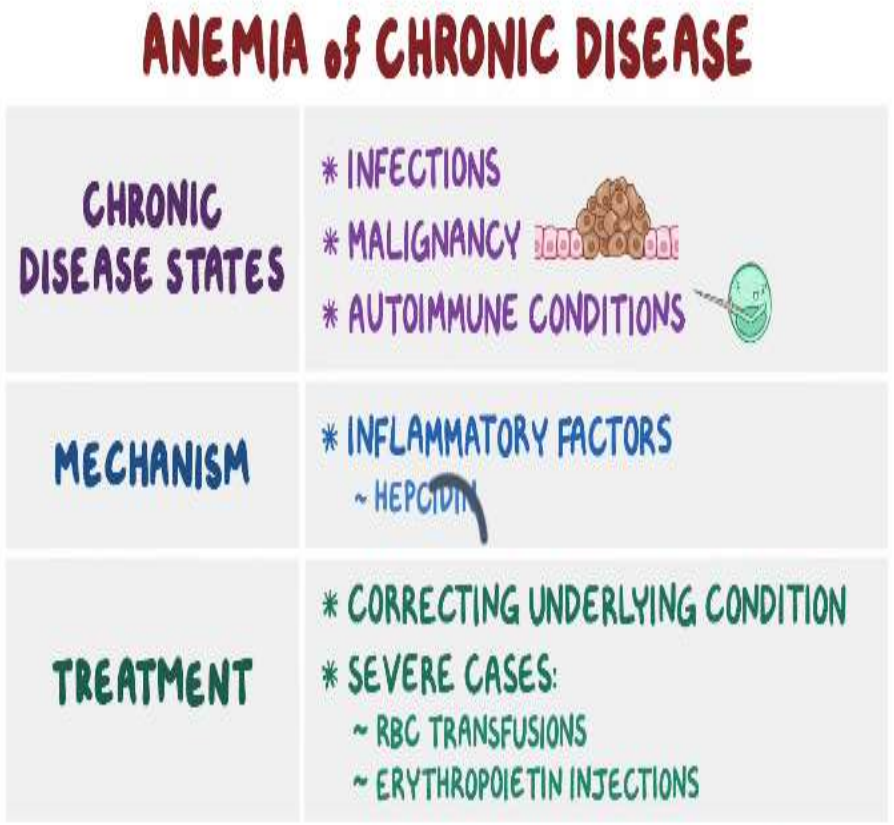
IV IRON FORMULATIONS WITH FDA-APPROVED INDICATIONS IN CHILDREN

Formulation	Approved pediatric indication	Approved dosing and administration notes*
Iron dextran†	Children over 4 months of age	Dose (mL) = 0.0442 (Desired Hgb – Observed Hgb) × LBW + (0.26 × LBW) Requires test dose prior to full therapeutic dose
Iron sucrose	Iron maintenance in patients ≥2 years with dialysis-dependent or non-dialysis-dependent CKD receiving erythropoietin therapy	Dose = 0.5 mg/kg, not to exceed 100 mg per dose every 2 weeks (for hemodialysis-dependent patients) or 4 weeks (for non-dialysis-dependent patients on erythropoietin therapy) for 12 weeks
Ferric gluconate	Treatment of IDA in pediatric patients ≥6 years undergoing chronic hemodialysis receiving erythropoietin therapy	Dose = 0.12 mL/kg (1.5 mg/kg of elemental iron) administered intravenously over 1 hour during 8 sequential dialysis sessions (maximum 125 mg per dose)
Ferric carboxymaltose	Treatment of children aged >1 year with IDA who are intolerant of oral iron or who have unsatisfactory response to oral iron	Patients <50 kg: 15 mg/kg/dose for 2 doses Patients ≥50 kg: 750 mg/dose for 2 doses Separate doses by at least 7 days Alternative dose is 15 mg/kg (maximum 1000 mg) as single infusion Associated with hypophosphatemia

CONCLUSIONS

- Anemia of inflammation is a highly prevalent syndrome associated with **systemic inflammation.**
- AI anemia:N**ormocytic, normochromic anemia** ,with **low transferrin saturation , high serum ferritin level.**
- **Treatment approaches; directed at the underlying disease**
- **Increased understanding of the pathogenesis ;ongoing development of targeted therapies that may offer additional treatment options in the future.**

ANEMIA OF INFLAMMATION / CHRONIC DISEASEANEMIA



Thank you