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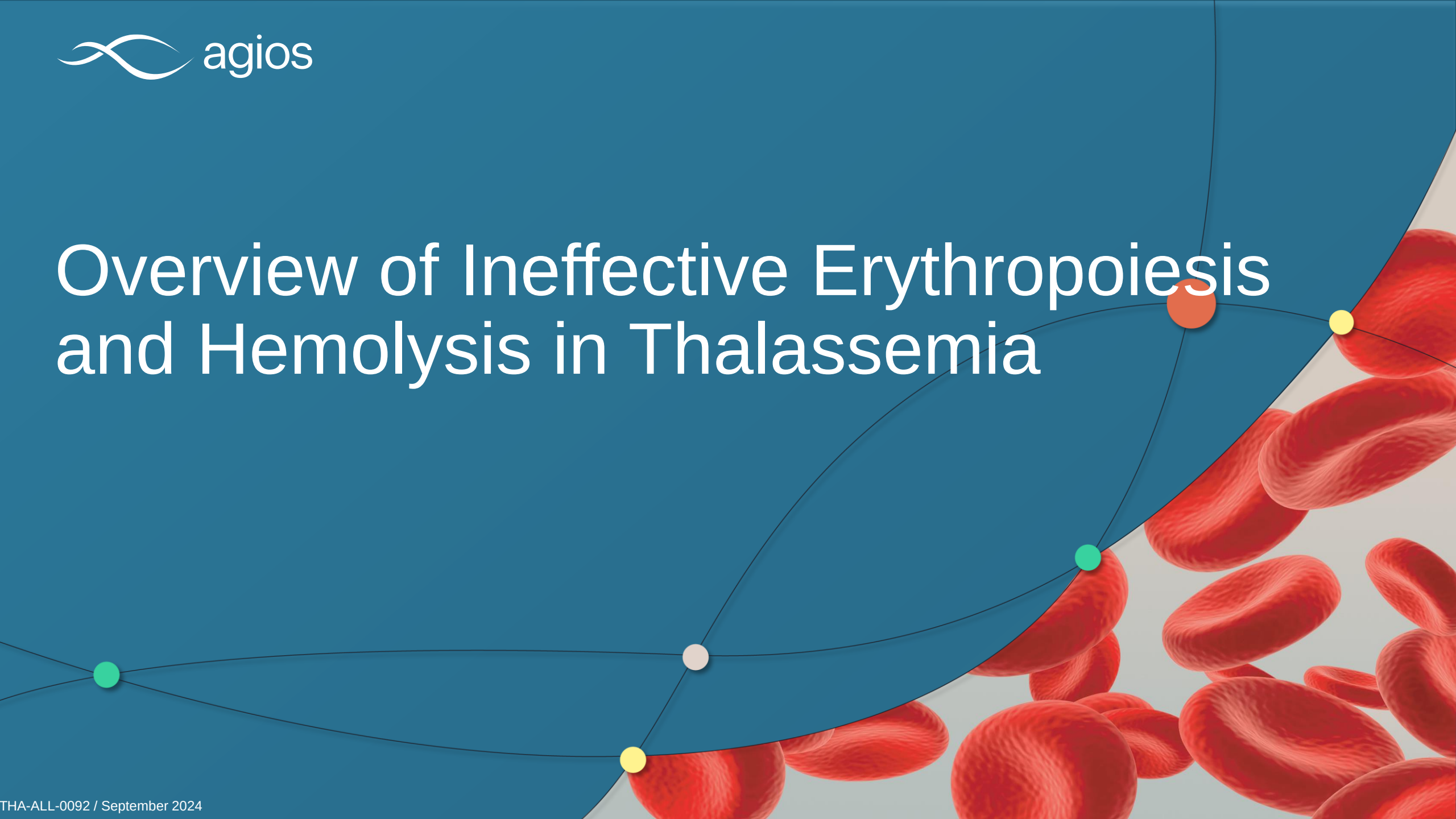
Overview of Ineffective Erythropoiesis and Hemolysis in Thalassemia



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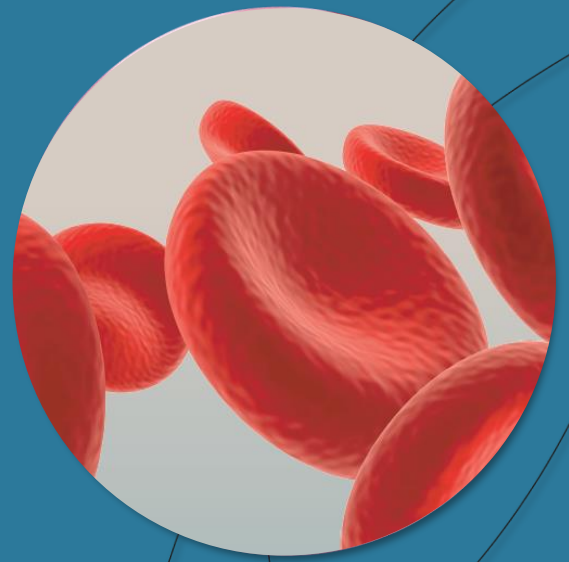
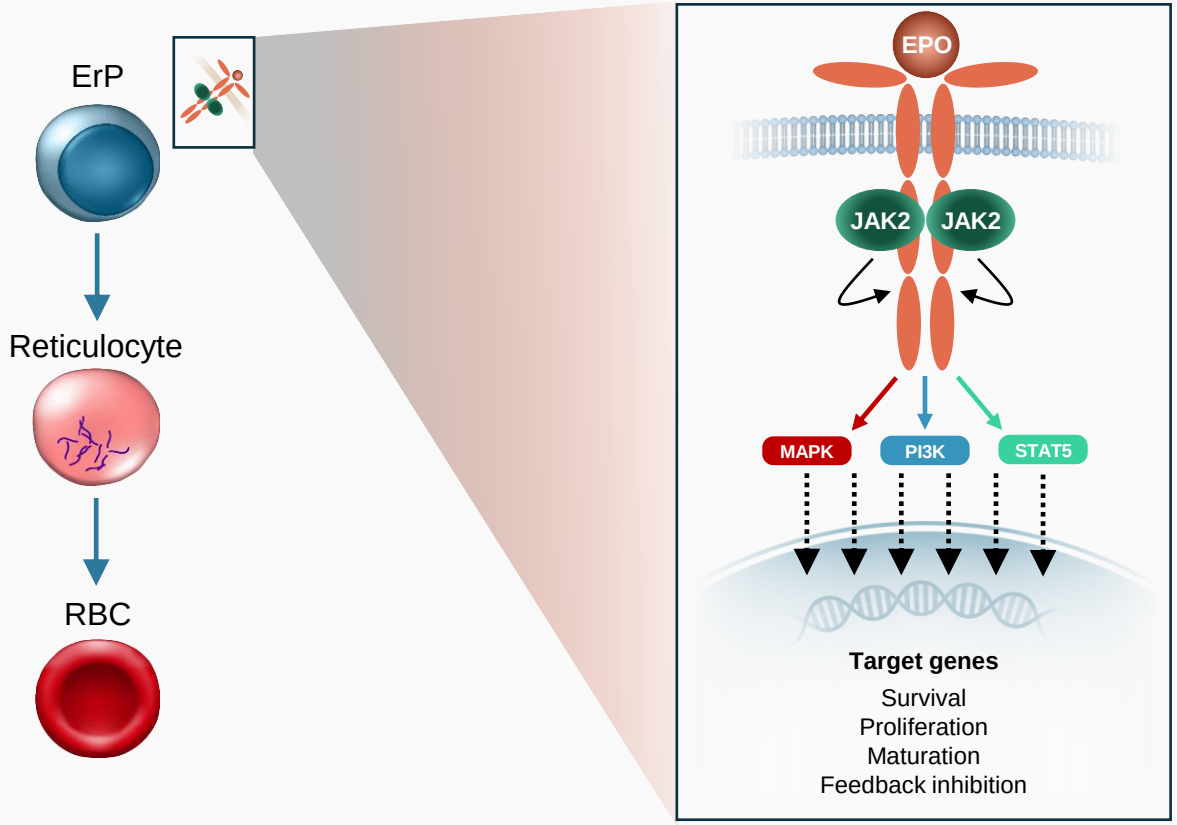
Overview of Anemia



Erythropoietin Plays a Central Role in Erythropoiesis

- Production of EPO is regulated by an **oxygen-sensitive** feedback loop[1–3]
  - Low levels of oxygen tension stimulate secretion of **EPO** by the kidneys
  - Circulating EPO binds to the **EpoR on ErP** cells of the bone marrow, leading to the stimulation of **JAK2**
    - Activation of JAK2 initiates multiple signaling pathways that support differentiation into **mature RBCs**
  - The major pathways activated by **EpoR-targeted genes** support survival, proliferation, and differentiation of ErP cells, a critical aspect in maintaining the **homeostasis** of RBCs

EPO binds to EpoR on ErP cells to initiate JAK2 activation[1,2,4,5]



Dysregulated EPO is a key contributor to pathogenesis in various forms of anemia[6]

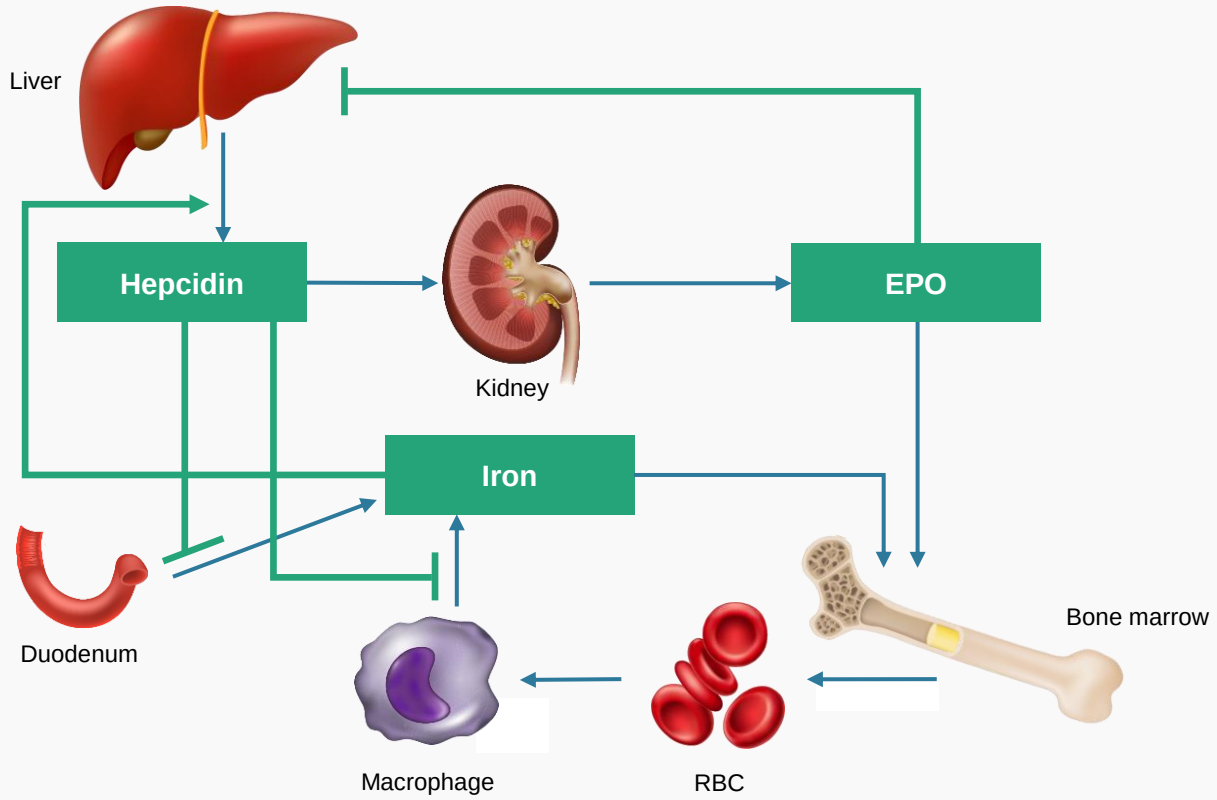
EPO, erythropoietin; EpoR, erythropoietin receptor; ErP, erythroid progenitor; JAK2, Janus kinase 2; MAPK, mitogen-activated protein kinase; PI3K, phosphoinositide 3-kinase; RBC, red blood cell; STAT, signal transducer and activator of transcription.

1. Bhoopalan SV, et al. *F1000Res* 2020;9:(Faculty Rev):1153. 2. Watowich SS. *J Investig Med* 2011;59(7):1067–72. 3. Elliott S, et al. *Ann Hematol* 2014;93(2):181–92. 4. Zhao W, et al. *Blood* 2006;107(3):907-15. 5. Gobert S, et al. *Eur J Biochem* 1995;234(1):75-83. 6. Turner J, et al. In: StatPearls [Internet]. StatPearls Publishing; 2023.

The Production of Healthy RBCs Depends on Iron Homeostasis and is Regulated by Erythropoietin and Hepcidin

- Produced by the liver, **hepcidin** regulates **iron homeostasis** by inhibiting enteral iron absorption and the release of iron into the circulation[1–3]
- **EPO** is produced by the kidneys and inhibits hepcidin synthesis, increasing the **availability of iron** in the bloodstream needed for erythropoiesis[4–6]

Mechanism of RBC production[9]



Iron homeostasis is crucial to the function of all organs in the body but is altered in some forms of anemia[7-9]

EPO, erythropoietin; RBC, red blood cell.

1. Pagani A, et al. *Front Physiol* 2019;10:1294. 2. Aschemeyer S, et al. *Blood* 2018;131(8):899–910. 3. Nemeth E, et al. *Science* 2004;306(5704):2090–93. 4. Jelkmann W. *Transfus Med Hemother* 2013;40(5):302–9. 5. Grootendorst S, et al. *Int J Mol Sci* 2021;22(4):2204. 6. Reissmann K. *Blood* 1950;5(4):372–80. 7. Pootrakul P, et al. *Blood* 1988;71(4):1124–29. 8. Cazzola M. *Blood* 2022;139(16):2460–70. 9. Correnti M, et al. *Int J Mol Sci* 2022;23(10):5341.

Processes Implicated in the Pathogenesis of Anemia

- Anemia is characterized by low concentrations of hemoglobin or hematocrit, resulting in decreased oxygen-carrying capacity of RBCs and **low oxygen conditions** that can impact any organ[1]

Ineffective erythropoiesis (IE)[2–6]

- Inability to produce an adequate number of RBCs in the presence of increased immature erythroid precursors in the bone marrow is associated with both α- and β-thalassemia
  - **β-thalassemia:** Unbound α-globin chains form unstable homotetramers, which accumulate and precipitate in RBC precursors in the bone marrow, leading to IE
  - **α-thalassemia:** Unstable HbH (a tetramer of β-globins) can be oxidized into intracellular precipitates, which cause IE

Hemolysis[4,7–9]

- The breakdown of erythrocytes results in expulsion of Hb and cytoplasmic contents into the surrounding fluid and circulation
  - **β-thalassemia:** α-globin tetramers promote generation of cytotoxic ROS in maturing reticulocytes and RBCs, resulting in hemolysis
  - **α-thalassemia:** Formation of HbH that aggregates in RBCs and results in hemolysis*

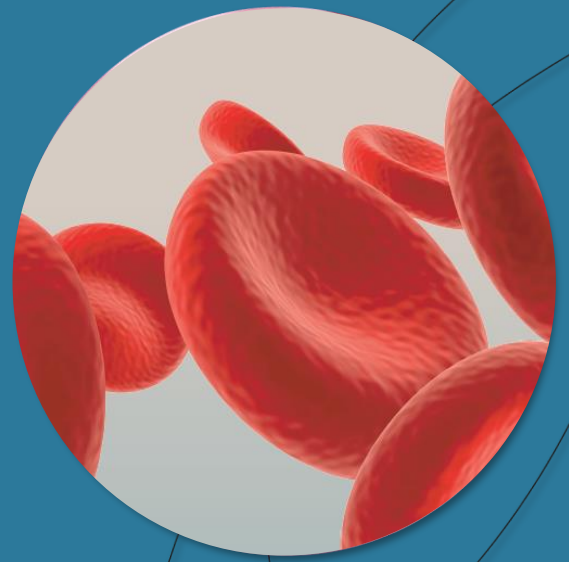
Disease Mechanisms Implicated in Thalassemia

Production of the correct ratio of α- and β-globin chains is important for proper function and survival of Hb, and health of RBCs[5,10]

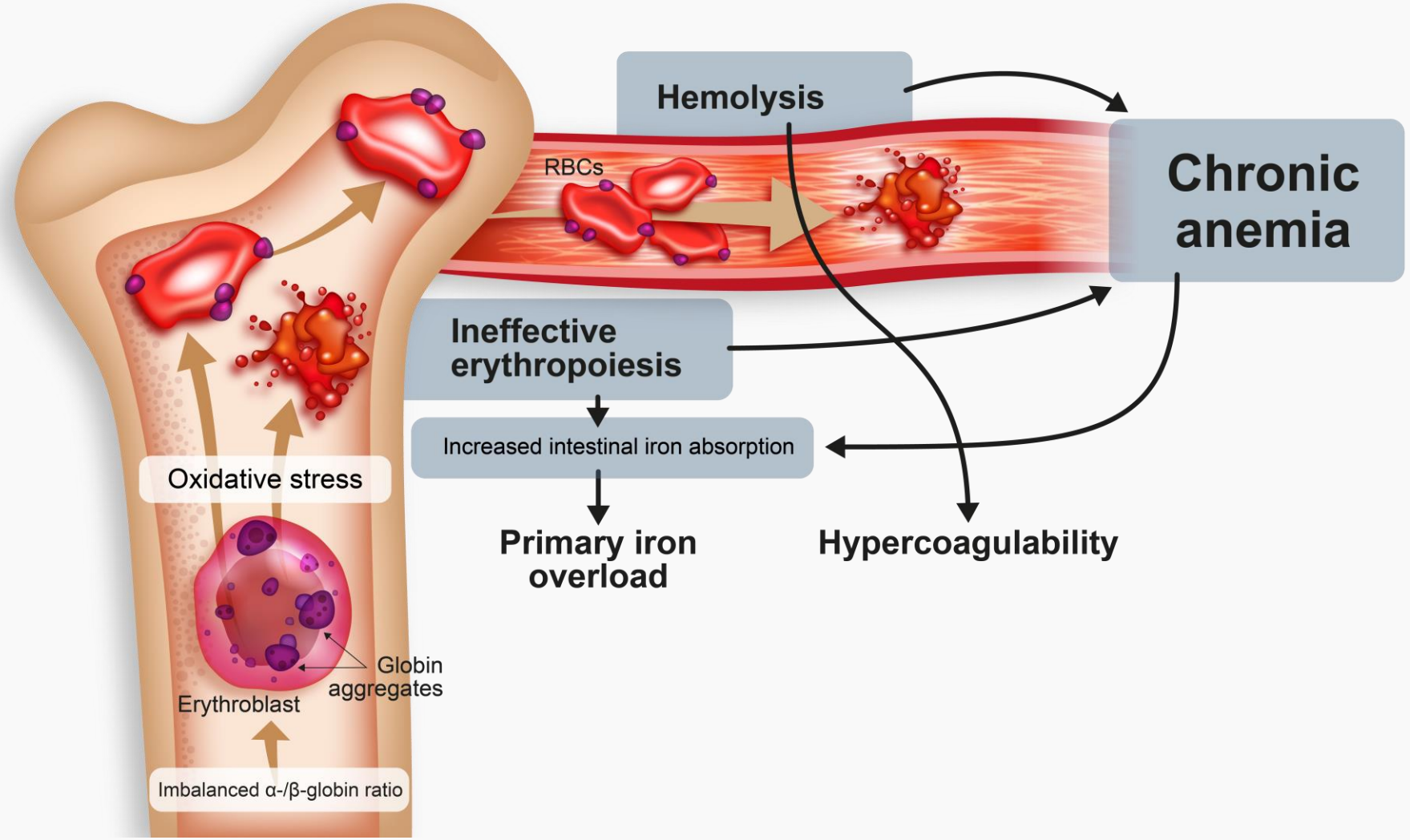
EPO, erythropoietin; Hb, hemoglobin; HbH, hemoglobin H; RBC, red blood cell; ROS, reactive oxygen species.

1. Fonseca AC, et al. *Curr Neurol Neurosci Rep* 2021;21:51. 2. Taher AT, et al. *N Engl J Med* 2021;384(8):727–43. 3. Mathias LA, et al. *Exp Hematol* 2000;28(12):1343–53. 4. Bajwa H, et al. Thalassemia [Updated 2023 Aug 8]. In: StatPearls [Internet]. StatPearls Publishing; 2023. 5. Muncie HL Jr, et al. *Am Fam Physician* 2009;80(4):339–44. 6. Chui DH, et al. *Blood* 2003;101(3):791–800. 7. Taher AT, et al. *Lancet* 2018;391(10116):155–67. 8. Orrico F, et al. *Biomolecules* 2023;13(8):1262. 9. Sikora J, et al. *Blood* 2014;124(13):2150–57. 10. Barbarani G, et al. *Front Genome Ed* 2020;2:571239.

Overview of Ineffective Erythropoiesis and Hemolysis in Thalassemia



Overview: Pathophysiology of Thalassemia



RBC, red blood cell

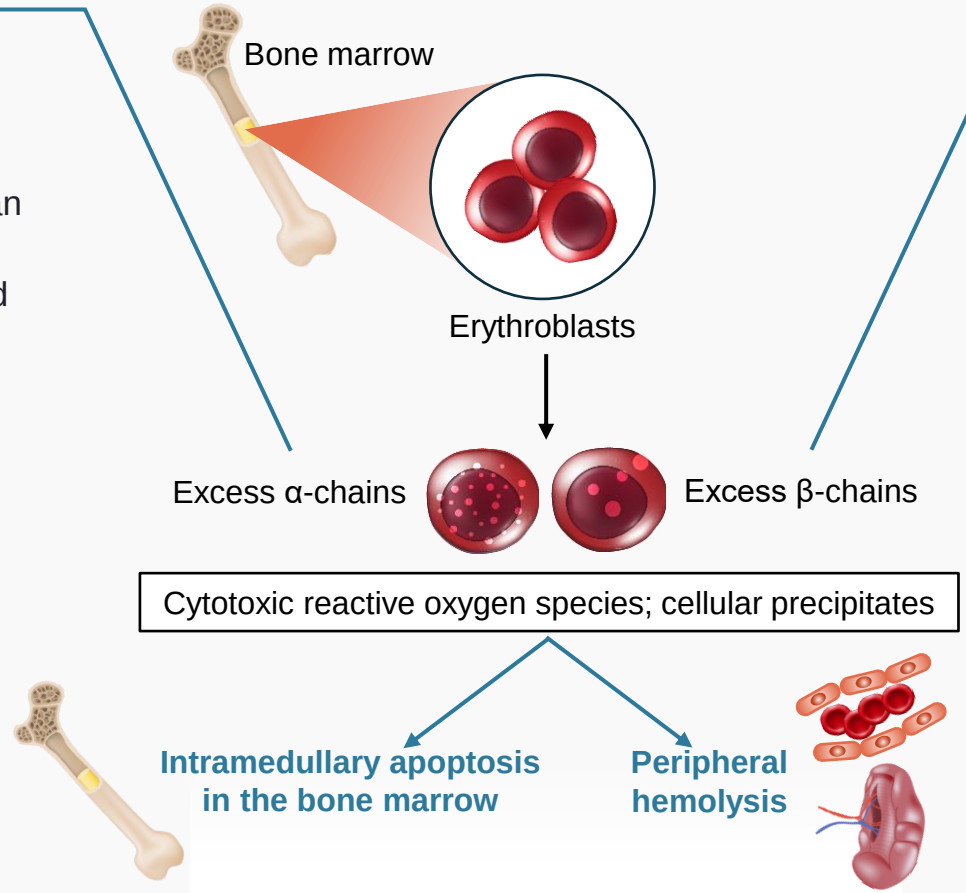
Taher A, et al. *N Engl J Med* 2021;384;(8)727–43.

IE and Chronic Hemolysis are Pathologic Drivers of Anemia in Thalassemia

Mechanism of IE and hemolysis in thalassemia[1–3]

β-thalassemia[1–5]

- Decrease or loss of **β-globin** chain production
- Excessive unstable **α-globin** chain precipitates, which are less soluble than HbH seen in α-thalassemia
- α-globin chains **precipitate** in erythroid precursors as well as mature RBCs, leading to IE and the generation of **defective RBC precursors**, seen in:
  - Intramedullary apoptosis of late-stage erythroblasts
  - Extramedullary hemolysis due to the presence of insoluble α-globin chains in circulating cells



α-thalassemia[6–9*]

- Decrease or loss of **α-globin** chain production or impaired function
- Excess unbound **β-globin** chains and accumulation of unstable HbH
- **Apoptosis** of maturing nucleated erythroid cells and **IE**
- **Non-deletional**
  - Inheritance of 2 deleted genes and 1 gene carrying a non-deletional abnormality (ie, point mutation) that disrupts normal α-globin chain formation
  - Results in unstable hemoglobin that precipitates in RBCs, forming insoluble inclusion bodies that damage and/or destroy the cell membrane
  - In non-deletional HbH disease, intramedullary death of erythroblasts leads to IE
- **Deletional**
  - HbH tetramers are soluble and do not aggregate during erythropoiesis, but are present in mature RBCs, leading to hemolysis

*γ-globin tetramers, called Hb Bart's, are mostly found *in utero* and in neonates[9]

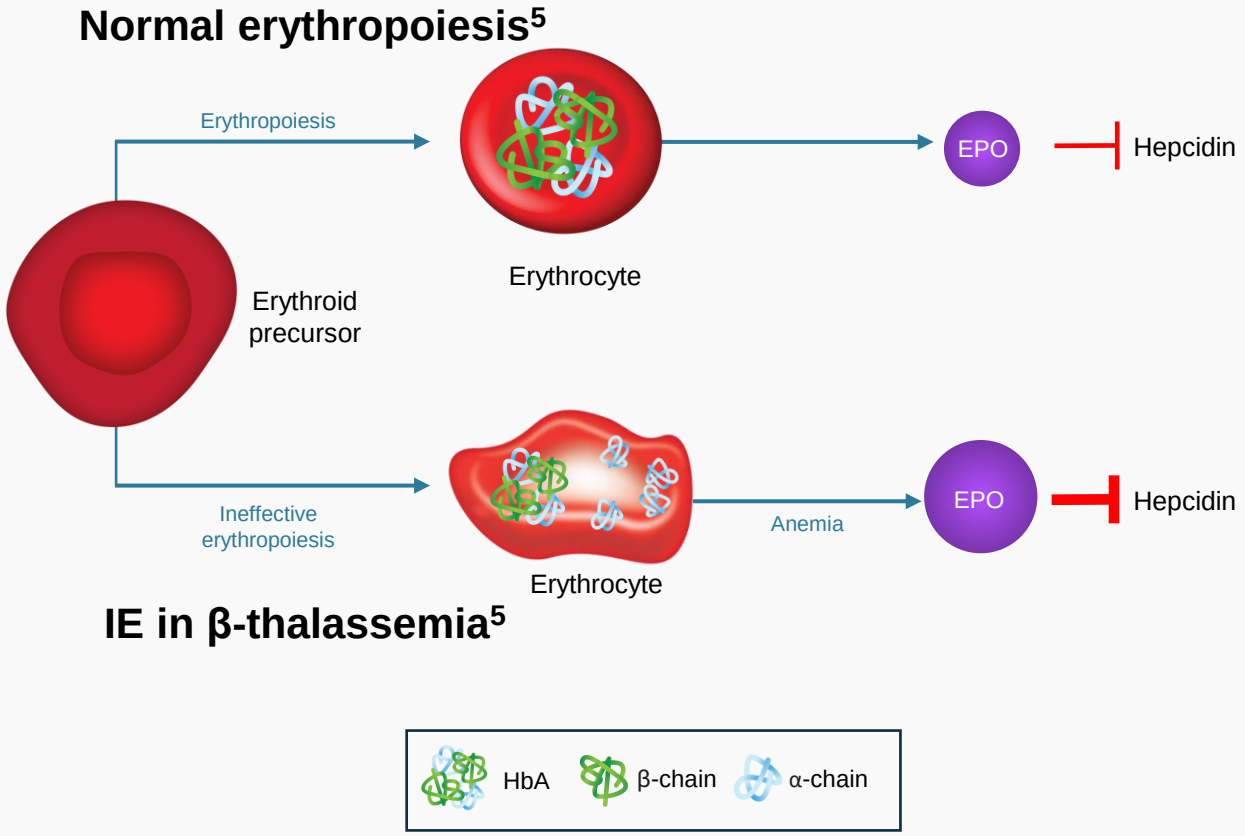
IE leads to cell death either within the marrow (apoptosis) or cell death outside the marrow (hemolysis)[10,11]

HbH, hemoglobin H; IE, ineffective erythropoiesis; RBC, red blood cell.

1. Rachmilewitz EA, et al. *Blood* 2011;118(13):3479–88; 2. Taher AT, et al. *N Engl J Med* 2021;384(8):727–43; 3. Bajwa H, et al. StatPearls [Internet]. StatPearls Publishing. 2023; 4. Khandros E, et al. *Blood* 2012;119(22):5265–75; 5. Sorenson S, et al. *Blood* 1990;75(6):1333–36; 6. Harewood J, et al. StatPearls [Internet]. StatPearls Publishing. 2023; 7. Kalle Kwaifa I, et al. *Orphanet J Rare Dis* 2020;15:166; 8. Taher AT, et al. *Lancet* 2018;391(10116):155–67; 9. Vichinsky EP, et al. *Cold Spring Harb Perspect Med* 2013;3(5):a011742; 10. Rivella S. *Curr Opin Hematol* 2009;16(3):187–94; 11. Centis F, et al. *Blood* 2000;96(10):3624-29.

Chronic Anemia from IE and Hemolysis Drives Dysregulation of EPO and Hepcidin

- In thalassemia, **IE and hemolysis** cause a chronic shortage of RBCs, leading to chronic **anemia**; the resultant hypoxia drives compensatory erythropoietic activity leading to a persistent increase in **EPO** and subsequent pathological inhibition of **hepcidin**[1–5]
- Erythroid marrow expands, unable to respond adequately to EPO, leading to **hyperplasia** and further perpetuating production of IE and EPO[3,4]
  - Erythroid expansion driven by IE also contributes to bone deformity and is associated with osteopenia[6,7]



Dysregulation of EPO and hepcidin signaling, and the subsequent compensatory responses, can lead to iron overload and its associated sequelae[3,4]

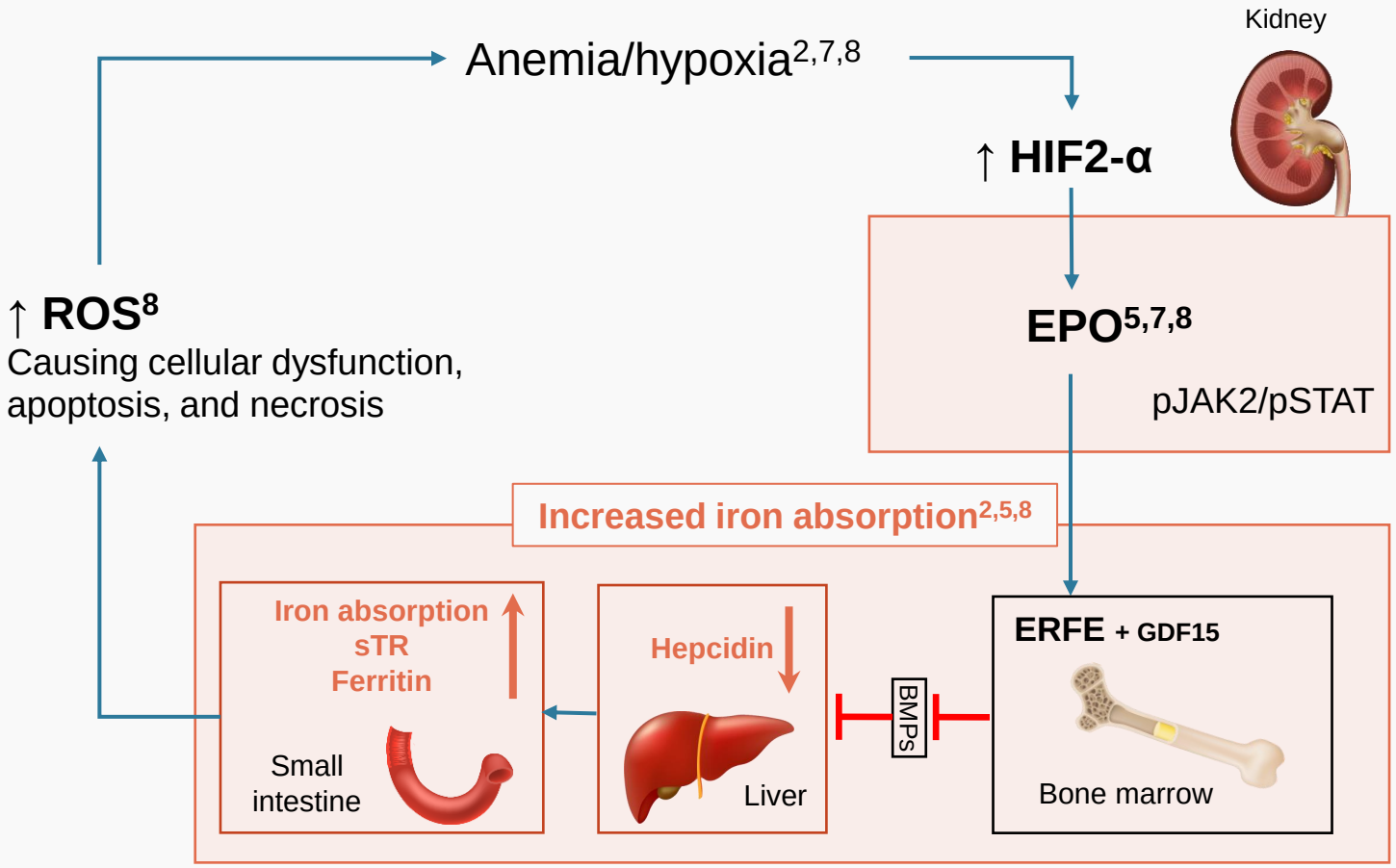
EPO, erythropoietin; HbA, hemoglobin A; IE, ineffective erythropoiesis; RBC, red blood cell.

1. Muncie HL et al. *Am Fam Physician* 2009;80(4):339–44. 2. Rivella S. *Blood Rev* 2012;26(1)(suppl 1):S12–S15. 3. Melchiori L, et al. *Adv Hematol* 2010;2010:938640.
4. Nicolas G, et al. *Blood Cells Mol Dis* 2002;29(3):327–35. 5. Gardenghi S, et al. *Hematol Oncol Clin North Am* 2010;24(6)1089–1107. 6. Morabito N, et al. *J Bone Miner Res* 2004;19(5):722–27.
7. De Sanctis V, et al. *Metabolism* 2018;80:66–79.

Iron Loading Anemia is Triggered by IE

- In response to **hypoxia** and **HIF2-α**, increased **EPO** released from the kidney suppresses hepcidin via **ERFE** secretion from erythroblasts in the marrow[1–4]
  - **GDF15** is another stress erythropoiesis factor that is being investigated in regulating production of hepcidin[5]
  - Excessive iron can also cause the generation of **ROS**, which may further damage cellular components and contribute to hypoxia[6]

Iron loading and erythropoiesis[2,5,7,8]



BMP, bone morphogenic protein; EPO, erythropoietin; ERFE, erythroferrone; GDF15, growth differentiation factor 15; HIF2α, hypoxia inducible factor 2α; IE, ineffective erythropoiesis; pJAK2, phosphorylated Janus activating kinase 2; pSTAT, phosphorylated signal transducer and activator of transcription; ROS, reactive oxygen species; sTR, soluble transferrin.

1. Scortegagna M, et al. *Blood* 2005;105(8):3133–40. 2. Kautz L, et al. *Nat Genet* 2014;46(7):678–84. 3. Nicolas G, et al. *J Clin Invest* 2002;110(7):1037–44. 4. Pak M, et al. *Blood* 2006;108(12):3730–35. 5. Tanno T, et al. *Nat Med* 2007;13(9):1096–101. 6. Jin X, et al. *Haematologica* 2018;103(10):1627–34. 7. Gupta R, et al. *Hematol Oncol Clin North Am* 2018;32(2):213–21. 8. Saad HKM, et al. *Biomedicines* 2022;10(1):189.

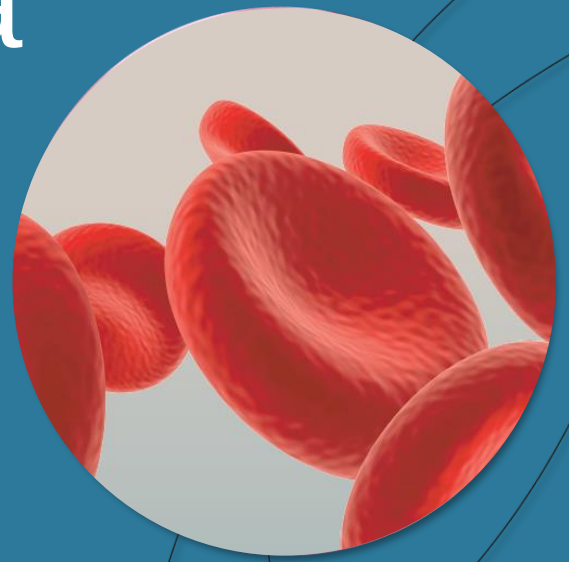
Biomarkers of IE, Hemolysis, and Iron Homeostasis

Biomarker	Healthy reference range	Patients with thalassemia
Hemoglobin concentration (g/dL)[1,2]	11.6–16.6	↓ Decreased
Hemolytic biomarkers[3-9]		
Lactate dehydrogenase (U/L)	122–222	↑ Increased
Haptoglobin (mg/dL)	30–200	↓ Decreased
Reticulocyte count (x109/L)	30.4–110.9	↑ Increased
Total bilirubin (mg/dL)	≤1.2	↑ Increased
Erythropoietic biomarkers[10-15]		
Erythropoietin (mIU/mL)	2.6–18.5	↑ Increased
Nucleated RBCs (%)	0–0.3	↑ Increased
Soluble transferrin receptor (mg/L)	1.8–4.6	↑ Increased
Iron biomarkers[16-20]		
Ferritin (mcg/L)	11–409	↑ Increased
Iron (mcg/dL)*	35–150	↑ Increased
Iron transferrin saturation (%)	14–50	↑ Increased
Hepcidin (nM)*	0.5–23.3	↓ Decreased

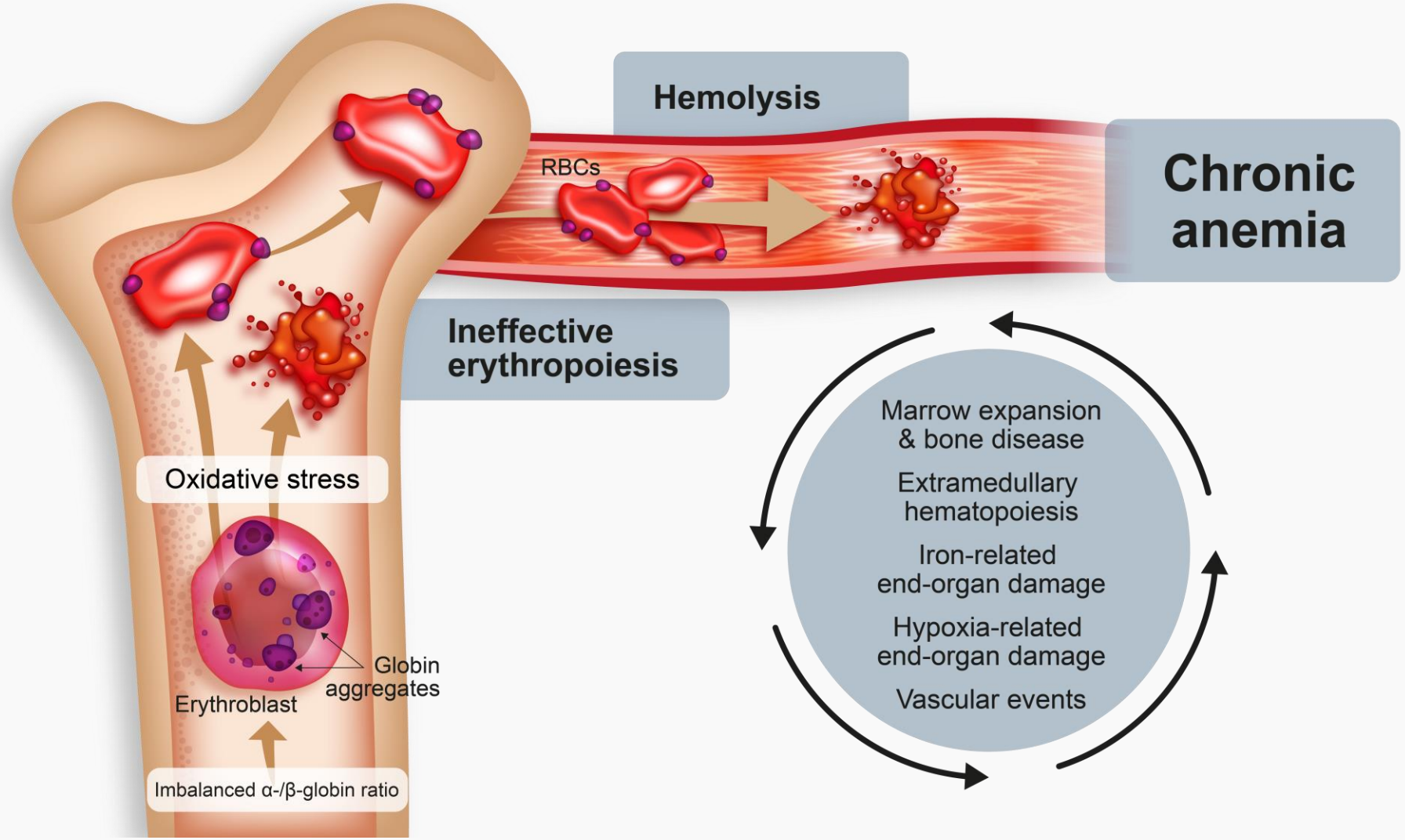
*Serum. IE, ineffective erythropoiesis; RBC, red blood cell.

1. Hemoglobin test. Mayo Foundation for Medical Education and Research. https://www.mayoclinic.org/tests-procedures/hemoglobin-test/about/pac-20385075. 2. Coates TD. *Free Radic Biol Med* 2014;72:23–40. 3. Test ID: LD. Lactate Dehydrogenase (LDH), Serum. Mayo Foundation for Medical Education and Research. https://www.mayocliniclabs.com/test-catalog/overview/8344#Clinical-and-Interpretive. 4. Test ID: HAPT. Haptoglobin, Serum. Mayo Foundation for Medical Education and Research. https://www.mayocliniclabs.com/test-catalog/overview/9168#Clinical-and-Interpretive. 5. Test ID: RTIC. Reticulocytes, Blood. Mayo Foundation for Medical Education and Research. https://www.mayocliniclabs.com/test-catalog/overview/9108#Clinical-and-Interpretive. 6. Test ID: BILI3. Bilirubin, Serum. Mayo Foundation for Medical Education and Research. https://www.mayocliniclabs.com/test-catalog/overview/8452#Clinical-and-Interpretive. 7. Toren A, et al. *Am J Hematol* 1996;51(2):166–167. 8. Ragab SM, et al. *Mediterr J Hematol Infect Dis* 2015;7(1):e2015019. 9. Borgna-Pignatti C, et al. *Haematologica* 2003;88(10):1106–1109. 10. Test ID: EPO. Erythropoietin, Serum. Mayo Foundation for Medical Education and Research. https://www.mayocliniclabs.com/test-catalog/overview/80173#Clinical-and-Interpretive. 11. CHH-CBC with Differential. OHSU. https://www.ohsu.edu/lab-services/chh-cbc-differential;. 12. Test ID: STFR. Soluble Transferrin Receptor (sTfR), Serum. Mayo Foundation for Medical Education and Research. https://www.mayocliniclabs.com/test-catalog/Overview/84283. 13. Chaisiripoomkere W, et al. *Southeast Asian J Trop Med Public Health*. 1999;30(4):786-788. 14. Danise P, et al. *Clin Chem Lab Med* 2009;47(12):1539–42. 15. Demir A, et al. *J Trop Pediatr* 2004;50(6):369–71. 16. Test ID: FERR1. Ferritin, Serum. Mayo Foundation for Medical Education and Research. https://www.mayocliniclabs.com/test-catalog/Overview/619953#Clinical-and-Interpretive. 17. Test ID: FEC. Iron and Total Iron-Binding Capacity, Serum. Mayo Foundation for Medical Education and Research. https://www.mayocliniclabs.com/test-catalog/overview/34624#Clinical-and-Interpretive. 18. Olivieri NF, et al. *N Engl J Med* 1994;331(9):574–78. 19. Sagare A, et al. *Res J Pharm Biol Chem Sci* 2014; 5(1):668–73. 20. Galesloot TE, et al. *Blood* 2011;117(25):e218–e225. All webpages accessed Aug 22/23, 2024.

Complications of Ineffective Erythropoiesis and Hemolysis in Thalassemia



Overview: Complications in Thalassemia

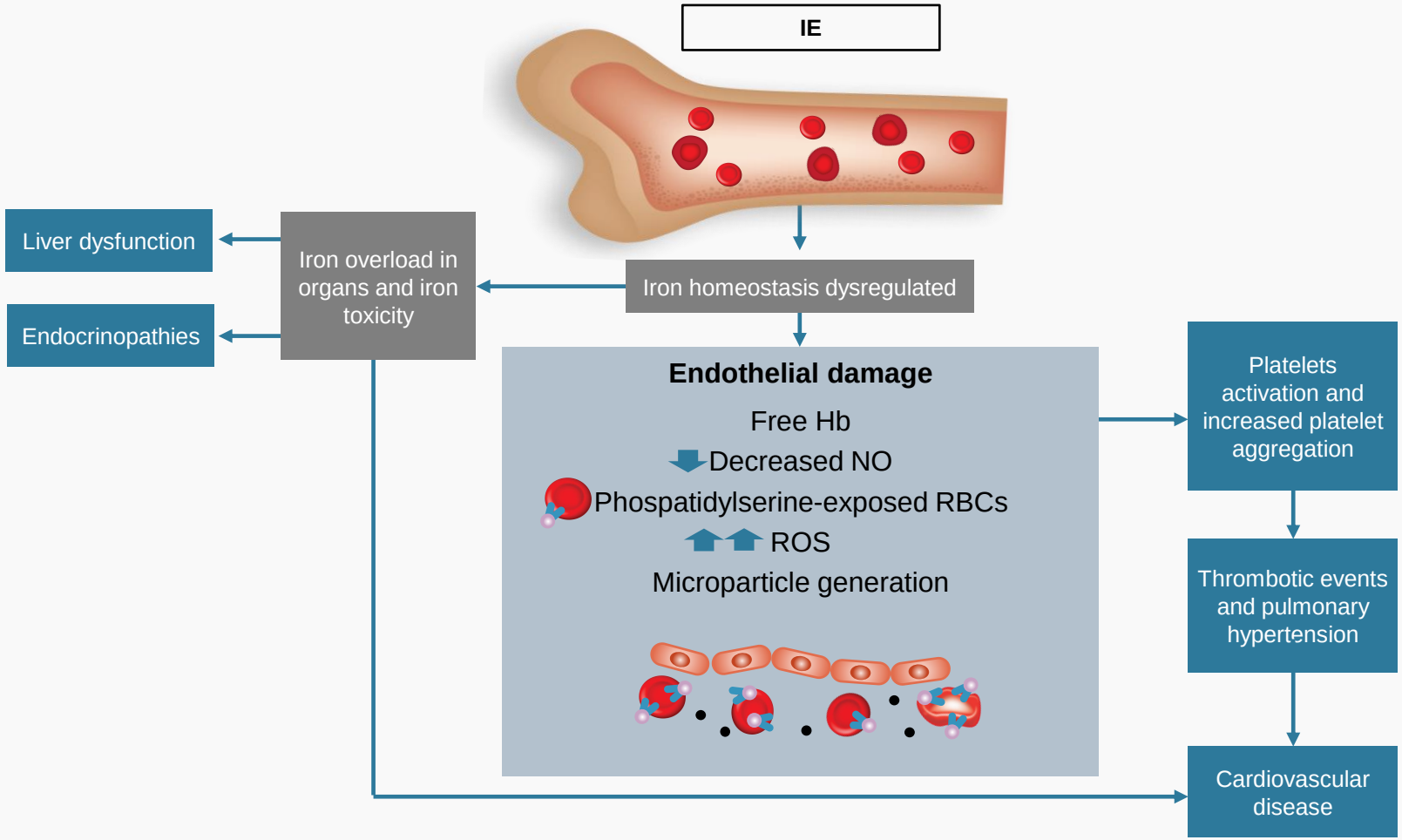


RBC, red blood cell.

Taher A, et al. *N Engl J Med* 2021;384;(8)727–43.

IE Contributes to Iron Overload, Which Drives Multiple Downstream Complications in Thalassemia

IE and iron overload in thalassemia[1]



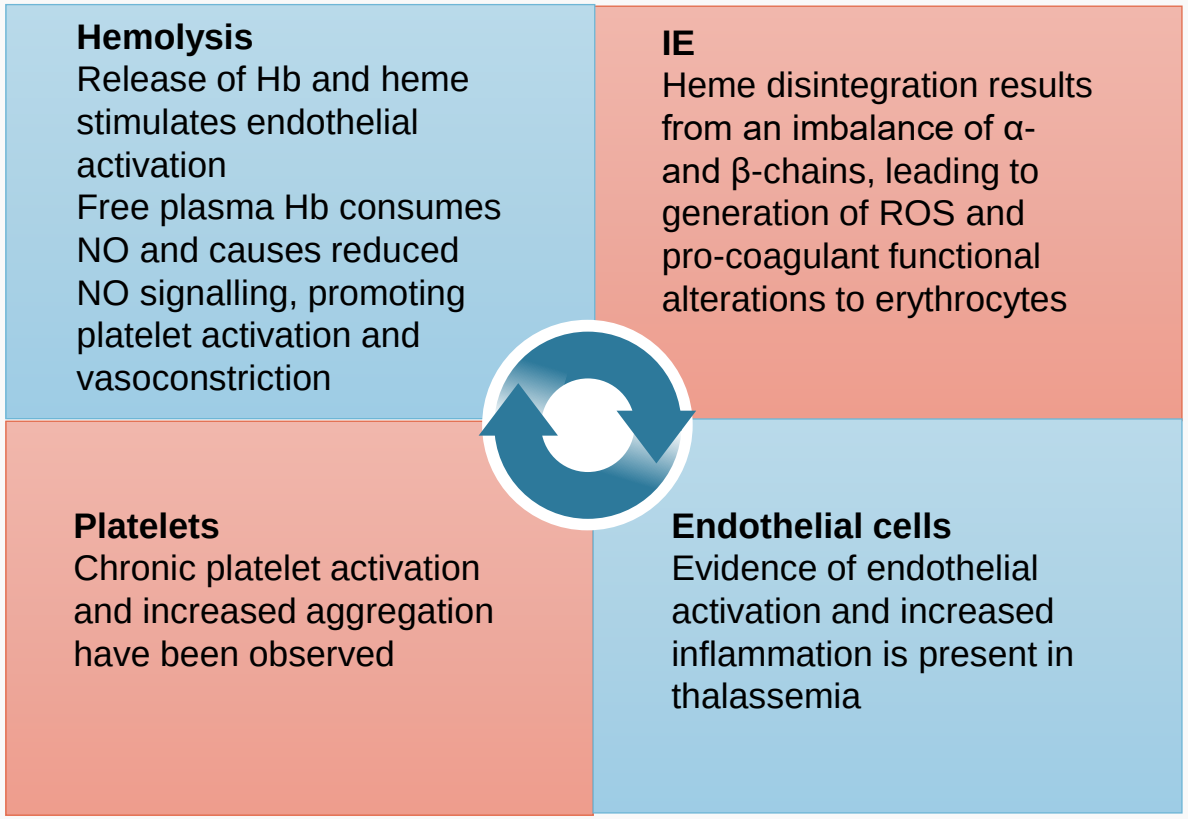
- **Iron overload** can lead to liver dysfunction, including fibrosis, cirrhosis, or endocrinopathies[1,2]
- Excessive iron deposits in organs are one of the leading causes of **morbidity** and **mortality** in thalassemia[3,4]

Hb, hemoglobin; IE, ineffective erythropoiesis; NO, nitric oxide; RBC, red blood cell; ROS, reactive oxygen species.

1. Kattamis A, et al. *Lancet* 2022;399(10343):2310–24. 2. Thalassemia: Complications and Treatment. Centers for Disease Control and Prevention. Updated Apr 27, 2023. Accessed Nov 16, 2023. https://www.cdc.gov/ncbddd/thalassemia/treatment.html 3. Taher AT, et al. *Hematology Am Soc Hematol Educ Program* 2017;2017(1):265–71. 4. Musallam KM, et al. *Haematologica* 2021;106(9):2489–91.

IE and Hemolysis Contribute to Hypercoagulation in Patients with Thalassemia via Several Mechanisms

Several mechanisms have been implicated in the pathogenesis of hypercoagulation in thalassemia[1–9]



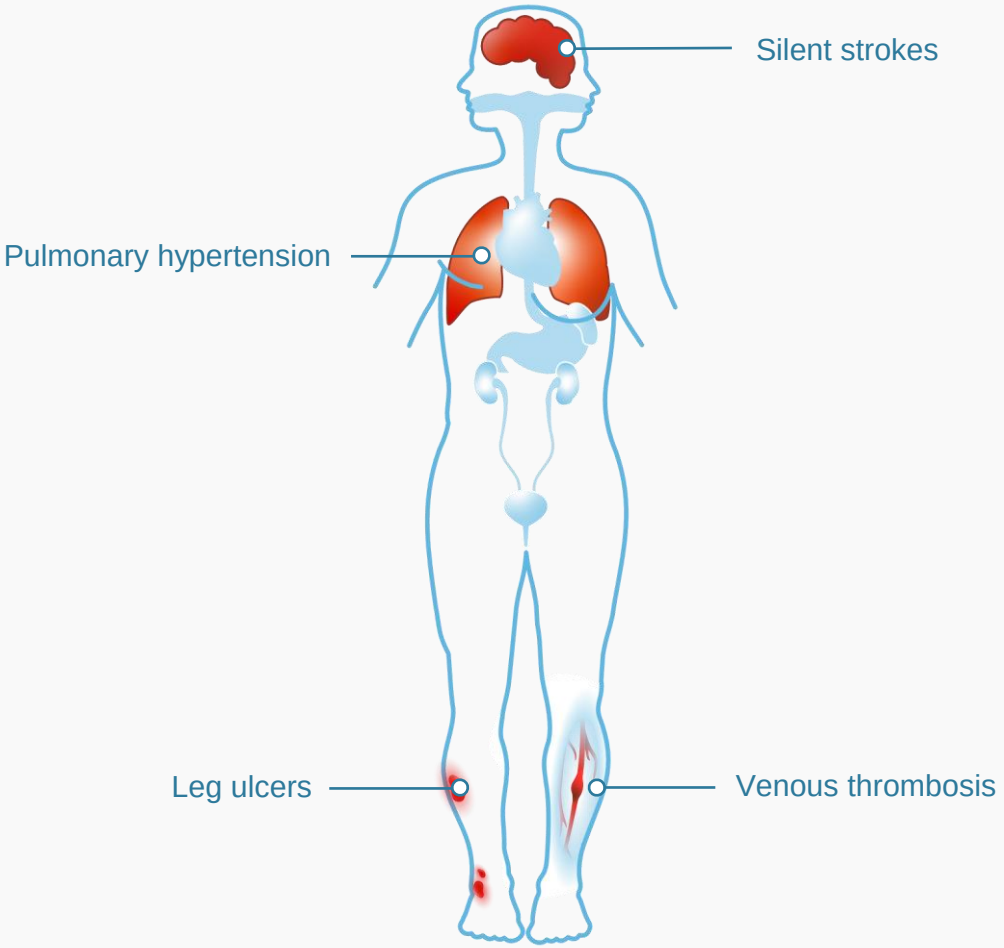
- An elevated (>4-fold) risk of **thromboembolic events** was found with **NTDT**, supported by an analysis of patients (n=8860) with **β-thalassemia major** vs **β-thalassemia intermedia**[10,11]
- Although less common in **TDT**, potentially due to the suppression of IE and hemolysis by transfusions, **thromboembolic events** can still occur in 4% of these patients[12–15]

Hb, hemoglobin; IE, ineffective erythropoiesis; NO, nitric oxide; NTDT, non–transfusion-dependent thalassemia; RBC, red blood cell; ROS, reactive oxygen species; TDT, transfusion-dependent thalassemia

1. Musallam KM, et al. *Haematologica* 2013;98(6):833–44. 2. Rivella S. *Curr Opin Hematol* 2009;16(3):187–94. 3. Rivella S. *Blood Rev* 2012;26(1)(Suppl 1):S12–S15. 4. Cappellini MD. *Hematology Am Soc Hematol Educ Program* 2007;74–8. 5. Rkiouak A, et al. *Clin Med Rev Case Rep* 2020;7(11):329. 6. Mahdi ZN, et al. *Hematol Oncol Stem Cell Ther* 2019;12(1):15–18. 7. Stoyanova E, et al. *PLoS One* 2012;7(6):e38089. 8. Abd Elghaffar AAE, et al. *J Blood Disord Transfus* 2015;6:3. 9. Vasilopoulou M, et al. *Thrombosis Update* 2022;7:100102.
10. Taher A, et al. *Thromb Haemostasis* 2006;96(4):488–91. 11. Taher A, et al. NTDT Guidelines: Thalassaemia International Federation; 2023. https://thalassaemia.org.cy/publications/tif-publications/guidelines-for-the-clinical-management-of-non-transfusion-dependent-thalassaemias-updated-version/. Accessed Dec 2023. 12. Cappellini MD, et al. *Expert Rev Hematol* 2012;5(5):505–11; 13. Pasricha S-R, et al. *Blood*;122:124–33; 14. Chen S, et al. *Am J Physiol* 1996; 270:H1951–56. 15. Borgna Pignatti C, et al. *Acta Haematol* 1998;99:76–9.

Hypercoagulability in NTDT may Lead to Downstream Vascular Anomalies and Mortality

Impact of hypercoagulability in NTDT[1,2,3]



- In a retrospective study of patients with **NTDT** (N=2,033), thrombosis was among the most common causes of death in this patient population[3]
- In a retrospective study of patients (N=584) with **β-thalassemia intermedia**, the prevalence of vascular comorbidities and complications was reported as[4]:
  - **Thrombosis:** 14.0%
  - **Pulmonary hypertension:** 11.0%
  - **Leg ulcers:** 7.9%

IE, ineffective erythropoiesis; NTDT, non–transfusion-dependent thalassemia.

1. Derchi G, et al. *Circulation* 2014;129(3):338–45. 2. Taher A, et al. NTDT Guidelines. Thalassaemia International Federation; 2023. https://thalassaemia.org.cy/publications/tif-publications/guidelines-for-the-management-of-non-transfusion-dependent-%ce%. Accessed Aug 2024. 3. Musallam KM, et al. *Haematologica* 2021;106(9):2489–92. 4. Taher AT, et al. *Blood* 2010;115(10):1886–92.

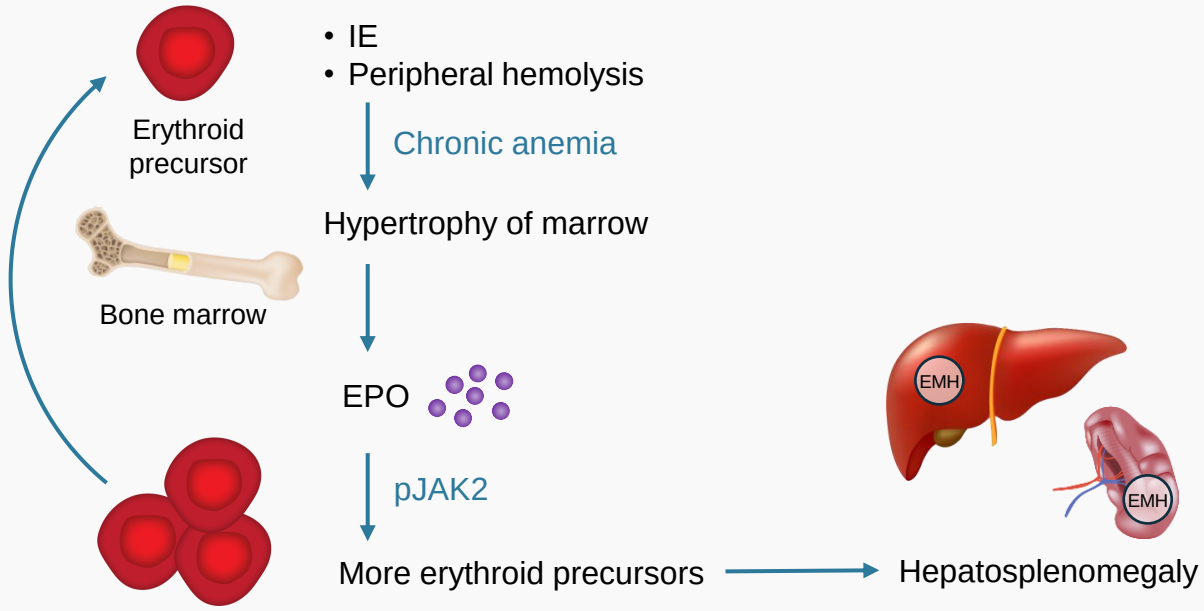
Extramedullary Hematopoiesis is a Complication of IE

- Erythroid expansion caused by IE is associated with extramedullary hematopoiesis (**EMH**), the homing and proliferation of erythroid precursors in the **spleen**, **liver**, **and other organs**[1,2]
  - EMH pseudotumors are more common in patients with more severe IE, and occur more frequently in **NTDT** (20%) vs **TDT** (<1%)

Localization of EMH in thalassemia[1,3–8]	
▪ Lymph nodes ▪ Thymus ▪ Heart ▪ Breast ▪ Prostate ▪ Ligaments ▪ Kidneys ▪ Adrenal glands	▪ Pleura ▪ Retroperitoneum ▪ Skin ▪ Peripheral/cranial nerves ▪ Brain ▪ Spinal canal

- In thalassemia, **anemia** and **hypoxia** increase levels of EPO, thus activating JAK2, which acts on erythroid precursors to drive pathologic EMH[2,9,10]

Pathogenesis of EMH in thalassemia[11–13]



~15% of patients with EMH may face paraspinal involvement, leading to severe clinical problems, including neurologic issues, and varied consequences, such as pain, deformities, and hematopoietic pseudotumors, depending on the location of EMH[1]

EMH, extramedullary hematopoiesis; EPO, erythropoietin; IE, ineffective erythropoiesis; JAK2, Janus kinase 2; NTDT, non–transfusion-dependent thalassemia; pJAK2, phosphorylated Janus activating kinase 2; TDT, transfusion-dependent thalassemia

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Erythroid Expansion Caused by IE Drives Pathological Changes in Bone Composition, Structure, and Morphology

Bone disease in thalassemia

- Erythroid expansion and IE are directly implicated as pathogenic drivers of **osteoporosis**[1]
- Although the exact cause of bone loss with IE is unclear, a proposed mechanism includes an imbalance in **OPG/RANKL ratio**[2-4]
- Expansion of the bone marrow space causes **thinning of the bone cortex**, particularly in the skull and hands[4,5]
  - Expansion of the osseous structures of the face

Pathogenesis of bone remodeling[6]

Osteoclast survival/activation

Osteopenia/osteoporosis

Decrease in OPG → **Leads to increased expression of RANKL by stromal cells or osteoblasts** → **Increased bone resorption by osteoclasts**

Osteoporosis and bone deformities are a feature of under-treated thalassemia[4,*]

IE, ineffective erythropoiesis; NTDT, non–transfusion-dependent thalassemia; OPG, osteoprotegerin; RANKL, receptor activator of nuclear factor kappa-B ligand; TDT, transfusion-dependent thalassemia.

*Regular use of transfusion support is implicated in reducing the prevalence of bone deformities and osteoporosis in TDT. Bone loss can still occur even with hyperperfusion regimens.[4]

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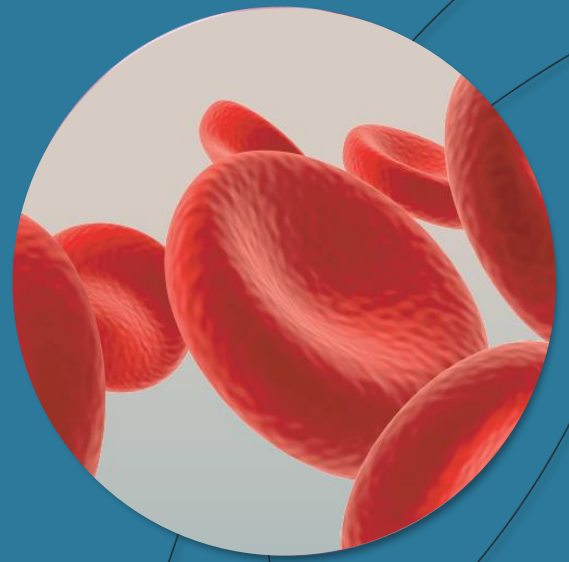
Summary



Summary

IE and hemolysis are key drivers of anemia and thalassemia[1–4]

Erythroid expansion is a compensatory feature of thalassemia and is driven by upregulation of EPO, which inhibits hepcidin and increases the availability of iron for erythropoiesis[5,6]

Chronic anemia caused by IE and hemolysis drives pathological dysregulation of EPO and hepcidin, which dysregulates iron homeostasis and causes iron overload, associated with increased morbidity[5,7,8]

IE and hemolysis induce hypercoagulation, which can lead to subsequent vascular disorders, such as venous thrombosis and pulmonary hypertension[9,10]

EMH is a common IE-related complication, along with osteoporosis and bone deformities, leading to erythropoietic tissue masses in the spleen, liver and lymph nodes[5,11–14]

EMH, extramedullary hematopoiesis; EPO, erythropoietin; IE, ineffective erythropoiesis; NTDT, non–transfusion-dependent thalassemia.

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