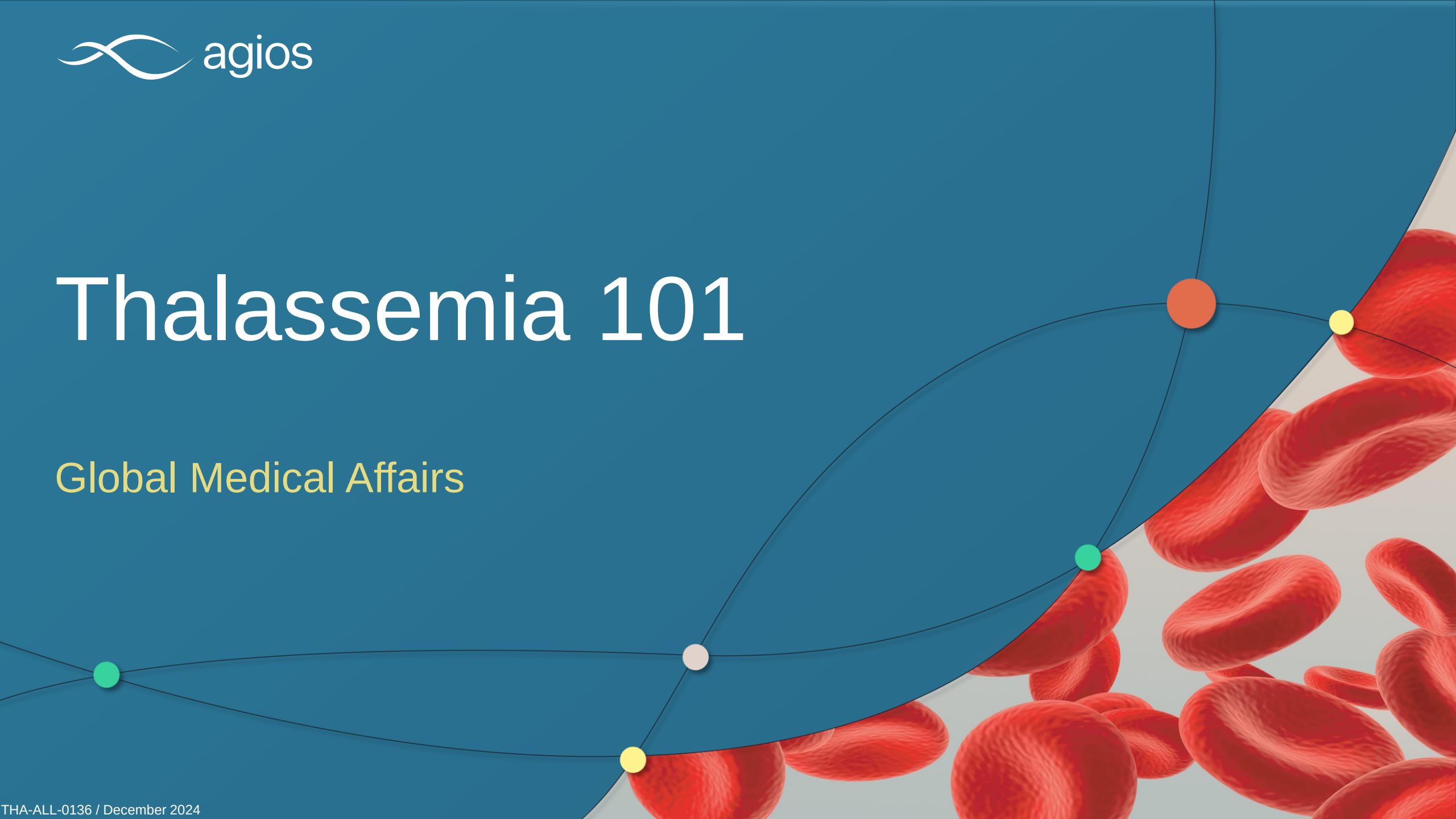
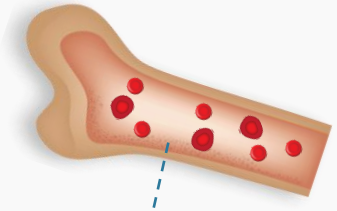
Thalassemia 101

Global Medical Affairs



Red Blood Cells (RBC) 101

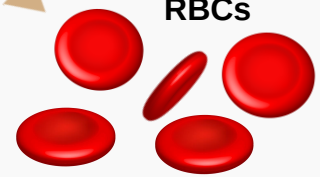
Origin and function of RBCs[1–3]



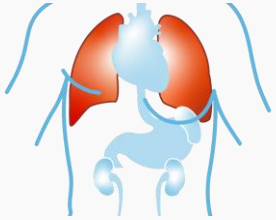
Bone marrow

1 RBCs are produced in the bone marrow through a process called 'erythropoiesis'[1,2]

Healthy RBCs



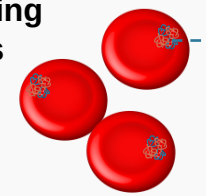
2 The lifespan of a healthy RBC is ~120 days[3]



3 RBCs travel in the bloodstream to the lungs, where oxygen binds to a molecule in the cell called hemoglobin[1]

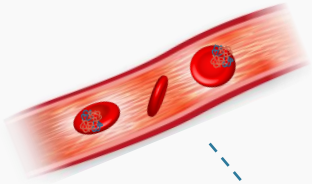
4 Hemoglobin is a specialized protein within the RBCs that enables them to carry oxygen[1]

Oxygen-carrying RBCs



Hemoglobin

5 Oxygen-carrying RBCs then travel in the blood vessels and deliver oxygen to tissues of the body[1]



Blood vessel

Key terms[2]

'erythro' = red

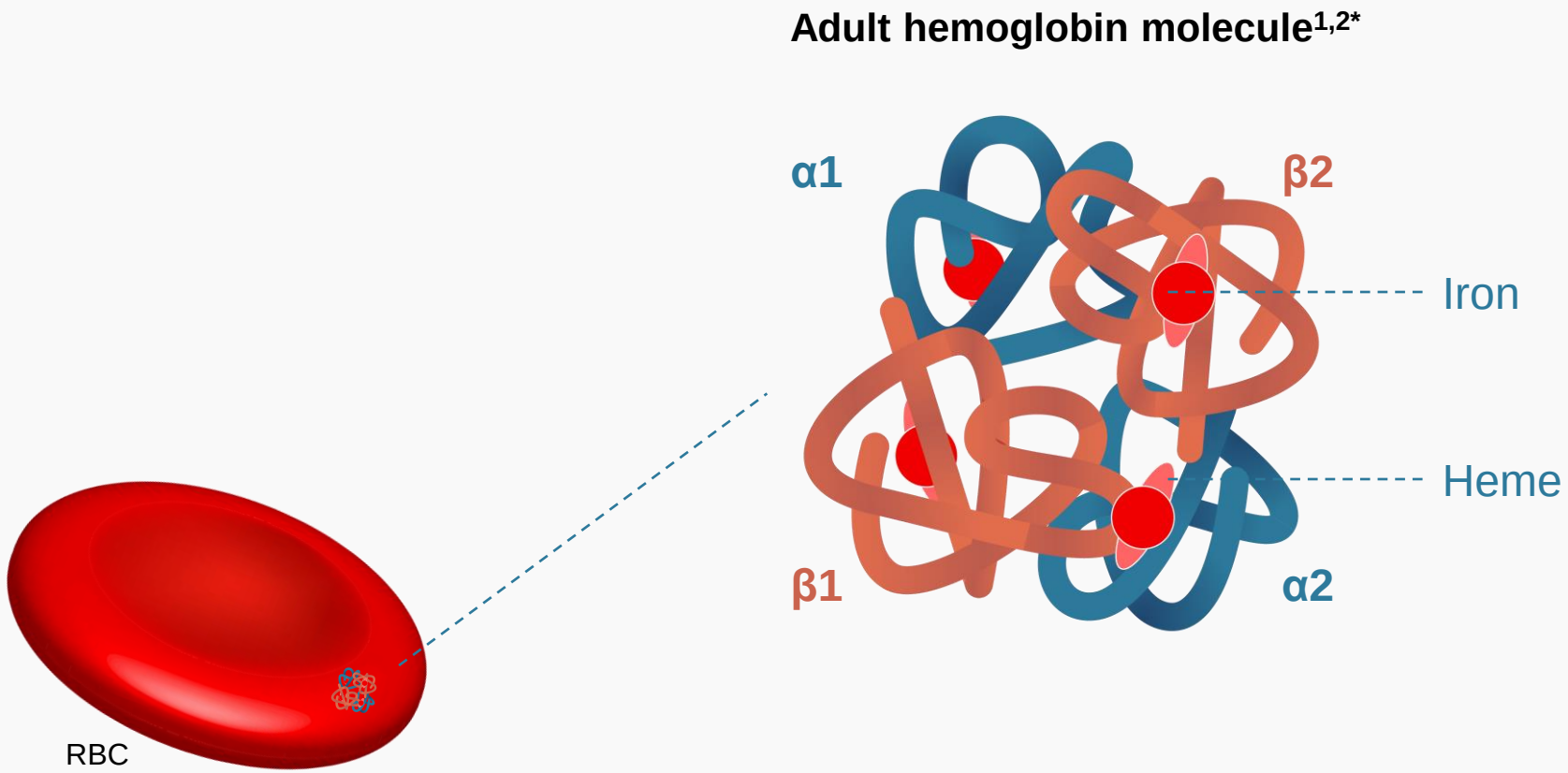
'poiesis' = to make

'erythrocyte' = RBC

'erythroblast' = immature RBC

1. Kuo HM. Fast facts for patients: alpha thalassemia. Karger; 2023. https://karger.com/books/book/3560/Fast-Facts-for-Patients-Alpha-Thalassemia.
2. Erythro, erythroblast, erythrocyte, erythropoiesis, poiesis. Collins Dictionary. https://www.collinsdictionary.com/dictionary/english/.
3. Scott MD. Model human β thalassemic erythrocytes: effect of unpaired purified α-hemoglobin chains on normal erythrocytes. Beta thalassemia. IntechOpen; 2020. https://www.intechopen.com/chapters/70197. All webpages accessed December 2024.

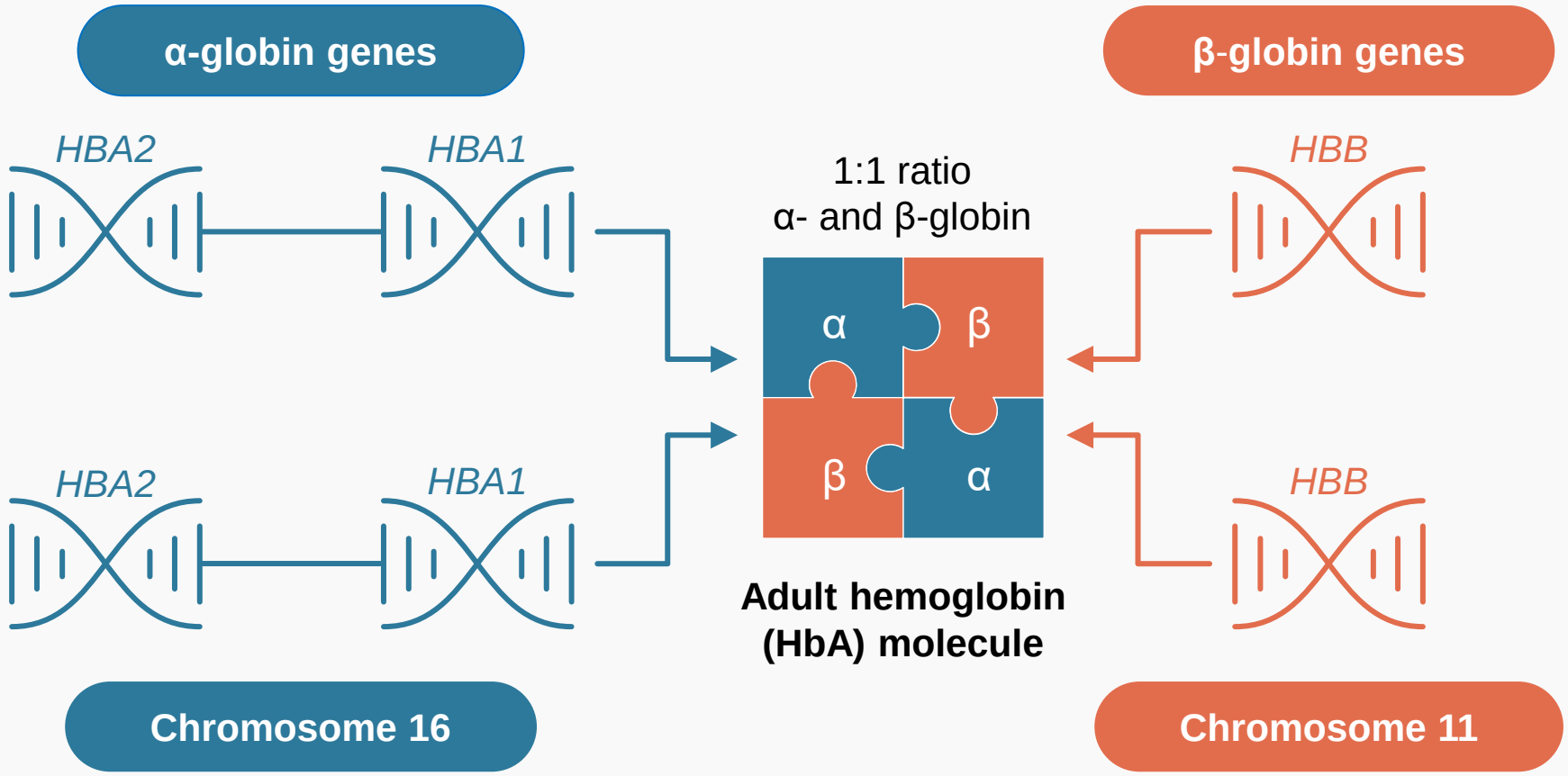
Adult hemoglobin is formed from two α-globin chains and two β-globin chains



RBC, red blood cell.
*Figure from reference 2. Modified with permission under CC BY 4.0.
1. Kwaifa IK, et al. *Orphanet J Rare Dis* 2020;15:166. 2. Bringas M, et al. *Sci Rep* 2017;7:10926.

In healthy RBCs, production of α- and β-globin chains is balanced

Healthy hemoglobin synthesis[1*]

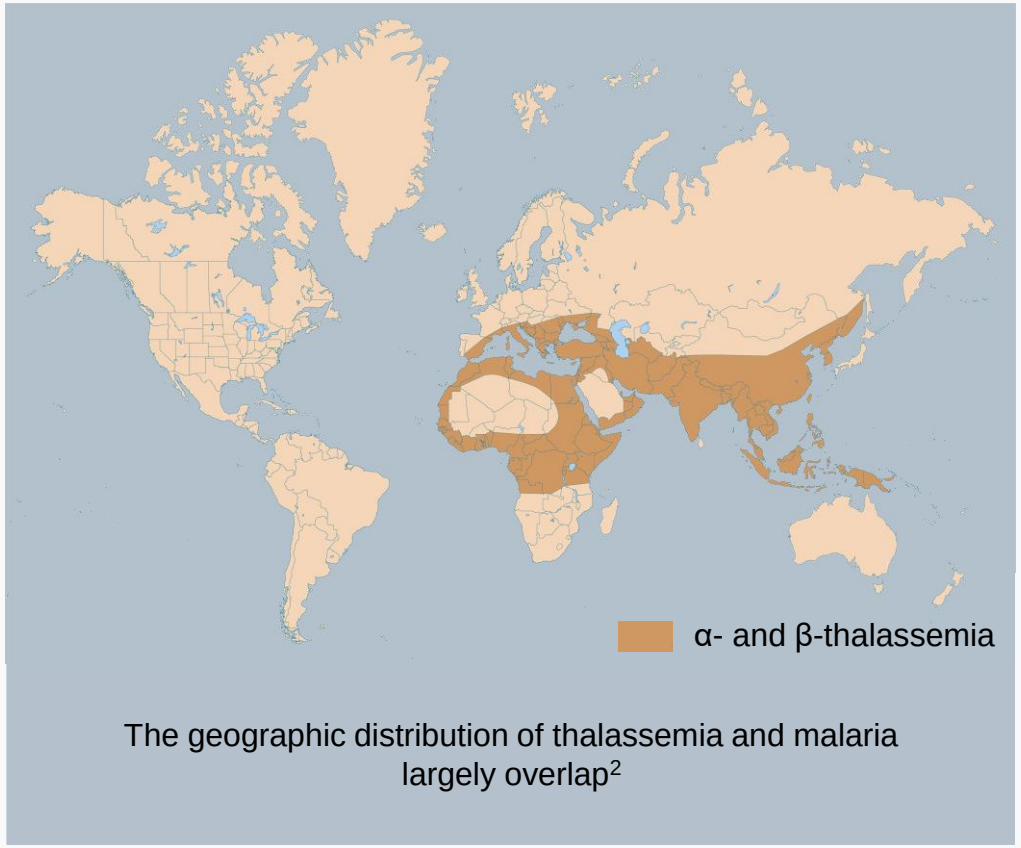


- Thalassemia is caused by mutations that lead to reduced production of α- or β- globin[2]

*Modified with permission under CC BY 4.0.
HBA, hemoglobin alpha gene; HBB, hemoglobin beta gene; RBC, red blood cell.
1. Kwaifa IK, et al. *Orphanet J Rare Dis* 2020;15:166. 2. Angastiniotis M, et al. *Int J Neonatal Screen* 2019;5:16.

Thalassemia has been historically more prevalent in regions where malaria is endemic

Regions where thalassemia is endemic[1*]



The geographic distribution of thalassemia and malaria largely overlap[2]

- Individuals who carry a thalassemia mutation on a single gene copy (‘trait’ or ‘thalassemia minor’) are thought to have a selective survival advantage to malaria[3–5]
- In more recent years, the prevalence of thalassemia has increased in the United States and Northern Europe due to population migration[6,7]

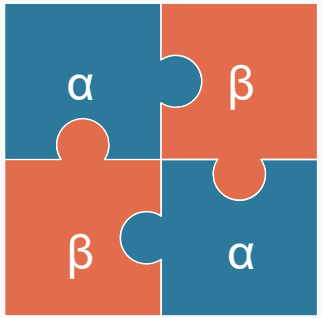
*Reproduced from *BMJ*, Weatherall, 314, 1675–8, 1997 with permission from BMJ Publishing Group Ltd.

1. Weatherall DJ. *BMJ* 1997;314:1675–8. 2. Vento S, et al. *Lancet Infect Dis* 2006;6:226–33 3. Roberts DJ, Williams TN. *Redox Rep* 2003;8:304–10.
4. Am Soc Hematol. Ash Clinical News: malaria and thalassemia in the Mediterranean basin. 2019. https://ashpublications.org/ashclinicalnews/news/4268/Malaria-and-Thalassemia-in-the-Mediterranean-Basin. Accessed December 2024. 5. Introini V, et al. *Sci Rep* 2022;12:8934.
6. Kattamis A, et al. *Eur J Haematol* 2020;105:692–703. 7. Kwaifa IK, et al. *Orphanet J Rare Dis* 2020;15:166.

Imbalanced production of α- and β-globin leads to unpaired excess chains and formation of abnormal hemoglobin

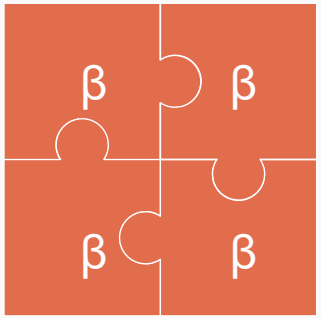
Adult hemoglobin[1*]

1:1 ratio
α- and β-globin



Healthy hemoglobin (HbA)

Reduced or
absent α-globin



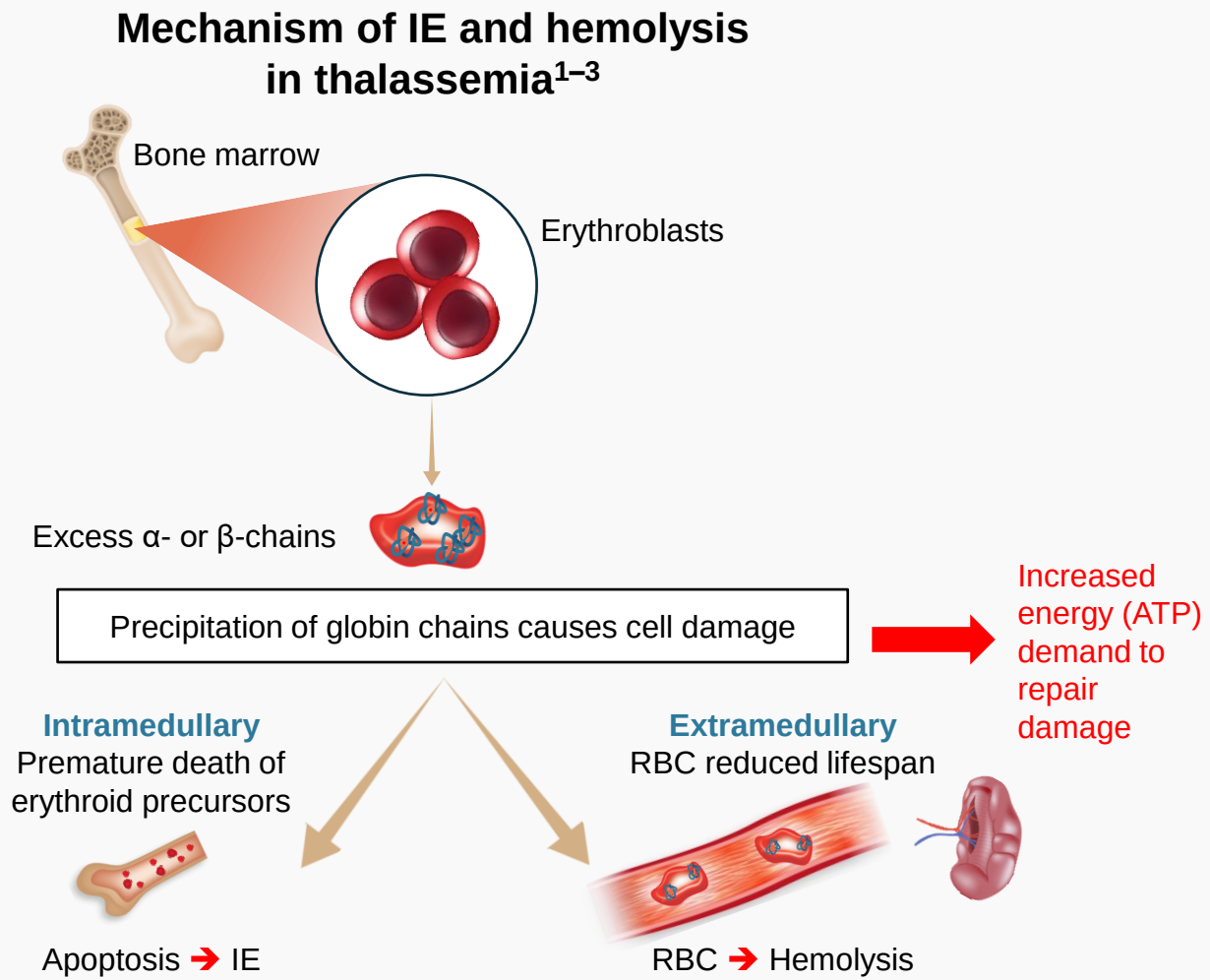
HbH tetramer

Example: α-thalassemia

- **Healthy RBCs**: α- and β-globin chains are balanced in a 1:1 ratio[1,2]
- **α-thalassemic RBCs**: reduced or absent synthesis of the α-globin chain, or alterations of α-globin chain stability or binding to β-globin, leads to a relative excess of the β-globin chains[1–3]

*Modified with permission under CC BY 4.0.
HbA, hemoglobin A; HbH, hemoglobin H disease; RBC, red blood cell.
1. Kwaifa IK, et al. *Orphanet J Rare Dis* 2020;15:166. 2. Angastiniotis M, Lobitz S. *Int J Neonatal Screen* 2019;5:16.
3. Bisconte MG, et al. *PLoS One* 2015;10:e0115738.

Unpaired excess globin chains damage RBCs and lead to premature cell death

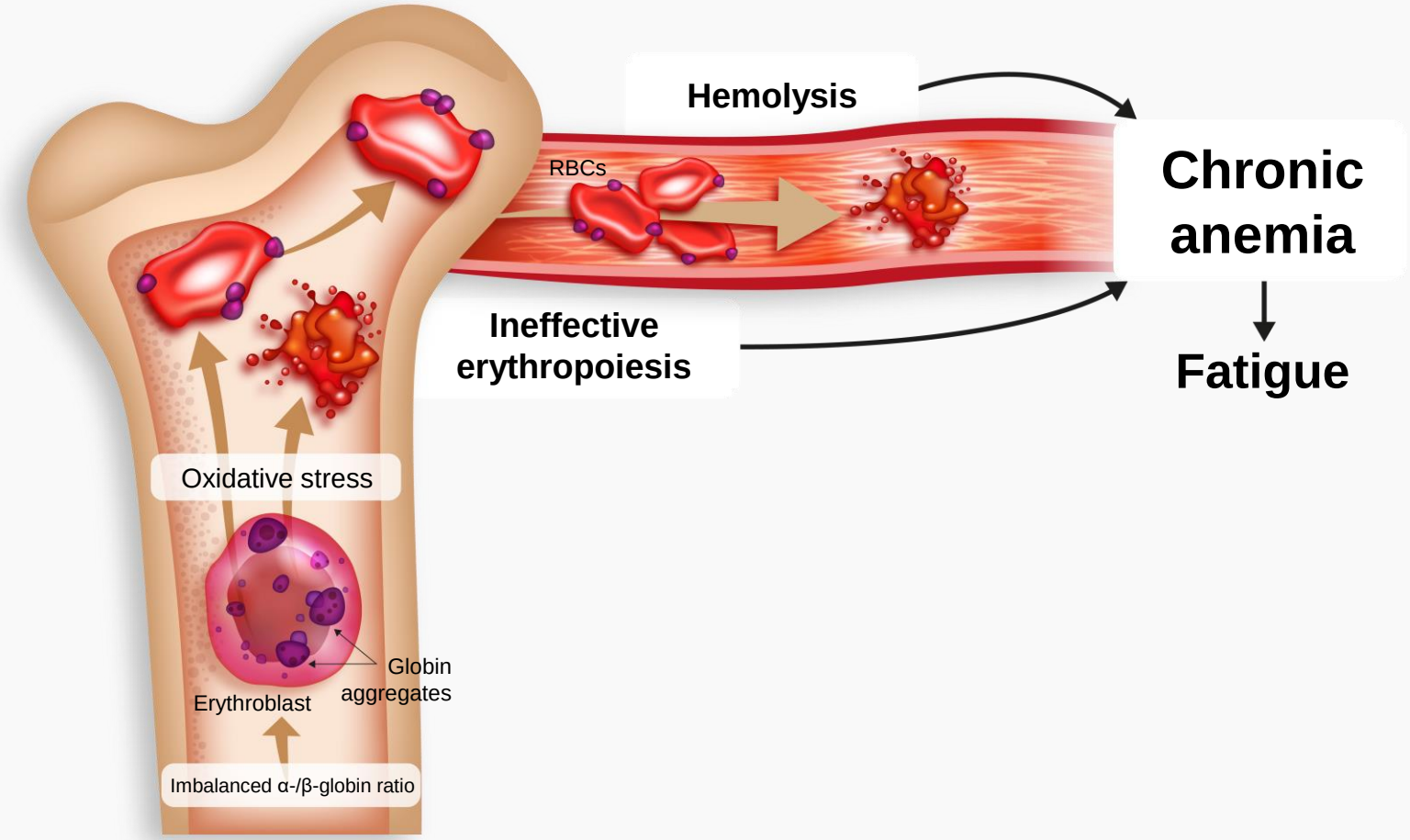


- Thalassemic RBC lifespan is ~6–10 days[4*]
- **Ineffective erythropoiesis (IE)**: insufficient production of RBCs due to death of erythroblasts (immature RBCs) in the bone marrow[1,3]
- **Hemolysis**: death of mature RBCs after leaving the bone marrow ('hemo' = blood; 'lysis' = cell rupture)[1,5]
- Decreased RBCs ➔ decreased hemoglobin (anemia) ➔ insufficient oxygen delivery to body ➔ fatigue, weakness, and tiredness[6,7]
- IE, hemolysis, and anemia can also lead to a multitude of downstream complications[6,8]

*In individuals with β-thalassemia without splenectomy.
ATP, adenosine triphosphate; RBC, red blood cell.

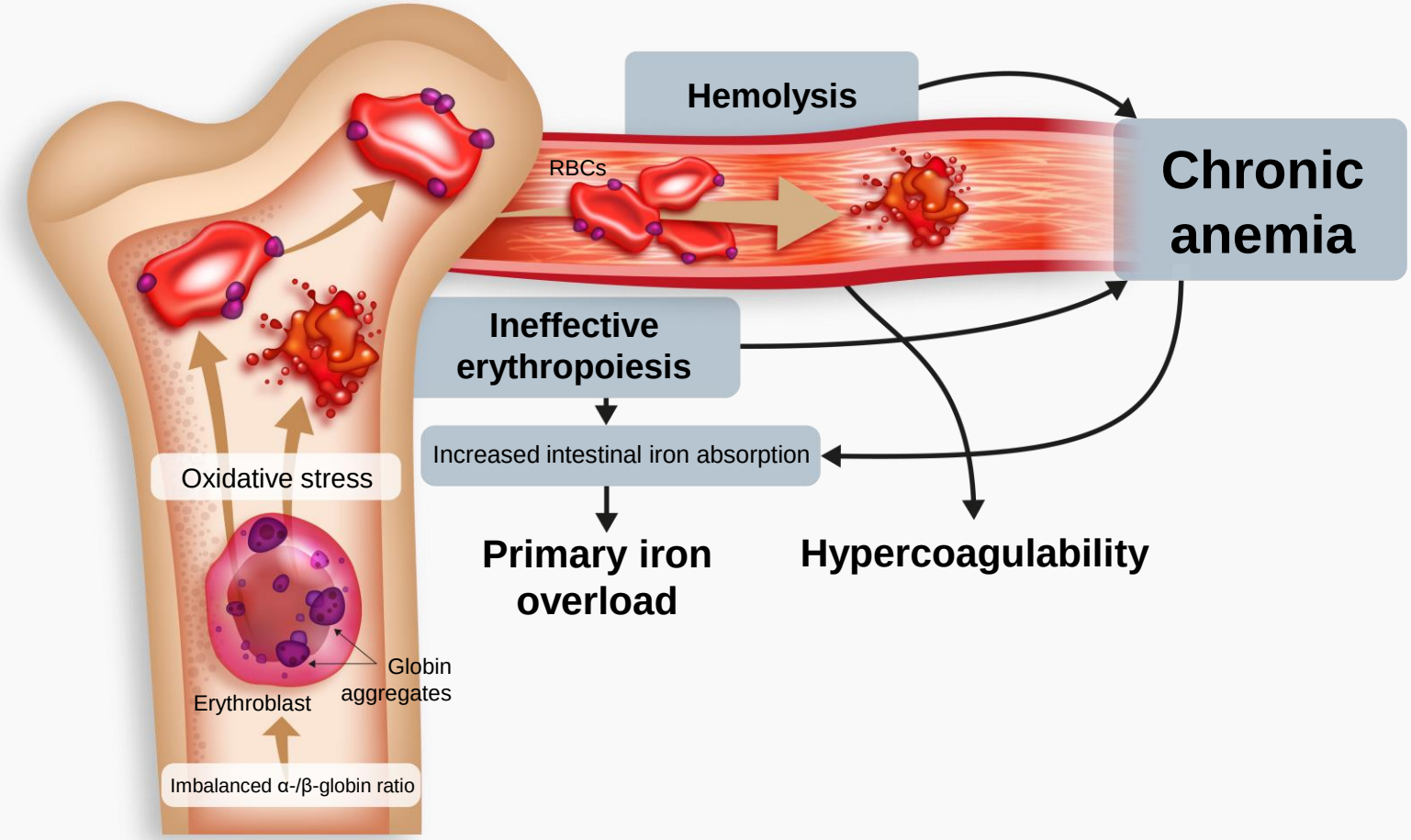
1. Rachmilewitz EA, Giardina PJ. *Blood* 2011;118:3479–88. 2. Sanchez-Villalobos M, et al. *Front Med (Lausanne)* 2022;9:880752. 3. Cazzola M. *Blood* 2022;139:2460–70.
4. Scott MD. Model human β thalassemic erythrocytes: effect of unpaired purified α-hemoglobin chains on normal erythrocytes. Beta thalassemia. IntechOpen; 2020. https://www.intechopen.com/chapters/70197. 5. Hemo, lysis. Merriam-Webster Dictionary. https://www.merriam-webster.com/. 6. Taher AT, et al. *N Engl J Med* 2021;384:727–43.
7. Kuo HM. Fast facts for patients: alpha thalassemia. Karger; 2023. https://karger.com/books/book/3560/Fast-Facts-for-Patients-Alpha-Thalassemia.
8. Kalle Kwaifa I, et al. *Orphanet J Rare Dis* 2020;15:166. All webpages accessed December 2024.

Pathophysiology of thalassemia



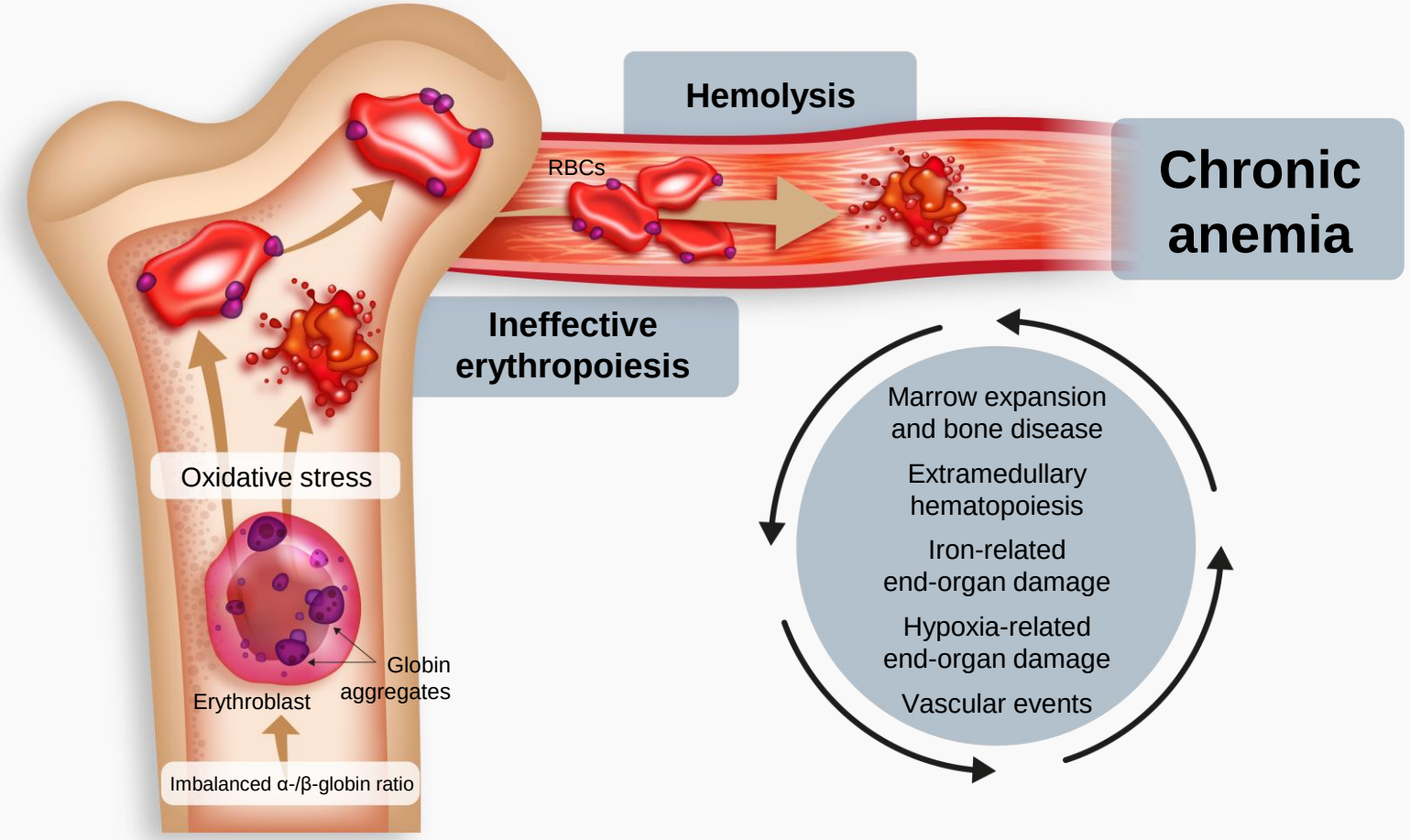
RBC, red blood cell.
Taher AT, et al. *N Engl J Med* 2021;384:727–43.

Pathophysiology of thalassemia



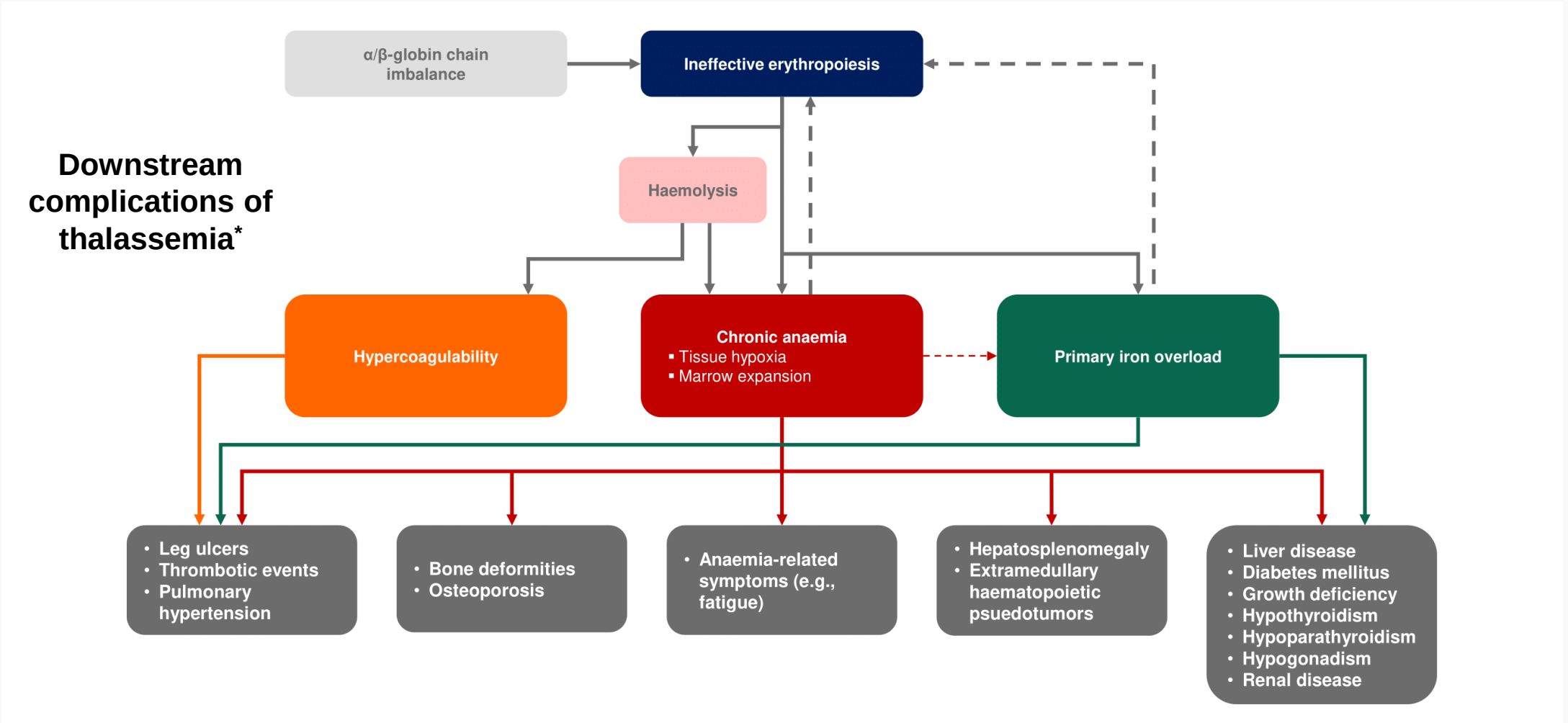
RBC, red blood cell.
Taher AT, et al. *N Engl J Med* 2021;384:727–43.

Pathophysiology of thalassemia



RBC, red blood cell.
Taher AT, et al. *N Engl J Med* 2021;384:727–43.

The causes of various complications in thalassemia are multifactorial and interrelated

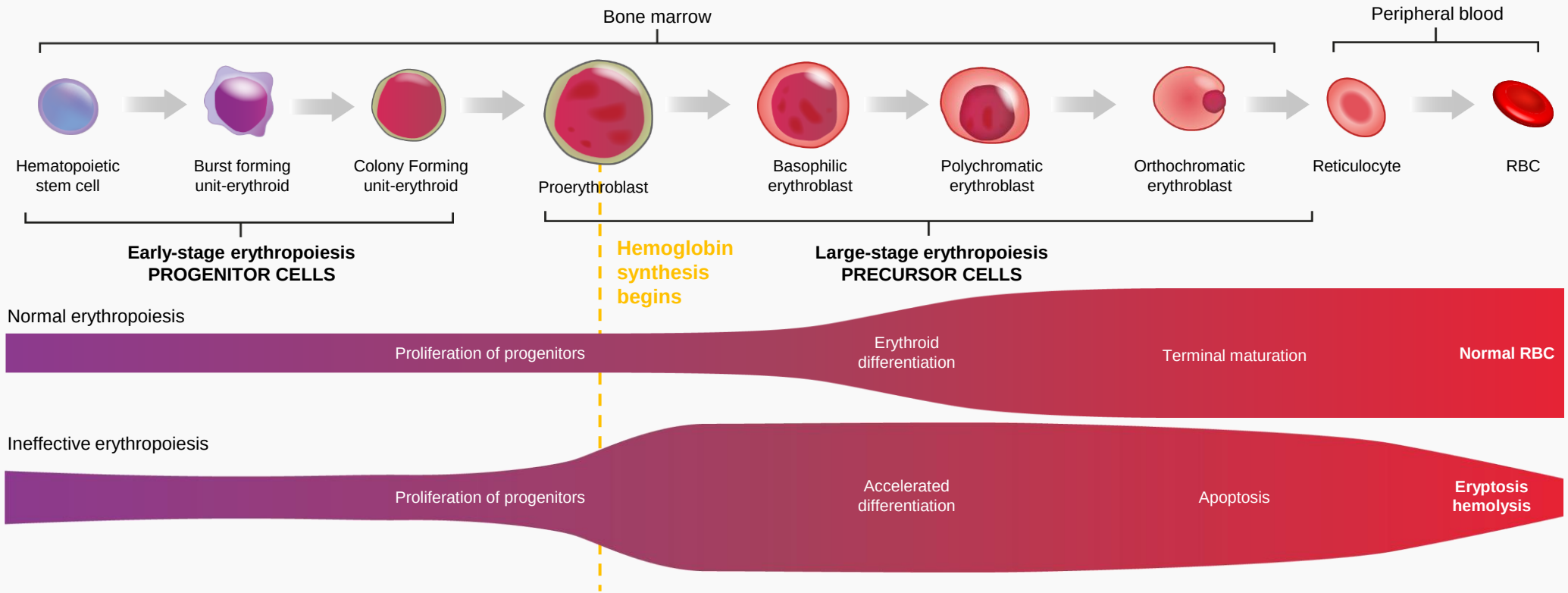


*Included with permission from the Thalassemia International Federation. Reproduction is prohibited.

Taher A, et al. Guidelines for the Management of Non-Transfusion-Dependent β-Thalassaemia. Thalassaemia International Federation; 2023. https://thalassaemia.org.cy/publications/tif-publications/guidelines-for-the-management-of-non-transfusion-dependent-%ce%b2-thalassaemia-3rd-edition-2023. Accessed December 2024.

Ineffective erythropoiesis occurs when there is a block in maturation of RBC precursors due to premature cell death

Temporal development of RBCs[1*–3]

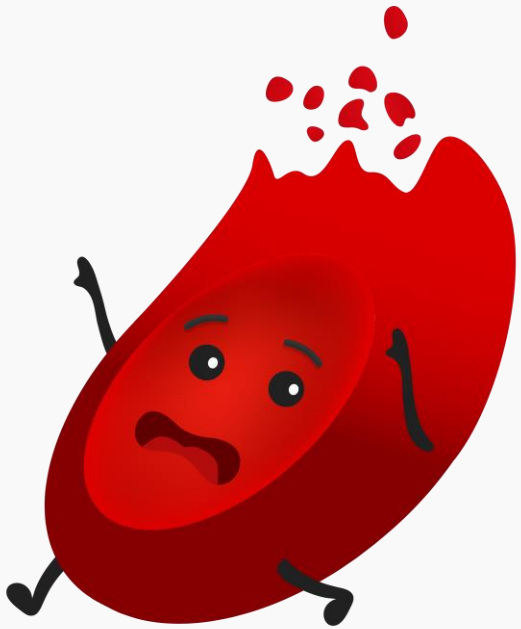


- The resulting anemia leads to the stimulation of more erythropoiesis, which further exacerbates the situation (bone marrow expansion and RBC formation in other sites of the body)[4,5]

- RBCs contain iron, and increased erythropoiesis stimulates absorption of more iron from the diet ➔ iron overload[1,4-7]

*Modified with permission under CC BY 4.0.
RBC, red blood cell.
1. Sanchez-Villalobos M, et al. *Front Med (Lausanne)* 2022;9:880752. 2. Klinken SP. *Int J Biochem Cell Biol*. 2002;34:1513–8.
3. Cazzola M. *Blood* 2022;139:2460–70. 4. Rivella S. *Blood Rev* 2012;26(Suppl 1):S12–5. 5. Melchiori L, et al. *Adv Hematol* 2010;2010:938640.
6. Saad HKM, et al. *Biomedicines* 2022;10:189. 7. Ginzburg Y, et al. *eLife* 2023;12:e90189.

Hemolysis can also lead to downstream complications



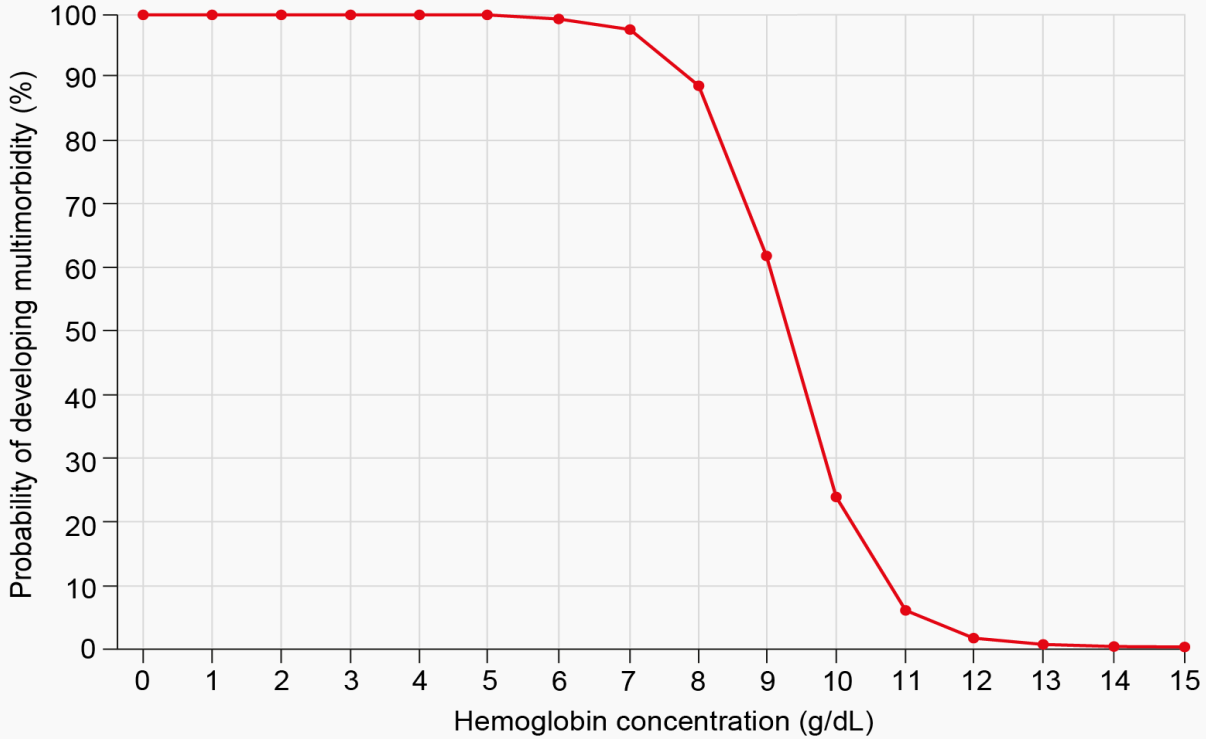
- The release of bits and particles from the damaged RBCs can make the blood stickier and induces a hypercoagulable state[1–3]
- **Hypercoagulation** can result in the formation of clots and impaired oxygen delivery, leading to:[1,4]
  - Pulmonary hypertension
  - Venous thrombosis
  - Stroke
  - Leg ulcers
- **Bilirubin** is a byproduct of RBC breakdown; excess bilirubin (‘hyperbilirubinemia’) as a result of hemolysis can lead to jaundice and gallstone formation[1,2]

RBC, red blood cell.

1. Taher A, et al. Guidelines for the Management of Non-Transfusion-Dependent β-Thalassaemia. Thalassaemia International Federation; 2023. https://thalassaemia.org.cy/publications/tif-publications/guidelines-for-the-management-of-non-transfusion-dependent-%ce%b2-thalassaemia-3rd-edition-2023.
2. Amid A, et al. Guidelines for the Management of α-Thalassaemia. Thalassaemia International Federation; 2023. https://thalassaemia.org.cy/publications/tif-publications/guidelines-for-the-management-of-%ce%b1-thalassaemia/. 3. Dimitrov JD, et al. *Arterioscler Thromb Vasc Biol* 2023;43:1349–61.
4. Taher AT, et al. *N Engl J Med* 2021;384:727–43. All webpages accessed December 2024.

Anemia has also been independently associated with a risk for developing complications

Probability of developing multiple morbidity at different hemoglobin levels*



Morbidities included

- Extramedullary hematopoietic pseudotumors
- Leg ulcers
- Thrombosis
- Pulmonary hypertension
- Abnormal liver function
- Heart failure
- Osteoporosis
- Hypogonadism
- Hypothyroidism
- Diabetes mellitus

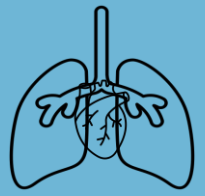
*Modified with permission.
Musallam KM, et al. *Ann Hematol* 2021;100:1903–5.

Iron overload occurs from the disease process and from transfusions, and can lead to organ damage

- Increased demand for RBC production ➔ increased intestinal iron absorption and release from macrophages ➔ primary iron overload[1,2]
- RBC transfusions ➔ to secondary iron overload[2]

Complications from iron overload may include[3–7]

Liver diseases
- Cirrhosis
- Hepatocellular carcinoma



Cardiopulmonary diseases
- Heart failure
- Pulmonary hypertension

Endocrine disorders
- Hypogonadism
- Hypothyroidism
- Hypoparathyroidism
- Diabetes mellitus

Skeletal manifestations
- Bone disease
- Osteoporosis
- Fractures

RBC, red blood cell.

1. Rivella S. *Blood Rev* 2012;26(Suppl 1):S12–5. 2. Taher AT, et al. *N Engl J Med* 2021;384:727–43.
3. Taher AT, Saliba AN. *Hematology Am Soc Hematol Educ Program* 2017:265–71. 4. Angastiniotis M, et al. *Int J Neonatal Screen* 2019;5:16.
5. Hsu CC. *Hepatol Commun* 2022;6:1842–54. 6. Fraidenburg DR, Machado RF. *Ann N Y Acad Sci 2016*;1368:127–39. 7. Wong P, et al. *Endocr Rev* 2016;37:320–46.

Thalassemia complications: overview

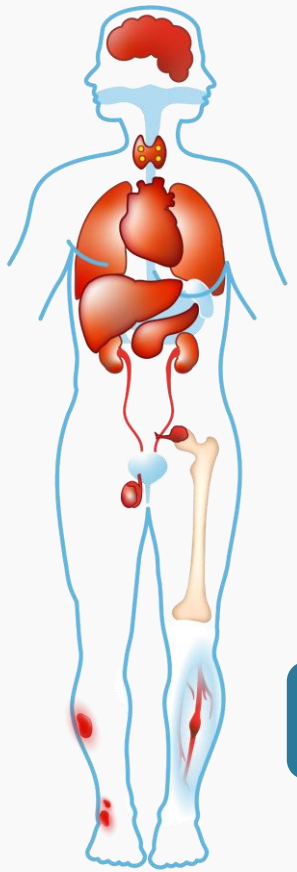
Build slide

α- and β-thalassemia risk factors

- Hemolysis
- Anemia
- Hypercoagulability
- 1° iron overload
- 2° iron overload

Treatments

- Splenectomy
- Transfusions
- Iron chelation



- Infections
- Facial and bone deformities
- Extramedullary hematopoietic pseudotumors
- Endocrinopathy
- Thrombosis and vascular events
- Growth and pubertal delay
- PHT and right heart failure
- Cardiac failure and arrhythmia
- Hepatosplenomegaly
- Liver fibrosis, cirrhosis, and HCC
- Hyperbilirubinemia and gallstones
- Renal complications
- Leg ulcers
- Cancers
- Iron chelator side effects
- Viral hepatitis
- Osteoporosis and bone disease

HCC, hepatocellular carcinoma; PHT, pulmonary hypertension.

Modified from Taher AT, et al. *N Engl J Med* 2021;384:727–43.
Amid A, et al. Guidelines for the Management of α-Thalassaemia. Thalassaemia International Federation; 2023. https://thalassaemia.org.cy/publications/tif-publications/guidelines-for-the-management-of-%ce%b1-thalassaemia/. Accessed December 2024.
Viprakasit V, et al. *Orphanet J Rare Dis* 2014;9:131. Viprakasit V, Ekwattanakit S. *Hematol Oncol Clin N Am* 2018;32:193–211.

Classification and transfusion requirements

- Thalassemia is now often classified phenotypically into two main groups:[1–3]
  - **Non–transfusion-dependent thalassemia (NTDT)**
  - **Transfusion-dependent thalassemia (TDT)**
- This classification moves away from the terms **thalassemia trait/minor**, **thalassemia intermedia** (TI), or **thalassemia major** (TM) used traditionally[1,2]

NTDT[2]

Patients do not require regular transfusion therapy for survival

TDT[2]

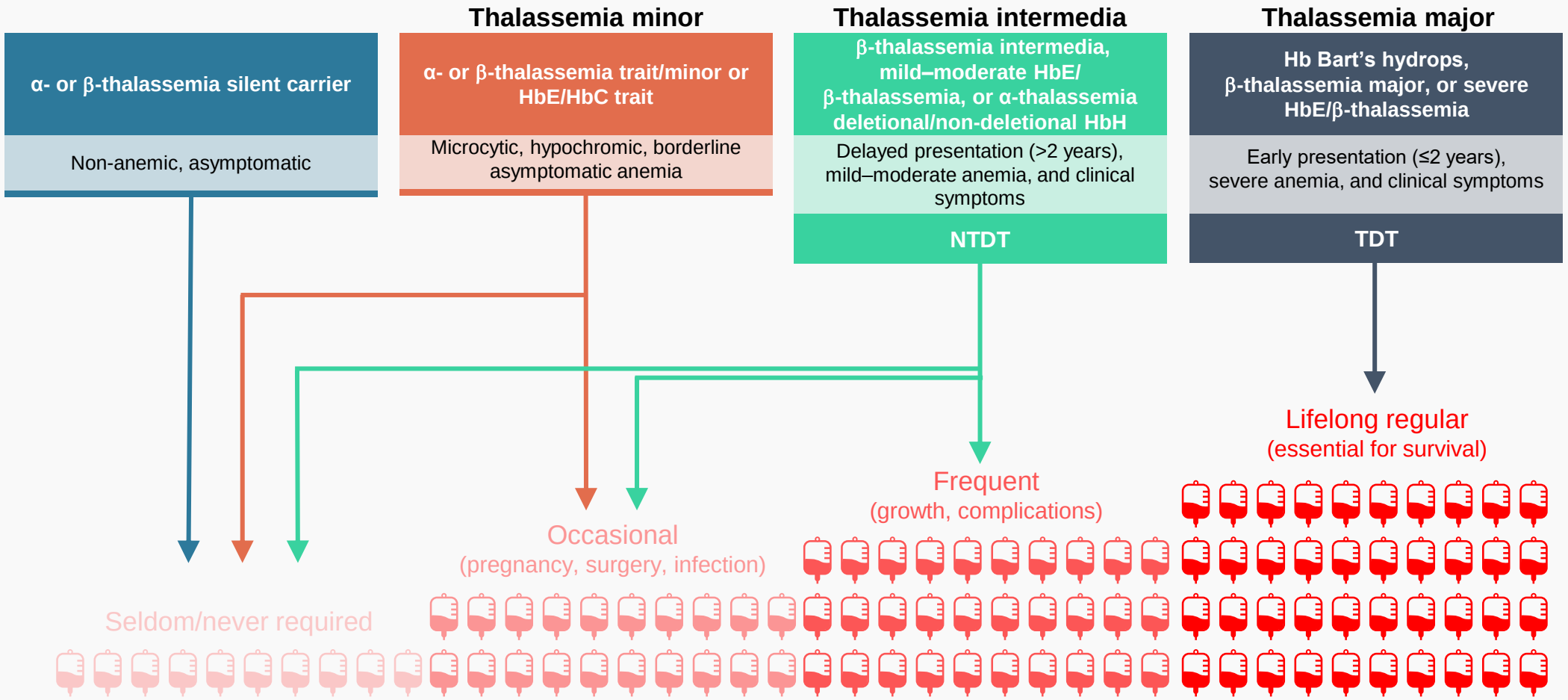
Patients who require lifelong regular transfusion therapy for survival

- However, the distinction between **NTDT** and **TDT** is fluid; **transfusion frequency is not always a measure of underlying disease severity**[2]
- **Transfusion requirements and frequency** may change over time due to age-specific factors and the changing biology of the patient[2–4]
- **Non-biologic factors** can also impact the decision to transfuse and the frequency of transfusions[2,3]
  - Patient preferences
  - Variations across regions, practices, and healthcare professionals (e.g. access to and cost of healthcare resources, management approaches, disease education)
  - Changes in management approaches over time

1. Farmakis D. A Short Guide for the Management of Transfusion-Dependent Thalassaemia. Thalassaemia International Federation; 2022. https://thalassaemia.org.cy/publications/tif-publications/a-short-guide-for-the-management-of-transfusion-dependent-thalassaemia-2022/.
2. Taher A, et al. Guidelines for the Management of Non-Transfusion-Dependent β-Thalassaemia Thalassaemia International Federation; 2023. https://thalassaemia.org.cy/download/guidelines-for-the-management-of-non-transfusion-dependent-%ce%b2-thalassaemia-3rd-edition-2023/.
3. Amid A, et al. Guidelines for the Management of α-Thalassaemia. Thalassaemia International Federation; 2023. https://thalassaemia.org.cy/publications/tif-publications/guidelines-for-the-management-of-%ce%b1-thalassaemia/. 4. Musallam KM, et al. *Am J Hematol* 2021;96:E54–6. All webpages accessed December 2024.

Transfusion burden across thalassemias

Thalassemia types and transfusion burden[1*–4]



*Modified with permission from the Thalassemia International Federation.
Hb, hemoglobin; HbC, hemoglobin C; HbE, hemoglobin E; HbH, hemoglobin H; NTDT, non–transfusion-dependent thalassemia; TDT, transfusion-dependent thalassemia.
1. Taher A, et al. Guidelines for the Management of Non-Transfusion-Dependent β-Thalassaemia. Thalassaemia International Federation; 2023. https://thalassaemia.org.cy/publications/tif-publications/guidelines-for-the-management-of-non-transfusion-dependent-%ce%b2-thalassaemia-3rd-edition-2023. 2. Farmakis D. A Short Guide for the Management of Transfusion-Dependent Thalassaemia. Thalassaemia International Federation; 2022. https://thalassaemia.org.cy/publications/tif-publications/a-short-guide-for-the-management-of-transfusion-dependent-thalassaemia-2022/. 3. Amid A, et al. Guidelines for the Management of α-Thalassaemia. Thalassaemia International Federation; 2023. https://thalassaemia.org.cy/publications/tif-publications/guidelines-for-the-management-of-%ce%b1-thalassaemia/.
4. Viprakasit V, Ekwattanakit S. *Hematol Oncol Clin North Am* 2018;32:193–211. All webpages accessed December 2024.

Q&A