AGGIORNAMENTO SU DIAGNOSI E TERAPIA DELLE EMOGLOBINOPATIE

Napoli, 7 novembre 2025 | Starhotels Terminus

La clinica delle Talassemie

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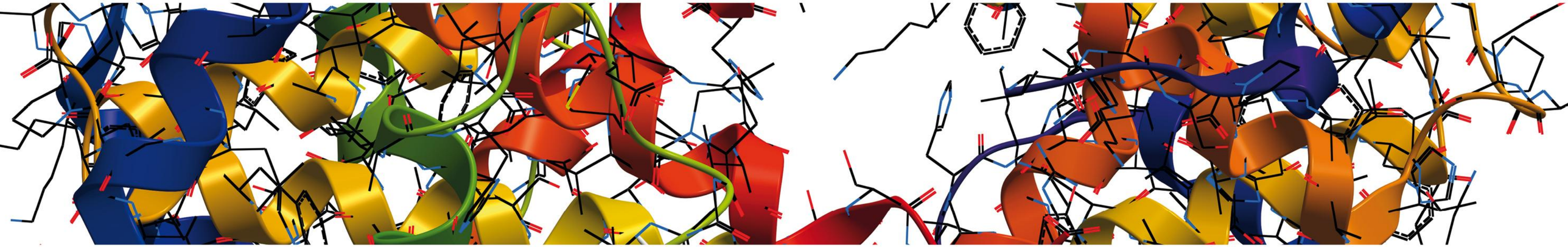
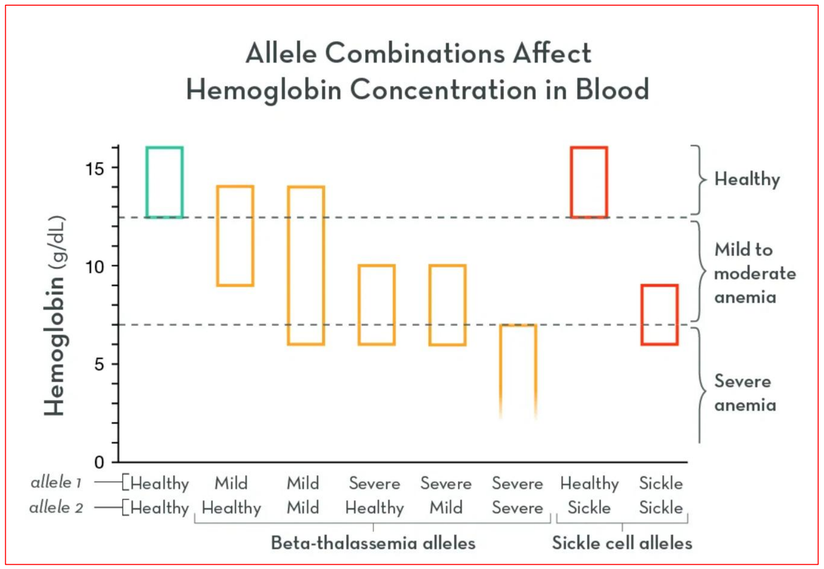


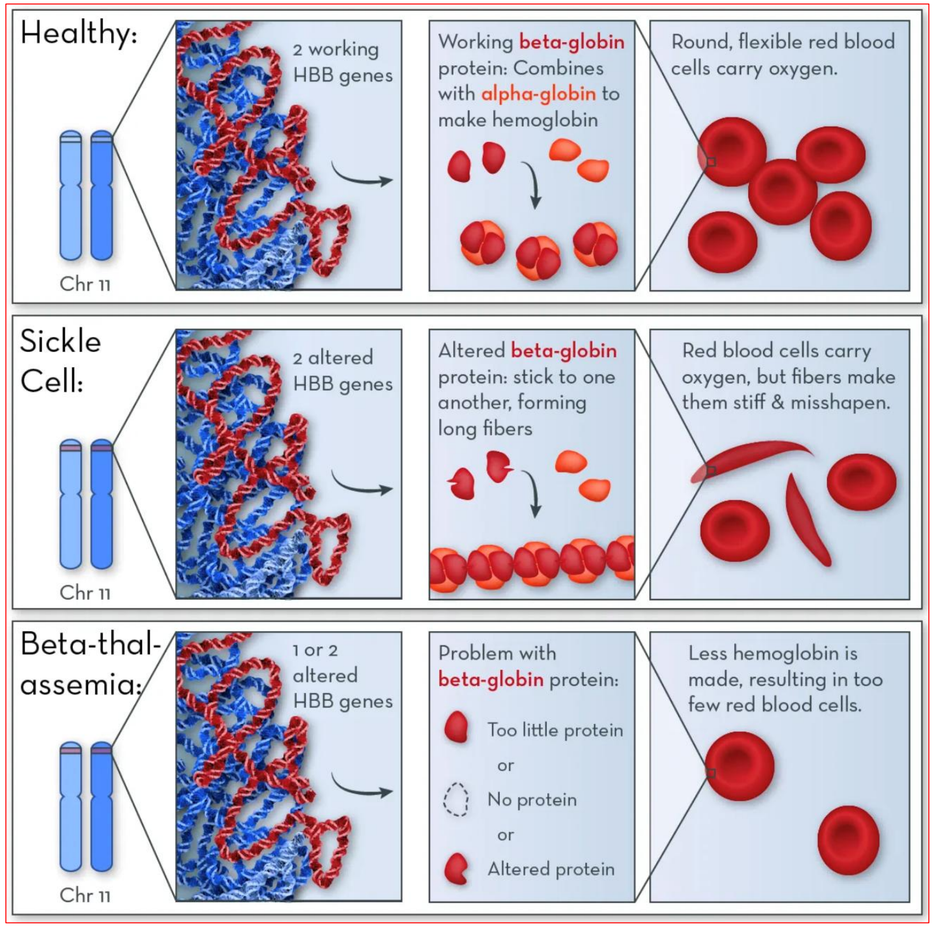
Disclosures of Name Surname

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
Nerviano Medical Sciences s.r.l.			X				

Le Emoglobinopatie

- I disturbi dell'emoglobina possono indurre una **minore produzione proteica** di globine o la produzione di una o più **catene alterate**;
- I **sintomi** sono estremamente variabili da persona a persona, da lievi a pericolosi per la vita, e possono comparire in determinati momenti della vita. Spesso, determinati disturbi hanno caratteristiche distintive.





https://learn.genetics.utah.edu/content/genetics/hemoglobin/

Le Emoglobinopatie

•Le talassemie sono riconosciute come **priorità di sanità pubblica globale**.

•L'OMS promuove un **approccio integrato e multidisciplinare** alla prevenzione e cura.

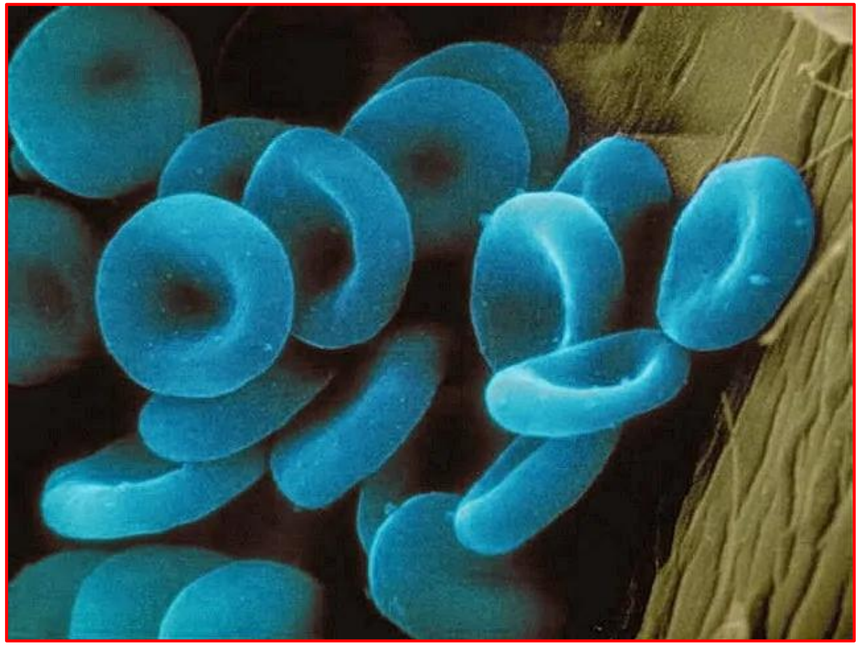
Obiettivi principali:

•Rafforzare i sistemi sanitari e la sorveglianza epidemiologica.

•Garantire **diagnosi precoce**, **trasfusioni sicure** e **accesso equo ai trattamenti**.

•Sostenere **formazione del personale sanitario** e **ricerca internazionale**.

•Integrare la cura delle talassemie nei programmi di **copertura sanitaria universale (UHC)**.



Emoglobinopatia "**O' sang' azzurr**"

Visione OMS: migliorare la qualità e l'aspettativa di vita delle persone affette, senza discriminazioni.

WHO response

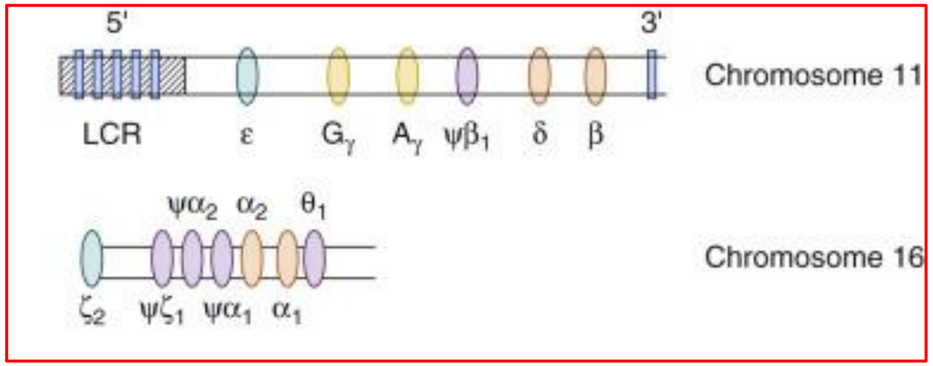
The governing bodies of WHO have adopted two resolutions on haemoglobin disorders. The resolution on sickle-cell disease from the 59th World Health Assembly in May 2006 and the resolution on thalassaemia from the 118th meeting of the WHO Executive Board call upon affected countries and the Secretariat of WHO to strengthen their response to these conditions. In addition, a resolution on the prevention and management of birth defects, including sickle-cell disease and thalassaemias, was adopted by the 63rd World Health Assembly in May 2010.

Specifically, WHO will:

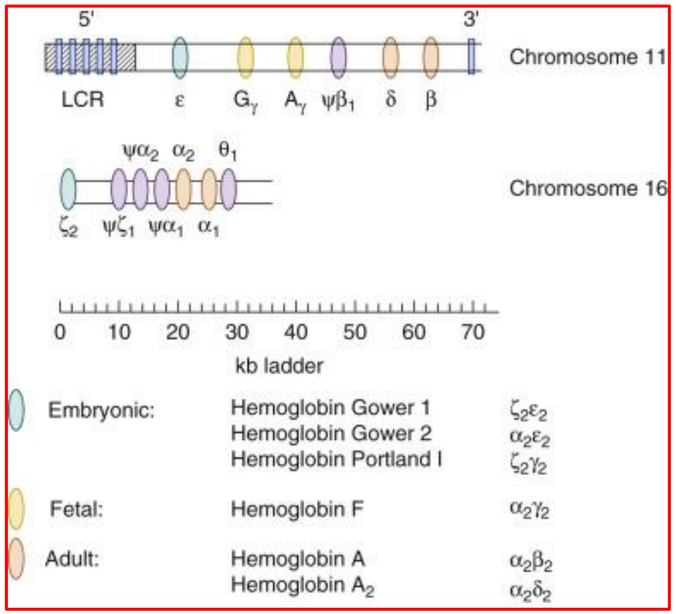
- increase awareness of the international community of the global burden of these disorders;
- promote equitable access to health services;
- provide technical support to countries for the prevention and management of these disorders; and
- promote and support research to improve quality of life for those affected.

Le Talassemie

- Le sindromi talassemiche sono dovute a uno squilibrio del **rapporto catene globiniche** e sono caratterizzate da vari gradi di **emopoiesi inefficace** e **aumento dell'emolisi**.
- Le sindromi cliniche sono suddivise principalmente in **α- e β-talassemie**, ciascuna con un numero variabile dei rispettivi geni globinici mutati.
- Le varianti dei geni della β-globina hanno una maggior prevalentenza nei bambini di origine mediterranea, meridionale e sud-orientale asiatica. Quelli delle α-globine sono più comuni in quelli di origine sud-orientale e africana.



Marjorie Leduc. *Analyse de la différenciation érythroïde humaine, murine et aviaire : évolution du protéome et des histones.* **Médecine humaine et pathologie. Université** Paris Cité, 2021.



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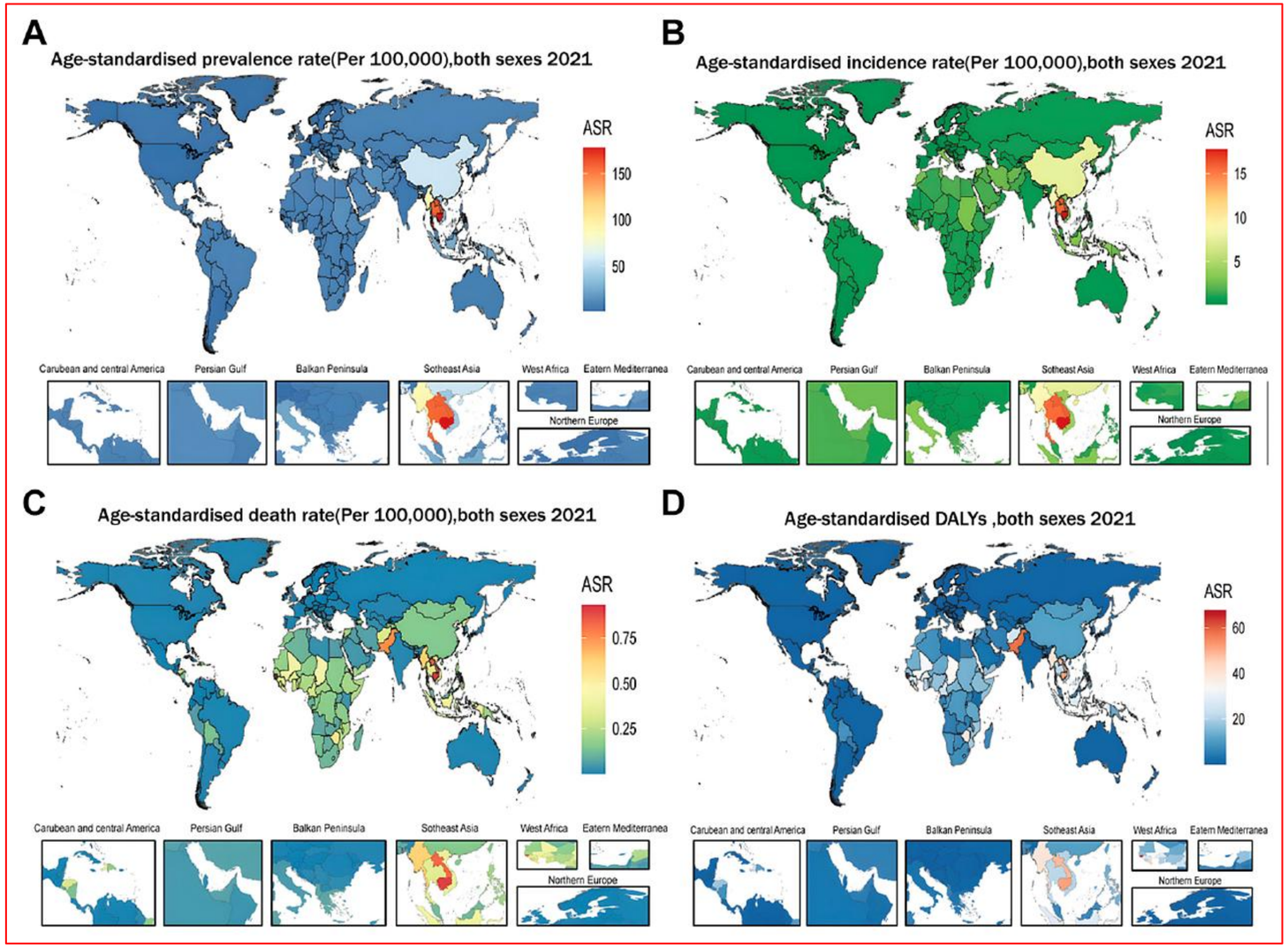
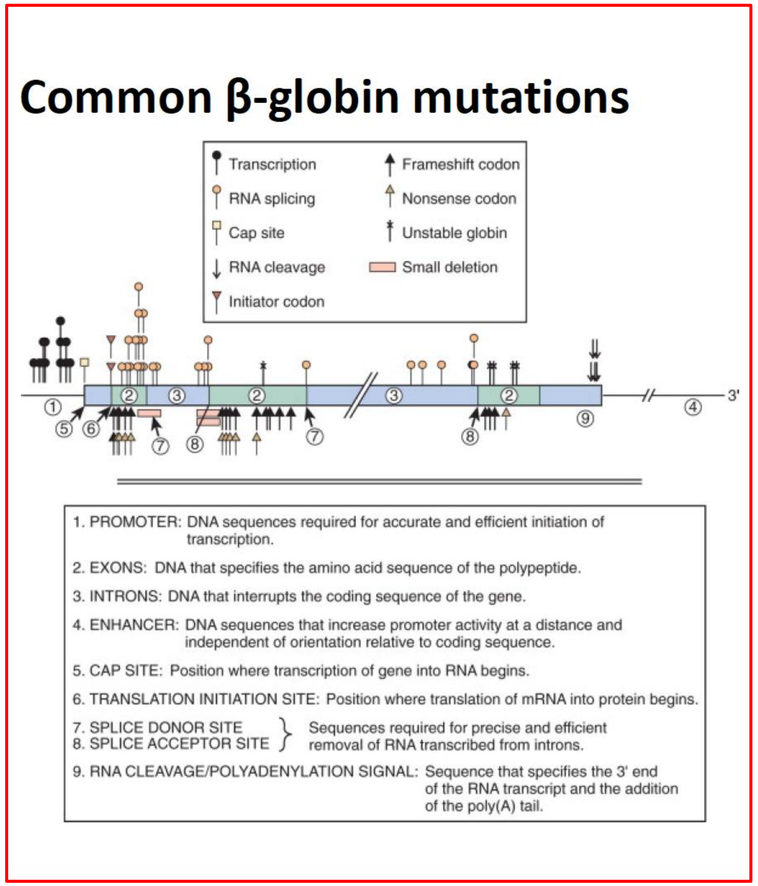
Epidemiologia

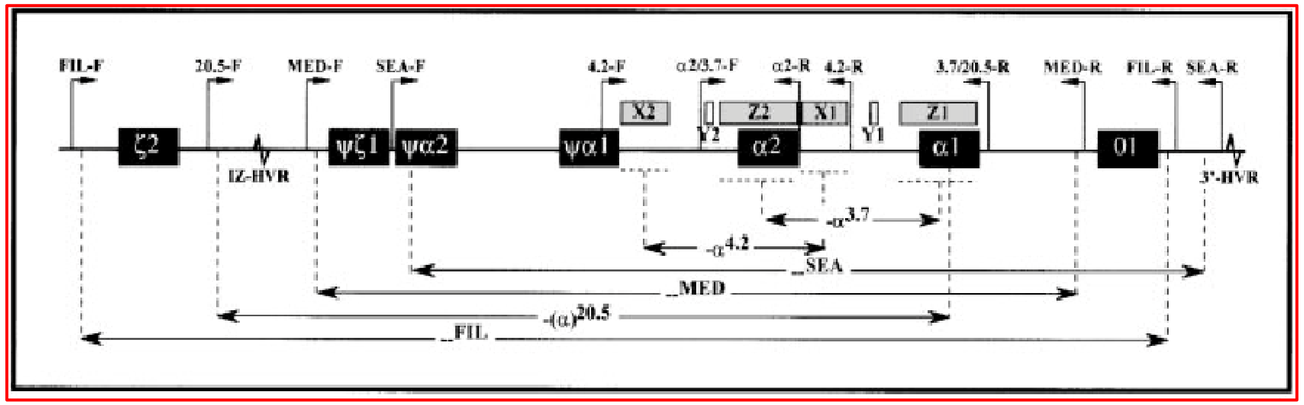


Tuo Y, et al. *Global, regional, and national burden of thalassemia, 1990-2021: a systematic analysis for the global burden of disease study 2021*. EClinicalMedicine. 2024 May 6;72:102619.

Le Talassemie



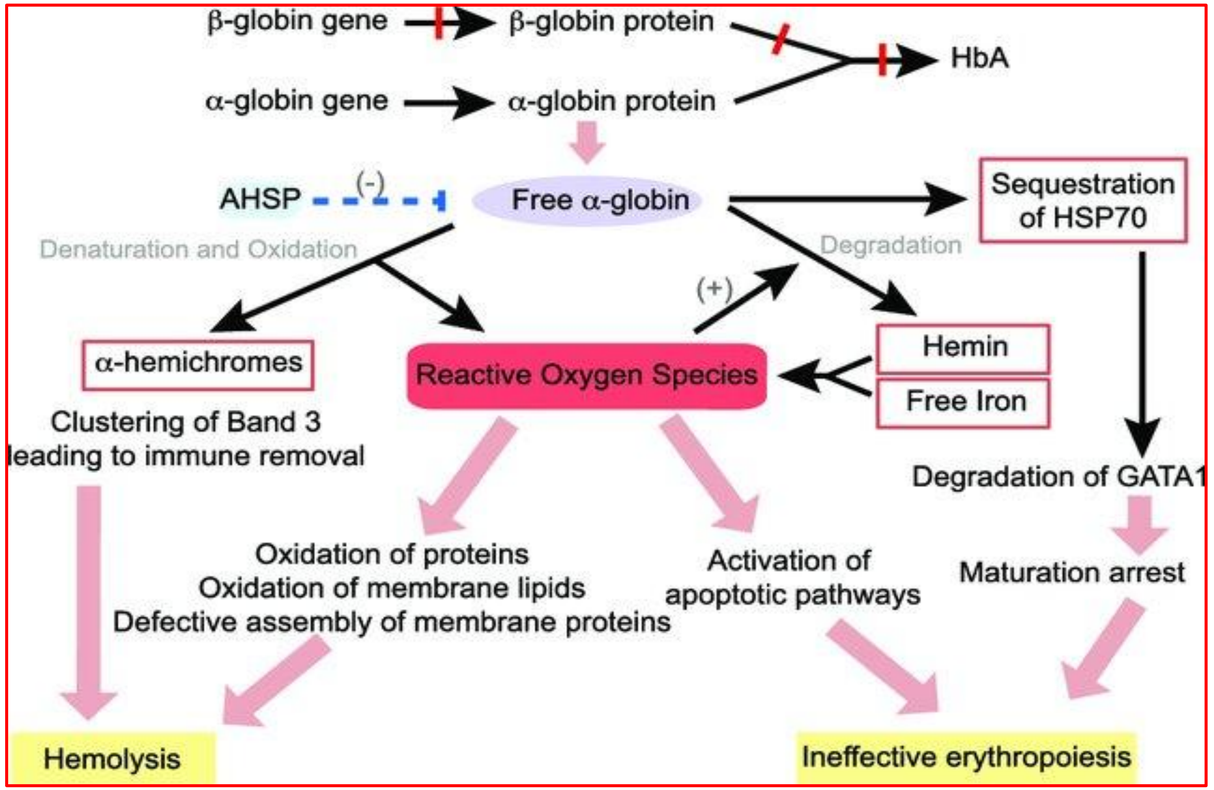
https://oncohemakey.com/thalassemias-2/



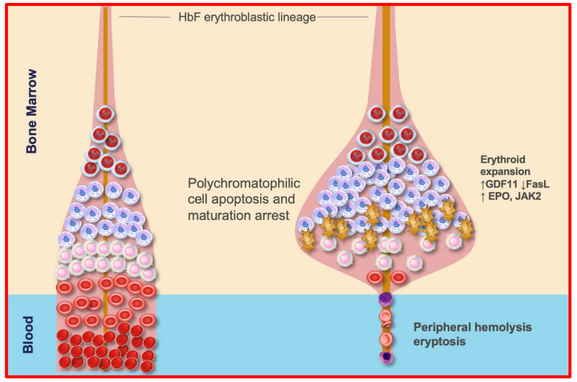
Sardón Estévez N, et al. *Diagnostic value of zinc protoporphyrin in a screening strategy for alpha-thalassemia*. **Eur J Haematol**. 2009 May;82(5):393-7.

Type of deletion	Phenotype	Number of examples recognized	Examples
RNA splice site mutation in α1 or α2 gene (donor or acceptor site)	α^+ thalassemia	3 (α2 donor site, α2 acceptor site, α1 acceptor site)	α2 IVS1 (−5nt) donor splice site mutation in Mediterranean area and Middle East
RNA polyadenylation signal mutations	α^+–α^0 thalassemia (ie, severe α^+) or α^+	4 (described only for α2 gene which is likely to account for the severe phenotype)	α2 AATAAA→AATAAG ($\alpha^{PA6A\rightarrow G}\alpha$, $\alpha^{TSaudi}\alpha$)
Imparied RNA translation consequent on initiation codon or intitiation consensus sequence mutation	α^+ thalassemia, α^+–α^0, or when the mutation occurs in association with deletional α thalassemia, α^0 thalassemia	5 (2 in α2 gene, 1 in α1 gene, 2 in single α gene)	α2 ATG→ACG, GTG or A–G; $-\alpha^{3.7}$ ATG→GTG (mutation in association with deletion gives α^0 phenotype)
Impaired RNA translation consequent on a frame shift or nonsense mutation	α^+ or α^0 thalassemia	5 (4 frame shift plus 1 nonsense)	Codon 30/31 (−4nt) frame shift and α2 CD116 GAG→TAG nonsense mutation
Impaired RNA translation consequent on a terminiation codon mutation leading to an elongated mRNA and α globin chain	α^+ thalassemia	5 (all α gene)	Hemoglobin Constant Spring TAA→CAA ($\alpha^{CS}\alpha$), hemoglobin Icaria TAA→AAA ($\alpha^{Ic}\alpha$), hemoglobin Koya Dora TAA→TCA, hemoglobin Seal Rock TAA→GAA, hemoglobin Paksé TAA→TAT
Production of highly unstable α chain as a result of point mutation or a small deletion	α^+ thalassemia	At least 18: 14 point mutations, 4 small deletions; 11 affecting α2 gene, 4 affecting α1 gene and 3 affecting a single α gene	Hemoglobin Arginia ($\alpha^{Agr}\alpha$), hemoglobin Petah Tikvah (α^{PT}), hemoglobin Quong Sze ($\alpha^{QS}\alpha$), hemoglobin Suan Dok ($\alpha^{SD}\alpha$) and hemoglobin Evaston (point mutations); hemoglobin Taybe (small deletion)
Lack of a transactivating factor encoded by the *ATRX* gene	α^+ thalassemia		ATR-X syndrome

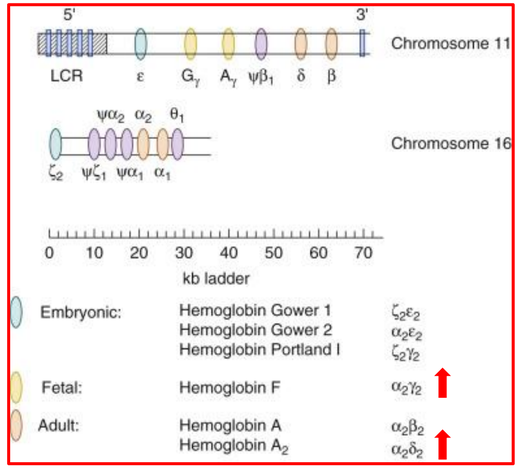
β-Talassemia



Mettananda S, Gibbons RJ, Higgs DR. *α-Globin as a molecular target in the treatment of β-thalassemia*. Blood. 2015 Jun 11;125(24):3694-701.



Sanchez-Villalobos M, Blanquer M, Moraleda JM, Salido EJ, Perez-Oliva AB. *New Insights Into Pathophysiology of β-Thalassemia*. Front Med (Lausanne). 2022 Apr 12;9:880752.



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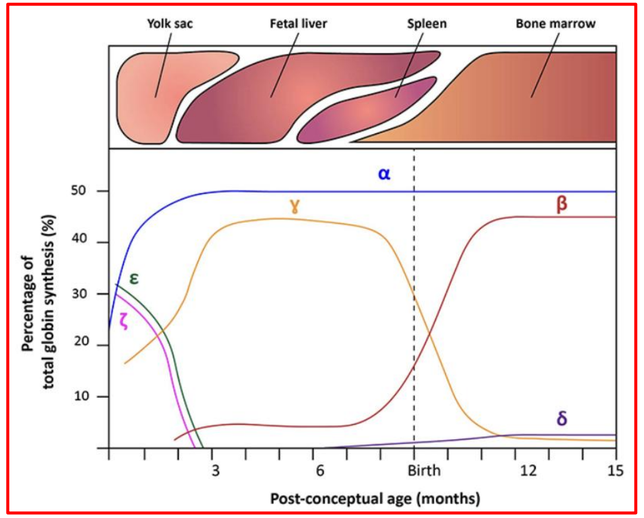
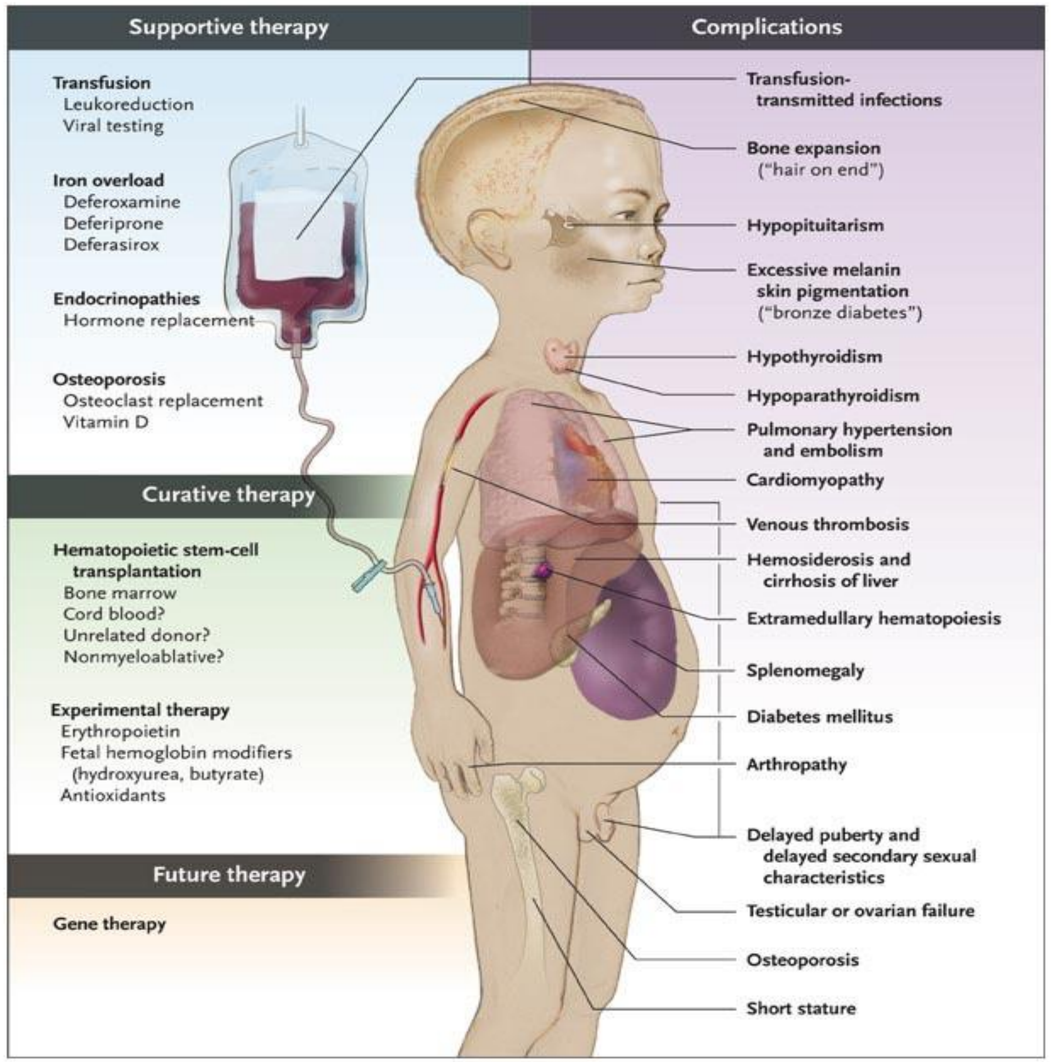


Forget BG. Progress in understanding the hemoglobin switch. **N Engl J Med**. 2011 Sep 1;365(9):852-4.

β-Talassemia

The ghost of Christmas Past

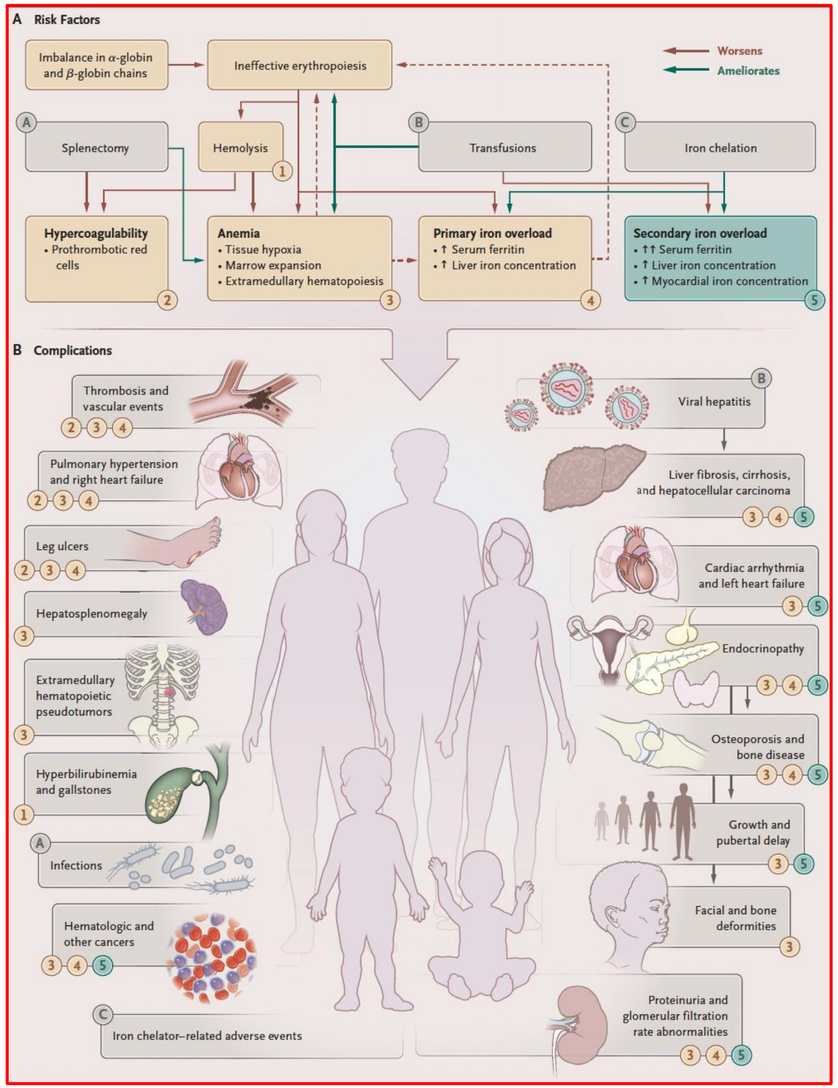


Rund D, Rachmilewitz E. *Beta-thalassemia.* N Engl J Med. **2005** Sep 15;353(11):1135-46.

1. **Midollo iperplastico** (espansione del midollo osseo con assottigliamento corticale e anomalie ossee).
2. **Emolisi/Aumento dell'assorbimento e del sovraccarico di ferro** (soprattutto con trasfusioni di sangue ripetute), con conseguente in:
   - **Fibrosi/cirrosi epatica**
   - **Disturbi endocrini** (ad esempio, diabete mellito, ipotiroidismo, ipogonadismo, ipoparatiroidismo, ipopituitrismo)
   - **Iperpigmentazione cutanea**
   - **Emocromatosi cardiaca** → aritmie e insufficienza cardiaca.
   - **Anomalie ossee**
3. **Ipersplenismo**:
   - Espansione del volume del plasma
   - Riduzione della vita dei globuli rossi (di cellule autologhe e di donatori)
   - Leucopenia
   - Trombocitopenia.

β-Talassemia

Quando pensarci?

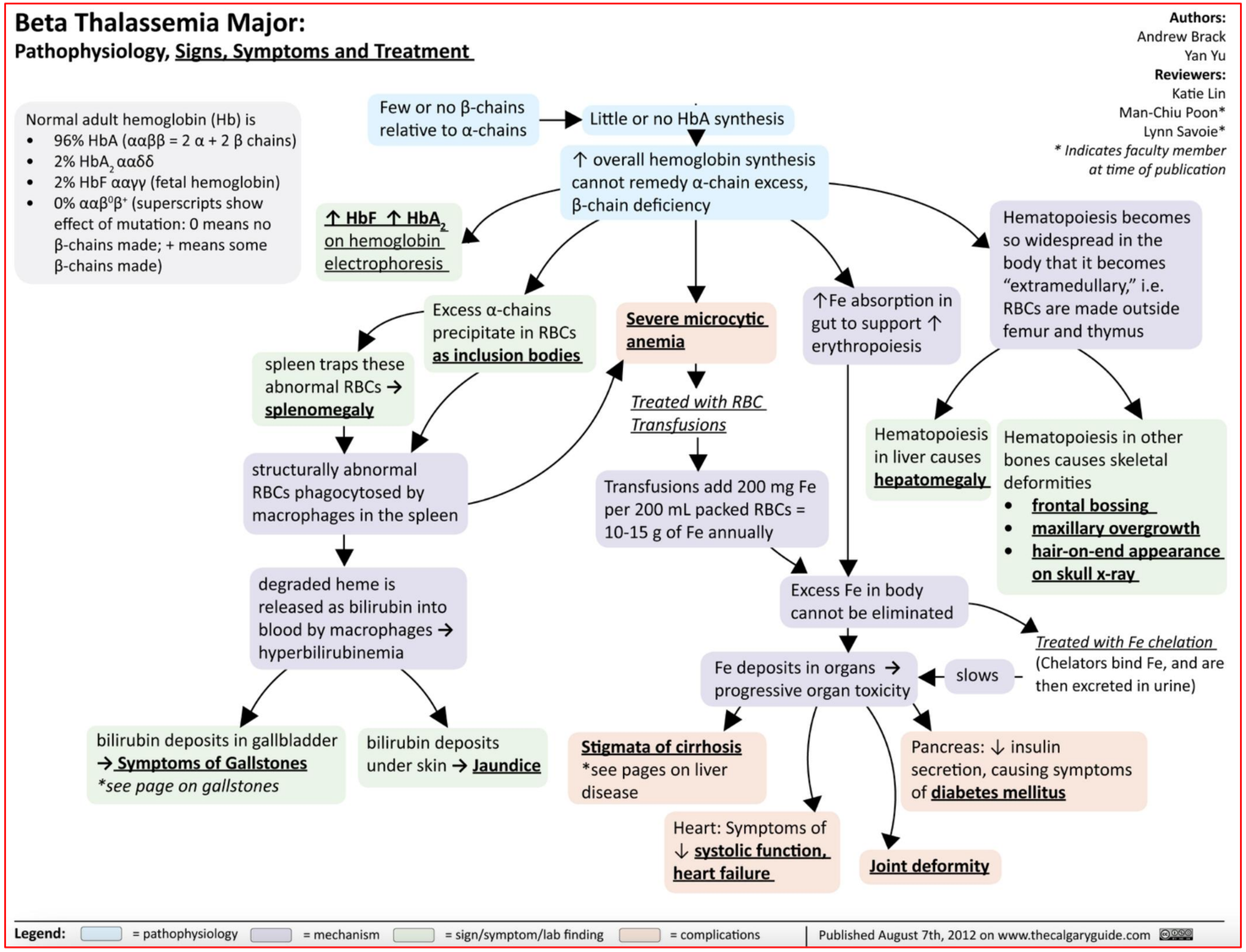


The ghost of Christmas Present

- Anamnesi familiare suggestiva;
- Ritardo della crescita;
- Stanchezza;
- Debolezza;
- Scarso appetito;
- Colorito itterico, pallido;
- Anomalie conformazione ossa cranio;
- Gonfiore addominale, splenomegalia;
- Urine scure.

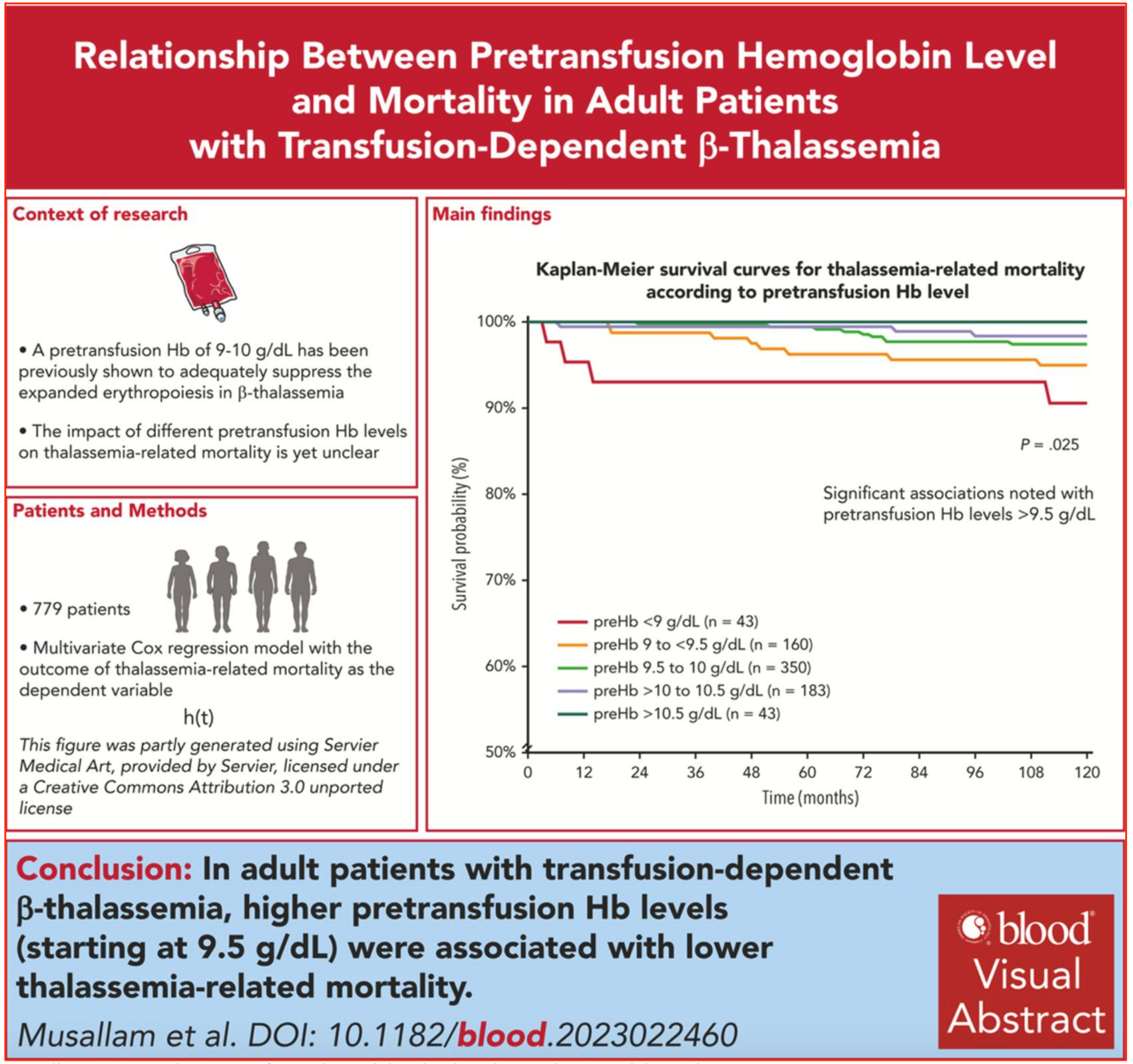
Taher AT, Musallam KM, Cappellini MD. *β-Thalassemias*. N Engl J Med. **2021** Feb 25;384(8):727-743.

β-Talassemia Trasfusione Dipendente



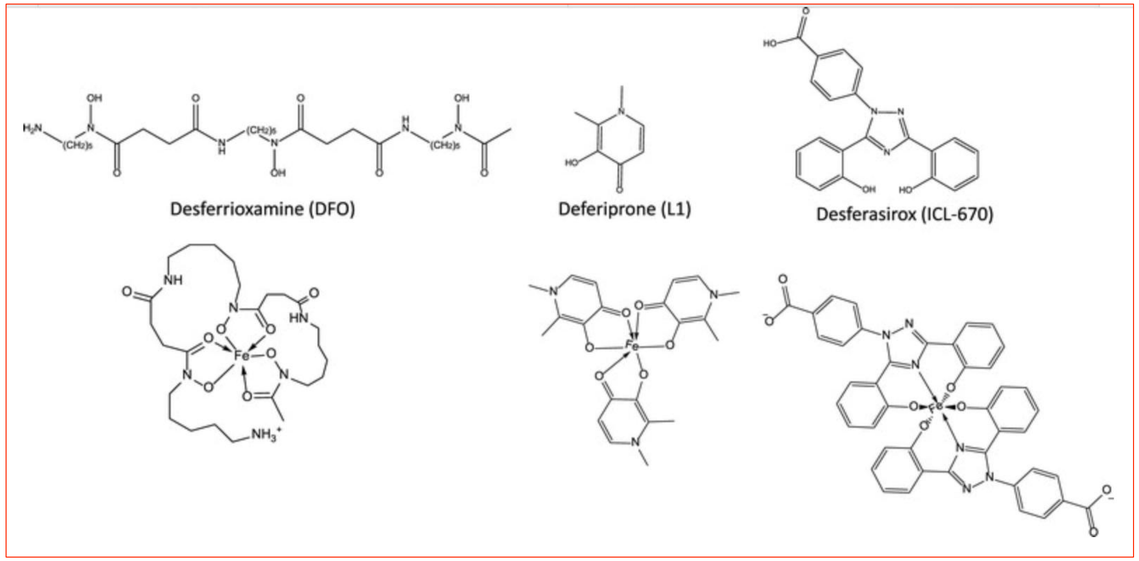
Trasfusioni

La pratica trasfusionale si è evoluta, negli anni, dall' "ipertrasfusione" (>10-12 g/dL) degli anni '60-'70 ad obiettivi più moderati e individualizzati (≈9,0-10,5 g/dL / 90-105 g/L) dagli anni '90 in poi, con raccomandazioni per aumentare tali target (≈11-12 g/dL) per pazienti con malattie cardiache o scarsa soppressione del midollo. Le attuali linee guida internazionali (TIF e organismi nazionali) raccomandano generalmente di mantenere l'Hb pre-trasfusionale ≈ 9,0-10,5 g/dL per la maggior parte dei pazienti dipendenti dalle trasfusioni.

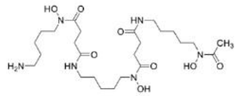
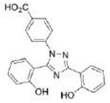


Musallam KM, et al. *Pretransfusion hemoglobin level and mortality in adults with transfusion-dependent β-thalassemia*. Blood. 2024 Mar 7;143(10):930-932.

Iron Chelators



Hamilton JL, Kizhakkedathu JN. *Polymeric nanocarriers for the treatment of systemic iron overload.* Mol Cell Ther. 2015 Mar 24;3:3

Chelator	DFO	DFP	DFX
Structure			
Molecular weight	560	139	373
First clinically available	1968	1999	2005
Administration route	Parental (subcutaneous or intravenous)	Oral (tablets or solution)	Oral (dispersible or film-coated tablets)
Administration frequency	8–12 h, 5–7 days per week; continuous infusion over 24 h in heart failure	Every 8 h, TID	Once daily, ongoing evaluations on BID dosing
Plasma half-life	30 min	3 h	8–16 h
Route of iron excretion	Urinary and fecal	Urinary	Fecal
Recommended dose	30–60 mg/g per day	75–100 mg/kg per day	20–40 mg/kg per day (dispersible tablets) or 14–28 mg/kg per day (film-coated tablets)
Main adverse event	Reaction at site of infusion, severe allergic reactions, bone abnormalities, growth failure, auditory (hearing loss), ophthalmologic (retinal damage), Yersinia infection	Gastrointestinal, arthralgia, transient increase in liver enzymes, neutropenia, agranulocytosis	Increased GFR and serum creatinine, proteinuria, rare renal failure, increased liver enzymes, rare liver failure, skin rash, gastrointestinal, rare gastrointestinal bleeding
Pregnancy	Contraindicated (can be used only at the end of the second trimester in patients with severe heart and liver IOL)	Contraindicated	Contraindicated
Licensed use—TDT	Treatment of chronic IOL resulting from transfusion-dependent anemia	Treatment of transfusional IOL in TDT where DFO is contraindicated or inadequate	US: Treatment of transfusional iron overload in patients 2 years or older Europe: Treatment of transfusional iron overload in patients 6 years and older, and when DFO is contraindicated or inadequate, in patients 2–5 years old
Licensed use—NTDT	No sufficient data, commonly used in clinical practice	Off-label	US: Treatment of chronic iron overload in patients 10 years of age and older with LIC ≥5 mg/g dry weight liver and SF ≥300 µg/L Europe: Treatment of chronic iron overload in patients 10 years of age and older with LIC ≥5 mg/g dry weight liver and/or SF ≥800 µg/L
Cost/year (£)	5584	5519	23,179

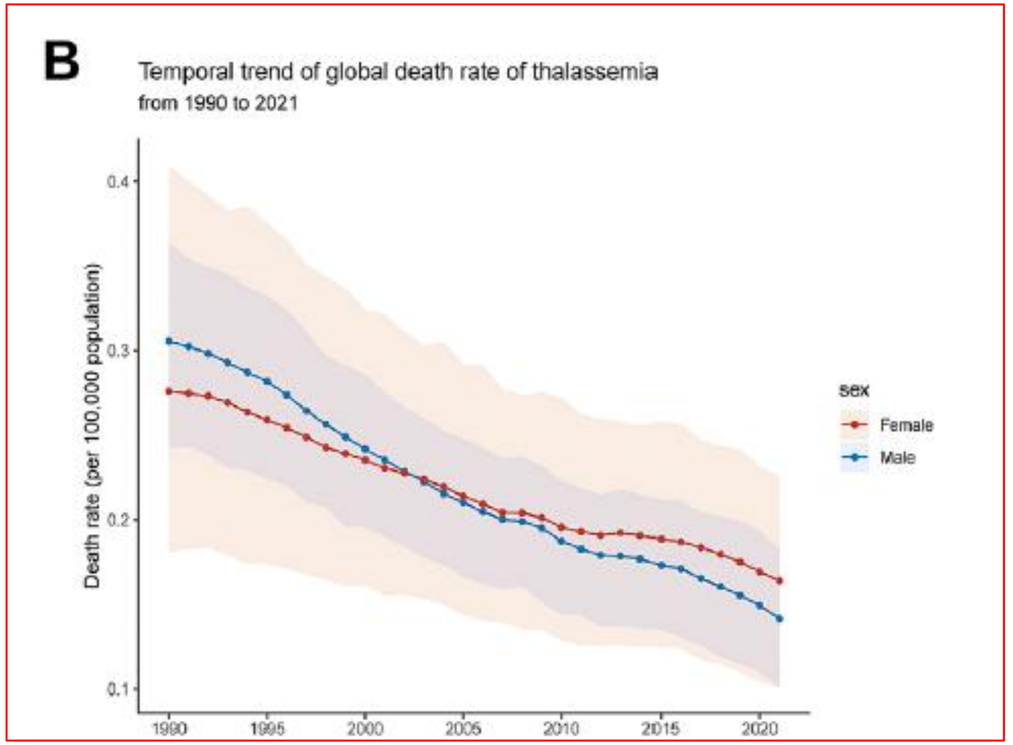
Pinto VM, et al. *Management of Iron Overload in Beta-Thalassemia Patients: Clinical Practice Update Based on Case Series*. Int J Mol Sci. 2020 Nov 20;21(22):8771.

β-Talassemia

Cause of Death & Epidemiology Trends

Parameter	All (*N* = 709)	Birth cohort			
		1970–1974 (*N* = 213)	1975–1979 (*N* = 245)	1980–1984 (*N* = 125)	1985–1997 (*N* = 126)
Male, *n* (%)	362 (51.1)	110 (51.6)	123 (50.2)	67 (53.6)	62 (49.2)
Age in years at last follow-up, median (IQR)	33.5 (21.3–43.3)	45.7 (24.5–48.1)	40.7 (26.2–43.4)	30.1 (19.2–39.4)	24.8 (16.4–31.2)
Patient-years of observation	22 443	7939	8217	3443	2843
BMT, *n* (%)	73 (10.3)	15 (7.0)	23 (9.4)	21 (16.8)	14 (11.1)
Age at BMT in years, median (IQR)	10.7 (7.9–15.5)	17.1 (15.6–19.1)	11.7 (10–13.4)	8.2 (6.5–10.4)	3.8 (2.7–10.3)
Splenectomy, *n* (%)	271 (38.2)	123 (57.7)	89 (36.3)	38 (30.4)	21 (16.7)
Age at splenectomy in years, median (IQR)	10 (8–16)	9 (7–12)	11 (8–17)	15 (10.2–20)	14 (6.8–23)
Deaths, *n* (%)	93 (13.1)	45 (21.1)	32 (13.1)	8 (6.4)	8 (6.3)
Age of death in years, median (IQR)	23.2 (16.9–30)	24.4 (19.8–31.3)	24.1 (18.3–31)	16.6 (10.9–21.8)	10.8 (8.4–17.3)
Cause of death, *n* (% of deaths)					
Heart disease	53 (57.0)	32 (71.1)	16 (50.0)	4 (50.0)	1 (12.5)
BMT complication	10 (10.8)	3 (6.7)	2 (6.3)	2 (25.0)	3 (37.5)
Infection	8 (8.6)	3 (6.7)	3 (9.4)	-	2 (25.0)
Liver disease	4 (4.3)	2 (4.4)	2 (6.3)	-	-
Cancer	3 (3.2)	1 (2.2)	1 (3.1)	1 (12.5)	-
Thromboembolism	2 (2.2)	-	2 (6.3)	-	-
Accident	2 (2.2)	1 (2.2)	1 (3.1)	-	-
Anemia	1 (1.1)	-	-	1 (12.5)	-
Unknown	10 (10.8)	3 (4.4)	5 (15.6)	-	2 (25.0)

Forni GL, et al. *Overall and complication-free survival in a large cohort of patients with β-thalassemia major followed over 50 years*. Am J Hematol. 2023 Mar;98(3):381-387.



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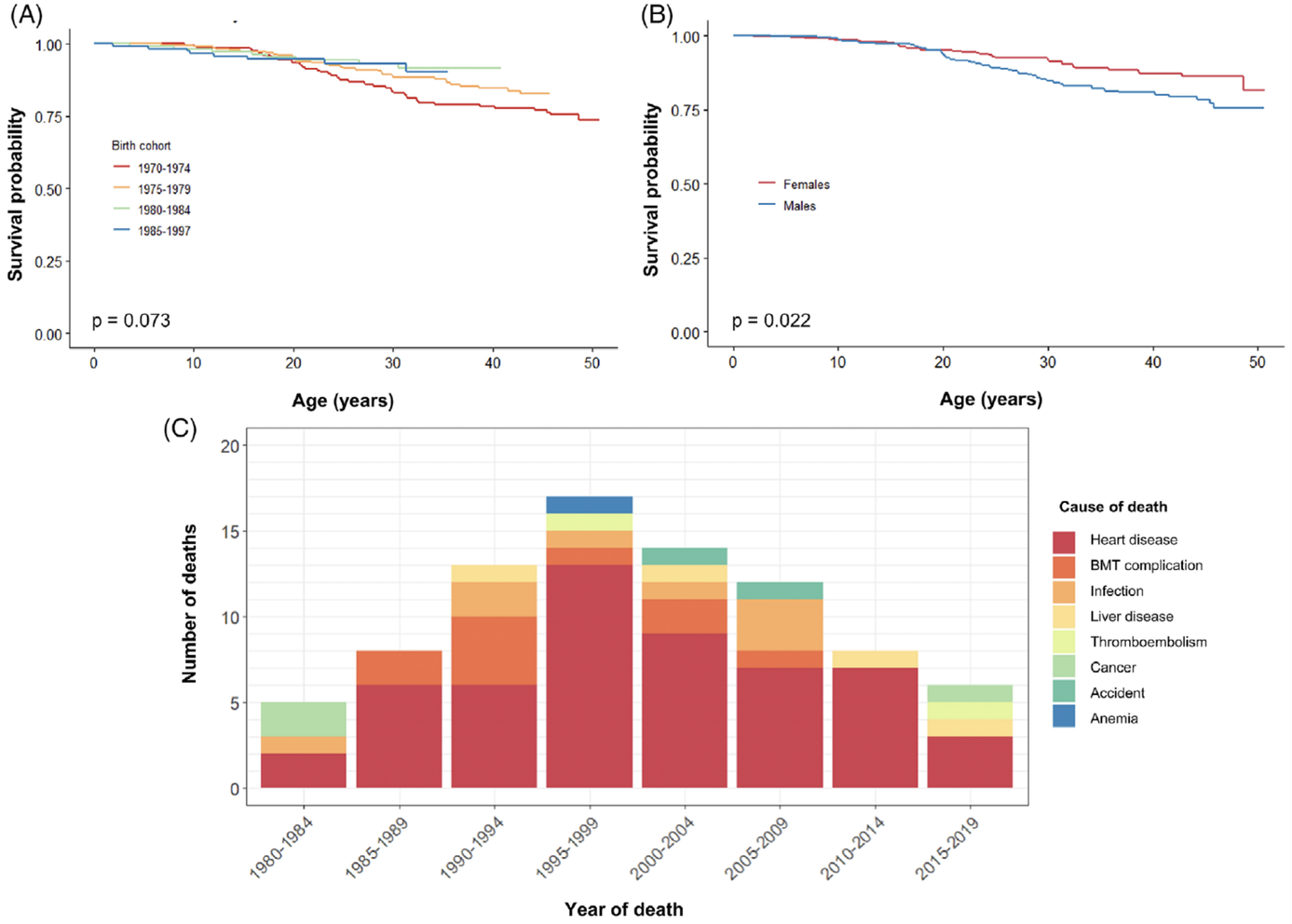
β-Talassemia

Cause of Death & Epidemiology Trends



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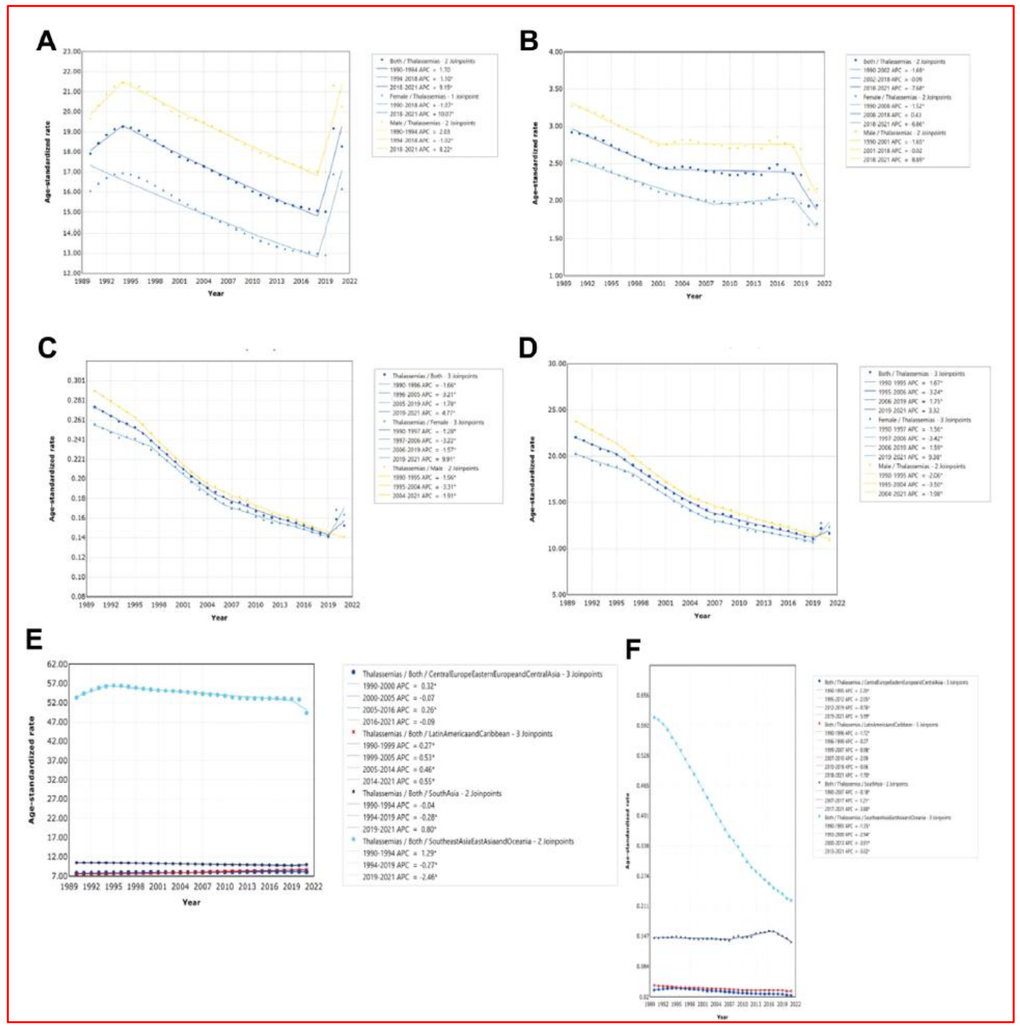

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β-Talassemia

Co-morbidities

	Risk factors	Monitoring	Management
Cardiovascular			
Left ventricle dysfunction	Anaemia; cardiac iron overload	Cardiac magnetic resonance (T2*); echocardiography (left ventricular ejection fraction)	Intensification of iron chelation therapy and cardiac medications
Pulmonary hypertension	Chronic hypoxia; splenectomy hypercoagulability; advanced age; non-transfusion-dependent thalassaemia	Echocardiography (tricuspid valve jet velocity); cardiac catheterisation for validation	Pulmonary vasodilator therapies
Arrhythmia	Anaemia; cardiac iron overload; thyroid disturbances	Cardiac magnetic resonance (T2*); electrocardiogram; Holter electrocardiogram	Intensification of iron chelation therapy and cardiac medications
Thromboembolic events	Splenectomy; hypercoagulability; iron-induced endothelial damage	Platelet count; nucleated red cell count	Education for avoiding other risk factors; possible aspirin prophylaxis for at-risk patients; standard anticoagulation therapy
Hepatobiliary			
Viral hepatitis	Red cell transfusions	Hepatitis serology and nucleic acid testing; biochemical evaluation; imaging studies (ultrasound, Fibroscan, magnetic resonance)	Timely vaccination, ensure safety of blood supplies, antiviral therapies
Fibrosis or cirrhosis	Liver iron overload	Hepatitis serology and nucleic acid testing; biochemical evaluation; imaging studies (ultrasound, Fibroscan, magnetic resonance); liver iron concentration (magnetic resonance)	Intensification of iron chelation therapy
Gallstones	Chronic haemolysis	Biochemical evaluation; imaging studies (ultrasound)	Cholecystectomy (if symptomatic)
Endocrinopathies			
Growth retardation; delayed puberty; hypogonadism	Pituitary iron deposition (thyroid hormone, hypothalamus-pituitary-gonadal axis, growth hormone-insulin like growth factor disturbances); nutrition; anaemia	Height; weight; Tanner stage; bone age; estradiol; testosterone; luteinising hormone, follicle-stimulating hormone (if required: growth hormone stimulation, luteinizing hormone-releasing hormone tests), T4/ thyroid-stimulating hormone	Appropriate transfusion and iron chelation; nutritional support; management strategy is considered on a case-by-case basis
Glucose intolerance; diabetes	Liver iron overload; pancreatic iron deposition; family predisposition	Fasting glucose; oral glucose tolerance test; fructosamine	Diet; physical activity; oral antidiabetics; insulin
Thyroid dysfunction	Anaemia; thyroid iron deposition; hypopituitarism	Thyroid function tests; pituitary evaluation; ultrasound	Timely evaluation and treatment
Adrenal insufficiency	Anaemia; adrenal iron deposition; hypopituitarism	Adrenal function tests; imaging studies	Glucocorticoid stress supplementation in patients with adrenal insufficiency
Bone disease	Ineffective erythropoiesis, iron predisposition and chelator toxicity; hypogonadism; hypoparathyroidism	Calcium, phosphorus, alkaline phosphatase, 25-hydroxy-vitamin D, parathormone, Dual Energy X-ray Absorptiometry at regular intervals	Calcium and vitamin D supplementation; bisphosphonates; denosumab
Neoplasia			
Hepatocellular carcinoma	Chronic hepatitis B or hepatitis C virus infections; liver iron overload	Imaging studies (ultrasound, MRI) at frequent intervals (6–12 months) after age 30 or 40 years	Viral hepatitis treatment; iron chelation therapy; referral for resection or transplantation if patients are at early stages of illness
Thyroid cancer; renal cancer; gastrointestinal cancer; breast cancer; haematological malignancies	Iron toxicity; chronic anaemia; advanced age	Surveillance with imaging studies or colonoscopy as per age-appropriate guidelines	Aggressive evaluation and treatment

(Table 2 continues on next page)

(Continued from previous page)

	Risk factors	Monitoring	Management
Others			
Renal dysfunction; tubular dysfunction; nephrolithiasis	Anaemia; renal iron deposition; and chelator (especially deferasirox) toxicity	Biochemical evaluation; urine analysis (calcium and total protein/creatinine ratio); imaging studies	Adjust iron chelation therapy; encourage fluid intake
Extramedullary haematopoiesis	Ineffective erythropoiesis	Symptom-directed imaging (x-ray, magnetic resonance)	Transfusion; hydroxyurea; radiotherapy; surgical decompression
Leg ulcers	Anaemia; hypercoagulability	Ineffective erythropoiesis indexes	Treatment of anaemia; topical antibiotics; occlusive dressing; leg elevation
Auditory disturbances	Chelator toxicity	Auditory evaluation at regular intervals	Careful titration of ototoxic iron chelation therapy (especially deferoxamine in low iron load concentrations)
Ophthalmologic disturbances	Chelator toxicity	Ophthalmologic evaluation at regular intervals	Adjust iron chelation therapy according to iron load concentrations
Infectious complications	Splenic dysfunction; transfusion-related infections; iron overload; use of iron chelation therapy (especially deferoxamine)	HIV and hepatitis C virus surveillance; aggressive evaluation in case of febrile episodes	Timely immunisation; prophylaxis; aggressive antibiotic treatment in patients who have had a splenectomy; monitoring for infections from pathogens with enhanced virulence in iron-rich environments
Spleen (splenomegaly, hypersplenism)	Ineffective erythropoiesis; extramedullary haematopoiesis	Hematological indexes for signs of hypersplenism, imaging studies (ultrasound, magnetic resonance, CT)	Consider splenectomy for symptomatic splenomegaly or hypersplenism

Table 2: **Monitoring and management of comorbidities**

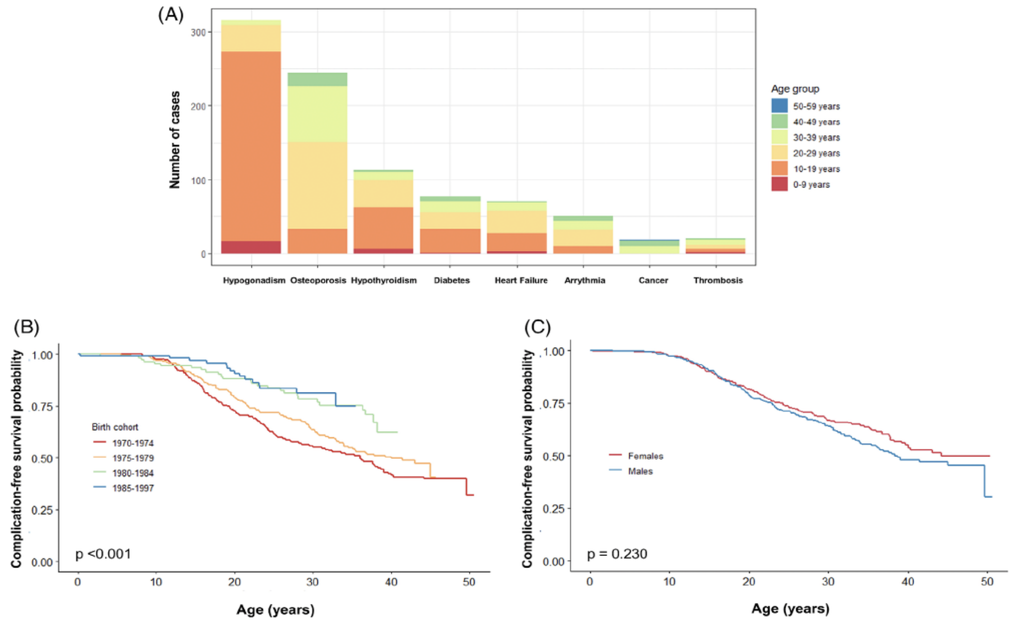
Kattamis A, et al. Thalassaemia. Lancet. 2022 Jun 18;399(10343):2310-2324.

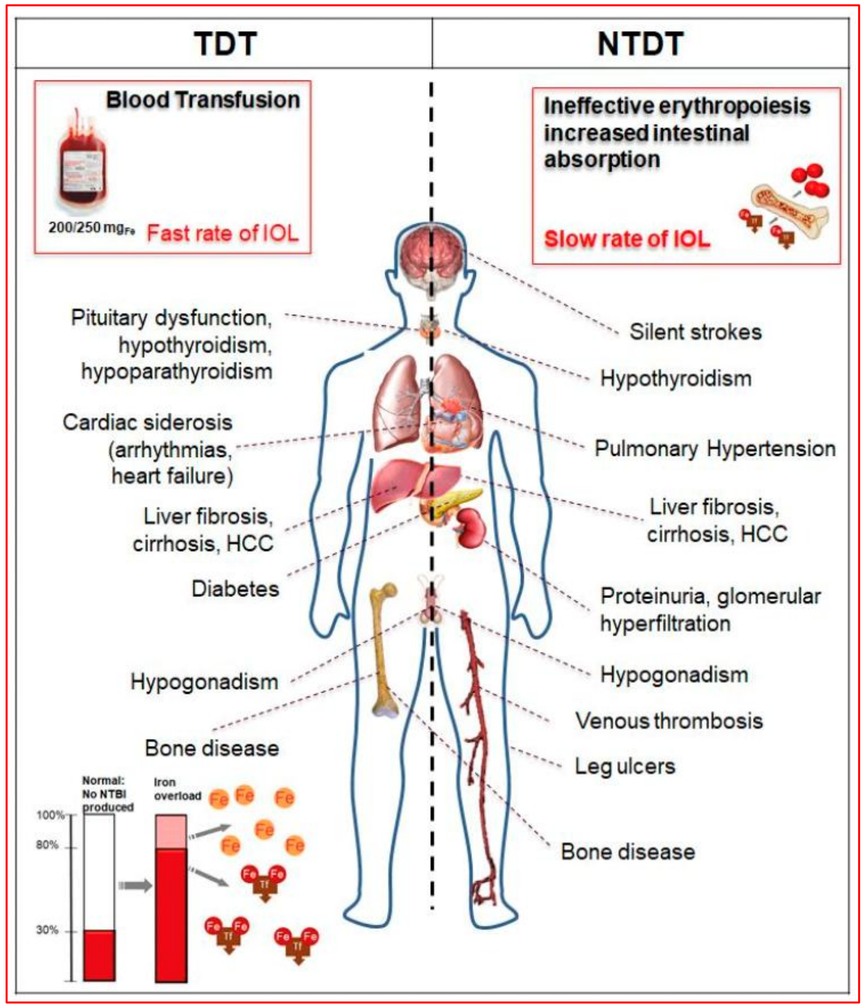
β-Talassemia

Co-morbidities

Parameter	Age at presentation in years, median (IQR)	All (*N* = 709)	Birth cohort 1970–1974 (*N* = 213)	1975–1979 (*N* = 245)	1980–1984 (*N* = 125)	1985–1997 (*N* = 126)
Any complication	-	480/709 (67.7)	178/213 (83.6)	185/245 (75.5)	70/125 (56.0)	47/126 (37.3)
Hearth failure	22.4 (18.5–28.5)	96/697 (13.8)	47/213 (22.1)	31/244 (12.7)	11/123 (8.9)	7/117 (6.0)
Arrhythmia	26.7 (22.7–34.2)	58/697 (8.3)	32/213 (15.0)	21/244 (8.6)	4/123 (3.3)	1/117 (0.9)
Diabetes	23.3 (16.1–30.9)	78/698 (11.2)	44/213 (20.7)	24/245 (9.8)	8/123 (6.5)	2/117 (1.7)
Hypothyroidism	19.4 (14.8–24.4)	120/698 (17.2)	55/213 (25.8)	52/245 (21.2)	10/123 (8.1)	3/117 (2.6)
Hypogonadism	16 (14.9–17)	335/683 (49.0)	148/213 (69.5)	144/245 (58.8)	33/121 (27.3)	10/104 (9.6)
Osteoporosis	27.6 (23–32.9)	263/402 (65.4)	82/118 (69.5)	100/139 (71.9)	50/71 (70.4)	31/74 (41.9)
Thrombosis	25.8 (19.4–34.7)	22/698 (3.2)	8/213 (3.8)	10/245 (4.1)	1/123 (0.8)	3/117 (2.6)
Cancer	39 (36–41.8)	21/709 (3.0)	15/213 (7.0)	6/245 (2.4)	0/125 (0.0)	0/126 (0.0)
HIV infection	11.2 (8.7–13.6)	10/698 (1.4)	5/213 (2.3)	5/245 (2.0)	0/123 (0.0)	0/117 (0.0)
≥2 complications	-	301/709 (42.5)	132/213 (62.0)	129/245 (52.7)	31/125 (24.8)	9/126 (7.1)
≥3 complications	-	137/709 (19.3)	69/213 (32.4)	54/245 (22.0)	13/125 (10.4)	1/126 (0.8)

Note: Data presented as *n*/*N* (%) unless otherwise indicated.
Abbreviations: HIV, human immunodeficiency virus; IQR, interquartile range.



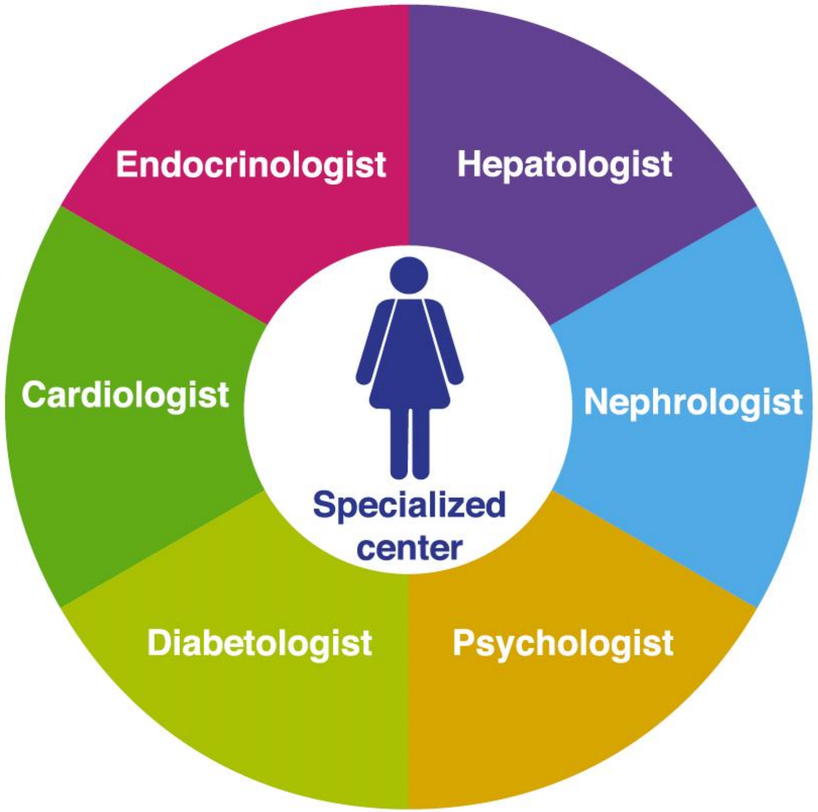


Pinto VM, et al. *Management of Iron Overload in Beta-Thalassemia Patients: Clinical Practice Update Based on Case Series*. Int J Mol Sci. 2020 Nov 20;21(22):8771.

Forni GL, et al. *Overall and complication-free survival in a large cohort of patients with β-thalassemia major followed over 50 years*. Am J Hematol. 2023 Mar;98(3):381-387.

β-Talassemia

Co-morbidities



Pinto VM, et al. *Management of the aging beta-thalassemia transfusion-dependent population - The Italian experience*. Blood Rev. 2019 Nov;38:100594.

• **Background**: la malattia coinvolge diversi organi e sistemi → gestione complessa.

• **Team multidisciplinare**: ematologo, trasfusionista, cardiologo, endocrinologo, epatologo, nefrologo, psicologo, dietista, infermiere.

Obiettivi:

• Prevenire e trattare precocemente le coplicanze d'organo.

• Migliorare qualità e aspettativa di vita

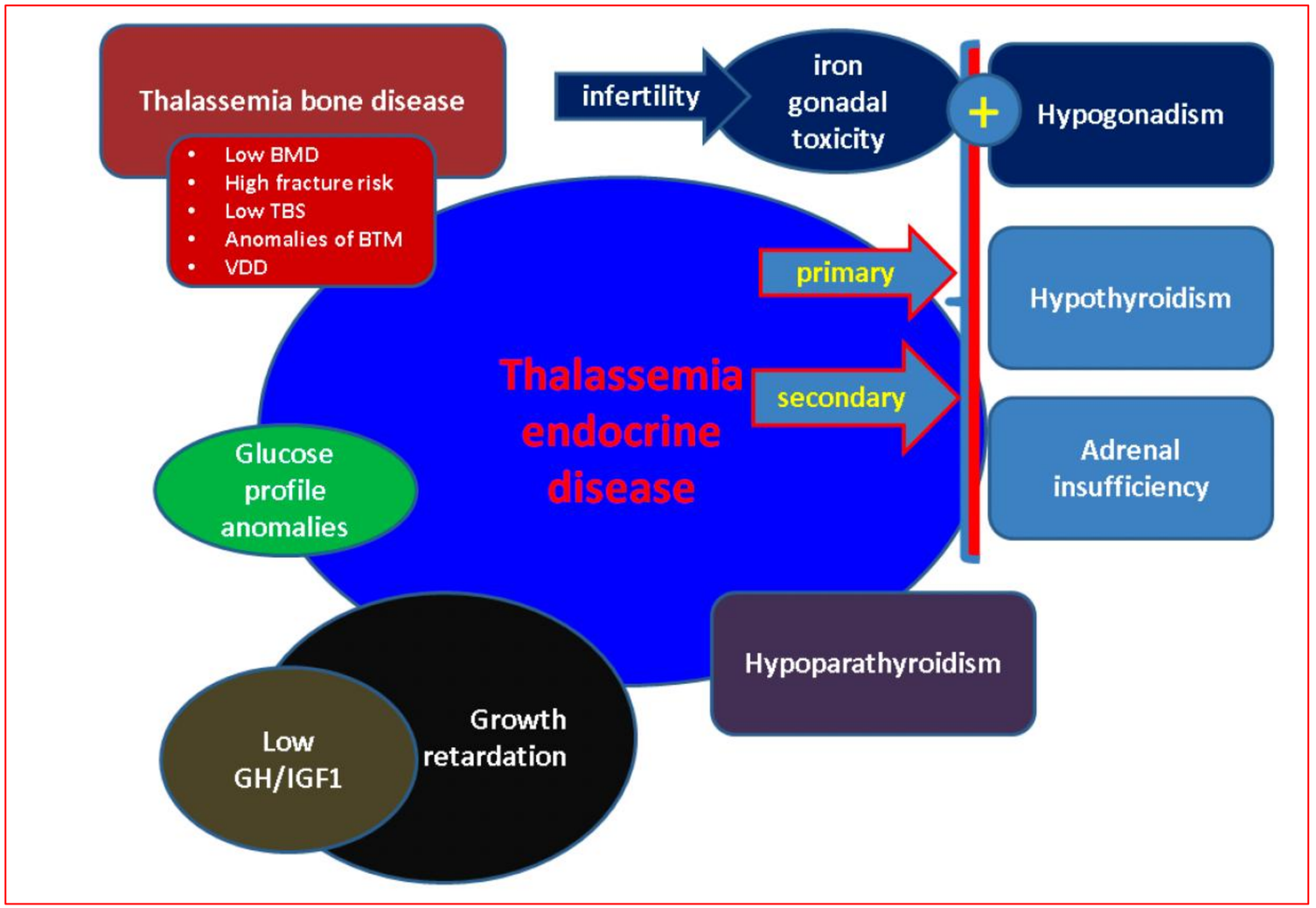
• Coordinare la transizione pediatrico-adulto.

• Personalizzare il percorso terapeutico.

Valore aggiunto: cura integrata, centrata sul paziente, con migliore esito clinico e benessere globale.

β-Talassemia

Thalassemic Endocrine Disease



Carsote M, et al. *New Entity-Thalassemic Endocrine Disease: Major Beta-Thalassemia and Endocrine Involvement*. Diagnostics (Basel). 2022 Aug 9;12(8):1921.

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β-Talassemia

Thalassemia-Associated mixed hypogonadism

Table 1 Characteristics of the population examined

CV risk and metabolic profile Mean (SD) or *N* (%)	NH-TDT	H-TDT	HH-C	*p*-value[1]	*p*-value[2]
Progetto Cuore score[3]	0.77 (1.04)	0.87 (0.83)	4.12 (7.86)	0.13	0.6
Framingham score[4]	3.2 (3.5)	4.0 (2.9)	8.0 (12.0)	0.046*	0.2
Total cholesterol (mg/dl)	113 (26)	136 (27)	185 (43)	0.004*	<0.001*
HDL-c (mg/dl)	35 (14)	39 (11)	51 (13)	0.15	<0.001*
Triglycerides (mg/dl)	93 (42)	106 (62.1)	118 (58.6)	0.907	0.446
LDL-c (mg/dl)	66 (23.8)	78 (32.3)	107 (38)	0.116	0.007*
PAs (mmHg)	112 (10)	107 (9)	119 (9)	0.083	<0.001*
PAd (mmHg)	61 (7.7)	61 (9.9)	74 (10.2)	0.814	<0.001*

[1] p-value NH-TDT vs. H-TDT

[2] p-value H-TDT vs. HH-C

[3] Low risk < 3%; intermediate risk 3–20%; high risk > 20%

[4] Low risk < 10%; intermediate risk 10–19%; high risk > 20%

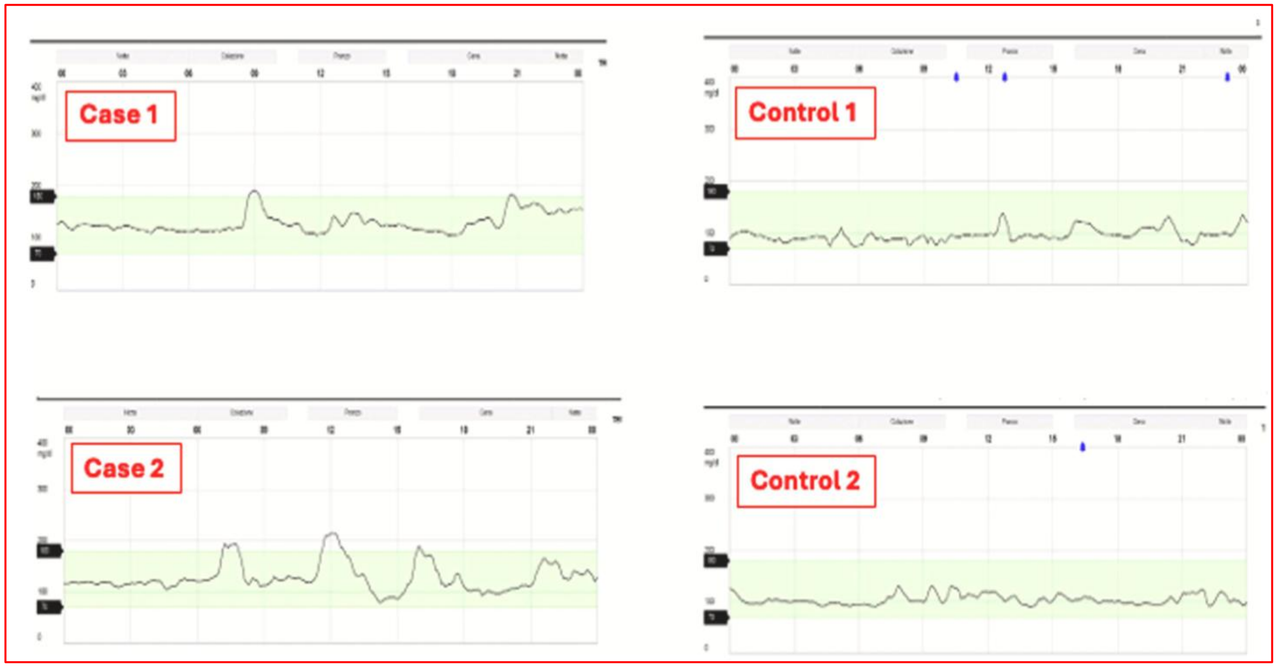
Casale M, et al. *Thalassemia-Associated mixed hypogonadism (TAMH): unraveling a unique endocrine pattern and its impact on cardiovascular risk.* Endocrine. 2025 Sep 20.

I pazienti TDT con ipogonadismo (H-TDT) avevano livelli significativamente più elevati di FSH e LH rispetto ai pazienti con ipogonadismo ipogonadotropo (HH-C) ($p < 0,001$).

Sono state riscontrate differenze significative nei livelli di colesterolo totale e rischio cardiovascolare tra i pazienti con TDT con e senza ipogonadismo ($p = 0,046$, $p = 0,004$, rispettivamente). Il rischio cardiovascolare era simile tra i pazienti con H-TDT e HH-C.

β-Talassemia

Continuous Glucose Monitoring



Zanfardino A, et al. *Characterisation of transfusion-dependent prediabetes using continuous glucose monitoring: The Haemoglycare study.* Diabetes Res Clin Pract. 2025 Apr;222:112076.

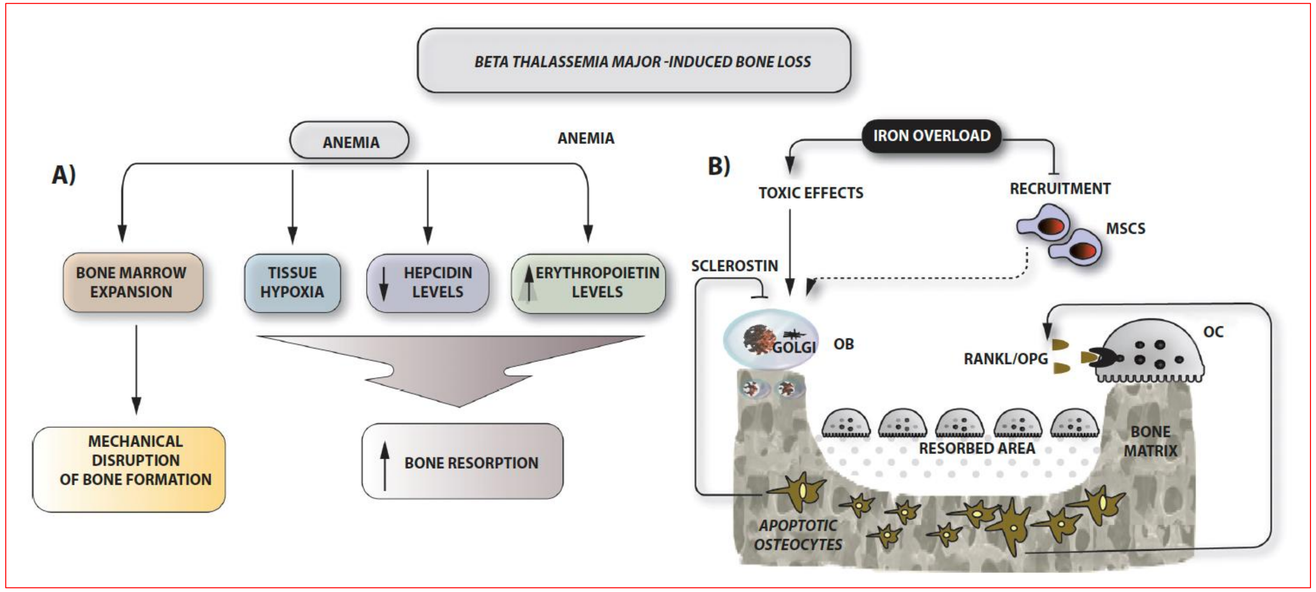
- HbA1c non e' un marcatore dello stato glicemico nei pazienti con thalassemia, trasfusione dipendenti.
- CGM rileva in modo affidabile stati di pre-diabete nel 37% dei pazienti con thalassemia trasfusione dipendente negativi al OGTT e con glicemia a digiuno nella norma

Linee guida internazionali confermano la necessità di effettuare lo screening dei disturbi del metabolismo del glucosio in tutti i pazienti con emoglobinopatie, in particolare nei pazienti trasfusione-dipendenti, a partire dai 10 anni di età.

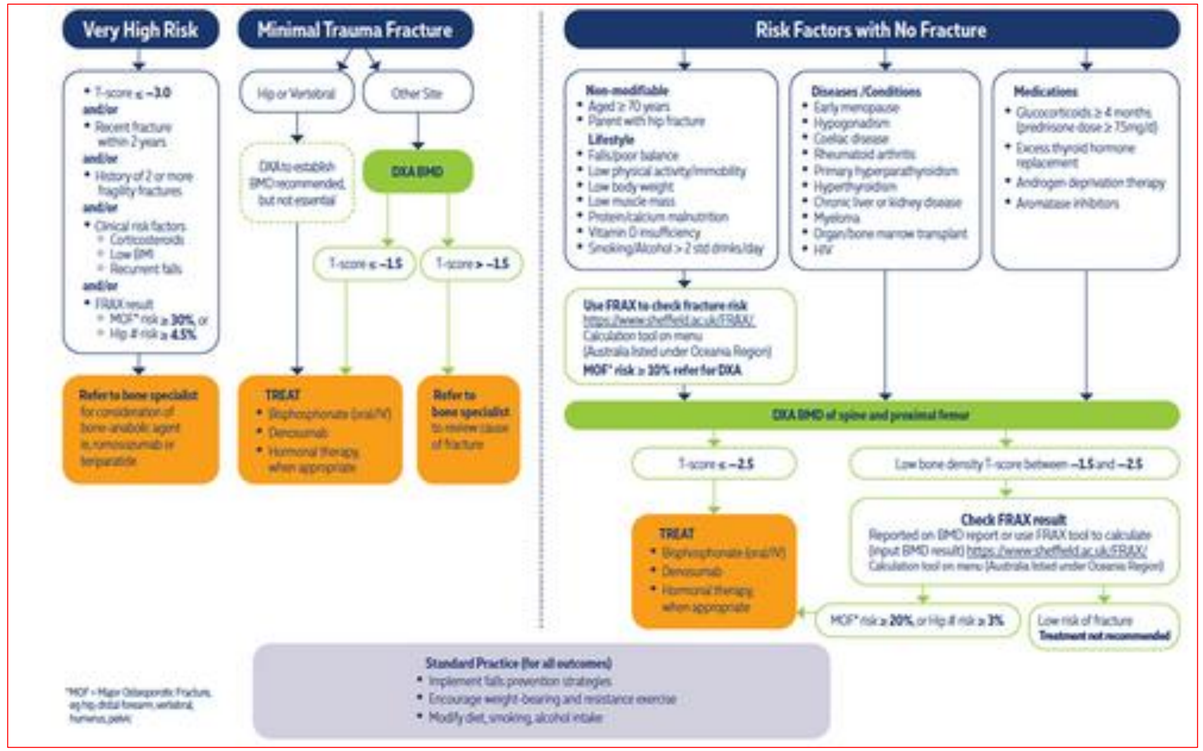
Sebbene la glicemia venosa a digiuno e l'OGTT siano gli unici test convalidati per la diagnosi di DM, IFG e IGT tra i pazienti con TDT, riteniamo che il CGM possa diventare sempre più rilevante per lo screening del diabete in questa popolazione.

β-Talassemia

Osteoporosis



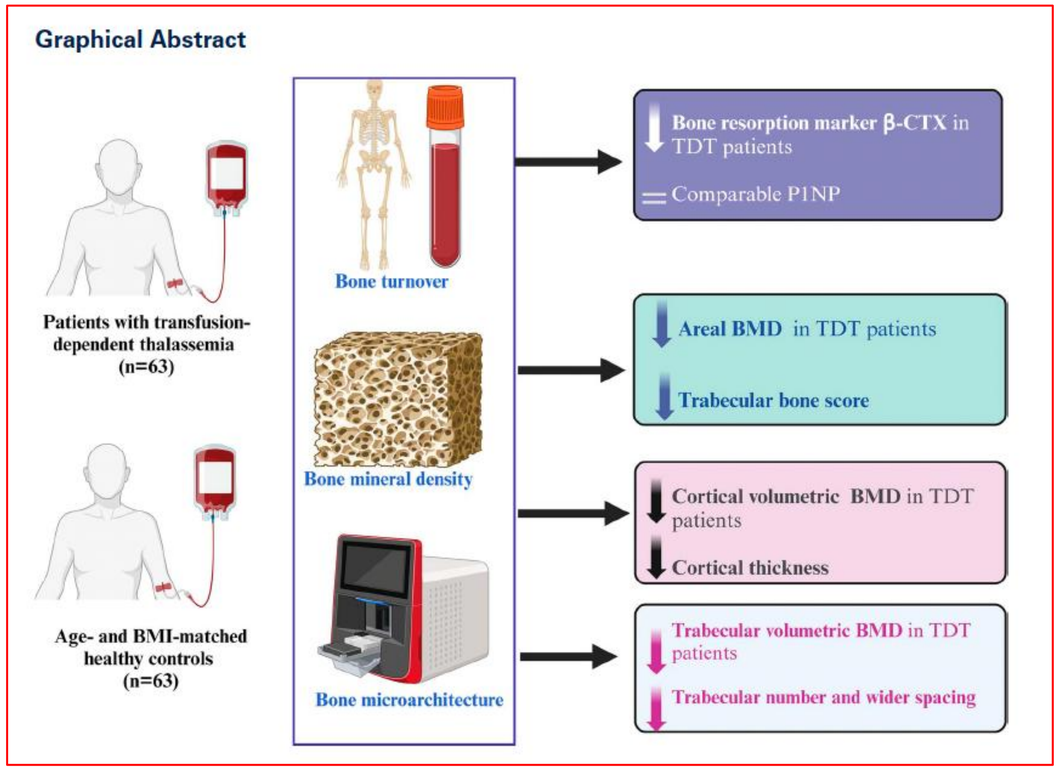
Yavropoulou MP, et al. *Approach to the management of β thalassemia major associated osteoporosis - A long-standing relationship revisited*. Acta Biomed. 2022 Oct 26;93(5):e2022305.



Healthy Bones Australia and RACGP Osteoporosis Australia. *Clinical Guidelines*. Healthy Bones Australia: Sydney, Australia; 2024.

β-Talassemia

Osteoporosis and Bone Architecture



Das L, et al. *Bone turnover, areal BMD, and bone microarchitecture by second-generation high-resolution peripheral quantitative computed tomography in transfusion-dependent thalassemia*. JBMR Plus. 2024 Aug 30;8(11):ziae117.

Factor	Key mechanism	Treatment	Prevention
Bone marrow expansion	Ineffective erythropoiesis	Transfusion at optimal Hb levels	Transfusion at optimal Hb levels
Iron overload	Iron toxicity	Optimal iron chelation	Early and regular iron chelation
Iron chelation	Overchelation; drug toxicity	Tune chelation intensity on iron overload; avoid high doses	Tune chelation intensity on iron overload
Hypogonadism	Iron toxicity	Replacement therapy	Early and regular iron chelation
Hypoparathyroidism	Iron toxicity	Replacement therapy	Early and regular iron chelation
Hyperparathyroidism	Vitamin D deficiency	Vitamin D2 or D3	Vitamin D2 or D3
Hypothyroidism	Iron toxicity	Replacement therapy	Early and regular iron chelation
GH	Iron toxicity	Replacement therapy	Early and regular iron chelation
Diabetes	Iron toxicity	Replacement therapy	Regular iron chelation; lifestyle
Liver disease	Viral hepatitis; iron toxicity	Antiviral therapy; regular iron chelation	Safe blood; regular iron chelation
Vitamin D deficiency	Iron toxicity	Vitamin D2 or D3	?
Renal disease	Hypercalciuria	Correct causes	?
Vitamin C deficiency	Iron toxicity	Vitamin C–rich diet	Optimal iron chelation

Piga A. Impact of bone disease and pain in thalassemia. Hematology Am Soc Hematol Educ Program. 2017 Dec 8;2017(1):272-277.

β-Talassemia

Osteoporosis or Thalassemic Osteopathy?

Treatment*	Outcome	Patients (N)
Alendronate and Clodronate	increase BMD at the lower back and hip compared with placebo after two years	25 patients
Neridronate	increased BMD at the lower back and femoral neck at six and 12 months but only at 12 months for the whole hip joint	125 patients
Pamidronate (60 vs 30 mg)	uncertain of the effect of the different doses on BMD at the lower back, hip, and forearm.	26 patients
Zinc	probably increases BMD at the lower back and hip after 12 months and after 18 months	42 patients
Denosumab	reduction in bone pain after 12 months	63 patients
Strontium ranelate	(Narratively) reported an increase in BMD at the lower back after 24 months and a decrease in back pain	24 patients

* calcitonin, colecalciferol ± calcium, hydroxyurea and hormone replacement therapy (HRT) are also used.

We recommend further long-term RCTs on different bisphosphonates and zinc supplementation therapies in people with beta thalassaemia-associated osteoporosis.

Bhardwaj A, Swe KM, Sinha NK. *Treatment for osteoporosis in people with beta-thalassaemia*. Cochrane Database of Systematic Reviews 2023, Issue 5. Art. No.: CD010429.

β-Talassemia

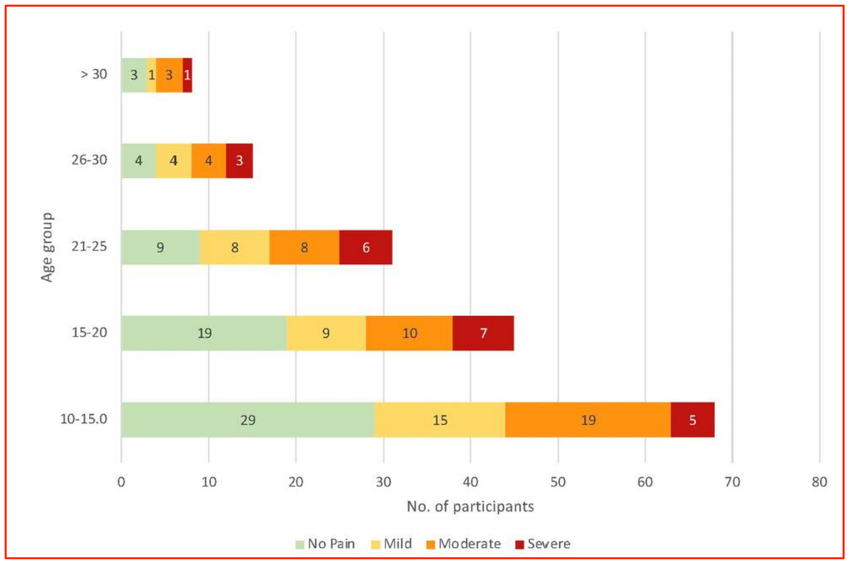
Thalassemic Osteopathy and Pain

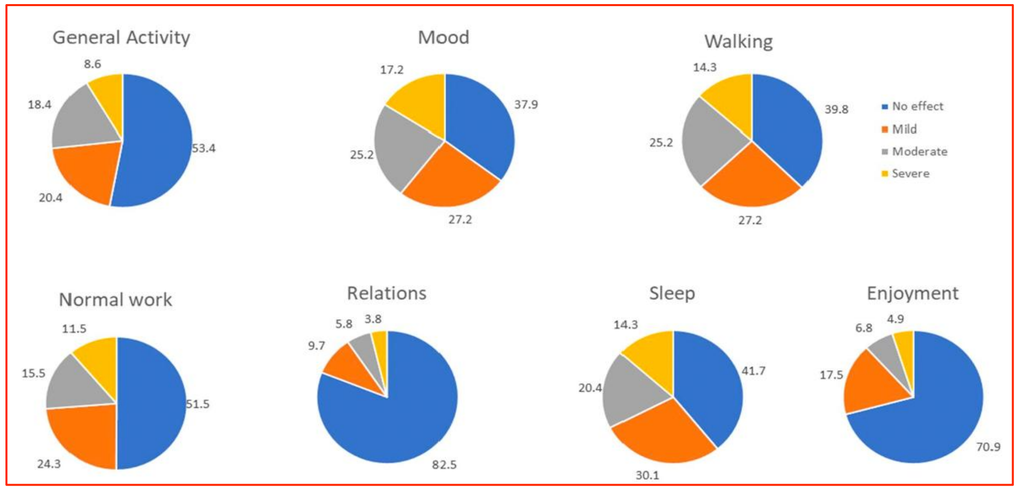
- A differenza dell'anemia falciforme, il dolore è raro durante i primi anni di vita e diventa frequente nella vita adulta.
- La maggior parte dei pazienti di età superiore ai 35 anni riferisce dolore cronico di intensità moderata-grave. La gravità del dolore aumenta con l'età, ma non varia significativamente con il sesso o con la diagnosi di talassemia.
- La qualità della vita, a causa del dolore, nella talassemia diminuisce notevolmente con l'età, rispetto alla popolazione generale.
- Il dolore cronico è più frequente nei pazienti che hanno iniziato trasfusioni regolari più tardi e hanno avuto una diagnosi di talassemia intermedia; è associata a un midollo osseo ipercellulare più espanso alla risonanza magnetica.
- Il sito più comune di dolore cronico è la parte bassa della schiena. Il dolore può essere scatenato da attività fisiche come stare in piedi a lungo e sollevare oggetti pesanti, ma il fattore scatenante del dolore più frequente è un basso livello di emoglobina, con sollievo dalle trasfusioni, specialmente nei pazienti con cicli trasfusionali più lunghi.
- L'imaging MRI della colonna vertebrale può rivelare una morfologia vertebrale anormale, degenerazione del disco e vari gradi di osteoporosi. Le alterazioni sono più estese rispetto ai pazienti con mal di schiena e assenza di talassemia.
- I pazienti con più siti di dolore o più visite con dolore hanno mostrato sintomi più elevati di depressione e ansia.

Piga A. Impact of bone disease and pain in thalassemia. Hematology Am Soc Hematol Educ Program. 2017 Dec 8;2017(1):272-277.

β-Talassemia

Pain





Grewal A, et al. *Prevalence, Severity, and Determinants of Pain in Thalassemia.* Hemoglobin. 2023 Sep;47(5):191-197.

	Youth $n = 21$	Adults $n = 50$	Total $n = 71$	p-Value [1]
Pain in past 24 h, count (% of cohort)	6 (28.6)	27 (54.0)	33 (46.5)	0.050
Back pain, count (%)	5 (23.8)	22 (44.9)	27 (38.6)	0.097
Pain in other body areas, count (%)	6 (28.6)	19 (38.8)	25 (35.7)	NS
Any pain medication use, count (%)	5 (23.8)	23 (46.0)	28 (39.4)	0.08
Average level of pain, 1–10 scale	1.8 ± 2.3	2.6 ± 2.5	2.3 ± 2.4	NS
Pain severity score [2]	6.3 ± 7.8	7.8 ± 8.4	7.4 ± 8.2	NS
Pain severity category [3]	Mild: 33% Moderate: 67% Severe: 0%	Mild: 59% Moderate: 30% Severe: 11%	Mild: 55% Moderate: 36% Severe: 9%	NS
Pain interference score [4]	13.4 ± 16.0	13.6 ± 17.8	13.6 ± 17.2	NS

Fung EB, et al. *Relationships among Physical Activity, Pain, and Bone Health in Youth and Adults with Thalassemia: An Observational Study*. Thalass Rep. 2022 Sep;12(3):90-100.

- La diminuzione dell'attività fisica e l'aumento del comportamento sedentario contribuiscono alla bassa massa ossea, che può essere correlata alla gravità del dolore in alcuni pazienti con Talassemia. Gli studi incentrati sull'aumento dell'attività fisica possono contribuire a migliorare la salute delle ossa e a ridurre il dolore nei pazienti con Thal.
- In alcune casistiche, il dolore è stato riportato dal 62,4% dei partecipanti con il 35,2% e il 59,4% dei partecipanti, che hanno riportato dolore rispettivamente nelle ultime 1 e 4 settimane.

Take Home Messages

- ✓ Le talassemie sono oggi patologie croniche gestibili, ma non ancora completamente risolte;
- ✓ La genetica molecolare ha rivoluzionato diagnosi, prognosi e counselling;
- ✓ La gravità clinica è correlata al grado di squilibrio tra catene globiniche;
- ✓ Oggi la prognosi, notevolmente migliorata negli anni, e' aperta e dipende più dalla gestione del ferro e dalle complicanze croniche che dalla malattia ematologica di base;
- ✓ La diagnosi precoce e la tipizzazione molecolare sono strumenti di prevenzione oltre che di cura;
- ✓ Stiamo passando da un approccio di supporto ad uno potenzialmente curativo e personalizzato;
- ✓ La talassemia oggi è una malattia cronica complessa che richiede team multi-disciplinari dedicati;
- ✓ Il futuro è nella combinazione di prevenzione e medicina di precisione.

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