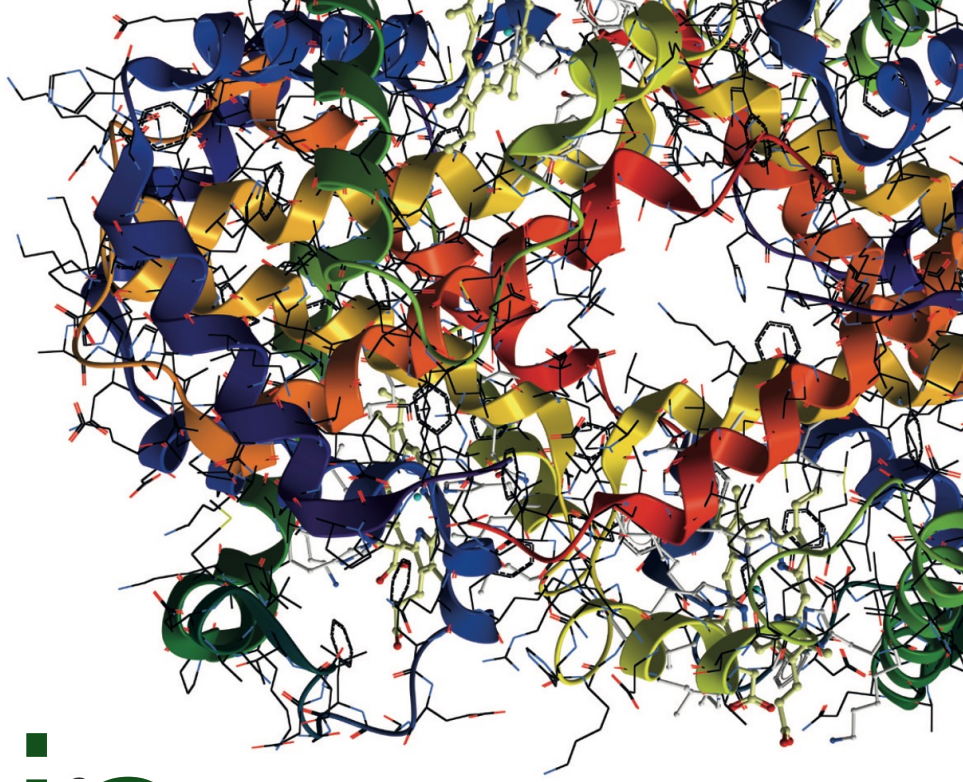
AGGIORNAMENTO SU DIAGNOSI E TERAPIA DELLE EMOGLOBINOPATIE



Alfa-Talassemie

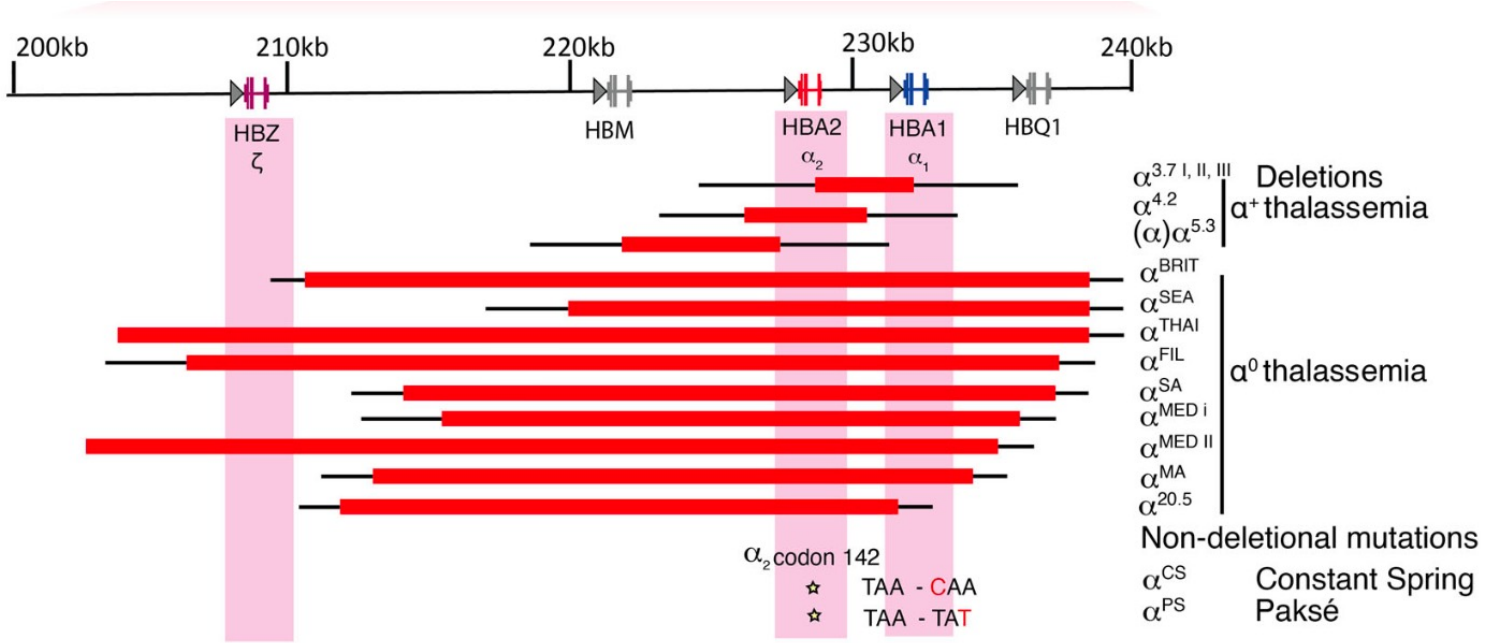
Natalia Scaramellini

SS Emoglobinopatie e disordini ereditari del metabolismo e del sistema immunitario. SC Medicina ad Indirizzo Metabolico Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milano

Dipartimento Scienze Cliniche e di Comunità Università degli Studi di Milano

Alfa Talassemia

Alterata sintesi delle catene alfa globiniche



Spettro fenotipico ampio e molto variabile

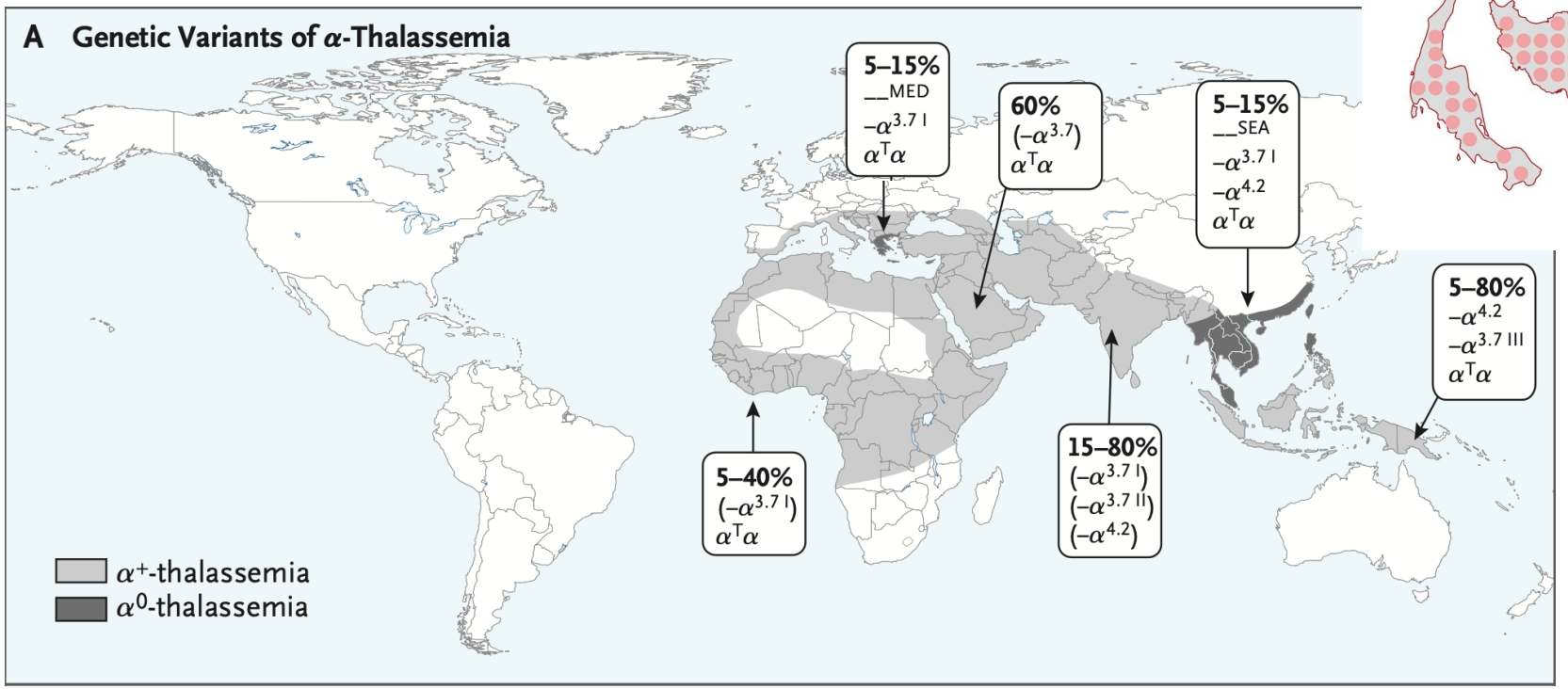
5% popolazione mondiale carrier

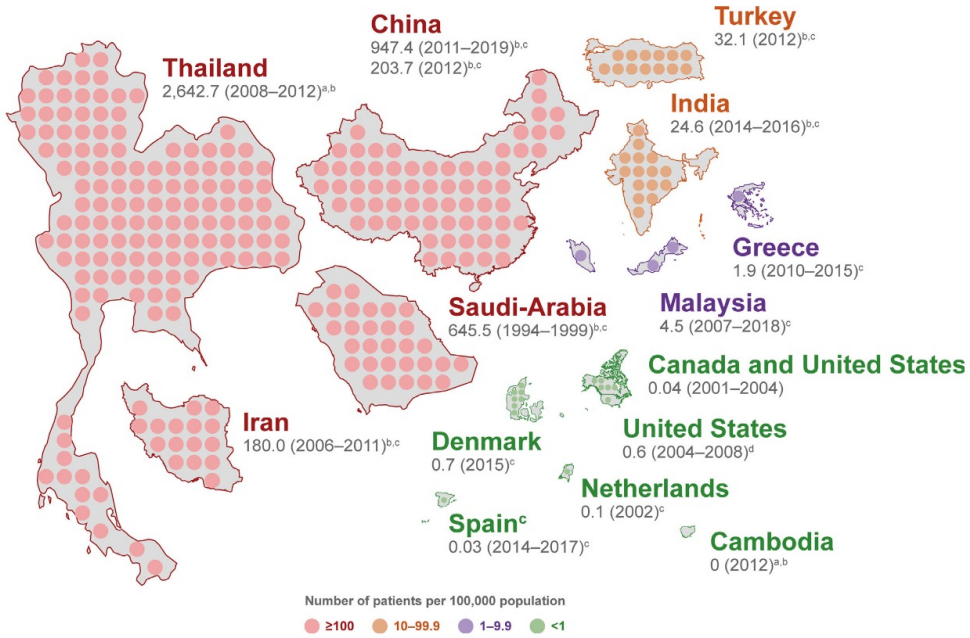
1 milione di persone affetto da

sindrome alfa talassemica

Galanello R, Alpha-thalassemia carrier identification by DNA analysis in the screening for thalassemia. Am J Hematol. 1998
Lal A, Disease burden, management strategies, and unmet needs in α-thalassemia due to hemoglobin H disease. Am J Hematol. 2024

Alfa Talassemia





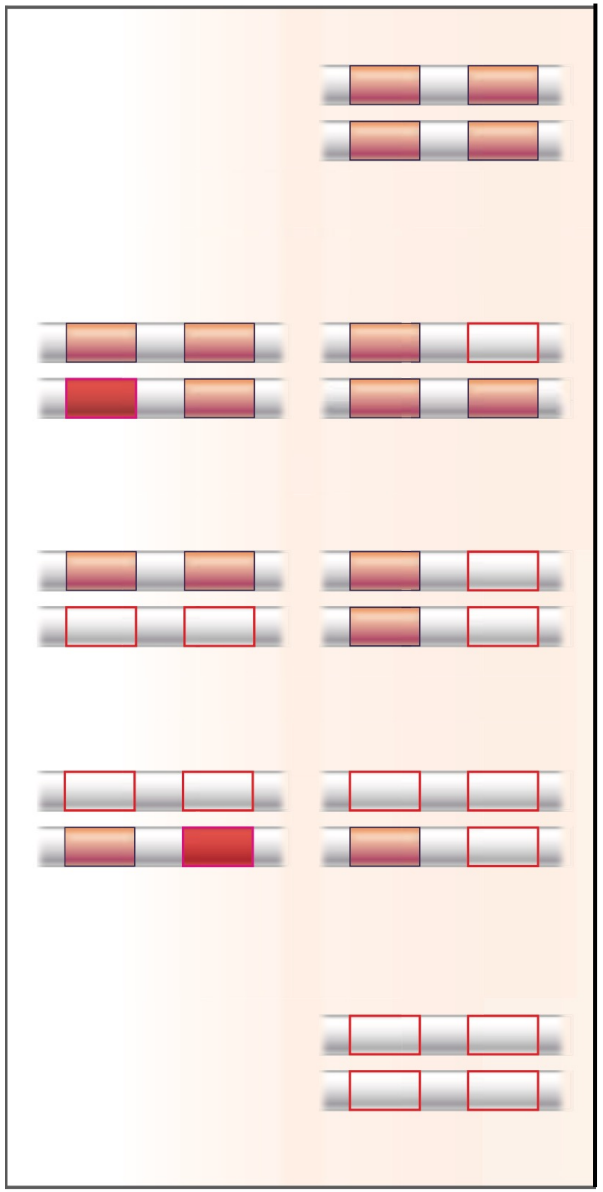
In Sardegna 38% popolazione ha almeno una mutazione

Piel FB, Weatherall DJ. The α-thalassemias. N Engl J Med. 2014

Galanello R, Alpha-thalassemia carrier identification by DNA analysis in the screening for thalassemia. Am J Hematol. 1998

Lal A, Disease burden, management strategies, and unmet needs in α-thalassemia due to hemoglobin H disease. Am J Hematol. 2024

Basi molecolari



Soggetto sano

Portatore sano o silente

Trait alfa

Malattia HbH

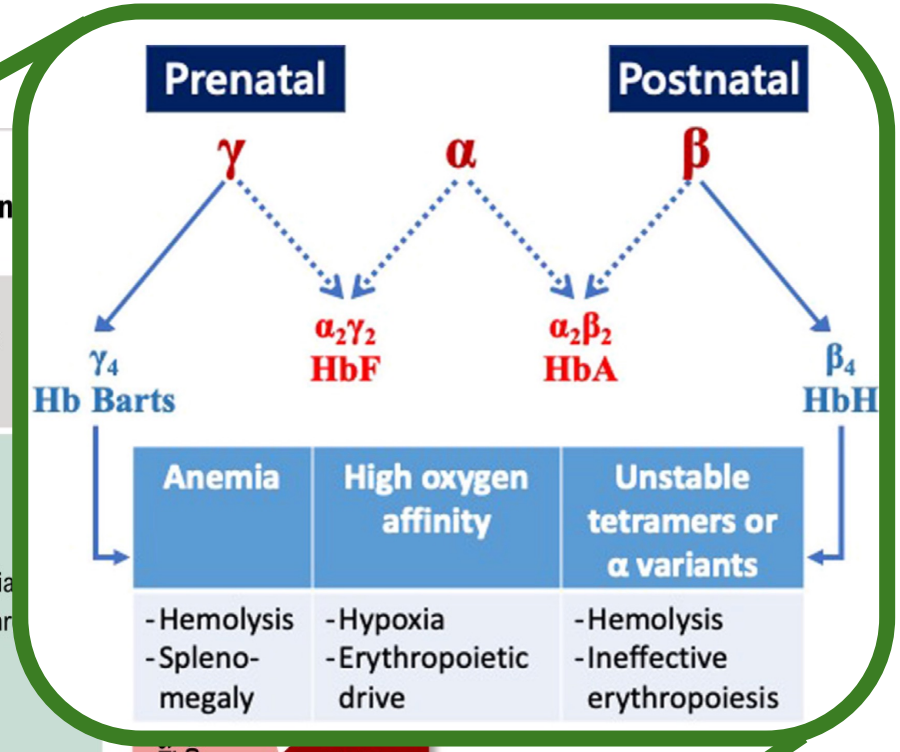
Malattia di Bart o Idrope fetale

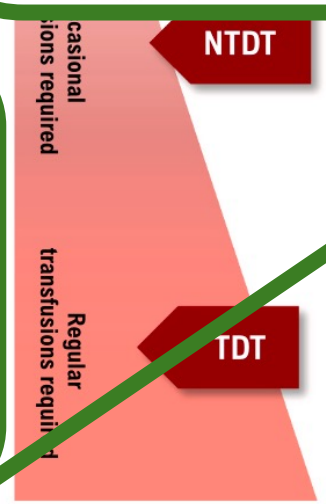
GRAVITA’

Piel FB, Weatherall DJ. The α-thalassemias. N Engl J Med. 2014

Basi molecolari

		Genotype	Phenotype	Clinical Presentation
Carrier States		−α/αα; α−/αα; αᵀα/αα; ααᵀ/αα (heterozygous α⁺-thalassemia)	Silent carrier / α-thalassemia minima	▪ Normal or mild decrease in MCH/MCV
		−−/αα; αᵀαᵀ/αα; −αᵀ/αα; αᵀ−/αα (α⁰-thalassemia)	α-thalassemia trait or α-thalassemia minor	▪ Normal or borderline anemia ▪ RBC microcytic and hypochr
		−α/−α or α−/α− αᵀα/αᵀα or −αᵀ/ααᵀ −α/αᵀα or α−/ααᵀ (homozygous α⁺-thalassemia)		
Clinically Relevant Forms		−−/−α or −−/α− (deletional)	HbH disease (α-thalassemia intermedia)	▪ Clinical severity is variable ▪ Mild to moderate anemia ▪ RBC markedly microcytic and hypochromic
		−−/αᵀα or −−/αᵀα αᵀαᵀ/−α or αᵀαᵀ/α− ααᵀ/−αᵀ or αᵀα/−αᵀ (nondeletional)		▪ More severe anemia ▪ RBC markedly microcytic and hypochromic
		Any combination of – or αᵀ resulting in deletion or inactivation of all 4 genes	Hb Barts hydrops fetalis syndrome (α-thalassemia major)	▪ Often die in utero or shortly after birth





Lal A, Disease burden, management strategies, and unmet needs in α-thalassemia due to hemoglobin H disease. Am J Hematol. 2024
Musallam KM. Systematic review and evidence gap assessment of the clinical, quality of life, and economic burden of alpha-thalassemia. EJHaem. 2024

Portatore silente

Sg-Esame Emocromocitometrico

Globuli Bianchi	**7.18**		10e9/L	[4.8 - 10.8]
Globuli Rossi	**5.87**	*	10e12/L	[4.50 - 5.30]
Emoglobina	**15.4**		g/dL	[13.5 - 17.5]
Ematocrito	**46.3**		%	[41.0 - 53.0]
Volume Globulare medio	**78.9**	*	fl	[80.0 - 94.0]
Emoglobina corpuscolare media	**26.2**		pg	[25.0 - 35.0]
Conc. Hb corpuscolare media	**33.3**		g/dL	[31.0 - 37.0]
Indice di anisocitosi (RDW)	**14.6**	*	%	[11.5 - 14.5]
Piastrine	**347**		10e9/L	[130 - 400]
MPV	**9.7**		fl	[9.5 - 13.1]

Sg-Formula Leucocitaria

Neutrofili	**3.43**		10e9/L	[1.50 - 6.50]
Linfociti	**2.98**		10e9/L	[1.20 - 3.40]
Monociti	**0.57**		10e9/L	[0.30 - 0.60]
Eosinofili	**0.16**		10e9/L	[0.10 - 0.80]
Basofili	**0.04**		10e9/L	[0.01 - 0.20]
Neutrofili %	**47.80**			
Linfociti %	**41.50**			
Monociti %	**7.90**			
Eosinofili %	**2.20**			
Basofili %	**0.60**			

Sg-Reticolociti

Reticolociti	**0.053**		10e12/L	[0.02 - 0.10]
Reticolociti %	**0.910**			[0.80 - 3.00]

$\alpha\,\alpha\,/\,\alpha\,-$
$\alpha^{T}\alpha/\,\alpha\,\alpha$

Normale valore Hb

Lievissima microcitosi

Asintomatico

Trait alfa talassemico

Sg-Esame Emocromocitometrico

Globuli Bianchi	**7.54**		10e9/L	[4.8 - 10.8]
Globuli Rossi	**5.76**	*	10e12/L	[4.50 - 5.30]
Emoglobina	**12.4**	*	g/dL	[13.5 - 17.5]
Ematocrito	**39.0**	*	%	[41.0 - 53.0]
Volume Globulare medio	**67.7**	*	fl	[80.0 - 94.0]
Emoglobina corpuscolare media	**21.5**	*	pg	[25.0 - 35.0]
Conc. Hb corpuscolare media	**31.8**		g/dL	[31.0 - 37.0]
Indice di anisocitosi (RDW)	**15.6**	*	%	[11.5 - 14.5]
Piastrine	**200**		10e9/L	[130 - 400]
MPV	**9.9**		fl	[9.5 - 13.1]

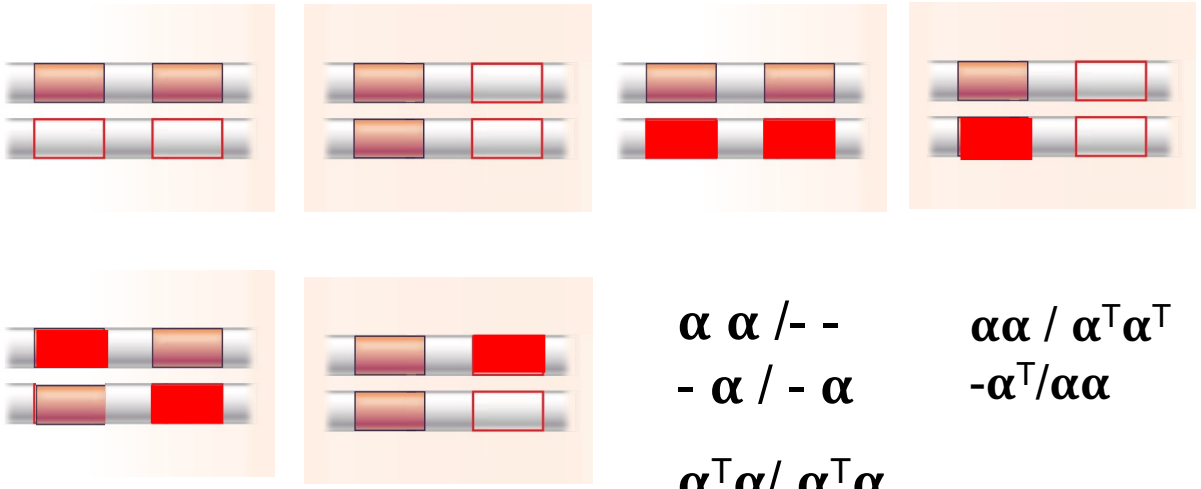
Sg-Formula Leucocitaria

Neutrofili	**2.96**		10e9/L	[1.50 - 6.50]
Linfociti	**3.62**	*	10e9/L	[1.20 - 3.40]
Monociti	**0.81**	*	10e9/L	[0.30 - 0.60]
Eosinofili	**0.09**		10e9/L	[0.10 - 0.80]
Basofili	**0.06**		10e9/L	[0.01 - 0.20]
Neutrofili %	**39.30**			
Linfociti %	**48.00**			
Monociti %	**10.70**			
Eosinofili %	**1.20**			
Basofili %	**0.80**			
NRBC (eritroblasti)	**0.00**		10e9/L	
NRBC% (eritroblasti)	**0.00**			

La morfologia cellulare è stata valutata al microscopio ottico

Sg-Reticolociti

Reticolociti	**0.061**		10e12/L	[0.02 - 0.10]
Reticolociti %	**1.060**			[0.80 - 3.00]



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-α^T/$\alpha\alpha$

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Hb normale o lieve anemia

microcitosi e ipocromia

Asintomatico

Malattia HbH – Delezionale

Sg-Esame Emocromocitometrico

Globuli Bianchi	**5,41**		10e9/L	[4,8 - 10,8]
Globuli Rossi	**5,07**		10e12/L	[4,50 - 5,30]
Emoglobina	**9,5**	*	g/dL	[13,5 - 17,5]
Ematocrito	**32,5**	*	%	[41,0 - 53,0]
Volume Globulare medio	**64,1**	*	fl	[80,0 - 94,0]
Emoglobina corpuscolare media	**18,7**	*	pg	[25,0 - 35,0]
Conc. Hb corpuscolare media	**29,2**	*	g/dL	[31,0 - 37,0]
Indice di anisocitosi (RDW)	**24,0**	*	%	[11,5 - 14,5]
Piastrine	**134**		10e9/L	[130 - 400]
Neutrofili	**3,44**		10e9/L	[1,50 - 6,50]
Linfociti	**1,44**		10e9/L	[1,20 - 3,40]
Monociti	**0,46**		10e9/L	[0,30 - 0,60]
Eosinofili	**0,06**		10e9/L	[0,10 - 0,80]
Basofili	**0,01**		10e9/L	[0,01 - 0,20]
Neutrofili %	**63,60**			
Linfociti %	**26,60**			
Monociti %	**8,50**			
Eosinofili %	**1,10**			
Basofili %	**0,20**			
NRBC (eritroblasti)	**0,00**		10e9/L	
NRBC% (eritroblasti)	**0,00**			

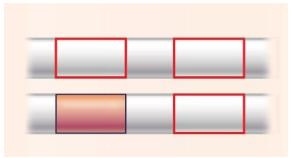
Sg-Reticolociti

Reticolociti	**0,133**	*	10e12/L	[0,02 - 0,10]
Reticolociti %	**2,620**			[0,80 - 3,00]

ASSETTO EMOGLOBINICO HPLC

Sg-Emoglobina A2	**0,8**	*	%	[2,0 - 3,2]
Sg-Emoglobina F	**3,2**	*	%	[<1]
Sg-Emoglobina Variante	**5,7**		%	Assente

CONCLUSIONI: Presenza di variante emoglobinica (HbH); a conferma/completamento diagnostico si consiglia la caratterizzazione con esame molecolare.



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Anemia moderata - grave

Microcitosi e ipocromia

Manifestazioni cliniche variabili

Reticolocitosi

Malattia HbH – Non Delezionale

ESAME EMOCROMOCITOMETRICO Sismex XT

Globuli Bianchi	**8.03**			10e9/L	[4.8 - 10.8]
Globuli Rossi	**5.31**		*	10e12/L	[4.10 - 5.10]
Emoglobina	**9.1**	7.1	*	g/dL	[12.0 - 16.0]
Ematocrito	**29.0**		*	%	[36.0 - 46.0]
Volume Globulare medio	**54.6**		*	fl	[78.0 - 99.0]
Emoglobina corpuscolare media	**17.1**		*	pg	[25.0 - 35.0]
Conc. Hb corpuscolare media	**31.4**			g/dL	[31.0 - 37.0]
Indice di anisocitosi (RDW)	**24.3**		*	%	[11.5 - 14.5]
Piastrine	**217**			10e9/L	[130 - 400]

FORMULA LEUCOCITARIA

Neutrofili	**5.16**	10e9/L	[1.50 - 6.50]
Linfociti	**2.27**	10e9/L	[1.20 - 3.40]
Monociti	**0.51**	10e9/L	[0.30 - 0.60]
Eosinofili	**0.06** *	10e9/L	[0.10 - 0.80]
Basofili	**0.03**	10e9/L	[0.01 - 0.20]
Neutrofili %	**64.20**		
Linfociti %	**28.30**		
Monociti %	**6.40**		
Eosinofili %	**0.70**		
Basofili %	**0.40**		

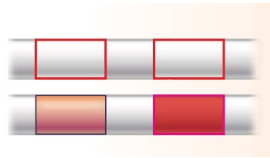
RETICOLOCITI

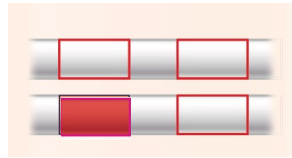
Reticolociti	**0.101**	*	10e12/L	[0.02 - 0.10]
Reticolociti %	**1.910**			[0.80 - 3.00]

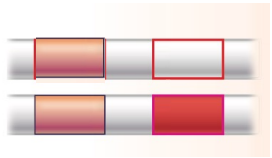
Separazione cromatografica Hb (HPLC) :	**HbA2:**	1.8	%	[2.0 - 3.2]
	HbF:	4.6	%	< 1
Hb ANOMALE: Hb H		5.7	%	

OSSERVAZIONI: Opportune indagini molecolari a conferma/completamento diagnostico.

CONCLUSIONI: Presenza di una condzione di alfa-talassemia; non si può escludere una forma del tipo "Malattia da Hb H".







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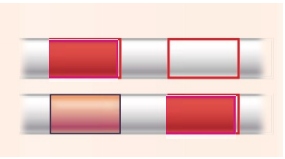


Anemia moderata - grave

Microcitosi e ipocromia

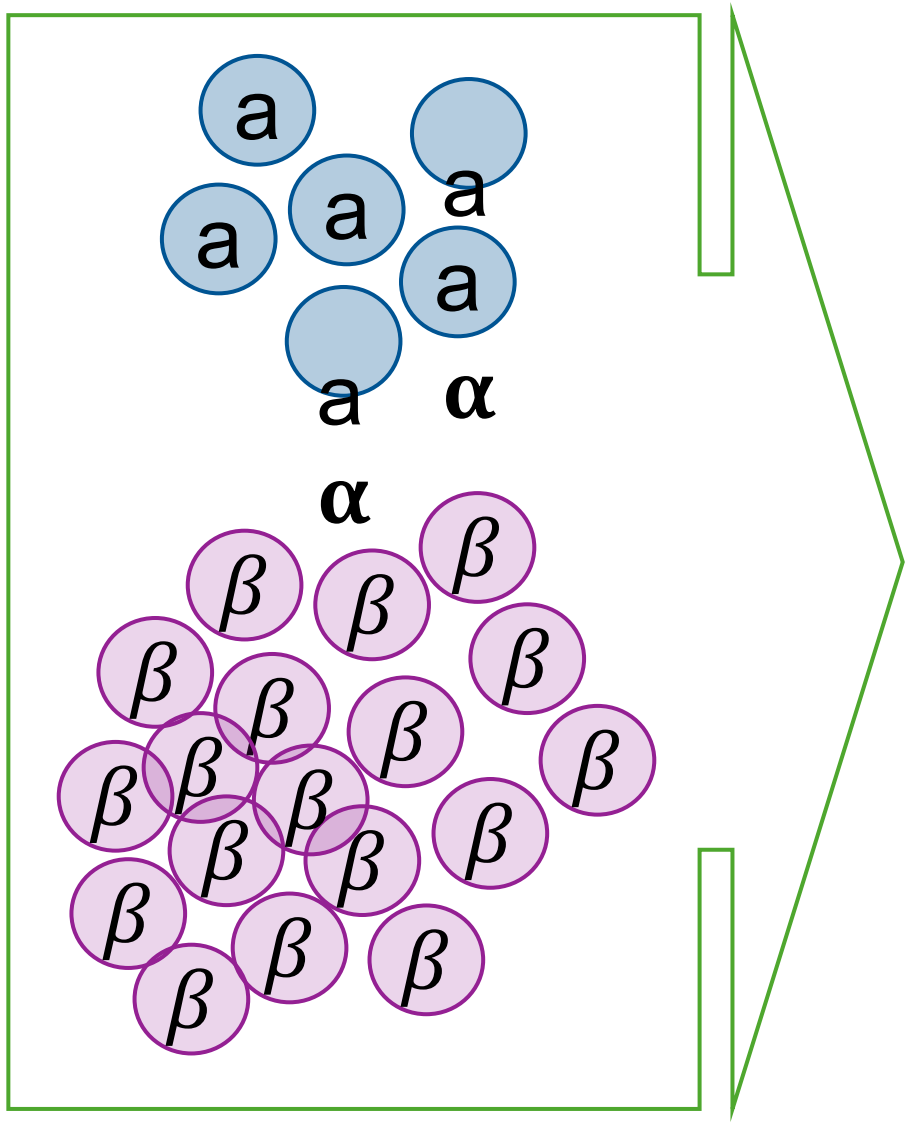
Reticolocitosi

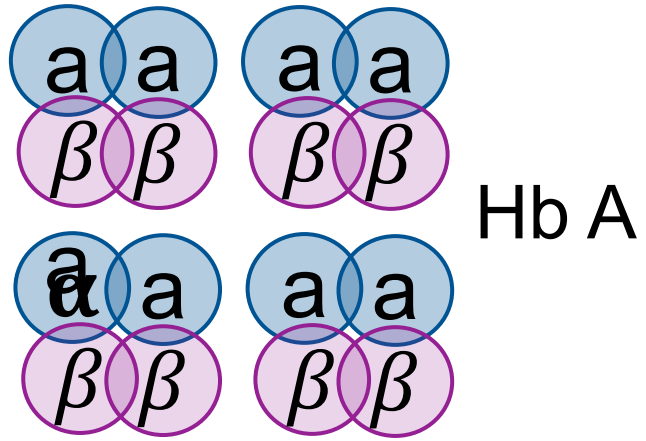
Produzione di catena alfa instabile

→ precipitazione nei globuli rossi

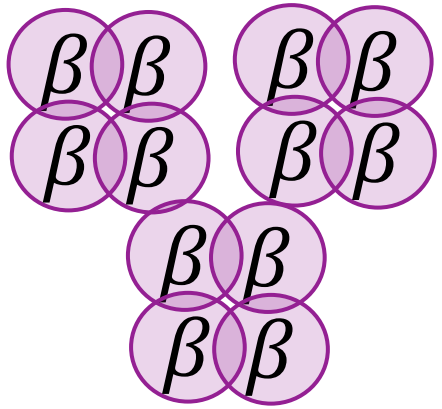
→ emolisi e eritropoiesi inefficace

Malattia HbH





Hb A



Hb H

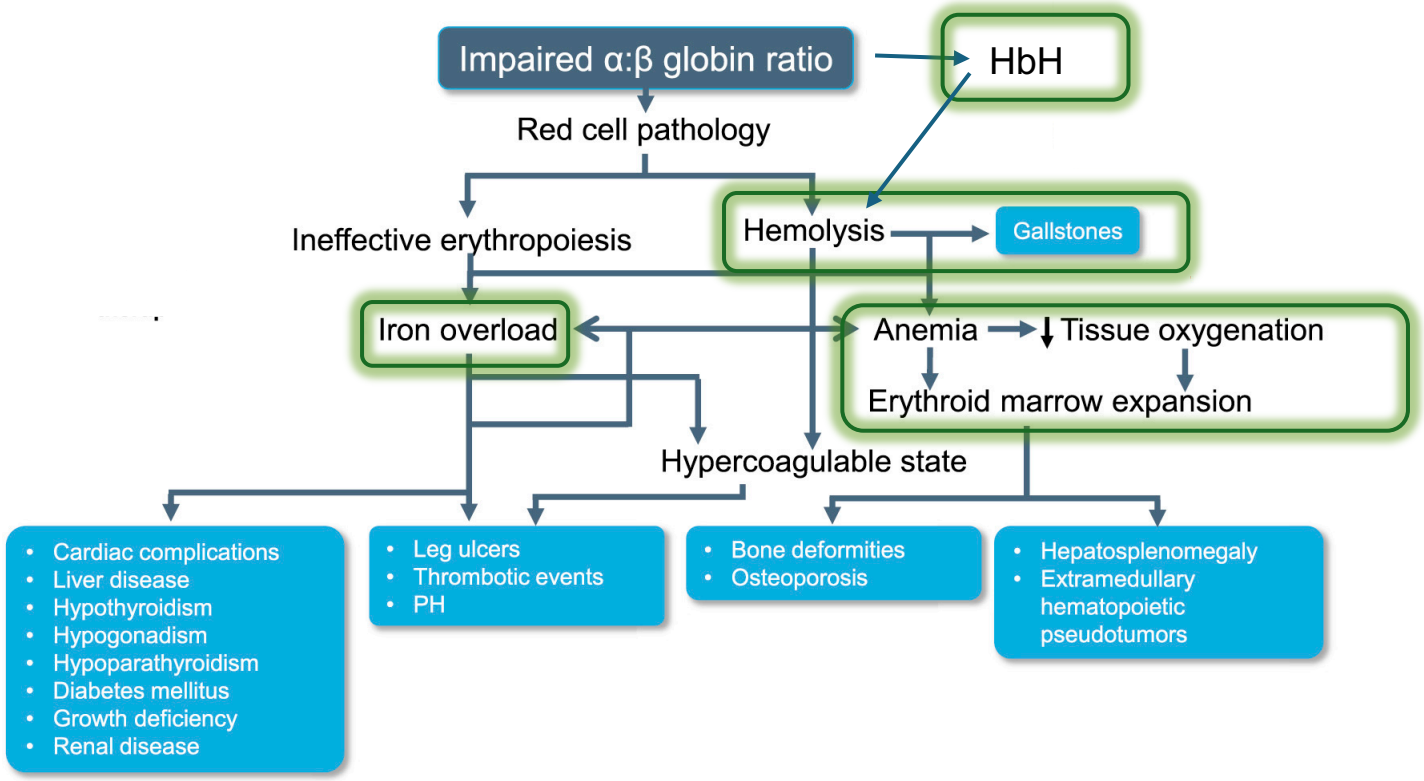
aumentata affinità per Ossigeno

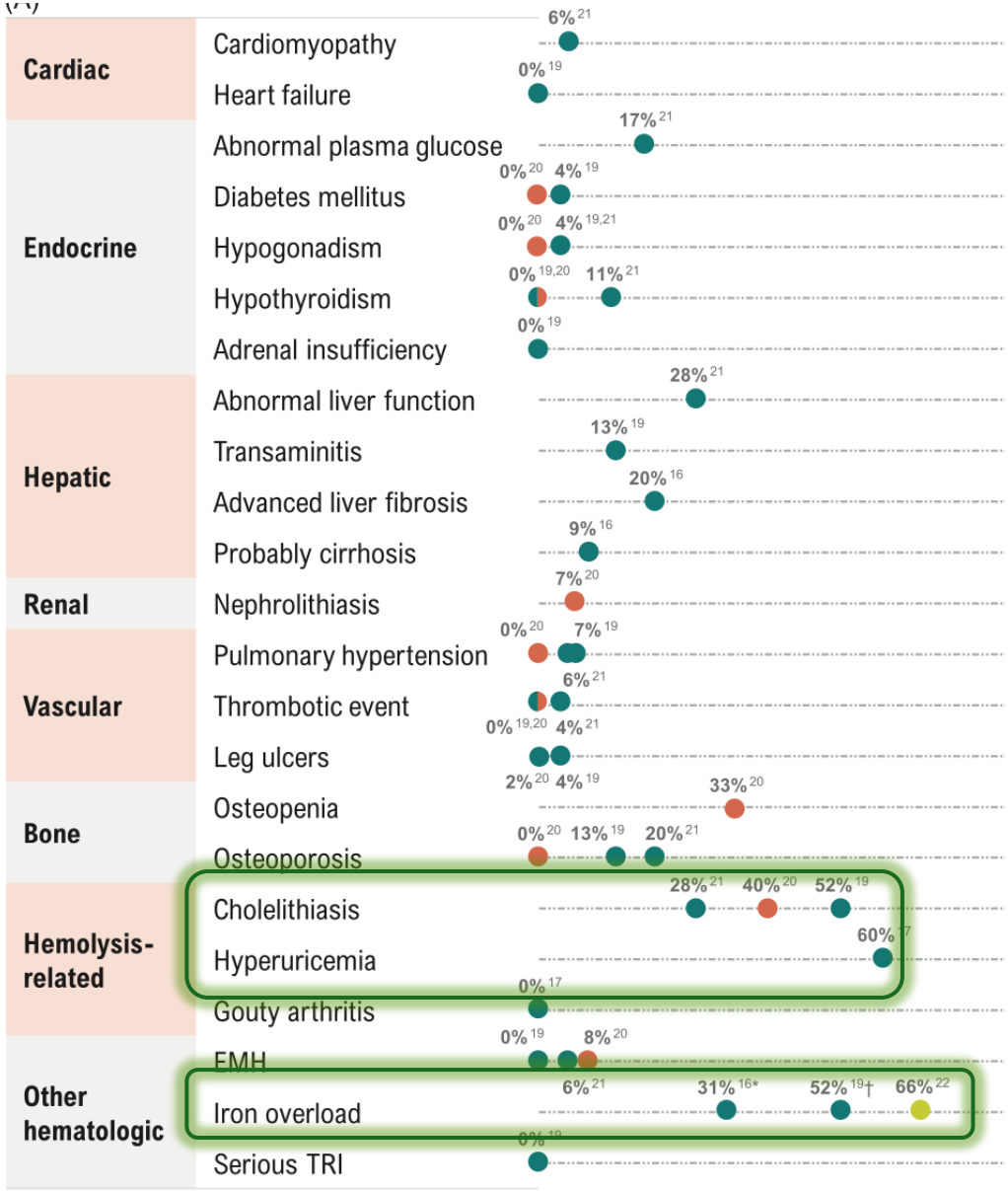
Hb effettiva (g/dL)
=
(1 - % Hb Bart + % HbH)
x Hb tot (g/dL)

Genetica alfa
Constant Spring
–a3.7, –a4.2, –SEA,
–FIL, –THAI, –MED,

Fattori secondari

Malattia HbH





Marcon A, Complications and Their Management. Hematol Oncol Clin North Am. 2018
Musallam KM. Systematic review and evidence gap assessment of the clinical, quality of life, and economic burden of alpha-thalassemia. EJHaem. 2024

Malattia HbH

	Delezionale	Non Delezionale
Hemoglobin, g/dL (range)	8.5 (6.9–10.7)	7.2 (3.8–8.7)
MCV, fL (range)	54.0 (46.0–76.0)	65.2 (48.7–80.7)
MCH, pg (range)	16.6 (14.3–24.7)	18.6 (14.8–24.8)
Reticulocytosis	+	++
Bilirubin	+	++
Age at first transfusion[a] (years)	11 ± 5.5	1.5 ± 2.1
History of blood transfusion (%)	3–29	24–80
Type of transfusion[b] (%)		
• Never transfused	92.4	46.2
• Intermittently transfused	7.6	44.9
• Regularly transfused	0	9.0
Splenomegaly	+	+++
Gallstones	+	++
Growth retardation	Rare	Common
Decreased bone density	Rare	Common

Musallam KM. Systematic review and evidence gap assessment of the clinical, quality of life, and economic burden of alpha-thalassemia. EJHaem. 2024

Malattia HbH _ Gravidanza

Non influenza fertilità

Malattia HbH aumenta rischio di pre eclampsia e scompenso cardiaco

Outcome	Control group (n = 437,382)	Women with α-thalassemia trait			P_1* (P_2†)
		Normal fetal group (n = 446)	Fetal group with α-thalassemia trait (n = 708)	Fetal group with HbH disease (n = 211)	
Cesarean delivery	127,851 (29.23)	137 (30.72)	208 (29.38)	63 (29.86)	0.889 (.914)
Postpartum hemorrhage	14,232 (3.25)	24 (5.38)	30 (4.24)	9 (4.27)	0.643 (.026)
Birth before 34 weeks of gestation	5221 (1.19)	8 (1.79)	6 (0.85)	4 (1.90)	0.283 (.398)
Birth before 37 weeks of gestation	25,205 (5.76)	25 (5.61)	48 (6.78)	17 (8.06)	0.477 (.333)
Fetal growth restriction	9198 (2.10)	7 (1.57)	15 (2.12)	6 (2.84)	0.551 (.758)
Low birth weight	22,695 (5.19)	23 (5.16)	40 (5.65)	19 (9.00)	0.129 (.088)
Macrosomia	12,986 (2.97)	13 (2.91)	27 (3.81)	6 (2.84)	0.640 (.622)
Apgar score < 7 at 1 min	4034 (0.92)	7 (1.57)	9 (1.27)	10 (4.74)	0.004 (< .001)
Apgar score < 7 at 5 min	1918 (0.44)	3 (0.67)	1 (0.14)	6 (2.84)	0.001 (.001)
Perinatal death	1874 (0.43)	1 (0.22)	1 (0.14)	2 (0.95)	0.147 (.359)

Gravidanza può portare a anemizzazione

Target Hb pre trasfusionale 9 g/dL

Supplementazione marziale con ferro in assenza di carenza non migliora i valori emoglobinici

Nelle pazienti splenectomizzate è consigliato acido acetilsalicilico in prevenzione per eventi trombotici

Non indicazioni assolute in merito alla tipologia di parto

Li J, Pregnancy outcomes in women affected by fetal alpha-thalassemia: a case control study. Sci Rep. 2021
Vaeusorn O, A study of thalassemia associated with pregnancy. Birth Defects Orig Artic Ser. 1988
Hui, D. H., Hemoglobin H disease: not necessarily a benign disorder. *Blood, The Journal of the American Society of Hematology*,

Malattia HbH _ Gravidanza

Sg-Esame Emocromocitometrico

Globuli Bianchi	**5.00**		10e9/L	[4.8 - 10.8]
Globuli Rossi	**3.74**	*	10e12/L	[4.10 - 5.10]
Emoglobina	**7.1**	*	g/dL	[12.0 - 16.0]
Ematocrito	**22.7**	*	%	[36.0 - 46.0]
Volume Globulare medio	**60.7**	*	fl	[78.0 - 99.0]
Emoglobina corpuscolare media	**19.0**	*	pg	[25.0 - 35.0]
Conc. Hb corpuscolare media	**31.3**		g/dL	[31.0 - 37.0]
Indice di anisocitosi (RDW)	**27.9**	*	%	[11.5 - 14.5]

Sg-Formula Leucocitaria

Neutrofili	**3.57**		10e9/L	[1.50 - 6.50]
Linfociti	**0.95**	*	10e9/L	[1.20 - 3.40]
Monociti	**0.42**		10e9/L	[0.30 - 0.60]
Eosinofili	**0.04**		10e9/L	[0.10 - 0.80]
Basofili	**0.02**		10e9/L	[0.01 - 0.20]
Neutrofili %	**71.40**			
Linfociti %	**19.00**			
Monociti %	**8.40**			
Eosinofili %	**0.80**			
Basofili %	**0.40**			

Sg-Reticolociti

Reticolociti	**0.137**	*	10e12/L	[0.02 - 0.10]
Reticolociti %	**3.670**	*		[0.80 - 3.00]

CHIMICA CLINICA

FERRO	*SIERO*	**160**	*	µg/dL	[37 - 145]

PROTEINE SPECIFICHE

FERRITINA	*SIERO*	**64**		µg/L	[15 - 150]
TRANSFERRINA	*SIERO*	**234**		mg/dL	[200 - 360]

ASSETTO EMOGLOBINICO

Sg-Emoglobina A2	**0,8**	*	%	[2,0 - 3,2]
Sg-Emoglobina F	**3,2**	*	%	[<1]
Sg-Emoglobina Variante	**5,7**		%	Assente

$\alpha^{-SEA}\alpha$ / - α

Malattia HbH _ Infezioni

Causa di crisi emolitiche

Causa di anemizzazione

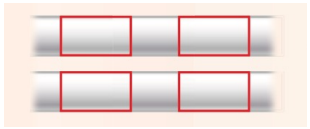
Supporto trasfusionale

Schedula vaccinale

Crisi aplastica da Parvovirus B19

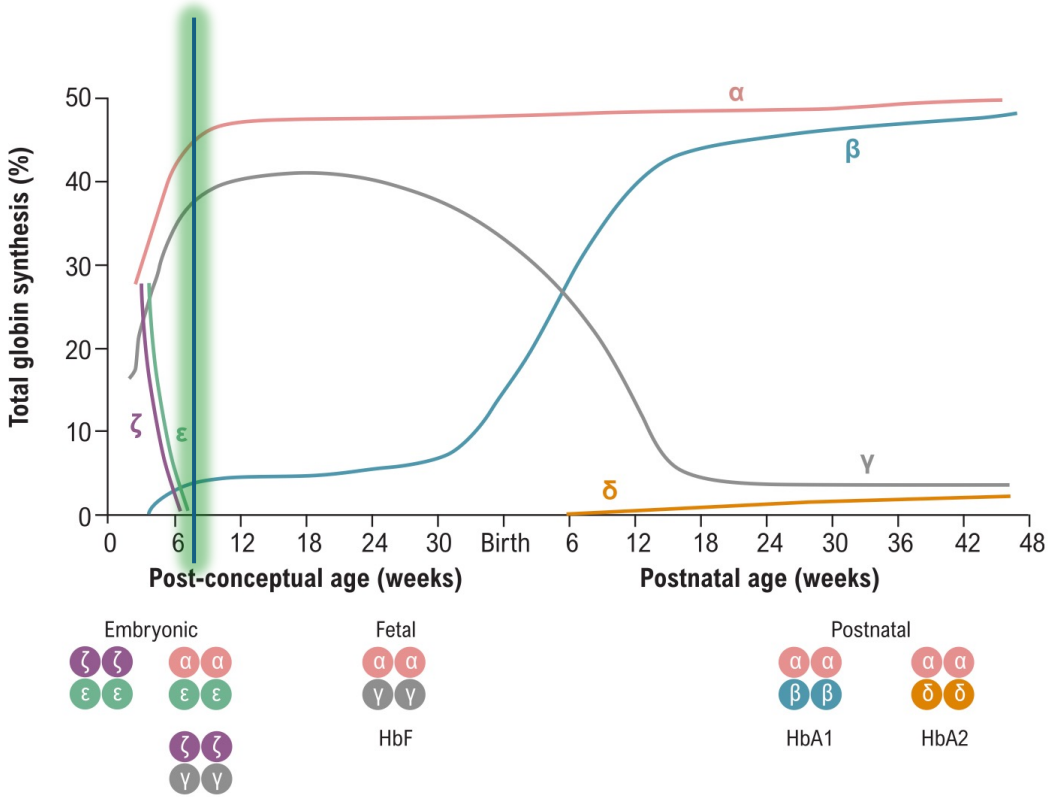
1. Restore patient's hemoglobin to 8-9 g/dL by red cell transfusion
   - Provide filtered red blood cells or leucocyte depleted blood 5-12 mL/kg/dose depending on the patients's clinical severity and levels of anemia
   - A close monitoring on total body fluid and cardiovascular status is highly recommended.
   - Serial Hb and Hct evaluation should be done at least daily since hemolysis could be continued as the cause has not been removed or properly treated.
2. Give adequate hydration
   - Intravenous fluid therapy should be provided to maintain circulation and withheld during transfusion support.
   - The amount and rate should be carefully calculated to avoid possible heart failure from volume overload.
3. Check blood electrolytes and provide appropriate correction
   - Metabolic acidosis is usually observed but mostly resolved by transfusion support and fluid therapy. Only rare cases require alkali therapy.
4. Try to control body temperature by various means
   - Frequent tepid sponge
   - Paracetamol 10-12 mg/kg every 4-6 hrs.
   - The usage of NSAIDs in hemolytic crisis of Hb H has limited data.
5. Identify the cause of infection/inflammation and provide appropriate treatment
   - Blood and urine culture should be done.
   - Empirical antibiotic with the coverage of gram-negative bacteria and/or encapsulated bacteria (depending on splenic condition) such as streptococcus, menigococcus and salmonella sps. should be promptly provided.

Idrope Fetale



Genotipo alfa
- - / - -

––SEA/ ––SEA
––SEA/––FIL



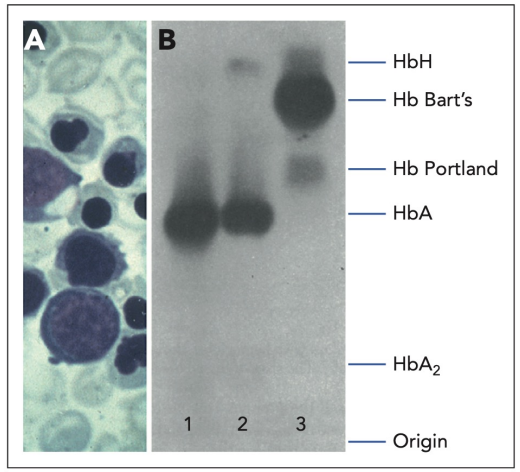
Impossibilità sintesi catene alfa

accumulo delle catene gamma

Aggregati Hb Bart

γ_4
Hb Barts

Anemia	High oxygen affinity	Unstable tetramers or α variants
-Hemolysis -Spleno-megaly	-Hypoxia -Erythropoietic drive	-Hemolysis -Ineffective erythropoiesis



Ali Amid, Hemoglobin Bart's hydrops fetalis: charting the past and envisioning the future. *Blood* 2024

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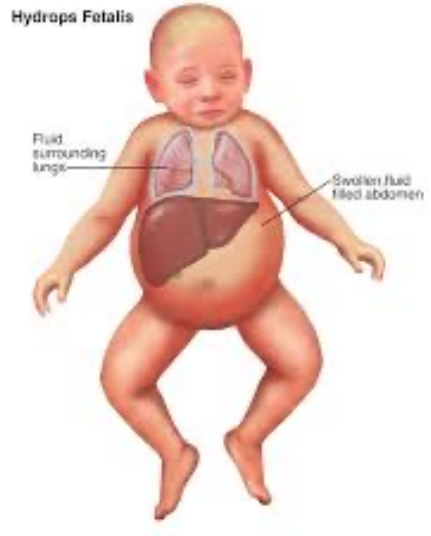

Fine del primo trimestre

Grave anem e ipossi

Iperbil inem
Organo a
Ipoalbum a
Scompen
cardiac nazioni cardia
Ascit versam o pleu o
M rmazioni del o genitourinario

Terapie

Trasfusioni epoca intrauterina
(18° settimana)
→ risoluzione del quadro clinico
→ trasfusione-dipendenza

Trapianto di Midollo intrafetale

Terapia genica

Ali Amid, Hemoglobin Bart's hydrops fetalis: charting the past and envisioning the future. *Blood* 2024
King AJ, HPotential new approaches to the management of the Hb Bart's hydrops fetalis syndrome: the most severe form of α-thalassemia. Hematology Am Soc Hematol Educ Program. 2018

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Forme inusuali di Alfa Talassemia

ATR 16

Anomalia telomero ch 16

Alfa talassemia e ritardo mentale

ATR X

Mutazione X linked che downregola gene alfa

Genere maschile

Alfa talassemia
Ritardo Mentale
Disfmorfismo volto
malformazioni multiorgano

ATMDS

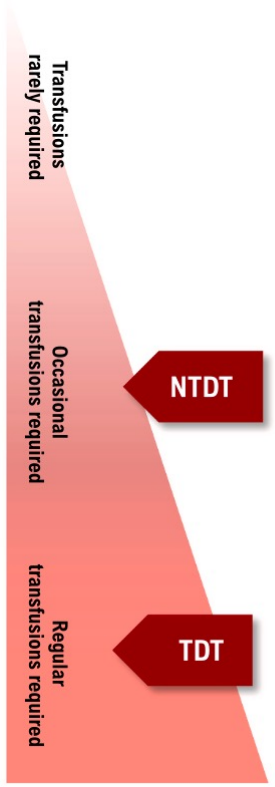
Forma acquisita di alfa talassemia

Disordini clonali ematopoiesi

Gibbons RJ. α-Thalassemia, mental retardation, and myelodysplastic syndrome. Cold Spring Harb Perspect Med. 2012

Take home messages

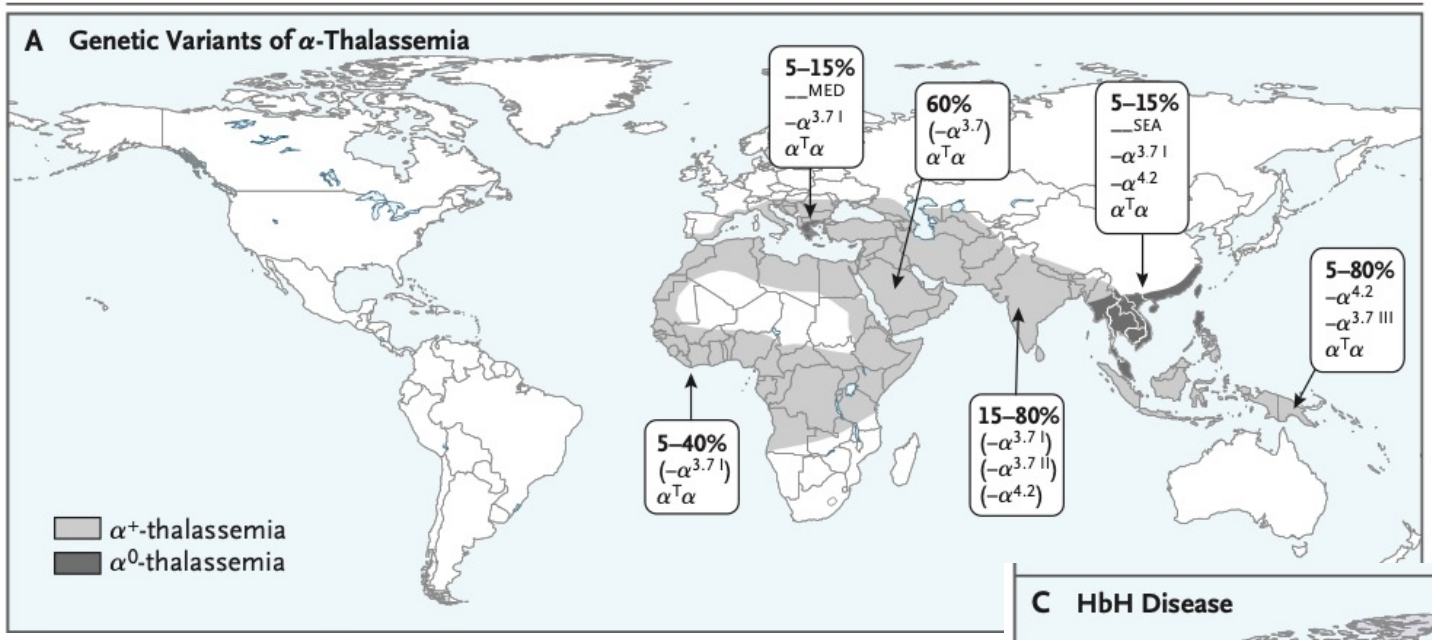
Genotype		Phenotype	Clinical Presentation
−α/αα; α−/αα; $\alpha^T\alpha$/αα; $\alpha\alpha^T$/αα (heterozygous α^+-thalassemia)	Carrier States	Silent carrier or α-thalassemia minima	▪ Normal or mild decrease in MCH/MCV
−−/αα; $\alpha^T\alpha^T$/αα; −α^T/αα; α^T−/αα (α^0-thalassemia)		α-thalassemia trait or α-thalassemia minor	▪ Normal or borderline anemia ▪ RBC microcytic and hypochromic
−α/−α or α−/α− $\alpha^T\alpha/\alpha^T\alpha$ or $\alpha\alpha^T/\alpha\alpha^T$ −α/$\alpha^T\alpha$ or α−/$\alpha\alpha^T$ (homozygous α^+-thalassemia)			
−−/−α or −−/α− (deletional)	Clinically Relevant Forms	HbH disease (α-thalassemia intermedia)	▪ Clinical severity is variable ▪ Mild to moderate anemia ▪ RBC markedly microcytic and hypochromic
−−/$\alpha^T\alpha$ or −−/$\alpha^T\alpha$ $\alpha^T\alpha^T$/−α or $\alpha^T\alpha$/α− $\alpha\alpha^T$/−α^T or $\alpha^T\alpha$/−α^T (nondeletional)			▪ More severe anemia ▪ RBC markedly microcytic and hypochromic
Any combination of – or α^T resulting in deletion or inactivation of all 4 genes		Hb Barts hydrops fetalis syndrome (α-thalassemia major)	▪ Often die in utero or shortly after birth

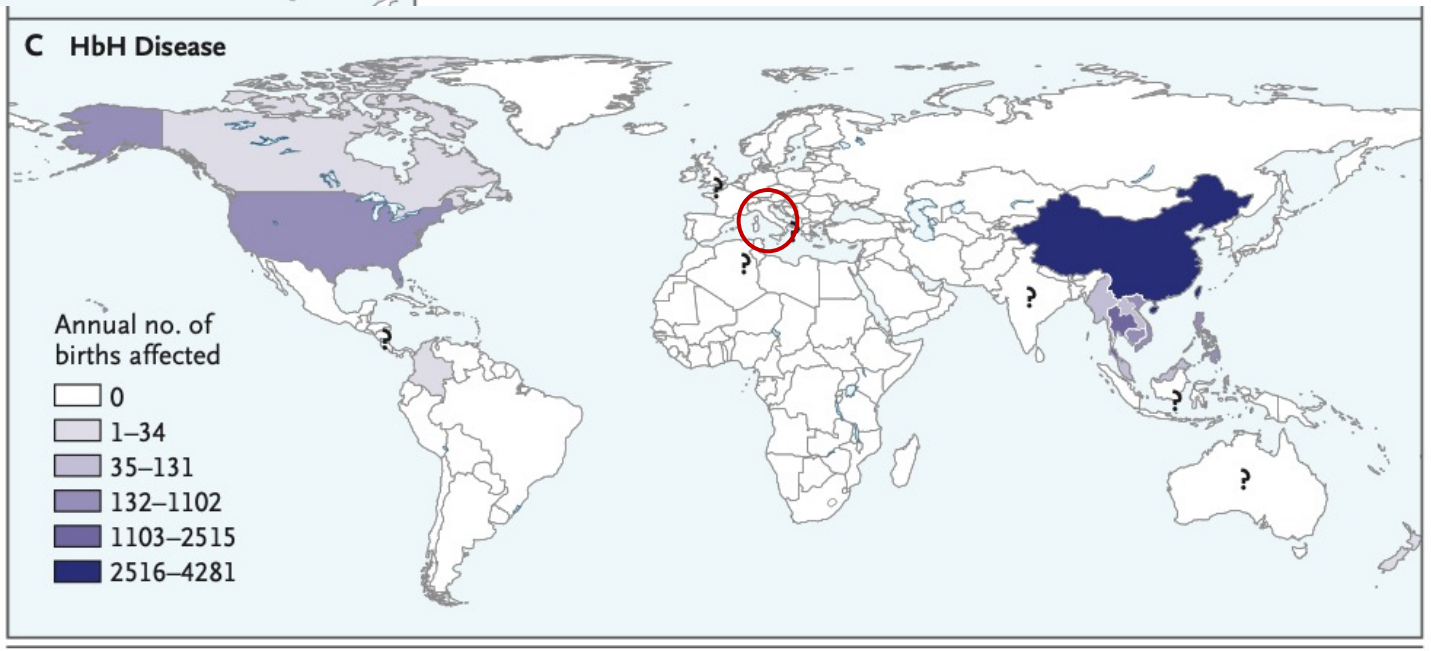


- mai sottovalutare microcitosi
- attenzione alle improvvise anemizzazioni in corso di eventi acuti o gravidanza
- attenzione provenienza geografica

Piel FB, Weatherall DJ. The α-thalassemias. N Engl J Med. 2014

Take home messages





Piel FB, Weatherall DJ. The α-thalassemias. N Engl J Med. 2014

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