UNIVERSITÀ DEGLI STUDI DELLA CAMPANIA
LUIGI VANVITELLI

UNIVERSITÀ DEGLI STUDI DELLA CAMPANIA
LUIGI VANVITELLI
SCUOLA DI MEDICINA E CHIRURGIA
DIPARTIMENTO DELLA DONNA, DEL BAMBINO E DI CHIRURGIA GENERALE E SPECIALISTICA

SITE
SOCIETA' ITALIANA TALASSEMIE ED EMOGLOBINOPATIE

XIV CONGRESSO NAZIONALE SITE

Roma, 11-13 Settembre 2025
Pontificia Università Urbaniana

EMOGLOBINE INSTABILI: ASPETTI CLINICI

Silverio Perrotta

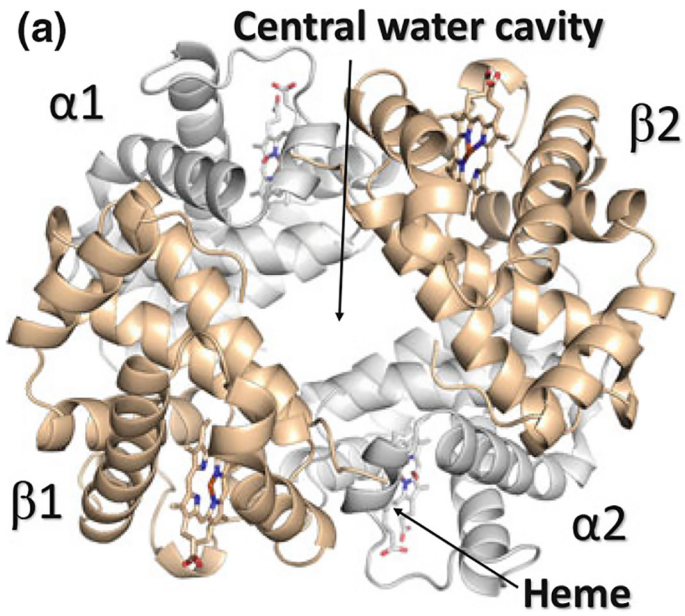
Università degli Studi della Campania "L. Vanvitelli"

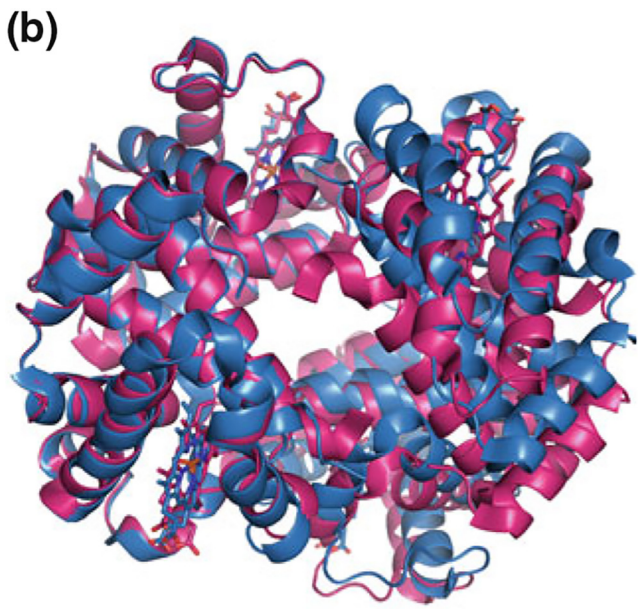
Ematologia ed Oncologia pediatrica

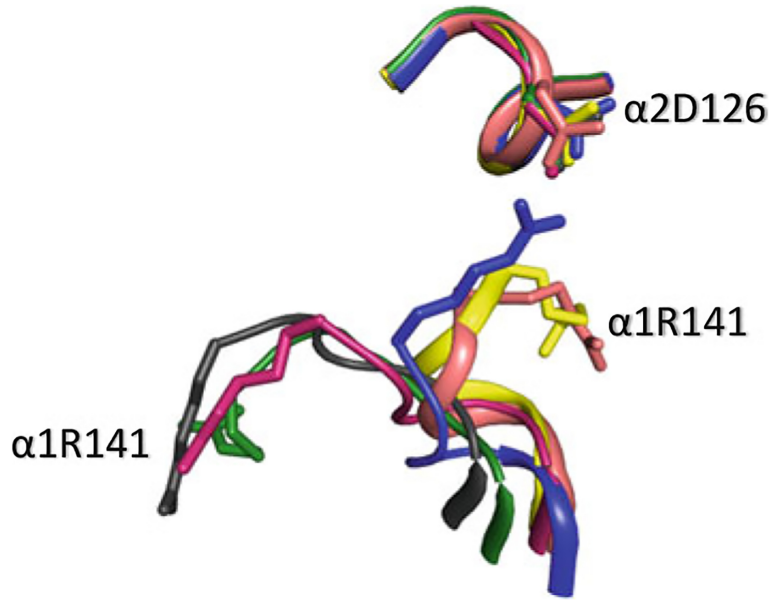
DAI Materno Infantile

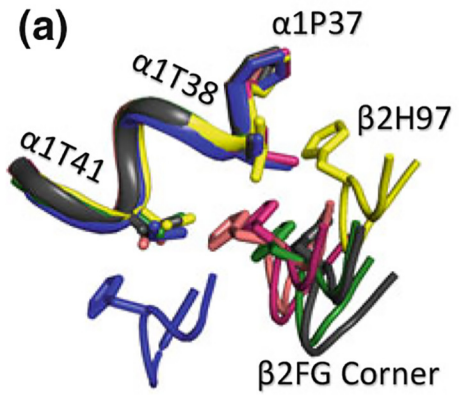
DICHIARAZIONE SILVERIO PERROTTA

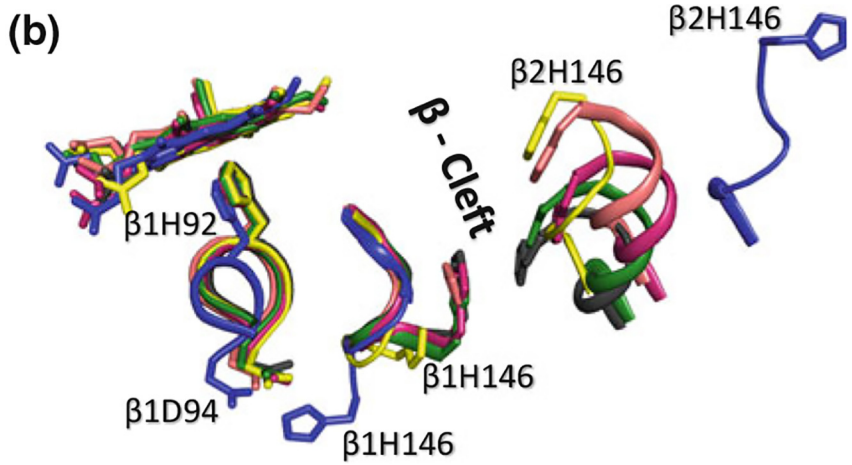
Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
NOVARTIS	YES					YES	
BMS	YES					YES	
Acceleron	YES					YES	
BlueBird bio						YES	
Vertex			YES			YES	
Novo Nordisk			YES				
AGIOS			YES				

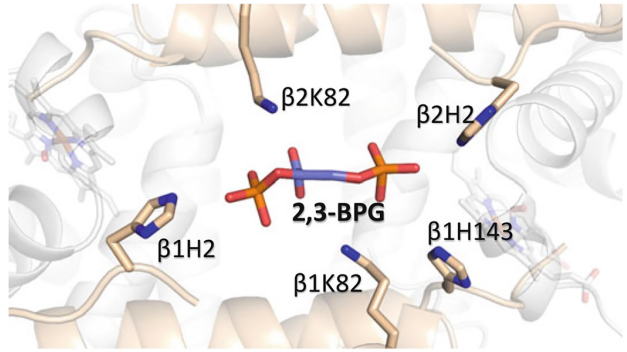

(a)
Central water cavity
α1
β2
β1
α2
Heme

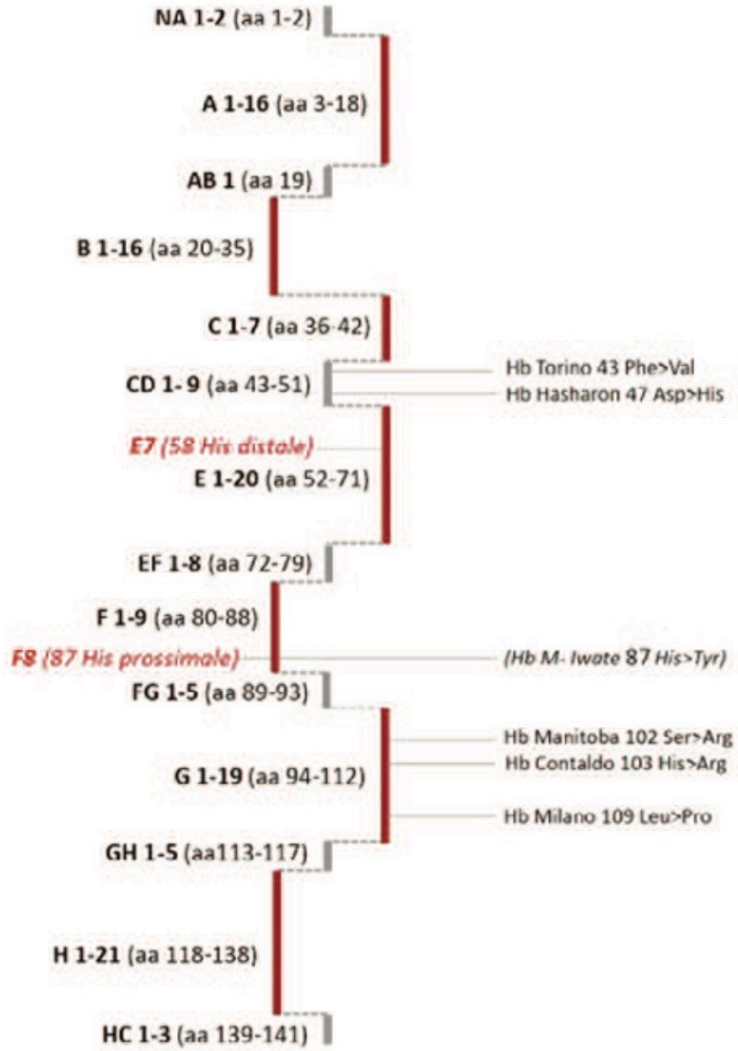

(b)


α2D126
α1R141
α1R141

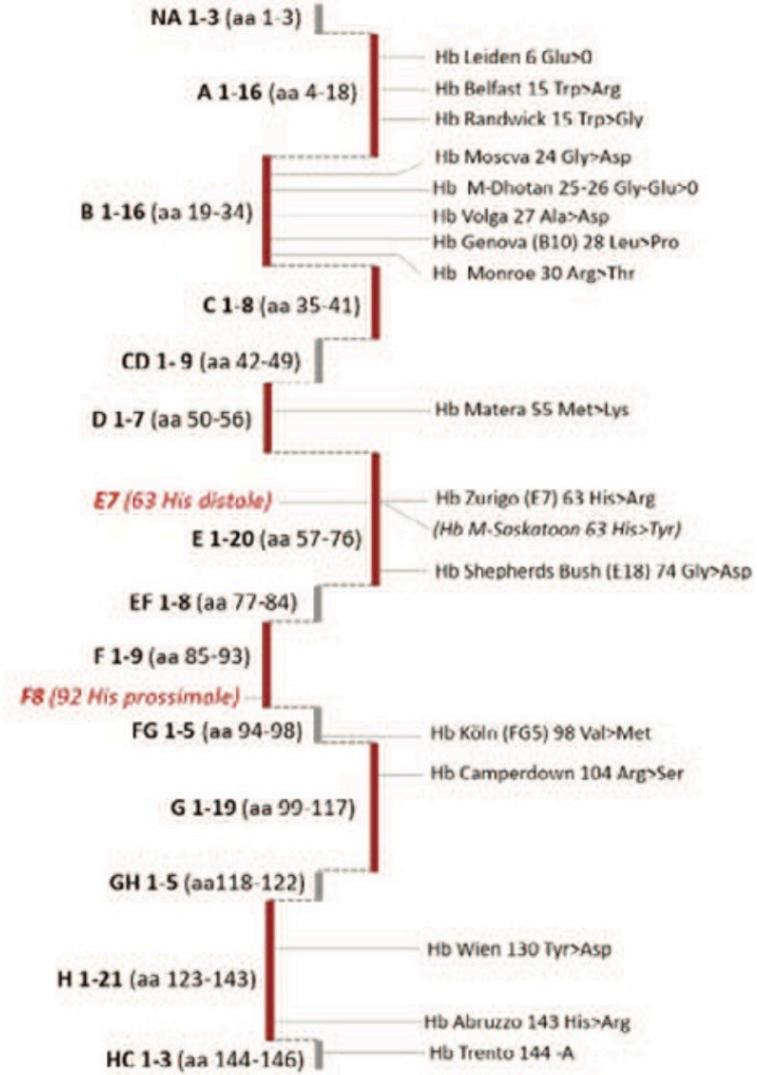

(a)
α1P37
α1T38
β2H97
α1T41
β2FG Corner


(b)
β2H146
β2H146
β - Cleft
β1H92
β1H146
β1D94
β1H146


β2K82
β2H2
2,3-BPG
β1H2
β1H143
β1K82

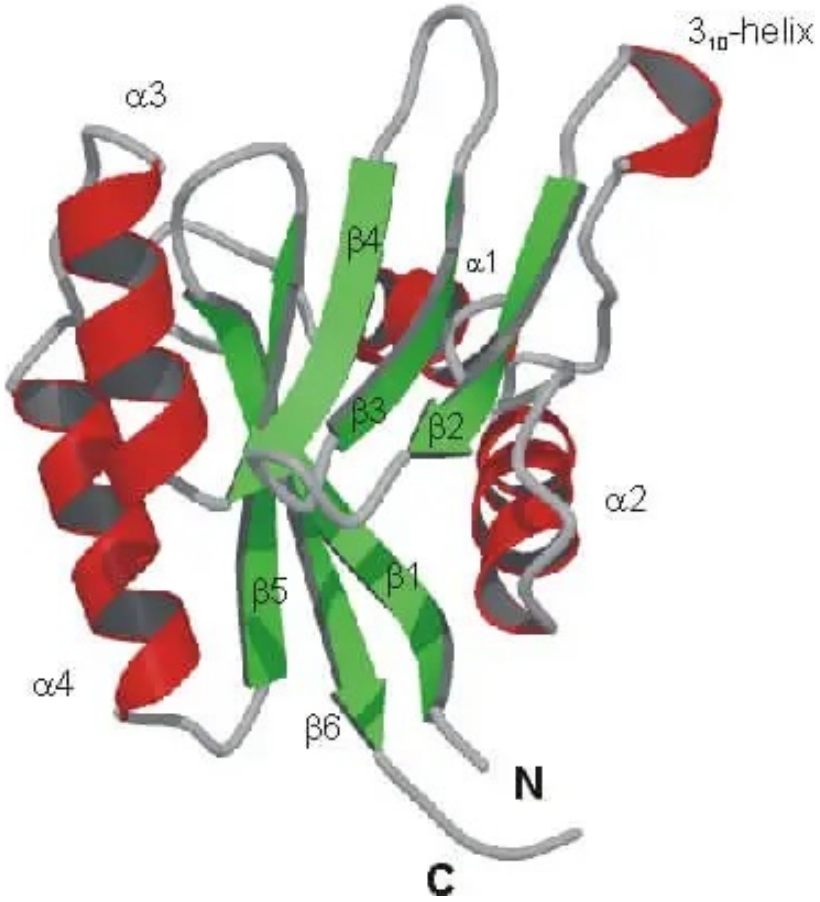


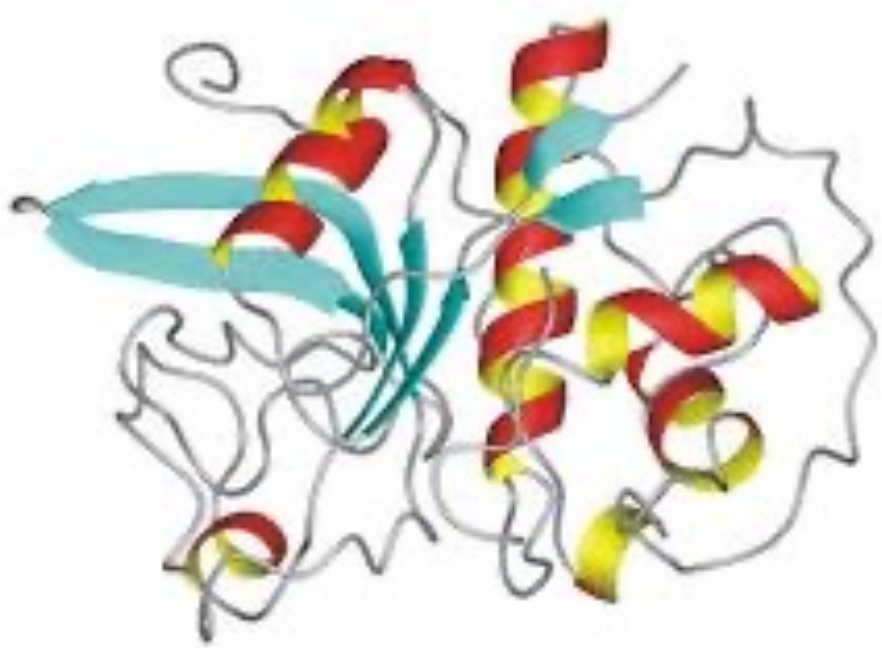
Catena α



Catena β

STRUTTURA α-ELICA DELL'HB





DIFETTI DI PUNTI DI LEGAME CON EME

Varianti delle catene α-globiniche che presentano sostituzioni amminoacidiche nei nove punti di contatto con l'eme fiancheggianti l'His distale [58 (E7)]

Varianti delle catene α globiniche che presentano sostituzioni amminoacidiche nei dieci punti di contatto con l'eme fiancheggianti l'His prossimale [87 (F8)]

Varianti delle catene β globiniche che presentano sostituzioni amminoacidiche nei dieci punti di contatto con l'eme fiancheggianti l'His distale [63 (E7)]

Varianti delle catene β globiniche che presentano sostituzioni amminoacidiche negli undici punti di contatto con l'eme fiancheggianti l'His prossimale [92 (F8)]

DIFETTI DI PUNTI DI LEGAME CON EME: AA DI DIVERSE DIMENSIONI

Varianti delle catene α-globiniche che presentano sostituzioni amminoacidiche nei nove punti di contatto con l'eme fiancheggianti l'His distale [58 (E7)]

Hb Vanvitelli: **α43(CE1) Phe>Leu; *HBA1*:c.130T>**
Hb Torino: **α43(CE1) Phe>Val; *HBA2*:c.130T>G**

Varianti delle catene α-globiniche che presentano sostituzioni amminoacidiche nei dieci punti di contatto con l'eme fiancheggianti l'His prossimale [87 (F8)]

Varianti delle catene β-globiniche che presentano sostituzioni amminoacidiche nei dieci punti di contatto con l'eme fiancheggianti l'His distale [63 (E7)]

Hb Sidney: β67(E11) Val>Ala; HBB:c.203T>C

Varianti delle catene β-globiniche che presentano sostituzioni amminoacidiche negli undici punti di contatto con l'eme fiancheggianti l'His prossimale [92 (F8)]

Hb Köln: β98(FG5) Val>Met; HBB:c.295G>A

DIFETTI DI PUNTI DI LEGAME CON EME: AA NELLA STESSA POSIZIONE

Varianti delle catene α-globiniche che presentano sostituzioni amminoacidiche nei nove punti di contatto con l'eme fiancheggianti l'His distale [58 (E7)]

Varianti delle catene α-globiniche che presentano sostituzioni amminoacidiche nei dieci punti di contatto con l'eme fiancheggianti l'His prossimale [87 (F8)]

Varianti delle catene β-globiniche che presentano sostituzioni amminoacidiche nei dieci punti di contatto con l'eme fiancheggianti l'His distale [63 (E7)]

Hb Zürich:	**β63(E7) His>Arg; HBB:c.191A>G**	**Hb instabile**
Hb M-Saskatoon:	**β63(E7) His>Tyr; HBB:c.190C>T**	**HbM**

Varianti delle catene β-globiniche che presentano sostituzioni amminoacidiche negli undici punti di contatto con l'eme fiancheggianti l'His prossimale [92 (F8)]

ALTRE CAUSE DI INSTABILITÀ

Sostituzione di aa con polarità diversa:	• **Hb Wien** [β130(H8) Tyr→Asp; *HBB*:c.391T>G]
Ruolo dell'aa prolina:	• **Hb Genova** [β28 (B10) Leu→Pro; *HBB*:c.86T>C] • **Hb Valletta** [β87(F3) Thr→Pro; *HBB*:c.262A>C] • **Hb Brigham** [β100(G2) Pro→Leu; *HBB*:c.302C>T]
Microdelezioni dell'ultimo esone dei geni α o β:	• **Varianti con fenotipo talassemico**

ESPRESSIONE CLINICA

Emoglobina instabile → **ANEMIA EMOLITICA**

Emoglobina con bassa affinità dell'ossigeno → **CIANOSI**

Emoglobina con alta affinità dell'ossigeno → **ERITROCITOSI**

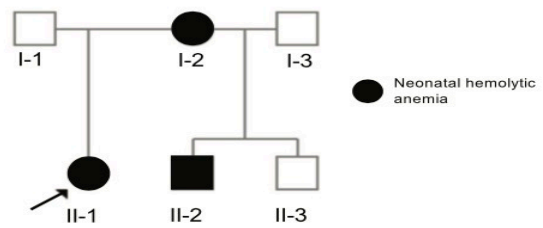
Metemoglobina → **CIANOSI E ERITROCITOSI/ANEMIA**

ANEMIA EMOLITICA

- **Anemia emolitica da ridotta sopravvivenza eritrocitaria**
- **Anemia emolitica**:
  Cronica (lieve o moderata) oppure con episodi occasionali di emolisi **acuta** (farmaci ossidanti o infezioni) oppure **emolisi compensata**
- **Indici di emolisi**: reticolocitosi, aumento bilirubina indiretta, aumento LDH, aptoglobina consumata
- **Splenomegalia**
- **Infezione da parvovirus B19**
- **Ipertensione polmonare**
- **Coeredità della S. di Gilbert**
- **Uso dell'EPO s.c. nei primi mesi di vita**

Unstable gamma globin variants can cause transient neonatal hemolytic anemia

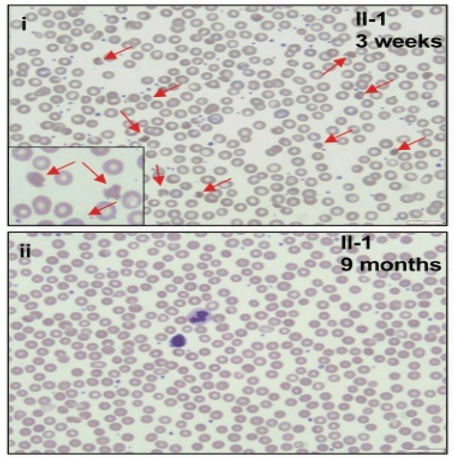
(A)

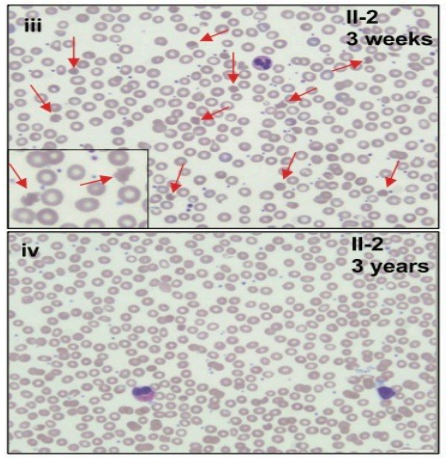


(B)

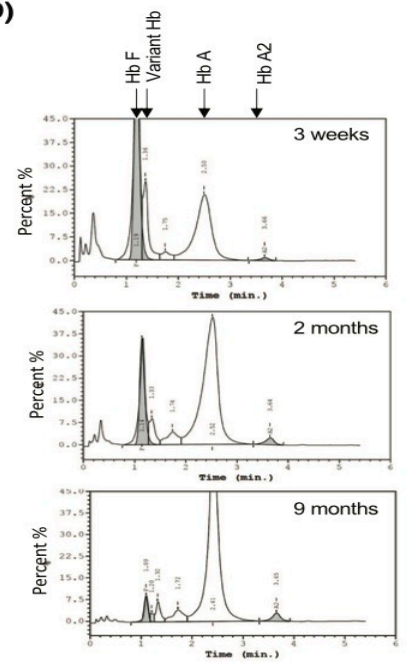
	Hemoglobin (g/dL)	Reticulocyte %	Total Bilirubin (mg/dL)	LDH (unit/L)	Hemoglobin Electrophoresis
II-1					
11 hours of life	18.9	14.1	7.4		
3 weeks	8.3	6.9	7.6	768	Hgb A1 53.4% Hgb A2 0.9% Hgb F* 45.7%
2 months	11.6	2.1	< 0.2	187	Hgb A1 78.7% Hgb A2 2.3% Hgb F* 19%
9 months	11	1.2	< 0.2	366	Hgb A1 92.9% Hgb A2 2.8% Hgb F* 4.3%
II-2					
2 weeks	8.6	7.8	18.3	440	
1 months	7.1	6.7			
3 months	10.5	1.3	0.2	292	
14 month	10.9	1.9	0.2	409	
20 month	11.8	0.7	< 0.2	358	Hgb A1 94.5% Hgb A2 3.1% Hgb F* 2.4%

(C)





(D)



SPLENECTOMIA

Table 1. Summary of splenectomy recommendations for hemolytic disorders.

Disease	When splenectomy recommended? *
Hereditary spherocytosis	Patient is transfusion-dependent or suffers severe anemia. Patient has moderate disease: decision based on spleen size and quality of life parameters. No need to perform cholecystectomy.
Pyruvate kinase deficiency	Consider if patient is transfusion-dependent or severely anemic. Cholecystectomy should be performed at time of splenectomy.
Splenectomy in congenital non-spherocytic hemolytic anemia due to G6PD deficiency	Consider if patient is transfusion-dependent and/or has massive splenomegaly and/or has symptomatic splenomegaly.
Hereditary stomatocytosis	Contraindicated.
Congenital dyserythropoietic anemia type II	Consider if patient is transfusion-dependent and/or has symptomatic splenomegaly.
Sickle cell disease	Patient has had two acute splenic sequestration crises and/or has massive splenomegaly and/or suffers symptomatic hypersplenism.
Unstable hemoglobin	Consider only if patient has transfusion-dependent anemia and/or symptomatic splenomegaly.

Splenectomy recommendations

In patients with unstable hemoglobin splenectomy should be considered ***when the spleen is very large and/or there is evidence of hypersplenism*** *(agreed by 95% of experts) (grade 2 recommendation, grade C evidence).*

haematologica | 2017; 102(8): 1304-1313

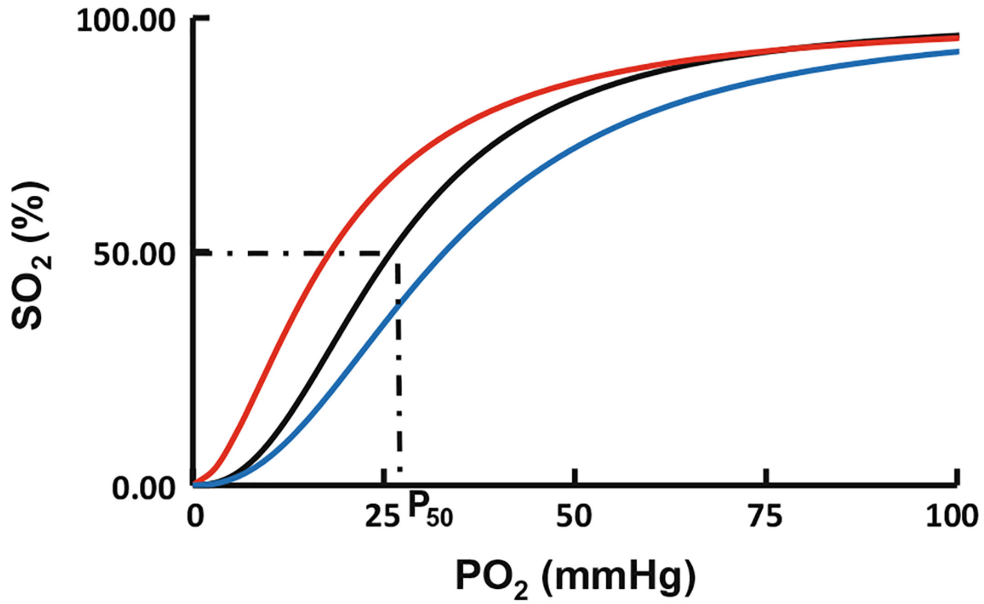
VARIANTI INSTABILI ED AFFINITÀ CON L'OSSIGENO

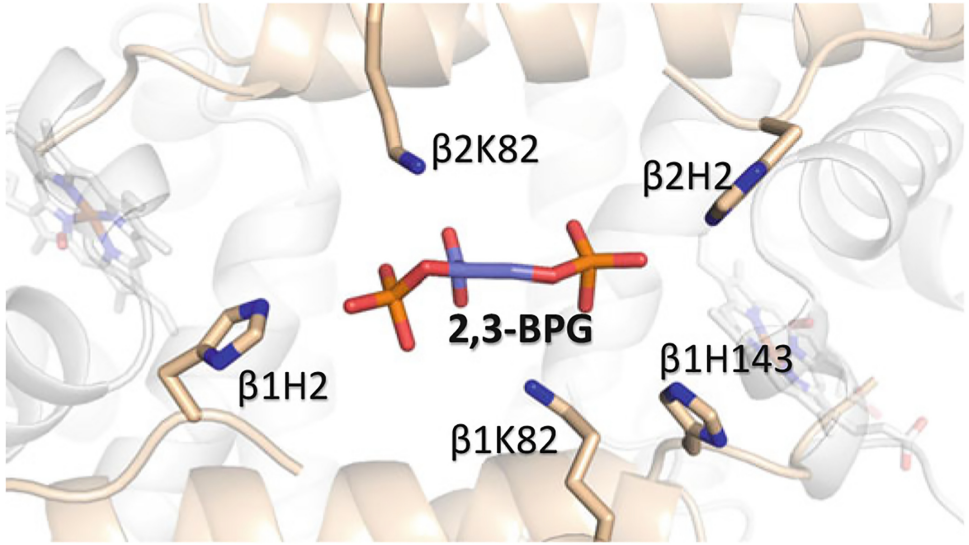
Varianti con affinità diminuita

Hb Torino
Hb Hammersmith
Hb Seattle

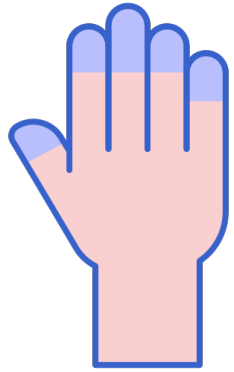
Varianti con affinità aumentata

Hb Koln
Hb Zurigo
Hb Freiburg





Hb con affinità per l'ossigeno ridotta

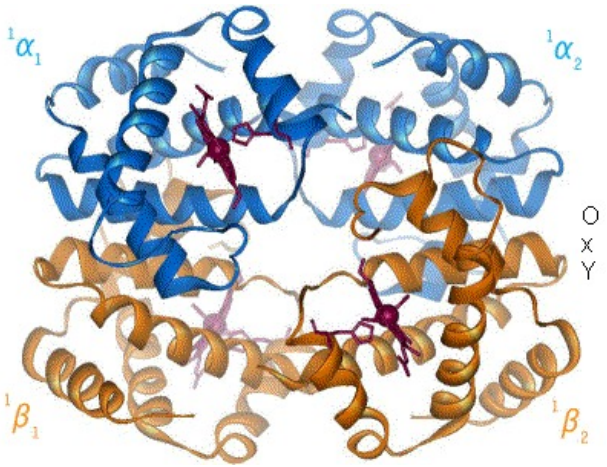


- Cianosi senza anemia ed emolisi (dd di un paziente cianotico)
- Cianosi presente dalla nascita nei casi di mutanti **alfa globina**
- Cianosi compare tra 6-12 mesi di vita nei casi di mutanti **beta globina**
- Cianosi è per lo piu presente alle dita, labbra, letto ungueale

Esposizione ad ossigeno
(dd tra cianosi dovuta ad emoglobina a bassa affinità vs HbM/metemoglobina)

Familial/Juvenile Erythrocytosis

Gene	Effect on protein	Type
JAK2	Gain of function, impaired auto-inhibitory domain	PV
EPOR	Gain of function, increased activation of signalling cascade	ECYT1
VHL	Loss of function, impaired degradation of HIF2α	ECYT2
EGLN1 (PHD2)	Loss of function, impaired degradation of HIF2α	ECYT3
EPAS1 (HIF2A)	Gain of function, increased stability in normoxia	ECYT4
EPO	Gain of function, increased expression in normoxia	ECYT5
HBB	Loss of function, increases Hb affinity for O2	ECYT6
HBA1 & HBA2	Loss of function, increases Hb affinity for O2	ECYT7
BPGM	Loss of function, impaired synthesis of 2,3-BPG	ECYT8



Class 1) Decreased released of oxygen to tissues with the physiological activation of the OS Pathway - Class 1 mutated genes are HBB, HBA, BPGM, PKLR;

More than **200 hemoglobin variants** with high oxygen affinity have been reported since 1966.

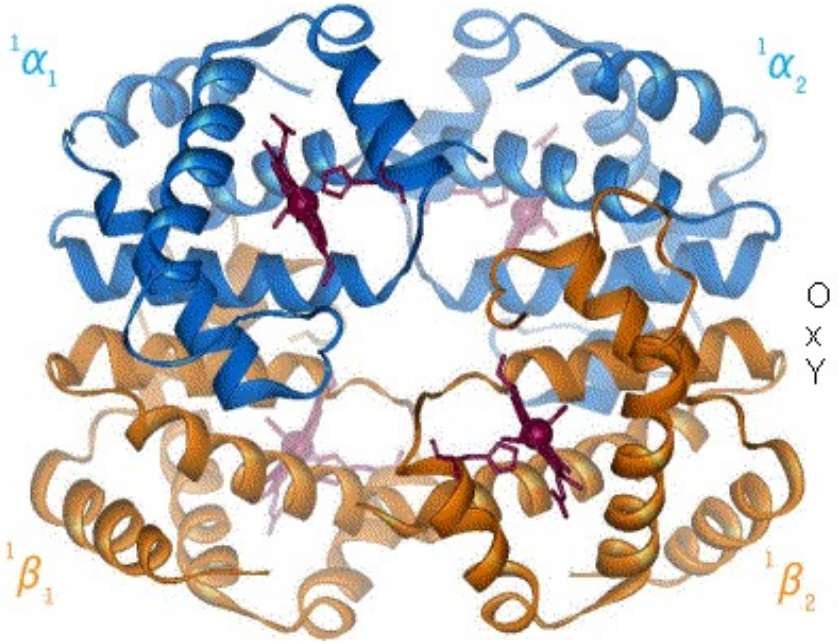
The **pathophysiologic** mechanism of altered oxygen affinity is often related to stabilization or destabilization of the T and R states in comparison to the normal Hb. A high oxygen affinity variant has either stabilization of the relaxed (R) state of the Hb tetramer (the high oxygen affinity state), or destabilization of the tense (T) state (the low oxygen affinity state) via mutations in critical regions of the globin chain that affect the R-T transition.

Affected individuals are generally **asymptomatic**, since erythrocytosis compensates to maintain adequate tissue O2 delivery. The **age at diagnosis varies** with the affected subunit. Germline mutations of alpha globin genes are associated with life-long erythrocytosis, while those of beta globin genes are silent at birth, but erythrocytosis develops after the fetal to adult Hb switch at approximately six months of age. Rare gamma globin mutations are associated with transient neonatal erythrocytosis that disappears by approximately six months of age, when most fetal Hb is replaced by adult Hb.

Familial deficiency of 2,3-BPG (previously known as 2,3-DPG) is a rare cause of congenital secondary erythrocytosis caused by a deficiency of the red blood cell (RBC) enzyme, bisphosphoglyceromutase (BPGM). The resultant increase in Hb-O2 affinity decreases the amount of O2 released peripherally, leading to **compensatory erythrocytosis**. In comparison to the high O2 affinity Hbs, the level of 2,3-BPG is very low in familial 2,3-BPG deficiency. Similar to high O2 affinity Hb mutants, the **p50** should be the first screening test that can be estimated from venous blood when the hemox-analyzer apparatus (described above) is not available.
EPO levels are not reliable to identify patients with BPGM variants.

HIGH–OXYGEN AFFINITY HB VARIANT

- Approximately **100** such variants have been described
- http://globin.bx.psu.edu/hbvar/menu.html
- **Autosomal dominant** transmission
- Structural alterations that occur at the **alpha1beta2 interface** and in regions involved in stabilizing the tense state of Hb.
- The resultant oxygen dissociation curve is **shifted to the left**, thereby **depressing the p50 value,** which is a measure of oxygen affinity.



P50

Affinity of Hb with oxygen is expressed as the P50, which is the **partial pressure of oxygen in blood at which 50% of the Hb is saturated with oxygen.**

The **venous P50** can be measured directly using a **cooximeter** which is no longer easily available in routine and even reference laboratories. Lichtman and colleagues have reported a mathematical formula which can be used to calculate P50 reliably (Ann Intern Med 1976, 84:517–520).

Calculating P50 using this formula requires the following **venous gas** parameters: partial pressure of oxygen (venous **pO2**), venous **pH** and venous **oxygen saturation**, and uses anti-log mathematical function that many clinicians find difficult to use for calculation

P50

The P50 of a healthy person with normal Hb is 26 ±1.3 mm Hg.

The 99% confidence interval for individual observations has been reported to be **22.6 to 29.4** mm Hg.

An abnormally **low P50 reflects an increased affinity** of hemoglobin for oxygen and vice versa.

Elevations and reductions in **2, 3- BPG level** in the erythrocyte will also lead to corresponding changes in P50 values

Confronto tra Varianti Hb con Alta Affinità per l'O2

Varianti Hb non instabili (blu) - Varianti Hb instabili (verde)

	Età/Sesso	G.R	Hb	Ht	MCV	Hb A_2	Hb F	Hb X	Variante Hb
	anni	x10 ^{6}/µl	g/dl	%	fl	%	%	%	
1.	45/ M	6.13	17.8	55.2	89.5	2.6	0.1	51.1	Hb Gambara
2.	18/ F	6.20	18.9	57.0	90.8	2.1	2.1	47.5	Hb Bologna-St.O.
3.	30/ F	5.66	14.5	44.2	78.0	2.8	0.1	42.7	Hb Bumbury
4.	25/ F	7.06	18.4	56.5	89.0	3.1	0.1	49.0 (b)	Hb Heathrow
5.	47/ M	6.50	17.3	51.0	78.4	2.5	0.1	46.8 (b)	Hb Johnstown
6.	31/ F	4.16	13.4	42.8	101.5	3.2	5.7	29.0	Hb Trento
7.	28/ F	4.30	12.5	41.2	95.2	4.1	1.1	n.d.	Hb Köln
8.	22/ F	4.50	12.4	39.6	90.0	3.8	2.4	n.d.	Hb Genova
9.	10/ M	4.92	13.3	41.6	85.5	3.5	0.8	25.2	Hb Sheph.Bush
10.	19/ M	4.45	13.1	42.4	96.0	3.3	1.1	27.4	Hb Zurigo
11.	30/ F	7.10	14.5	41.0	57.7	5.2	6.5	88.3	Hb Abruzzo (c)

(c) Hb Abruzzo + Beta Talassemia

Confronto tra Varianti Hb con Alta Affinità per l'O2

Varianti Hb non instabili (blu) - Varianti Hb instabili (verde)

	Test Instabilità	Bilirubina indiretta	2,3-DPG	P_{50}	Eritropoietina	Reticolociti	Variante Hb
1.	N	N	↓	↓	N	↑	Hb Gambara
2.	N	N	↓	↓	N	N	Hb Bologna-St.O.
3.	N	N	N	↓	N	N	Hb Bumbury
4.	N	N	↓	↓	N	N	Hb Heathrow
5.	N	N	n.d.	↓	N	N	Hb Johnstown
6.	P	↑	↓	↓	N	↑	Hb Trento
7.	P	↑	N	↓	N	↑↑	Hb Köln
8.	P	↑	(↑)	(↑)	n.d.	↑↑↑	Hb Genova
9.	P	↑	↓	↓	n.d.	↑↑	Hb Sheph. Bush
10.	P	↑	N	↓	N	N (↑)	Hb Zurigo
11.	P	↑	n.d.	↓	n.d.	↑	Hb Abruzzo (c)

(c) Hb Abruzzo + Beta Talassemia

HIGH OXYGEN AFFINITY HAEMOGLOBINS (venesection)

- Presence of **symptom**s such as dizziness, dyspnoea or angina, for which a raised Hct is considered to be a contributory factor.
- One or more **previous thrombotic episodes**.
- **Asymptomatic individuals in whom a family member** with a high oxygen affinity haemoglobin, similar haemoglobin concentration, and comparable risk factors for thrombosis, has developed thrombotic problems.

METHEMOGLOBINEMIA

- Methemoglobinemia is a **rare** disorder associated with **oxidization of divalent ferro-iron of hemoglobin (Hb) to ferri-iron of methemoglobin** (MetHb).
- The presence of iron in the **ferric** [Fe3+] state results in allosteric changes that permit the **binding of oxygen irreversibly**.
- The corresponding ferro-globins in the tetramer shifts the oxygen-dissociation curve of Hb to the **left**.
- This shift leads to **increased affinity of the Hb** for oxygen and thus impaired oxygen release to the tissue, resulting in hypoxia with the so called“functional anemia” without Hb decrease.
- Methemoglobinemia can result from either **inherited or acquired processes**

Disease	Transmission	Cyanosis	Anemia	Other symptoms	Gene(s)	MetHb level %	CYB5R activity	Hb electrophoresis/ HPLC
Drug exposure	Acquired	Yes	No	-	-	Variable	Normal	Normal
Methemoglobinemia, type I	Autosomal recessive	Yes since birth	No	-	*CYB5R3*	20–30	Decreased	Normal
Methemoglobinemia, type II	Autosomal recessive	Yes since birth	No	Neurological involvement	*CYB5R3*	8–40	Decreased	Normal
Methemoglobinemia, type IV	Autosomal recessive	Yes	No	46,XY DSD Ambiguous genitalia	*CYB5A*	12–19	Normal	Normal
HbM disease	Autosomal dominant	Yes since birth or after HbF/A switching	Yes	-	*HBA1*, *HBA2*, *HBB*, *HBG1*, *HBG2*	12–25	Normal	Abnormal
Unstable Hb	Autosomal dominant	Yes	Yes	-	*HBA1*, *HBA2*, *HBB*, *HBG1*, *HBG2*	Variable (Stressor induced)	Normal	N or Abnormal

AJH 2021, 96:1666-1678

Hereditary methemoglobinemia

Enzyme deficiency

- It is a **rare** genetic condition caused by **NADH cytochrome b5 reductase deficiency** due to **biallelic mutations in the CYB5R3 gene** that codes the enzyme (CYB5R)

- More than 80 different disease-causing variants in the CYB5R3 gene have been reported

- Patients with biallelic causative variants in CYB5R3 gene often exhibit **erythrocytosis**

➢ Based on the severity of the enzyme deficiency, this condition can be classified into two different subtypes:

Disease	Transmission	Cyanosis	Anemia	Other symptoms	Gene(s)	MetHb level %	CYB5R activity	Hb electrophoresis/ HPLC
Methemoglobinemia, type I	Autosomal recessive	Yes since birth	No	-	*CYB5R3*	20–30	Decreased	Normal
Methemoglobinemia, type II	Autosomal recessive	Yes since birth	No	Neurological involvement	*CYB5R3*	8–40	Decreased	Normal

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Hemoglobin M

Disease	Transmission	Cyanosis	Anemia	Other symptoms	Gene(s)	MetHb level %	CYB5R activity	Hb electrophoresis/ HPLC
HbM disease	Autosomal dominant	Yes since birth or after HbF/A switching	Yes	-	*HBA1*, *HBA2*, *HBB*, *HBG1*, *HBG2*	12–25	Normal	Abnormal

TABLE 1 Signs, symptoms, and causes of methemoglobinemia

MetHb level	Signs	Symptoms	Causes
<10%	Low pulse oximeter readings, alteration of the skin color (pale, gray, blue)	Asymptomatic	Acquired
10%-30%	Cyanosis Dark brown blood	Asymptomatic/confusion	Enzymopenic methemoglobinemia, HbM, acquired
30%-50%	Dyspnea, dizziness, syncope	Confusion, chest pain, palpitations, headache, fatigue	Acquired ± hereditary
50%-70%	Tachypnea, metabolic acidosis, dysrhythmias, seizure, delirium, coma	Confusion, chest pain, palpitations, headache, fatigue	Acquired ± hereditary
>70%	Severe hypoxemia, death	-	Acquired ± hereditary

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When should congenital methemoglobinemia be considered as a possible diagnosis?

- ✓ Known **family history** of methemoglobinemia.
- ✓ **Cyanosis** in a newborn baby, infant, child, or adult **not associated with hypoxemia**, cold exposure or other known explanation
- ✓ **Incidental finding** of increased MetHb level.
- ✓ **Pulse oximetry showing unexpected or discordant results** compared to clinical assessment or other measures of oxygenation
- ✓ **Severe neurodevelopmental disorder**, typically presenting in the first year of life

Treatment of toxic methemoglobinemia

- The **agent precipitating** methemoglobinemia should be **stopped or removed**.
- **Supportive therapy**: intravenous hydration with glucose and oxygen supplementation
- **Methylene Blue**: The usual starting dose is **1–2 mg/kg** (0.2 mL/kg of a 1% solution) infused **intravenously over 3 to 5 min**. The dose may be **repeated** at 1 mg/kg if methemoglobinemia does not significantly decrease within 30–60 min (dose max 7 mg/Kg)
- **Exchange transfusion**: urgent, in cases of worsening methemoglobinemia after MB treatment, must be performed.
- **Ascorbic acid**: dosing is not standardized
- Case reports have described treatment of refractory methemoglobinemia with **blood transfusions, exchange transfusion, hemodialysis, hyperbaric oxygen and N-acetylcysteine**

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Treatment of inherited methemoglobinemia

- **Methylene blue (MB) with or without ascorbic acid** is prescribed in more severe cases of congenital methemoglobinemia.
- In some countries, **oral MB** 100–300 mg per day is administered with dose adjustment according to MetHb levels.
- Many patients are adequately treated with **ascorbic acid alone**, given in varying dosing regimens, from 0.2–1.0 g/day orally in divided doses
- **Riboflavin** can accelerate reduction of MetHb levels via the nicotinamide adenine dinucleotide-flavin reductase system (limited data)
- In methemoglobinemia associated with hemoglobin disorders, both **HbM and unstable Hb**, **MB and ascorbic acid treatment are ineffective** and should be avoided.
- In patients who have developed **erythrocytosis, phlebotomy is not recommended** as higher erythrocyte mass allows provision of normal tissue oxygenation.

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Conclusioni (1)

- Una variante instabile delle catene **beta** può causare **anemie** gravi, moderate o lievi in seguito ad emolisi croniche o acute e ciò dipenderà dalle caratteristiche del difetto
- Le varianti instabili **beta** possono esordire **dopo i sei mesi** al termine dello switch dell'HbF
- Le varianti instabili **beta** sono in genere clinicamente **più espresse rispetto alle varianti alfa**
- Le varianti instabili **alfa** possono esordire alla **nascita** in forme clinicamente più importanti rispetto a come possono manifestarsi in età adulta per la presenza delle catene gamma con le quali possono formare tetrameri più instabili
- Raramente le varianti instabili delle catene **alfa** producono fenomeni emolitici rilevanti in età adulta
- Le varianti instabili del gene **gamma** possono manifestarsi con **una transitoria anemia emolitica neonatale** e poi diventano «asintomatiche»
- L'associazione con **difetti talassemici** può produrre condizioni **emolitiche clinicamente significative**. La **splenectomia** in genere **non** risulta utile e deve essere valutata con attenzione
- Alcune varianti instabili vengono definite "**iperinstabili**" e presentano talvolta un comportamento "**talassemico**"
- L'**associazione** con **HbS o con difetti di membrana** può produrre forme clinicamente piu importanti che talvolta necessitano di trasfusioni o suggeriscono la splenectomia
- La presenza di un paziente con **anemia e segni di emolisi** in cui si escludono le cause piu frequenti di anemia emolitica congenita (es SE, EE) è giusto ipotizzare la presenza di una **Hb instabile**

Conclusioni (2)

- Una variante dell'Hb con **ridotta affinità per l'ossigeno** si manifesta con generalmente **cianosi** localizzata **senza anemia ed emolisi**: nessuna terapia
- Una variante dell'Hb con **aumenta affinità per l'ossigeno** si manifesta con **Hb nella norma** ma con reticolocitosi e iperbilirubinemia indiretta se la variante è **instabile** oppure con **eritrocitosi** se la variante è **stabile**
- La valutazione della **P50** con un **emogasanalisi venosa** è importante per stabilire l'affinità per l'ossigeno
- La **salassoterapia** è raramente indicata nelle varianti dell'Hb con aumenta affinità per l'ossigeno se il paziente non ha fattori di rischio o manifestazioni cliniche
- La **metemoglobinemia ereditaria** da mutazione del gene CYB5R3 è rara e si manifesta con **eritrocitosi, cianosi e sintomi neurologici** soprattutto nel tipo II.
- **Hb M** è trasmessa con meccanismo autosomico dominante e si manifesta con **anemia e cianosi**
- Nella metemoglobinemia la sintomatologia è legata alla **percentuale di MetHb presente**
- Terapia della metemoglobinemia: **blu di metilene e acido ascorbico**
- Nei pazienti con **metemoglobinemia ereditaria ed eritrocitosi** la **salassoterapia** deve essere evitata

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Ematologia ed Oncologia Pediatrica, Centro ERN malattie rare ematologiche, Università della Campania “L. Vanvitelli

Francesca Rossi
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Daniela Di Pinto
Elvira Pota
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