Highlights in Ematologia
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Emoglobinopatie frequenti e meno frequenti

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Conflitto d’interesse

Nessun conflitto d’interesse

Agenda

Definition of hemoglobinopathies

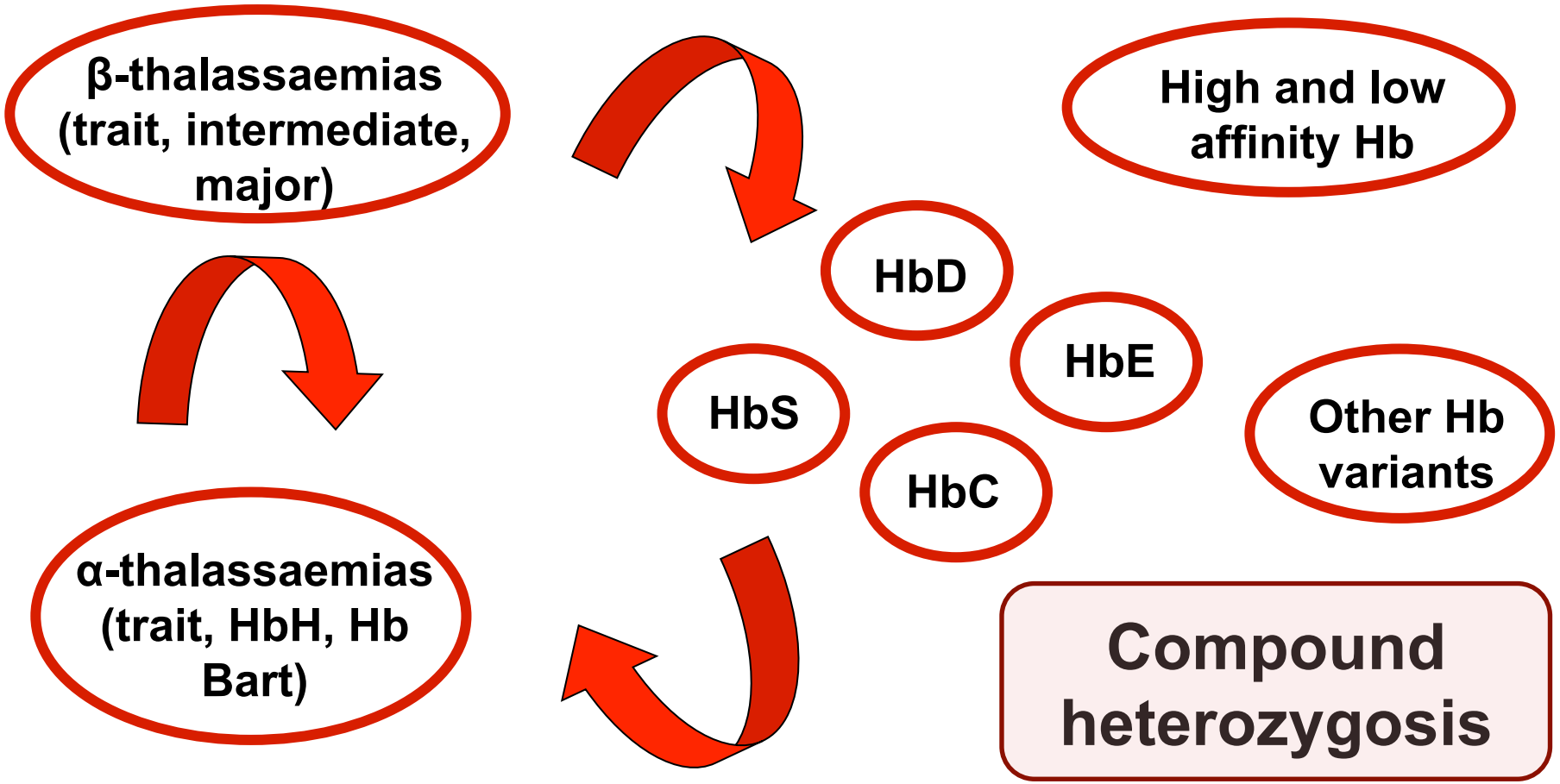
Case reports

Pathophysiology

Clinical spectrum

Hemoglobinopathies

Group of inherited disorders



Thalassemia International Federation (TIF) guidelines

CASE REPORT 1

Donna, 52 anni

- Proveniente dalle Filippine
- Padre di 88 anni affetto da artrite reumatoide
- Madre deceduta a 88 anni per ictus, con anemia
- Fratello di 57 anni, in buona salute, iperteso

CASE REPORT 1

Donna, 52 anni

In APR:

- All'età di 15 anni: tonsillectomia ed adenoidectomia

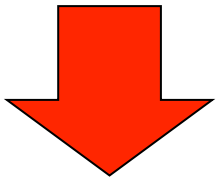
- All'età di 19 anni: ricovero per febbre ed ittero con diagnosi di anemia emolitica

- Riferisce valori di Hb stabili tra 8 e 9 g/dl; segnalata splenomegalia e iperferritinemia

CASE REPORT 1

Donna, 52 anni

Ricorso in PS per febbre ed Hb 6.7 g/dl.



Esami Ematici

- **GB normali**
- **Hb 6.7 g/dl**
- **MCV 68.7 fl**
- **PLT normali**
- **RDW 34.9%**
- **LDH 595 U/l**
- **Ferritina 1171 ng/ml, Sat transf: 62%**
- **Bil. tot/dir: 1,23/0,41 mg/dl**

CASE REPORT 1

Donna, 52 anni

Origini Filippine

Anemia

Iperferritinemia

Microcitosi

Splenomegalia

Aumento indici emolisi

HPLC: identificazione di Hb H

CASE REPORT 2

Due fratelli D.M. ed F.M. di 40 e 32 anni

- Provenienti dal Bangladesh
- Madre diabetica, zio paterno e padre con pregresso IMA.

CASE REPORT 2

D.M. 40 anni

Facies talassemica

Ipogonadismo

Splenomegalia

Iperferritinemia

Calcolosi colecisti

Cardiopatia (FE 45%)

Non chelazione

ET regolari*

Genova 2006

Arrivo in Italia

F.M. 32 anni

Facies composita

Normale fx gonadica

Splenomegalia

Iperferritinemia

Colecisti alitiasica

FE nella norma

Non chelazione

ET regolari*

*dall'età di 8-9 anni

CASE REPORT 2

D.M. 40 anni

Ipogonadismo

Splenectomia

Iperferritinemia

Colecistectomia

Cardiopatia dilatativa

Aritmie (FA)

Chelazione

"Percorso"
negli anni

F.M. 32 anni

Nascita di un figlio

Splenomegalia

Iperferritinemia

Colecisti alitiasica

FE nella norma

Non aritmie

Chelazione

CASE REPORT 2

D.M. 40 anni

Genetica:
HbE/Beta-thal

F.M. 32 anni

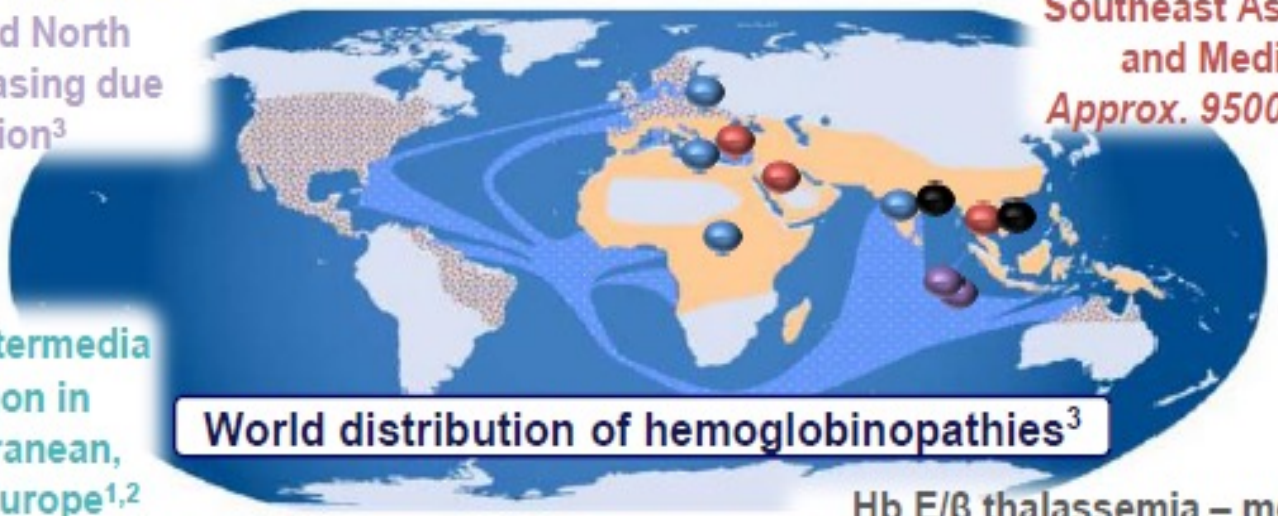
Genetica:
HbE/Beta-thal

Hemoglobinopathies in the world

A different distribution of hemoglobinopathies is detected in each country

Prevalence of Hb H disease in Europe and North America increasing due to migration[3]

Hb H – most common in Southeast Asia, Middle East and Mediterranean[3]
Approx. 9500 annual births[4]



β thalassemia intermedia – most common in Africa, Mediterranean, India and East Europe[1,2]

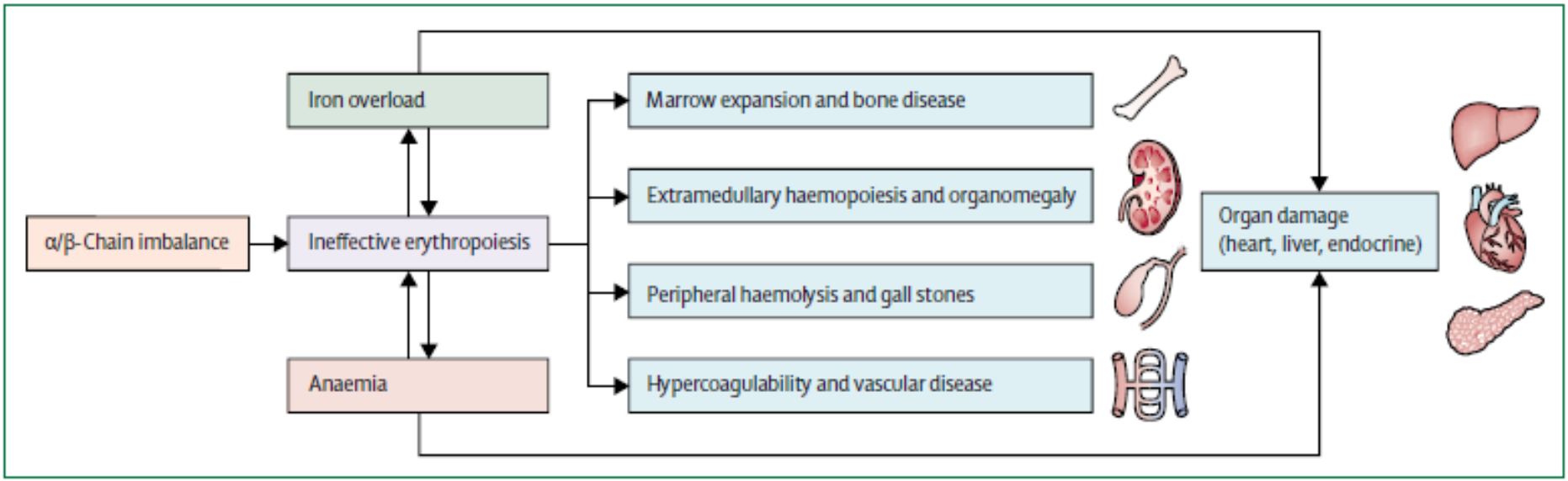
World distribution of hemoglobinopathies[3]

Hb E/β thalassemia – most common in East India, Bangladesh and Southeast Asia[1]
Approx. 19,000 annual births[4]

The increased migration flow expands the reach of these diseases

[1]Weatherall DJ. *Blood Rev* 2012;26 Suppl 1:S3–S6;
[2]Available from: http://emedicine.medscape.com/article/959122-overview#a0156;
[3]Harteveld CL and Higgs DR. *Orphanet J Rare Dis* 2010;5:13; [4]Weatherall DJ. *Blood* 2010;115:4331–4336.

Pathophysiology



"Points" of pathophysiology:

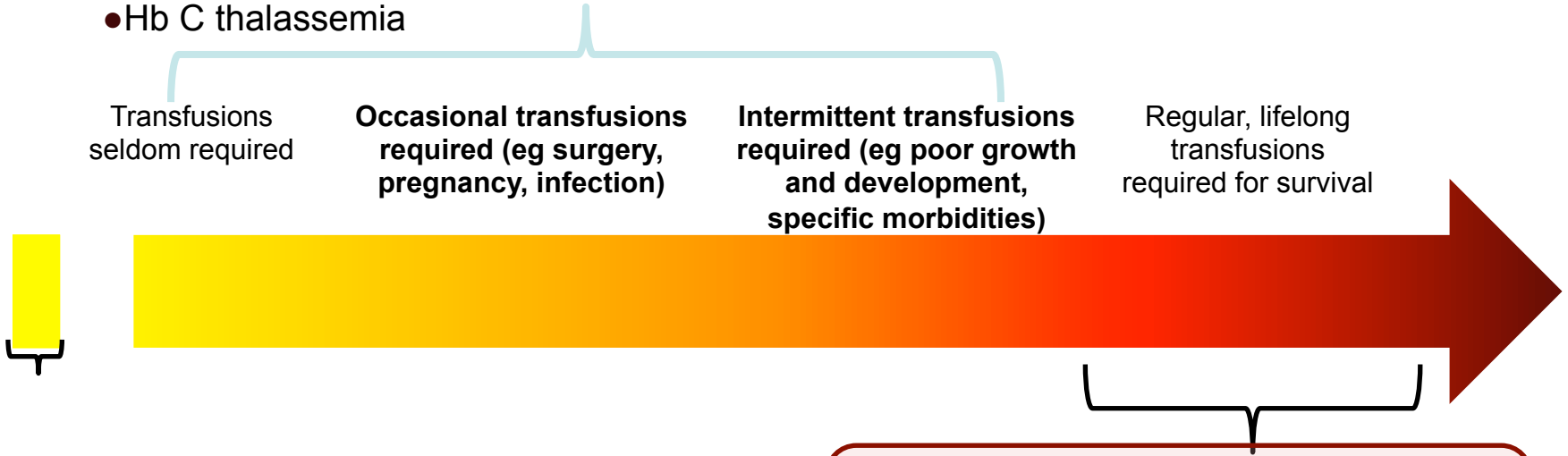
- Ineffective erythropoiesis
- Anemia
- Iron overload

Ali T Taher, David J Weatherall, Maria Domenica Cappellini
Published online July 31, 2017 http://dx.doi.org/10.1016/S0140-6736(17)31822-6

Thalassemia has a broad clinical spectrum, complicating diagnosis and management

NTDT

- β thalassemia intermedia
- Mild/moderate Hb E/β thalassemia
- Hb H disease (α thalassemia)
- Hb S β thalassemia
- Hb C thalassemia



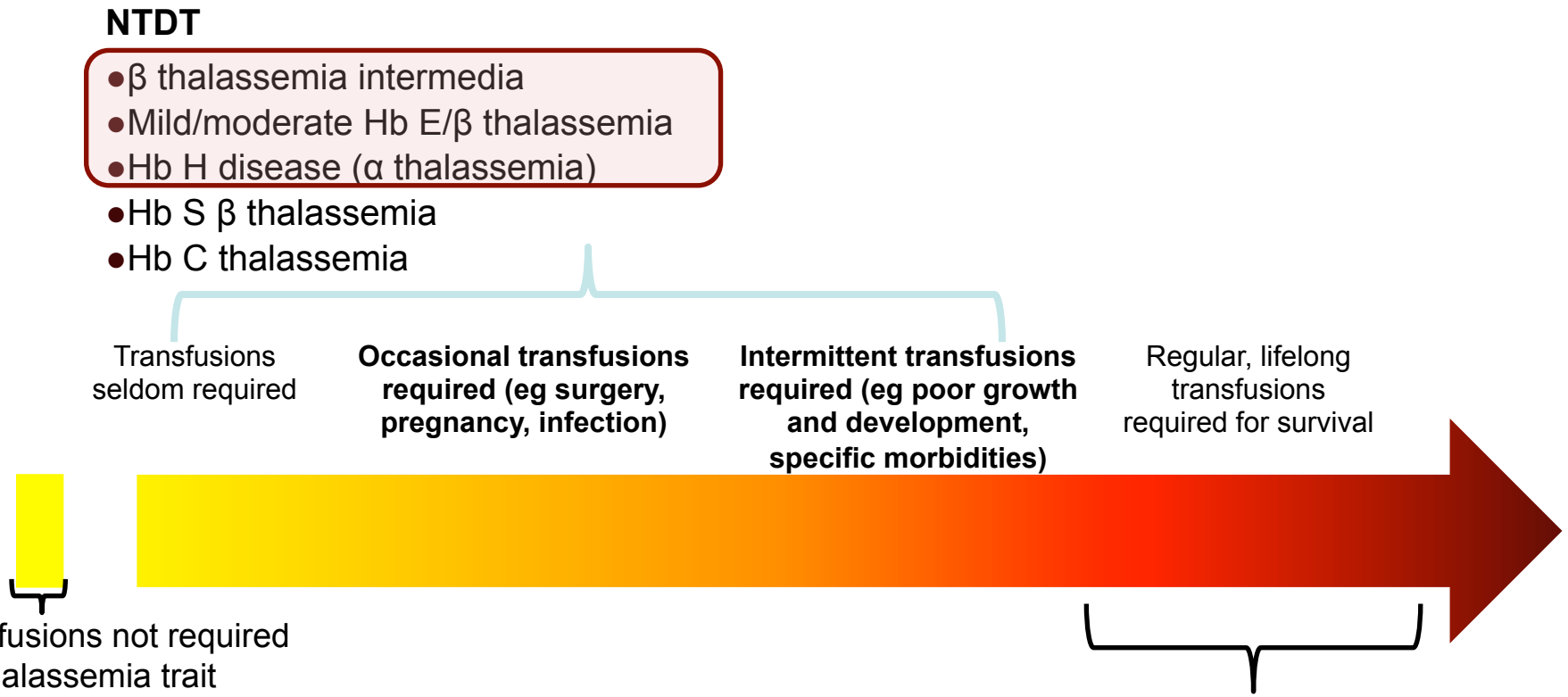
Transfusions not required
- α thalassemia trait
- β thalassemia minor

Transfusion-dependent thalassemia (TDT)
- β thalassemia major
- Severe Hb E/β thalassemia
- Hb Barts hydrops (α thalassemia major)

Taher AT *et al. Br J Haematol* 2011;152:512–523; 2. Galanello R and Origa R. *Orphanet Journal of Rare Diseases* 2010;5:11; 3. Vichinsky E. *Hematology Am Soc Hematol Educ Program* 2007;79–83; 4. Muncie HL and Campbell JS. *Am Fam Physician* 2009;80:339–344; 5. Figure adapted from Musallam KM *et al*. *Haematologica* 2013;98:833–844.

Thalassemia has a broad clinical spectrum, complicating diagnosis and management

NTDT patients do not require regular red cell transfusions but may require occasional transfusions for growth failure, pregnancy, infections and other specific situations[1–4]



Taher AT *et al. Br J Haematol* 2011;152:512–523; 2. Galanello R and Origa R. *Orphanet Journal of Rare Diseases* 2010;5:11; 3. Vichinsky E. *Hematology Am Soc Hematol Educ Program* 2007;79–83; 4. Muncie HL and Campbell JS. *Am Fam Physician* 2009;80:339–344; 5. Figure adapted from Musallam KM *et al*. *Haematologica* 2013;98:833–844.

Phenotypic classification of the β thalassemias is based on clinical grounds

- Severe anemia presenting early in life (<2 years)
- Requires lifelong blood transfusions and chelation
- If untreated, leads to death usually in first decade

β thalassemia major

- Mild-to-moderate anemia (7–10 g/dL), usually diagnosed in later childhood (>2 years) ± splenomegaly
- Blood transfusions not necessary for survival (NTDT)
- Some exceptions at the severe end of the spectrum:
  - Transfusions recommended in children with Hb 50–60 g/L to prevent skeletal deformities
  - Transfusions often required later in life as a result of splenomegaly, infections, pregnancy, or other disease-related factors

β thalassemia intermedia

- Clinically asymptomatic
- Microcytic, hypochromic anemia
- Requires genetic counseling

β thalassemia minor/trait

1. Musallam KM *et al. Cold Spring Harb Perspect Med* 2012;2:a013482;
2. Galanello R and Origa R. *Orphanet J Rare Dis* 2010;5:11;
3. Taher AT *et al. Blood Reviews* 2012;26S:S24–S27

Genotype-phenotype association in α thalassemia leads to variable clinical severity

- Overall clinical phenotype: very mild – may not be noticed other than when a blood count is examined[1]

NTDT

Phenotype	Genotype	Clinical severity
Major (Hb Barts hydrops)	• --/--	• Most develop hydrops fetalis syndrome and die in utero during pregnancy, or shortly after birth • Survivors are transfusion dependent
Non-deletional Hb H disease	• --/$\alpha^T\alpha$	• Moderate-to-severe anemia • May require occasional or frequent transfusions (10–12/year)[2,3]
Deletional Hb H disease	• --/-α	• Mild-to-moderate anemia • Transfusion independent • Clinical severity is variable and ranges between minor to major
Trait/minor	• -α/-α • --/αα	• Borderline asymptomatic anemia • Microcytosis and hypochromia
Silent carrier	• -α/αα	• Asymptomatic • No hematological abnormalities

Severity of disease

Hb H disease is the most severe non-fatal form of α thalassemia[2]

1. Adapted from Musallam KM *et al*. *Haematologica* 2013;98:833–844.
2. Harteveld C and Higgs D. *Orphanet Journal of Rare Diseases* 2010;5:13;
3. Fucharoen S and Viprakasit V. *Hematology Am Soc Hematol Educ Program* 2009:26–34;
4. Laosombat V *et al. Ann Hem* 2009;88:1185–1192

Hb E/β thalassemia is associated with a highly variable clinical phenotype, with mild-to-moderate disease being classified as NTDT

	Hb E/β thalassemia category	Clinical phenotype
TDT	Severe	• Hb level as low as 4–5 g/dL • Clinical symptoms similar to β thalassemia major
NTDT	Moderate	• Hb levels between 6 and 7 g/dL • Clinical symptoms similar to β thalassemia intermedia
NTDT	Mild	• Hb levels between 9 and 12 g/dL • Usually do not develop clinically significant problems

1. Galanello R and Origa R. *Orphanet J Rare Dis* 2010;5:11

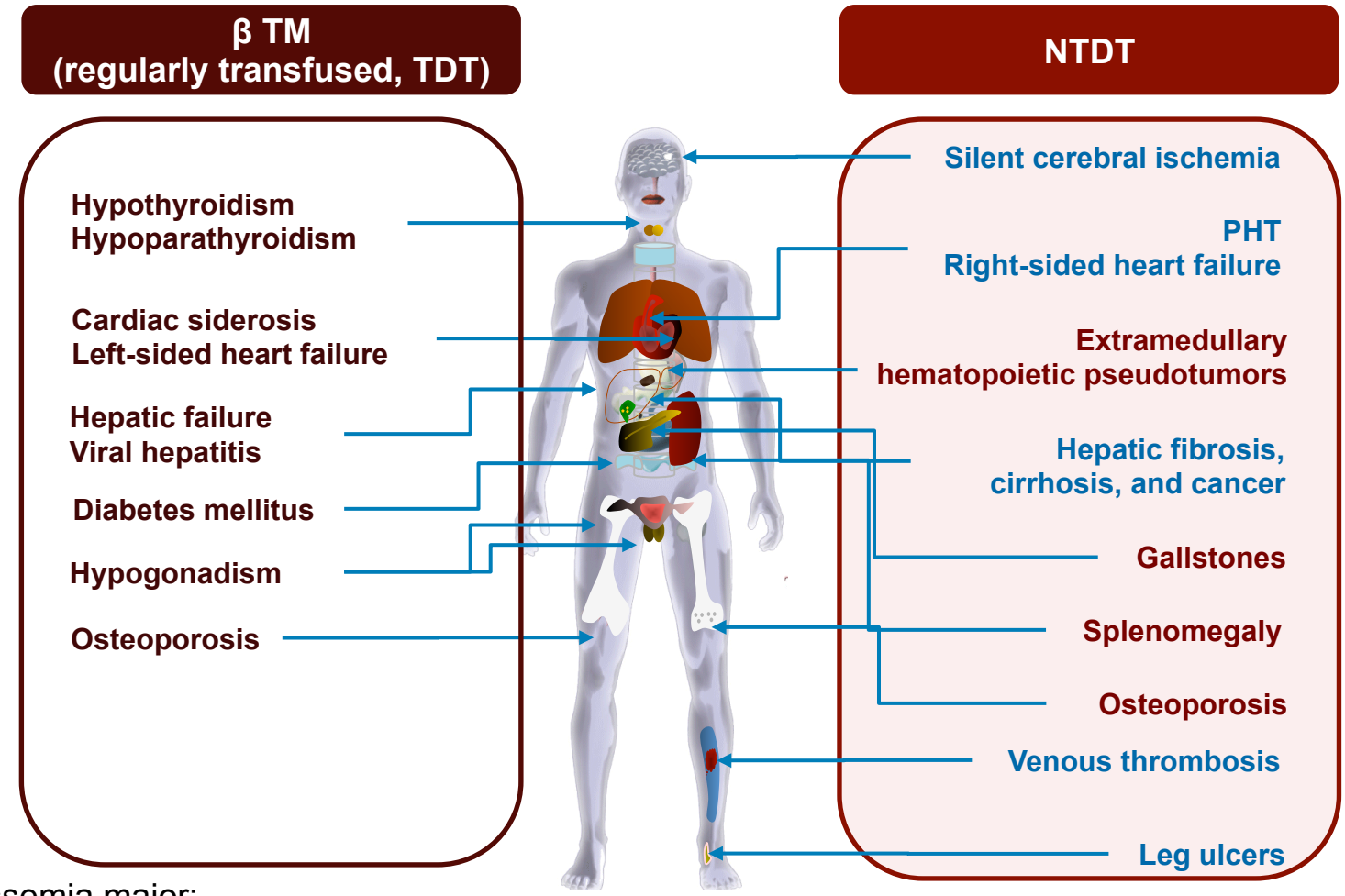
Distinct genetic modifiers can contribute to the phenotypic diversity of Hb E/β thalassemia

- **Type of β thalassemia mutations**
  - Hb E with β^+ thalassemia mutations are likely to have a mild disease phenotype
- **Co-inheritance of α thalassemia**
  - α thalassemia mutations can reduce free α globin precipitation
- **Co-inheritance of determinants that increase Hb F**
  - Up-regulated γ globin expression will further normalize globin imbalance due to Hb E/β thalassemia
  - Hb E/HPFH has a very mild clinical phenotype
- **Modifiers of complications**:
  - QTL with increased F on chromosome 6q23, 8q, Xp22 and 2p16.1
  - XMN1 polymorphism/ SNPs within the *β* gene cluster (chromosome 11p15)
  - Polymorphism of the *UGT1*1* gene
  - Serum erythropoietin concentration

QTL, quantitative trait loci;
SNP, single nucleotide polymorphisms

1. Galanello R. *Blood Rev* 2012;26S:S7–S11;
2. Olivieri NF *et al*. *Br J Haematol* 2008;141:388–397;
3. Winichagoon P *et al*. *Br J Haematol* 1993;83:633–639;
4. Premawardhena A *et al*. *Lancet* 2001;357:1945–1946;
5. Olivieri NF *et al*. *Hematol Oncol Clin North Am* 2010;24:1055–1070;
6. O'Donnell A *et al*. *Proc Natl Acad Sci* USA 2009;106:18716–18721

Clinical complications in TDT and NTDT



β TM, β thalassemia major;
IOL, iron overload;
PHT, pulmonary hypertension;
TDT, transfusion-dependent thalassemia

Musallam KM *et al*. *Haematologica* 2013;98:833–844.

Conclusions

The increased migration flows in our country lead to a particular attention for hemoglobinopathies and their diagnosis

Hemoglobinopathies, previously letal from childhood, can be treated as chronic conditions

Conclusions

Predominant forms of hemoglobinopathies are:

- β thalassemia major (TDT)
- Sickle cell disease
- β thalassemia intermedia (NTDT)
- Hb E/β thalassemia
- Hb H disease (α thalassemia)

NTDT leads to ineffective erythropoiesis and anemia, which can ultimately lead to several complications including iron overload

Conclusions

Underlying molecular pathology and a variety of **genetic modifiers** lead to a variable clinical phenotype for all NTDTs

The broad clinical spectrum of NTDT complicates diagnosis and management, requiring a **personalized approach** to patient treatment

Conclusions

Correction of globin chains imbalance (gene teraphy), amelioration of ineffective erythropoiesis (sotatercept, luspatercept, JAK2 inhibitors) and regulation of iron overload (chelators, drugs for iron metabolism) represent the **future treatment strategies**

Ringraziamenti

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Dott.ssa Irene Motta

Dott.ssa Migone De Amicis Margherita

Personale infermieristico

PER L'ATTENZIONE