

# AGGIORNAMENTO SU DIAGNOSI E TERAPIA DELLE EMOGLOBINOPATIE

Milano, 15 Novembre 2024 | Starhotels E.C.H.O.

Con il patrocinio di



## DREPANOCITOSI

**Giovanna Graziadei**

SS Emoglobinopatie e Disordini Ereditari del  
Metabolismo e del Sistema Immunitario  
SC Medicina ad Indirizzo Metabolico  
Fondazione IRCCS Ca' Granda Ospedale  
Maggiore Policlinico di Milano



FONDAZIONE IRCCS CA' GRANDA  
OSPEDALE MAGGIORE POLICLINICO

# Anemia a Cellule Falciformi

- Gruppo di **Anemie Emolitiche Croniche Ereditarie** trasmesse secondo modalità mendeliana come **carattere autosomico recessivo**
- **Variante emoglobinica HbS** causata dalla sostituzione aminoacidica [Glu6Val, rs334] da mutazione nucleotidica missenso (GAT →GTG) sul gene  $\beta$ -globinico [HBB]
- **Patologia multisistemica**, caratterizzata da ampia eterogeneità clinica, con **episodi di acuzie e progressivo danno d'organo**

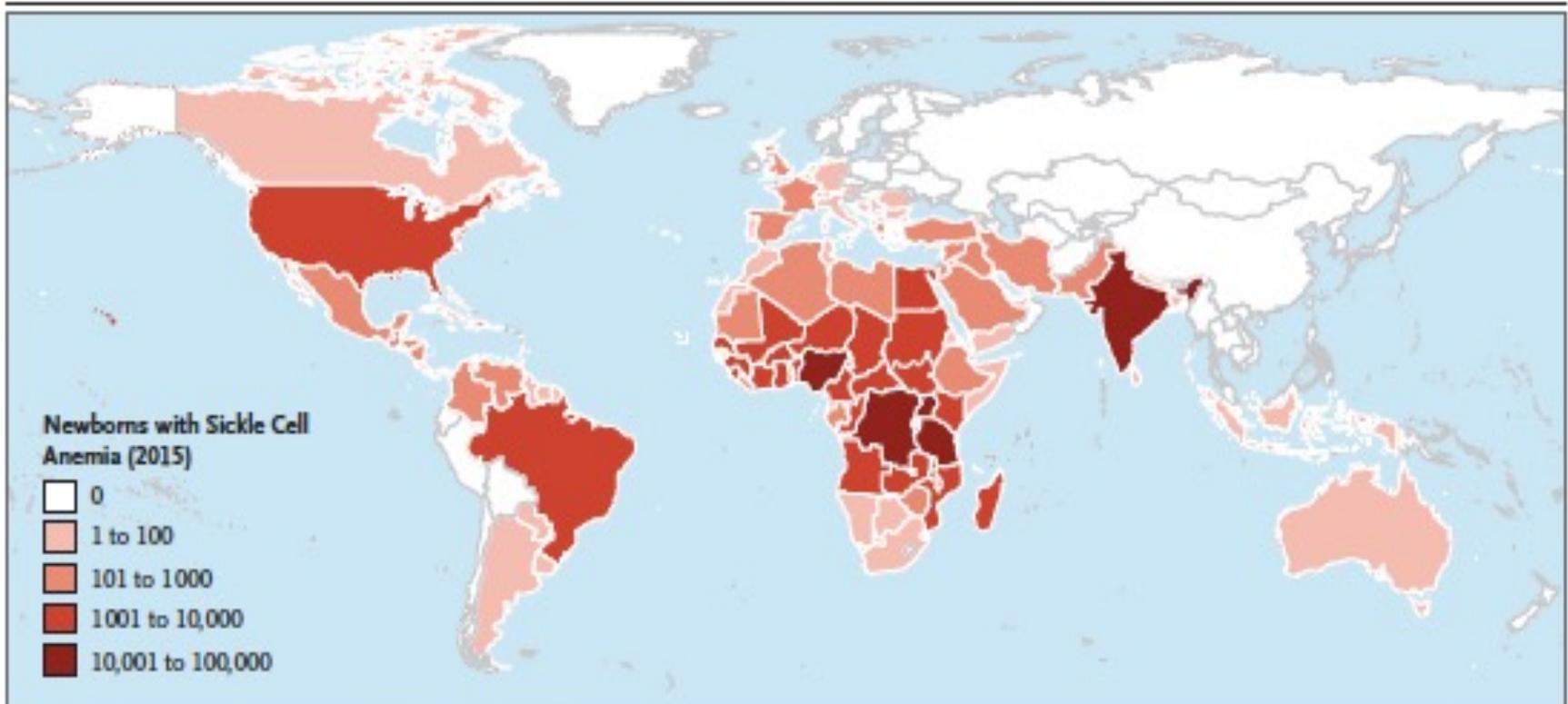
Discovery	Importance
1910 Sickled erythrocytes in Grenadan dental student <sup>2</sup>	First description of disease linked to abnormal erythrocytes
1924 Haemolysis in sickle-cell disease <sup>3</sup>	Explanation for anaemia, jaundice, and cholelithiasis
1924 Vaso-occlusion as cause of some pathological features <sup>4</sup>	Explanation for ischaemic tissue damage
1948 Abnormal electrophoretic mobility of sickle haemoglobin <sup>5</sup>	Identified pathophysiology to have a molecular basis
1948 No symptoms in infants noted <sup>6</sup>	Beneficial effects of high concentrations of fetal haemoglobin identified
1951 Characteristics of polymerisation of deoxygenated HbS <sup>7</sup>	Primary molecular mechanism identified
1980s Value of penicillin in young children with sickle-cell anaemia <sup>8,9</sup>	Reduced mortality, role of neonatal screening
1984 Bone marrow transplant in child with sickle-cell anaemia and leukaemia <sup>10</sup>	Identified potential cure
1995 Efficacy of hydroxycarbamide <sup>11</sup>	Only disease-modifying drug identified
1998 Reduced stroke incidence in children with abnormal transcranial dopplers who were given blood transfusion <sup>12</sup>	Primary stroke prevention with fall in stroke occurrence

Table 1: Important discoveries in the pathological and clinical features of sickle-cell disease in chronological order

# Sindromi falcemiche: genotipi

	Characteristics
<b>Severe sickle-cell disease</b> HbS/S ( $\beta 6\text{Glu}\rightarrow\text{Val}/\beta 6\text{Glu}\rightarrow\text{Val}$ ); sickle-cell anaemia HbS/ $\beta^0$ thalassaemia Severe HbS/ $\beta^+$ thalassaemia HbS/OArab ( $\beta 6\text{Glu}\rightarrow\text{Val}/\beta 121\text{Glu}\rightarrow\text{Lys}$ ) HbS/D Punjab ( $\beta 6\text{Glu}\rightarrow\text{Val}/\beta 121\text{Glu}\rightarrow\text{Gln}$ ) HbS/C Harlem ( $\beta 6\text{Glu}\rightarrow\text{Val}/\beta 6\text{Glu}\rightarrow\text{Val}/\beta 73\text{Asp}\rightarrow\text{Asn}$ ) HbC/S Antilles ( $\beta 6\text{Glu}\rightarrow\text{Lys}/\beta 6\text{Glu}\rightarrow\text{Val}, \beta 23\text{Val}\rightarrow\text{Ile}$ )  HbS/Quebec-CHORI ( $\beta 6\text{Glu}\rightarrow\text{Val}/\beta 87\text{Thr}\rightarrow\text{Ile}$ )	The most common form of sickle-cell disease Most prevalent in the eastern Mediterranean region and India <sup>14</sup> Most prevalent in the eastern Mediterranean region and India; 1–5% HbA present <sup>14</sup> Reported in north Africa, the Middle East, and the Balkans; relatively rare <sup>14</sup> Predominant in northern India but occurs worldwide <sup>14</sup> Electrophoretically resembles HbSC, but clinically severe; double mutation in $\beta$ -globin gene; very rare <sup>25</sup> Double mutation in $\beta$ -globin gene results in severe sickle-cell disease when co-inherited with HbC; very rare <sup>26</sup> Two cases described; resembles sickle-cell trait with standard analytical techniques <sup>7</sup>
<b>Moderate sickle-cell disease</b> HbS/C ( $\beta 6\text{Glu}\rightarrow\text{Val}/\beta 6\text{Glu}\rightarrow\text{Lys}$ ) Moderate HbS/ $\beta^+$ thalassaemia HbA/S Oman ( $\beta^0/\beta 6\text{Glu}\rightarrow\text{Val}, \beta 121\text{Glu}\rightarrow\text{Lys}$ )	25–30% cases of sickle-cell disease in populations of African origin <sup>13</sup> Most cases in the eastern Mediterranean region; 6–15% HbA present <sup>14</sup> Dominant form of sickle-cell disease caused by double mutation in $\beta$ -globin gene; very rare <sup>28</sup>
<b>Mild sickle-cell disease</b> Mild HbS/ $\beta^{++}$ thalassaemia HbS/E ( $\beta 6\text{Glu}\rightarrow\text{Val}/\beta 26\text{Glu}\rightarrow\text{Lys}$ )  HbA/Jamaica Plain ( $\beta^0/\beta 6\text{Glu}\rightarrow\text{Val}, \beta 68\text{Leu}/\text{Phe}$ )	Mostly in populations of African origin; 16–30% HbA present <sup>14</sup> HbE predominates in southeast Asia and so HbSE uncommon, although frequency is increasing with population migration <sup>19</sup> Dominant form of sickle-cell disease; double mutation results in Hb with low oxygen affinity; one case described <sup>29</sup>
<b>Very mild sickle-cell disease</b> HbS/HPPH  HbS/other Hb variants	Group of disorders caused by large deletions of the $\beta$ -globin gene complex; typically 30% fetal haemoglobin <sup>14</sup> HbS is co-inherited with many other Hb variants, and symptoms develop only in extreme hypoxia
Genotypes that have been reported to cause sickle-cell disease are listed. All include at least one copy of the $\beta^S$ allele, in combination with one or more mutations in the $\beta$ -globin gene. HbS= sickle haemoglobin. HbA= haemoglobin variant A. HbE= haemoglobin variant E. Hb= haemoglobin.	
<b>Table 2: Different types of sickle-cell disease</b>	

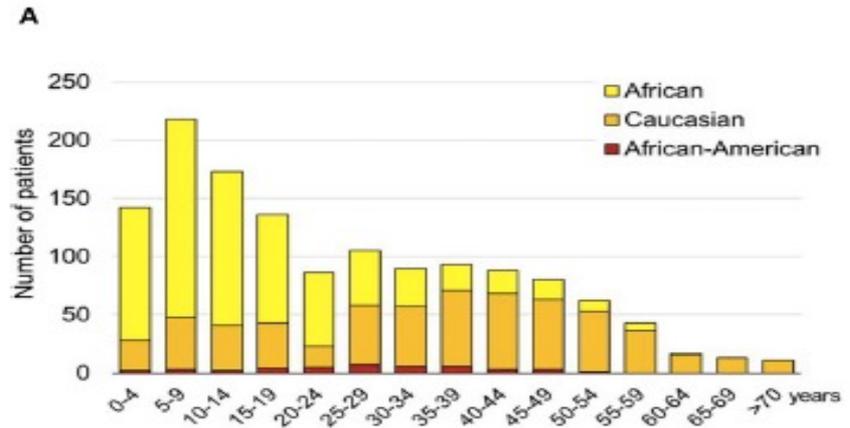
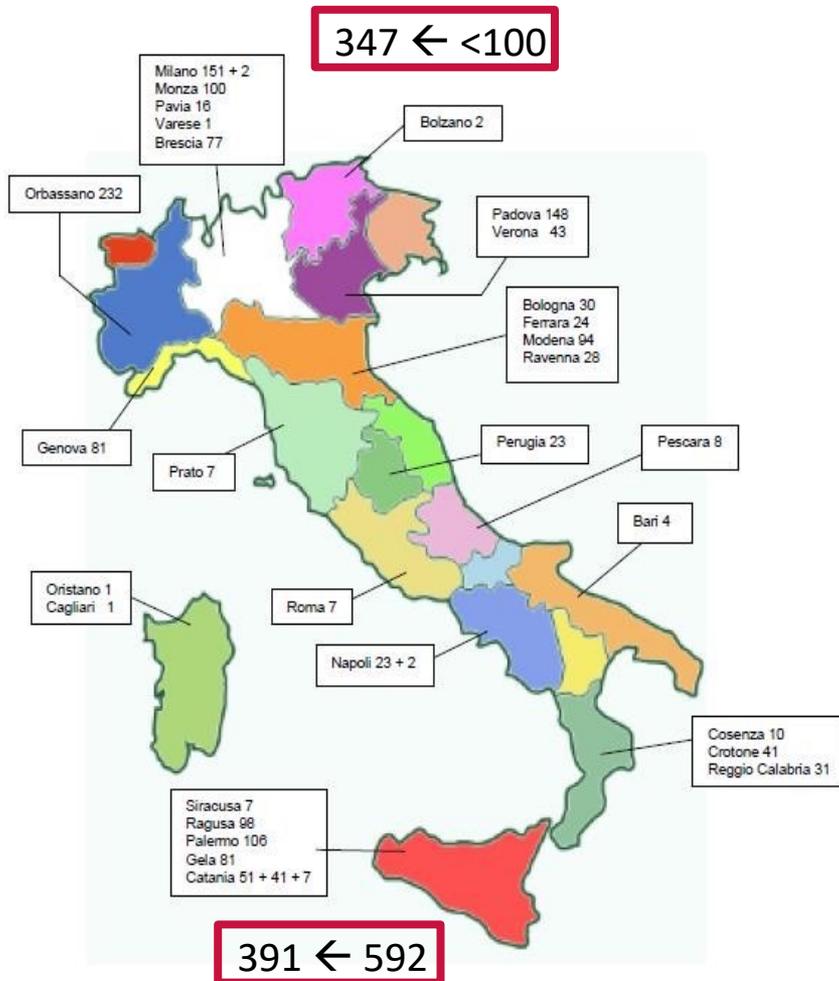
# Una delle più comuni patologie ereditarie monogeniche



**Figure 1.** Number of Newborns with Sickle Cell Anemia in Each Country in 2015.

Data are based on estimates from Piel et al.<sup>1</sup> Alaska is shown separately from the rest of the United States.

# Survey SITE del 2018: 1579 pazienti



Ethnicity	Genotype	Counts (%)	Males (%)	Median age (IQR), yr
<b>African (n = 769)</b>	HbSS	548 (71.3)	280 (51.2)	11 (6.9–19.8)
	HbS/β <sup>0</sup> -thalassemia	18 (2.3)	12 (66.7)	14.5 (9.5–19.8)
	HbS/β <sup>+</sup> -thalassemia	30 (3.9)	16 (53.3)	26.5 (15.6–37.5)
	HbSC	160 (20.8)	78 (48.8)	16.9 (7.8–27.0)
	Not defined	13 (1.7)	3 (23.1)	40 (12–46)
<b>Caucasian (n = 756)</b>	HbSS	162 (21.4)	76 (46.9)	35.4 (18–48)
	HbS/β <sup>0</sup> -thalassemia	263 (34.8)	38 (52.5)	40 (27–50)
	HbS/β <sup>+</sup> -thalassemia	300 (39.7)	61 (53.7)	39 (25–51)
	HbSC	4 (0.5)	3 (75.0)	31.5 (20–40.8)
	Not defined	27 (3.6)	14 (51.9)	31.9 (22–45)
<b>African-American (n = 45)</b>	HbSS	24 (53.3)	9 (37.5)	29 (22.6–36.2)
	HbS/β <sup>0</sup> -thalassemia	4 (8.9)	2 (50.0)	12.5 (6.8–23.2)
	HbS/β <sup>+</sup> -thalassemia	4 (8.9)	1 (25.0)	25 (9.5–41.5)
	HbSC	13 (28.9)	4 (30.8)	27.5 (21–35)

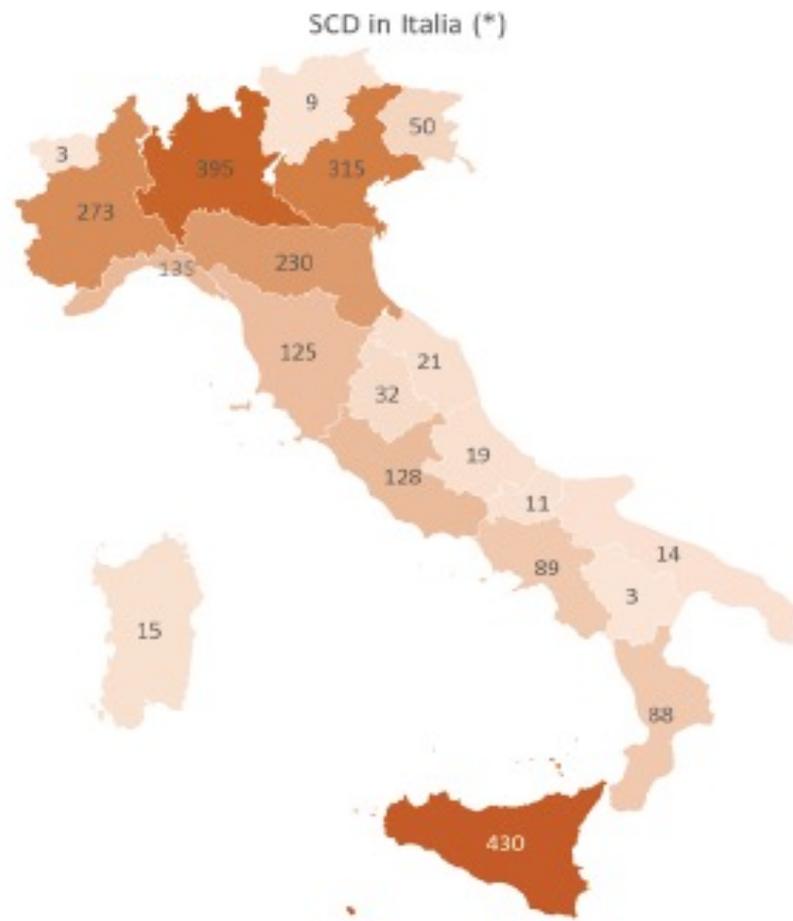
Dati Caritas del 2000: 928 pazienti

Graziadei G, De Franceschi L, *Frontiers in Medicine* 2022

# Survey SITE del 2024: 2385 pazienti (totale 9570)



(\*) <https://www.site-italia.org/contatti/centri-regionali.html>

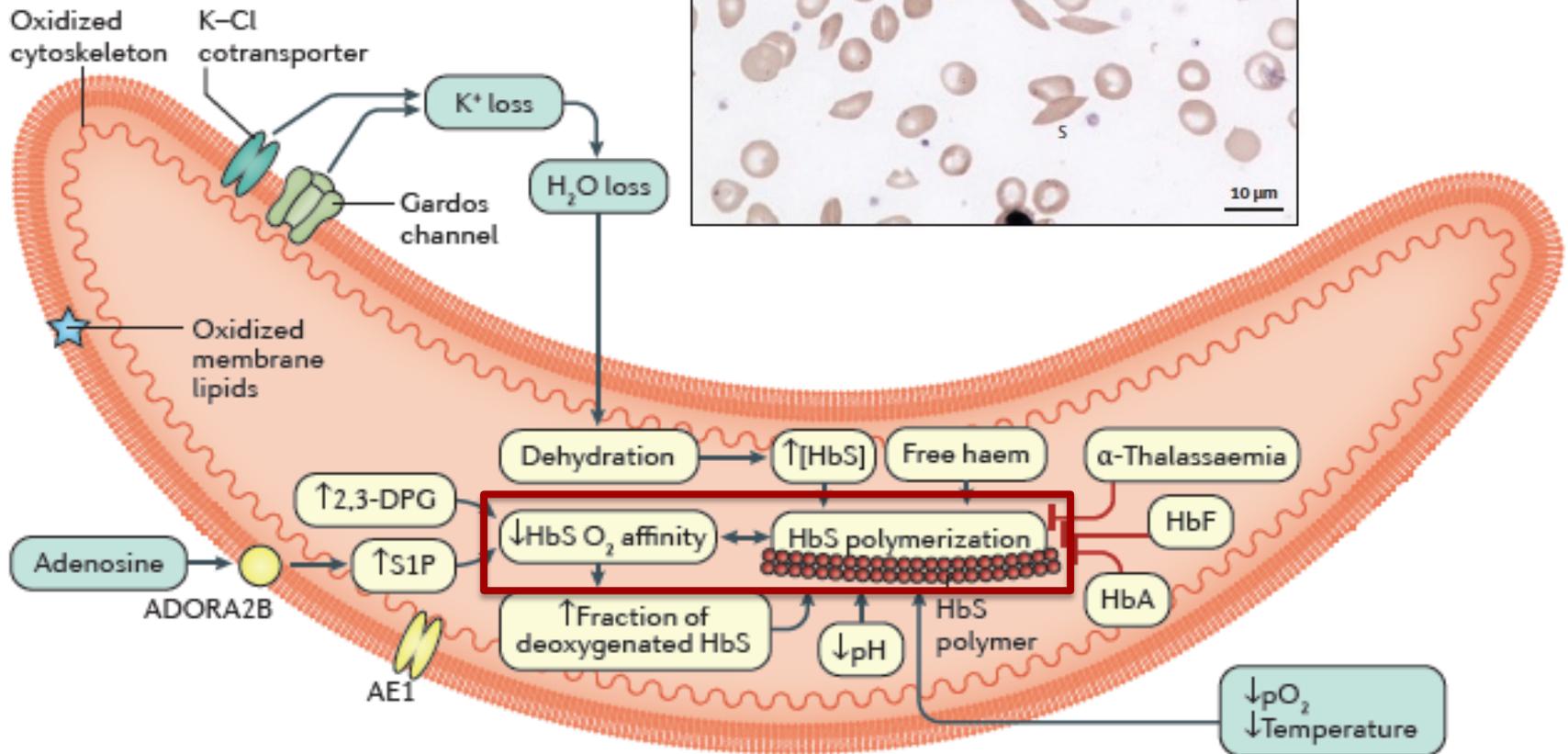
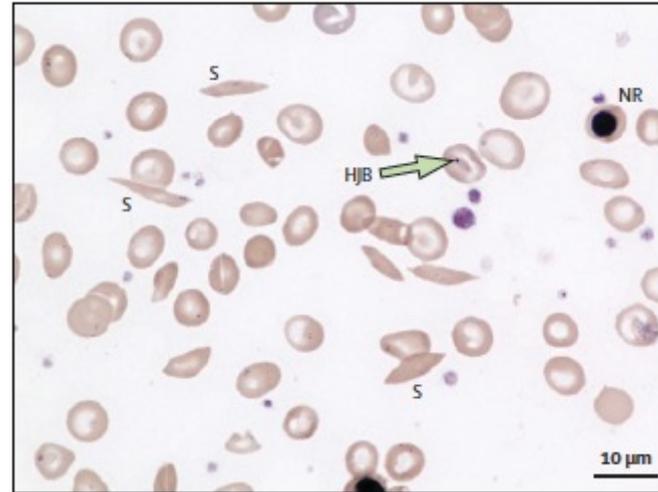


(\*) <https://www.site-italia.org/contatti/centri-regionali.html>

Con tecnologia Bing  
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(\*) <https://www.site-italia.org/contatti/centri-regionali.html>

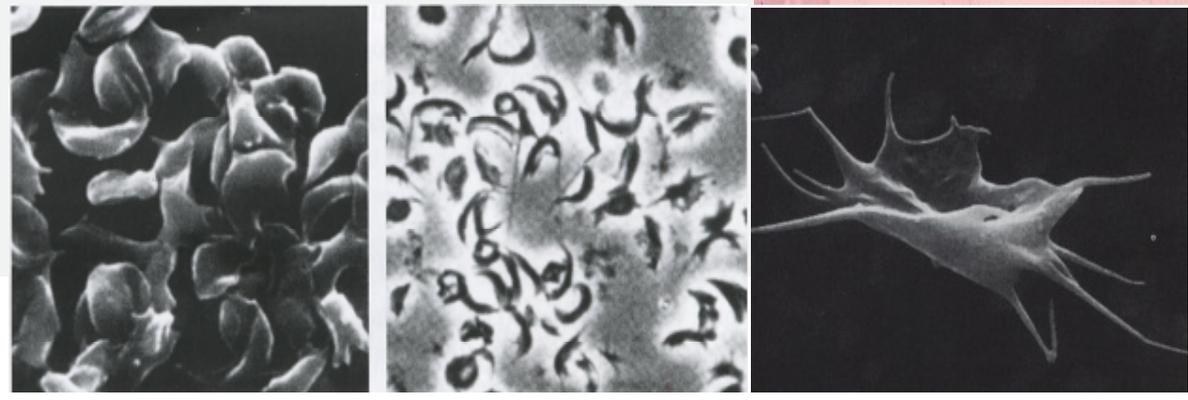
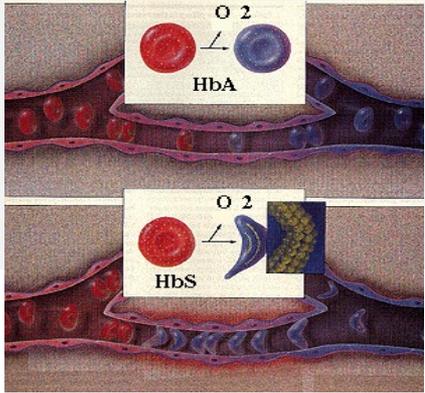
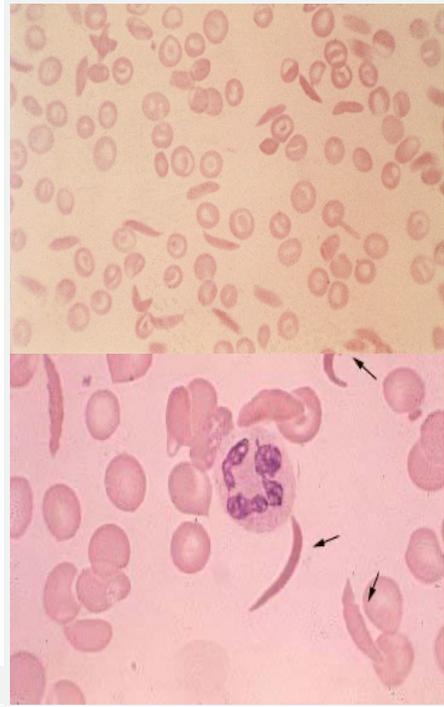
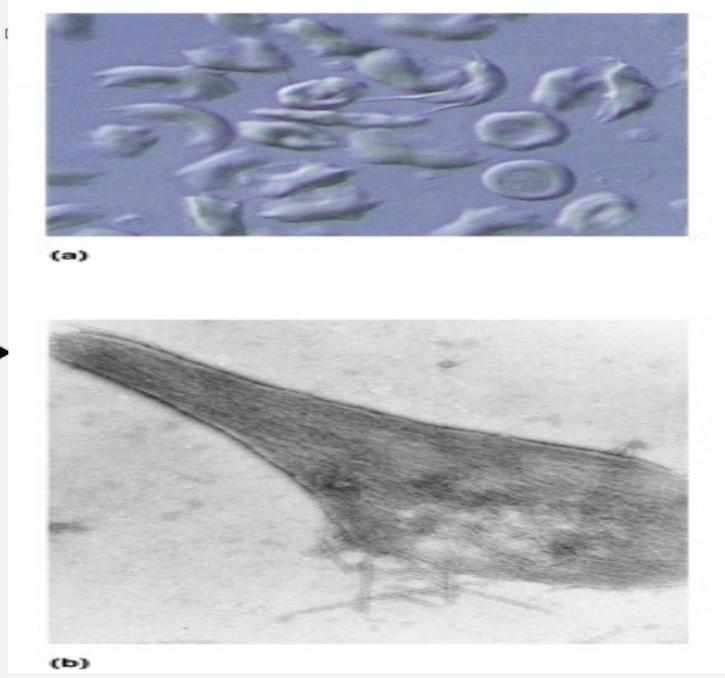
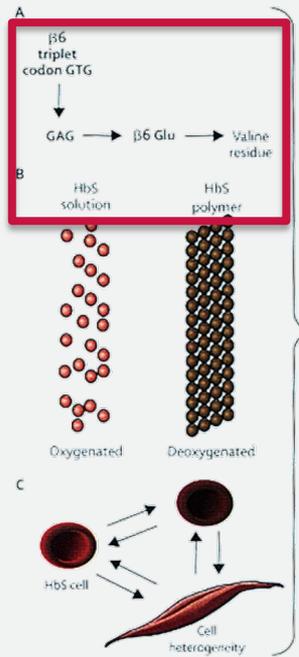
# Eritrocita falcemico



$\beta^S \rightarrow \alpha_2\beta^S_2 - \text{HbS} \rightarrow$  peculiari caratteristiche biochimiche ( $\downarrow$ affinità per l' $\text{O}_2$ )

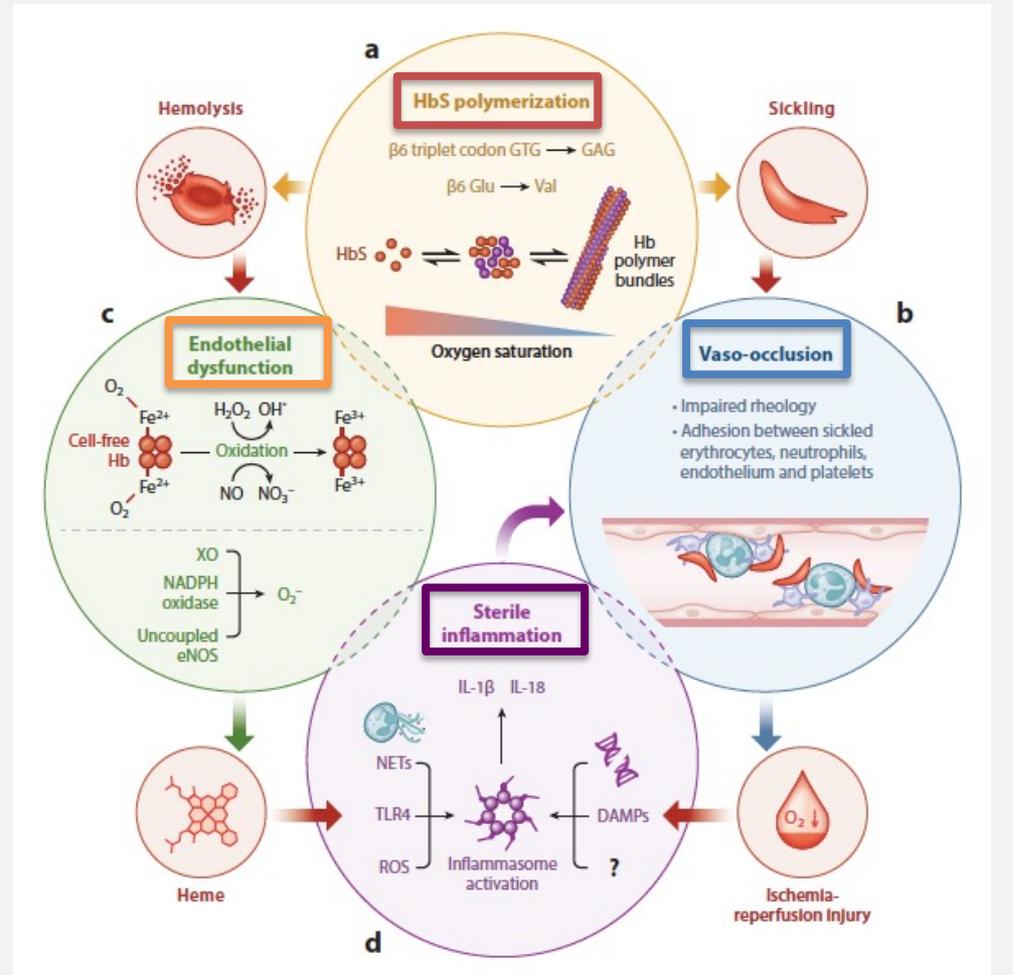
*Kato GJ, Nature Review Disease Primers 2018  
Piel FP, N Engl J Med 2017*

# Morfologia eritrocitaria e falcizzazione



# Fisiopatologia e targets terapeutici

- a. Polimerizzazione HbS, falcizzazione, emolisi, anemia
- b. Vasocclusione, adesione
- c. Danno endoteliale da emolisi
- d. Infiammazione "asettica"

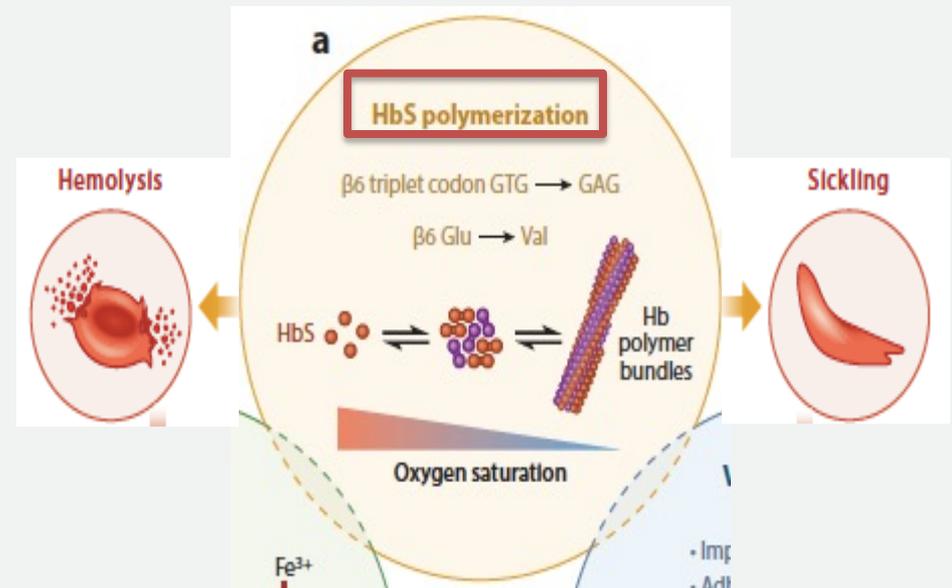


Prithu Sundd,<sup>1,2,3,\*</sup> Mark T. Gladwin,<sup>1,2,3,\*</sup>  
 and Enrico M. Novelli<sup>2,3,4,\*</sup>

Annu. Rev. Pathol. Mech. Dis. 2019. 14:263–92

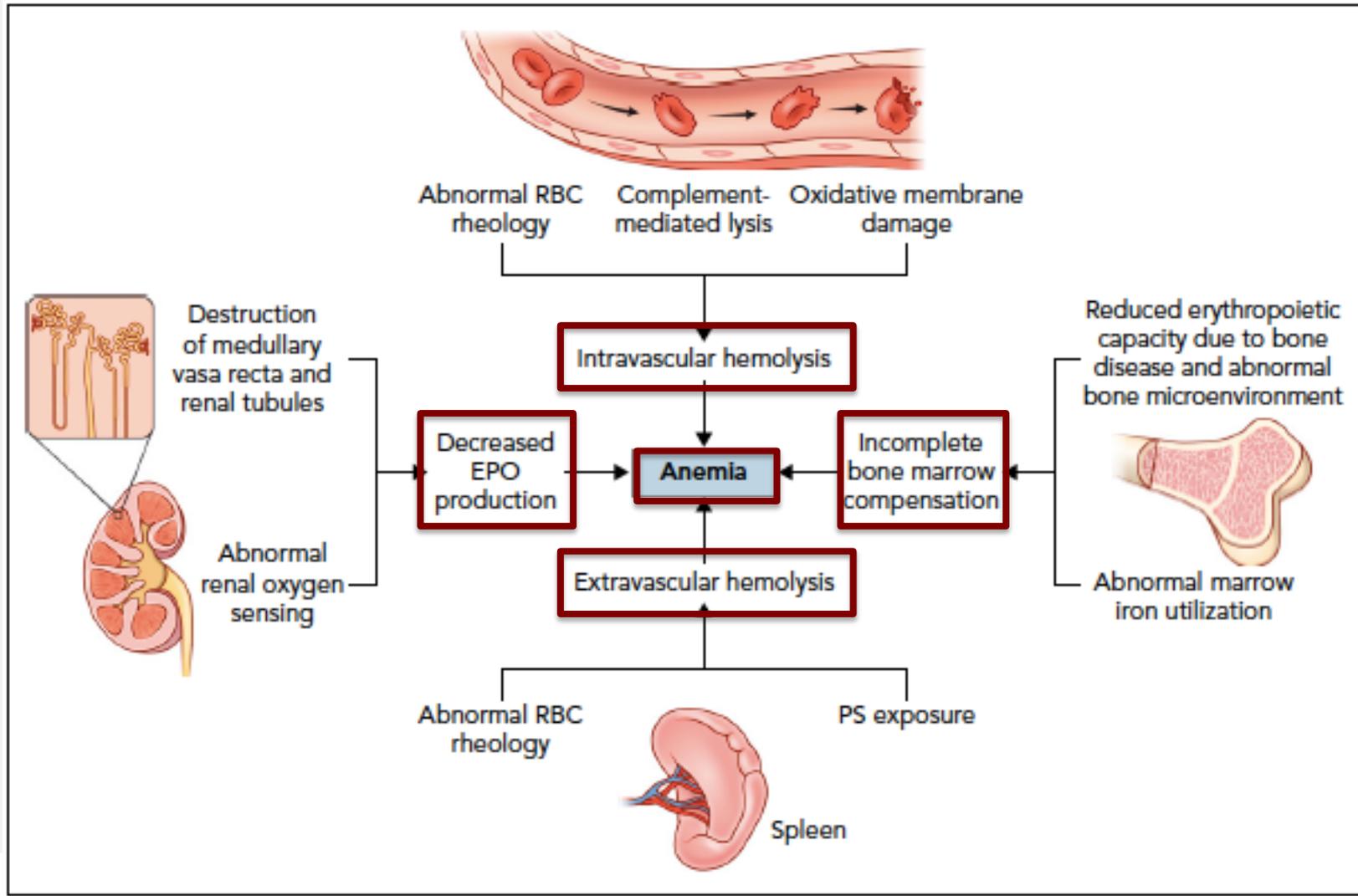
# Polimerizzazione - Emolisi

- **Variante emoglobinica HbS:** mutazione missenso di un singolo nucleotide in posizione 17 (GAT → GTG) sul gene  $\beta$ -globinico [HBB] e **sostituzione di acido glutammico con valina del sesto aminoacido [Glu6Val, rs334]** sulla catena  $\beta$ -globinica
- → sacca idro-fobica nel tetramero di HbS deOx → legame tra le catene  $\beta 1$  e  $\beta 2$  di due molecole Hb
- **Cristallizzazione** → polimeri che saturano l'eritrocita e ne alterano l'architettura e la flessibilità → **deidratazione**
- Il tasso e l'estensione della polimerizzazione è proporzionale alla durata della disidratazione ed alla concentrazione di HbS intraeritrocitaria



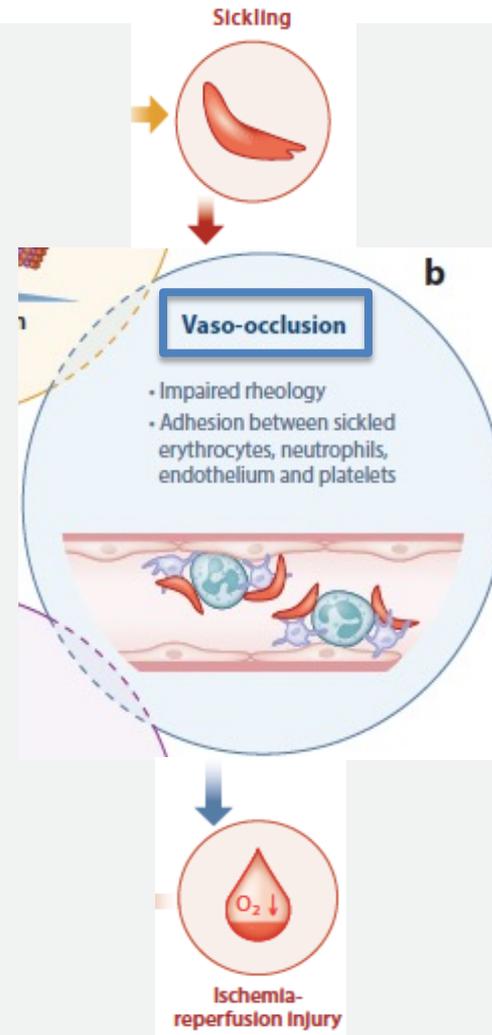
$\beta^S \rightarrow \alpha_2\beta^S_2$  - HbS → peculiari caratteristiche biochimiche:  
↓ **affinità per l'O<sub>2</sub>**

# Fisiopatologia dell'anemia in SCD

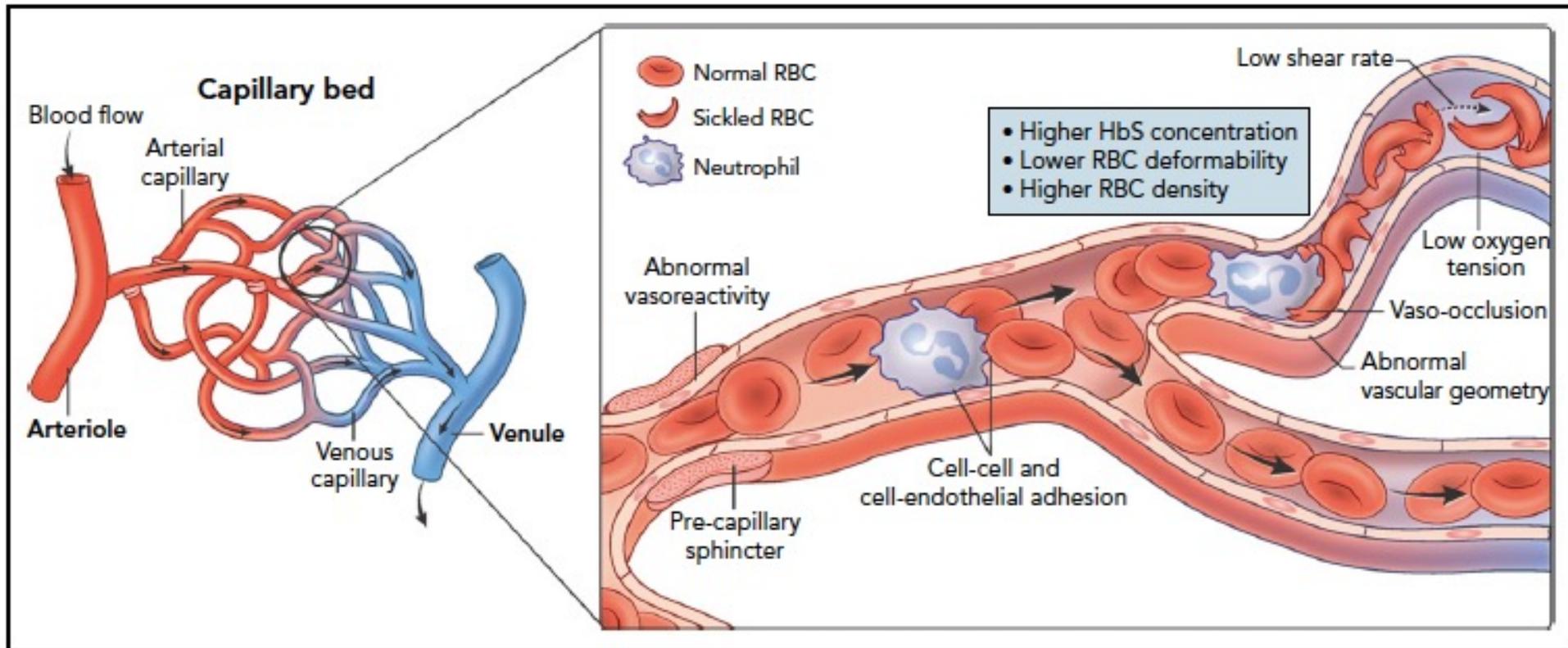


# Vaso-occlusione

- **Polimeri di HbS** →
  - falcizzazione eritrocitaria →
    - alterazione della reologia
    - aggregazione degli eritrociti falcemici
    - adesione con neutrofili, piastrine e cellule endoteliali
  - stasi ematica
  - vaso-occlusione
- **Vaso-occlusione** →
  - fenomeno di ischemia-riperfusion (I-R)
  - emolisi con rilascio di Hb libera nel sangue

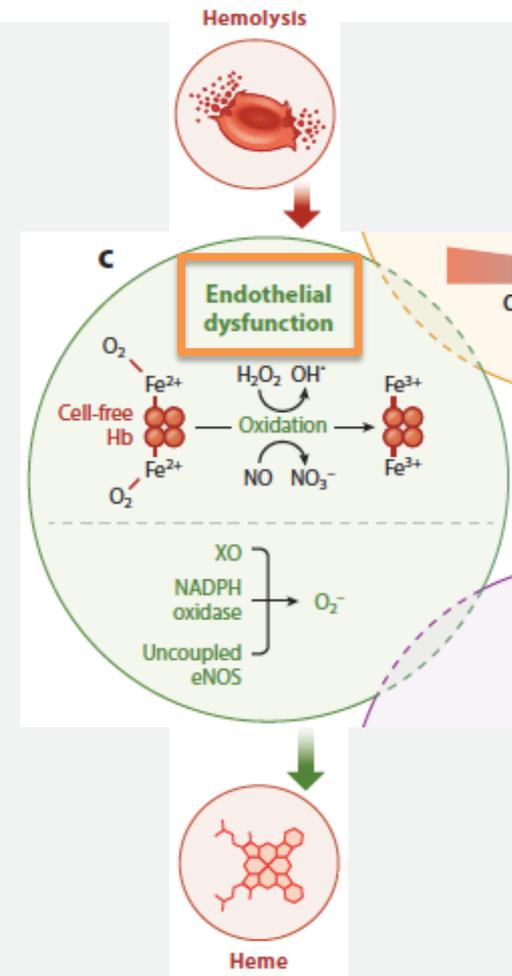


# Fisiopatologia della vaso-occlusione in SCD



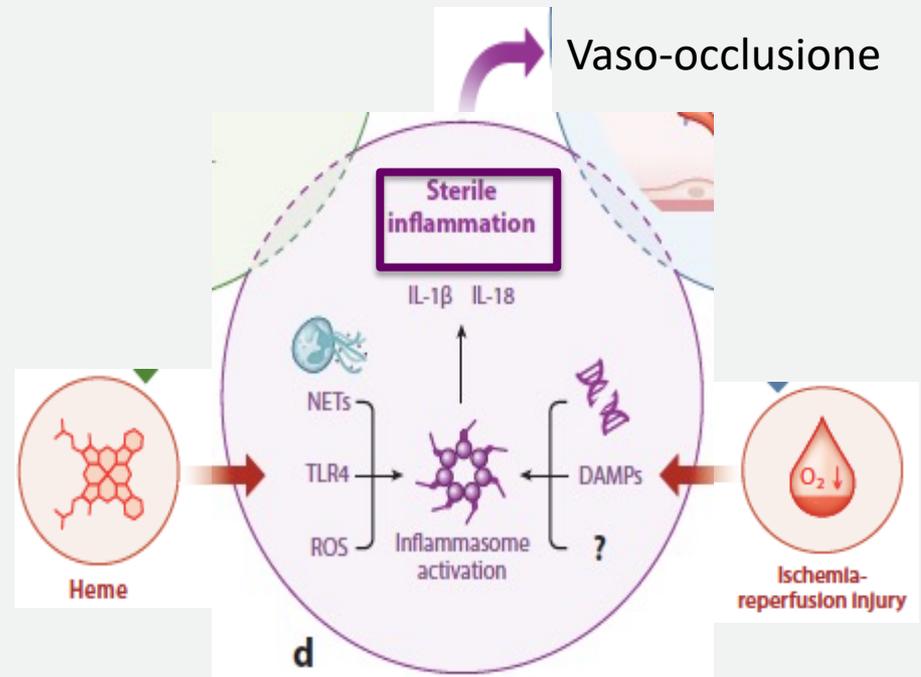
# Danno endoteliale

- **Hb Ox** Hb Ox ( $\text{Fe}^{2+}$ ) →
  - **disfunzione endoteliale** →
    - **inattivazione di NO da parte di Hb libera e di  $\text{O}^-$  da degradazione di arginina**
    - deplezione di NO per formare nitrati ( $\text{NO}^3$ ) e metaemoglobina ( $\text{Fe}^{3+}$ )
    - reazione di  $\text{O}_2$  con  $\text{H}_2\text{O}_2$  (Reazione di Fenton) → idrossi radicali liberi ( $\text{OH}\bullet$ ) e metaemoglobina ( $\text{Fe}^{3+}$ )
    - NADPH e xantina ossidasi e NO sintasi endoteliale (eNOS) genera radicali liberi  $\text{O}_2^-$
    - degradazione di metaemoglobina ( $\text{Fe}^{3+}$ ) causa **rilascio di eme plasmatico libero, che costituisce il “major erythrocyte damage associated molecular pattern” (DAMP)**
    - esposizione di fosfatidilserina su outlayer
    - overexpression di Tissue Factor



# Infiammazione asettica

- **L'eme o il danno da ischemia-riperfusion inducono la formazione di Reactive Oxygen Species (ROS)** generation, Toll-like receptor 4 (TLR4) activation, neutrophil extracellular trap (NET) generation, release of tissue or cell-derived DAMPs, DNA, and other unknown factors (?) → infiammazione asettica, tramite
- **Attivazione della via infiammatoria nelle cellule endoteliali ed "infiammatorie" → rilascio di IL-1 $\beta$**
- L'infiammazione asettica promuove la vaso-occlusione attraverso lo stimolo all'adesione di neutrofili, piastrine e cellule endoteliali



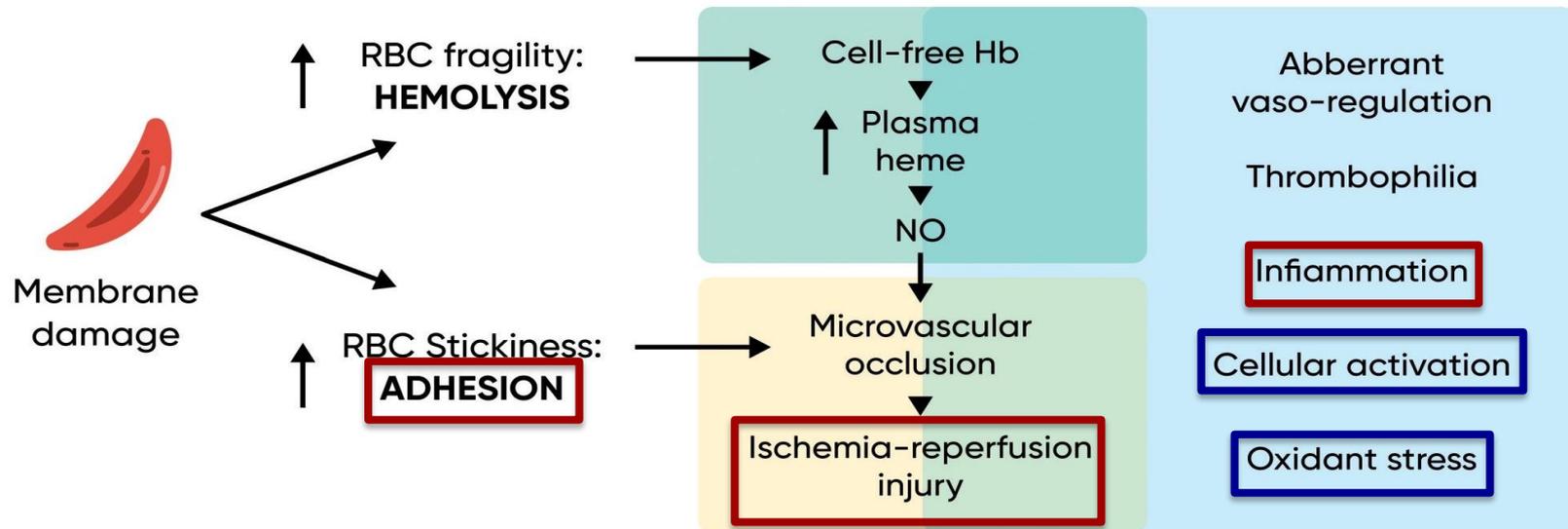


# New insights into the pathophysiology and development of novel therapies for sickle cell disease

Scott Moerdler<sup>1,2</sup> and Deepa Manwani<sup>1,3</sup>

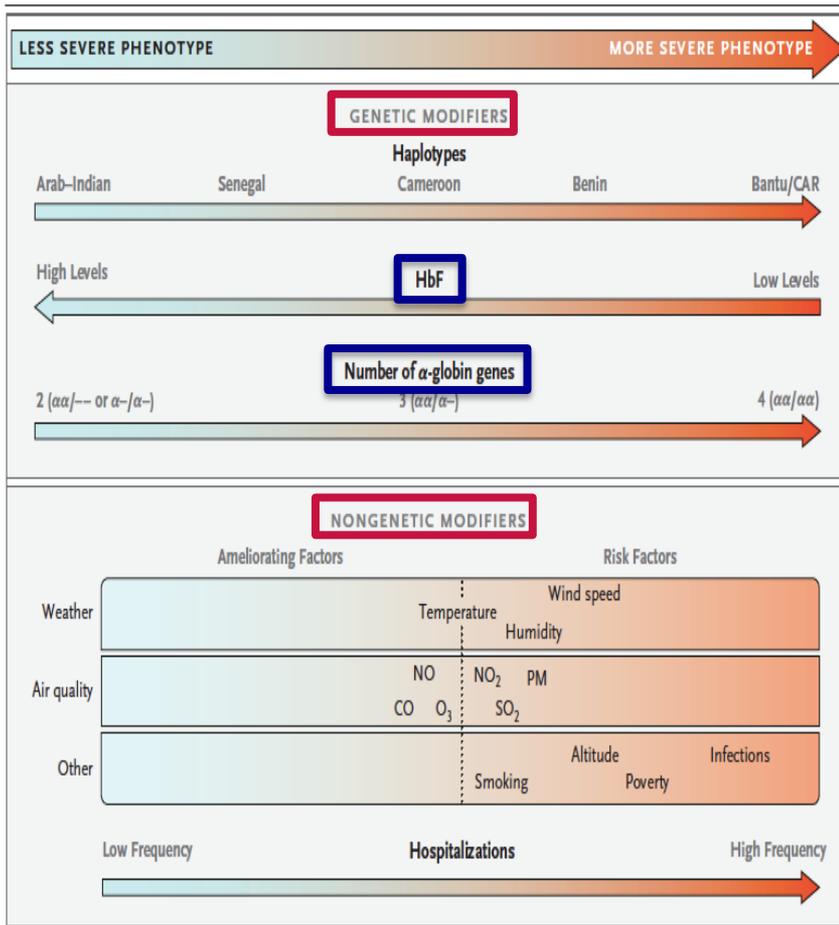
<sup>1</sup>Children's Hospital, Montefiore Medical Center, Bronx, NY; and <sup>2</sup>Department of Microbiology and Immunology and <sup>3</sup>Division of Pediatric Hematology, Oncology, Marrow and Blood Cell Transplantation, Albert Einstein College of Medicine, Bronx, NY

Hematology 2018

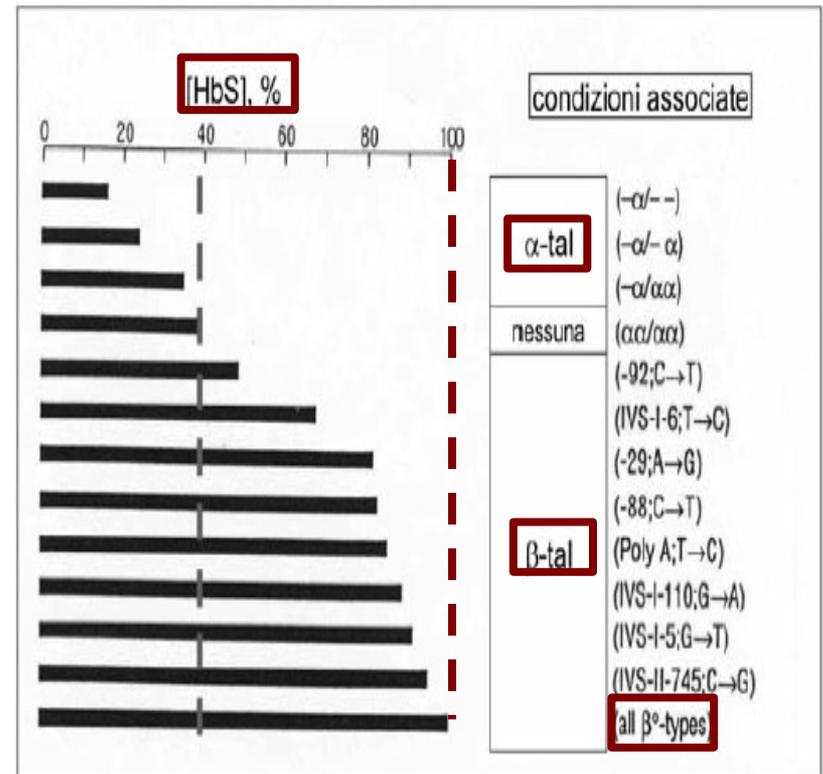


Carden MA, Haematologica 2019

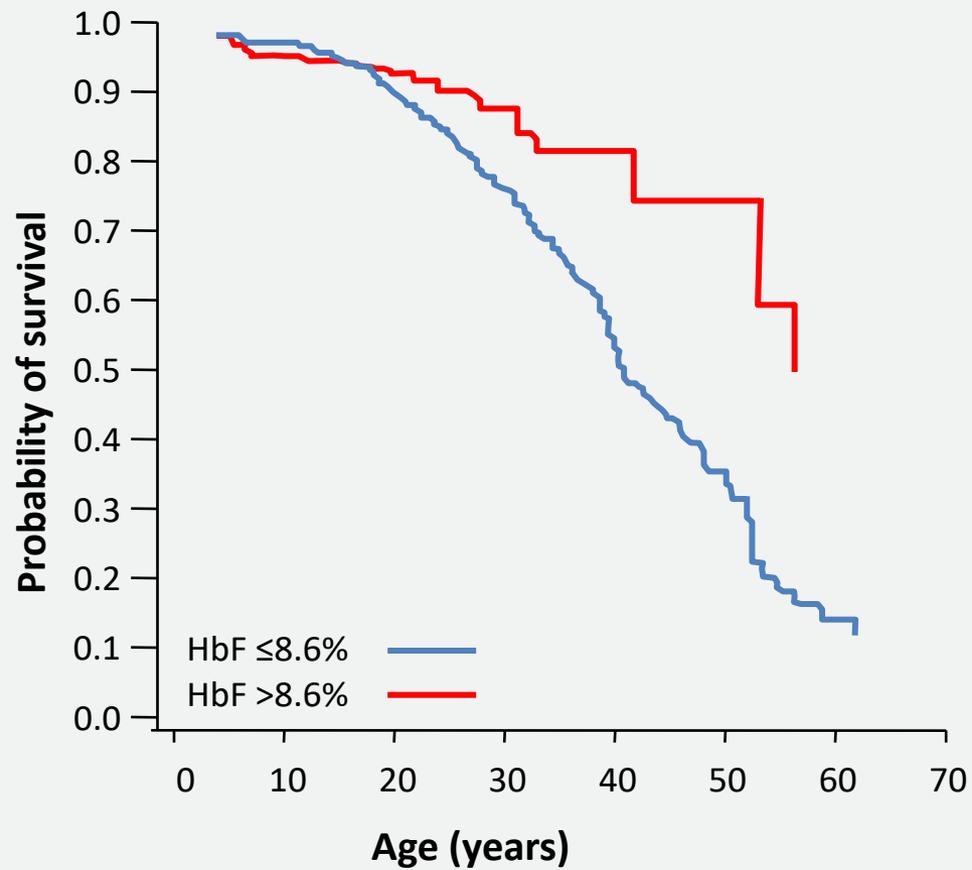
# Modificatori della gravità del quadro clinico



## Coeredità di alleli talassemici

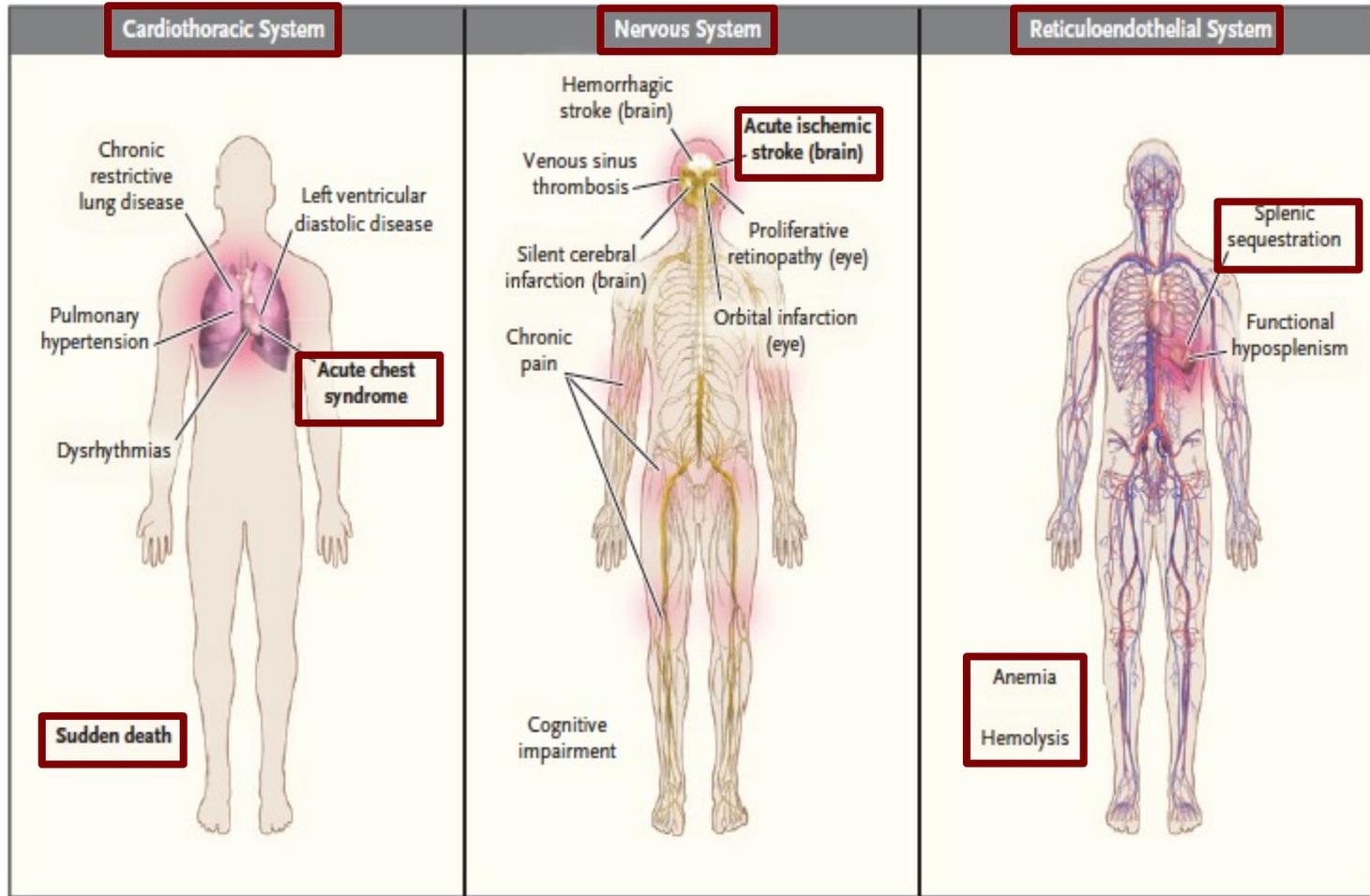


# Sopravvivenza

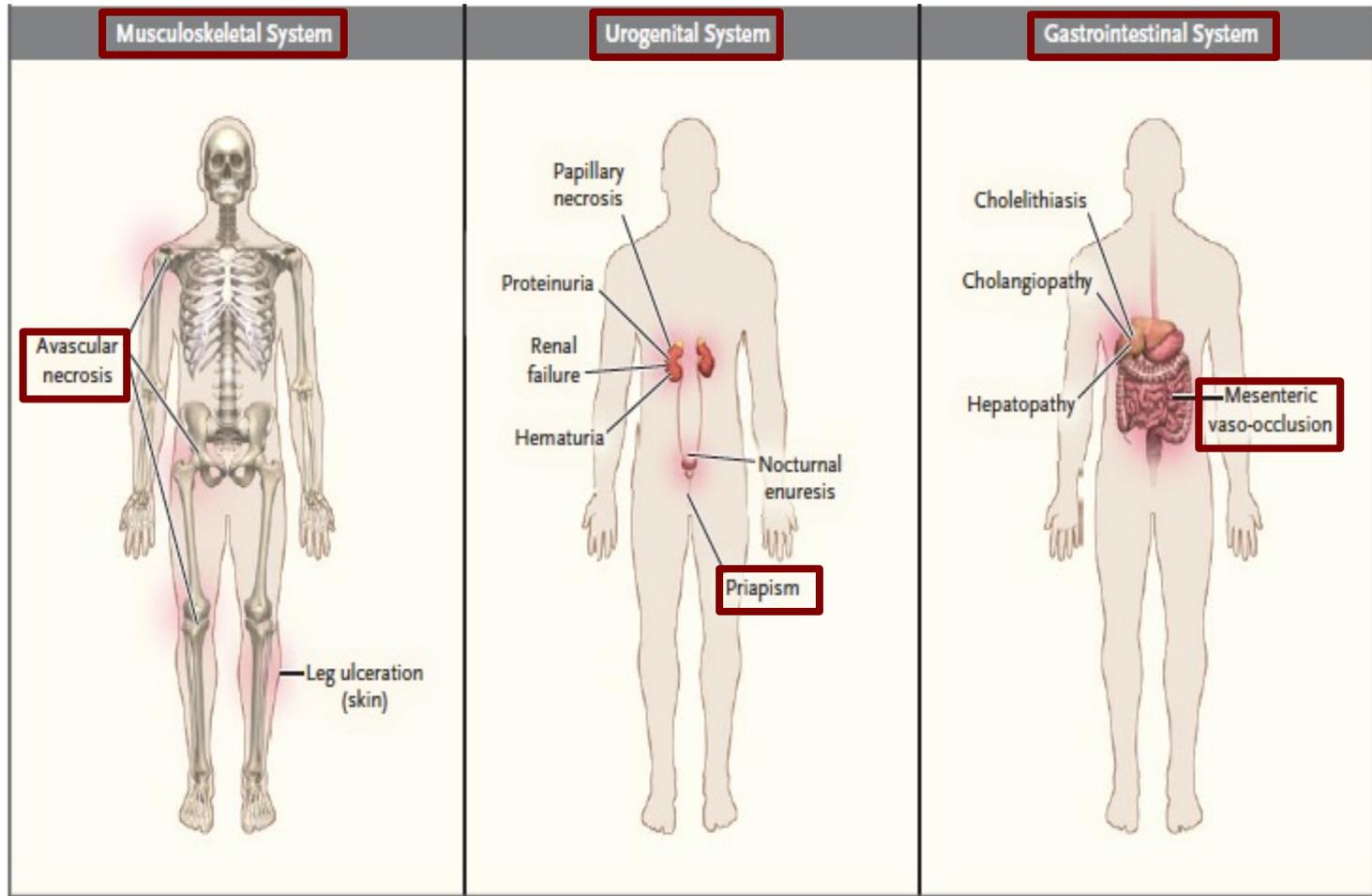


Platt OS, et al. N Engl J Med 1994

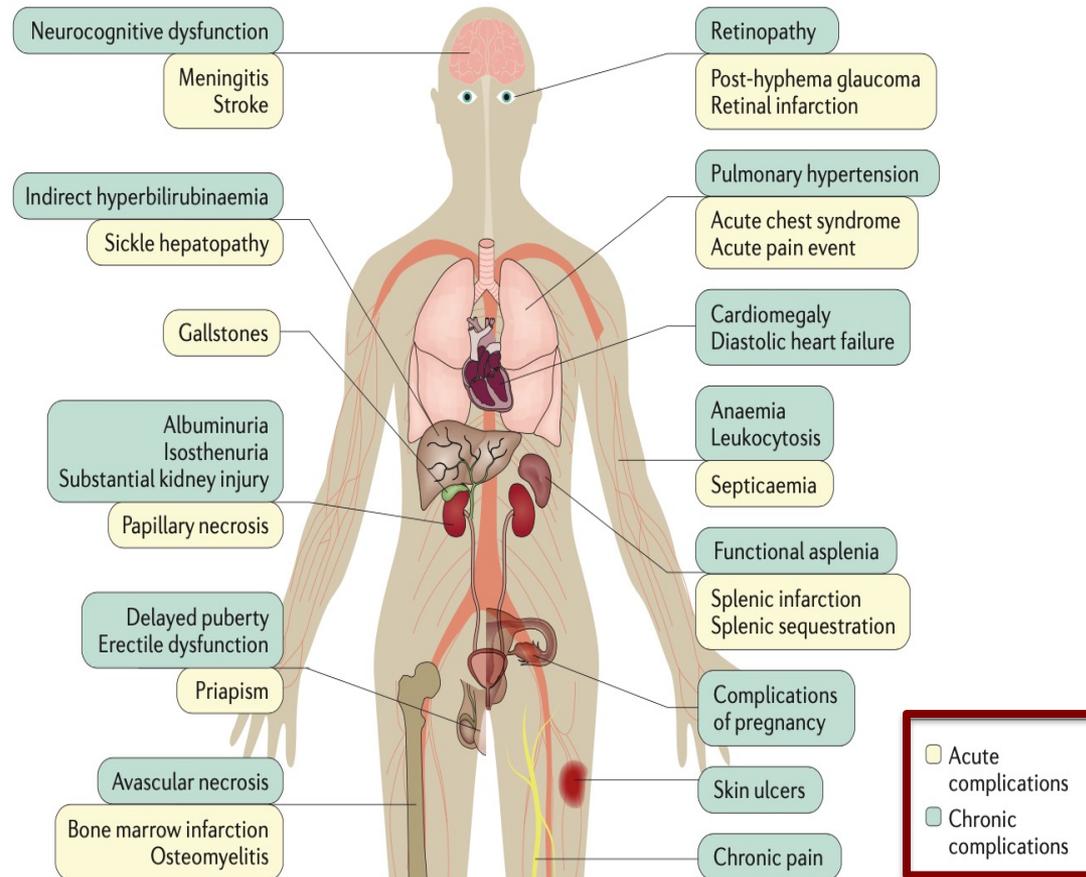
# Clinica: complicate



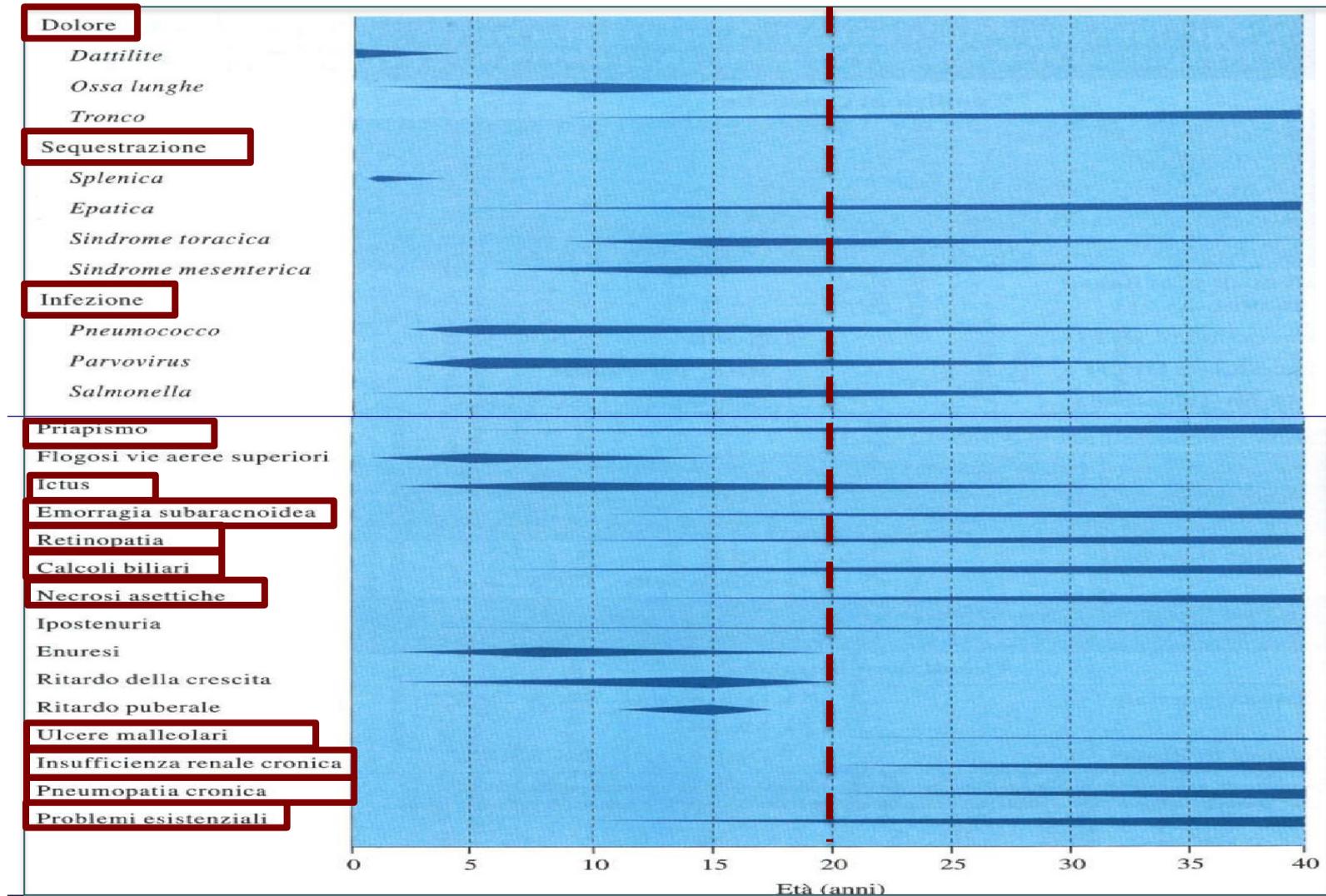
# Clinica: complicanze



# Complicanze acute e croniche



# Complicanze: insorgenza e sedi coinvolte



# Criteri di depistage e di accesso in Pronto Soccorso

	ELEMENTO	NOTE
Anamnesi	<ul style="list-style-type: none"> <li>Gruppo etnico</li> <li>Anemia emolitica cronica</li> <li>Dolori ricorrenti</li> <li>Infezioni ricorrenti</li> <li>Episodi di priapismo</li> <li>Sindrome mani-piedi nei primi 5 anni di vita</li> </ul>	Ossei, addominali, migranti etc Polmonari, ossee etc.
Esame obiettivo	<ul style="list-style-type: none"> <li>Pallore cute e mucose</li> <li>Sub-ittero o ittero franco</li> <li>Splenomegalia</li> </ul>	Tende a diminuire con l'età
Possibile presentazione clinica confondente	<ul style="list-style-type: none"> <li>Crisi aplastica</li> <li>Osteomielite</li> <li>Broncopolmonite</li> <li>Stroke</li> <li>Sequestro splenico</li> </ul>	Queste manifestazioni possono costituire l'esordio della SCD

SINTOMI	LABORATORIO
<ul style="list-style-type: none"> <li>Aspetto sofferente</li> <li>Temperatura <math>\geq 39^{\circ}\text{C}</math> o febbre con precedente storia di sepsi da <i>S.pneumoniae</i></li> <li>Sintomi respiratori e/o dolore toracico</li> <li>Sintomi neurologici rilevanti</li> <li>Dolore addominale</li> <li>Ittero franco</li> <li>Ematuria macroscopica</li> <li>Eventi successivi alla trasfusione (da quattro ore a quindici giorni)</li> <li>Ipotensione</li> <li>Disidratazione</li> <li>Crisi falcemica in gravidanza</li> <li>Priapismo prolungato</li> </ul>	<ul style="list-style-type: none"> <li>WBC <math>\geq 30.000/\mu\text{l}</math> o <math>\leq 5.000/\mu\text{l}</math></li> <li>PLT <math>\leq 100.000/\mu\text{l}</math></li> <li>Hb <math>\leq 7</math> gr/dl</li> <li>Alterata disfunzione renale (creatinina, azotemia, eGFR)</li> <li>Segni di DIC (PLT <math>\leq 70.000/\mu\text{l}</math>; allungamento dei tempi di coagulazione e riduzione significativa del fibrinogeno)</li> </ul>

# Drepanocitosi: un'emergenza clinica

- La Drepanocitosi è la **terza emergenza medica dopo Infarto Miocardico Acuto e Stroke**
- Le manifestazioni cliniche acute della Drepanocitosi sono definite **“time-dependent”**

*Forni GL, Intern Emerg Med. 2019 Oct;14(7):1051-1064*



**TO THE EDITOR:**

## Access to emergency departments for acute events and identification of sickle cell disease in refugees

Lucia De Franceschi,<sup>1</sup> Caterina Lux,<sup>2</sup> Frédéric B. Piel,<sup>3</sup> Barbara Giansin,<sup>4</sup> Federico Bonetti,<sup>5</sup> Maddalena Casale,<sup>6</sup> Giovanna Graziadei,<sup>7</sup> Roberto Lisi,<sup>8</sup> Valeria Pinto,<sup>4</sup> Maria Caterina Putti,<sup>9</sup> Paolo Rigano,<sup>10</sup> Rossellina Rosso,<sup>11</sup> Giovanna Russo,<sup>12</sup> Vincenzo Spadola,<sup>13</sup> Claudio Pulvirenti,<sup>14</sup> Monica Rizzi,<sup>1</sup> Filippo Mazzi,<sup>1</sup> Giovanbattista Ruffo,<sup>15</sup> and Gian Luca Forni<sup>4</sup>

 **blood**\* 9 MAY 2019 | VOLUME 133, NUMBER 19

# Algoritmo

Forni et al. *Orphanet Journal of Rare Diseases* 2014, **9**:91  
<http://www.ojrd.com/content/9/1/91>



LETTER TO THE EDITOR

Open Access

## Development of interactive algorithm for clinical management of acute events related to sickle cell disease in emergency department

Gian Luca Forni<sup>1</sup>, Gabriele Finco<sup>2</sup>, Giovanna Graziadei<sup>4</sup>, Manuela Balocco<sup>1</sup>, Paolo Rigano<sup>5</sup>, Silverio Perrotta<sup>6</sup>, Oliviero Olivieri<sup>7</sup>, Maria Domenica Cappellini<sup>3,4\*</sup> and Lucia De Franceschi<sup>7</sup>

### Abstract

Sickle cell disease (SCD ORPHA232; OMIM 603903) is a rare hereditary red cell disorder, which global distribution is changed in the last decade due to immigration-fluxes from endemic areas to Western-countries. One of the main clinical manifestations of SCD are the acute painful vaso-occlusive crisis, which cause frequent accesses of SCD patients to the emergency departments (EDs). This has generated the requirement of feasible tools for emergency givers. In the context of the scientific-Italian-Society for the study of Thalassemias and Hemoglobinopathies (SITE), we developed an algorithm with interactive windows to guide physicians in managing SCD patients in EDs.

**Keywords:** Sickle cell disease, Acute vaso-occlusive crisis, Emergency departments, Pain



Collana Scientifica SITE  
Opinione di esperti

## ALGORITMO PER LA GESTIONE IN PRONTO SOCCORSO DEGLI EVENTI ACUTI NEI PAZIENTI AFFETTI DA ANEMIA FALCIFORME

Gian Luca Forni<sup>1</sup>, Manuela Balocco<sup>1</sup>, Maddalena Casale<sup>2</sup>, Paolo Cremonesi<sup>3</sup>, Gabriele Finco<sup>4</sup>, Giovanna Graziadei<sup>5</sup>, Silverio Perrotta<sup>2</sup>, Valeria Pinto<sup>1</sup>, Enrico Polati<sup>6</sup>, Paolo Rigano<sup>7</sup>, Giacomo Robello<sup>1</sup>, Alessandra Rosa<sup>1</sup>, Giovanna Russo<sup>8</sup>, Laura Sainati<sup>9</sup>, Vittorio Schweiger<sup>6</sup>, Aurora Vassanelli<sup>10</sup>, Pietro Bonomo<sup>11</sup>, Oliviero Olivieri<sup>12</sup>, Maria Domenica Cappellini<sup>5</sup>, Lucia De Franceschi<sup>12</sup>

<sup>1</sup> Centro della Microcitemia e Anemie Congenite, E.O. Ospedali Galliera, Genova

<sup>2</sup> Dipartimento della Donna, del Bambino, Università della Campania "L. Vanvitelli, Napoli

<sup>3</sup> S.C. Medicina e Chirurgia d'Accettazione e d'Urgenza E.O. Ospedali Galliera, Genova

<sup>4</sup> Rianimazione e Terapia Intensiva Presidio San Giovanni di Dio, Università di Cagliari, Cagliari

<sup>5</sup> Centro anemie congenite, Policlinico di Milano, Milano

<sup>6</sup> Dipartimento di Chirurgia, sezione di Anestesia, Università di Verona, Verona

<sup>7</sup> U.O.C. Ematologia II con Talassemia, Ospedali Riuniti P.O. Cervello Palermo, Palermo

<sup>8</sup> Centro di riferimento di ematologia pediatrica, Università di Catania, Catania

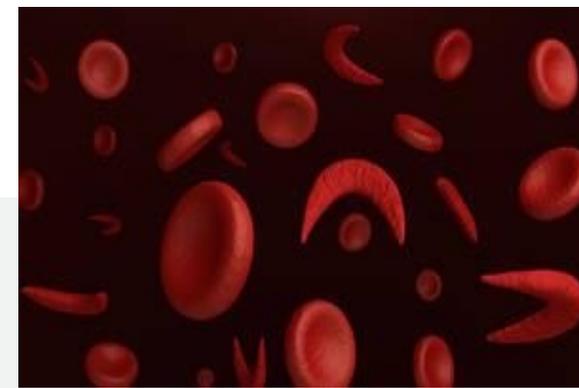
<sup>9</sup> Clinica di Pediatria Oncoematologica, Università degli Studi di Padova, Padova

<sup>10</sup> U.O.C. di Medicina Trasfusionale, Azienda Ospedaliera Universitaria Integrata, Verona

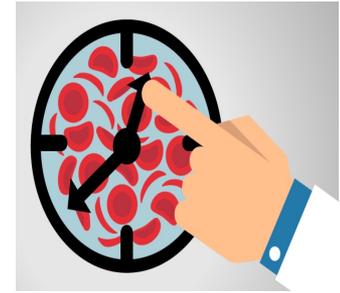
<sup>11</sup> Dipartimento di Medicina Trasfusionale, Ospedale Arezzo, Ragusa

<sup>12</sup> Dipartimento di Medicina, sezione di Medicina Interna B-AOUI, Università di Verona, Verona

Scaricabile dal sito: [http://www.site-italia.org/file/Triage\\_SCD.pdf](http://www.site-italia.org/file/Triage_SCD.pdf)  
release 3 (marzo 2019)



# Eventi acuti: tempo-dipendenti



- Terapia del dolore
- Terapia trasfusionale
- Idratazione
- Terapia antibiotica empirica
- Profilassi antitrombotica LMWH

- NRS <7: FANS + paracetamolo
- NRS >7: oppioidi

**TRIAGE**  
**SCD patient** with established or **suspected** diagnosis

It is essential that all patients receive at least a yellow code

**FATTORI PROGNOSTICI POSITIVI**  
 rapida identificazione ed inizio tempestivo della terapia

Administration of the first dose of appropriate analgesic within 30 minutes from access to the hospital

**RED CODE:**

- Failure of at least one of the vital functions (respiratory system, cardiovascular system or state of consciousness)
- Acute cephalalgia with associated neurological symptoms
- Acute psychotic crisis
- Acute **anemia** symptoms (< 2gr/dl compared to the steady state or marked paleness)
- **Painful symptomatology** with **VAS > 8/10** (or pain resistant to the analgesic therapy at home)
- Severe jaundice

**YELLOW CODE:**  
**painful symptomatology with VAS 5-7**

- Cases of (also induced by minor traumas)
  - >38° fever or persistent for at least 2 days
- Cases of infection
- Modest non-traumatological cephalalgical symptomatology
- Reported virus alterations
- Intense jaundice in apparent wellness without anemia

**GREEN CODE:**

- Minor skin diseases
- Minor ORL diseases
- Modest anxiety state
- Minor skin wounds
- Excoriations and abrasions
- First-degree burns

**WHITE FLAG:**

- Certificate issues
- Medical-legal issues
- Diagnostic-therapeutical prescriptions
- Non-urgent advice requests
- Pregnancy assessment requests

**ADULT management**

**CHILD management**

**ADULT management**

**CHILD management**

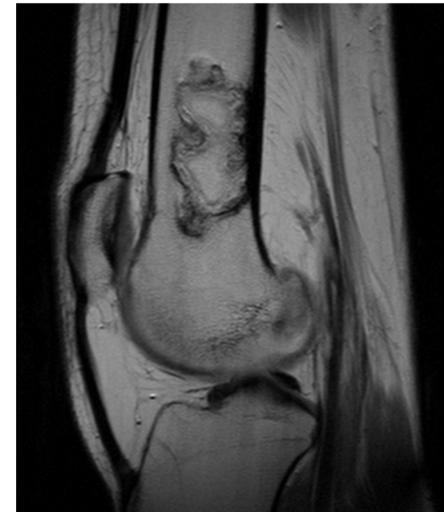
**Patient with surgical framework (e.g. acute abdomen)**

# Dolore, crisi falcemica

- **Principale complicanza acuta (incidenza 0.8 episodi/anno)**
- Episodio di dolore acuto di entità variabile
- **Distretto osteo-muscolare più frequentemente coinvolto** (estremità, rachide, torace)

- **Organi target: osso, milza, fegato, rene, polmone**
- Esordio acuto vs subacuto
- Durata variabile da ore a giorni
- Caratteristiche diverse (pulsante, continuo, migrante)

- **Crisi dolorosa acuta ossea**
- **Acute chest syndrome**
- **Evento neurologico acuto**
- **Priapismo**
- **Anemizzazione acuta**
- **Colestasi intraepatica acuta**



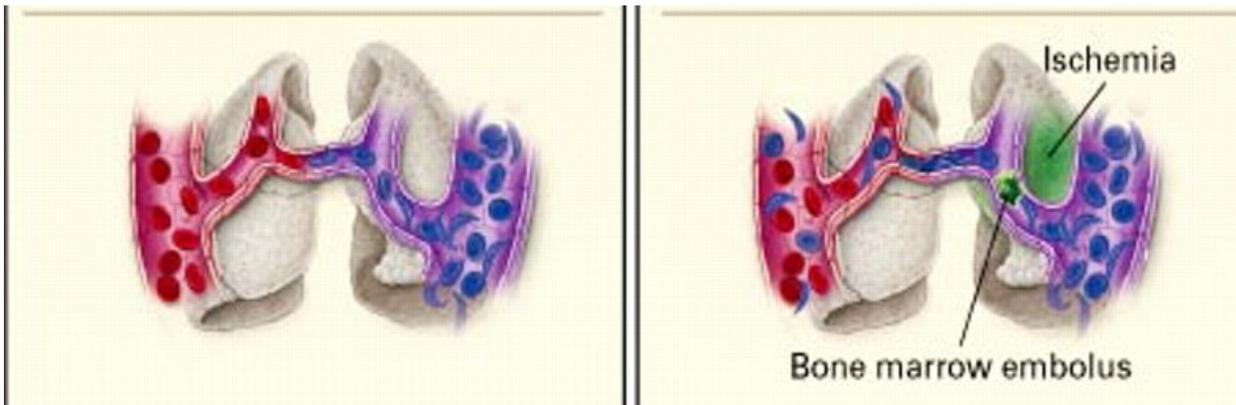
# Dolore osseo

- **Dolore osteo-muscolare**
- Infarto osseo
- Necrosi ossea asettica:
  - segmenti epifisari
  - testa di omero e femore
- Osteoporosi
- Fratture/cedimenti vertebrali
- Osteomieliti; dattilite
- Artrite asettica o settica, se infiammazione

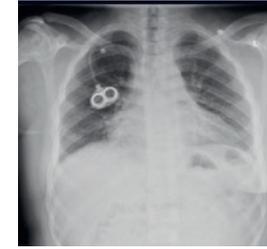
**Struttura ossea: trabecole** con singola arteria e unica vena  
**Sickle dense cells:** in capillari **lento flusso ematico ed elevata pressione**

→ - ipossia di midollo e osso  
- diminuzione del tempo per la polimerizzazione  
- aumento disidratazione GR

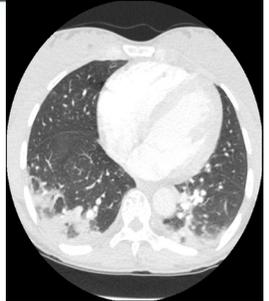
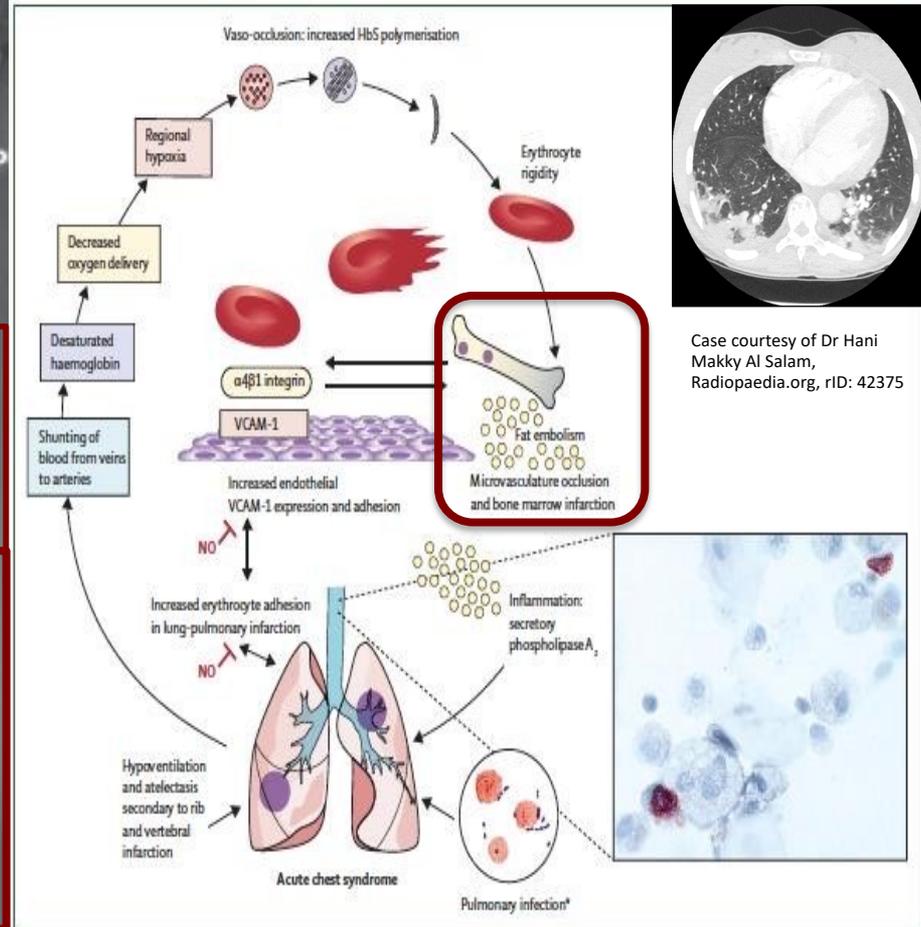
→ **dolore osseo e rilascio di emboli necrotici** dal midollo



# Acute Chest Syndrome



- Febbre e/o sintomi respiratori associati ad un nuovo infiltrato polmonare all'Rx torace o, se negativa, alterazioni del parenchima polmonare alla TC torace
- Seconda più comune complicanza e causa di ospedalizzazione
- Mortalità 9% se non trattata tempestivamente
- Radiologicamente indistinguibile da polmonite multilobare
- Eziologia multifattoriale



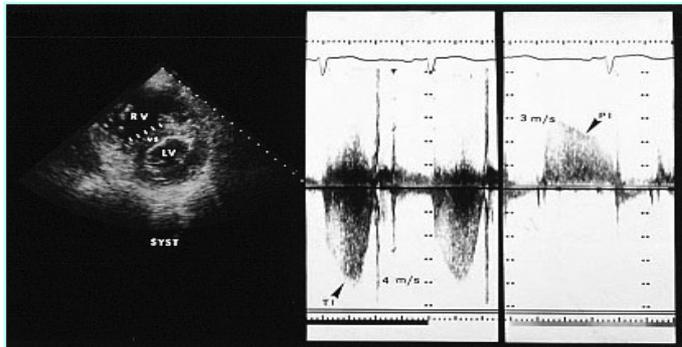
Case courtesy of Dr Hani Makky Al Salam, Radiopaedia.org, rID: 42375

# Ipertensione Polmonare

- Emolisi ed alterazione endoteliale

Emolisi  Disregolazione dell'omeostasi di NO

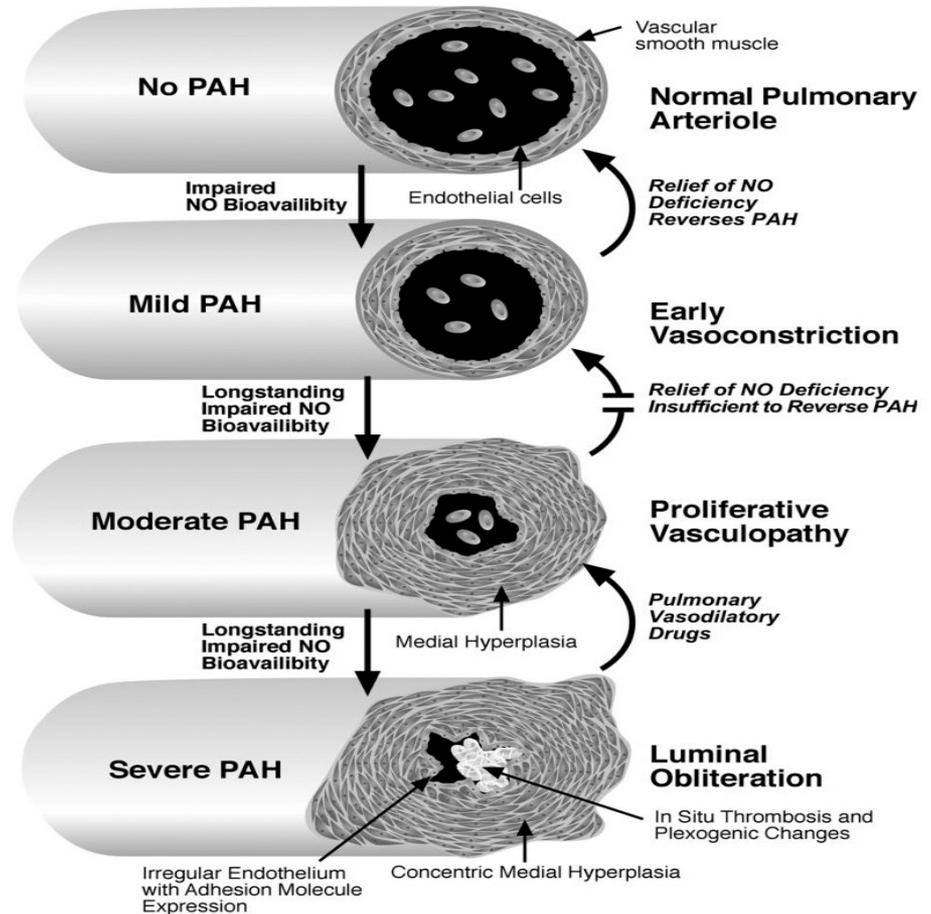
- Stato cronico di deossigenazione
- Vasculopatia proliferativa** ← danno d'organo progressivo, polmonare
- Micro-macro tromboembolismi ← vaso-occlusione e viscosità
- Elevata pressione polmonare dovuta all'anemia



Gladwin MT. NEJM 2008; JACC, CHEST 2004

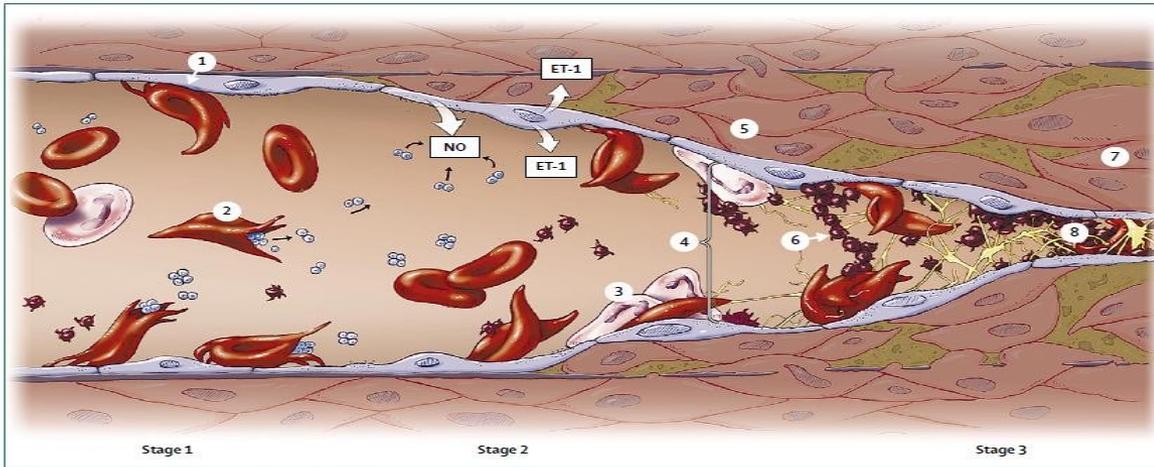
Ipertensione arteriosa polmonare

- PAPs 35-40 mmHg
- Velocità di rigurgito tricuspidalico 2.5–3.4 m/sec



Hematology 2005; Educational ASH 2005  
Kato GJ Pediatr Hematol Oncol 2007

# Stroke



**Figure 4: Vasculopathy and stroke in sickle-cell disease**

The sickle erythrocyte is pre-eminent in the development of cerebrovascular disease as a result of abnormal adherence to the vascular endothelium (1) and haemolysis (2). These factors result in a proinflammatory state manifested, in part, by leucocyte adhesion (3) and platelet aggregation (6). Increased secretion of endothelin (ET-1) and scavenging of nitric oxide (NO) by cell-free haemoglobin dimers result in increased vasomotor tone (4). Luminal narrowing occurs secondary to proliferation of smooth-muscle cells and fibroblasts within the intimal layer (5). The end result is vasculopathy (7) and occlusion (8).

## VASCULOPATIA CEREBRALE

- Ictus ischemico
- TIA reiterati
- Ictus emorragico
- Infarti cerebrali silenti (anomalie fino a 55% pz in RM) → deterioramento delle funzioni cognitive (10-30%)

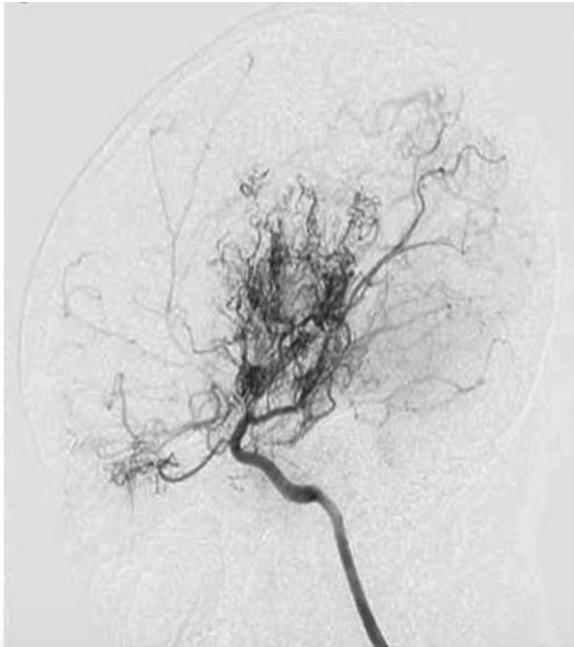
## ICTUS EMORRAGICO

- Più frequente tra 20-29 anni
- Rottura di aneurismi cerebrali/emorragia intra-parenchimale o ventricolare (vasculopatia cronica tipo Moyamoya con neoangiogenesi e aumentato rischio emorragico)

## ICTUS ISCHEMICO/TIA

- 7.4% <14 anni; 11% <20 anni; 24% <45 anni
- Fattori precipitanti: anemizzazione, sepsi
- Stenosi/occlusione di vasi del circolo anteriore (carotide interna distale/parte prossimale delle a. cerebrali medie), vasi distali (trombosi in situ, embolizzazione)

# Stroke



**Angiografia**

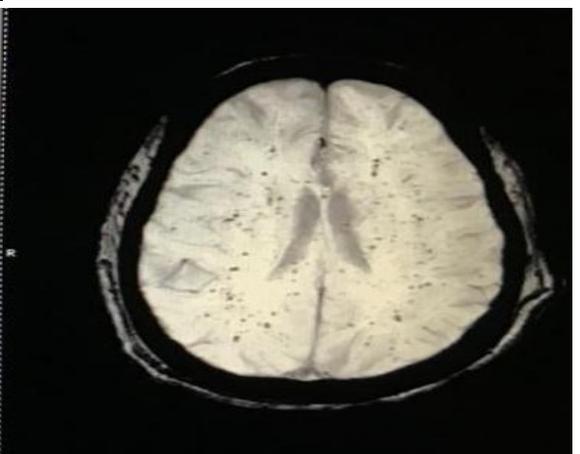
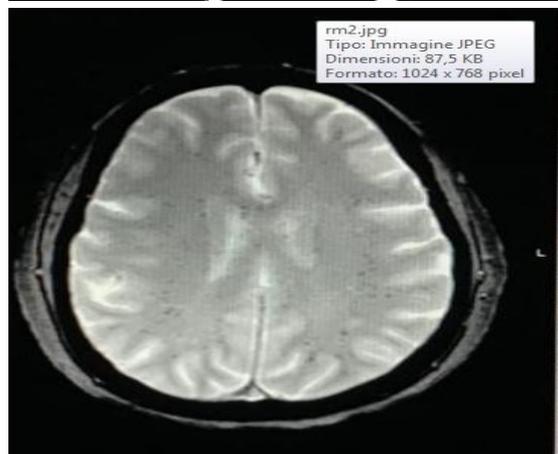
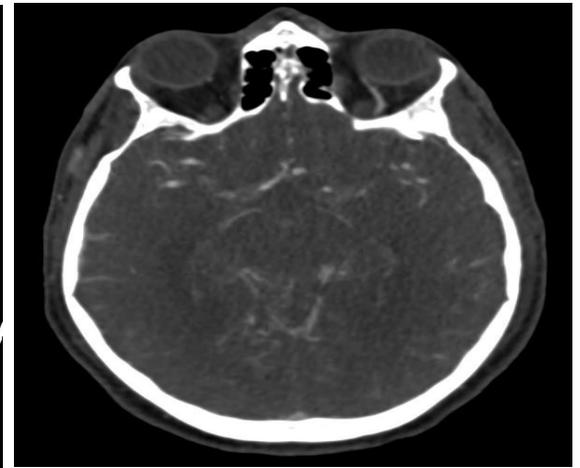
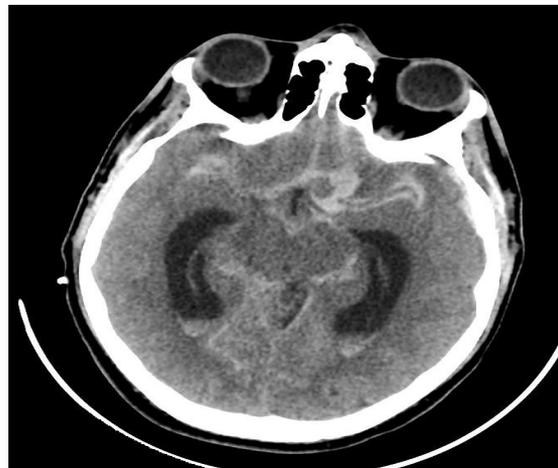
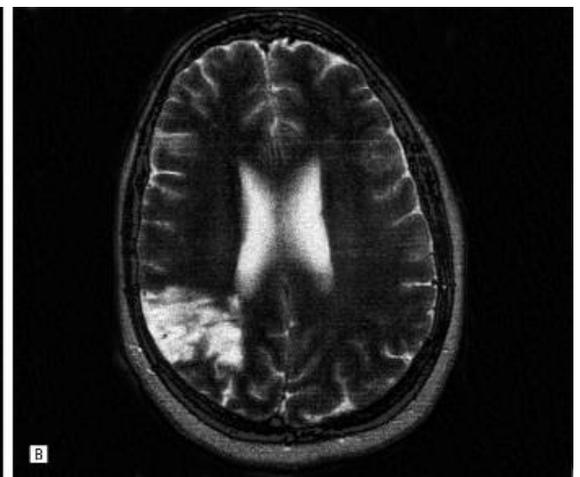
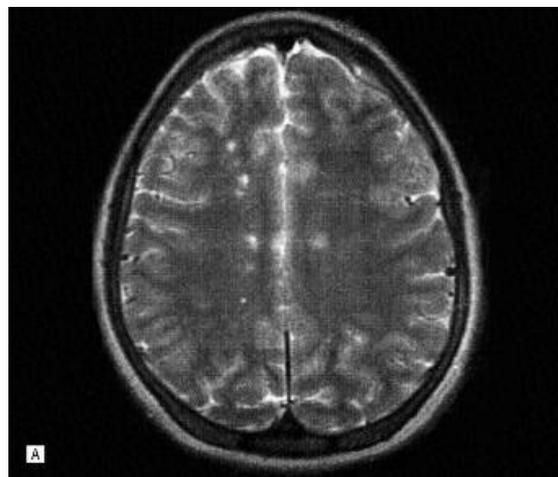
**RMN cerebri con mdc (Gadol)**

**TAC cerebri**

**Angio-TAC**

*Scott RM, N Engl J Med. 2009*

*Pinto VM, Intern Emerg Med. 2019*



rm2.jpg  
Tipo: Immagine JPEG  
Dimensioni: 87,5 KB  
Formato: 1024 x 768 pixel

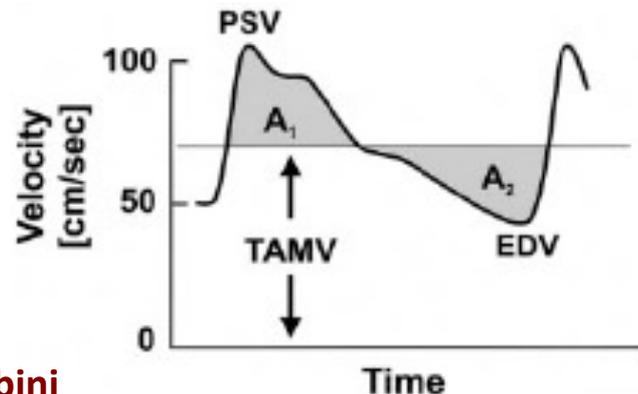
# Fattori Prognostici

## Transcranial Doppler Correlation With Cerebral Angiography in Sickle Cell Disease

Robert J. Adams, MD; Fenwick T. Nichols, MD; Ramon Figueroa, MD; Virgil McKie, MD; and Thomas Lott, MD

*Stroke* 1992, 23:1073-1077

STOP Trial



Bambini

**Normale:** TAMMX: <170 cm/sec e PSV <200

**Condizionale 2A:** TAMMX 170-199 cm/sec e PSV 200-249, in uno o più di: M1, MCA, BIF, dICA

**Condizionale 2B:** TAMMX 170 cm/sec e PSV 200, in uno o più di: PCA, BA

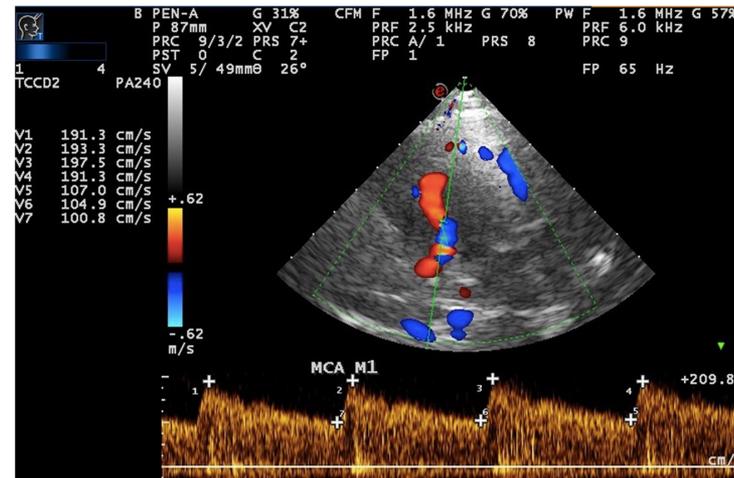
**Condizionale 2C:** TAMMX 170 cm/sec e PSV 200, in uno o più di: ACA

**Anormale:** TAMMX: >200 cm/sec e PSV >250, in uno o più di: MCA, BIF, dICA

## Adulti

MCA-PSV (cm/s)	SCD patients	Controls	Total
>132.7	28 (53.8%)	0	28
<132.7	24 (46.2%)	26 (100%)	50
Total	52	26	78

Variables	SCD patients (n = 53)		Controls (n = 27)		p value
	Median	Q1-Q3	Median	Q1-Q3	
MCA-TAMM (cm/s)	96.9	84.6-103.8	75.9	72.3-83.4	<.0001
MCA-PSV (cm/s)	133.7	112.9-144.1	112.2	104.5-120.2	=.0001
MCA-PI	0.80	0.73-0.88	0.89	0.80-1.06	=.0021



Graziadei G, Ann Hematol 2017

# Anemizzazione acuta

## SEQUESTRO SPLENICO

- Splenomegalia e anemia
- Reticolocitosi, possibile piastrinopenia da ipersplenismo
- Bambini, **Talasso-drepanocitosi**

## SEQUESTRO EPATICO

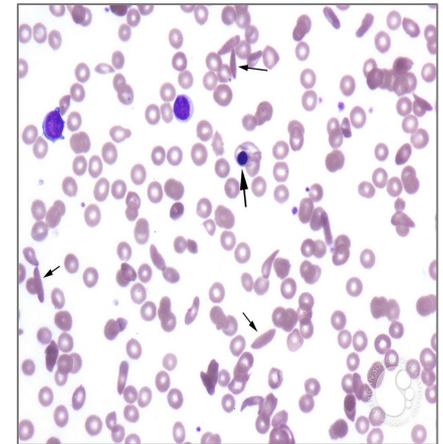
- Epatomegalia e anemia
- Reticolocitosi
- Bambini e adulti

## CRISI APLASTICA

- Riduzione Hb di almeno 2 g/dL rispetto ai valori baseline del paziente
- Aplasia transitoria della serie eritroide dovuta solitamente a infezione virale (Parvovirus B19)
- Valore di reticolociti inappropriatamente basso per il livello di anemia
- Bambini e adulti



*Acute splenic sequestration  
Inherited Hemoglobin  
Disorders, A. Munshi*



*Aplastic crisis. ASH  
Image Bank.*

# Colestasi intraepatica acuta e Priapismo

## **COLESTASI INTRAEPATICA ACUTA**

- Complicanza rara, ma potenzialmente fatale
- Insorgenza improvvisa di dolore addominale in ipocondrio destro, epatomegalia, iperbilirubinemia +/- rialzo delle transaminasi, coagulopatia
- Può complicarsi con insufficienza epatica, diatesi emorragica, encefalopatia epatica e insufficienza renale acuta

## **PRIAPISMO**

- Complicanza frequente nel giovane adulto
- <1 ora: priapismo discontinuo; >3 ore: priapismo prolungato
- Urgenza urologica: se non trattato precocemente può esitare in danno tissutale (fibrosi) e successiva disfunzione erettile

# Retinopatia falcemica

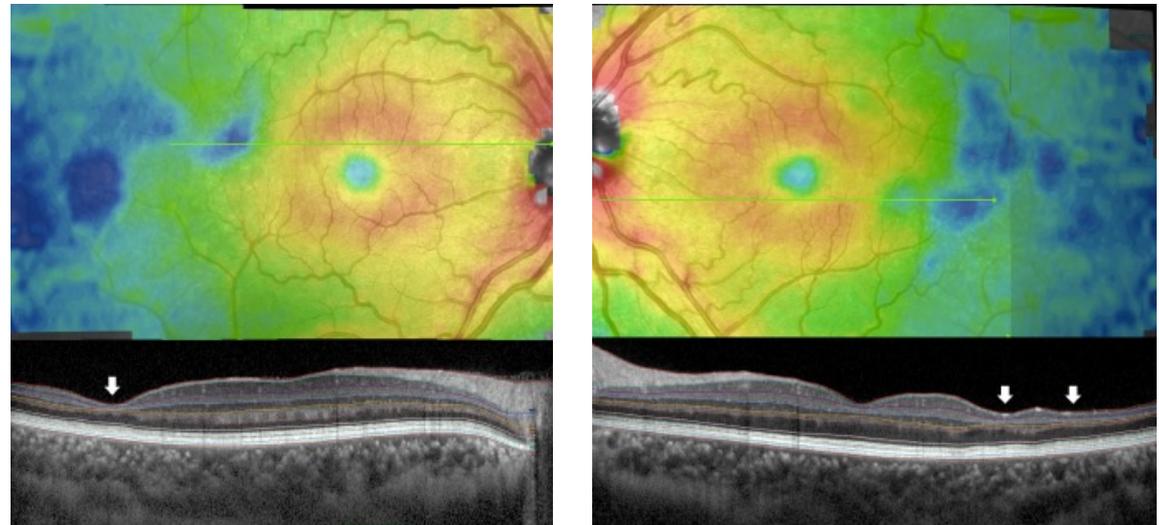
## RESEARCH ARTICLE

### Sickle cell maculopathy: Identification of systemic risk factors, and microstructural analysis of individual retinal layers of the macula

Laura Dell'Arti<sup>1,2</sup>, Giulio Barteselli<sup>3</sup>, Lorenzo Riva<sup>2</sup>, Elisa Carini<sup>2</sup>, Giovanna Graziadei<sup>4</sup>, Eleonora Benatti<sup>2</sup>, Alessandro Invernizzi<sup>5</sup>, Maria D. Cappellini<sup>1,4</sup>, Francesco Viola<sup>1,2,\*</sup>

1 Department of Clinical Sciences and Community Health, University of Milan, Milan, Italy, 2 Ophthalmological Unit, Ca' Granda Foundation, IRCCS Ospedale Maggiore Policlinico, Milan, Italy, 3 Genentech Inc, South San Francisco, California, United States of America, 4 Rare Diseases Center, Department of Medicine and Medical Specialties, Ca' Granda Foundation, IRCCS Ospedale Maggiore Policlinico, Milan, Italy, 5 Eye Clinic, Department of Biomedical and Clinical Science "L. Sacco", Luigi Sacco Hospital, University of Milan, Milan, Italy

forms of sickle cell retinopathy. A subtle thinning of the overall macula occurs in SCD patients and involves multiple retinal layers, suggesting that ischemic vasculopathy may happen in both superficial and deep capillary plexi. Thinning of the outer retinal layers suggests that an ischemic insult of the choriocapillaris may also occur in SCD patients.



**Fig 2. Example of sickle cell maculopathy.** (First and third rows) Patchy areas of markedly reduced retinal thickness are visible as blue areas on retinal thickness maps. (Second and fourth row) Automatic segmentation of the B-scans passing through thinned areas demonstrates thinning of multiple individual retinal layers (white arrows).

# Opzioni terapeutiche

**Table 1. Summary of Recommended Treatment Approaches for Sickle Cell Disease.\***

Treatment Approach	Dose and Frequency	Duration	Recommendation	Evidence Quality	Availability in Low-Resource Areas
<b>Prevention of infection</b>					
Penicillin V	62.5–250 mg, twice daily	At least until 5 yr of age	Strong	Moderate	Available
Pneumococcal vaccines	Every 5 yr, starting at 2 yr of age	Lifelong	Strong	Moderate	Limited availability
Malarial prophylaxis when appropriate	Daily (e.g., proguanil), weekly (e.g., pyrimethamine), or intermittent (e.g., mefloquine–artesunate or sulfadoxine–pyrimethamine plus amodiaquine)	Lifelong (in malarious area)	Strong	Low	Available
<b>Blood transfusion</b>					
<b>Acute care</b>					
Treatment of anemia	Simple transfusion; target hemoglobin level, 10 g/dl	Limited	Strong	Low	Limited availability
Preoperative transfusion (if hemoglobin <8.5 g/dl)	Simple transfusion, performed once; target hemoglobin level, 10 g/dl		Strong	Moderate	Limited availability
<b>Ongoing care</b>					
Primary stroke prevention	Target HbS, <30%; transfusions every 3–6 wk	Indefinite	Strong	High	Very limited availability
Secondary stroke prevention	Target HbS, <30% or <50%; transfusions every 3–6 wk	Indefinite	Moderate	Low	Very limited availability
Prevention of additional silent cerebral infarctions	Target HbS, <30%; transfusions every 3–6 wk	Indefinite	Moderate	Moderate	Very limited availability
<b>Hydroxyurea</b>					
Universal use	20–35 mg/kg/day	Indefinite	Moderate	Moderate	Limited availability
Prevention of acute complications	15–35 mg/kg/day	Indefinite	Strong	High	Limited availability
Primary stroke prevention	15–35 mg/kg/day	Indefinite	Strong	Moderate	Limited availability

Ferro-chelazione

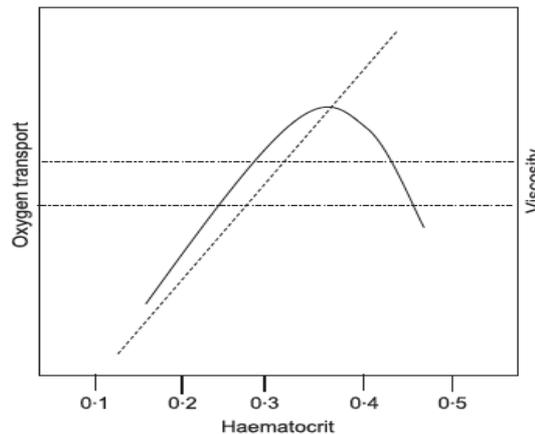
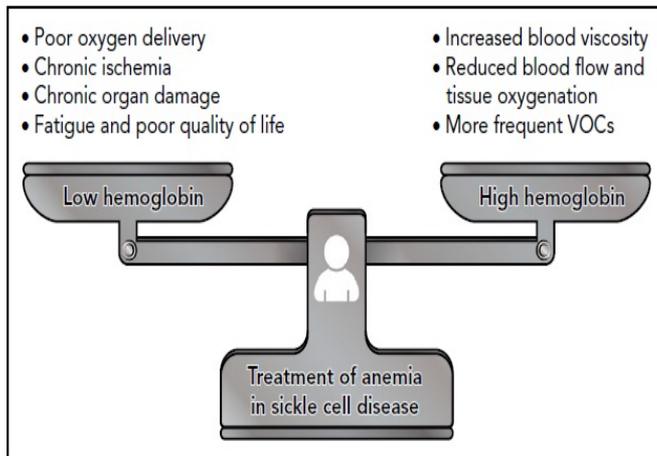
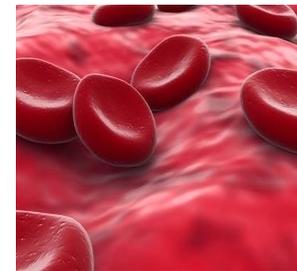
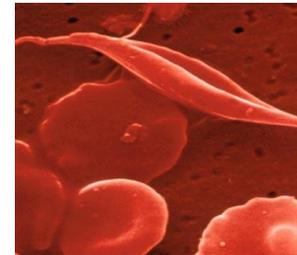
Trapianto di midollo

# Terapia trasfusionale: obiettivi e strategie

- Eliminare i fattori di rischio pro-falcizzanti
- Interrompere la falcizzazione, i fenomeni vaso-occlusivi, il danno endoteliale
- Correggere l'anemia, ridurre la percentuale di HbS, prevenire il danno d'organo



- **Due opzioni: Trasfusione semplice**
  - Hb non >10-11 g/dl
  - iperviscosità
- **Eritroexchange, manuale o automatica**  
→ Rimozione GR o sangue intero + ET



Adams RJ, et al. *N Engl J Med* 1998  
Vichinsky EP, et al. *N Engl J Med* 1995  
Pinto VM, *Intern Emerg Med* 2019

# Opzioni terapeutiche: indicazioni

The choice of transfusion method, i.e., simple (top up) or exchange, should be based on clinical judgement of individual cases, taking into account the indication for transfusion, the need to avoid hyperviscosity and minimise alloimmunisation, maintenance of iron balance, venous access issues and available resources (Grade 1C).

ACUTO

CRONICO

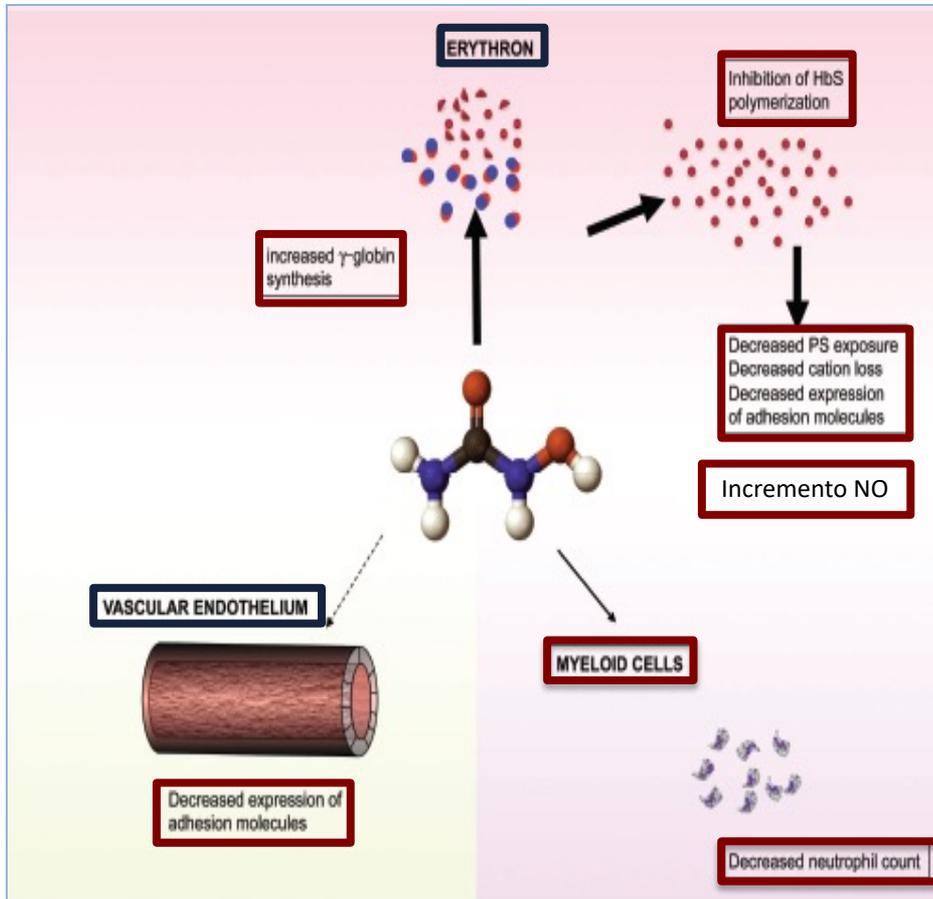
	GRADE evaluation	Type of transfusion*
<b>Indications where primary goal of transfusion is to correct acute anaemia</b>		
Aplastic crisis	1B	Simple (top up)
Acute splenic sequestration	1B	Simple
Acute hepatic sequestration	1B	Simple
Delayed haemolytic transfusion reaction (transfusion should be avoided unless the anaemia is severe or life-threatening)	1C	Simple
<b>Indications where primary goal of transfusion is to reduce HbS concentration in relation to HbA</b> → <b>HbS &lt;30%</b>		
GRADE evaluation		
Type of transfusion*		
<u>ACS</u>	1B	Simple or exchange <sup>†</sup>
<u>Acute stroke or other neurological deficit (e.g. TIA)</u>	1B	Exchange
<u>Acute multi-organ failure</u>	1C	Exchange
<u>Mesenteric/girdle syndrome</u>	1C	Exchange
Severe sepsis	2C	Exchange
Acute intrahepatic cholestasis	1C	Exchange
Primary stroke prevention	1A	Simple or exchange
Prevention of silent cerebral infarct recurrence	1A	Simple or exchange
Secondary stroke prevention	1B	Simple or exchange
<u>Surgery</u>		
• SS patients – elective low or medium risk surgery	1A	Simple or exchange
• SC patients – elective low or medium risk surgery	1C	Exchange
• All sickle genotypes – elective high risk surgery	1C	Exchange
• Emergency surgery	1D	Individual considerations <sup>‡</sup>
<u>Pregnancy</u>		
• Sickle complications (e.g. painful crises, ACS, stroke)	1B	Simple or exchange
• Severe anaemia	1C	Simple
• High obstetric, medical or fetal risk	1C	Simple or exchange
Recurrent ACS <sup>§</sup>	2C	Simple or exchange
Recurrent painful crises <sup>§</sup>	2C	Simple or exchange

**Emazie concentrate leucodeplete compatibili per Gruppo ABO-Rh-Kell e match di II livello Alloimmunizzazione**

# Idrossiurea

Indicazioni: 2-3 VOCs/anno che hanno richiesto l'uso di analgesia maggiore e ricovero senza gravi complicanze d'organo, progressa ACS o frequenti ospedalizzazioni

SITE 2014



**Table 1.** Definite, probable and possible indications for hydroxycarbamide in sickle cell disease.

## Definite

- More than three episodes of severe acute pain per year
- Two or more episodes of acute chest syndrome

## Probable

- Frequent episodes of acute pain requiring analgesia
- Persistent albuminuria or other evidence of renal disease
- Hypoxemia or other evidence of lung disease
- Sickle hepatopathy
- Tricuspid jet velocity  $>2.5\text{m/s}$  on echocardiography or pulmonary hypertension
- Primary or secondary stroke prevention when blood transfusions are unacceptable
- Hemoglobin  $<7\text{g/dL}$

## Possible

- Poor growth
- Conditional transcranial Doppler velocities
- Patient or family request
- Elevated steady state white cell count
- Pre-operative management
- Significant coexistent disease likely to exacerbate SCD, such as asthma, SLE
- Strong wish to avoid blood transfusions, including Jehovah's Witnesses
- Living in low-income country with greatly increased early mortality

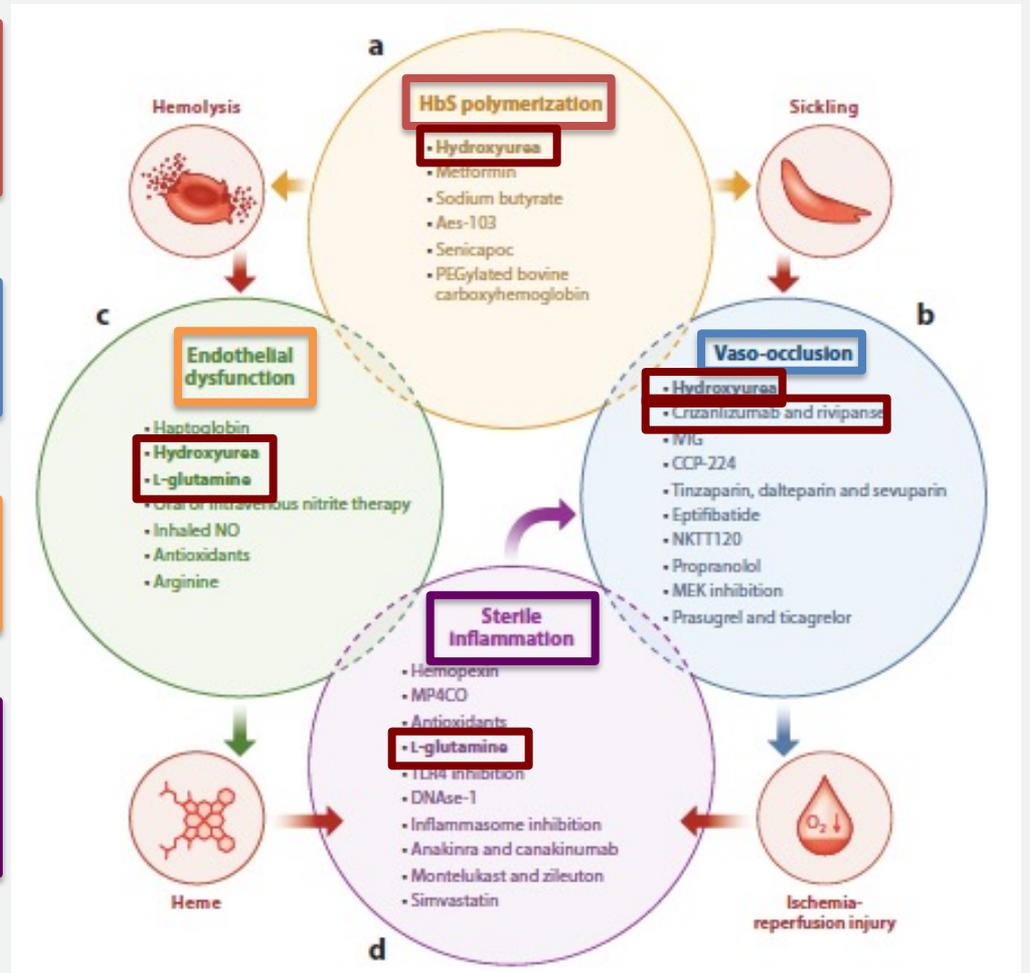
# Nuovi approcci terapeutici

a. **Modulatori di polimerizzazione** di Hb, dell'affinità dell'Hb per l'O<sub>2</sub> e disidratazione GR

b. **Inibitori dell'adesione** tra GR, GB, PLT e cellule endoteliali

c. **Leganti di Hb libera plasmatica e ROS**; sintesi di NO

d. **Leganti di eme e ROS**; neutralizzanti di molecole infiammatorie (NETs, TLR4, IL-1 $\beta$ )

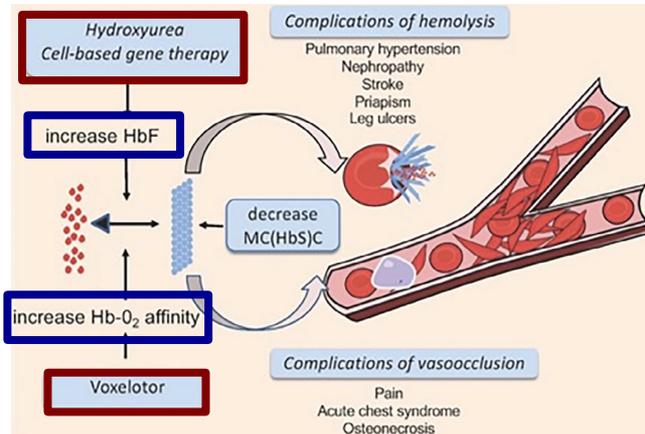


Prithu Sundd,<sup>1,2,3,\*</sup> Mark T. Gladwin,<sup>1,2,3,\*</sup>  
and Enrico M. Novelli<sup>2,3,4,\*</sup>

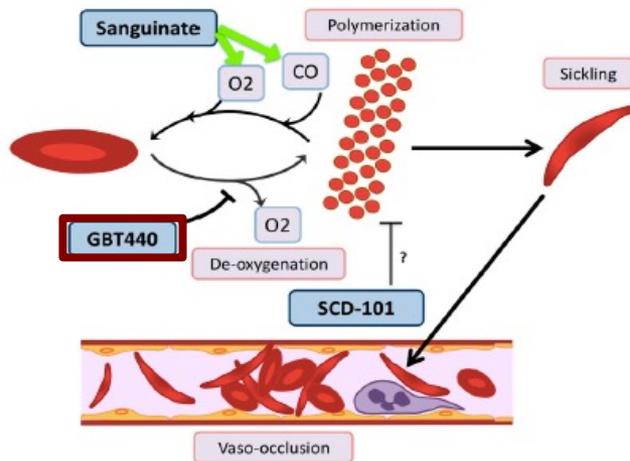
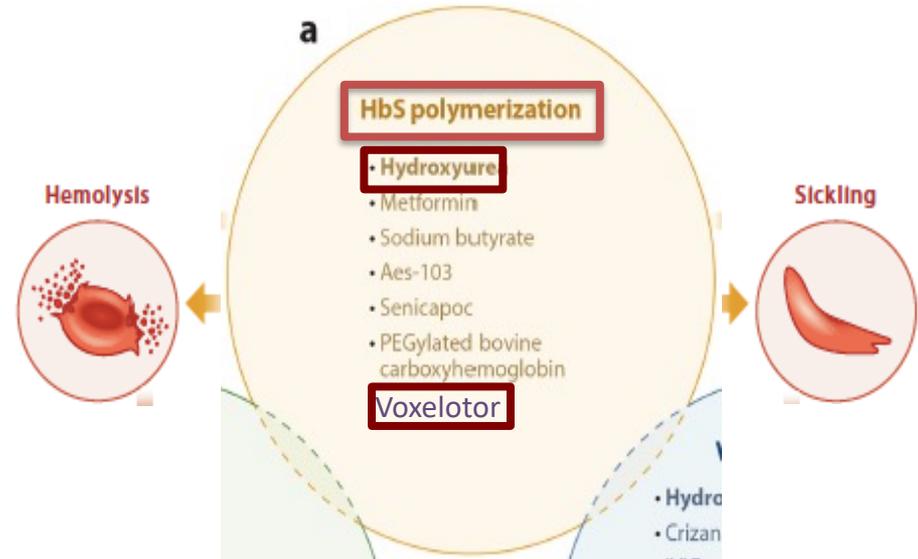
Annu. Rev. Pathol. Mech. Dis. 2019. 14:263–92

Farmaci approvati da US FDA: **Idrossiurea e L-glutamina**

# Modulatori della polimerizzazione: Voxelotor



Steinberg MH, Am J Hematol 2020



Moerdler S, Hematology 2018

**Voxelotor (GBT440):** inibitore diretto della polimerizzazione. Lega in modo reversibile  $\alpha$ -catene di HbS ed incrementa l'affinità per l'O<sub>2</sub> tramite modificazioni allosteriche a favore di R-state  $\rightarrow$  decremento sickle cells ed emolisi ed incremento Hb

Adapted by Sunnd P, Annu. Rev. Pathol. Dis 2019

# The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812

AUGUST 8, 2019

VOL. 381 NO. 6

## A Phase 3 Randomized Trial of Voxelotor in Sickle Cell Disease

Elliott Vichinsky, M.D., Carolyn C. Hoppe, M.D., Kenneth I. Ataga, M.D., Russell E. Ware, M.D., Ph.D., Videlis Nduba, M.B., Ch.B., M.P.H., Amal El-Beshlawy, M.D., Hoda Hassab, M.D., Maureen M. Achebe, M.D., M.P.H., Salam Alkindi, M.B., B.Ch., R. Clark Brown, M.D., Ph.D., David L. Diuguid, M.D., Paul Telfer, M.D., Dimitris A. Tsitsikas, M.D., Ashraf Elghandour, M.D., Victor R. Gordeuk, M.D., Julie Kanter, M.D., Miguel R. Abboud, M.D., Joshua Lehrer-Graiwer, M.D., Margaret Tonda, Pharm.D., Allison Intondi, Ph.D., Barbara Tong, Ph.D., and Jo Howard, M.D., for the HOPE Trial Investigators\*

### CONCLUSIONS

In this phase 3 randomized, placebo-controlled trial involving participants with sickle cell disease, voxelotor significantly increased hemoglobin levels and reduced markers of hemolysis. These findings are consistent with inhibition of HbS polymerization and indicate a disease-modifying potential. (Funded by Global Blood Therapeutics; HOPE ClinicalTrials.gov number, NCT03036813.)

N Engl J Med 2019;381:509-19.  
DOI: 10.1056/NEJMoal1903212

✓ **Authorised**  
This medicine is authorised for use in the European Union

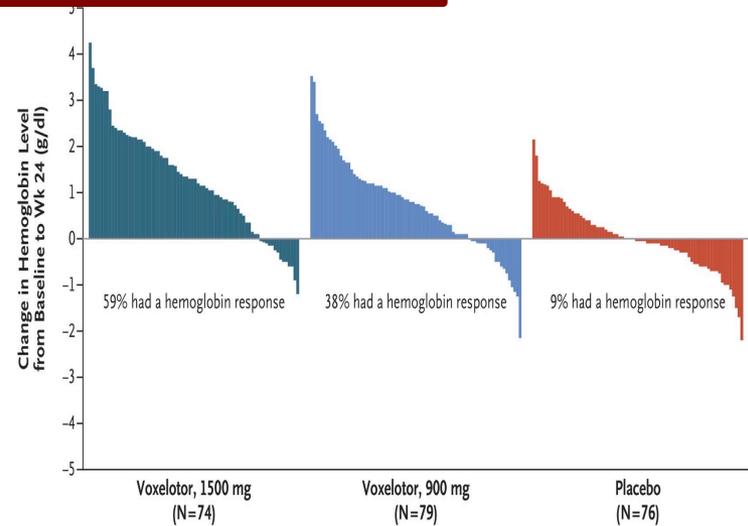
✗ **Suspended**  
This medicine is currently suspended from use in the European Union

EMA/H/C/004869 - 18/11/2016  
Orphan Designation (EU/3/16/1769)  
11/2019 Autorizzazione in USA  
14/02/2022 in EU

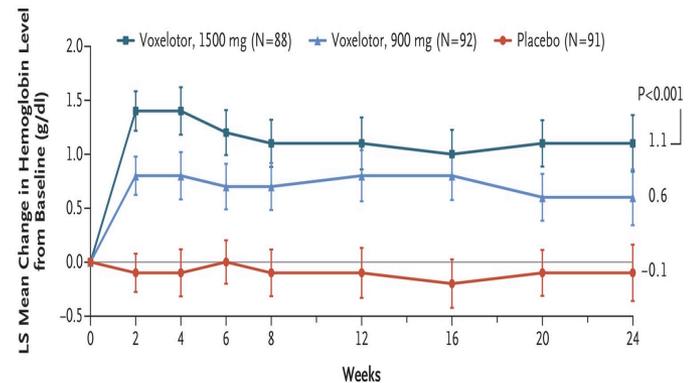
29/07/2024 Inizio di revisione dei trials / due registri  
26/09/2024 Sospensione



A Waterfall Plot of Change in Hemoglobin Level from Baseline to Wk 24



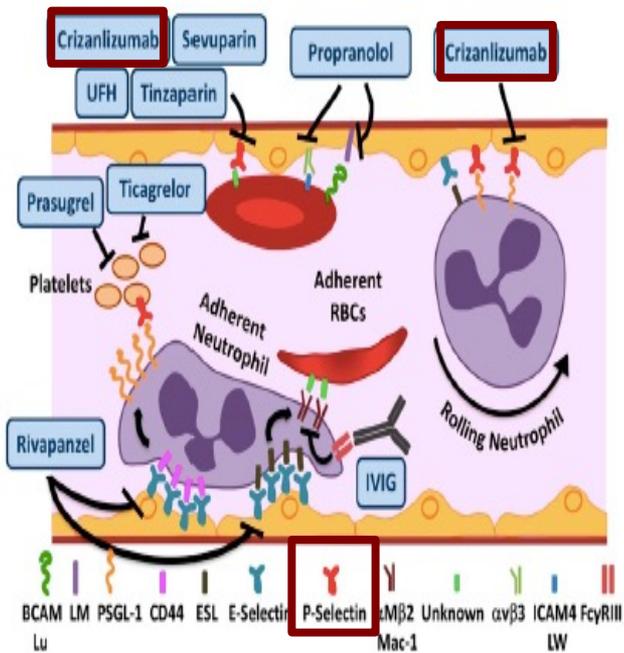
B LS Mean Change in Hemoglobin Level from Baseline to Wk 24



No. at Risk	0	2	4	6	8	12	16	20	24
Voxelotor, 1500 mg	76	78	74	74	71	76	77	72	72
Voxelotor, 900 mg	82	78	69	74	76	77	73	78	78
Placebo	82	79	81	74	81	77	78	72	72

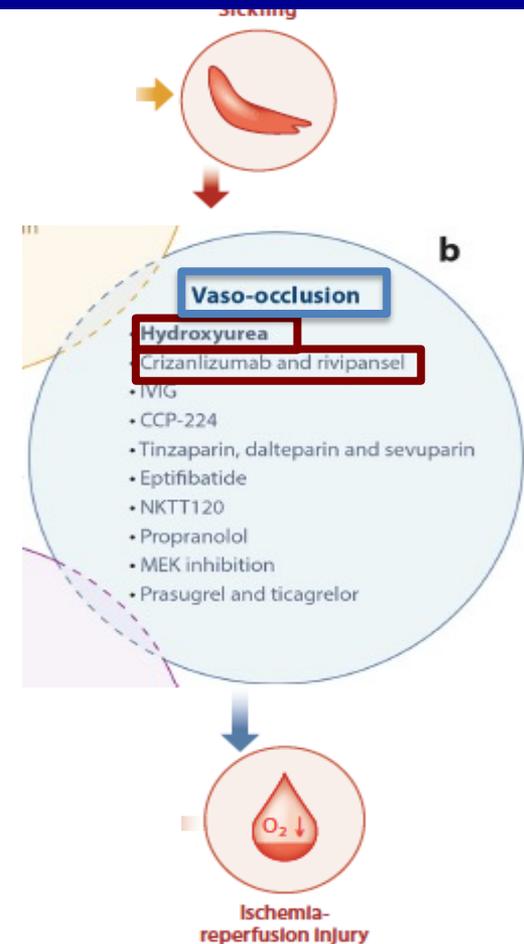
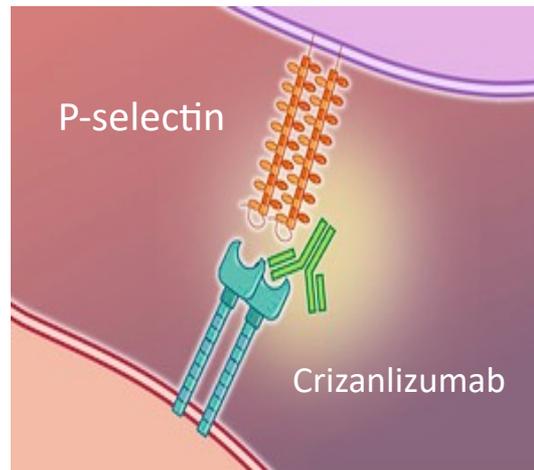
Vichinsky E, N Engl J Med 2019

# Inibitori della vaso-occlusione e dell'adesione: Crizanlizumab



Moerdler S, Hematology 2018

**Ab monoclonale umanizzato che lega P-selectina e blocca la sua interazione con il P-selectin glycoprotein ligand 1 (PSGL-1)**



Sunnd P, Annu. Rev. Pathol. Dis 2019

ORIGINAL ARTICLE

# Crizanlizumab for the Prevention of Pain Crises in Sickle Cell Disease

K.I. Ataga, A. Kutlar, J. Kanter, D. Liles, R. Cancado, J. Friedrisch, T.H. Guthrie, J. Knight-Madden, O.A. Alvarez, V.R. Gordeuk, S. Gualandro, M.P. Colella, W.R. Smith, S.A. Rollins, J.W. Stocker, and R.P. Rother

## CONCLUSIONS

In patients with sickle cell disease, crizanlizumab therapy resulted in a significantly lower rate of sickle cell-related pain crises than placebo and was associated with a low incidence of adverse events. (Funded by Selexys Pharmaceuticals and others; SUSTAIN ClinicalTrials.gov number, NCT01895361.) *N Engl J Med* 2017;376:429-39. DOI: 10.1056/NEJMoa1611770

✓ **Authorised**

This medicine is authorised for use in the European Union

Autorizzazione subordinata  
28/10/2020  
EMA/446082/2020  
EMA/H/C/004874

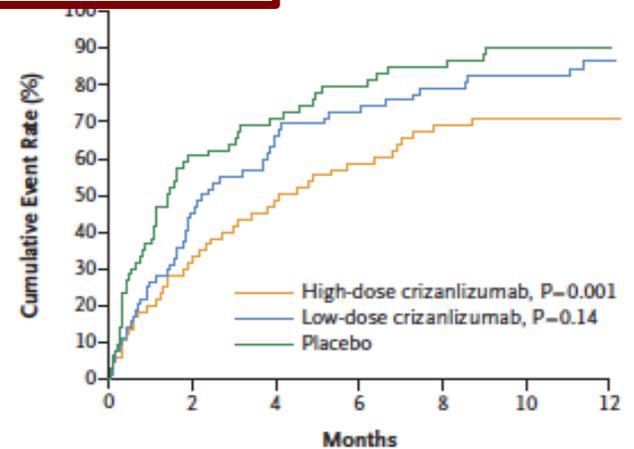
✗ **Revoked**

This medicine's authorisation has been revoked

3 August 2023  
EMA/359200/2023



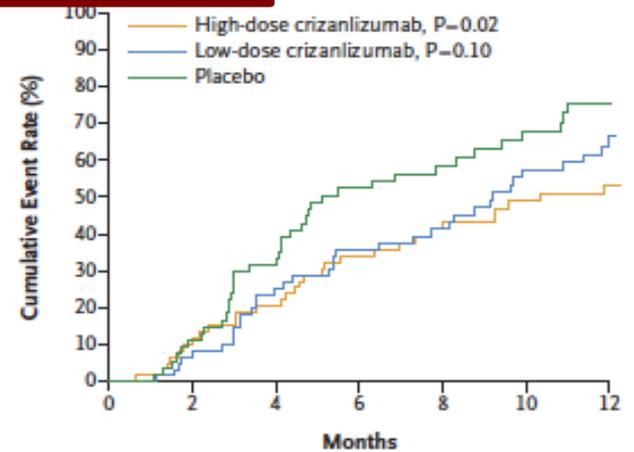
**A First Sickle Cell-Related Pain Crisis**



**No. at Risk**

High-dose crizanlizumab	67	49	41	35	30	26	24	20	18	17	16	15	7
Low-dose crizanlizumab	66	47	34	28	21	19	17	15	12	10	10	10	3
Placebo	65	37	23	21	17	13	12	9	8	6	5	4	1

**B Second Sickle Cell-Related Pain Crisis**



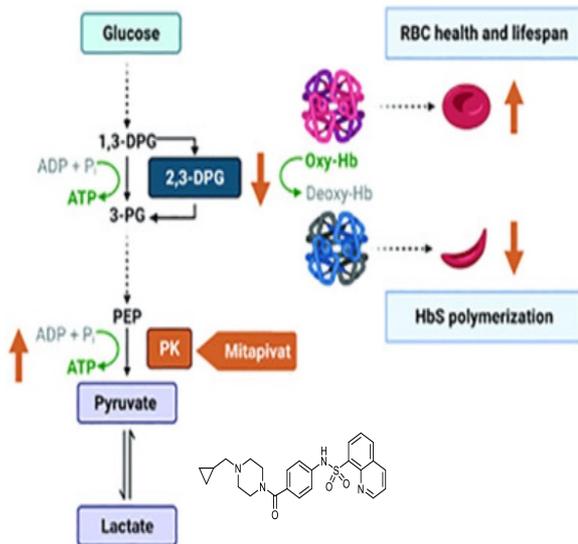
**No. at Risk**

High-dose crizanlizumab	67	60	52	50	46	41	38	35	31	30	26	22	9
Low-dose crizanlizumab	66	62	56	50	43	40	36	34	31	26	21	20	7
Placebo	65	55	48	38	36	27	25	22	18	16	13	10	3

# Agenti sul metabolismo eritrocitario: Mitapivat

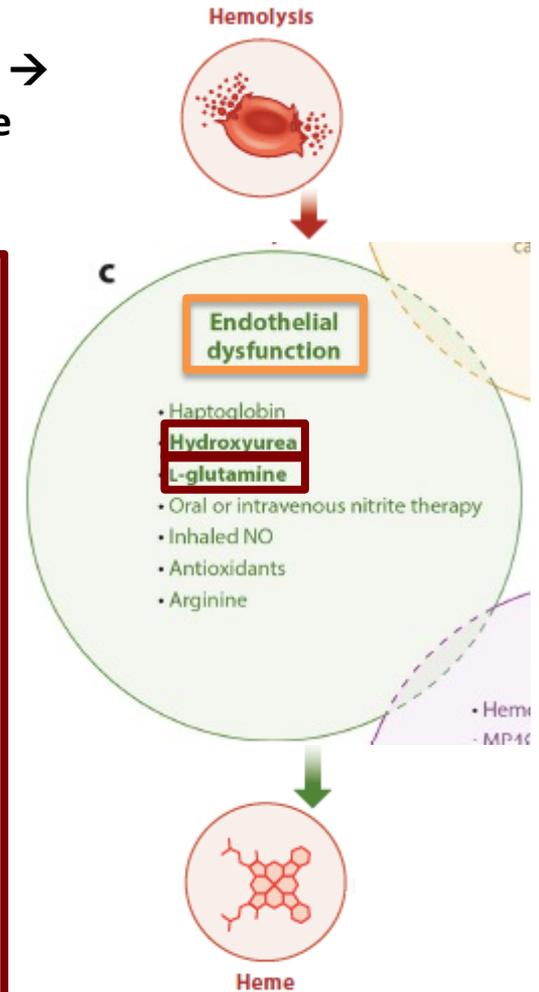
- **Idrossiurea**
- **L-Glutamina**

- Aptoglobina      **Hb libera:**
- Nitriti - **NO**      **neutralizza NO →**
- Antiossidanti      **vasocostrizione**
- Arginina



**Azione sul metabolismo GR**  
**In SCD PK è meno stabile:**  
**adeguata produzione di ATP, ma**  
**incrementata richiesta**

- **Mitapivat:** attivatore allosterico di PK-R (PKR) che agisce nell'ultimo step della glicolisi per produrre ATP
- **Mitapivat ricostituisce attività** e termostabilità di PK, riduce 2,3-DPG e p50, **incrementa ATP migliorando lo stato redox intracellulare per riduzione di emolisi e sickling**



Van Dijk, MJ, Blood Advances 2023



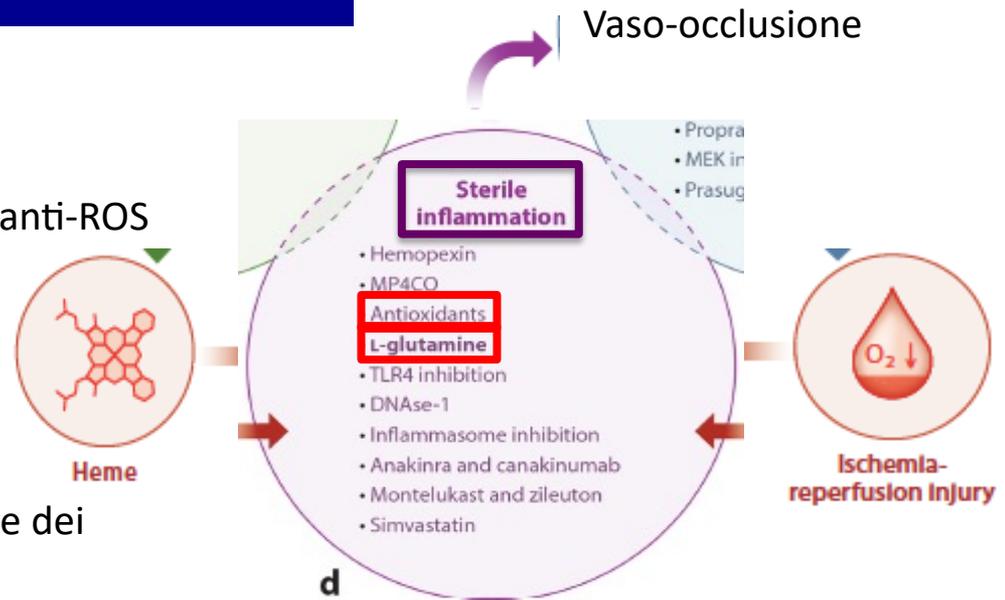
✓ **Authorised**

This medicine is authorised for use in the European Union

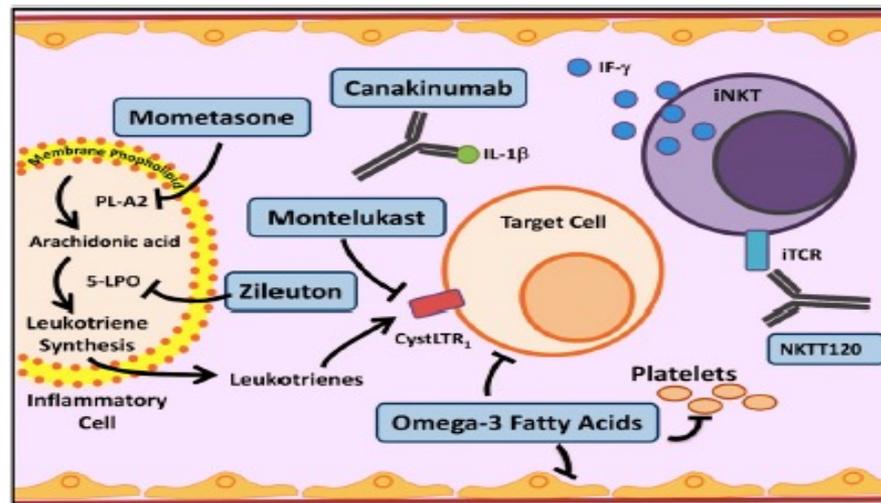
Per deficit di Piruvato Kinasi

# Anti-ossidanti – Anti-infiammatori

- **L-Glutamina**
- **N-AcetilCisteina (NAC):** antiossidante anti-ROS
- Emopexina
- Anti-ossidanti
- Anakinra
- Canakinumab
- **Montelukast:** antagonista del recettore dei leucotrieni
- **Simvastatina:** previene danno endoteliale up-regolando la sintesi di NO



*Sunnd P, Annu. Rev. Pathol. Dis 2019*



# Trapianto di midollo, Gene Therapy, Gene Editing

## Bone Marrow Transplantation In Sickle Cell Disease

Damilola Ashorobi; Ruchi Bhatt.

NCBI Bookshelf. A service of the National Library of Medicine, National Institutes of Health.

StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022 Jan-.

## Gene Therapy in a Patient with Sickle Cell Disease

Jean-Antoine Ribeil, M.D., Ph.D., Salima Hacein-Bey-Abina, Pharm.D., Ph.D., Emmanuel Payen, Ph.D., Alessandra Magnani, M.D., Ph.D., Michaela Semeraro, M.D., Ph.D., Elisa Magrin, Ph.D., Laure Caccavelli, Ph.D., Benedicte Neven, M.D., Ph.D., Philippe Bourget, Pharm.D., Ph.D., Wassim El Nemer, Ph.D., Pablo Bartolucci, M.D., Ph.D., Leslie Weber, M.Sc., Hervé Puy, M.D., Ph.D., Jean-François Meritet, Ph.D., David Grevent, M.D., Yves Beuzard, M.D., Stany Chrétien, Ph.D., Thibaud Lefebvre, M.D., Robert W. Ross, M.D., Olivier Negre, Ph.D., Gabor Veres, Ph.D., Laura Sandler, M.P.H., Sandeep Soni, M.D., Mariane de Montalembert, M.D., Ph.D., Stéphane Blanche, M.D., Philippe Leboulch, M.D., and Marina Cavazzana, M.D., Ph.D.

N Engl J Med 2017;376:848-55.

DOI: 10.1056/NEJMoa1609677

## CRISPR-Cas9 Gene Editing for Sickle Cell Disease and $\beta$ -Thalassemia

H. Frangoul, D. Altshuler, M.D. Cappellini, Y.-S. Chen, J. Domm, B.K. Eustace, J. Foell, J. de la Fuente, S. Grupp, R. Handgretinger, T.W. Ho, A. Kattamis, A. Kernysky, J. Lekstrom-Himes, A.M. Li, F. Locatelli, M.Y. Mapara, M. de Montalembert, D. Rondelli, A. Sharma, S. Sheth, S. Soni, M.H. Steinberg, D. Wall, A. Yen, and S. Corbacioglu

N Engl J Med 2021;384:252-60.

DOI: 10.1056/NEJMoa2031054

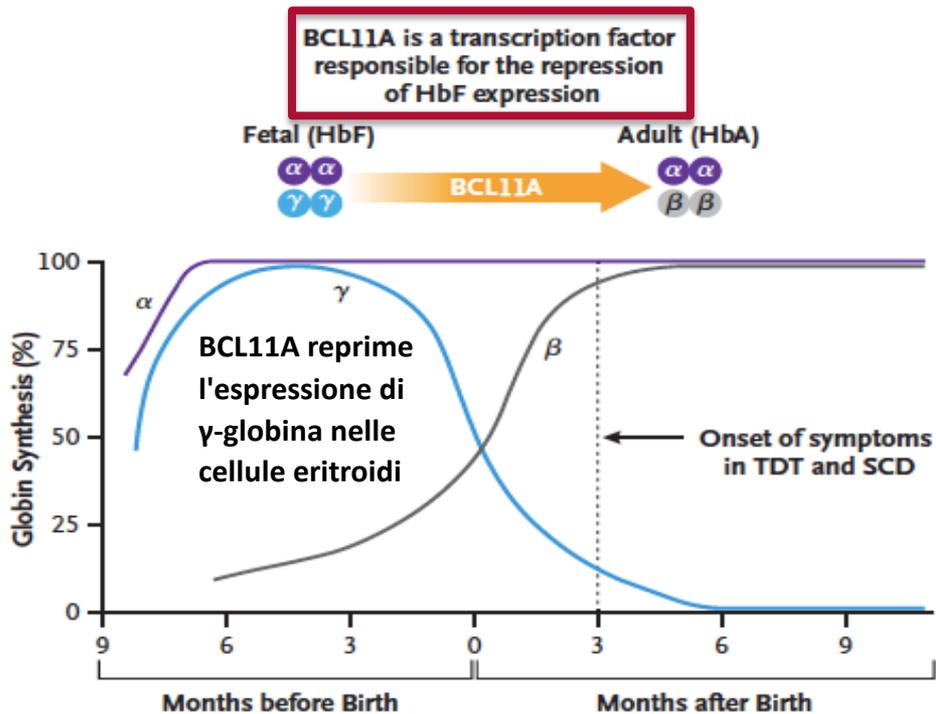
# CRISPR-Cas9 Gene Editing for Sickle Cell Disease and $\beta$ -Thalassemia

H. Frangoul, D. Altshuler, M.D. Cappellini, Y.-S. Chen, J. Domm, B.K. Eustace, J. Foell, J. de la Fuente, S. Grupp, R. Handgretinger, T.W. Ho, A. Kattamis, A. Kernysky, J. Lekstrom-Himes, A.M. Li, F. Locatelli, M.Y. Mapara, M. de Montalembert, D. Rondelli, A. Sharma, S. Sheth, S. Soni, M.H. Steinberg, D. Wall, A. Yen, and S. Corbacioglu

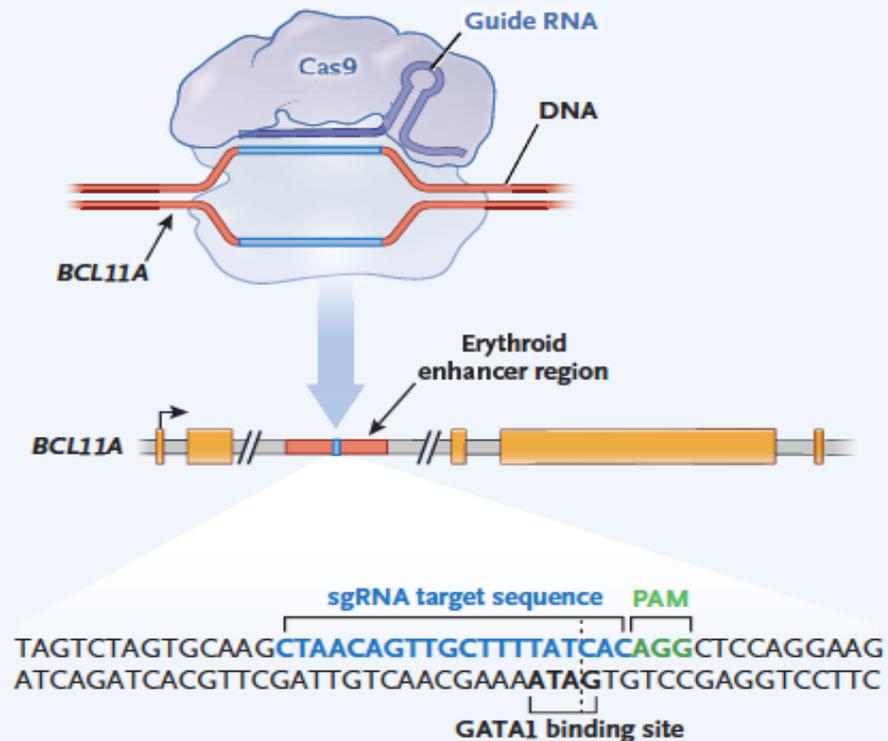
N Engl J Med 2021;384:252-60.  
DOI: 10.1056/NEJMoa2031054

CLIMB SCD-121 trial

## A Transition from Fetal to Adult Hemoglobin

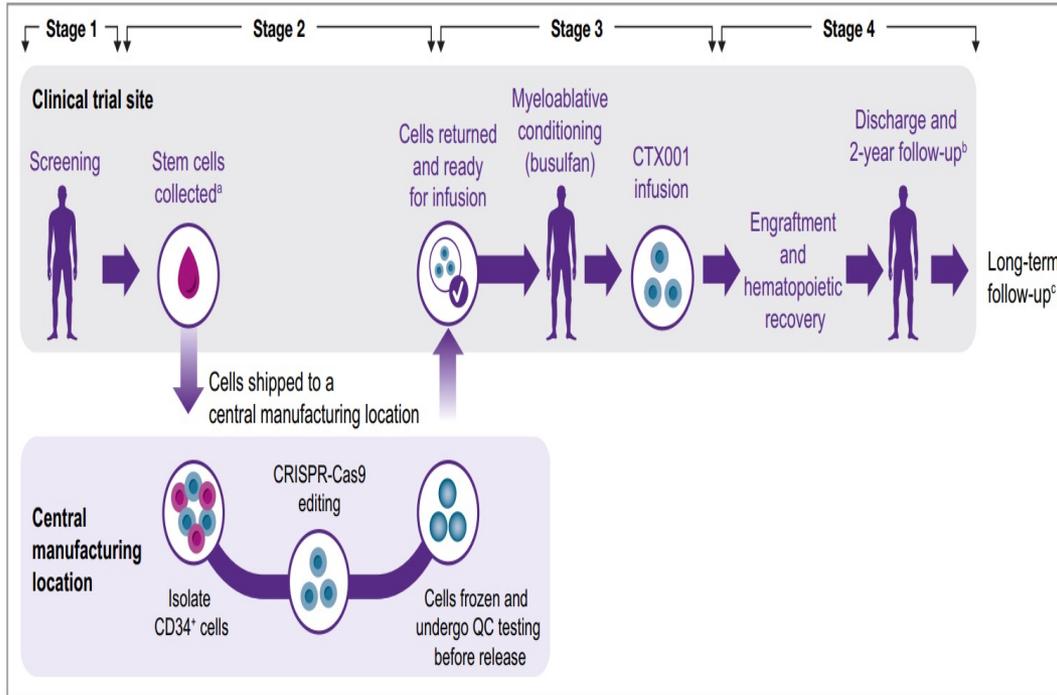


## B Targeting of Editing Site



**Non-viral cell therapy.** Riattivazione dell'HbF mediante gene editing con CRISPR-Cas9 delle regioni enhancer eritroide-specifiche di *BCL11A* in cellule staminali ematopoietiche CD34+ autologhe e in progenitori eritroidi (HSPCs) di donatori sani modificate

# Exagamglogene Autotemcel



Adapted from *The New England Journal of Medicine*, Frangoul H et al. CRISPR-Cas9 Gene Editing for Sickle Cell Disease and  $\beta$ -Thalassemia, 384., 252-260. Copyright © (2020) Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society. QC, quality control.

- Phase 3, open-label, single-dose
- Mobilizzazione HSPCs con plerixafor

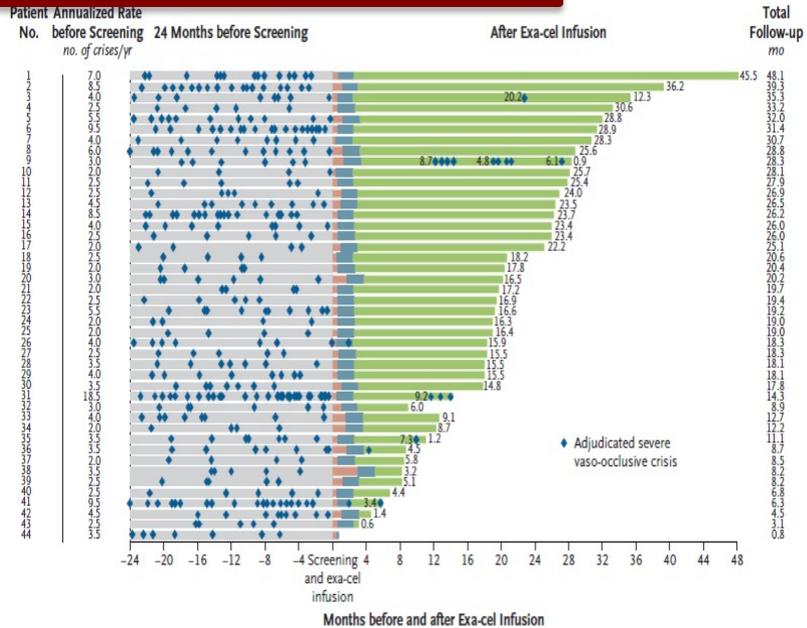
- **Scopo:** ridurre l'espressione di BCL11A nelle linee cellulari eritroido-specifiche, riattivare la sintesi della  $\gamma$ -globina e di conseguenza la quota di HbF
- **Risultati:** dopo un anno di terapia (post-mieloablazione) in due pazienti (TDT e SCD) → livelli elevati di editing allelico nel midollo osseo e nel sangue con incremento dell'emoglobina fetale con distribuzione pancellulare → **trasfusione-indipendenza in TDT**  
**assenza di VOCs in SCD**

✓ Authorised

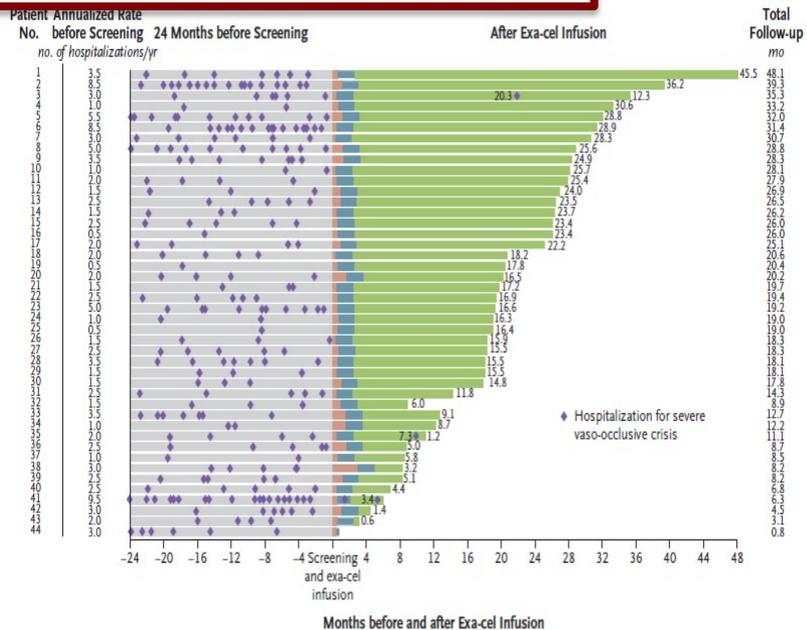
This medicine is authorised for use in the European Union

■ Baseline period ■ Time from exa-cel infusion to last red-cell transfusion in the initial period ■ 60-Day washout period after last red-cell transfusion ■ Time from washout period to data cutoff or end of study

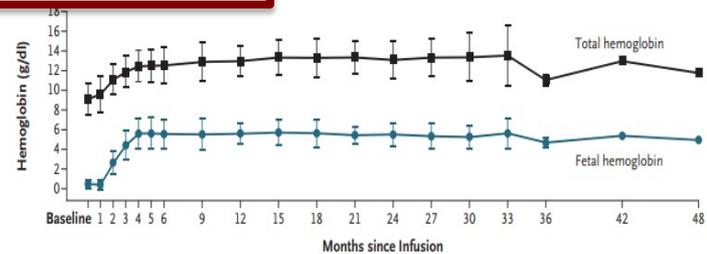
### A Duration of Periods Free from Severe Vaso-Occlusive Crises after Exa-cel Infusion in All Patients



### B Duration of Periods Free from Inpatient Hospitalization for Severe Vaso-Occlusive Crises in All Patients

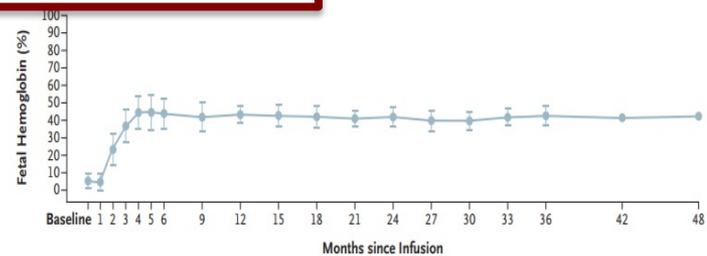


### A Mean Total Hemoglobin and Fetal Hemoglobin Levels



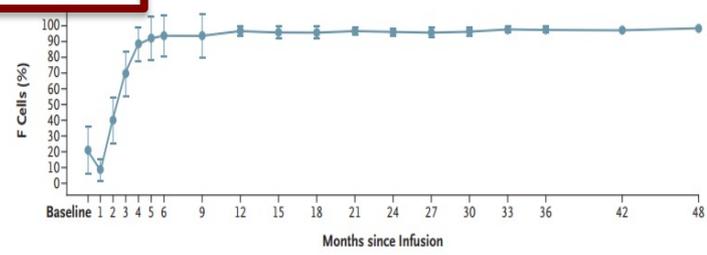
No. of Patients	43	42	43	43	41	41	38	34	31	29	27	16	17	10	7	4	2	1	1
Total hemoglobin	43	42	43	43	41	41	38	34	31	29	27	16	17	10	7	4	2	1	1
Fetal hemoglobin	43	42	43	43	41	40	38	34	31	29	27	16	17	10	7	4	2	1	1

### B Mean Fetal Hemoglobin as Percentage of Total Hemoglobin



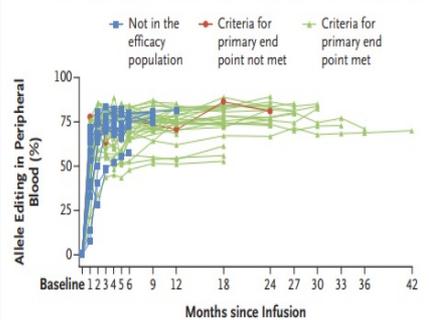
No. of Patients	44	42	43	43	41	40	38	34	32	29	27	16	17	10	7	4	2	1	1
Total hemoglobin	44	42	43	43	41	40	38	34	32	29	27	16	17	10	7	4	2	1	1
Fetal hemoglobin	44	42	43	43	41	40	38	34	32	29	27	16	17	10	7	4	2	1	1

### C Mean Percentages of F Cells

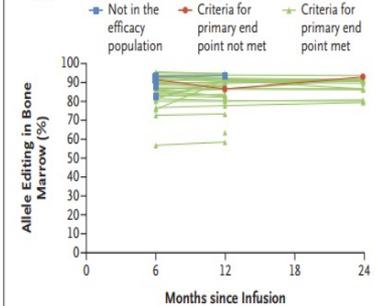


No. of Patients	44	43	43	41	41	39	34	32	29	27	17	17	10	7	4	2	1	1
Total hemoglobin	44	43	43	41	41	39	34	32	29	27	17	17	10	7	4	2	1	1
Fetal hemoglobin	44	43	43	41	41	39	34	32	29	27	17	17	10	7	4	2	1	1

### D Individual Percentages of Edited Alleles in Peripheral-Blood Nucleated Cells



### E Individual Percentages of Edited Alleles in Bone Marrow CD34+ Cells



# Take Home Messages

- **La drepanocitosi è una patologia multisistemica, caratterizzata da eterogeneità clinica, con episodi di acuzie e progressivo danno d'organo, gravata da elevata morbilità e mortalità, con frequente utilizzo delle risorse sanitarie**
- **Meccanismi Fisiopatologici: emolisi, vaso-occlusione, danno endoteliale ed infiammazione asettica**
- Essenziale la diagnosi precoce e l'inizio tempestivo della terapia per la prevenzione delle complicanze
- Conoscenza di modificatori dell'espressione clinica e dei fattori prognostici negativi essenziale nella prevenzione dello sviluppo del danno d'organo
- **Nuova era per la terapia della drepanocitosi; alla complessità della fisiopatologia, corrisponde la complessità del trattamento**
- Identificati nuovi target; **numerosi agenti in fase pre-clinica, fase I/II/III - difetto genetico**

# Grazie al Centro Emoglobinopatie



**Grazie per l'attenzione**

