# La drepanocitosi

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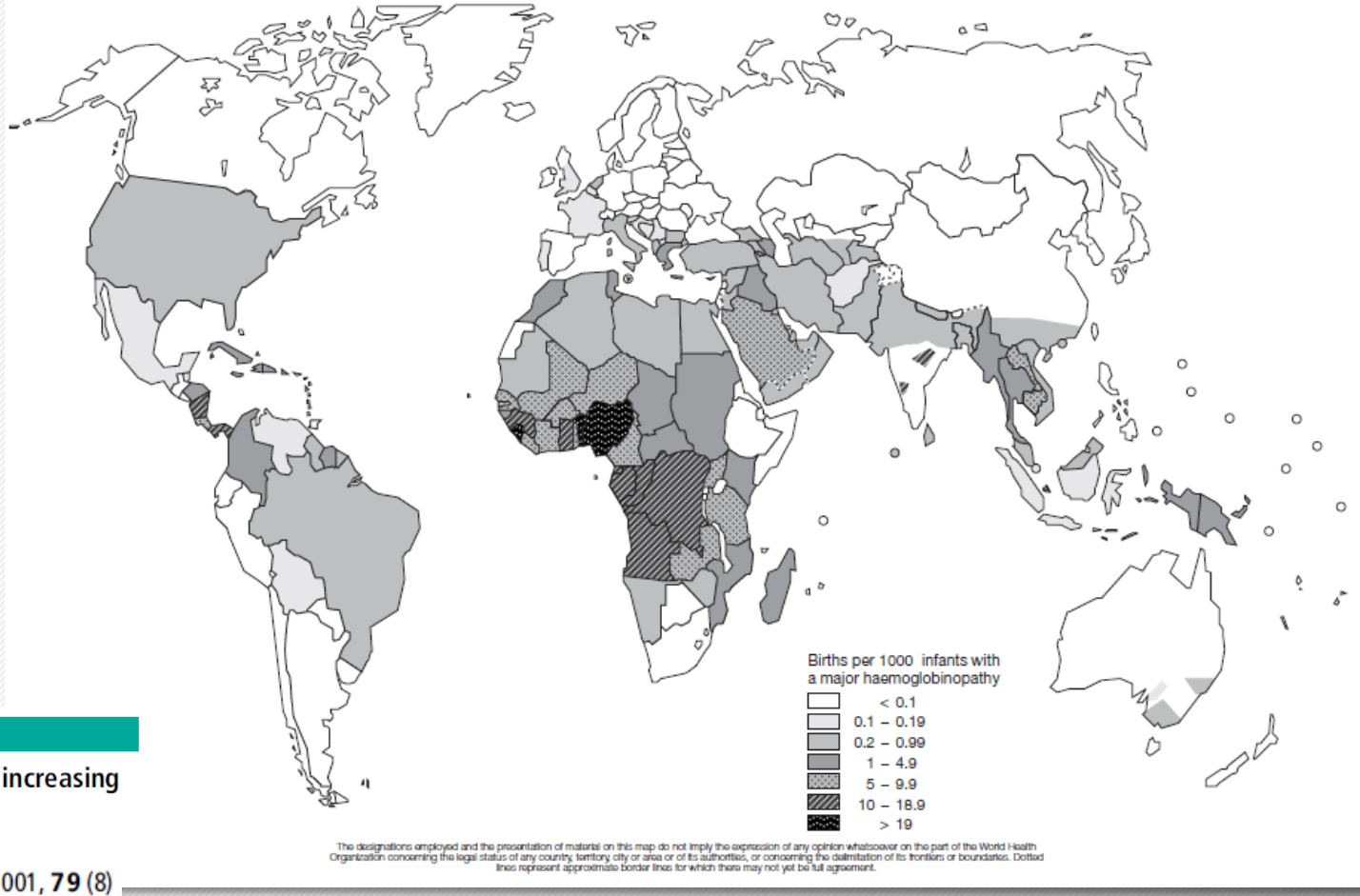
# Distribuzione globale delle emoglobinopatie

Figure 7
**Global distribution of haemoglobin disorders, in terms of births of affected infants per1000 births**




**Public Health Reviews**

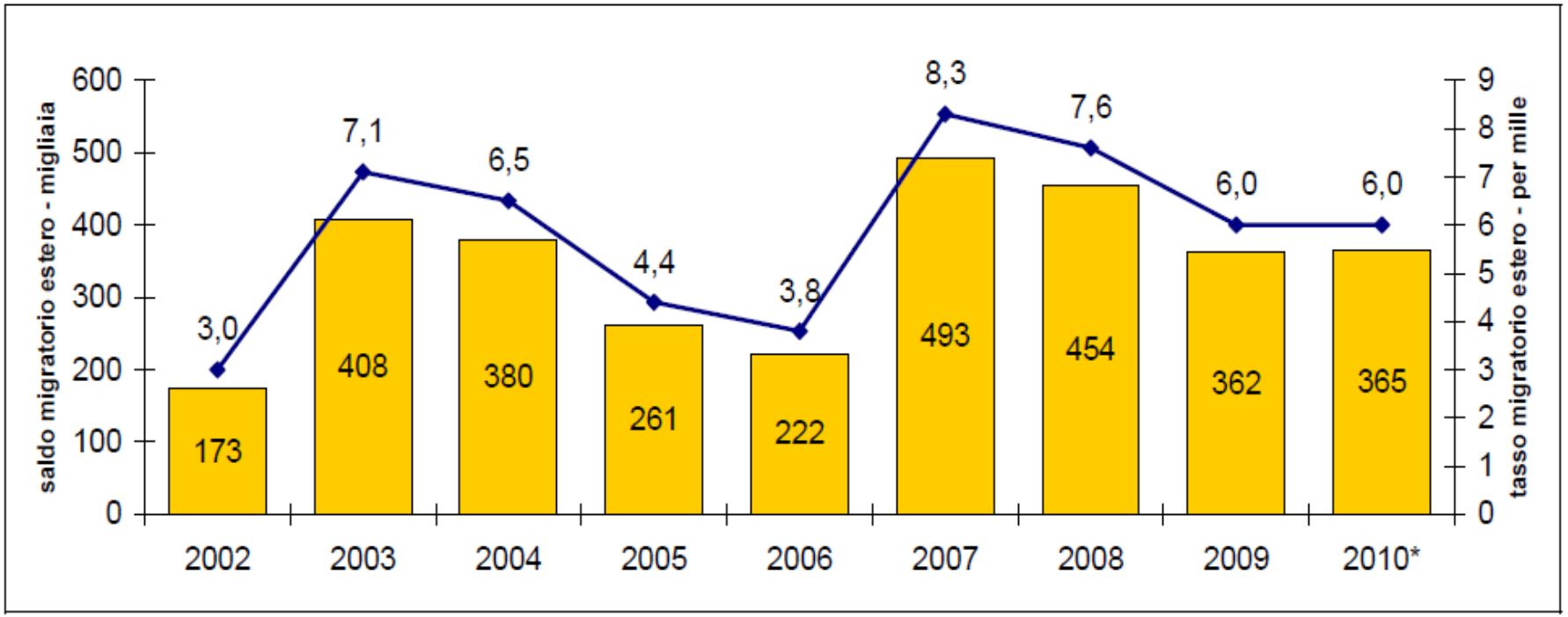
Inherited haemoglobin disorders: an increasing global health problem

D.J. Weatherall[1] & J.B. Clegg[2]

Bulletin of the World Health Organization, 2001, **79** (8)

# La situazione italiana

Figura 5 – Saldo migratorio con l'estero (migliaia) e tasso migratorio con l'estero (per mille) – Italia, Anni 2002-2010




* stima

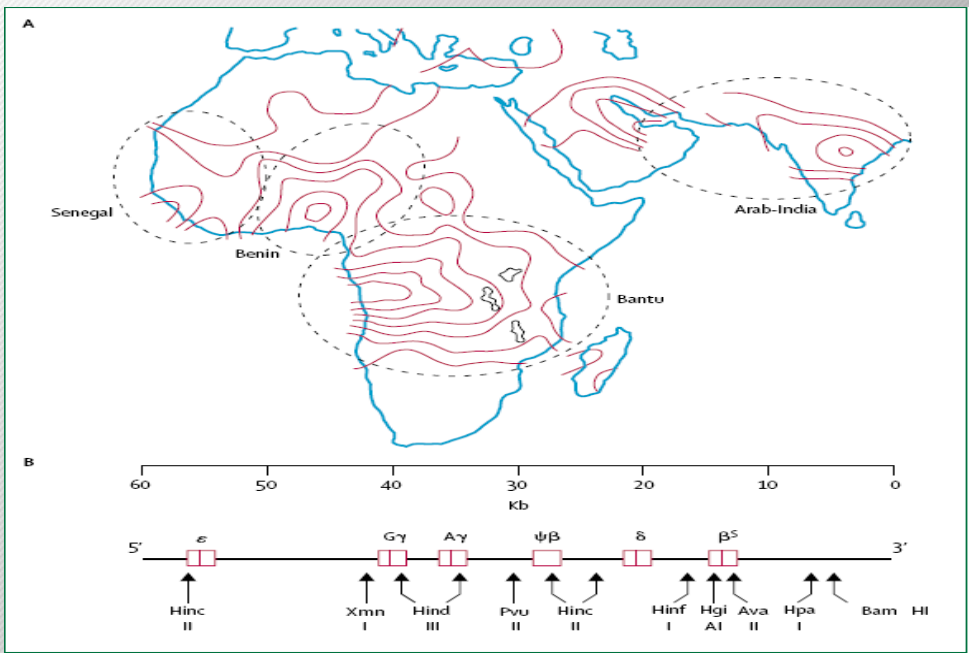
| | N. medio figli per donna | Età media al parto |
|---|---|---|
| DONNE ITALIANE | 1.29 | 31.8 |
| DONNE STRANIERE | 2.13 | 28.9 |

Nel 2010 oltre **104.000** nascite (18.8%) attribuibili a madri straniere (nel 2000: **35.000**, pari al 6,4%)

Dati ISTAT 2011

# Drepanocitosi

- Sempre esistita in Africa la nozione di una malattia caratterizzata da crisi dolorose e morte in giovane età, legata a varie credenze tribali.
- Incidenza > 1:3.000 negli Stati Uniti
- Terza causa di morte in africa per bambini ospedalizzati (dopo malaria e gastroenteriti)
- Lo stato di portatore eterozigote conferisce resistenza all'infezione da *Plasmodium falciparum* (selezione, polimorfismo bilanciato)
- 4 aplotipi principali legati alla mutazione
- 3 africani, 1 indo-europeo)
- → migrazioni → diffusione



# La situazione italiana

## LETTERS TO THE EDITOR

### Hospitalization of children with sickle cell disease in a region with increasing immigration rates

Sickle cell disease (SCD) has become a paradigm of immigration hematology in Europe. Accurate up-to date information is needed to determine SCD prevalence, define real burden of disease and develop appropriate clinical networks of care, especially in regions lacking screening programs. We used two independent sources of data (Regional Register of Rare Disorders and Regional Register of Hospital Discharge Records) to determine extent of SCD and pattern of hospitalization of pediatric patients in the Veneto Region of North-East Italy. A steady increase of case notifications and hospitalizations has been observed in the past five years. Ninety-five percent of patients are immigrants with HbS/HbS SCD. Specialized regional registers can be used to define disease extent and guide targeted interventions in regions still lacking comprehensive care screening programs.

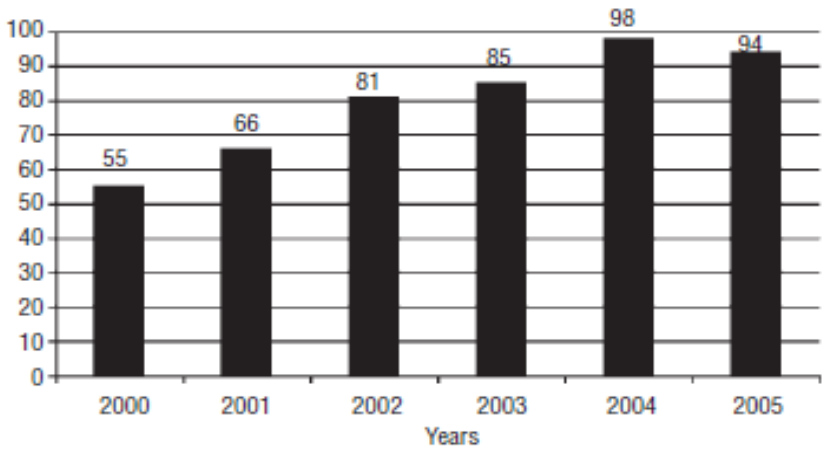



Figure 1. Inpatient admissions due to sickle cell disease in the Veneto Region per year from 2000 to 2005.

# Sickle cell disease as a paradigm of immigration hematology: new challenges for hematologists in Europe

***Irene Roberts, Mariane de Montalembert***

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**Table 1.** Carrier frequencies for HbS (*modified from Weatherall & Clegg, 2001*).

| *Country* | *Carrier frequency (%)* |
|---|---|
| **Africa** | |
| Nigeria | 19-27 |
| The Gambia | 6-24 |
| Senegal | 5-15 |
| Liberia | 1-23 |
| Cote d'Ivoire | 3-22 |
| Mali | 7-29 |
| Ghana | 3-22 |
| Benin | 7-29 |
| Niger | 5-33 |
| Cameroon | 8-34 |
| Central African Republic | 1-21 |
| Gabon | 8 |
| Democratic Republic of Congo | 2-0 |
| Angola | 4-24 |
| Zambia | 6-27 |
| Uganda | 4-30 |
| United Republic of Tanzania | 10-38 |
| Kenya | 2-32 |
| Sierra Leone | 16-30 |

| *Country* | *Carrier frequency (%)* |
|---|---|
| **Eastern Mediterranean** | |
| Saudi Arabia | 1-29 |
| Iraq | 0-22 |
| **India** | |
| Madras | 20 |
| Andhra Republic Pradesh | 17 |
| Madhya Pradesh | 20 |
| Gujarat | 30 |
| Orissa | 25 |

# Drepanocitosi: la genetica

- Sostituzione di un **singolo nucleotide** (GTG al posto di GAG) nel sesto codone del gene per la β-globina → valina al posto di acido glutamico
- Omozigoti → "**Anemia a cellule falciformi**" (HbS>90%)
- "**Malattia a cellule falciformi**": per eterozigoti composti in cui un gene della beta-globina porta la mutazione per HbS e l'altro un'altra mutazione (HbS>50%)
- Se la malattia è monogenica, lo stesso non si può dire della sua espressione fenotipica (geni pleiotropici)

**I genotipi della malattia a cellule falciformi**

- **HbSS o anemia falciforme**: soggetto omozigote per il gene $\beta^s$, con un quadro grave o moderatamente grave.
- **HbS/$\beta^0$**: doppia eterozigosi per HbS e thalassemia $\beta^0$. Quadro clinico pressoché indistinguibile dall'anemia falciforme.
- **HbSC**: doppia eterozigosi per HbS ed HbC, con un quadro clinico a gravità intermedia.
- **HbS/$\beta^+$**: doppia eterozigosi per HbS e thalassemia $\beta^+$. Quadro clinico in genere moderato, ma variabile nei diversi gruppi etnici.
- **HbS/ persistenza ereditaria di HbF (S/HPHP)**: quadro clinico lieve o privo di sintomi.
- **HbS/HbE**: combinazione molto rara e generalmente con un quadro clinico estremamente lieve.
- Rare combinazioni di **HbS** con **HbD Los Angeles**, **Hb Punjab**, **HbO Arabia** o **HbG-Philadelphia** tra le altre.

# Fisiopatologia della falcizzazione

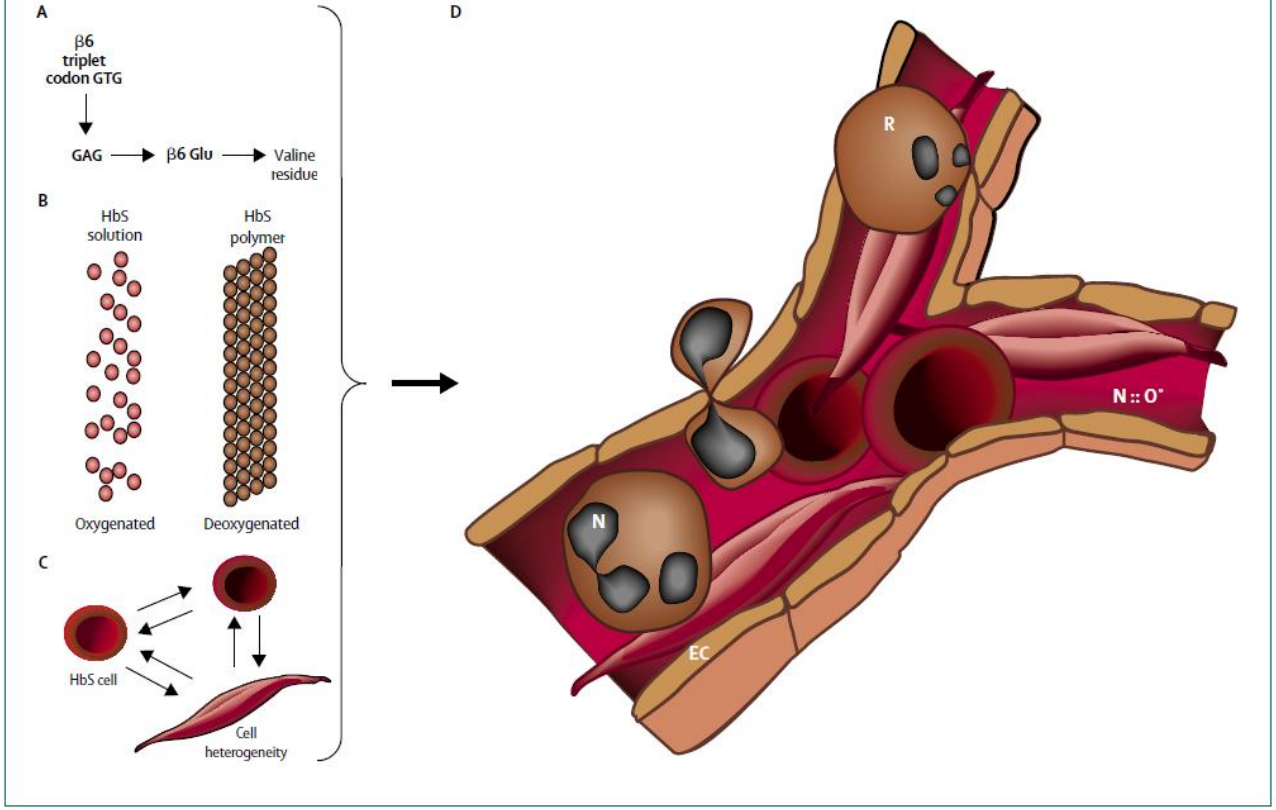
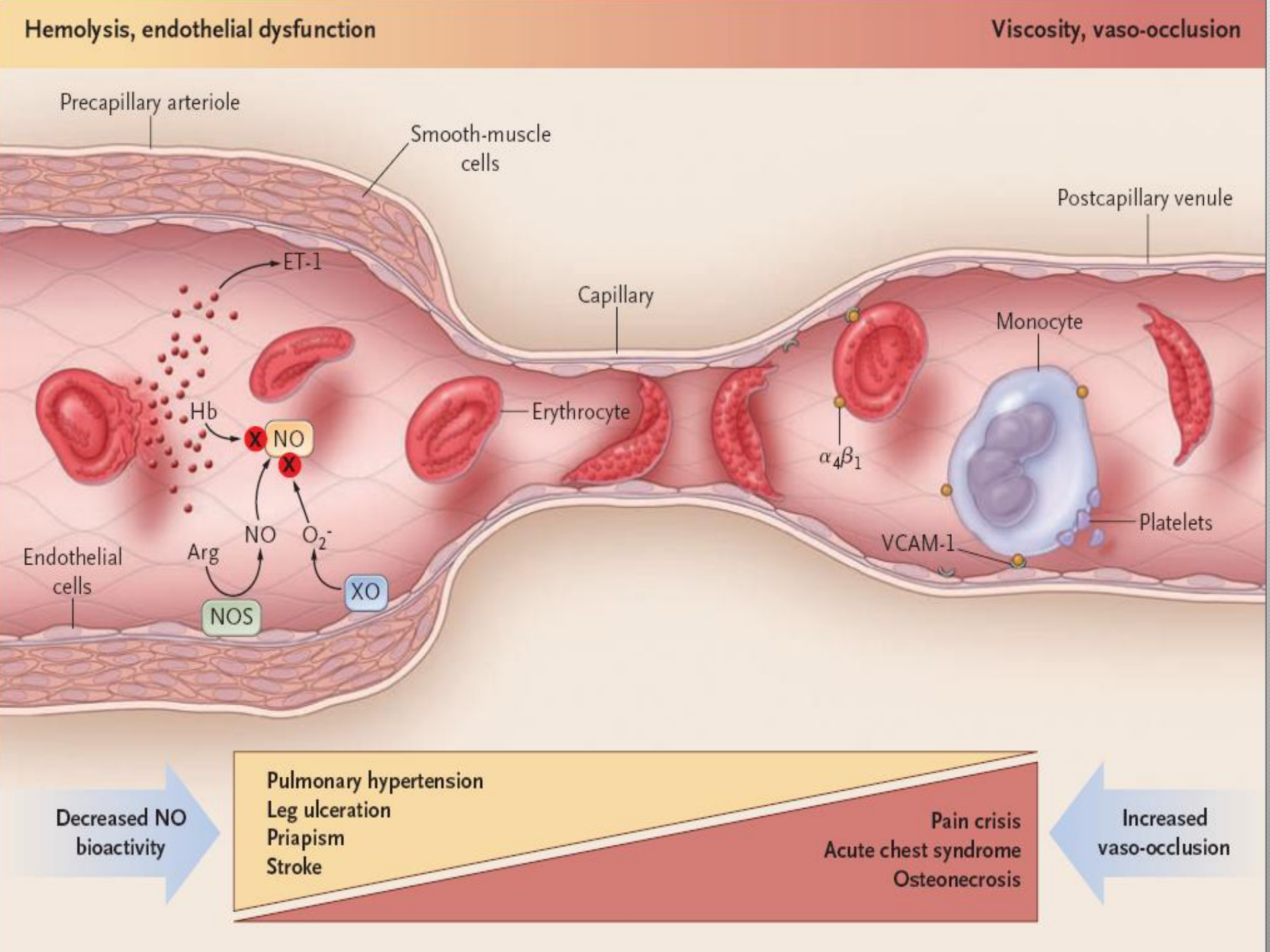



***Figure 2:*** **Pathophysiology of vaso-occlusion**
(A) Single nucleotide substitution (GTG for GAG). (B) HbS polymerisation. (C) Cell shape changes of HbS-polymer-containing erythrocyte. (D) Cross-section of microvascular bifurcation. EC=endothelium. R=reticulocyte. ISC=irreversibly sickled cell. N=leucocyte. N::O˙=NO bioavailability. RBC=red blood cell. Luminal obstruction has been initiated by attachment of proadhesive reticulocyte to endothelium with secondary trapping of irreversible sickled cells. Leucocytes participate in formation of heterocellular aggregates, and NO bioavailability crucial to vasodilation is impaired. Figure adapted from reference 13, by permission of M H Steinberg.


Hemolysis, endothelial dysfunction
Viscosity, vaso-occlusion
Precapillary arteriole
Smooth-muscle cells
Postcapillary venule
ET-1
Capillary
Monocyte
Hb
NO
Erythrocyte
$\alpha_4\beta_1$
Platelets
VCAM-1
Endothelial cells
Arg
NO
$O_2^-$
NOS
XO
Decreased NO bioactivity
Pulmonary hypertension
Leg ulceration
Priapism
Stroke
Pain crisis
Acute chest syndrome
Osteonecrosis
Increased vaso-occlusion

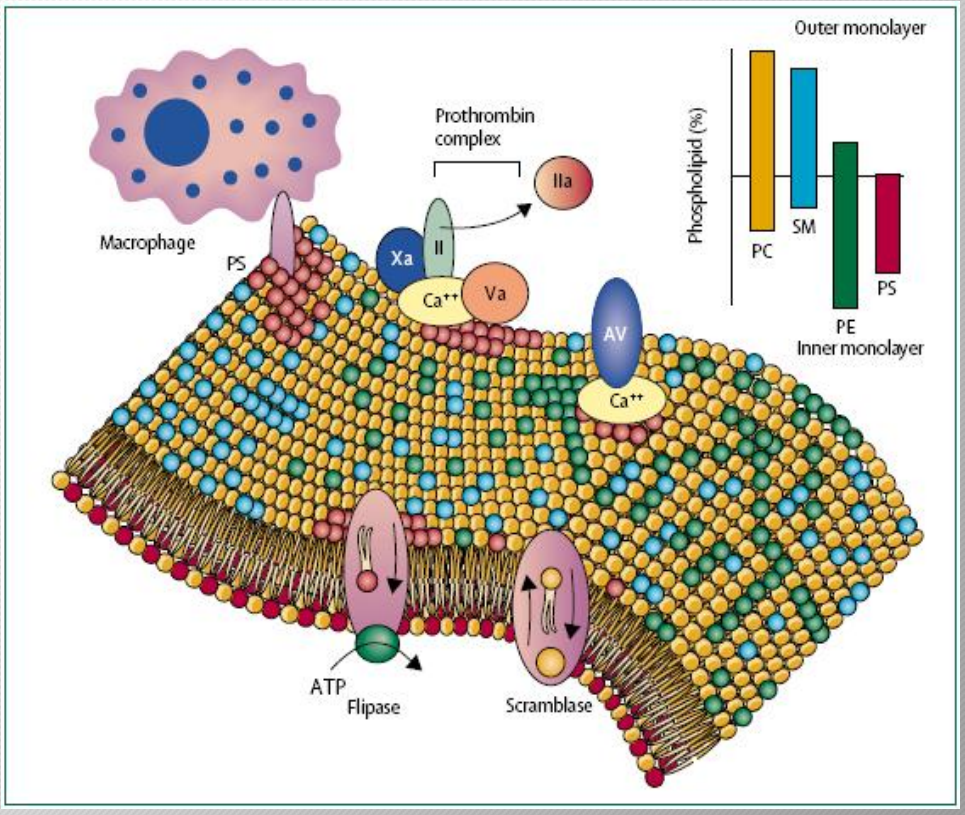
# Drepanocitosi - fisiopatologia

**Meccanismi intra-eritrocitari**

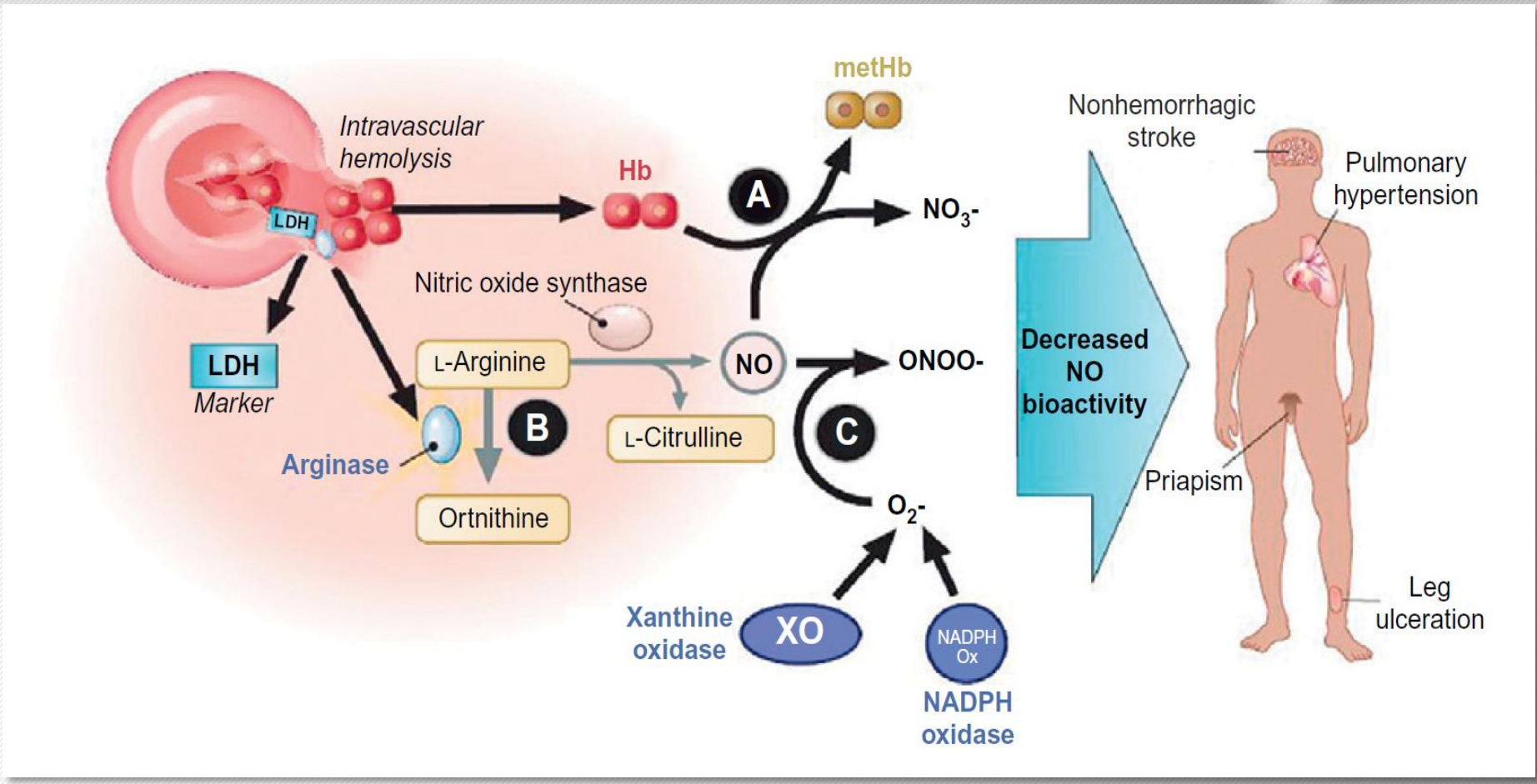
- Polimerizzazione HbS (grado di desaturazione dell'Hb, pH, percentuale di HbF)
- Emolisi intravascolare
  → Riduzione NO
- Omeostasi cationica
- Sovraespressione molecole di adesione
- Disfunzione del doppio layer lipidico

**Meccanismi extra-eritrocitari**

- Aumentata viscosità ematica
- Leucociti (e significato prognostico)
- Piastrine
- Danno endoteliale
- Fattori della coagulazione



# Drepanocitosi – Deplezione NO



# Drepanocitosi – quadri clinici

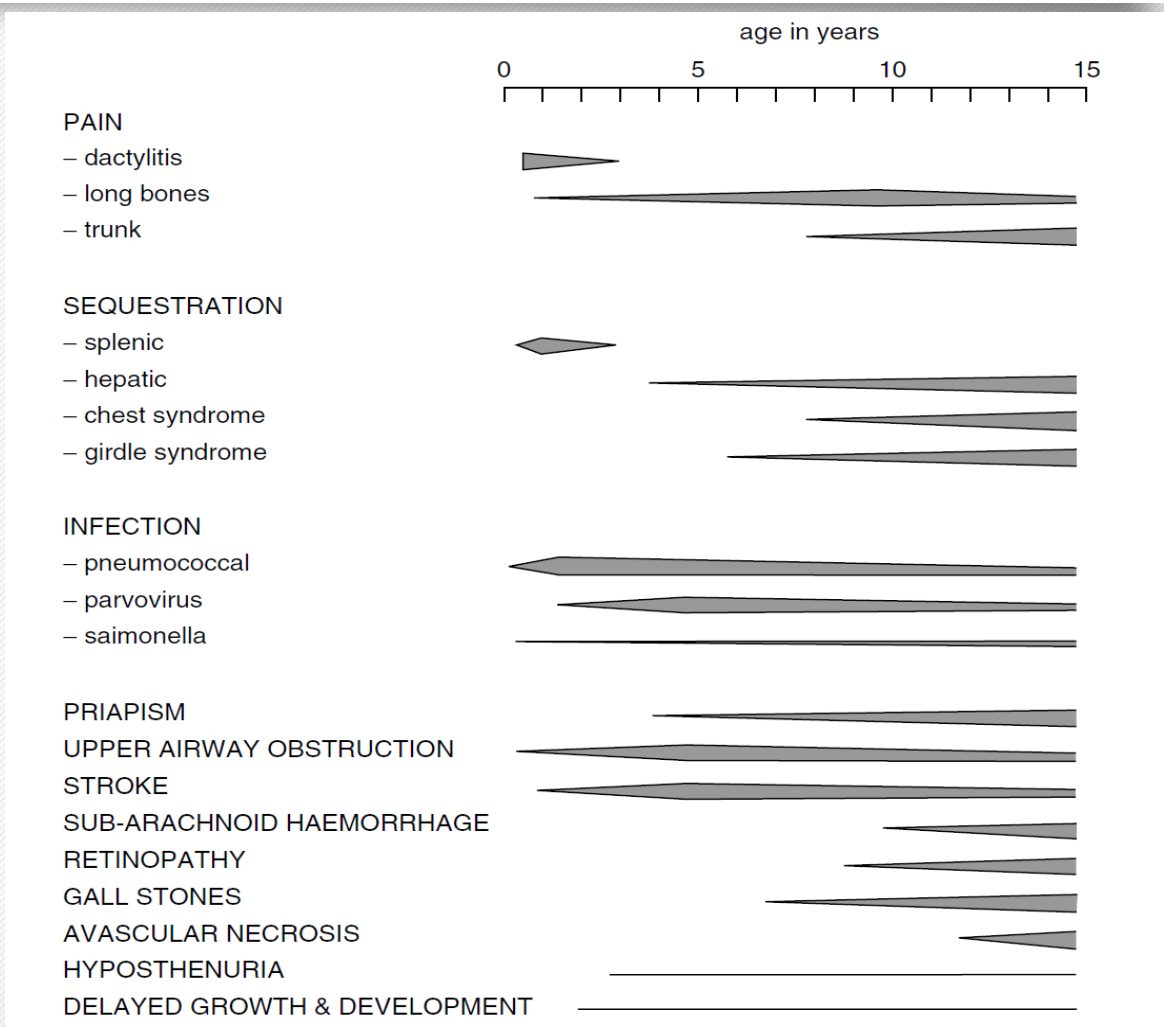
- Sintomi clinici in caso di omozigosi legati a:
  - **anemia emolitica cronica**:
    - normocitica e normocromica;
    - anisopoichilocitosi, emazie a bersaglio, policromatofilia;
    - reticolocitosi.
  - **asplenia** (infarti splenici);
  - **fenomeni vaso-occlusivi** a carico di piccoli e grossi vasi con crisi dolorose e danno d'organo (causa più importante di morbidità e mortalità).

# Drepanocitosi – quadri clinici

**Manifestazioni cliniche acute**

- *“hand-foot syndrome”* (dattilite, spesso la prima manifestazione)
- crisi vaso-occlusive (crisi dolorose)
- sindrome toracica acuta
- sequestro splenico
- crisi aplastiche
- accidenti cerebrovascolari
- priapismo
- infezioni ricorrenti: osteomieliti, sepsi

# Drepanocitosi – quadri clinici




Bailliere's Clinical Hematology. London: Bailliere Tindall, 1991;361.

# Drepanocitosi - clinica

**Manifestazioni cliniche acute**

- **“*hand - foot syndrome*” o sindrome mani – piedi:**
  - spesso è la prima manifestazione clinica della drepanocitosi nel bambino (in particolare nei primi 2 anni di vita);
  - colpisce le estremità con dolore e tumefazioni del dorso delle mani e dei piedi per occlusione del microcircolo;
  - *dattilite*: interessamento delle piccole ossa delle mani e dei piedi, che appaiono  tumefatte, calde e dolenti.

# Drepanocitosi - clinica

**Manifestazioni cliniche acute**

- **Crisi vaso-occlusive (crisi dolorose):**
  - manifestazione clinica distintiva della drepanocitosi;
  - interessano sia il micro- che il macro-circolo, generalmente a livello degli organi con flusso ematico lento (milza, ossa, fegato, midollare del rene) o di quelli ad attività metabolica più elevata (muscoli, cervello, placenta);
  - causa scatenante: processi infettivi, freddo, fatica fisica, disidratazione, immobilizzazione prolungata. A volte causa ignota.

# Drepanocitosi - clinica

**Manifestazioni cliniche acute**

- **Sindrome toracica acuta *(acute chest syndrome)*:**
  - comparsa di lesione polmonare all'Rx torace in associazione con febbre, dispnea, dolore toracico, ipossiemia;
  - Rx: addensamenti prevalentemente ai lobi superiori o medi;
  - causa scatenante: nei bambini al di sotto dei 4 anni le infezioni respiratorie;
  - quadro clinico che può evolvere in senso peggiorativo anche in poche ore.

# Drepanocitosi - clinica

**Manifestazioni cliniche acute**

- **Sequestro splenico:**
  - intrappolamento e distruzione delle emazie all'interno dei sinusoidi splenici ed epatici:
    - bambino: più frequente il sequestro splenico;
    - adulto: più frequente il sequestro epatico.
  - importante causa di morbilità e mortalità;
  - rapida anemizzazione, associata ad improvvisa splenomegalia e reticolocitosi.
  - collasso cardio-circolatorio dovuto all'ipovolemia improvvisa, shock;
  - mortalità elevata: 7 – 30% (necessità di tempestivo inizio del trattamento medico).

# Drepanocitosi - clinica

**Manifestazioni cliniche acute**

- **Crisi aplastiche:**
  - fanno parte della storia naturale di tutte le anemie emolitiche e quindi anche della drepanocitosi;
  - il tempo di sopravvivenza degli eritrociti è ridotto anche nelle fasi di benessere;
  - reticolocitopenia e rapido calo dell'emoglobina fino anche a 2 – 3 g/dL;
  - causata soprattutto da stimoli di natura infettiva, prevalentemente virale: ***Parvovirus B19***;
  - citotossicità diretta del *Parvovirus B19* sui precursori eritroidi midollari (nel 15-25% dei casi vengono coinvolti anche i precursori mieloidi e megacariocitari);
  - l'immunità contro il *Parvovirus B19* è considerata permanente.

# Drepanocitosi - clinica

**Manifestazioni cliniche acute**

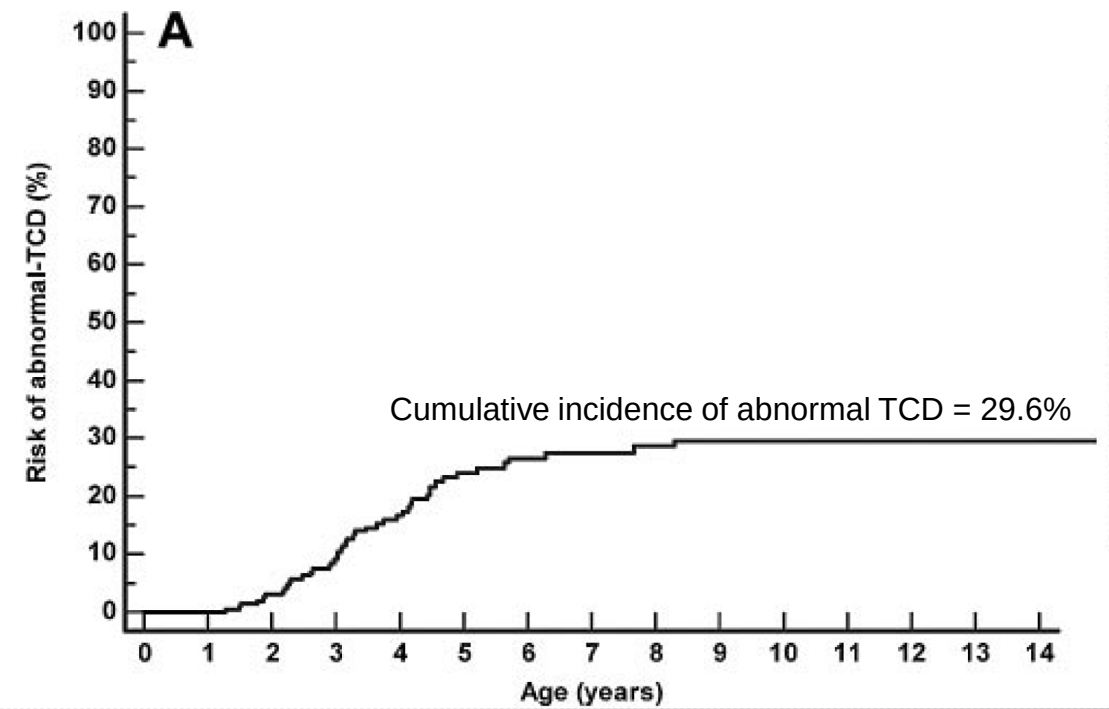
- **Eventi cerebrovascolari:**
  - rappresentano una delle più gravi complicanze della drepanocitosi;
  - stroke ischemico (arterial ischemic stroke);
  - infarto silente: alterata immagine RMN in assenza di storia clinica o deficit neurologico (fino al 20% dei bambini con drepanocitosi ha lesioni cerebrali silenti alla RMN). Deterioramento delle funzioni cognitive.
  - attacco ischemico transitorio (TIA);
  - stroke emorragico: comprende l'emorragia sub-aracnoidea e l'emorragia intra-cerebrale (mortale nel 25% dei casi);
  - valore predittivo dell'eco-doppler trans-cranico: permette di identificare restringimenti delle arterie intracraniche misurando la velocità del flusso ematico.

CME article

# Impact of early transcranial Doppler screening and intensive therapy on cerebral vasculopathy outcome in a newborn sickle cell anemia cohort

Françoise Bernaudin,[1,2] Suzanne Verlhac,[3] Cécile Arnaud,[1] Annie Kamdem,[1] Sylvie Chevret,[4] Isabelle Hau,[1] Lena Coïc,[1] Emmanuella Leveillé,[1] Elisabeth Lemarchand,[1] Emmanuelle Lesprit,[1] Isabelle Abadie,[1] Nadia Medejel,[1] Fouad Madhi,[1] Sophie Lemerle,[1] Sandra Biscardi,[1] Josiane Bardakdjian,[5] Frédéric Galactéros,[5] Martine Torres,[6] Mathieu Kuentz,[7] Christelle Ferry,[2] Gérard Socié,[2] Philippe Reinert,[1] and Christophe Delacourt[1]

## Probability of abnormal TCD (TAMMX ≥ 200 cm/sec)




- SS / Sβ0
  - 45/217 patients
  - at a median age of 3,2 years (range, 1.3 – 8.3).
  - Cumulative incidence = 29.6% at 9 years.
  - Independent risk factors:
    - Absence of α thalassemia
    - G6PD deficiency
    - Hemolysis

Bernaudin F *et al*. Blood 2011; 117(4):1130-1140.

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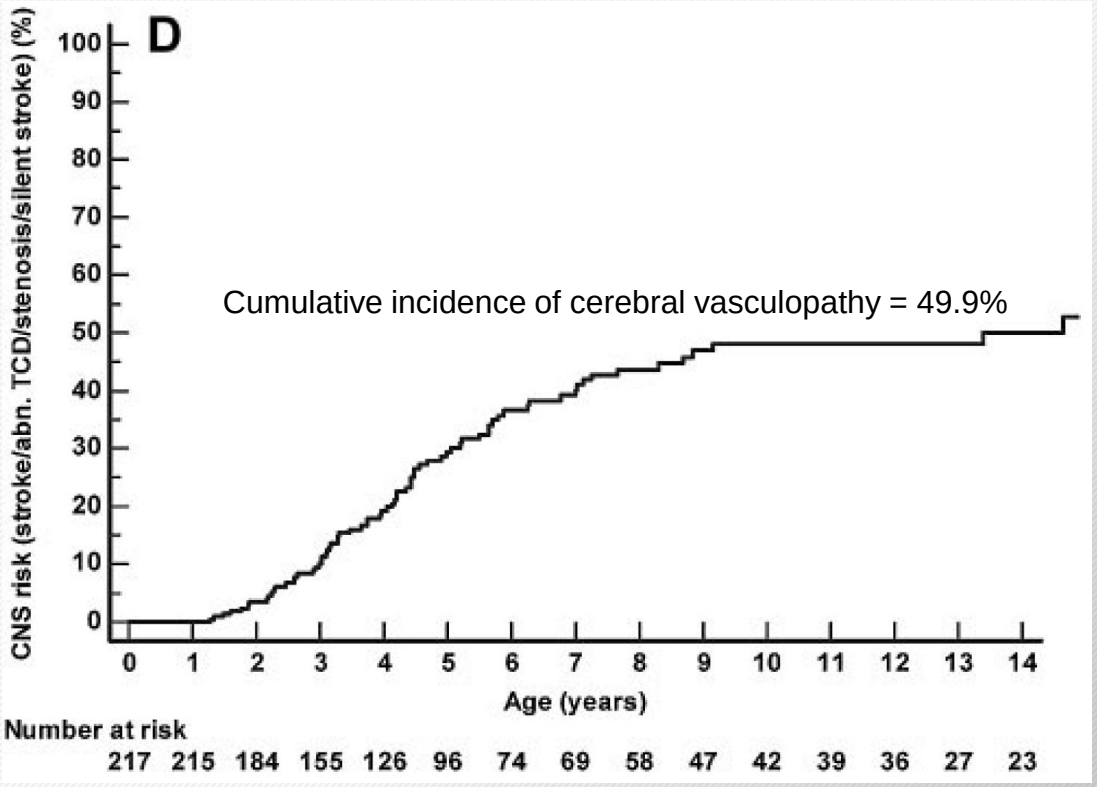
## **Probability of cerebral vasculopathy**
(stroke, abn TCD, stenosis or silent stroke)




- SS / Sβ0
  - 49.9% by 14 years of age.

Bernaudin F *et al*. Blood 2011; 117(4):1130-1140.

# Drepanocitosi - clinica

**Manifestazioni cliniche acute**

- **Infezioni ricorrenti, osteomielite, sepsi:**
  - le infezioni sono la principale causa di morte nei soggetti affetti da drepanocitosi, soprattutto nei bambini di età inferiore ai 5 anni;
  - atrofia splenica -> asplenia funzionale -> deficit linfociti B IgM memory;
  - **sepsi** da *Streptococcus pneumoniae*, *Hemophilus influenzae* e *Neisseria meningitidis*;
  - **acute chest syndrome** da *Mycoplasma pneumoniae*, *Chlamidya pneumoniae* e *Streptococcus pneumoniae*;
  - **osteomielite ed artrite settica** da *Salmonella*, *Staphylococcus aureus* e *Streptococcus pneumoniae*.
  - Importanza delle **vaccinazioni**.
  - **Profilassi antibiotica** (amoxicillina o benzilpenicillina benzatinica) in tutti i bambini (**indicazione assoluta nei primi 5 anni di vita**).

| | Major clinical manifestations | Underpinning mechanisms | Management issues |
|---|---|---|---|
| Eye | Retinitis proliferans occurs with greatest frequency in HbSC disease and can lead to visual impairment. | Peripheral retinal vascular occlusion due to red-cell and leucocyte-endothelial adhesion (via surface adhesion molecules). Angiogenic factors seem crucial to seafan formation. | Periodical ophthalmic assessment with early identification of peripheral retinal disease. |
| Kidney | Hypertrophy: occurs in all sickle genotypes, especially HbSS. Also age-dependent. | Renal enlargement is due to glomerular hypertrophy and increased renal blood volume. | .. |
| | Alterations in distal nephron function, resulting in hyposthenuria and nocturia. Tubular acidosis (type IV or incomplete distal acidosis) can also arise. | Hyposthenuria mainly due to hyperosmolar-induced loss of deep juxtamedullary nephrons, which also causes acidosis due to perturbation in bicarbonate reabsorption. | Hyposthenuria can lead to childhood enuresis. Urine-specific gravity is a poor index of hydration status. |
| | Tubular deficiencies in adults include increased secretion of creatinine and uric acid. Heightened reabsorption of phosphates (aldosterone-independent) leading to hyperphosphataemia can also take place. | Proximal tubular dysfunction. | Creatinine clearance might overestimate GFR. |
| | Glomerular abnormalities: increases in GFR and ERPF occur in children, preceded by microalbuminuria. GFR and ERPF decline towards normal rates in adolescence, and fall to subnormal rate levels in older individuals. Proteinuria could progress to nephrotic syndrome, and end-stage renal disease. HbSS patients develop renal failure earlier than those with HbSC disease (median age of onset 23 *vs* 50 years). | Mesangial phagocytosis of sickle-cells, glomerular hypertrophy, immune-complex glomerulonephritis, and hyperfiltration-induced glomerular injury have all been implicated. NSAID used for pain control further impairs renal function. | ACE inhibitors reduce microalbuminuria and reduce glomerular damage. NSAID to be used with caution in patients with sickle nephropathy. Transplantation is a recourse in some patients with end-stage renal insufficiency. |
| Lung | Most serious complication is PH (mean pulmonary artery pressure of >25 mm Hg, and/or a tricuspid jet velocity on echocardiogram >2·5 m/s). PH occurs in 5–30% of patients, with a median survival time of 2 years. | Recurrent ACS is a predisposing factor for SCD-related PH. Chronic anaemia with hypoxia, pulmonary release of inflammatory cytokines, reduction in NO synthase in small pulmonary arterioles with increase in endothelin-1, and platelet-derived factors have been implicated in pathogenesis. | Often asymptomatic in early stages. Should be suspected in those with unexplained $O_2$ desaturation, syncope, or fixed dyspnoea. Ominous prognosis justifies experimental treatments including epoprostenol infusions, NO inhalation, oral L-arginine, or use of the endothelin antagonist bosentan. |
| Chronic leg ulcers | Usually occur over medial malleoli in chronic haemolytic anaemias, including HbSS, thalassaemia, and spherocytosis. | Possible incompetence of venous valves draining ankle region and a reduction in venous refilling time. Hydroxyurea treatment in SCD can cause leg ulcers. | Unna boot (gauze impregnated with zinc oxide) is effective. IV arginine butyrate also reported to cause rapid healing. Hydroxyurea to be used with caution in SCD individuals with previous history of leg ulcers. |
| Osteonecrosis | Osteonecrosis of the femoral and humeral heads occur in all sickle genotypes, most commonly in SS α-thalassaemia and in HbSS individuals with a high haemoglobin concentration. | Expansion of red-cell marrow with increased pressure or end-arterial vascular occlusion of the femoral and humeral heads have been postulated. | Disease frequently asymptomatic; T1 and T2-weighted images on MRI detect early lesions not seen on radiographs. Hip coring used for early disease; surgical hip replacement indicated for more advanced lesions. |
| Spleen | Autoinfarction in patients with HbSS before age 2 years. Hyposplenism has slower onset in those with HbSC disease. | Distinct sinusoidal blood flow, high rates of oxygen extraction, and acidosis provide ideal conditions for HbS polymerisation, leading to autoinfarction. | Elevated susceptibility to infection. Use of prophylactic penicillin and pneumococcal vaccine standard. |

GFR=glomerular filtration rate. ERPF=effective renal plasma flow. NSAID=non-steroidal anti-inflammatory drugs. ACE=angiotensin-converting enzyme. PH=pulmonary hypertension. ACS=acute chest syndrome. SCD=sickle-cell disease.

The NEW ENGLAND JOURNAL of MEDICINE

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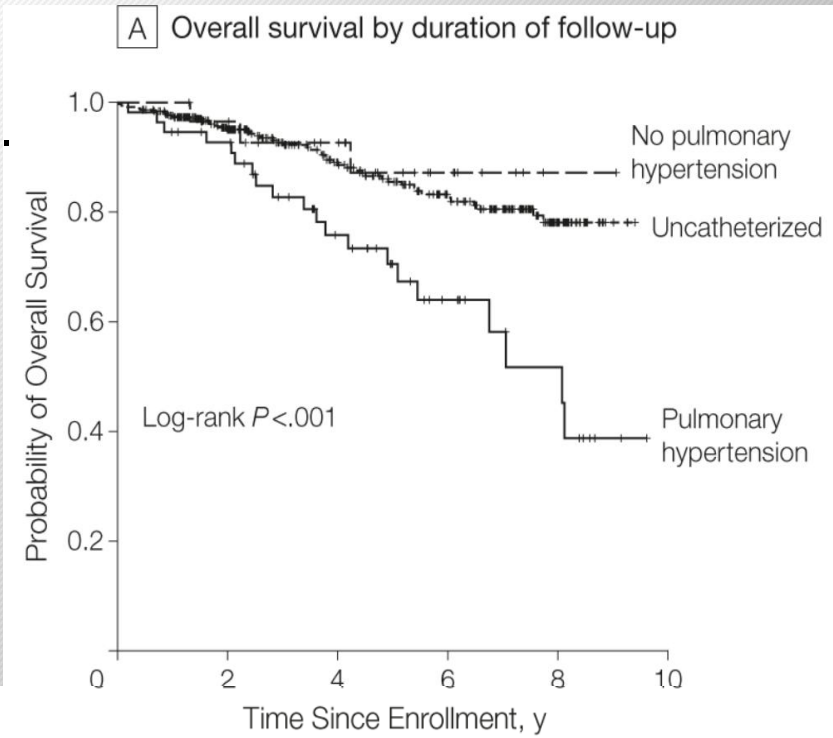
# Controlled Trial of Transfusions for Silent Cerebral Infarcts in Sickle Cell Anemia

M.R. DeBaun, M. Gordon, R.C. McKinstry, M.J. Noetzel, D.A. White, S.A. Sarnaik, E.R. Meier, T.H. Howard, S. Majumdar, B.P.D. Inusa, P.T. Telfer, M. Kirby-Allen, T.L. McCavit, A. Kamdem, G. Airewele, G.M. Woods, B. Berman, J.A. Panepinto, B.R. Fuh, J.L. Kwiatkowski, A.A. King, J.M. Fixler, M.M. Rhodes, A.A. Thompson, M.E. Heiny, R.C. Redding-Lallinger, F.J. Kirkham, N. Dixon, C.E. Gonzalez, K.A. Kalinyak, C.T. Quinn, J.J. Strouse, J.P. Miller, H. Lehmann, M.A. Kraut, W.S. Ball, Jr., D. Hirtz, and J.F. Casella

- Silent Cerebral Infarcts:
  - Prevalence approximately 33% (higher than abnormal TCD)
    - 13% at 1 year — Pediatr Blood Cancer 2008; 51:643-6.
    - 27% at 6 years — Br J Haematol 2009; 146:300-5.
    - 37% at 14 years — Blood 2011; 117:1130-40.
  - Cognitive deterioration:
    - IQ scores 5 points lower — Am J Haematol 2014; 89:162-7.
    - 10% reduction in annual income when adults — Intelligence 2007; 35:489-501.
  - Benefit of regular transfusion therapy for secondary prevention:
    - How long ?

# Pulmonary hypertension: risk factor for early death in adults

- Gladwin MT *et al*. N Engl J Med 2004; 350:886-95.
  - High risk of death in patients with tricuspidal regurgitant jet velocity (TRJV) ≥ 2.5 m/s.
- Parent F *et al.* N Engl J Med 2011; 365:44-53.
  - Prevalence of TRJV ≥ 2.5 m/s = 27%
  - But only 6% pulmonary hypertension confirmed with right heart catheterization.
- Mehari A *et al.* JAMA 2012; 3017:1254-56.
  - 37% risk of death at 6 years of follow-up for patients with pulmonary hypertension documented by RHC
  - 20% risk of death at 6 years of follow-up for non catheterized.

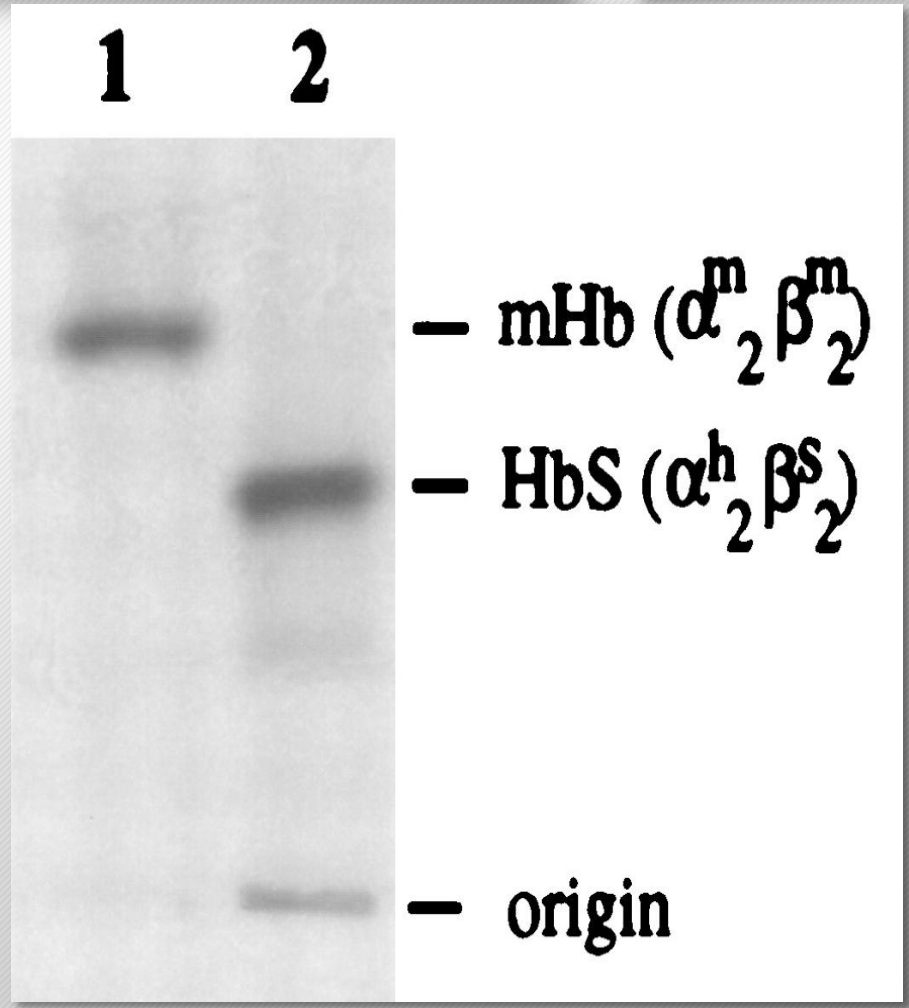



No. at risk

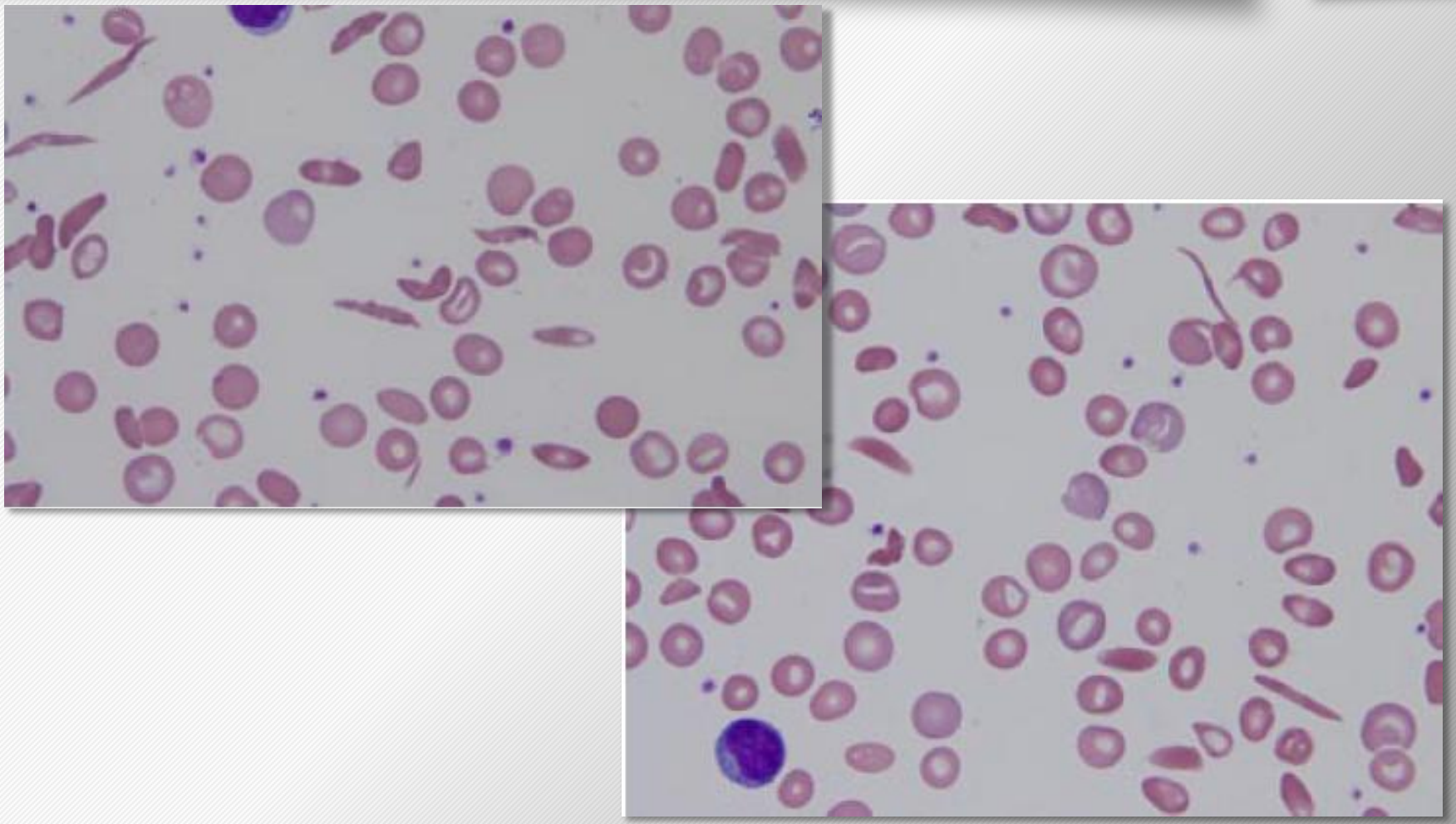
| | | | | | |
|---|---|---|---|---|---|
| No pulmonary hypertension | 29 | 25 | 20 | 8 | 1 |
| Uncatheterized | 381 | 284 | 187 | 128 | 37 |
| Pulmonary hypertension | 55 | 48 | 30 | 15 | 8 |

# Drepanocitosi - diagnosi

- **Emocromo, indici di emolisi**
- Striscio di sangue periferico
- Test di falcizzazione
- **Elettroforesi (HPLC,…)**
- Genetica
- Diagnostica dei vari quadri clinici



# Drepanocitosi: sangue periferico



# Drepanocitosi - terapia

**Terapia del dolore:** paracetamolo, oppioidi, idratazione.

**Sorveglianza infettivologica:**
- profilassi con penicillina
- trattare aggressivamente ogni episodio febbrile
- vaccinazioni (in particolare contro i germi capsulati; influenza)

**Trasfusionale**:
- Trasfusione semplice
- Scambio manuale (flebotomia seguita da trasfusione)
- **Eritrocitoaferesi**

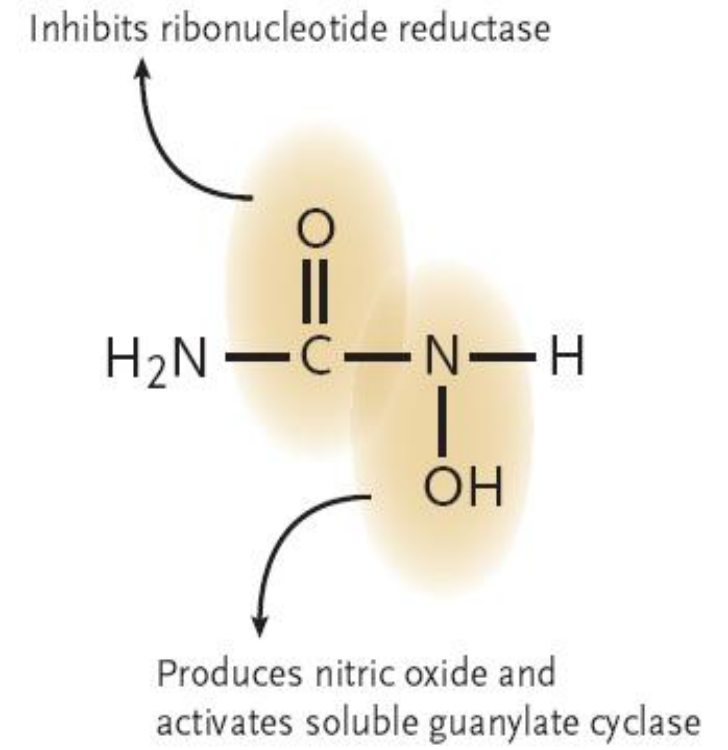
**Farmacologica:**
- **idrossiurea**
- nuovi farmaci

Splenectomia profilattica
- Nel sequestro splenico cronico

4) **Trapianto di cellule staminali emopoietiche**

# Drepanocitosi - idrossiurea

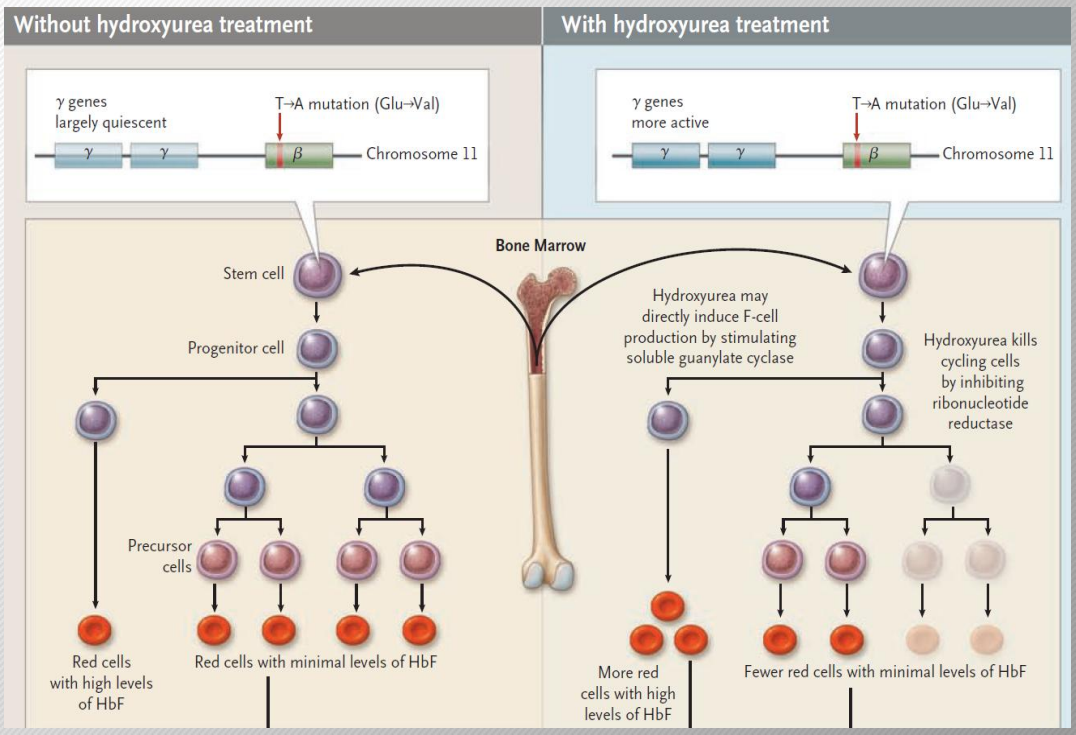
- Inibitore della ribonucleotide reduttasi largamente usata nel trattamento delle sindromi  mieloproliferative.
- Effetto pleiotropico:
  - induce la sintesi di catene $\gamma$ e quindi di HbF;
  - riduce la disidratazione cellulare;
  - migliora la deformabilità delle cellule;
  - riduce l'espressione delle molecole di adesione VLA-4 e CD36 sui reticolociti.
- Effetto mielosoppressivo:
  - riduce il numero di neutrofili, piastrine e reticolociti diminuendo la viscosità ematica.
- Perossidazione dell'drossiurea:
  - Formazione di ossido nitrico (NO), potente vasodilatatore che aumenta anche l'affinità dell'HbS per l'O2, diminuendone la polimerizzazione.



# Drepanocitosi - idrossiurea

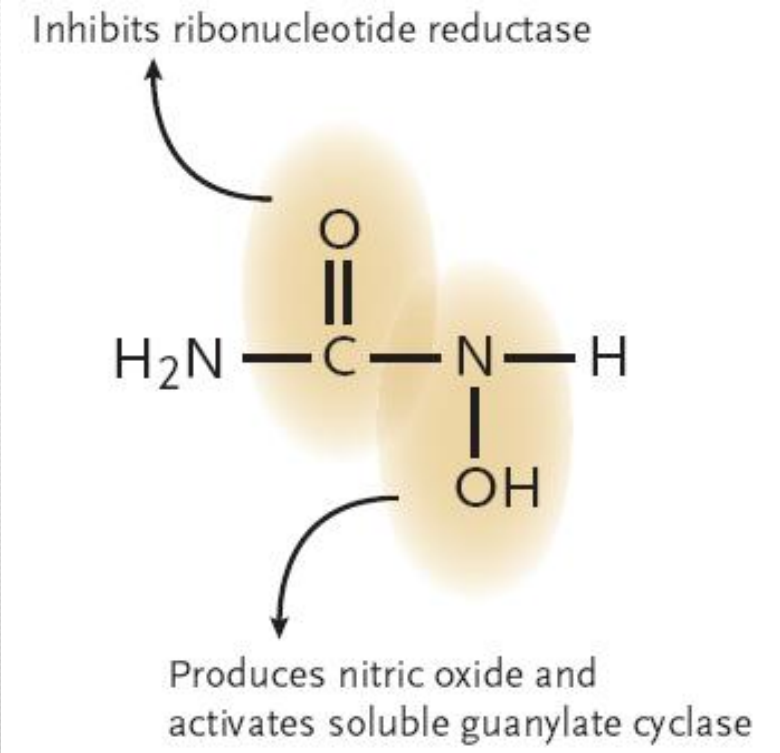
**Aumentata sintesi di HbF:**

- Inibizione della ribonucleotide reduttasi:
  - L'effetto citotossico dell'idrossiurea riduce la produzione di globuli rossi contenenti alti livelli di HbS, che derivano da progenitori in fase di attiva e rapida moltiplicazione.
  - Viene così favorita la produzione di eritrociti contenenti elevati livelli di HbF, che derivano da progenitori che si dividono più lentamente.



# Drepanocitosi - idrossiurea

- Dosaggio
  - -Iniziare con 15-20 mg/kg/die
  - -Incrementare di 5-10 mg/kg/die ogni 4 settimane
  - -Massimo 35 mg/kg/die
- Efficacia provata su:
  - -Riduzione delle crisi vaso-occlusive
  - -Riduzione degli episodi di ACS
  - -Minor richiesta trasfusionale
- Sorveglianza
  - -a breve termine (mielosoppressione)
  - -a lungo termine (Infertilità? Carcinogenesi?)



## 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 >2.5m/s on echocardiography or pulmonary hypertension |
| Primary or secondary stroke prevention when blood transfusions are unacceptable |
| Hemoglobin <7g/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 |

Rees, D. C. Haematologica 2011;96:488-491

haematologica
the hematology journal

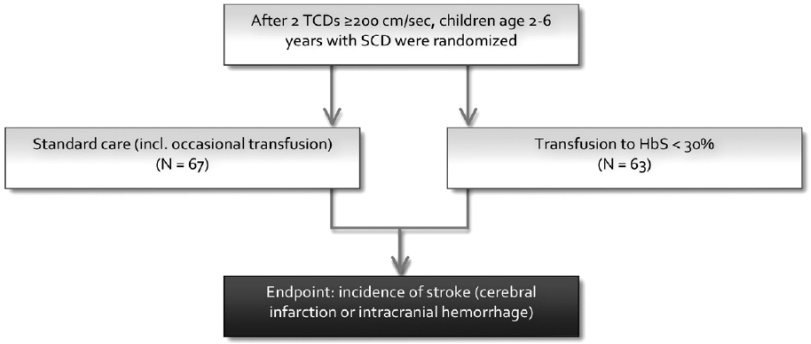
Stroke
Journal of the American Heart Association

# Toward a Stroke-Free Childhood in Sickle Cell Disease: The 2013 Sherman Lecture

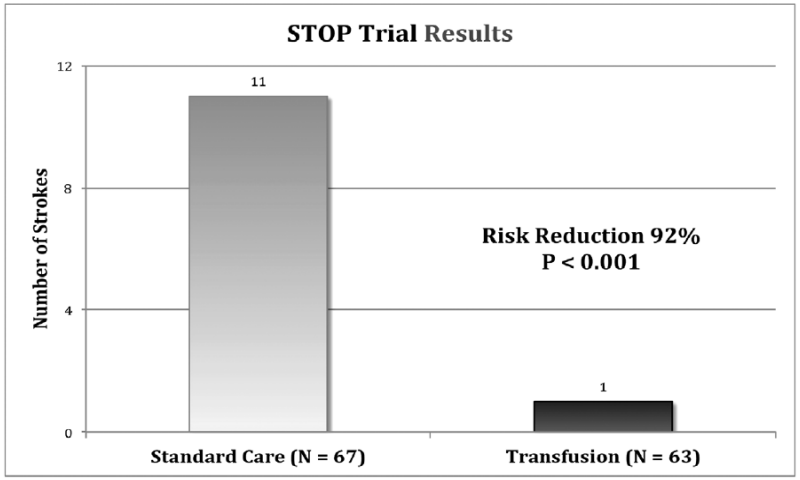
Robert J. Adams

*Stroke.* 2013;44:2930-2934; originally published online September 5, 2013;

**A** **Stroke Prevention Trial in Sickle Cell Anemia: STOP Trial Design**




**B**

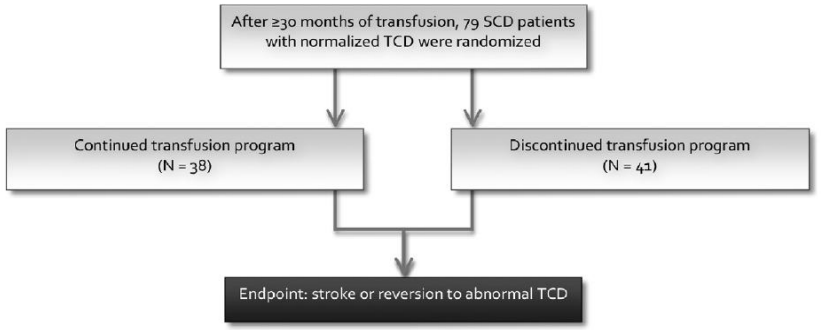



STOP Study halted prematurely in 1997

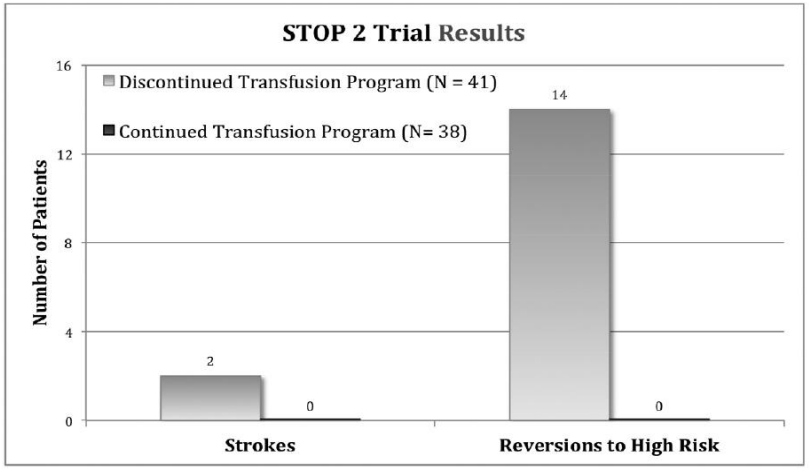
NIH recommends that all children with SCD should be screened for stroke risk using TCD; **those at high risk should receive transfusion therapy**.

N Engl J Med 1998; 339:5-11

**A** **Optimizing Primary Stroke Prevention In Children With Sickle Cell Anemia: STOP 2 Trial Design**




**B**




STOP 2 Study halted prematurely in 2004

NIH recommends that transfusions **be continued indefinitely** in children with SCD at high risk for stroke.

N Engl J Med 2005; 353:2769-2778

# The bioethical dilemma

To transplant, or not to transplant - that is the question.

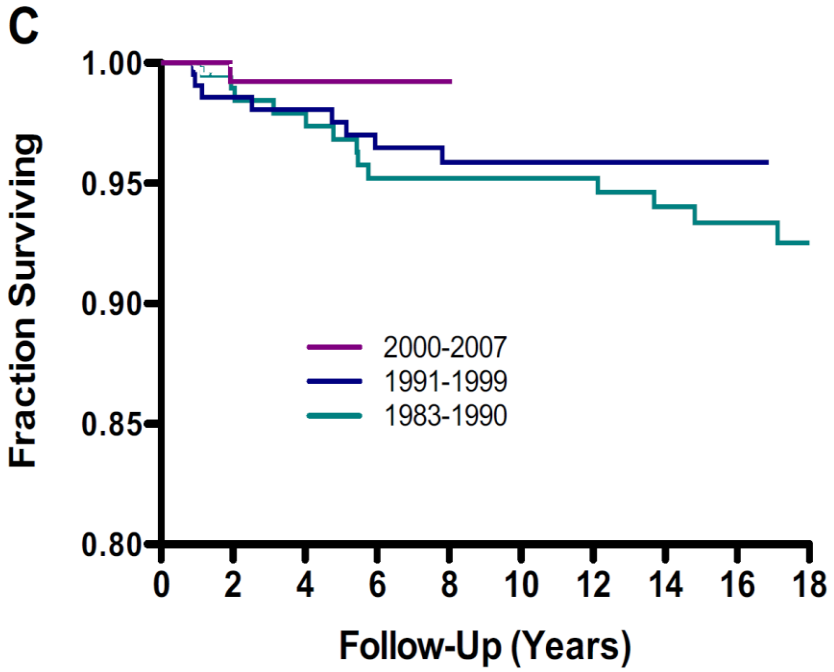
Shakespeare W. Hamlet 1600; Act III: Scene 1.

# Improved survival of children and adolescents with sickle cell disease

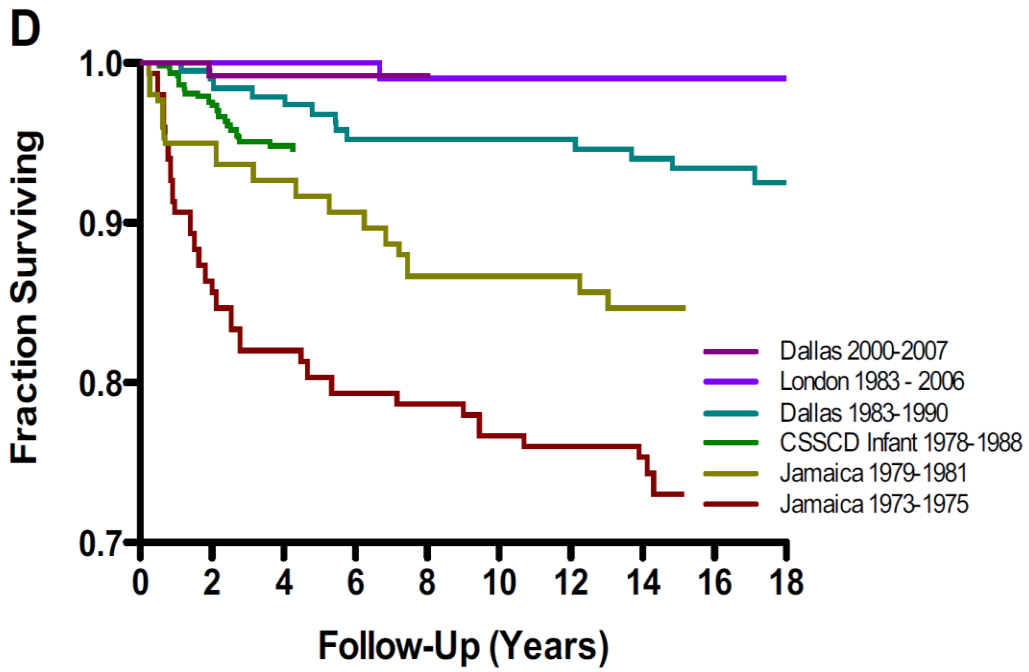
Charles T. Quinn,[1-3] Zora R. Rogers,[1-3] Timothy L. McCavit,[1-3] and George R. Buchanan[1-3]

[1]Division of Hematology-Oncology, Department of Pediatrics, The University of Texas Southwestern Medical Center, Dallas; [2]Southwestern Comprehensive Sickle Cell Center, Dallas, TX; and [3]Children's Medical Center Dallas, TX

## Trends in overall survival by cohort era




## Overall survival by cohort



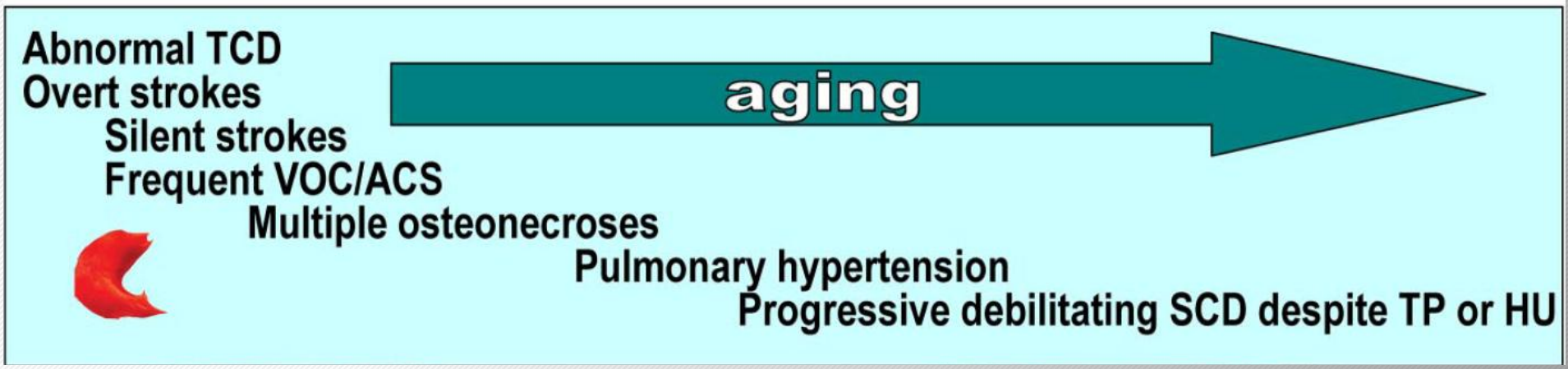

Quinn T.C. *et al*. Blood 2010; 115(17):3447-3452.

RESEARCH ARTICLES

# Mortality Rates and Age at Death from Sickle Cell Disease: U.S., 1979–2005

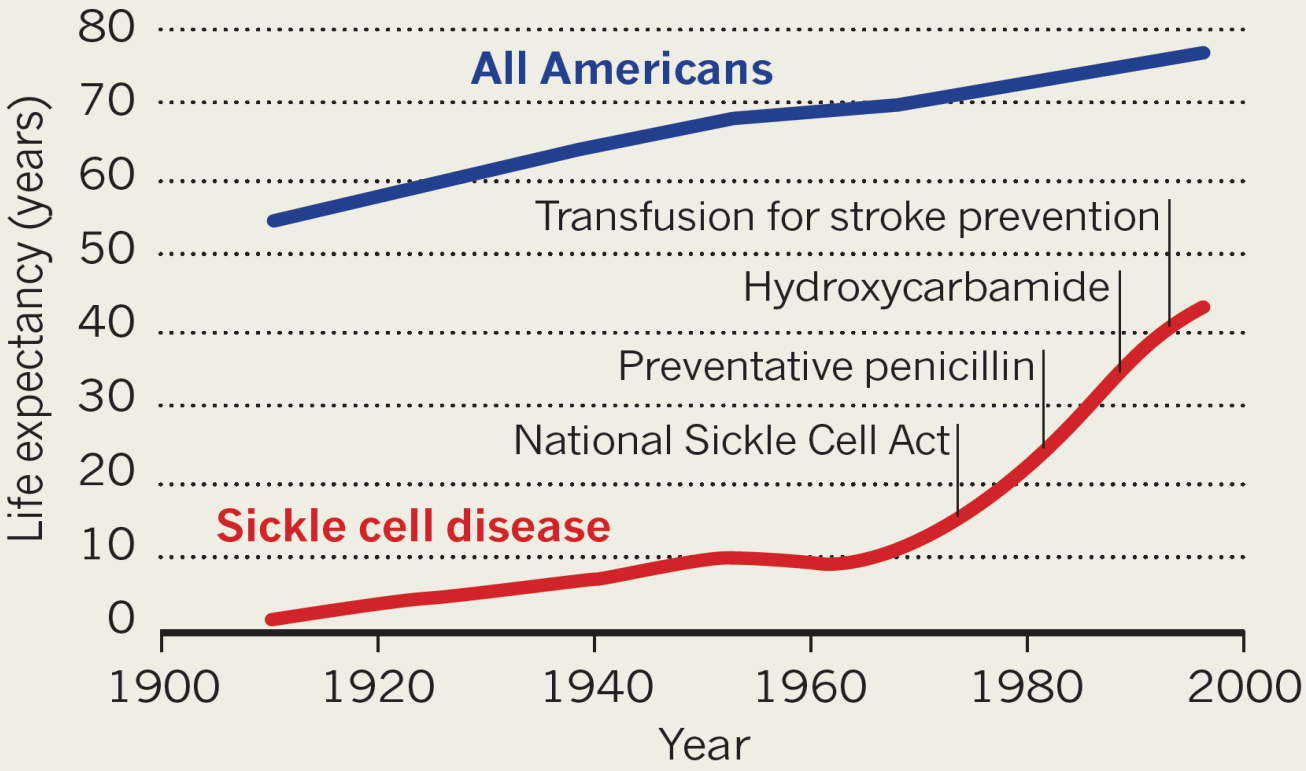
SOPHIE LANZKRON, MD, MHS[a]
C. PATRICK CARROLL, MD[b]
CARLTON HAYWOOD JR., PHD, MA[a,c]

- The pediatric mortality rate decreased by 3% each year during the period studied ($P < 0.001$)
- The adult mortality increased by 1% each year during the time period studied ($P < 0.001$).
- And high morbidity…



## HEALTH IMPROVEMENT

As a result of more effective treatments, the life expectancy of people with sickle-cell disease in the United States has increased dramatically. Most developing nations, however, have yet to see such a change[3].



blood

# How I treat acute strokes and long-term management in sickle cell disease

Adetola A. Kassim, Najibah A. Galadanci, Sumit Pruthi, and Michael R. DeBaun.

Blood First edition Paper, prepublished online March 30, 2015; doi:10.1182/blood-2014-09-551564

- «Four studies, with a minimum follow-up of 5 years, demonstrated the efficacy of HSCT for secondary prevention of strokes.»
  - Vermylen C *et al*. Bone Marrow Transplant 1998; 22(1):1-6.
  - Bernaudin F *et al*. Blood 2007; 110(7):2749-2756.
  - Walters MC *et al*. Biol Blood and Marrow Transplant 2010; 16(2):263-272.
  - Dallas MH *et al*. Biol Blood Marrow Transplant 2013; 19(5):820-830.

- «Based on these studies, we believe that blood transfusion therapy for secondary stroke prevention is palliative and HSCT offers both a chance of cure from the disease and is effective in secondary stroke prevention.»

## **Table 1.** Indications for HSCT in Sickle Cell Anemia

| **Matched sibling donor (if available)** | **Matched unrelated donor** | **Mismatched marrow donor, haploidentical donor, unrelated cord blood transplant** |
|---|---|---|
| Consider early,* prior to or at onset of SCD symptoms, with the highest priority given to patients with HbSS and HbSβ° | Stroke | Recurrent stroke despite adequate chronic transfusion therapy; progressive CNS changes |
| Stroke | Elevated TCD velocity | Severe SCD symptoms and inhability to tolerate supportive care resulting in symptom persistence / progression |
| Elevated TCD velocity | Recurrent acute chest syndrome despite supportive care | |
| Recurrent acute chest syndrome despite supportive care | Reccurrent severe VOE despite supportive care | |
| Reccurrent severe VOE despite supportive care | Red cell alloimmunization despite intervention in established indication for chronic transfusion therapy | |
| Red cell alloimmunization despite intervention in established indication for chronic transfusion therapy | Pulmonary hypertention | |
| Pulmonary hypertention | Recurrent priapism | |
| Recurrent priapism | Sickle nephropathy | |
| Sickle nephropathy | Bone and joint involvement | |
| Bone and joint involvement | | |
| Sickle rethinopathy | | |

Blood 2014; 123:3089-3094.

# TCSE allogenico nell'anemia falciforme

| | N. | (%) |
|---|---|---|
| **Number of patients** | **30** | **(100%)** |
| Gender: | | |
| • Female | 15 | (50%) |
| • Male | 15 | (50%) |
| Genotype: | | |
| • HbS / S | 21 | (71%) |
| • HbS / $\beta^0$ | 7 | (23%) |
| • HbS / HbC | 1 | (3%) |
| • HbS / HbO-Arab | 1 | (3%) |
| Age at BMT (years, median and range) | 8 | (2 – 18) |
| Pre-transplant SCD complications: | | |
| • Vaso-occlusive pain episodes | 30 | (100%) |
| • Acute chest syndrome | 7 | (23%) |
| • Stroke | 3 | (10%) |
| • Avascular necrosis | 7 | (23%) |
| • Transfusions | 24 | (80%) |



Br J Haematol 2015; 169:726-736.

# TCSE allogenico nell'anemia falciforme

| | N. | (%) |
|---|---|---|
| Donor: | | |
| • Matched family donor (MFD) | 24 | (80%) |
| • Matched unrelated donor (MUD) | 6 | (20%) |
| Donor gender: | | |
| • Female | 12 | (40%) |
| • Male | 18 | (60%) |
| Gender mismatch: | | |
| • Female donor and male recipient | 5 | (17%) |
| • Other combinations | 25 | (83%) |
| Donor age (years, median and range) | 15 | (4 – 47) |



Br J Haematol 2015; 169:726-736.

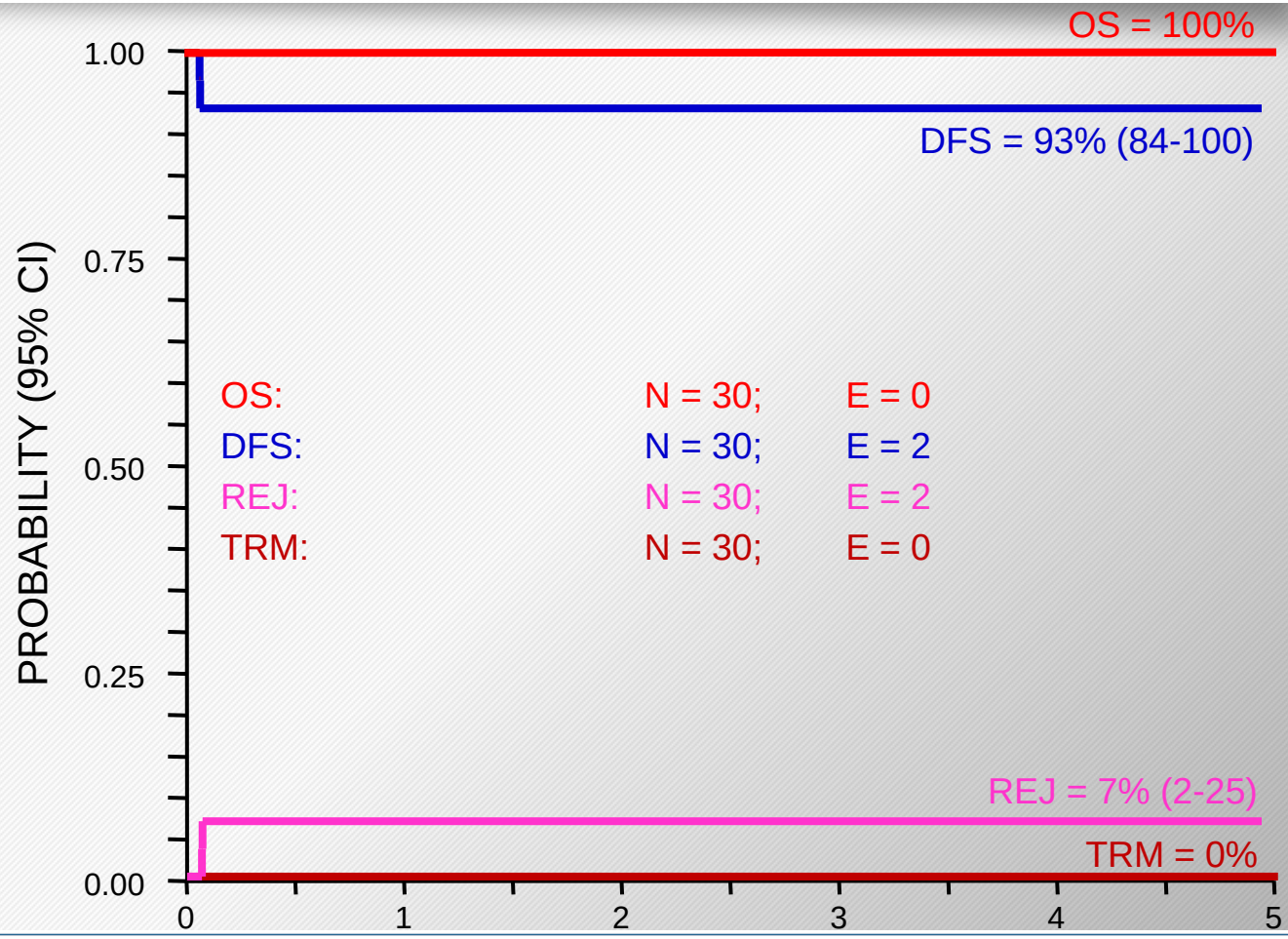
# TCSE allogenico nell'anemia falciforme

| | N. | (%) |
|---|---|---|
| Conditioning regimen: | | |
| • Busulfan + Thiotepa + Fludarabine ± ATG | 15 | (50%) |
| • Thiotepa + Treosulfan + Fludarabine ± ATG | 15 | (50%) |
| Stem cell source: | | |
| • Bone marrow | 22 | (74%) |
| • Cord blood | 4 | (13%) |
| • Bone marrow + cord blood | 3 | (10%) |
| • Peripheral blood | 1 | (3%) |
| Cell dose infused (median and range) | | |
| • Bone marrow (TNC x $10^8$/kg) | 5.4 | (1.2 – 10) |
| • Peripheral blood (CD34+ x $10^6$/kg) | 6.5 | - - |
| GVHD prophylaxis: | | |
| • Cs-A + short-term MTX | 18 | (60%) |
| • Cs-A + short-term MTX + ATG | 12 | (40%) |



Br J Haematol 2015; 169:726-736.

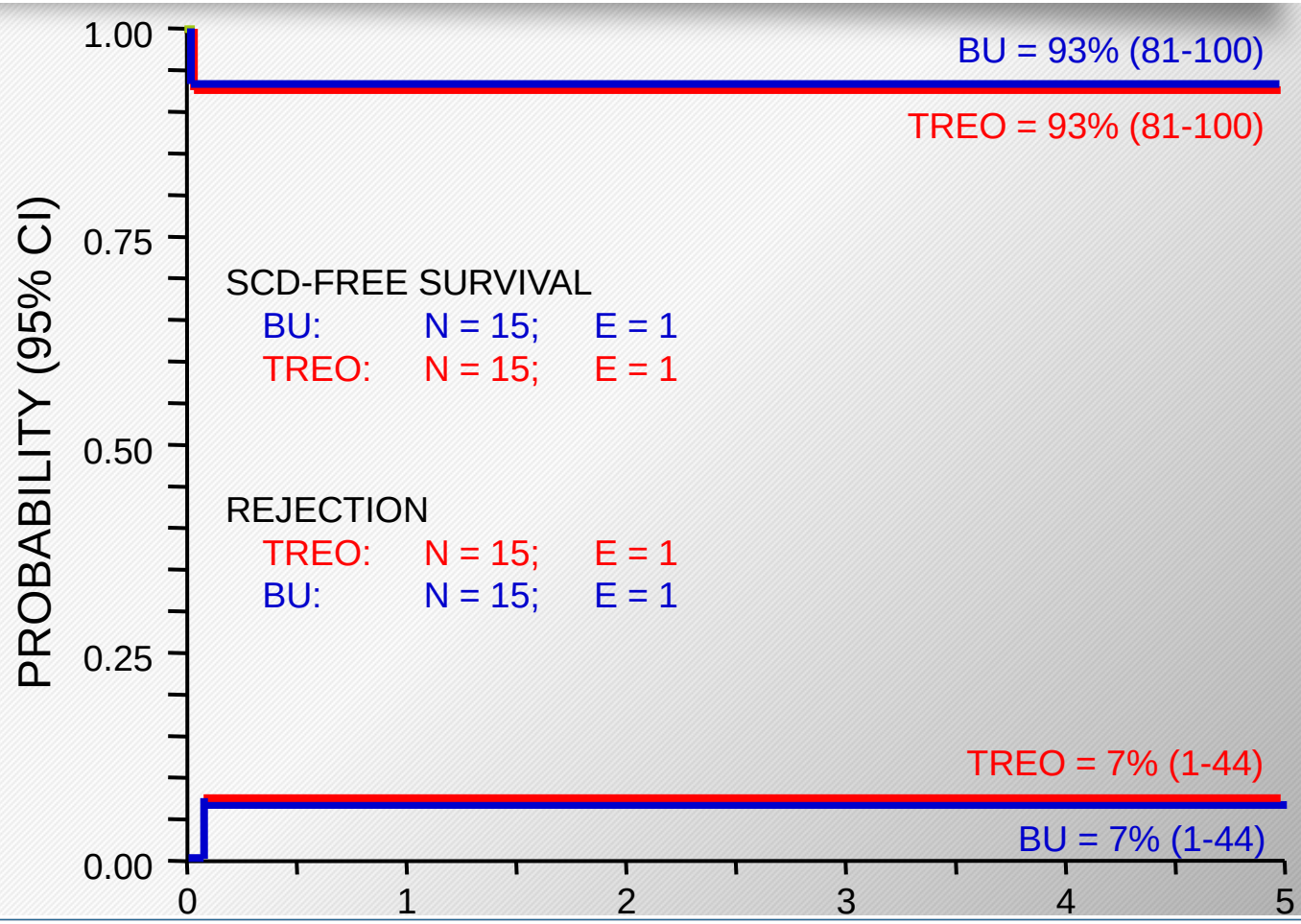
# TCSE allogenico nell'anemia falciforme




bjh BRITISH JOURNAL OF HAEMATOLOGY

Br J Haematol 2015; 169:726-736.

# TCSE allogenico nell'anemia falciforme

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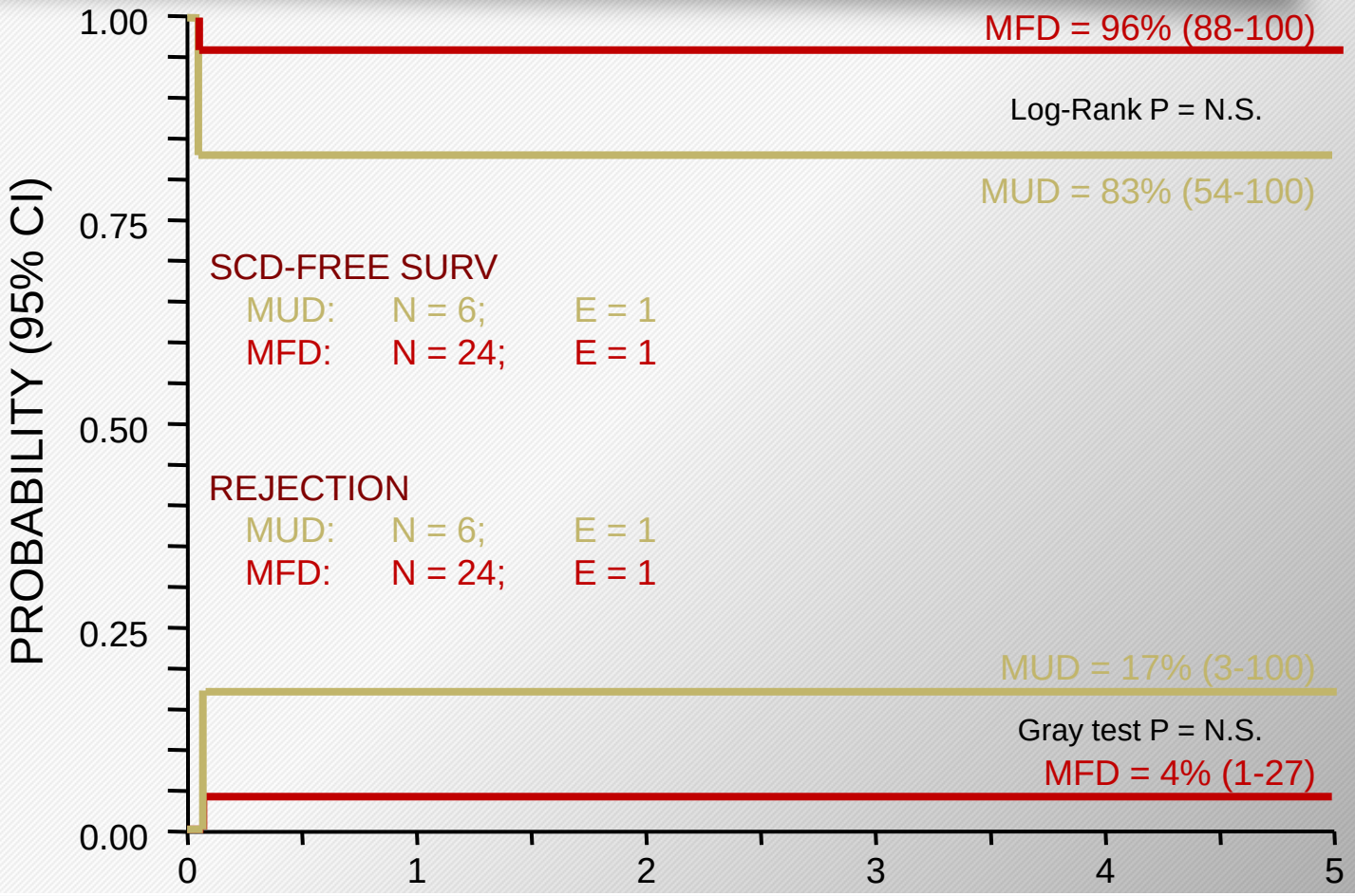



bjh BRITISH JOURNAL OF HAEMATOLOGY

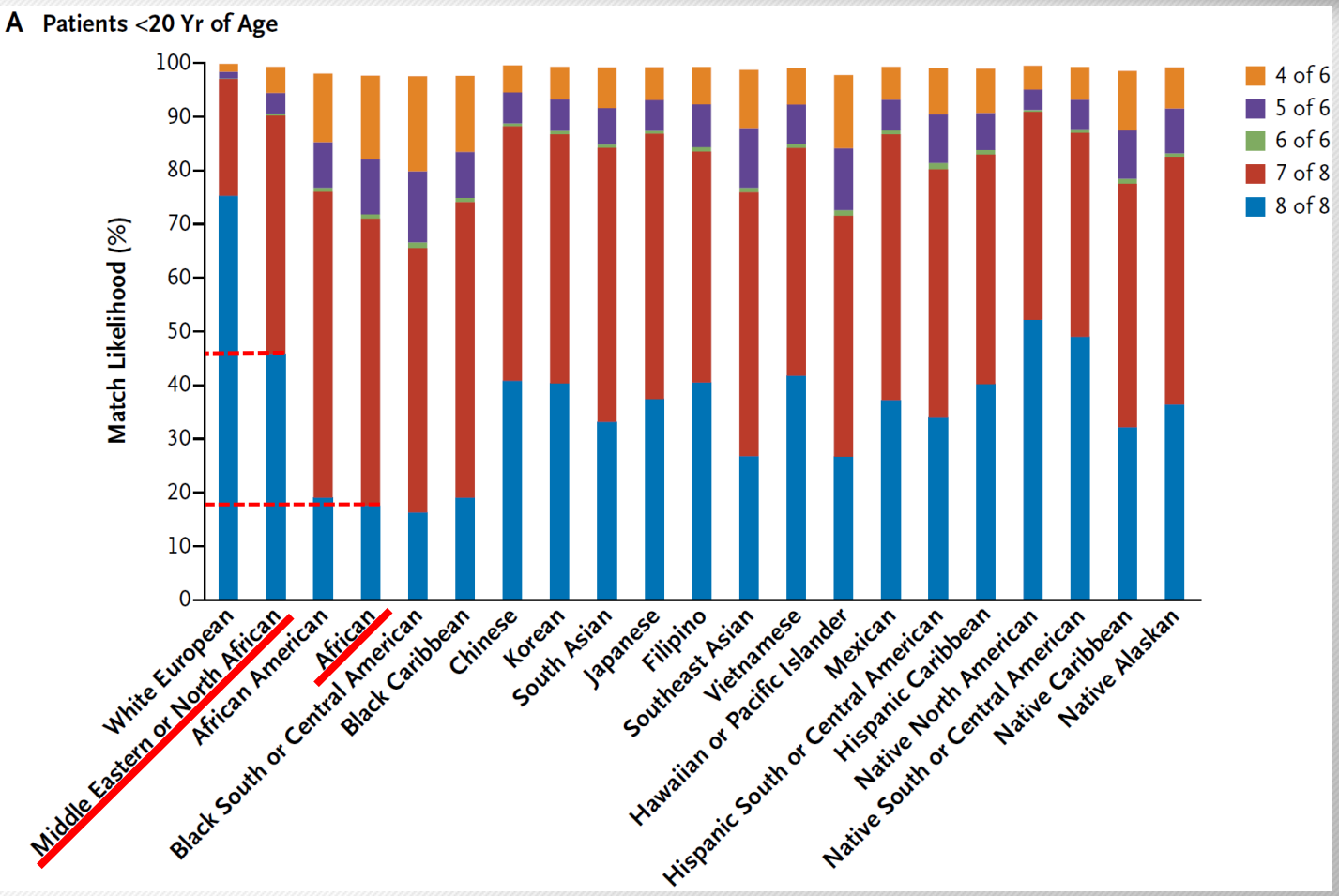
Br J Haematol 2015; 169:726-736.

The NEW ENGLAND JOURNAL of MEDICINE

SPECIAL ARTICLE

# HLA Match Likelihoods for Hematopoietic Stem-Cell Grafts in the U.S. Registry

Loren Gragert, B.S., B.A., Mary Eapen, M.B., B.S., Eric Williams, Ph.D., John Freeman, B.S., Stephen Spellman, M.B.S., Robert Baitty, M.P.P., Robert Hartzman, M.D., J. Douglas Rizzo, M.D., Mary Horowitz, M.D., Dennis Confer, M.D., and Martin Maiers, B.A.




**Match likelihood according to racial and ethnic group.**
The likelihood of finding a match with the use of a search strategy win which an 8/8 HLA-matched donor is sought first, then a 7/8 HLA-matched donor, and thereafter a cord-blood unit with an adequate cell dose is shown.

# Conclusions (1)
# Genotypically identical family donor HSCT

- Still underutilized:
  - (only 611  and 627 patients reported to EBMT and CIBMTR, respectively)
- Standard of care:
  - Survival = 96% and SCD-fee survival = 93% in 135 patients from the 4 most recent publications.
- Not systematic but for patients requiring intensive therapy.
- Early discussion with parents.
- Family HLA typing.
- Sibling cord blood cryopreservation.
- Myeloablative conditioning regimen for children:
  - Treosulfan instead of Busulfan?
- Non myeloablative conditioning regimen for adults.
- CB is as affective as BM.

# Conclusions (2)
# Matched unrelated donor HSCT

- Low probability to find an 8/8 matched bone marrow donor for ethnic minorities:
  - 75% for white recipients of European descent.
  - 16% for central Africa patients.
- Results of unrelated donor cord blood transplants are still unsatisfactory:
  - Premature stop of the CBT arm of the SCURT trial
  - Overall disease-free survival probability < 60%.
  - High cell dose is necessary ( > 5 x $10^7$/kg).

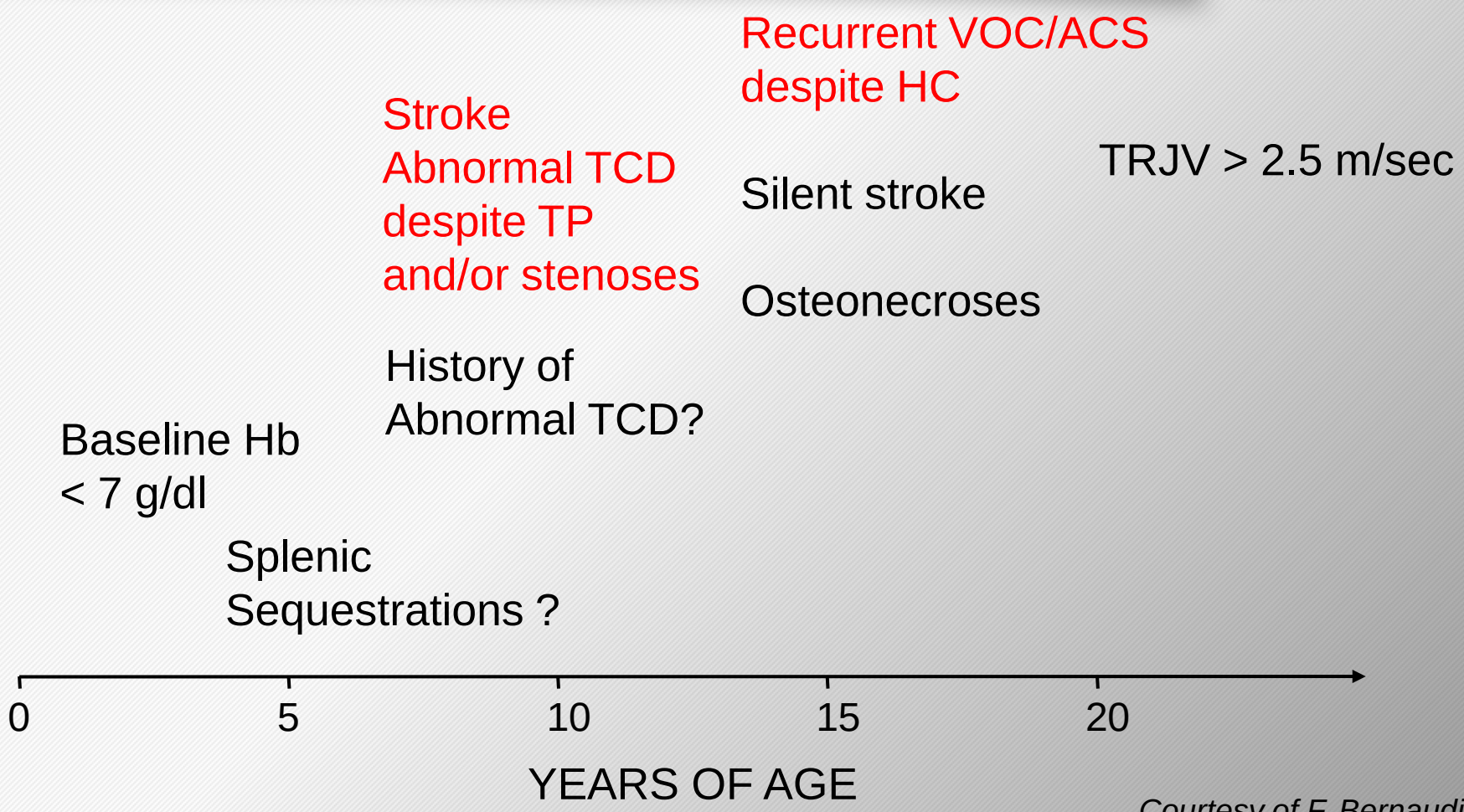
# Conclusions (3)
# Haploidentical transplants

- Cy + Flu + ATG + 200 cGy TBI and PT-HDCY:
  - 50% had stable donor engraftment and cessation of sickle-related complications.

- 70% disease-free survival in children with thalassemia using T-cell depletion with positive CD34+ selection.
  - Role of pre-conditioning?
  - Negative CD3+ TCR$\alpha\beta$+ and CD19+ selection?

- Haploidentical HSCT could be proposed to patients lacking a matched donor an with progressively debilitating SCD despite transfusion program and hydroxicarbamide therapy.
  - in centres with experience in transplanting SCD patients;
  - with specific haplo transplant programs;
  - in prospective clinical trials.

# When ?




*Courtesy of F. Bernaudin*

A.I.E.O.P.
Associazione Italiana Ematologia Oncologia Pediatrica

## Associazione Italiana Ematologia Oncologia Pediatrica

### Gruppo di Lavoro "Patologia del globulo rosso"
### Coordinatore: Dr. Silverio Perrotta

# RACCOMANDAZIONI PER LA GESTIONE DELLA MALATTIA DREPANOCITICA IN ETA' PEDIATRICA IN ITALIA

**Coordinamento**
Giovanna Russo[1]

**Revisione**
Giovanna Russo[1], Piera Samperi[1], Laura Sainati[2], Raffaella Colombatti[2]