WBMT
worldwide network for blood and marrow transplantation
WWW.WBMT.ORG
www.wbmt.org

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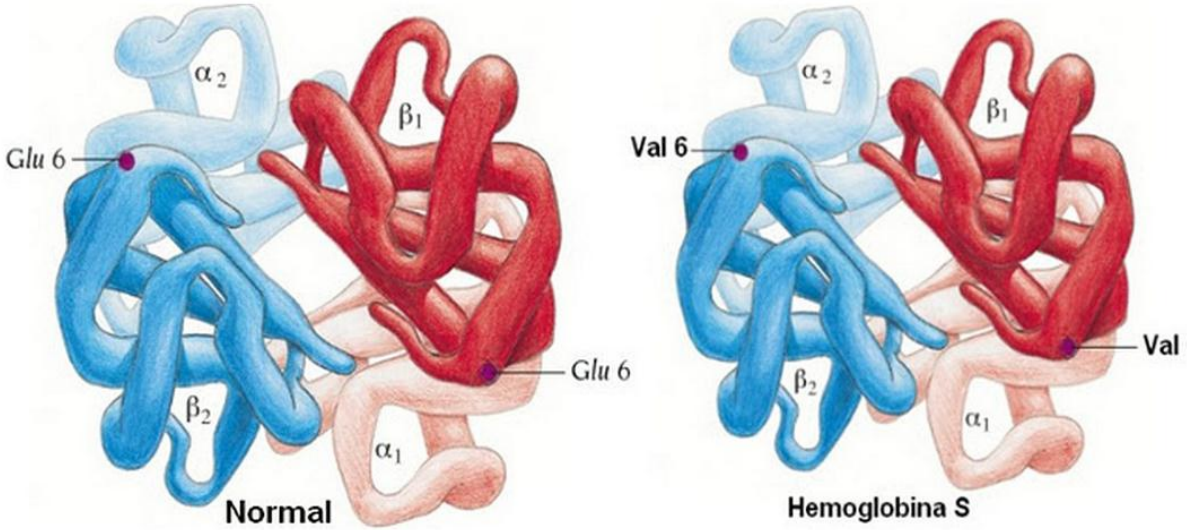
BONE MARROW TRANSPLANT IN HEMOGLOBINOPATHIES

National Network for Blood and Marrow Transplatatation

Hemoglobinopathies

- Normal hemoglobines
  - 2 α and 2 β = Hb A
  - 2 α and 2 δ = Hb A2
  - 2 α and 2 γ = HbF

- In sickle cell there is a point mutation on beta chain (beta S or hemoglobine S).

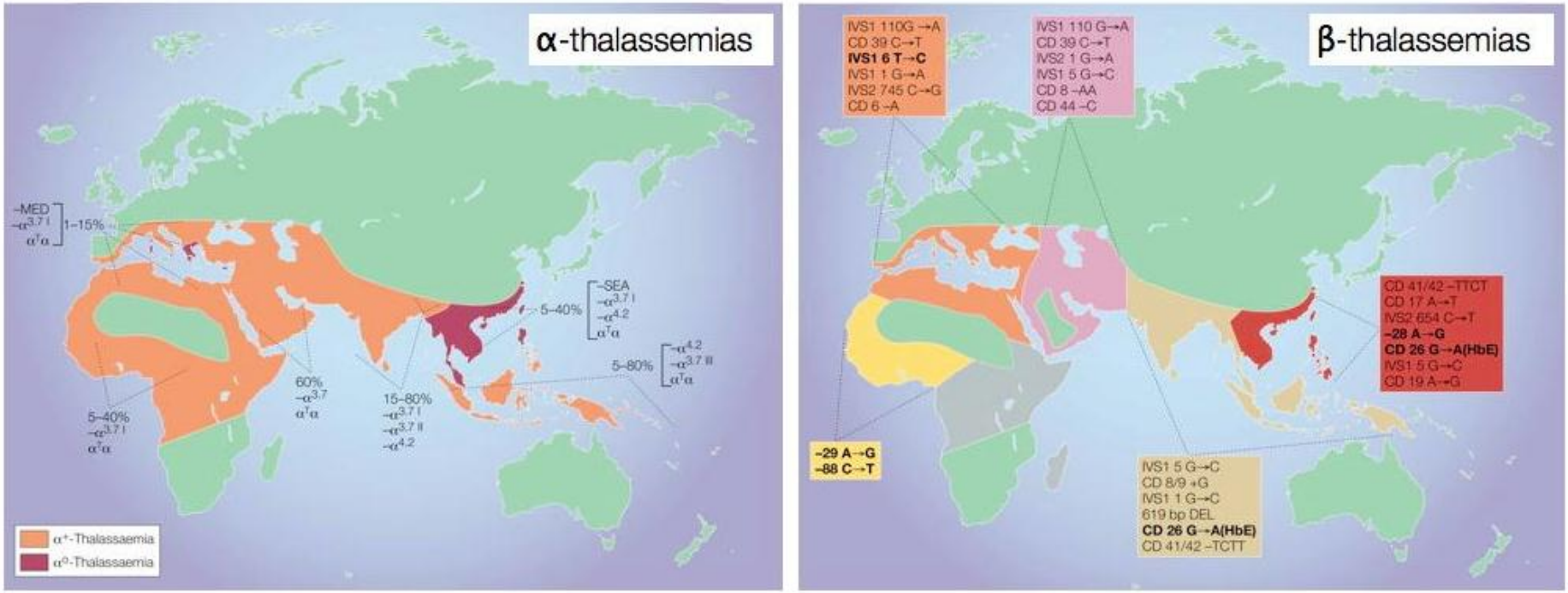


Hemoglobinopathies

- Thalassemia
  - Inherited disease requiring chronic long-life transfusions to treat the anemia caused by enhanced red blood cell destruction.
  - Major complication is a progressive iron overload and consequent organ deterioration.
    - Regular iron chelation by parenteral and oral chelators
    - Blood born infections

Thalassemias

Worldwide distribution of α- and β-thalassemias



Weatherall DJ *Nat Rev Genetics* 2:245, 2001

Thalassemia Major

- First allogeneic BM transplant more than 30 years ago
- BMT standart clinical practice
- In Pesaro more than 1000 patients were transplanted in the 80s and 90s
  - After 20 years of follow up thalassemia free survival was reported as 73% in 900 unselected patients transplanted from an HLA-identical sibling donor.
- More recently even better results
  - modern transplantation approaches
  - careful patient selection
- Survival without transplantation has also improved
  - Survival into the fourth or fifth decade of life is now possible for well-treated patients

Angelucci et al. Haematologica 2014

BMT in Thalassemia major

- EBMT survey on 1061 TM patients
  - Donor matched sibling
  - Overall survival (OS) 91±0.01 months
  - Disease-free survival (DFS) 83±0.01 months
  - Age threshold of 14 years for optimal results
    - 96% *vs.* 82% for OS
    - 86% *vs.* 74% for DFS

Pesaro risk classification is based on
liver size by physical examination, fibrosis detected on liver biopsy, and chelation history

Baronciani et al. ASH 2011

BMT in Thalassemia major

- For whom?
  - All transfusion dependent patients
- Which graft source?
  - HLA identical sibling BM (avoid PBSC)
  - Related cord blood (> $3.5x10^7$/kg)
- When?
  - As soon as possible
  - Results better in Pesaro class 1 and 2
    - With less than 14 years

Angelucci et al. Haematologica 2014

Hemoglobinopathies

Hemoglobinopathy	No. Newborn/Year
Sickle Cell Anemia (SS)	217.331
Hbglp SC	54.736
S β thalassemia	11.074
β thalassemia maior	22.989
HbE β thalassemia	19.128
HbH disease	9.568
Hb Barts	5.183

Weatherhall DJ Blood 2010
Modell B, Darlison M. Bull World Health Organ. 2008

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83,2% Sickle Cell Diseases

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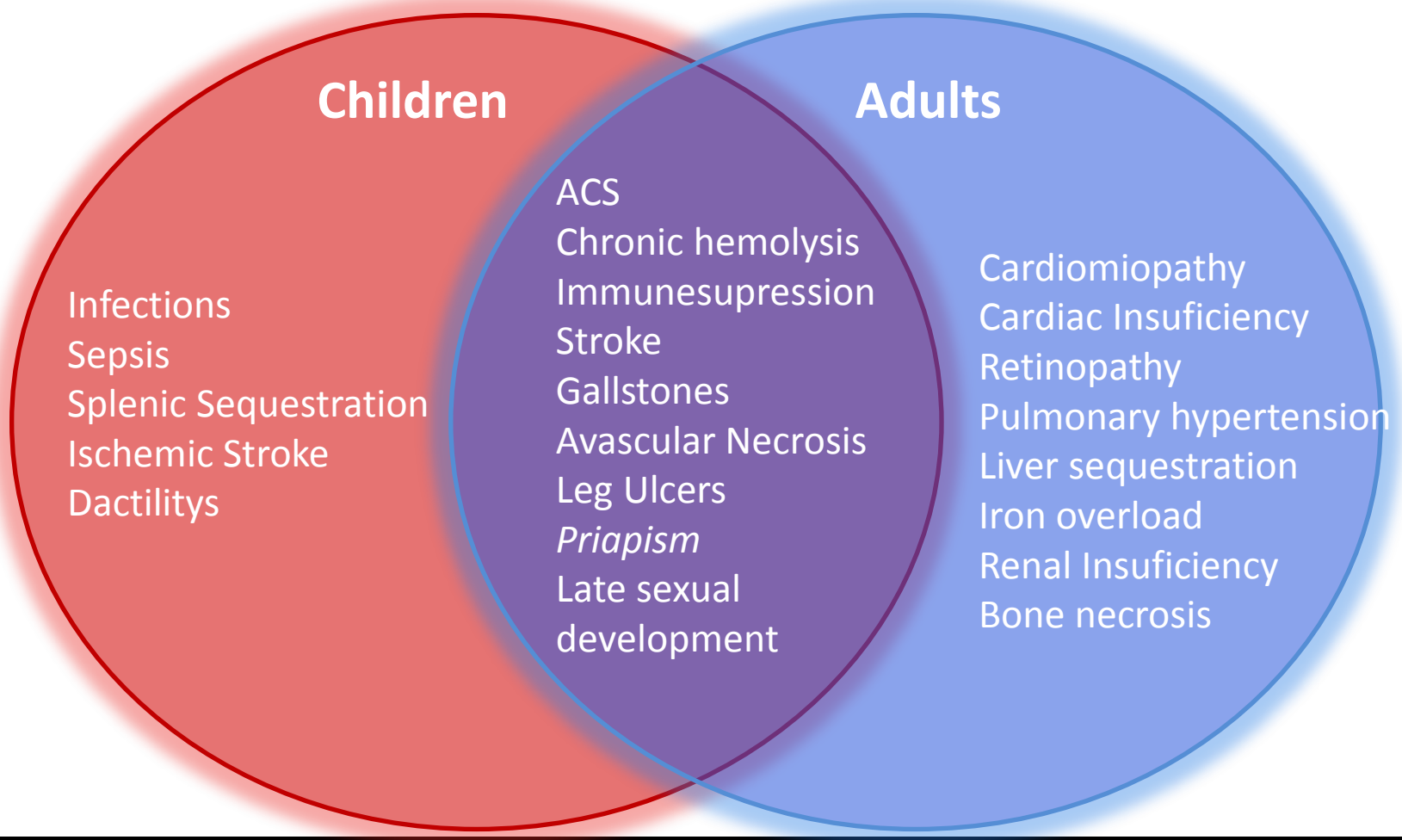
Hemoglobinopathies

- Sickle Cell Disease
  - Inherited disease caused by a point mutation
  - Variable phenotype depending of the haplotype and partner gene
    - SS
    - SC
    - S thalassemia
  - Most severe forms SS and $S\beta^0$
  - No severity predictors

Clinical Course



Hemoglobinopathies

Genotype	Genes involved	Typical severity	% hemoglobin/ total Hemoglobine in a typical patient				
			HbS	HbA	HbF	HbC	HbA2
HbAA	β e β	Normal	-	96	2	-	2
HbSS	β^S e β^S	Severe	95	-	3	-	2
HbSC	β^S e β^C	Not severe	48	-	3	47	2
$HbSb^0$	β^S e β^0 talassemia	Severe	93	-	2	-	5
$HbSb^+$	β^S e β^+ talassemia[1]	Moderate	85	6	5	-	4
$HbSb^+$	β^S e β^+ talassemia[2]	Not severe	70	23	3	-	4

[1]mutation that causes severe thalassemia
[2]mutacao that causes not severe thalassemia

Frenette & Atweh, JCI 2007

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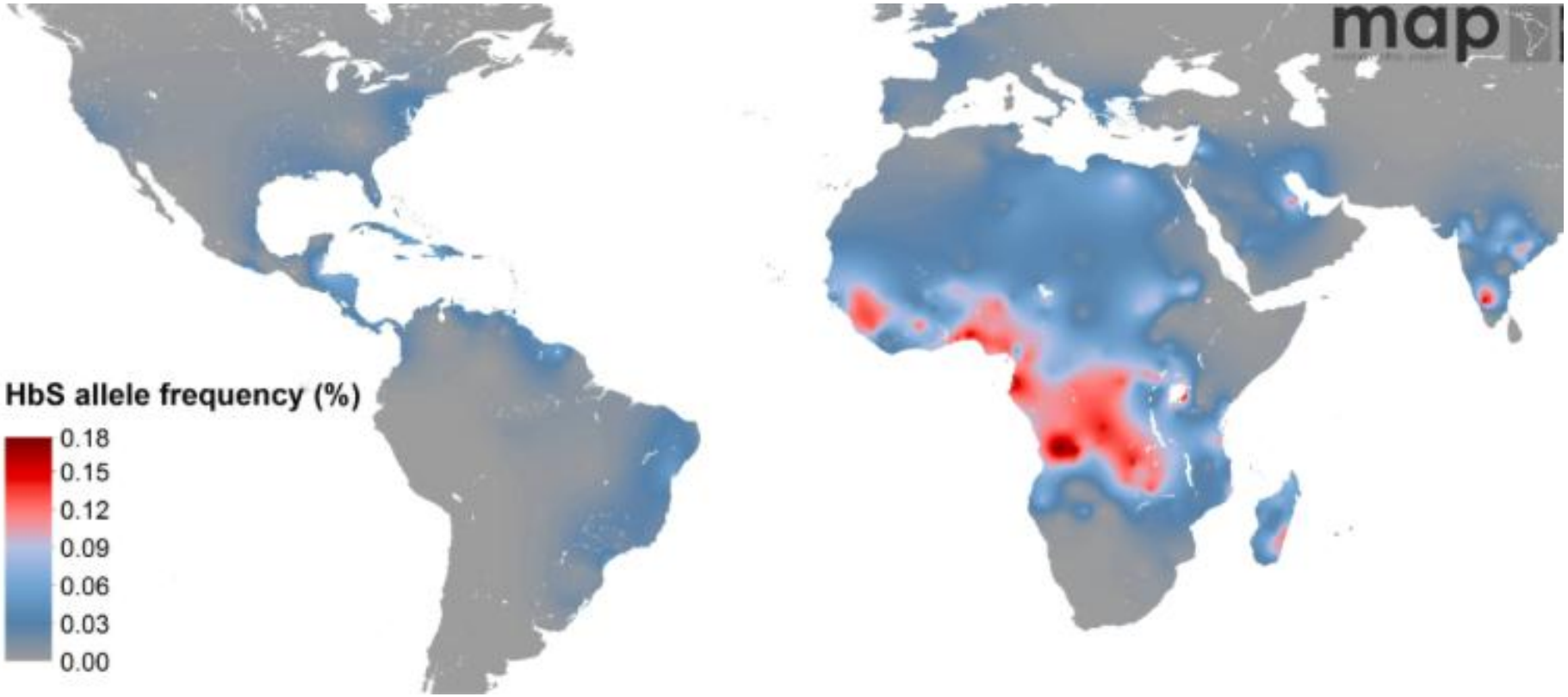
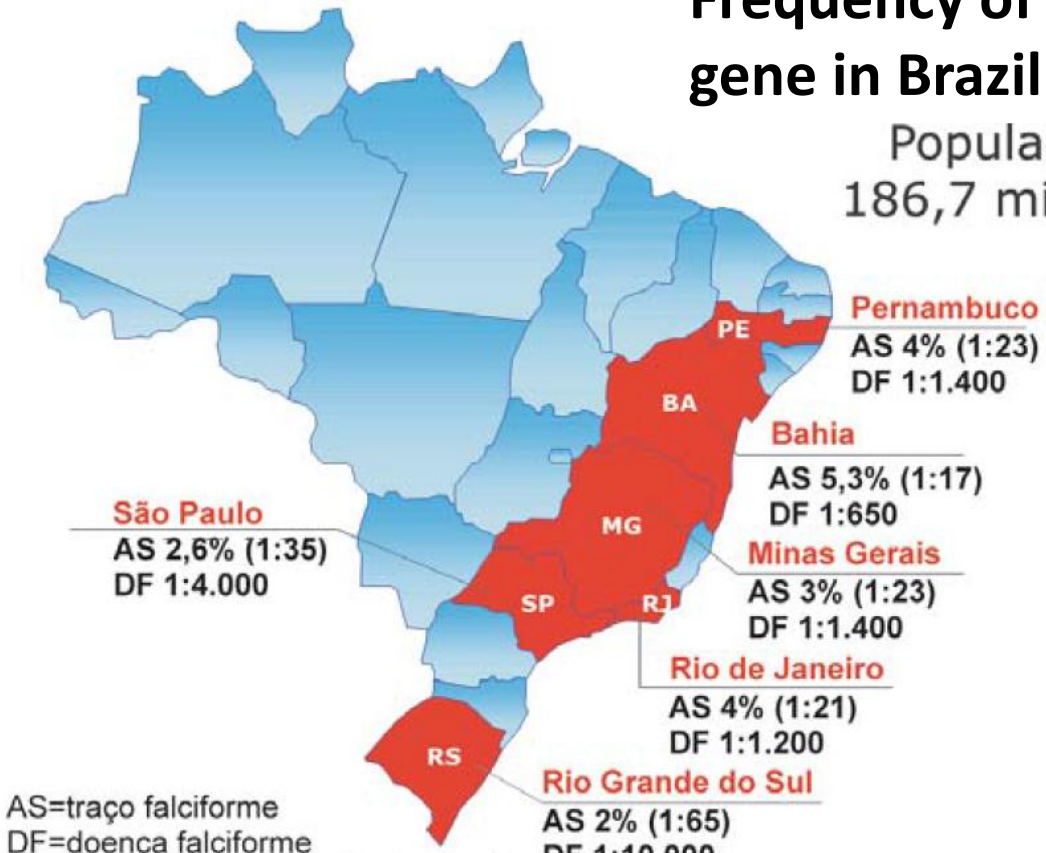
HbS allele frequency



S gene in Brazil

Frequency of the S gene in Brazil



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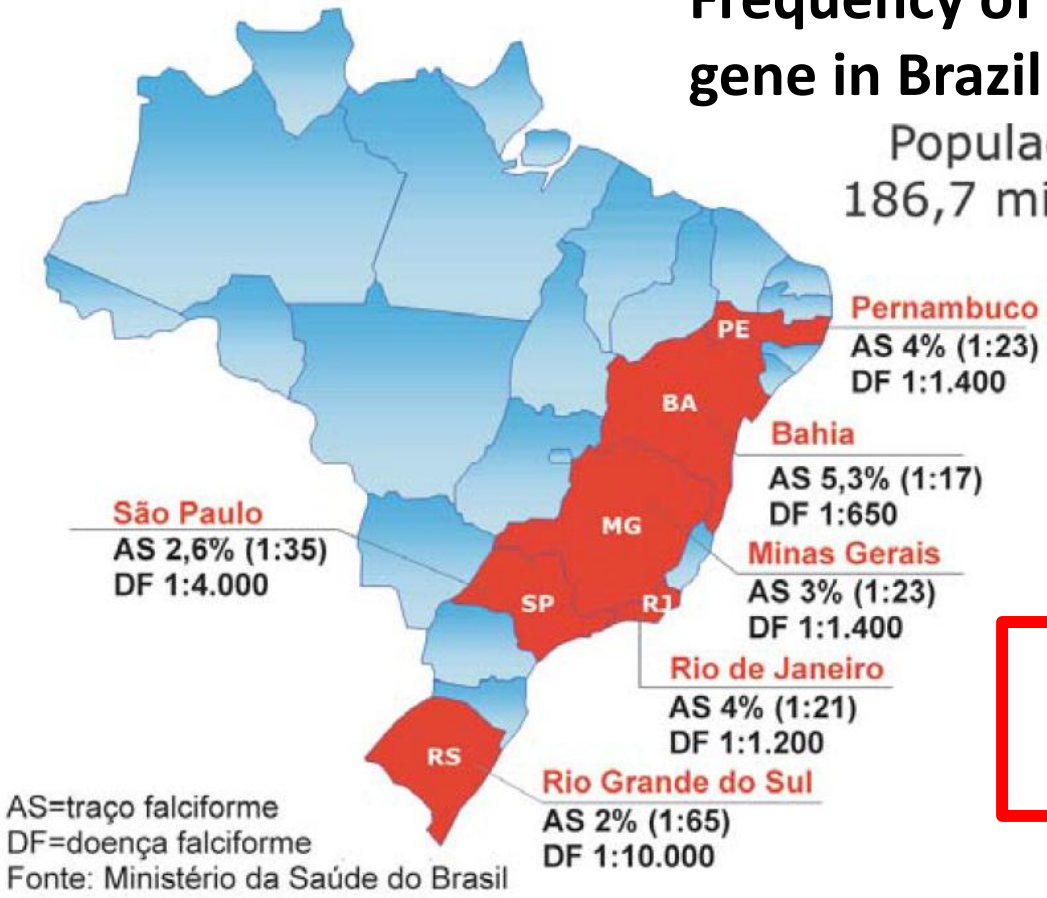
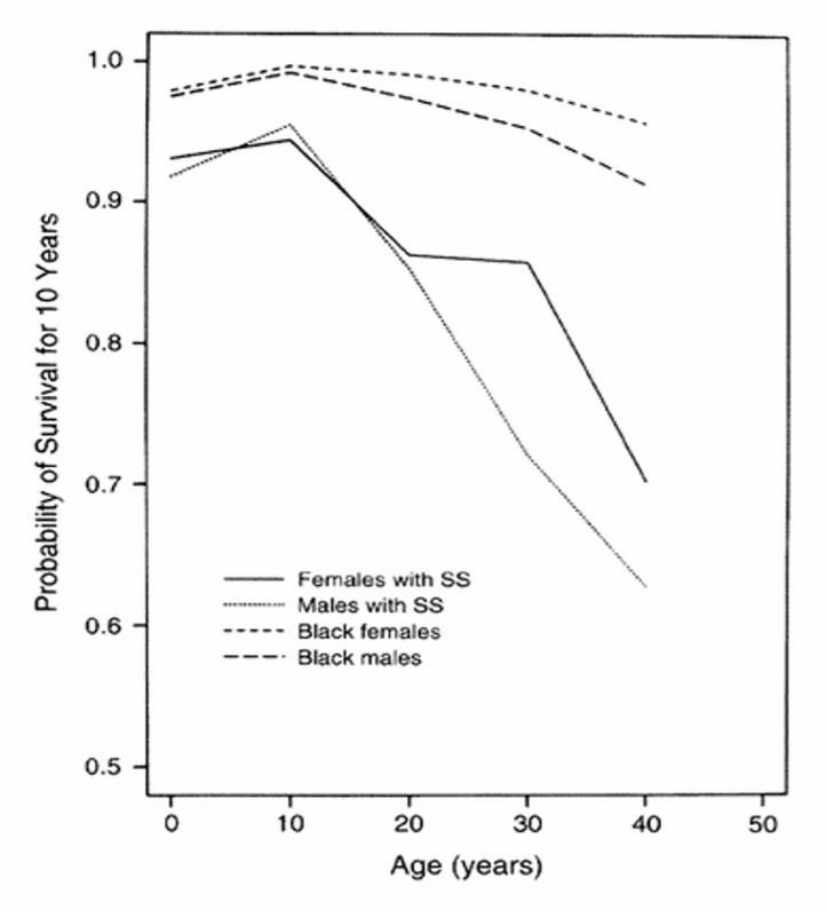


About 4000 newborns with SCD/year in Brazil

Survival in SCD

- **Rational**
  - Survival of affected afrodescendents are shortened in 25 to 30 years when compared to non affected group
  - First case of SCT in a patient with acute leukemia and SCD



Platt O, NEJM 1994

Bone Marrow Transplant for SCD

- First allogeneic BMT in 80s for a patient with acute leukemia
- In the 90s first results from Europe and USA
- More than 80% long term disease free survival and >90% overall survival with transplant from HLA identical siblings
- Related cord bloods similar results

Bone Marrow Transplant for SCD
USA and EUROPA

Transplants for SCD	EBMT- Eurocord (1986- 2013)	CIBMTR (1986- 2012)
Total	611	627
Type of donor		
HLA-identical	487	430
CB related and unrelated	73	71
Haploidentical donor	34	61
Other unrelated donor	17	65
Overall survival		
1 year	95±1%	96±2%
2 years	94±1%	94±1%

Data kindly provided by prof. Eliane Gluckman

Indications for BMT in SCD

Stroke or central nervous system event lasting longer than 24 h, acute chest syndrome with recurrent hospitalizations or previous exchange transfusions
Recurrent vaso-occlusive pain (more than 2 episodes per year over several years) or recurrent priapism
Impaired neuropsychological function with abnormal cerebral MRI scan
Stage I or II sickle lung disease
Sickle nephropathy (moderate or severe proteinuria or a glomerular filtration rate 30 to 50% of the predicted normal value)
Bilateral proliferative retinopathy with major visual impairment in at least one eye
Osteonecrosis of multiple joints
Red-cell alloimmunization during long-term transfusion therapy

Suggested by Walters et al and the EBMT

Angelucci et al. Haematologica 2014

Indications for SCT in SCD

Brazilian Protocol

Organ	One of the findings
Age	No limit
Vasoclusive crisis	a. Two ACSD in the last 2 years b. ≥ 3 episods of severe pain crisis per year in the last 2 years
CNS	a. Neurologic event (stroke or neurologic deficit that last for > 24 hours) b. Neurologic sign or symptom c. TCD > 200 cm/seg (2x)
Organ damage	a. Pneumopathy b. Pulmonary Hypertension c. Reduced kidney function d. Osteonecrosis in more than one articulation e. Retinopathy
Alloimunization	≥ 2 antibodies in patients in regular transfusion program
Hydrea	Reduction < 50% of algic crisis under HU treatment or intolerance to HU

Indications for SCT in SCD

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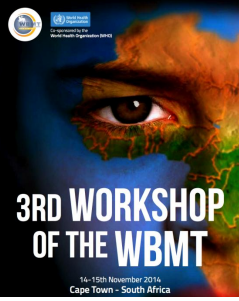
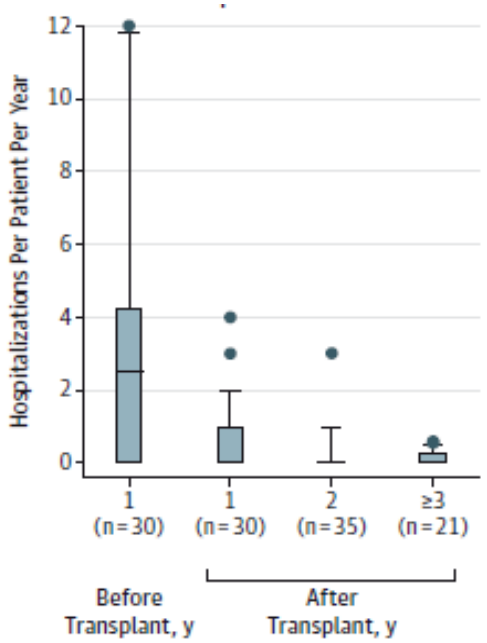
ONLY HLA IDENTICAL SIBLINGS OR RELATED CORD BLOOD

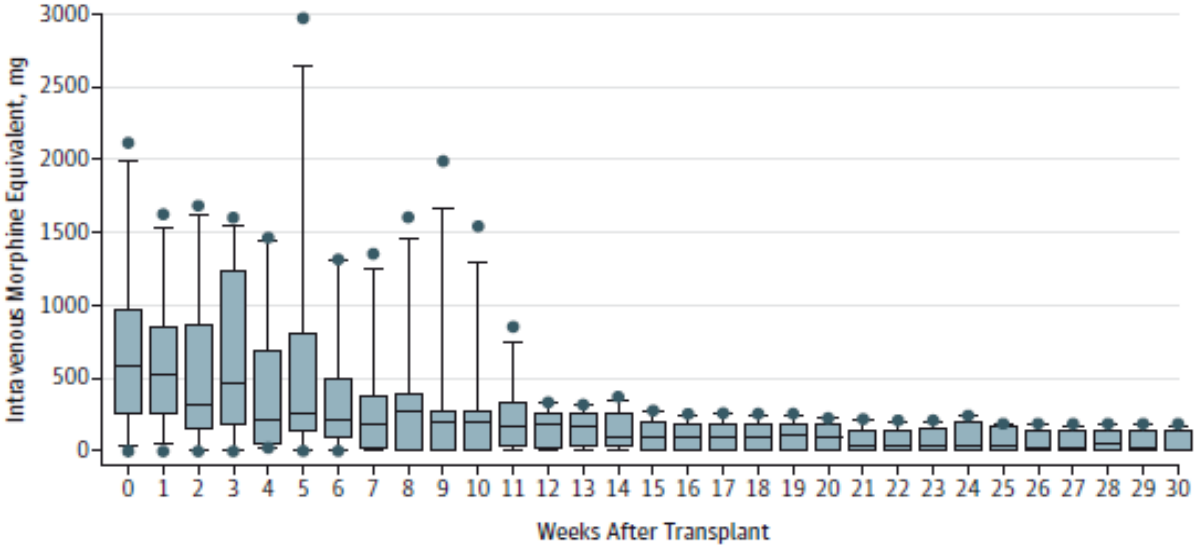
Outcome after BMT



Hospitalization rate



Narcotic use

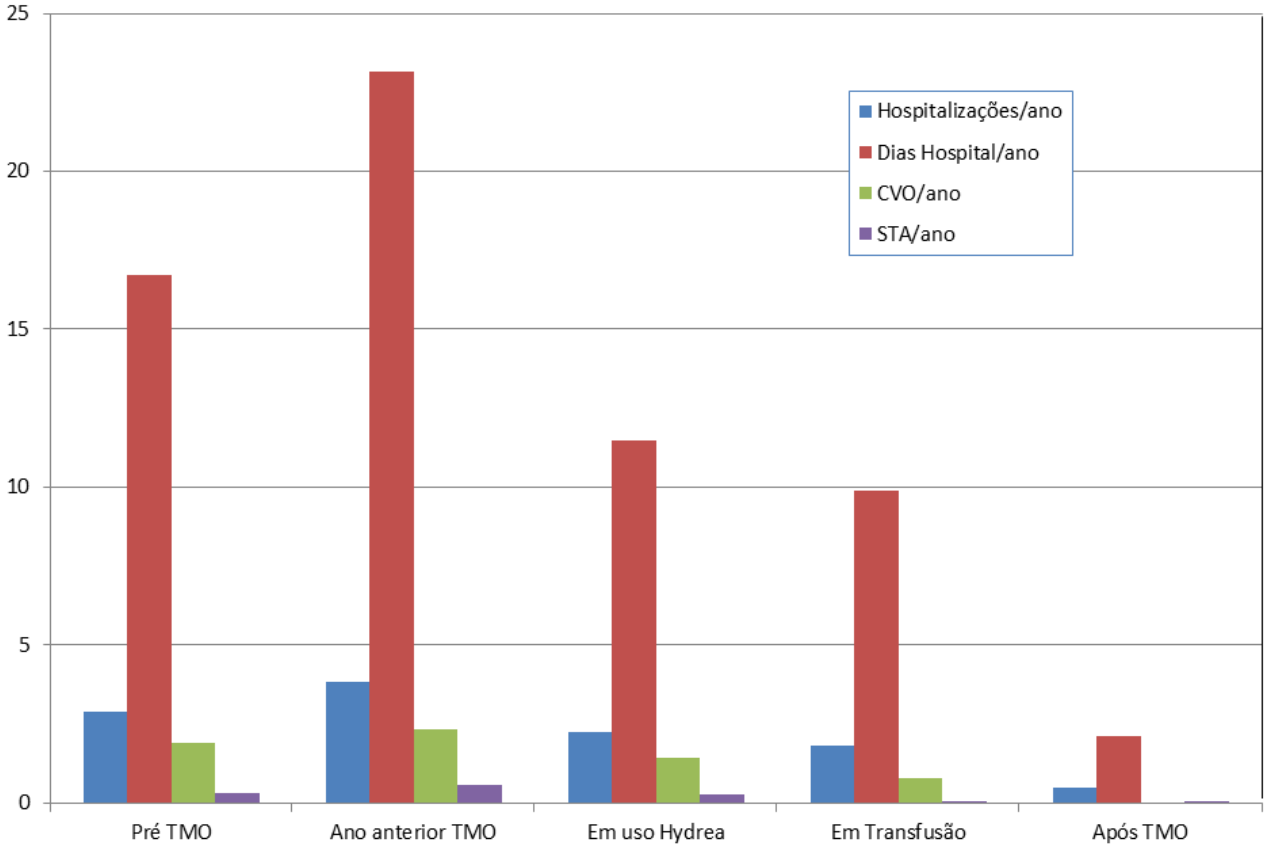


A, Median hospital admission rate per patient a year before, 1 year after, 2 years after HSCT, and 3 years after Hematopoietic Stem Cell transplantation (HSCT) and later per year. B, Among 11 participants who took narcotics long-term, median intravenous morphine equivalent doses of narcotics per week are shown with respect to time after HSCT. The boxes refer to 25th and 75th percentile; the whiskers, 10th and 90th percentile; and the dots, values outside the 10th and 90th percentile.

JAMA. 2014;312(1):48-56.

Outcome after BMT

N = 114 pacientes

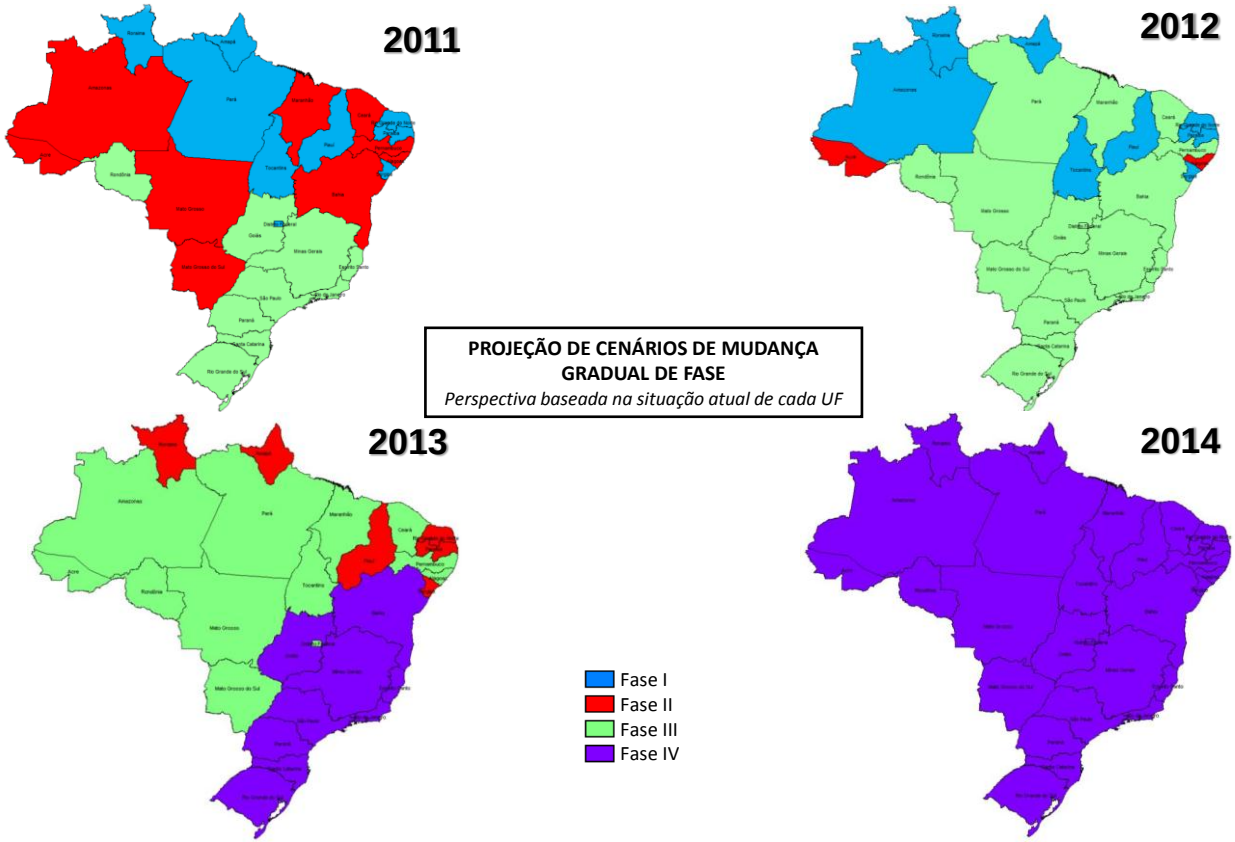


Situation in Brazil

- Few thalassemia major patients
  - Less than 800 probably
- Sickle Cell very frequent
  - About 4000 new cases per year
  - Already about 40.000 – 50.000 cases

Newborn screening programm

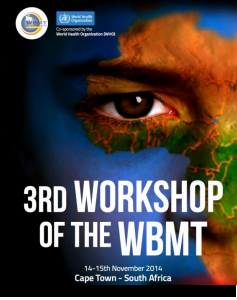
Programa Nacional de Triagem Neonatal



Public SCD Programm in Brazil

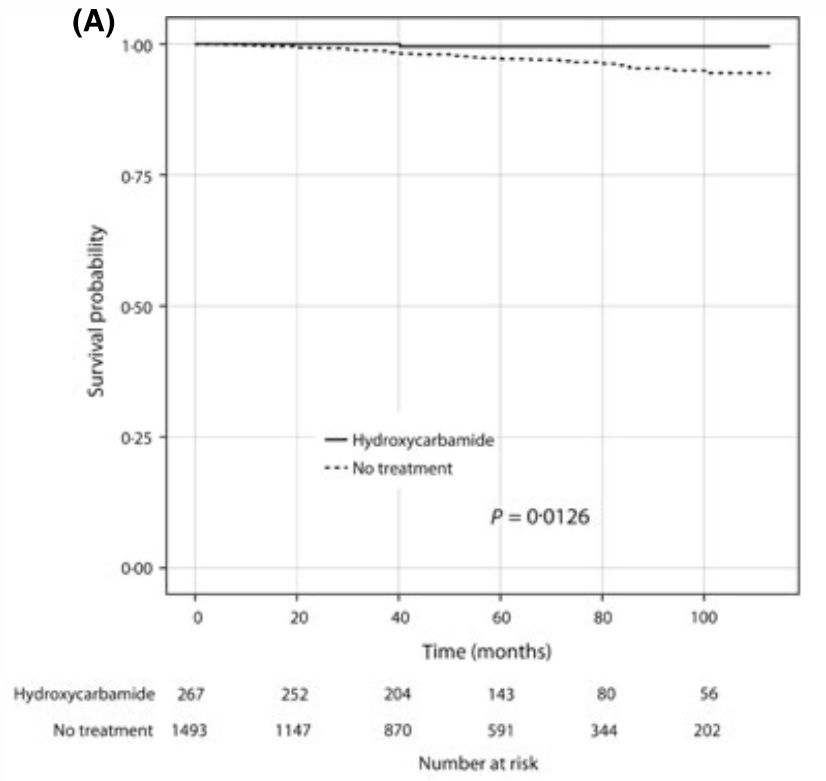
- 2005 – First public regulation for SCD
- 2009 – oral iron chelator approved
- 2010 – first public Hydrea programm
- 2011 – specific hydroxicarbamide and oral chelator programm for SCD
- 2013 – Hb electrophoresis included as routine in pregnant women
- 2013 – Transcranial Doppler reimbursed
- 2014 – BMT for SCD officially indicated in patients with defined criterias

Hydroxicarbamide in SCD Brazil



- Control Group
  - N = 1493 pts
  - Med Age 7 years
- Treated Group
  - N = 267
  - Med Age 5,5 years

- Hydroxycarbamide vs support



Lobo CL et al, Brit Journal Haematol 2013

SCT for SCD in Brazil

- N = 34 patients (35 transplants)
  - 21 patients transplanted in one center
    - 3 new patients short follow up
  - 13 patients transplanted in other 6 centers

- Alive
  - 20 (21) cases
  - 7 (13) cases*

Transplantation in SCD

Problems before transplant

- Heavily transfused patients
  - Antibodies
  - Iron overload
- Comorbidities
  - Stroke
  - Pulmonary dysfunction
  - Hepatic dysfunction
- Predicitve factors of severity

Transplantation in SCD

Problems after transplant….

- Acute and chronic toxicity of chemotherapy
  - Mucositis
  - Infections
  - Fertility
  - Second neoplasia
- Immunesupression
- Graft versus Host diseases

BMT for SCD In Ribeirão Preto

- N= 21 patients
  - (22 transplants)
- Median Age – 18 years (8-39 years)
- Median Follow up – 2 years
- Overall Survival
  - 20 patients alive
  - 1 death 1 year after 2. BMT and 3,8 years after 1.
    - Hemorrhagic stroke – Moya-Moya prévio before BMT

BMT for SCD In Ribeirão Preto

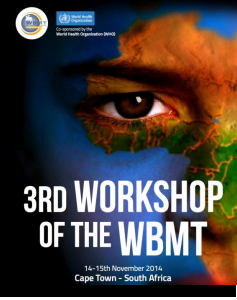
- Indications
  - Priapism
  - Stroke
  - Altered Transcranial doppler
  - Repeted acute chest syndromes
  - Severe leg ulcers

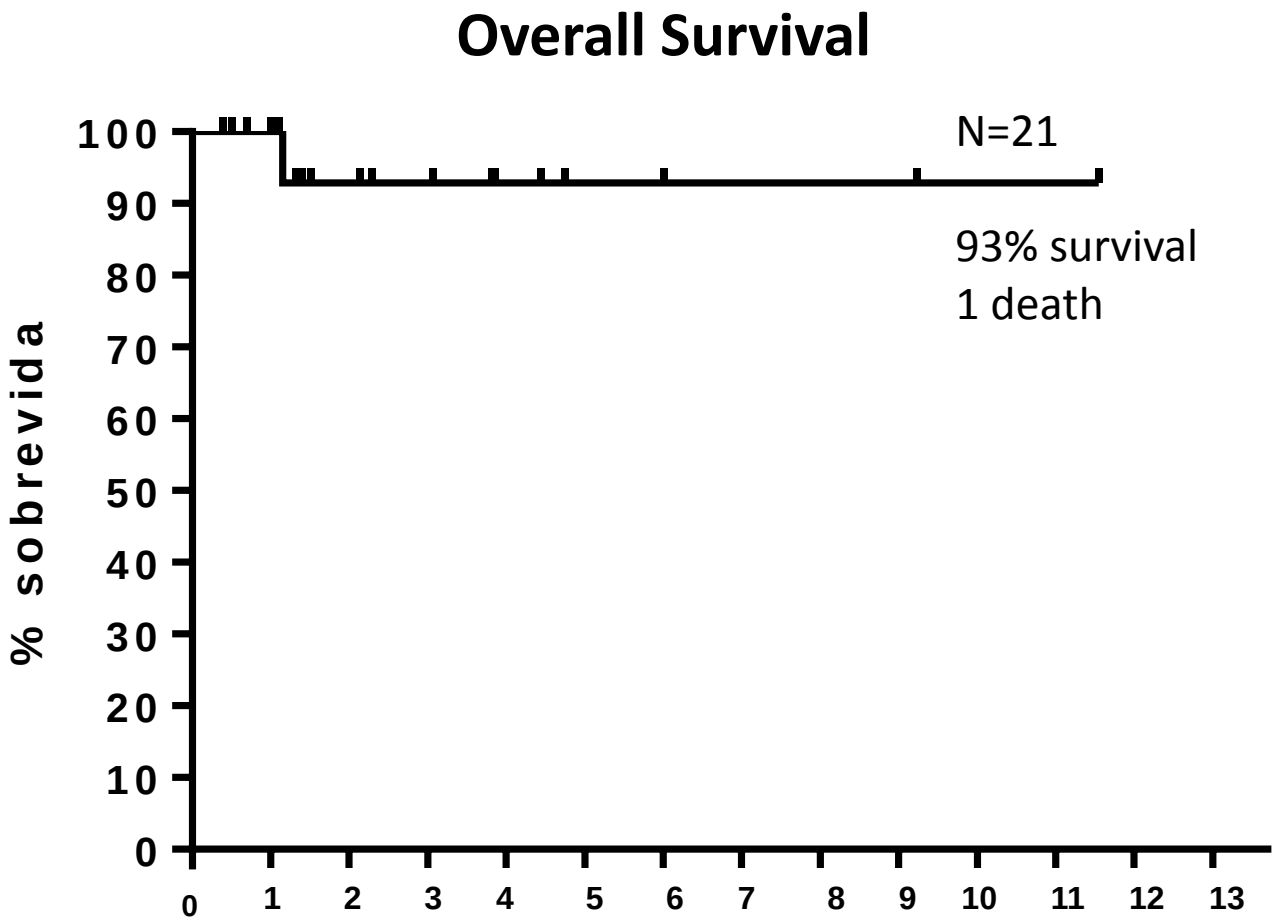
BMT for SCD In Ribeirão Preto

- GVHDa
  - 5 cases grade II
- GVHDc
  - None of our patients until today

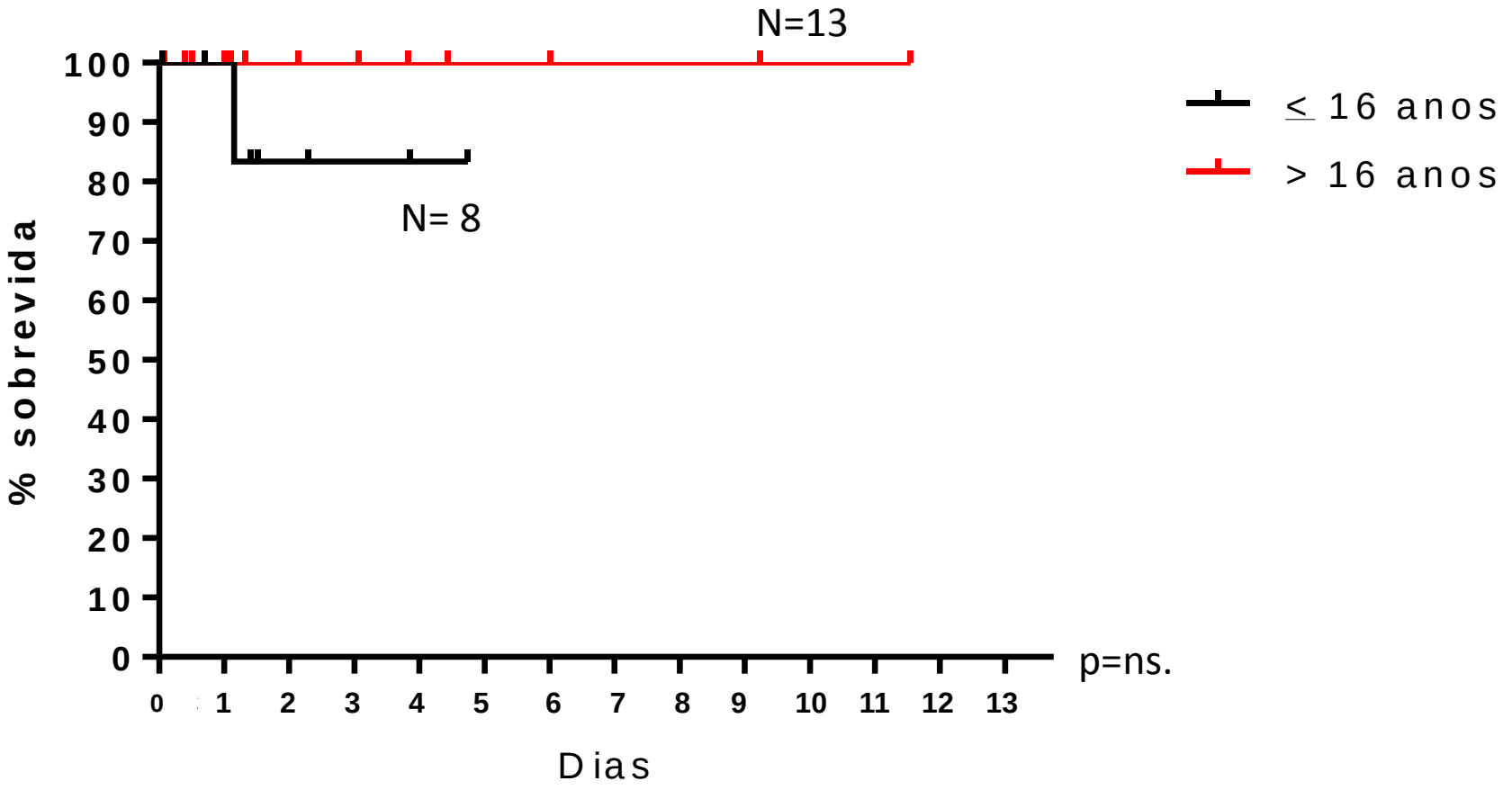
* obs: all patients were carefully evaluated and prepared for transplant! None of them were transplanted less than 6 months after first apointmet!! HbS < 30%, Hydrea until initiated conditioning, anticonvulsivants as long as they take CsA, platelets between 50.000, Hb between 9,0 and 10,0 g/dL

BMT for SCD In Ribeirão Preto





BMT for SCD In Ribeirão Preto



BMT for SCD

- Why should we wait until they have irreversible complications?
- Very high mortality after complications
- Poor quality of life
- We dont have good severity predictors for the disease

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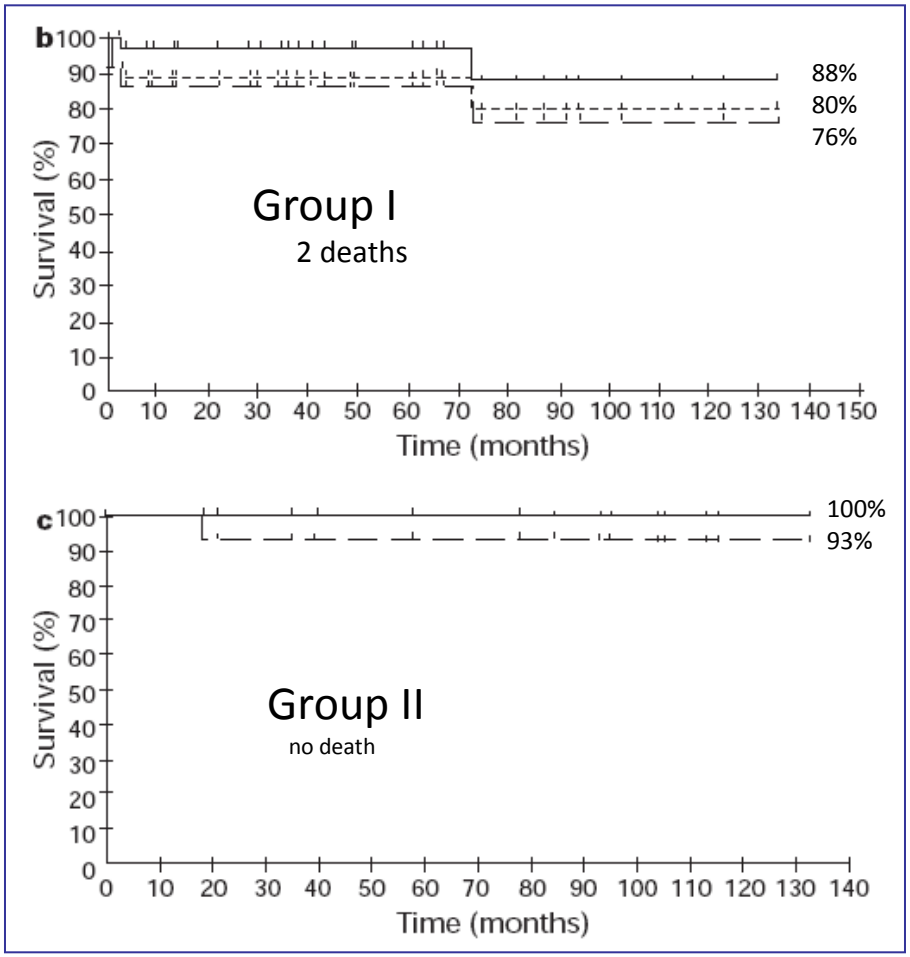
The ethics of a proposed study of hematopoietic stem cell transplant for children with "less severe" sickle cell disease

Robert S. Nickel,[1] Jeanne E. Hendrickson,[2] and Ann E. Haight[1]

BMT in SCD – How early?

- N= 50
- Group I – 36 patients
  - Stroke, ACS
  - Med Age 8,6 years (1,7 a 23 a)
- Group II – 14 patients
  - Families returning to Africa wanted to take the kids cured home
  - Med Age 2 years (0,9 a 15 years)
- Graft failure and rejection
  - 25% group I
  - 7% group II

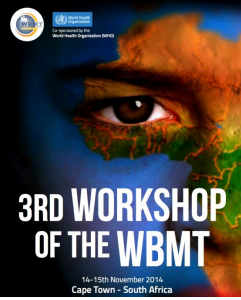


Vermylen C, 1998 BMT

Conclusions

- Health problem in Brazil and worldwide
- Compromise the quality of life
- Pain is the hallmark of sickle cell disease
- BMT can cure Sickle Cell Disease and Thalassemia major
- The procedure can be safely offered not only to children, but also to adults
- Since they have several comorbidities sometimes a careful selection and treatment of complications should performed before transplant
- A strong collaboration with a transfusion agency is necessary for the best outcome

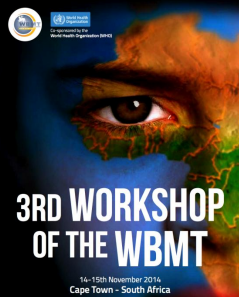
BMT in Sickle Cell Disease



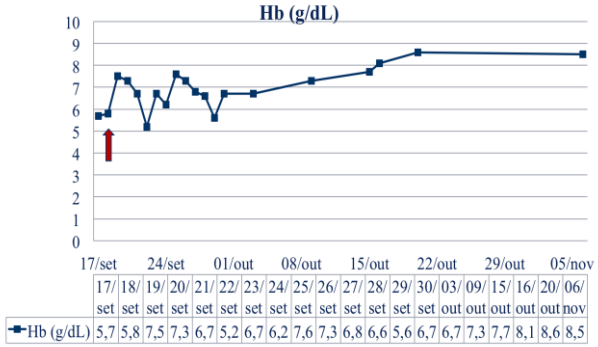
- Female 22 years
  - Transfused since 9 months
  - With 9 years started with frequent transfusion reactions
  - Since 2 years ago reactions with all transfusions
  - Hb 6,3 g/dL
  - HbS 85%
  - Antibodies anti-E, anti-e and anti-C

- Female 29 years old
- Transfused irregularly since childhood
- With 20 years started with complications of the disease
- Refractory leg ulcer
- Antibodies identified
  - Anti-K, Anti-Kpa, Anti-Fya , Anti-S impossible to rule aout Anti-Jkb, Dia and Cw.

BMT in Sickle Cell Disease



- Female 22 years
  - Transfusion block
  - No blood available
  - Rituximab 3x, IV immunoglobulin 2x plasmapheresis



	17/set	18/set	19/set	20/set	21/set	22/set	23/set	24/set	25/set	26/set	27/set	28/set	29/set	30/set	03/out	09/out	15/out	16/out	20/out	06/nov
Hb (g/dL)	5,7	5,8	7,5	7,3	6,7	5,2	6,7	6,2	7,6	7,3	6,8	6,6	5,6	6,7	6,7	7,3	7,7	8,1	8,6	8,5

45 days after BMT doing fine!

- Female 29 years old
  - After first phenotyped transfusion severe hyperhemolisys Hb 3,5 g/dL
  - 48 donors were called but only 2 compatible
  - Rituximab, Ciclophosphamide and plasmapheresis
- 4 months after transplant doing fine!!

Acknowledgments

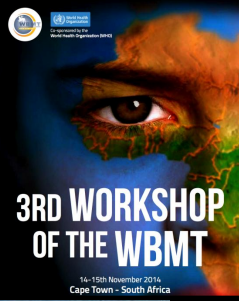
Hemocentro Ribeirão Preto

- Ana Cristina Pinto
- Gil de Santis
- Ivan Angulo

Dermatologista

- Marco Andrey Cipriani Frade

National Network for Blood and Marrow Transplatatation



To my patients

Salvador, Bahia

National Network for Blood and Marrow Transplatatation

National Network for Blood and Marrow Transplatatation

Hemoglobinopathies

Major differences TM and SCD

	Thalassemia	Sickle cell disease
Prognostic criteria for disease severity	Homogenous pattern for β thalassemia major	Wide genetic variability; inconsistent development of complications
Currently accepted indication for allogeneic HSCT	Transfusion dependency. For patients with an HLA identical sibling donor or well-matched related or unrelated donor: as soon as possible to avoid transfusion associated complications	Patient with matched sibling donor and complication requiring treatment with hydroxurea or transfusion
Total number of HSCT reported	> 3000 patients transplanted	500-600 patients transplanted
Risk factors for transplant-related complications	Age, organ dysfunction due to iron overload	Age, history of cerebral events
Alternative effective medical therapy	Life-long transfusion with chelation	Hydroxyurea: not curative, but ameliorates some complications. Chronic transfusion and chelation therapy.
Key issue for transplant outcome	Control of iron overload and related tissue damage	Cure from chronic inflammation and prevention of future SCD-related organ damage
Conditioning regimen	Needs to ablate an expanded bone marrow	Reduced intensity regimens seem to induce stable chimerism and full donor erythropoiesis
Possibility for gene therapy	First successful case reported. Phase I clinical trial ready to start	No successful case reported. Phase I clinical trial ready to start

Angelucci et al. Haematologica 2014

A doença vs TMO

Primum non nocere!

Dano	TMO
Death	Low death rate after BMT
Infections	Long term imunesupression after SCT
Acute complications	Mucosite, alopecia, SOS, hemorragia cerebral, PRES
Chronic complications	GVHDc
Reproduction	Possível por toxicidade do condicionamento
Social	Problema intenso de curta duração

BLOOD, 7 AUGUST 2014 • VOLUME 124, NUMBER 6

A doença vs TMO

Primum non nocere!

Dano	TMO	Doença Falciforme
Óbito	Baixa chance de morrer de complicações do TMO	Risco muito baixo na infância com cuidados adequados de suporte, alto risco de morrer prematuramente quando adulto
Infecções	Pacienes muito imunossuprimidos por longo tempo pós TMO	Função esplenica defeituosa ou ausente
Complicações Agudas	Mucosite, alopecia, SOS, hemorragia cerebral, PRES	CVA, sequestro esplenico, STA, colecistite, priapismo, crise aplástica, AVC
Complicações Crônicas	GVHDc	Dor crônica, necrose asséptica, lesões orgânicas (rim, pulmão, retina)
Problemas reprodutivos	Possível por toxicidade do condicionamento	Possível por lesão órgãos (disfunção erétil, problemas na gestação) ou hidroxiurea
Social	Problema intenso de curta duração	Pela vida toda…. Doença crônica

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