Stem Cell Transplantation in Sickle Cell Anemia

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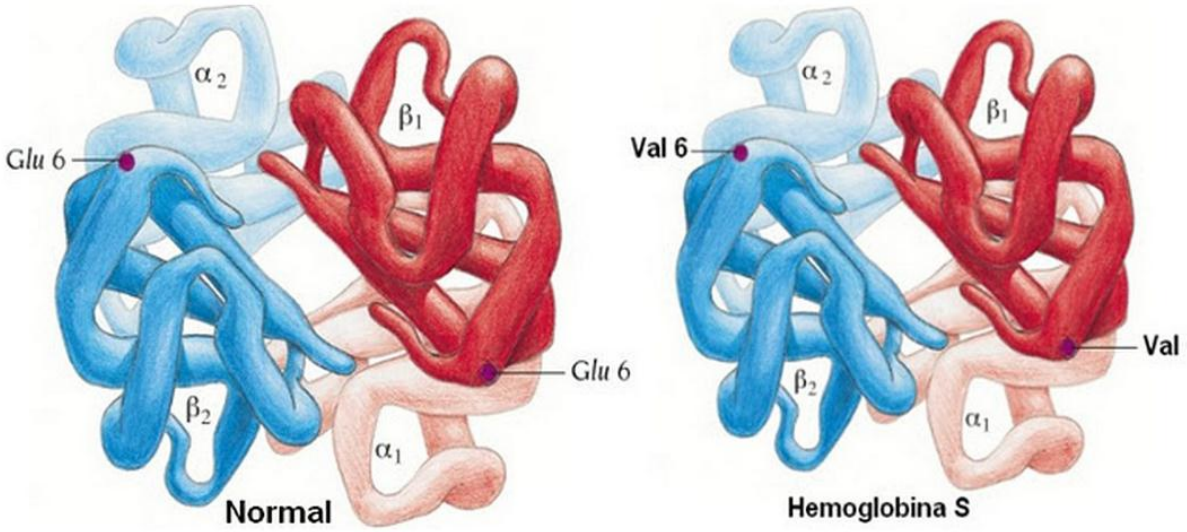
Hemoglobinopathies

- 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).



The Hemoglobinopathies

Hemoglobinopathy	No. Newborns/year
Sickle Cell Anemia (SS)	217.331
SC Disease	54.736
S β thalassemia	11.074
β thalassemia major	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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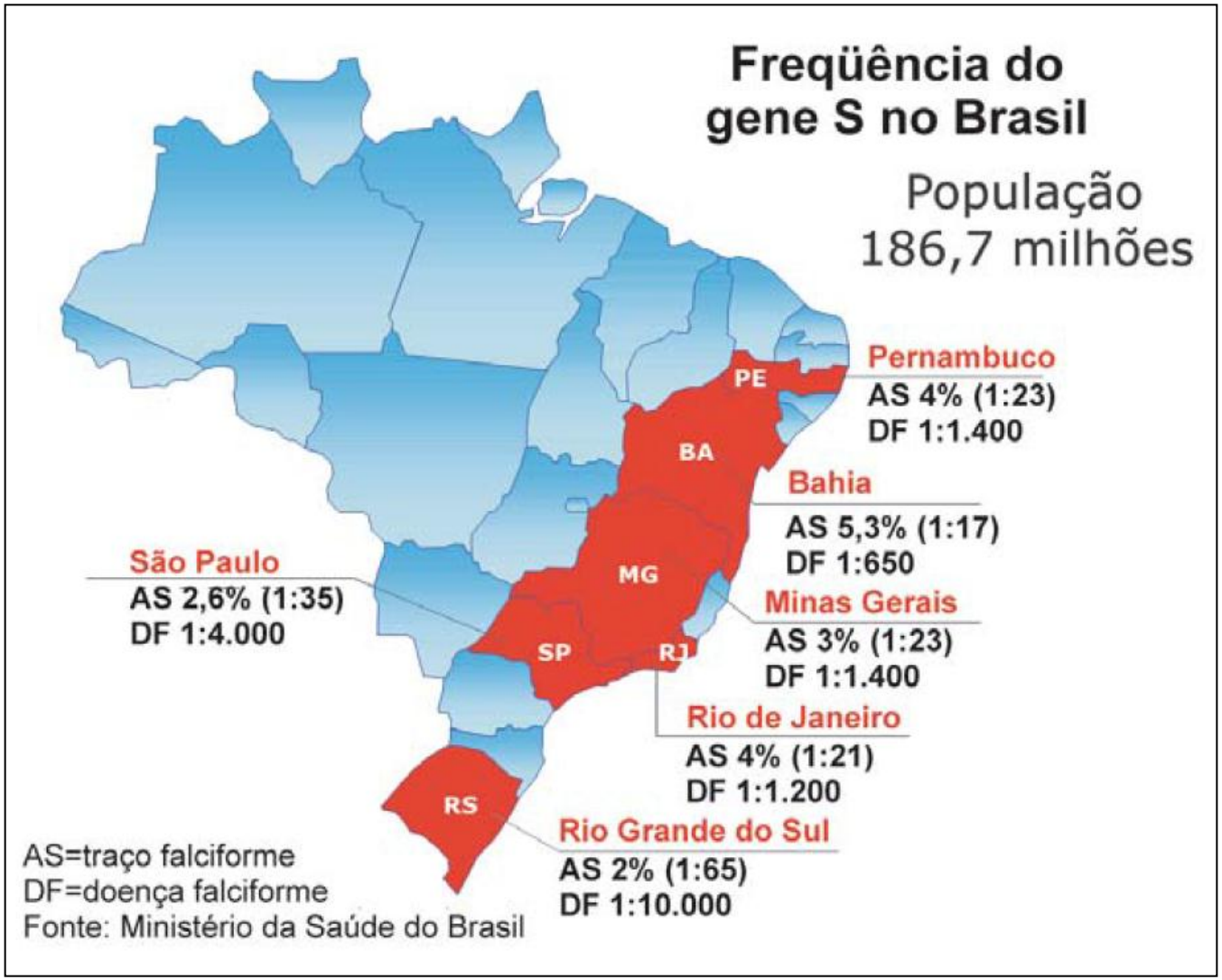
Sickle Cell Disease in Brazil

- SCD are the most common hereditary monogenic disease in Brazil
  - 4 % of the brazilian population carry the S gene. Until 10% of the afrodescedents
  - We estimate that about 3500 kids with sickle cell disease are born in Brazil
  - We estimate 200.000 sickle cell carriers in Brazil
  - We estimate about 30.000 – 50.000 brazilians with SCD
- Health problem in Brazil

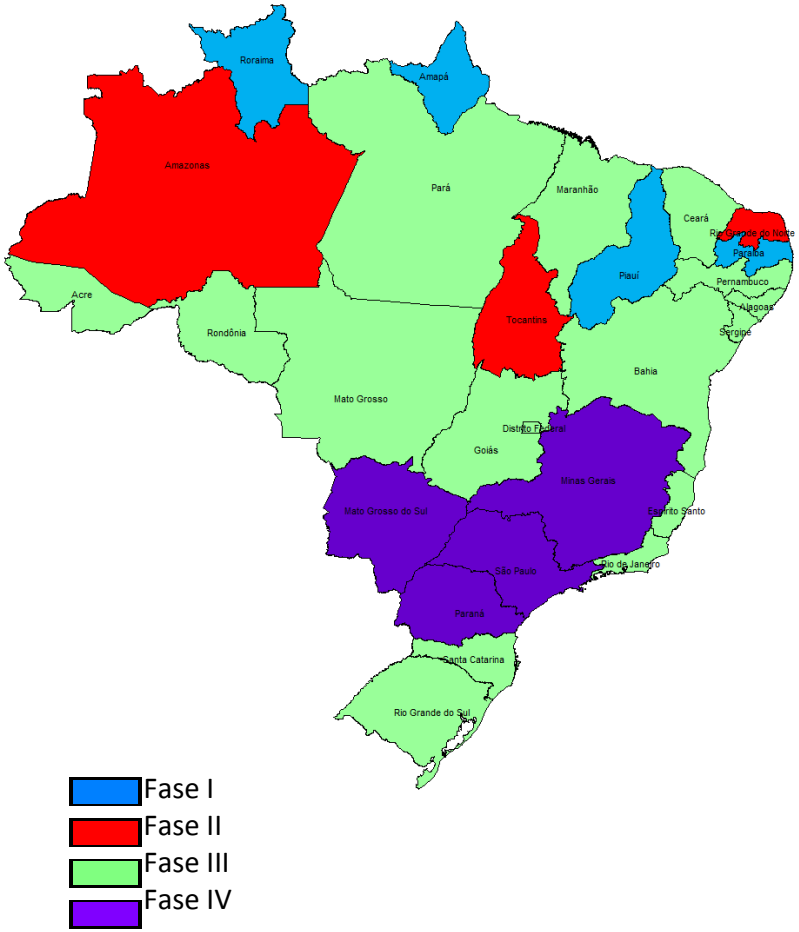
Documento Dr. Rodolfo Cancado

S gene in Brazil

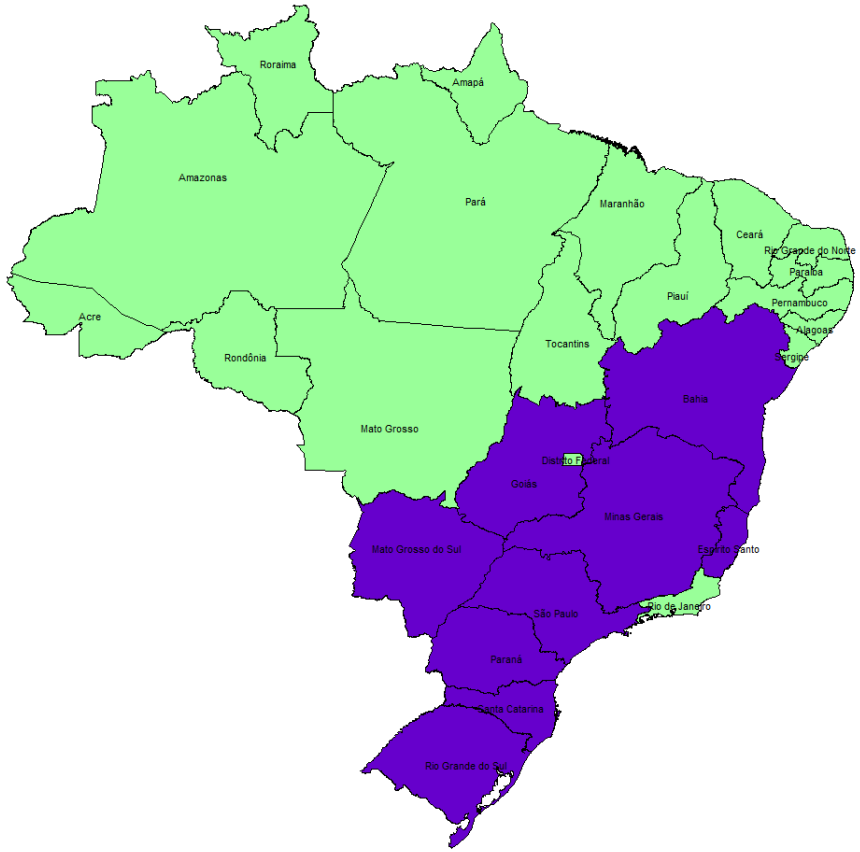


Neonatal Screening Program

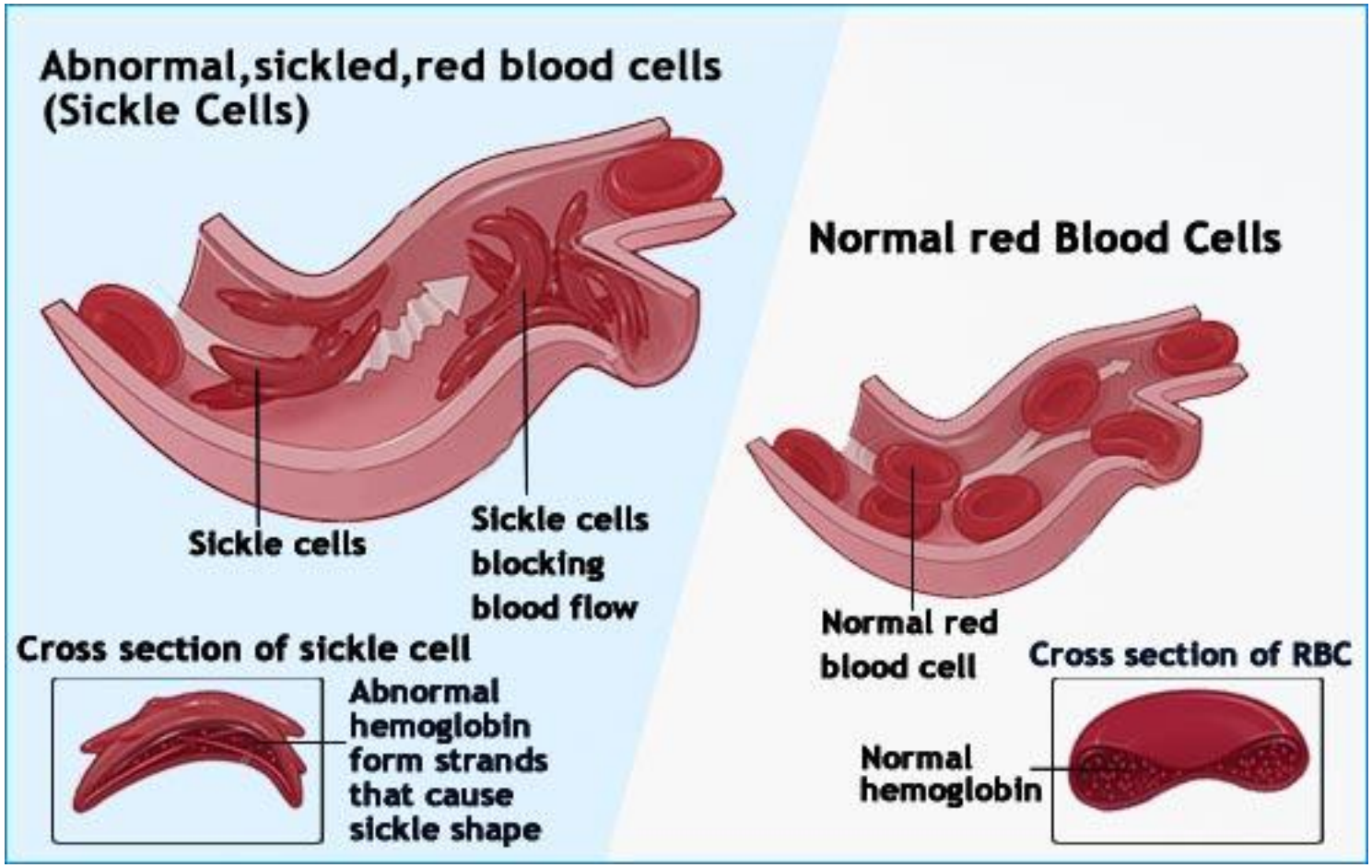
May 2013



Goals for end of 2013



Pathophysiology



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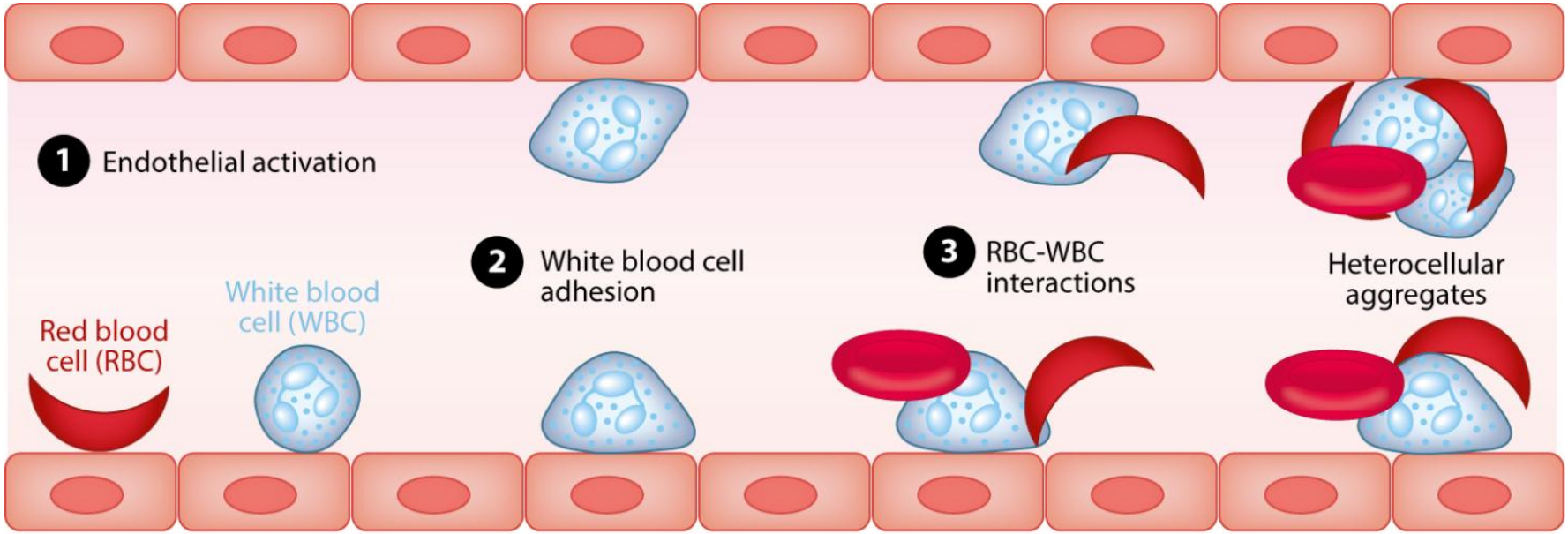
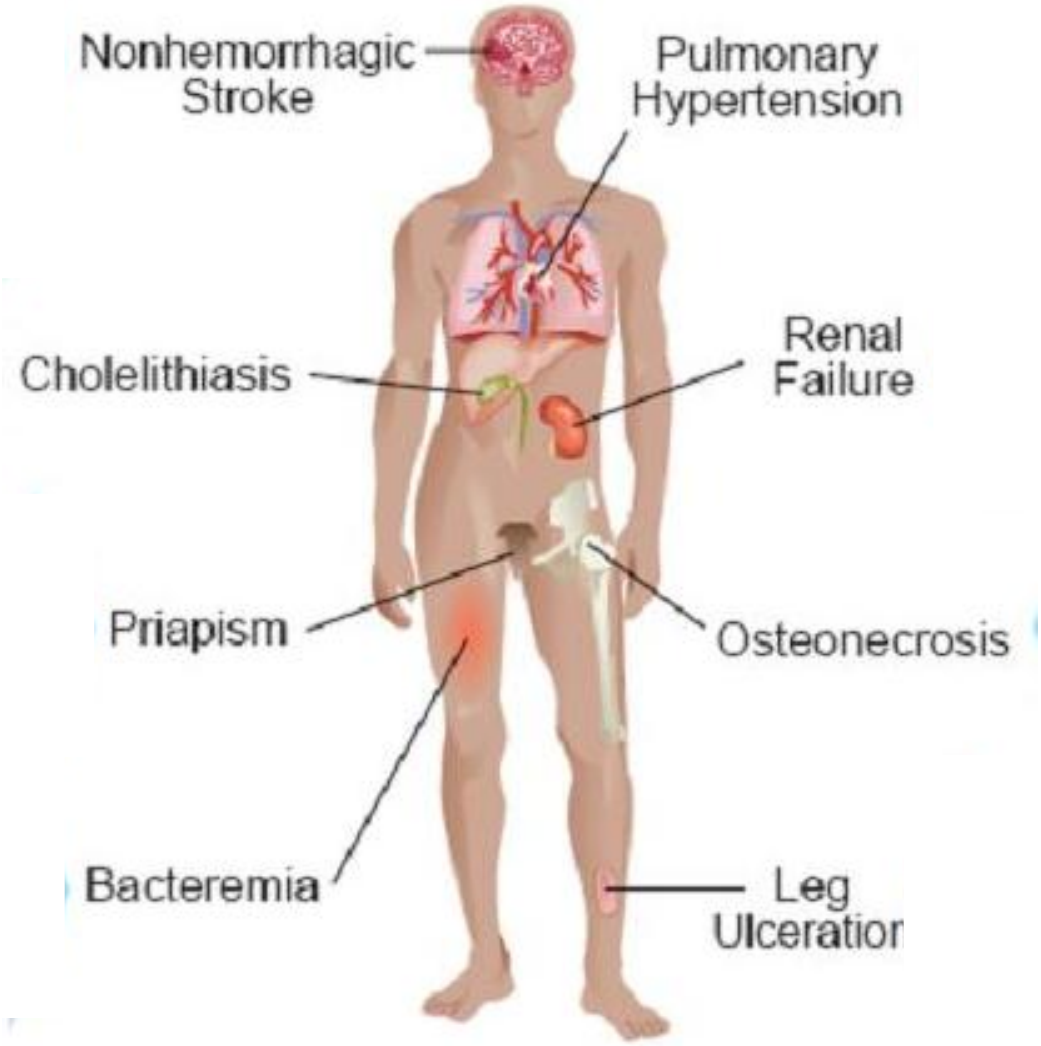


Kassim AA, DeBaun MR. 2013. Annu. Rev. Med. 64:451–66

Clinical Manifestations SCD



Clinical Evolution in SCD

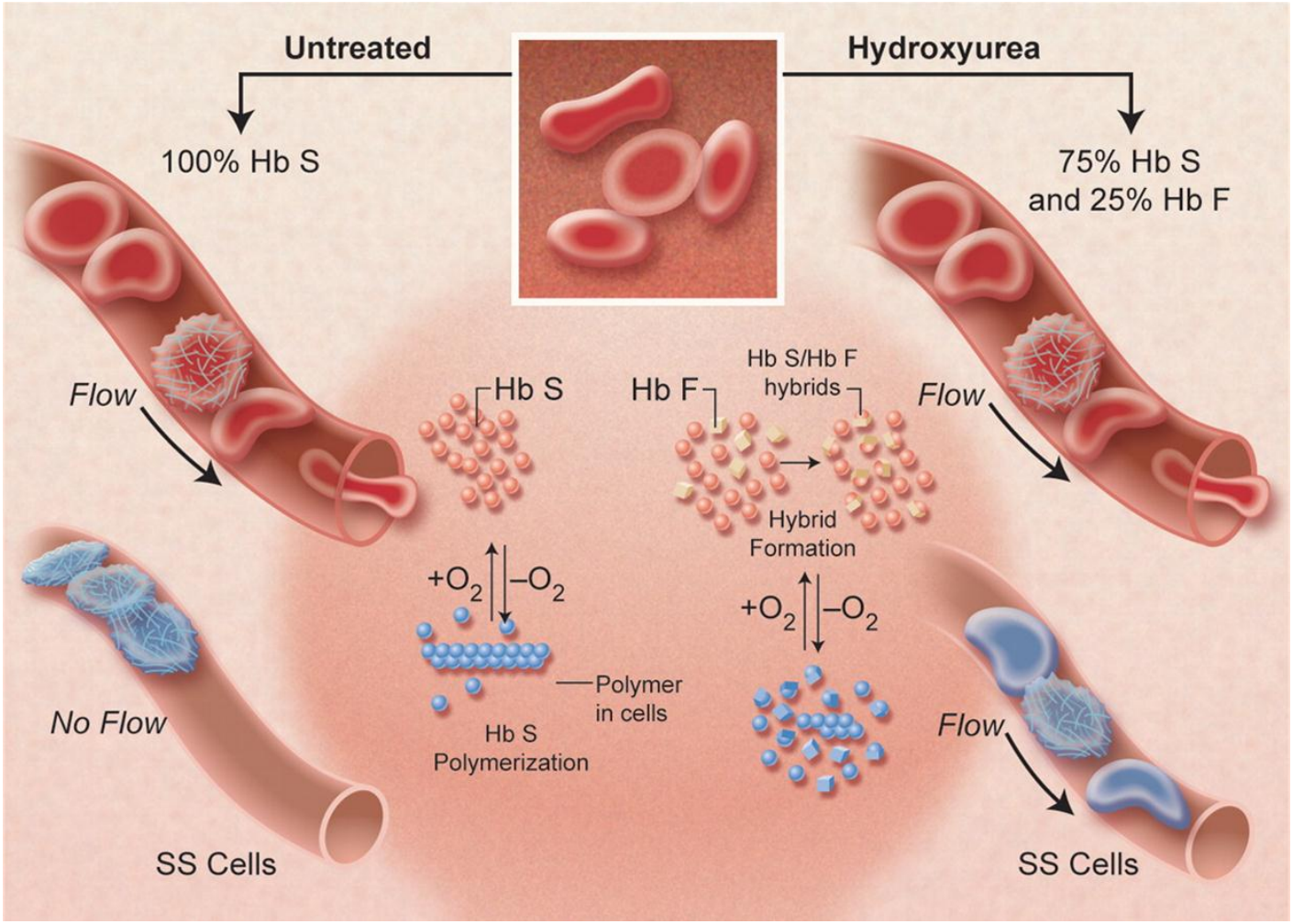
Infections
Sepsis
Splenic Sequestration
Ischemic Stroke
Dactilitys

Vosoclusive crises
Acute chest syndrome
Pulmonary hypertension
Priapism
Hemossiderosis

Kidney disease
Retinopathy
Leg ulcers
Asspetic necrosis femur
Hemorrhagic stroke
Multiple organ failure

A G E

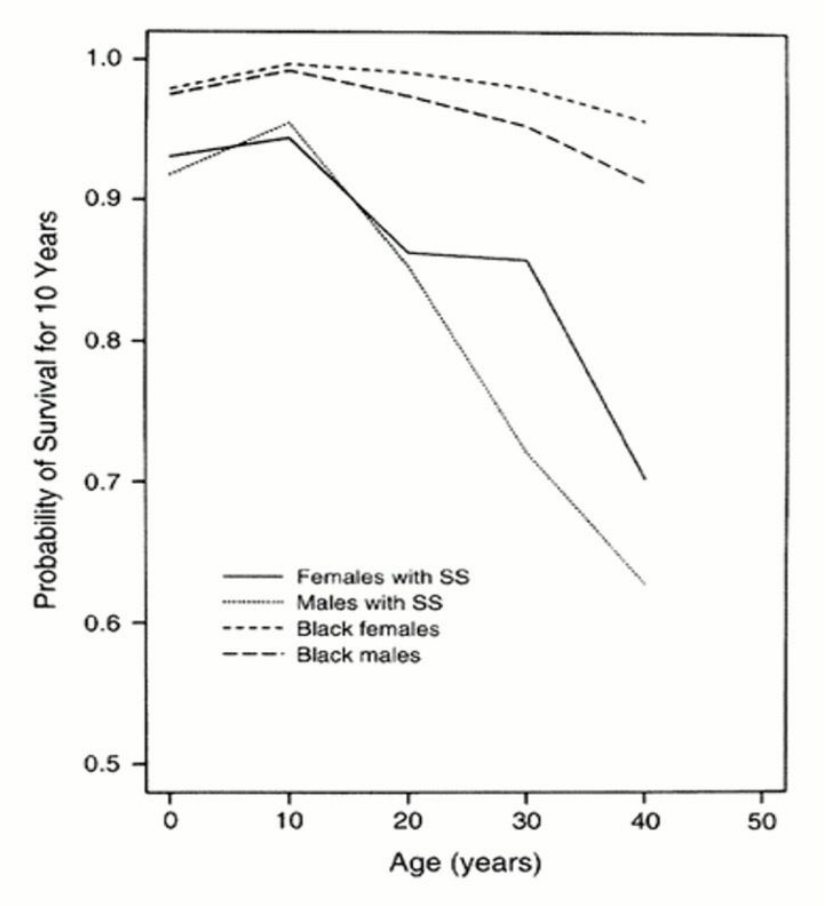
Hydroxicarbamide



Schechter A N Blood 2008;112:3927-3938

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

Mortality in SCD

- Time evaluated 1979 to 2005
  - N=16654 deaths due to sickle cell anemia
  - National Center for Health Statistics
- Death rate 1979
  - Median age
    - mens: 33,4 years
    - Women: 36,9 years
- Death rate 2005
  - Median age
    - Man: 38 years
    - Woman: 42 years

Lanzkron S et al. 2013 Public Health Rep

Mortality in SCD

- Time evaluated 1979 to 2005
  - N=16654 deaths due to sickle cell anemia
  - National Center for Health Statistics
- Death rate 1979

> 19 years: mortality rate increased 1% for each year
< 19 years: mortality decreased 3% for each year

- Death rate 2005
  - Median age
    - Man: 38 years
    - Woman: 42 years

Lanzkron S et al. 2013 Public Health Rep

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

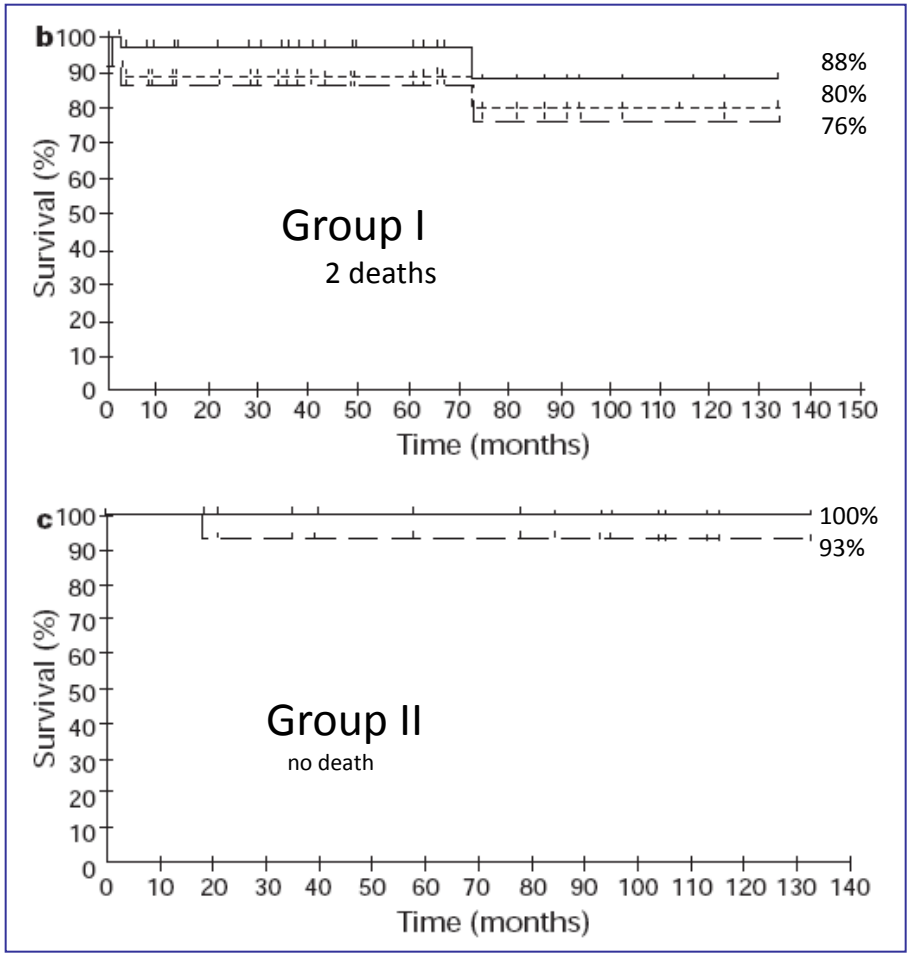
Problems after transplant….

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

What transplant can do for our patients?

Stem Cell Transplantation in SCD

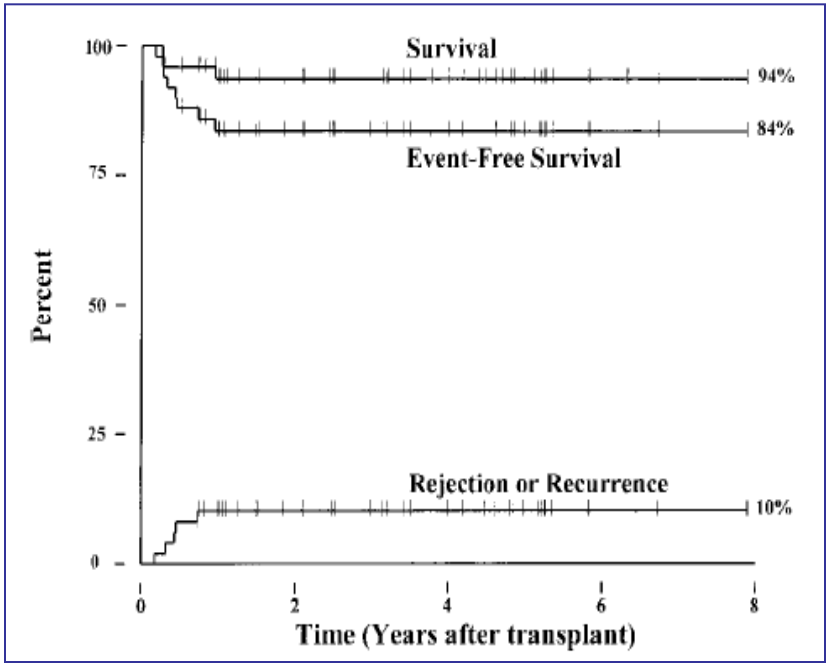
- N= 50
- Group I – 36 patients
  - Stroke, ACS, Vasocclusion
  - Med Age 8,6 years (1,7 to 23 y)
- Group II – 14 patients
  - Families with affected kids who wanted to go back to their countries cured!
  - Med Age 2 years (0,9 a 15 y)
- Graft failure or rejection
  - 25% group I
  - 7% group II



Vermylen C, 1998 BMT

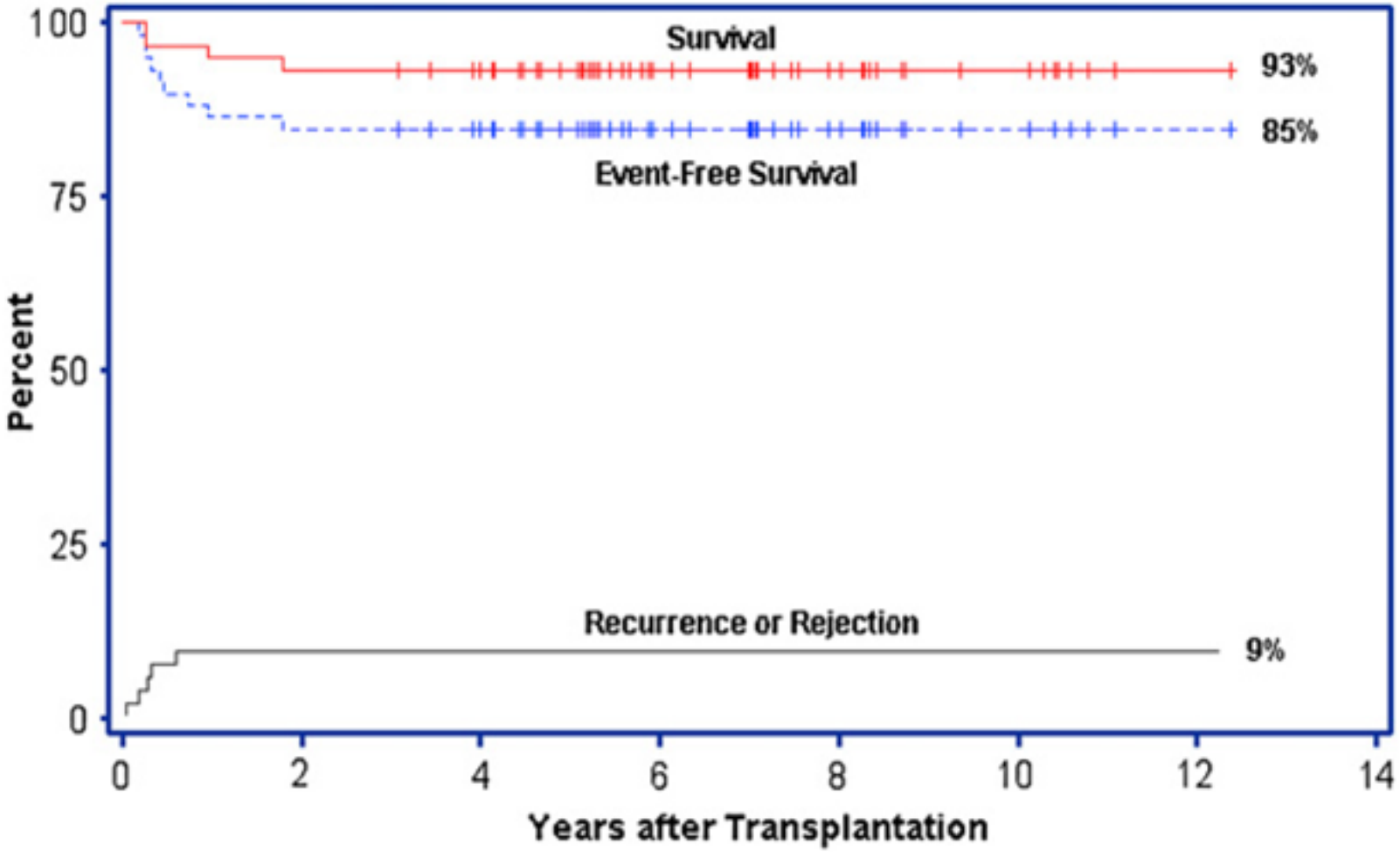
Stem Cell Transplantation in SCD

- N = 50 (48 SS)
- Med Age 9,9 (3,3 to 15,9)
- Indications
  - Stroke
  - Acute Chest syndrome
  - Vasocclusive crisis
- Evolution
  - 3 deaths
    - 1 stroke
    - 2 GVHD
- Chimerism
  - 5 graft failures/rejections



Walters M, 2000 Blood

Stem Cell Transplantation in SCD USA



Walters MC et al. Bone Marrow Transplantion 2010

SCT for Sickle Cell Anemia
French Cohort

- N= 144 patients
  - 84M; 60F
- **Median Age**: 9 years
- **Indications**
  - Vasculopatia cerebral (89)
  - CVO frequentes (41)
  - Osteonecrose (7)
  - Aloimunização (4)
  - Hipertensão Pulmonar (1)
  - Leucemia (2)
- **Stem Cell Source**
  - BM (121)
  - CB (21)
  - PBSC (1)
  - BM+CB (1)

Conditioning regimen: BuCy ATG

Median Follow Up
3.1 years (0.2-15.5)

F. Bernaudin et al, EBMT 2011 #396

SCT for Sickle Cell Anemia
French Cohort

- Results
  - Take: 142/144 (2 cords)
    - 1 late rejection after 3 years
  - Acute GVHD
    - ≥ II in 23%
    - ≥ III in 4,9%
  - Chornic GVHD
    - 9,7% (4 extensive)
- Deaths N=6 (4,1%)
  - 4 GVHD related, 1 Stroke, 1 sepsis in aplasia

SCT for Sickle Cell Anemia
French Cohort

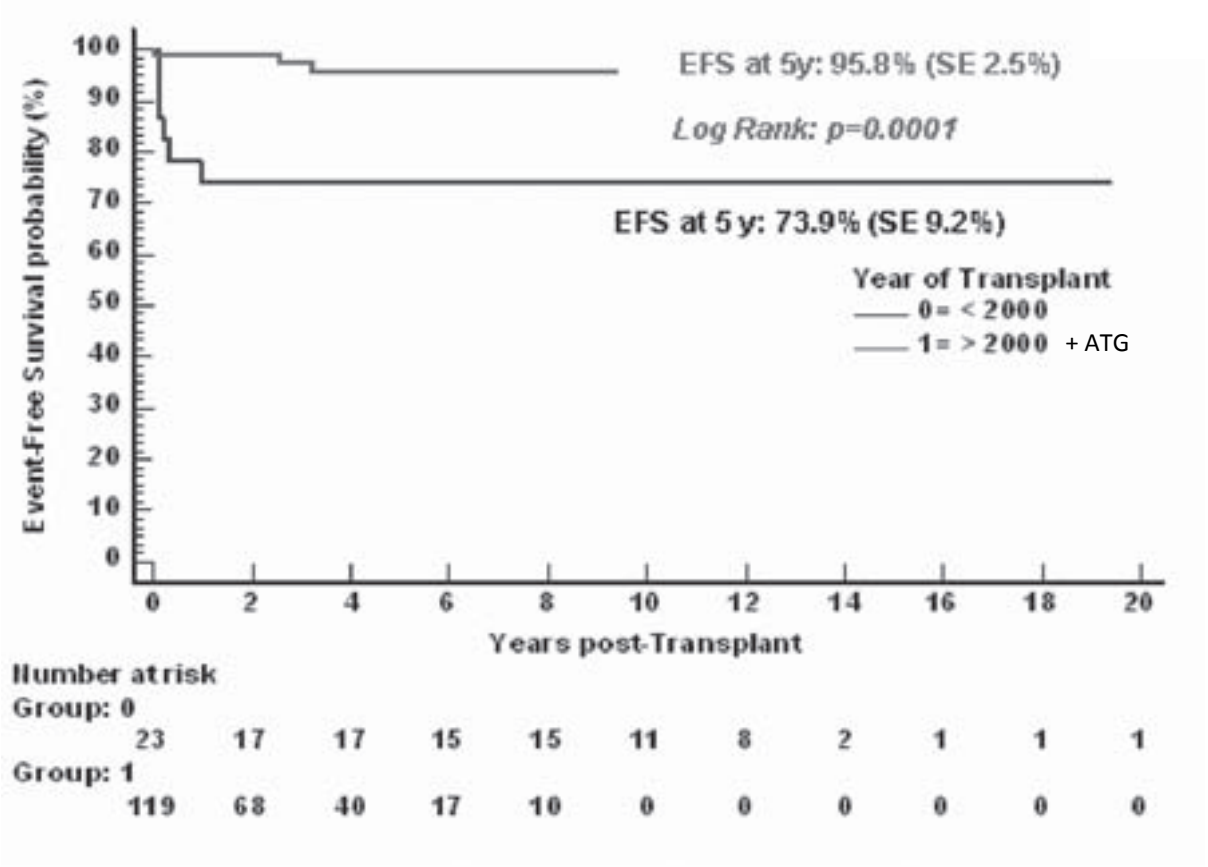
- CNS
  - No new strokes
- Lungs
  - Estabilization of lung function
- Reversion of chronic “Inflammatory state”
  - Increased BMI (body mass index)

SCT for Sickle Cell Anemia

French Cohort

5 year Overall Surival 95%

Event free surival 92,2%



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SCT for Sickle Cell Anemia

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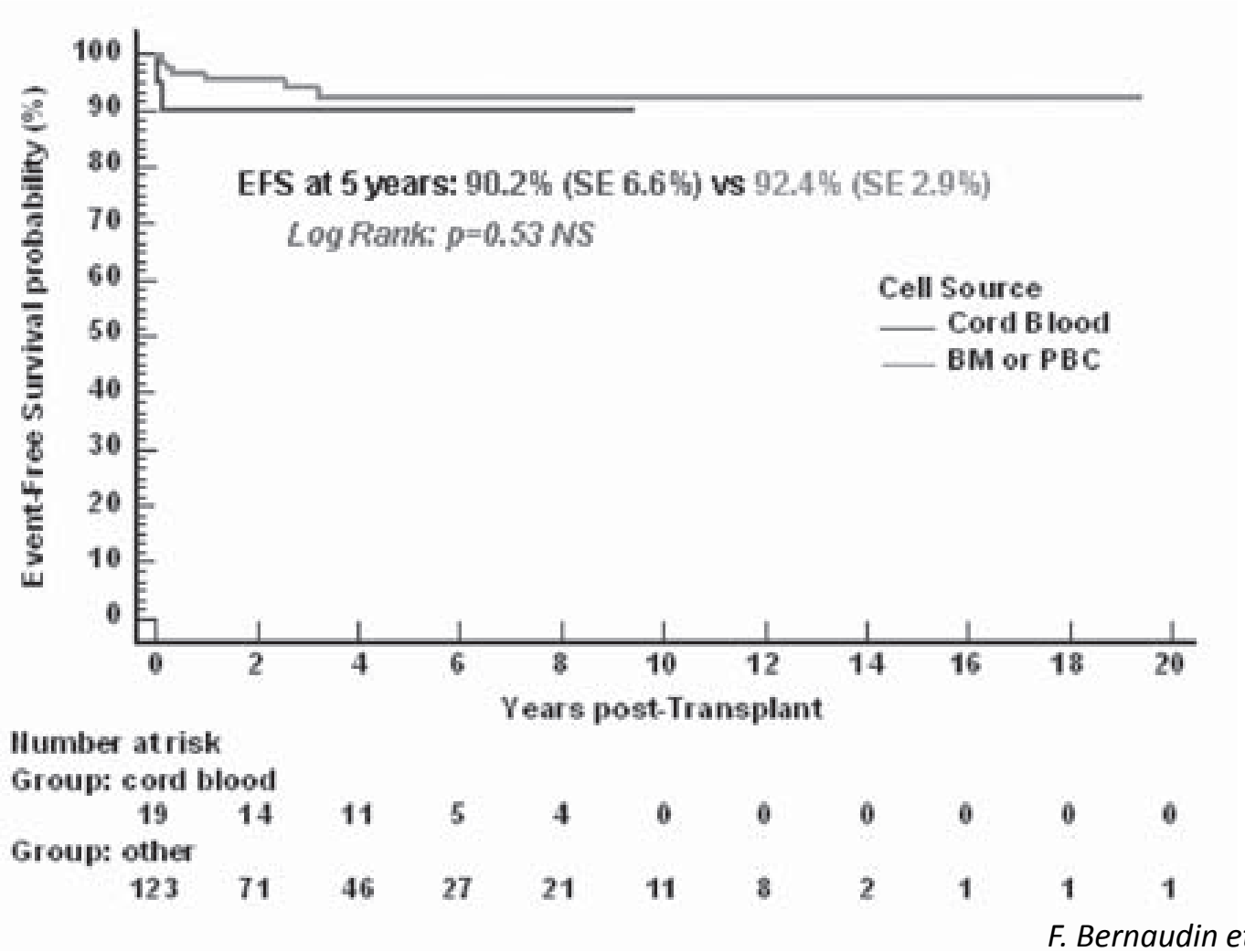


F. Bernaudin et al, EBMT 2011 #396

Hemoglobinopathies

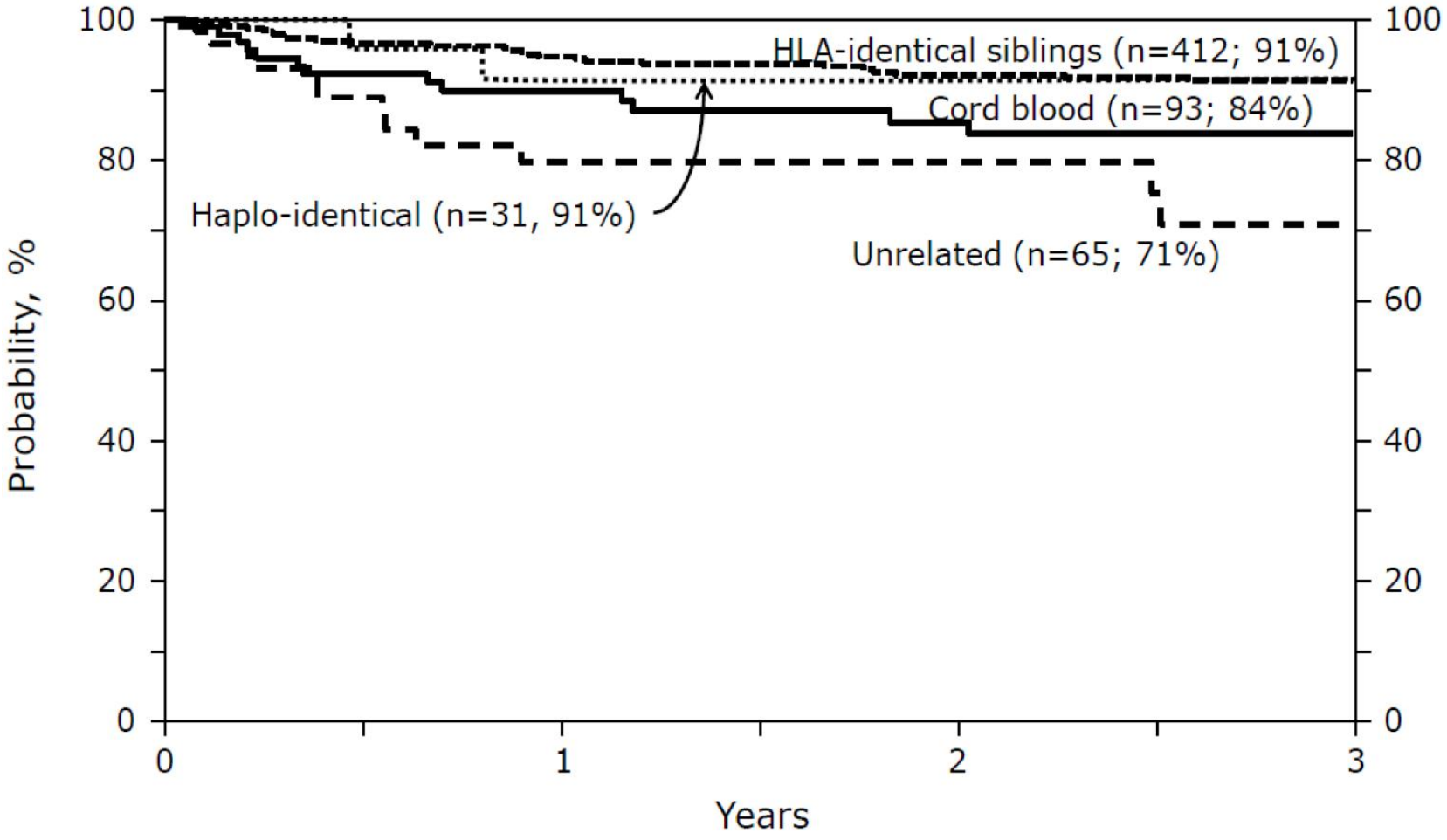
	Thalassemia	Sickle Cell
In Brazil	**485 cases**	**30 a 50.000 cases**
SCT results		
Overall Survival	66% (grau I a III)*	**94%**
Disease Free Survival	68% (graus I a III)**	**85%**
Mortality	12 a 37% (grau III)	**4 a 7%**
Acute and chronic GVHD	4 a 31%	**10 a 22%**
* Class I – 93% **Class II – 83%		

SCT in SCD – Europe and USA

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%

Unpublished data kindly provided by prof. Eliane Gluckman

SCT in SCD – USA - CIBMTR



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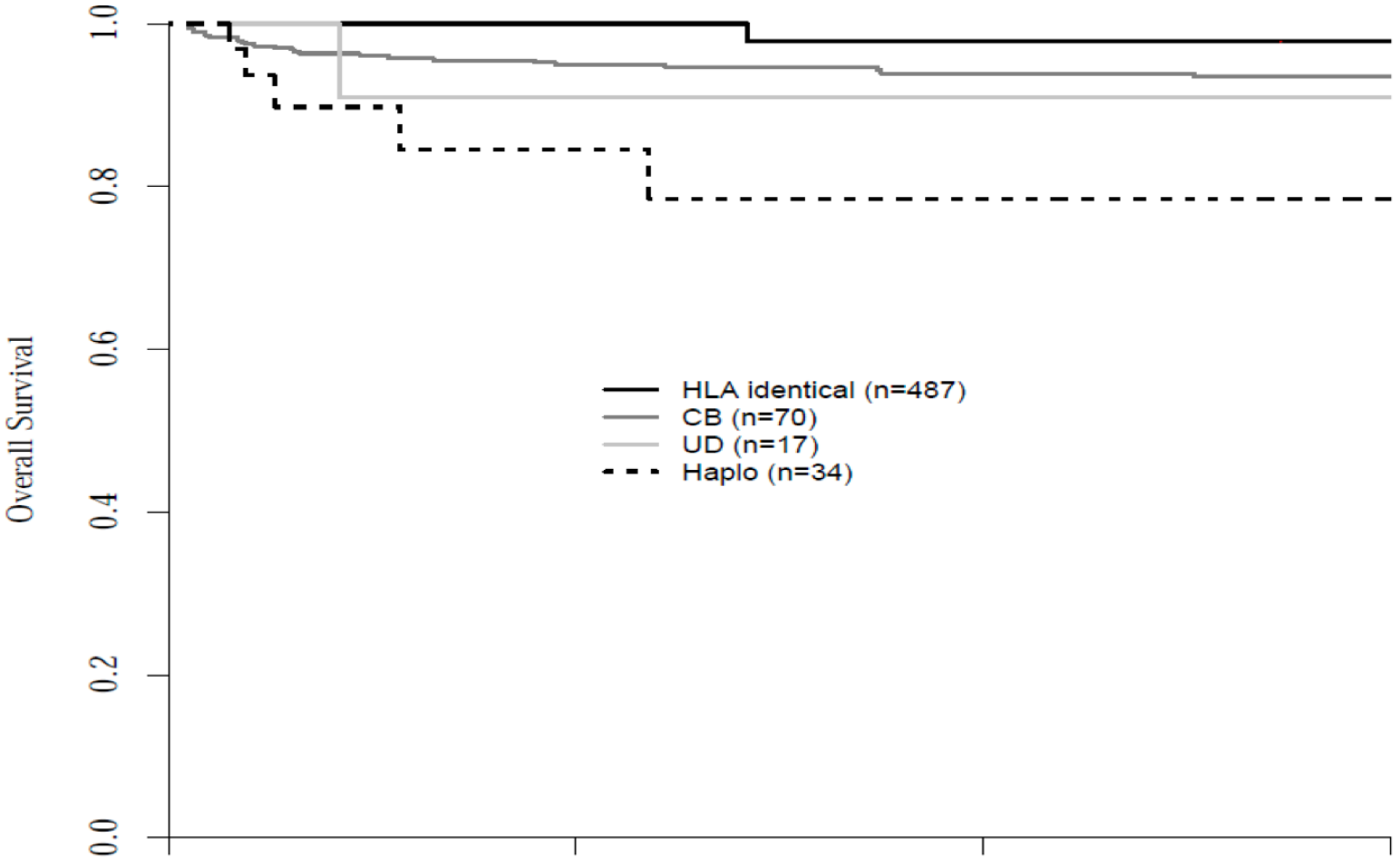
SCT in SCD – Europe - EBMT



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Indications for SCT in SCD

Brazilian Protocol

Organ	Some 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

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Indications for SCT in SCD

Brazilian Protocol

- **N=21 patients**
  - 22 transplants
- **Median Age 14 years (7 to 38 years)**
  - Median Age Ribeirão Preto : 16 years
- **Median follow up** 3 years (30 days – 13 years)
- **Major Indications**
  - Stroke
  - Priapism
  - Vasoclusive crisis
  - Alosensibilization
  - Altered TCD velocity
- **Conditioning**
  - Fludarabine e Bussulfan 12 mg/kg (Ribeirão Preto)
  - Fludarabinaee Cyclophosfamide (2 cases)
  - Bussulfan e Cyclophosphamide

	Center	Age	Indication	Conditioning regimenr	Follow Up
1	HCUFMG	14	Stroke + Moya-Moya	BuCy + ATG	
2	HCUFMG	33	Hodgkin lymphoma	BU+FLU+CY	
3	HC-UFPR	7	Stroke	Bu14Cy+ATG	
4	HC-UFPR	11	Stroke	BU14+Cy+ ATG	
5	HC-UFPR	10	4 strokes	BU12Cy+ATG	
6	HIAE	7	Repeated vasoclusive crisis	BUCY+/ ATG	
7	UNICAMP	24	Repeated vasoclusive crisis	FluBu+ATG +2G TBI	
8	HC-FMRP	16	Acute Chest syndrome	BuCY + ATG	
9	HC-FMRP	38	Priapism	FluCy + ATG	
10	HC-FMRP	13	Stroke + MoyaMoya	FluCy+ATG	
11	HC-FMRP	27	Priapism	FluBu12+ATG	
12	HC-FMRP	15	Stroke	FluBu12+ATG	
13	HC-FMRP	34	Vasoclusive crisis	FluBu12+ATG	
14	HC-FMRP	9	TCD + alosensibilization	FluBu12+ATG	
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2	HCUFMG	33	Hodgkin lymphoma	No	43 days
3	HC-UFPR	7	Stroke	Yes	13 years
4	HC-UFPR	11	Stroke	Yes	1264 days (3,4 years)
5	HC-UFPR	10	4 strokes	No	84 days
6	HIAE	7	Repeated vasoclusive crisis	Yes	818 days (2,2 years)
7	UNICAMP	24	Repeated vasoclusive crisis	Yes	691 days (1,9 years)
8	HC-FMRP	16	Acute Chest syndrome	Yes	3650 days (10 years)
9	HC-FMRP	38	Priapism	Yes	2785 days (7,6 years)
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15	HC-FMRP	20	Repeated vasoclusive crisis	Yes	809 days (2,2 years)
16	HC-FMRP	27	Repeated vasoclusive crisis	Yes	540 days (1,5 years)
17	HC-FMRP	13	Repeated vasoclusive crisis	Yes	378 days (1 year
18	HC-FMRP	7	Stroke	Yes	11 months
19	HC-FMRP	14	Repeated vasoclusive crisis	Yes	90 days
20	HC-FMRP	10	Repeated vasoclusive crisis	Yes	50 days
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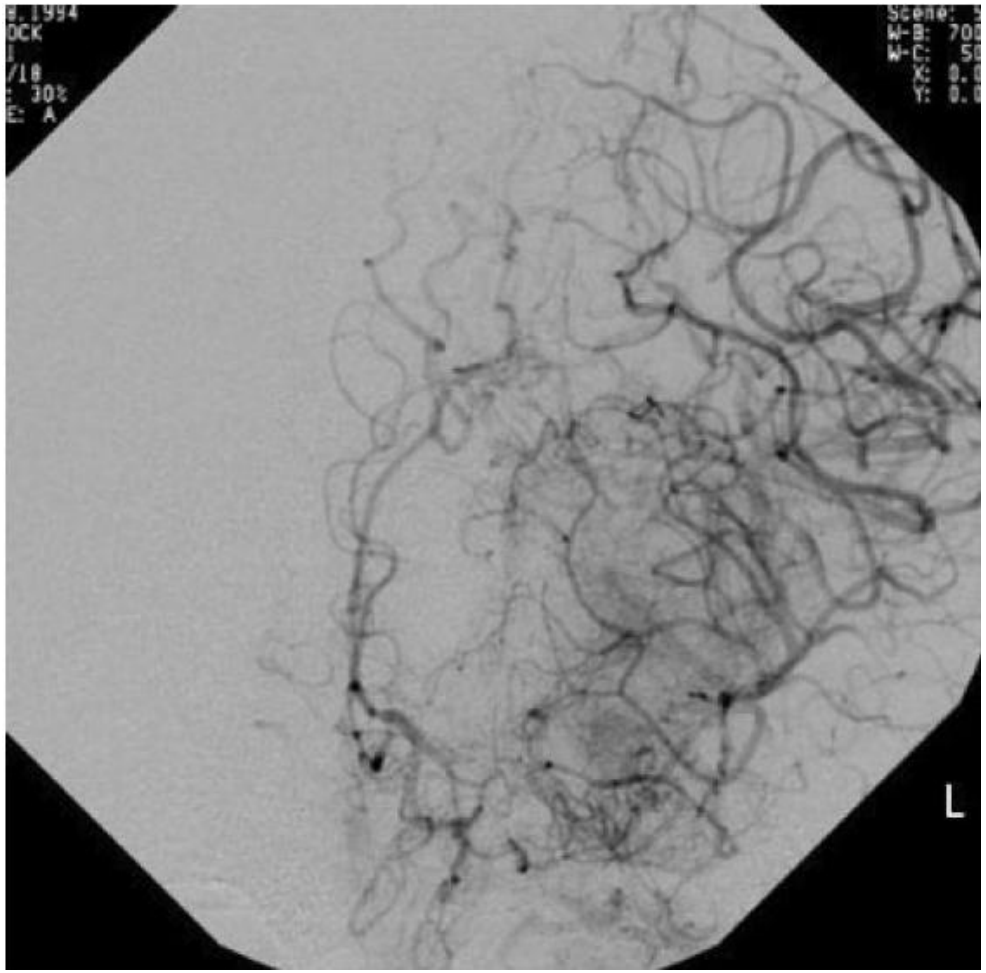
SCT in Ribeirão Preto

- N= 16 patients (+2)
- Age median 18 (6-38)
- 1 death Moya Moya
- Median follow up 2 years
- Acute GVHD
  - 3 cases grade II easily treated
- None chronic GVHD of evaluable patients

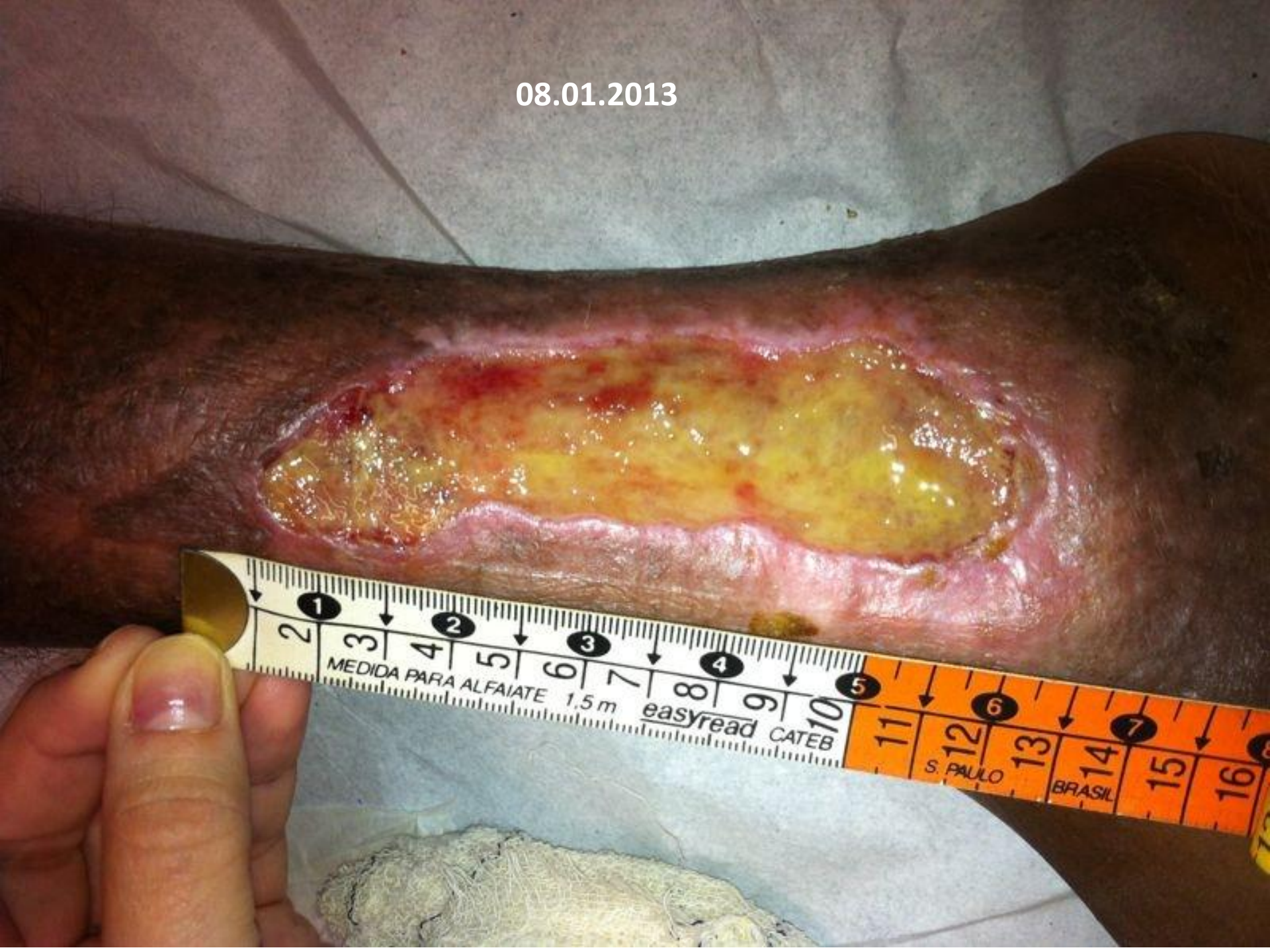
MoyaMoya



Stem Cell Transplant in SCD

Importance of careful preparation for SCT

- Patients with severe comorbidities
- Politransfused patients
- Alosensitized
- Leg Ulcers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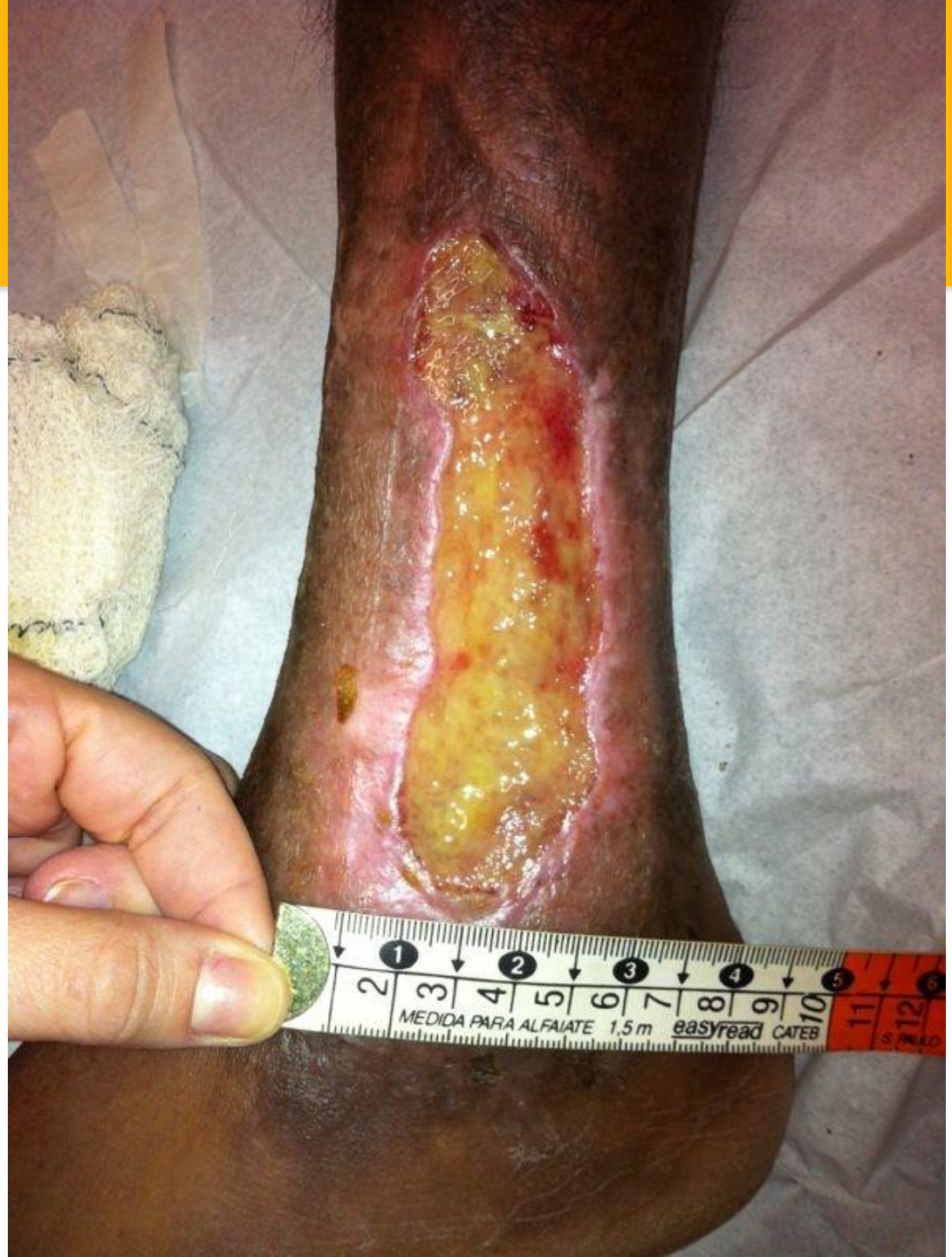


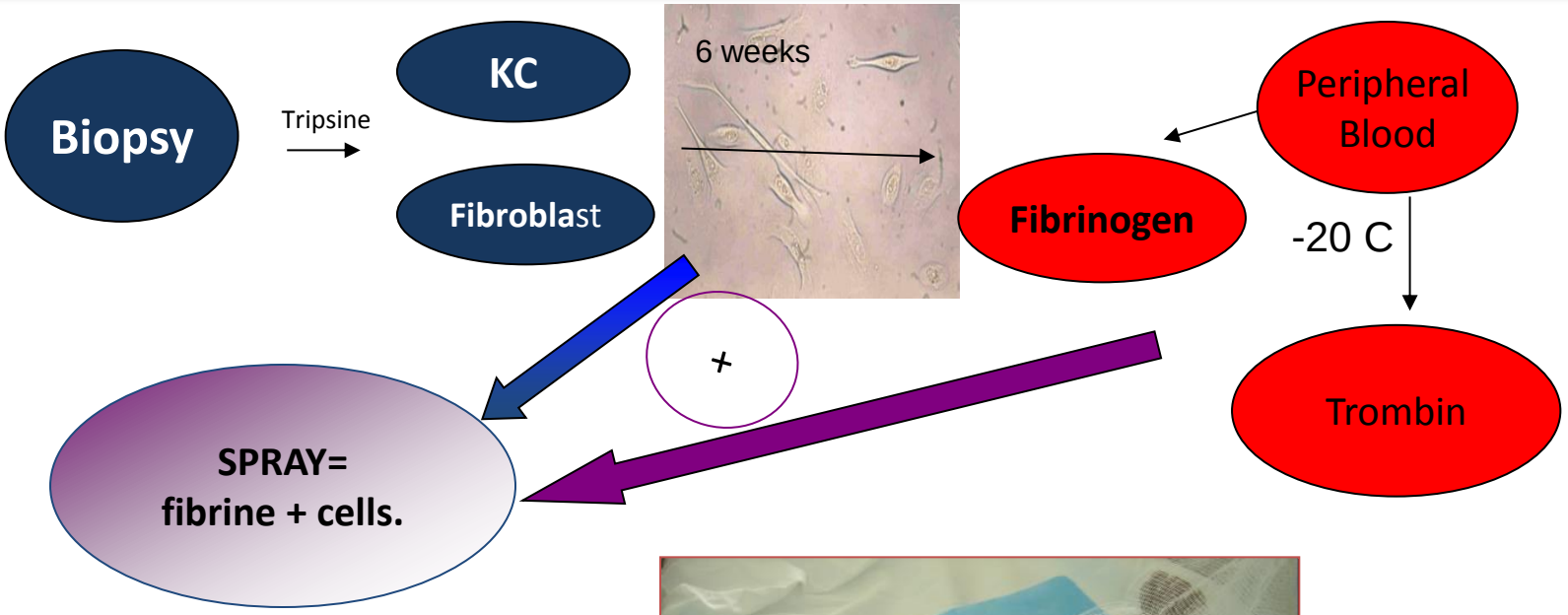
08.01.2013

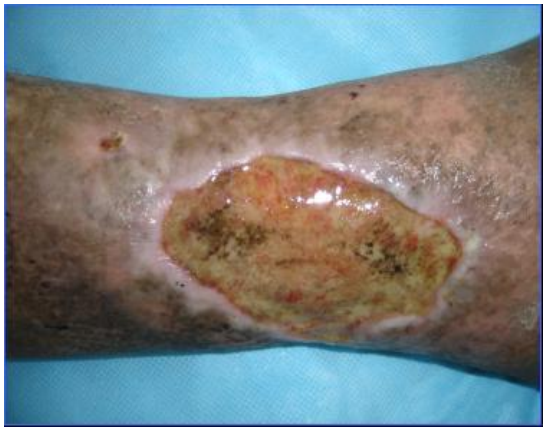
Wound history since 1993

Ulcer with pale and inflammatory bottom

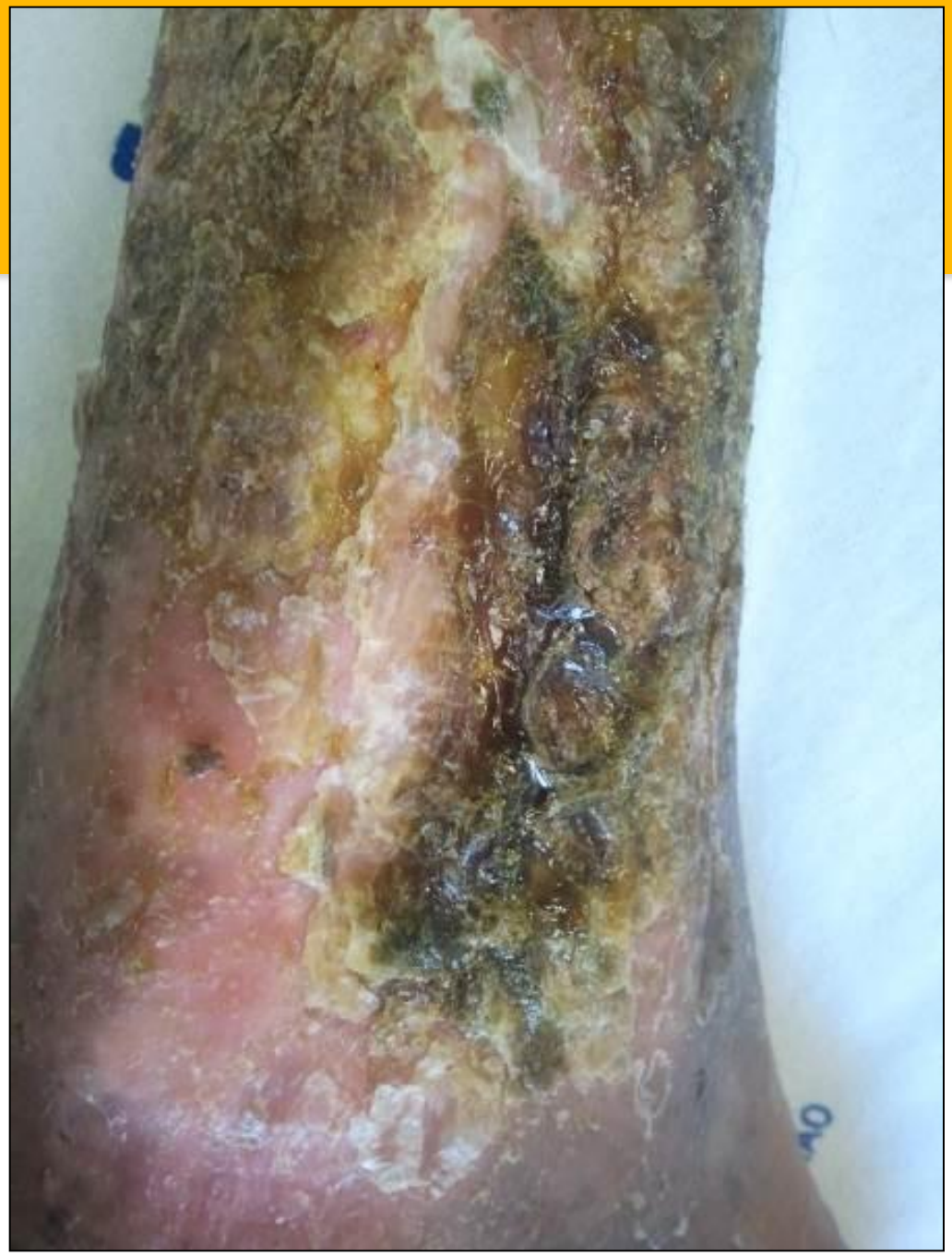
Severe pain

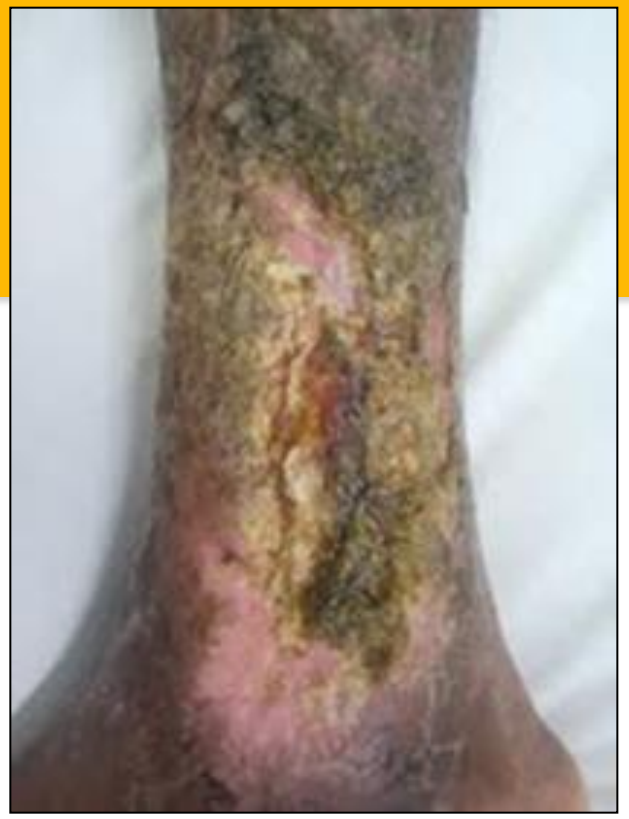
Keratinocyte Culture and fibrinogen glue





Prof. Dr. Marco Andrey Cipriani Frade - Dermatology



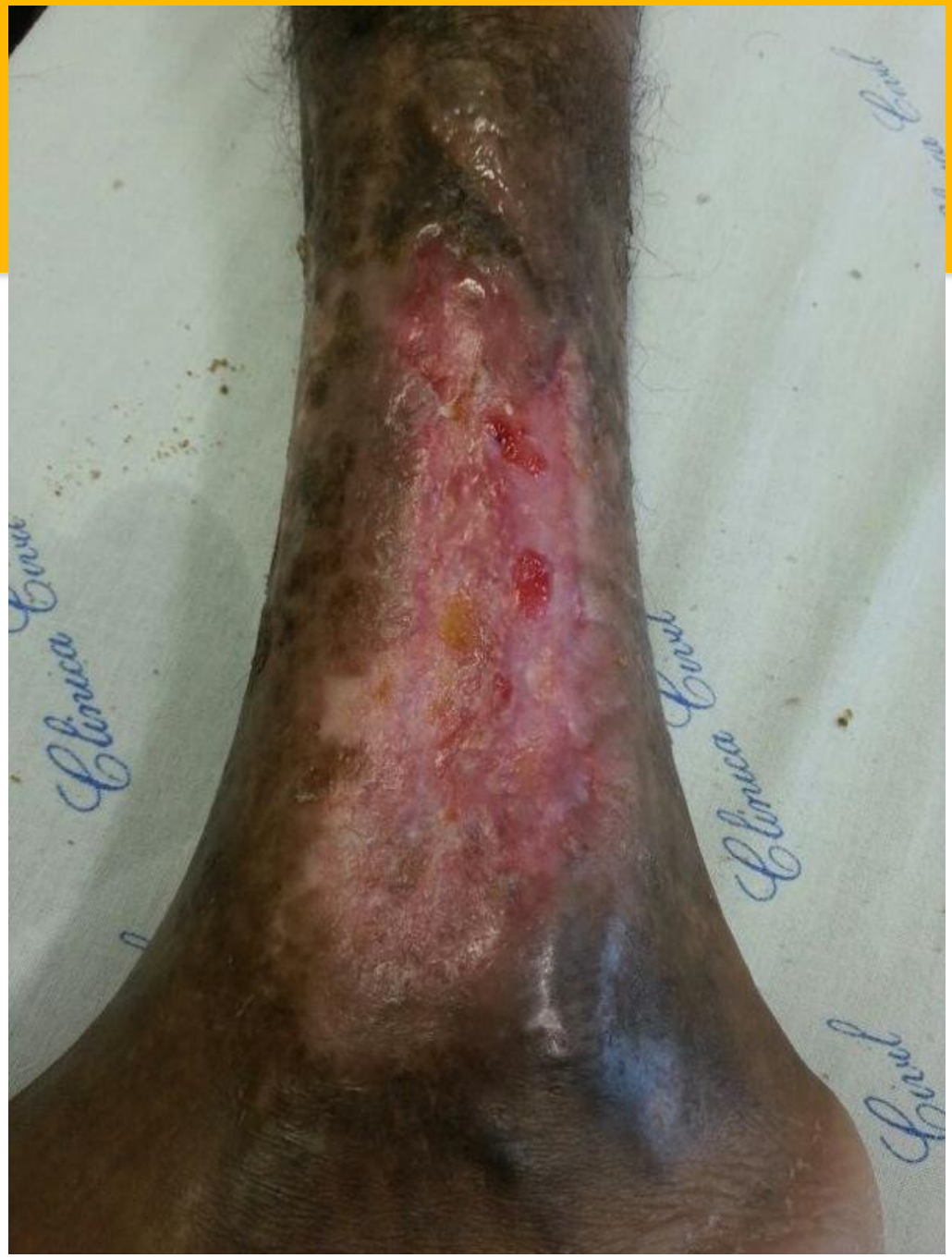


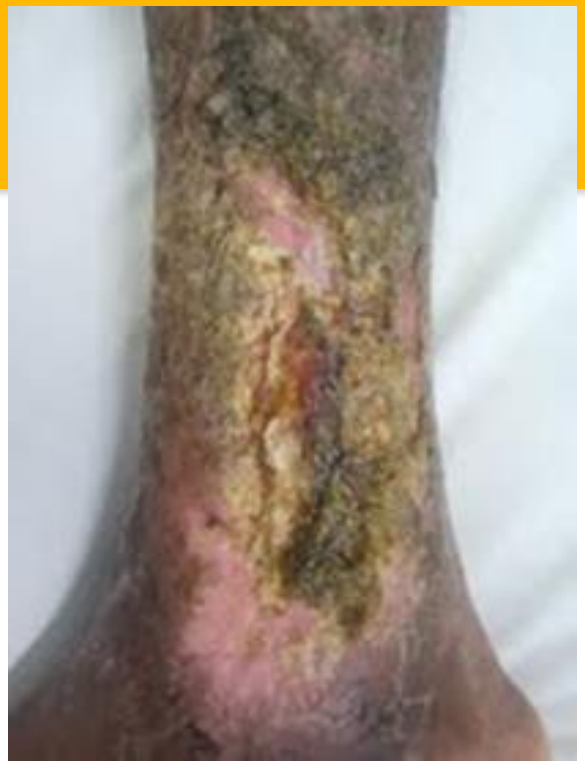
10.04.2013

06.04.2013

Day Zero of BM transplant

24.04.2013

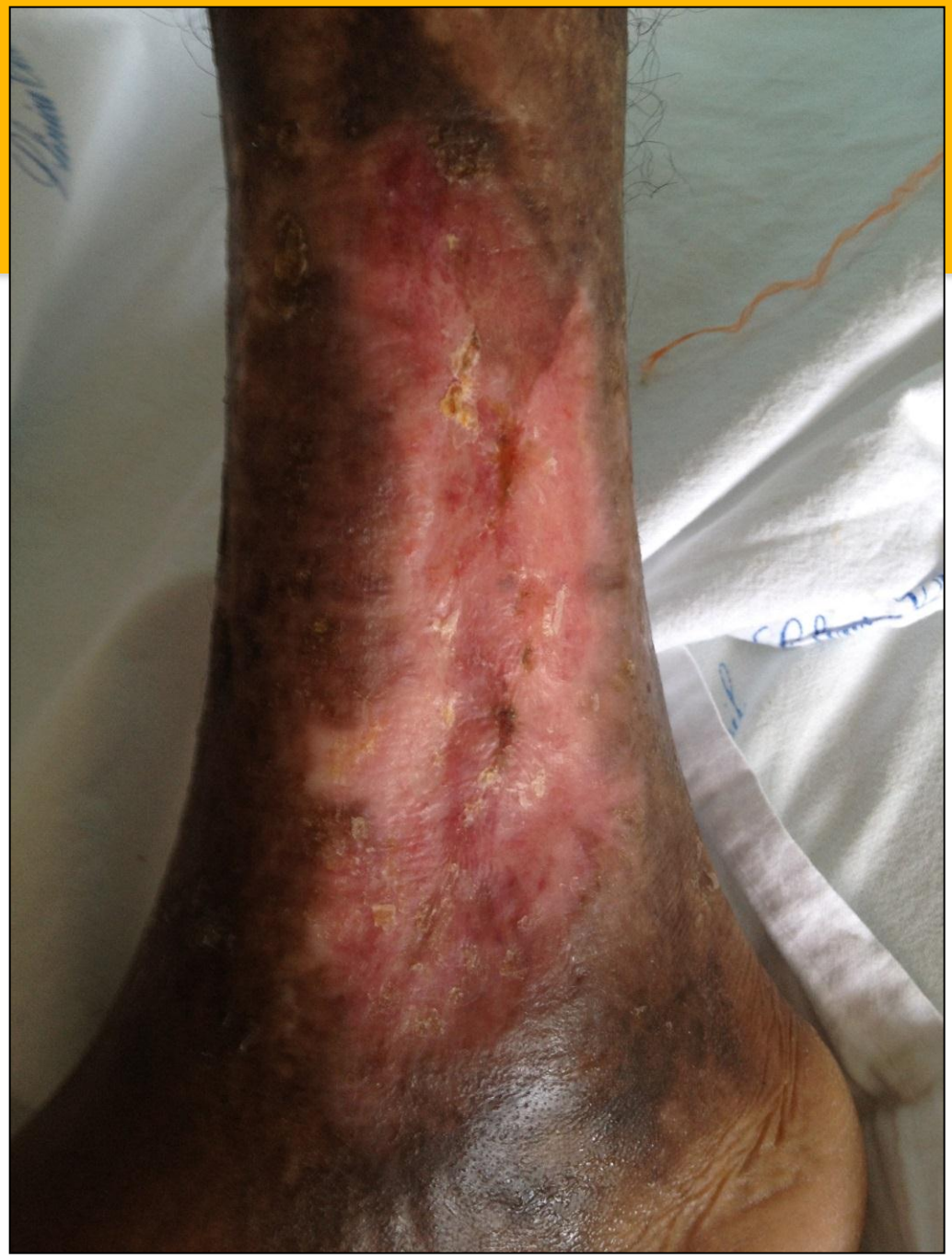




Follow up
50th days after KC transplant

12th day after BM Transplant

Clinical aspect of wounded area after mechanic debridment

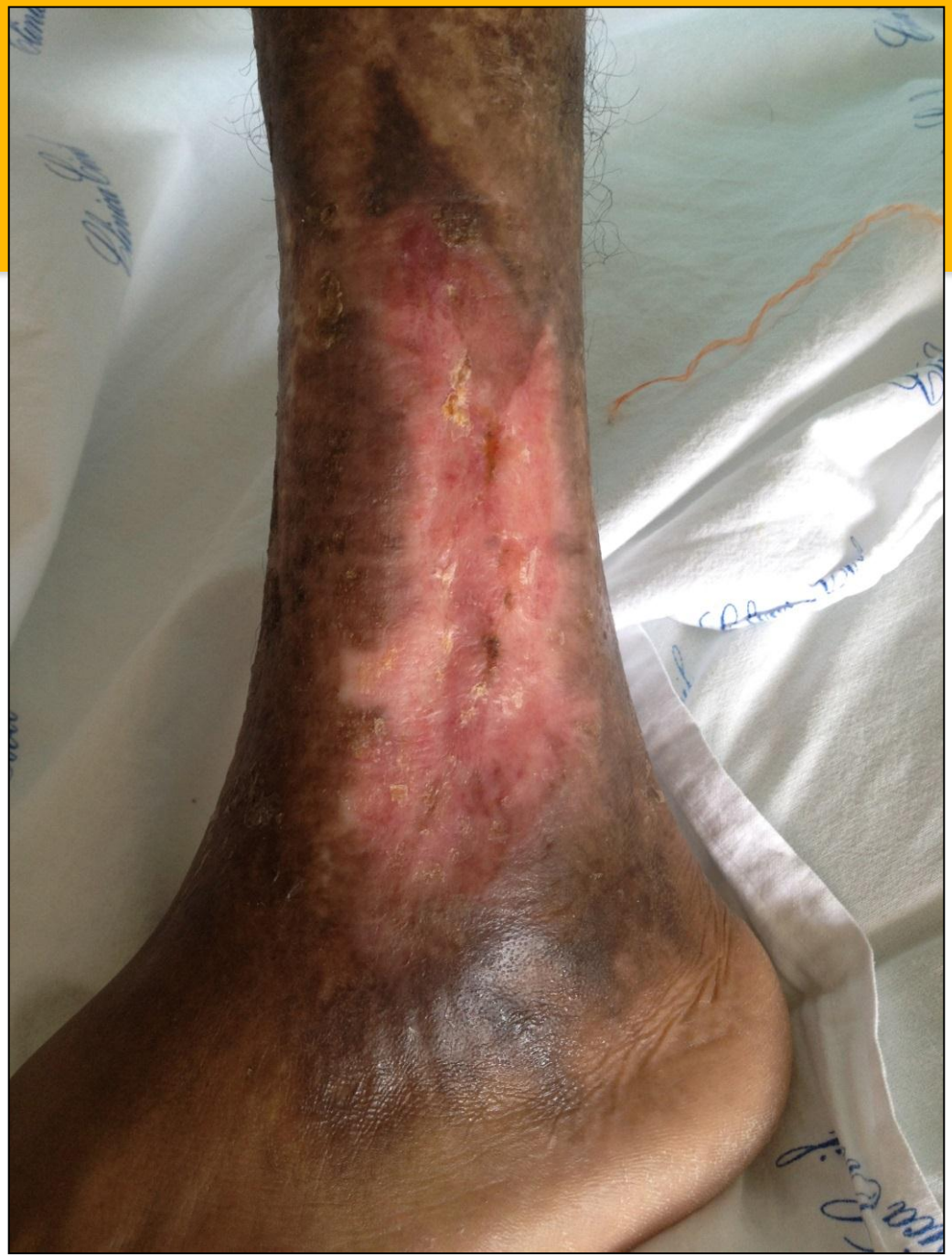


06.05.2013

Follow up

68th day after KC transplant

24th day after BM Transplant



06.05.2013

This ulcer was open since 1993

Sickle Cell Disease

- Health problem in Brazil
- Compromise the quality of life
- Pain is the hallmark of the disease
- SCT can cure SCD
- 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

Acknowledgements

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  - Carlos E. Setanni Grecco
  - Ana Carolina S Paixão
- Dermatologist
  - Marco Andrey Cipriani Frade

Special thank for the patients

- **When I asked them what transplant represented to them:**

- If I die tomorrow, at least I will have known what it is to live without pain for a year of my life.
  - fem, 34 years old, one year after transplant.
  - She is now 3 years after transplant having a normal life.

- Transplant gave me the freedom of not being always concerned about my health everyday, something I had to do for 38 years of my life!
  - Male, 46 years, 8 years after transplant having a normal life