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Transplant In Sickle Cell Anemia Patients

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At the conclusion of this activity, participants should be able to:

- Describe the basics of Sickle Cell Anemia Pathophysiology and identify clinical presentation of Sickle Cell Anemia patients
- Summarize the current role of Hematopoietic Stem Cell Transplantation in Sickle Cell Anemia patients
- Identify Gene Therapy as an emerging trend and a potentially curative strategy for Sickle Cell Anemia

What is Sickle Cell Disease ?

- Sickle Cell Disease is an inherited autosomal recessive disorder that is expressed as Sickle Cell Anemia, Sickle Cell Thalassemia and Sickle-Hb C Disease .

- Sickle Cell Anemia in its most severe form is an homozygous form and is characterized by the presence of an abnormal form of Hemoglobin – *Hemoglobin S (Hb S)*

- Sickle Cell –Thalassemia and Sickle cell-Hb C Disease are heterozygous forms in which the child simultaneously inherits another type of abnormal hemoglobin from one parent

- Sickle Cell trait, in which the child inherits Hb S from one parent and normal hemoglobin (Hb A) from the other, is a heterozygous carrier state that rarely has clinical manifestations

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Sickle Cell Anemia is Inherited

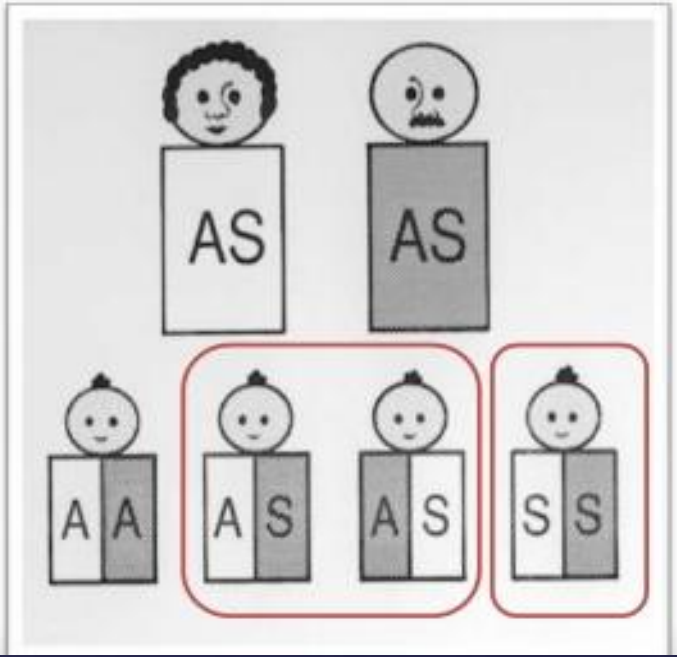
Genetics

- It's autosomal recessive blood disease.
- It's not contagious "You can't catch it".
- You inherit it from your parents.

*The gene defect is a known mutation of a single nucleotide.

*The person that receives the defective gene from both his parents will develop Sickle-cell disease.

*The person who receives only one defective gene from either one of his parents will develop Sickle-cell trait.



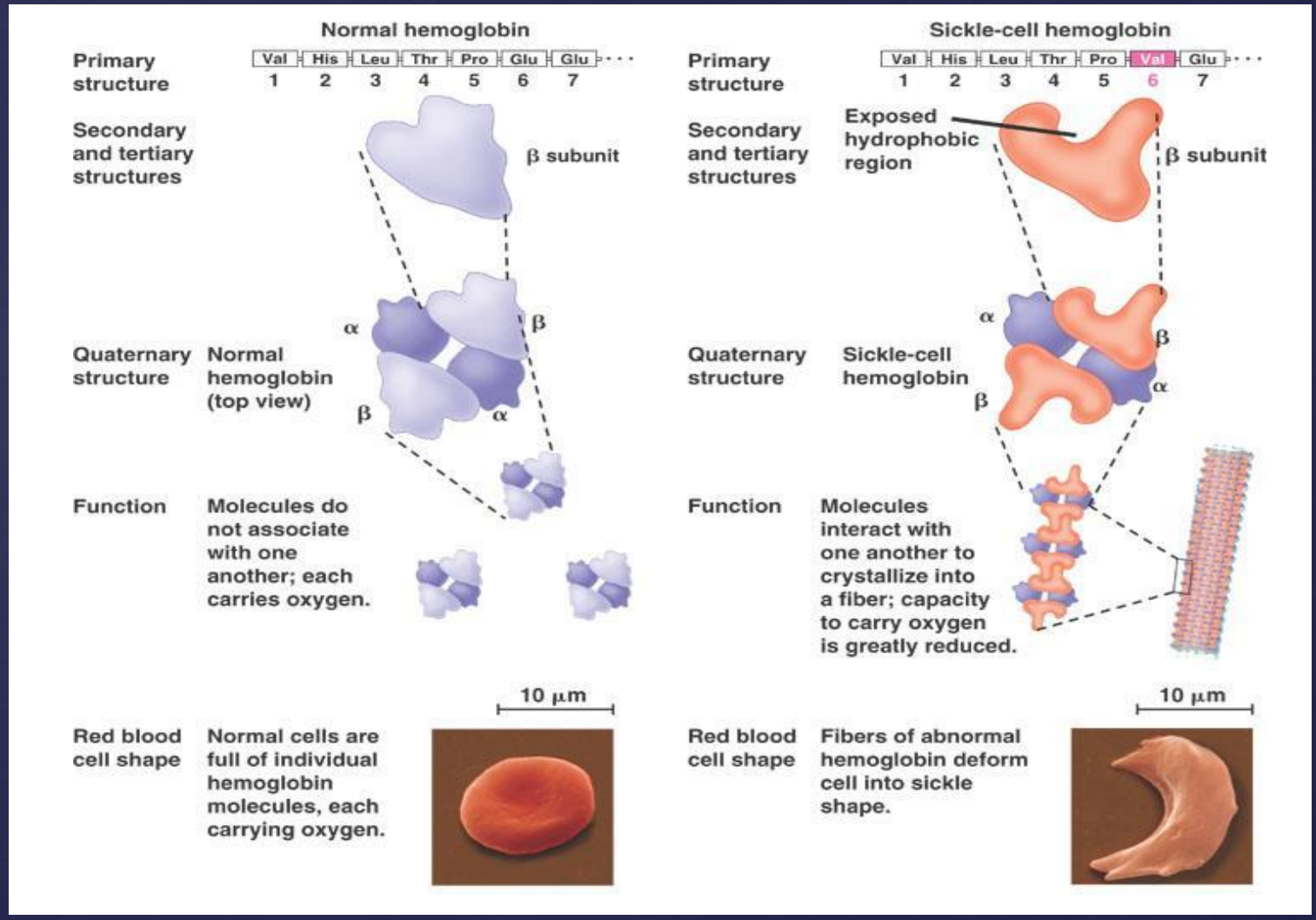
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Hemoglobin S (Hb S)

- Hb S is formed by a genetic mutation in which one amino acid (Valine) replaces another (Glutamic Acid)
- Hb S, the so-called sickle Hemoglobin, reacts to deoxygenation and dehydration by solidifying and stretching the erythrocytes into an elongated sickle shape.
- Red blood cells typically live 90 to 120 days but Sickle Cells only survive 10 to 20 Days

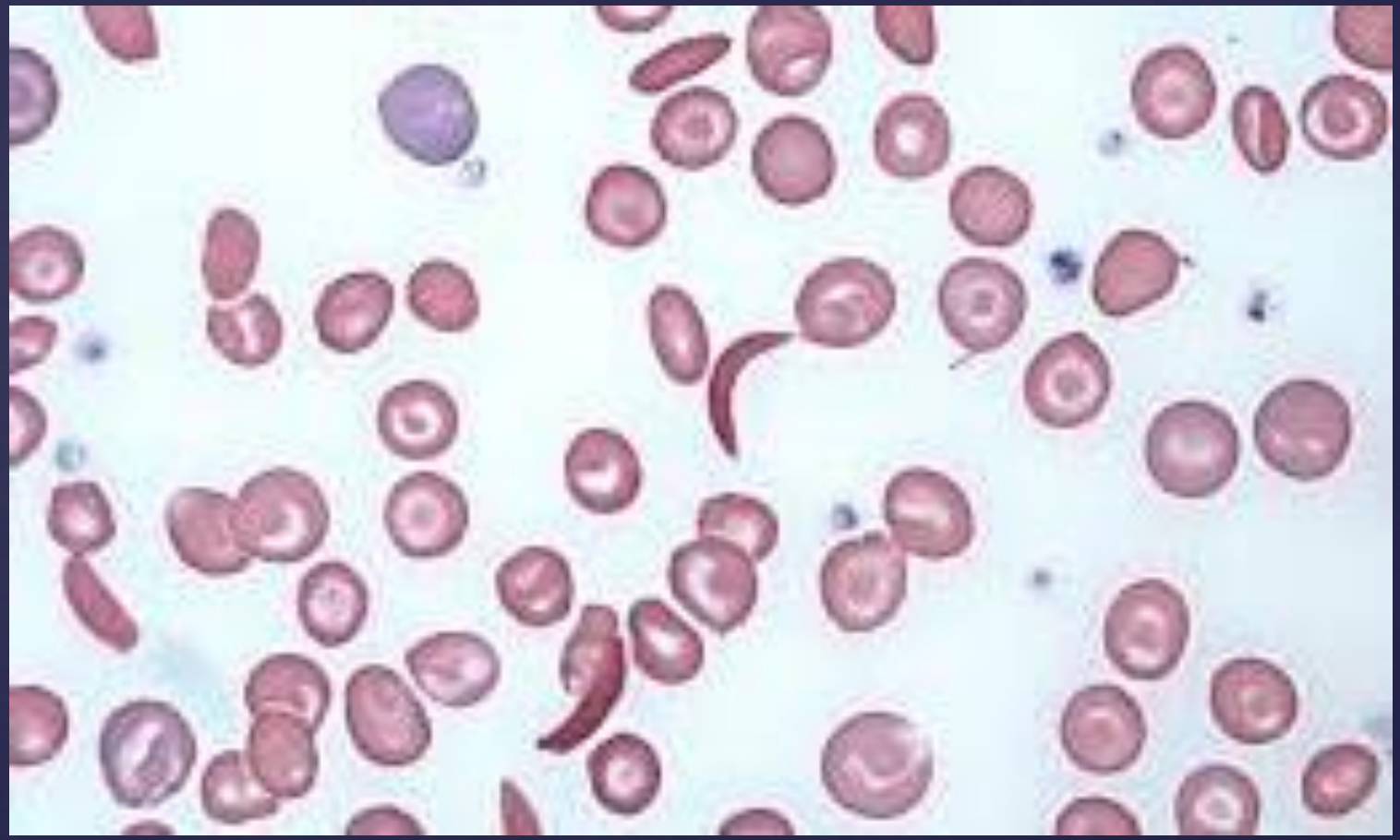
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Normal Hemoglobin vs Sickle-Cell Hemoglobin



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Are you able to identify the diseased Erythrocytes ?



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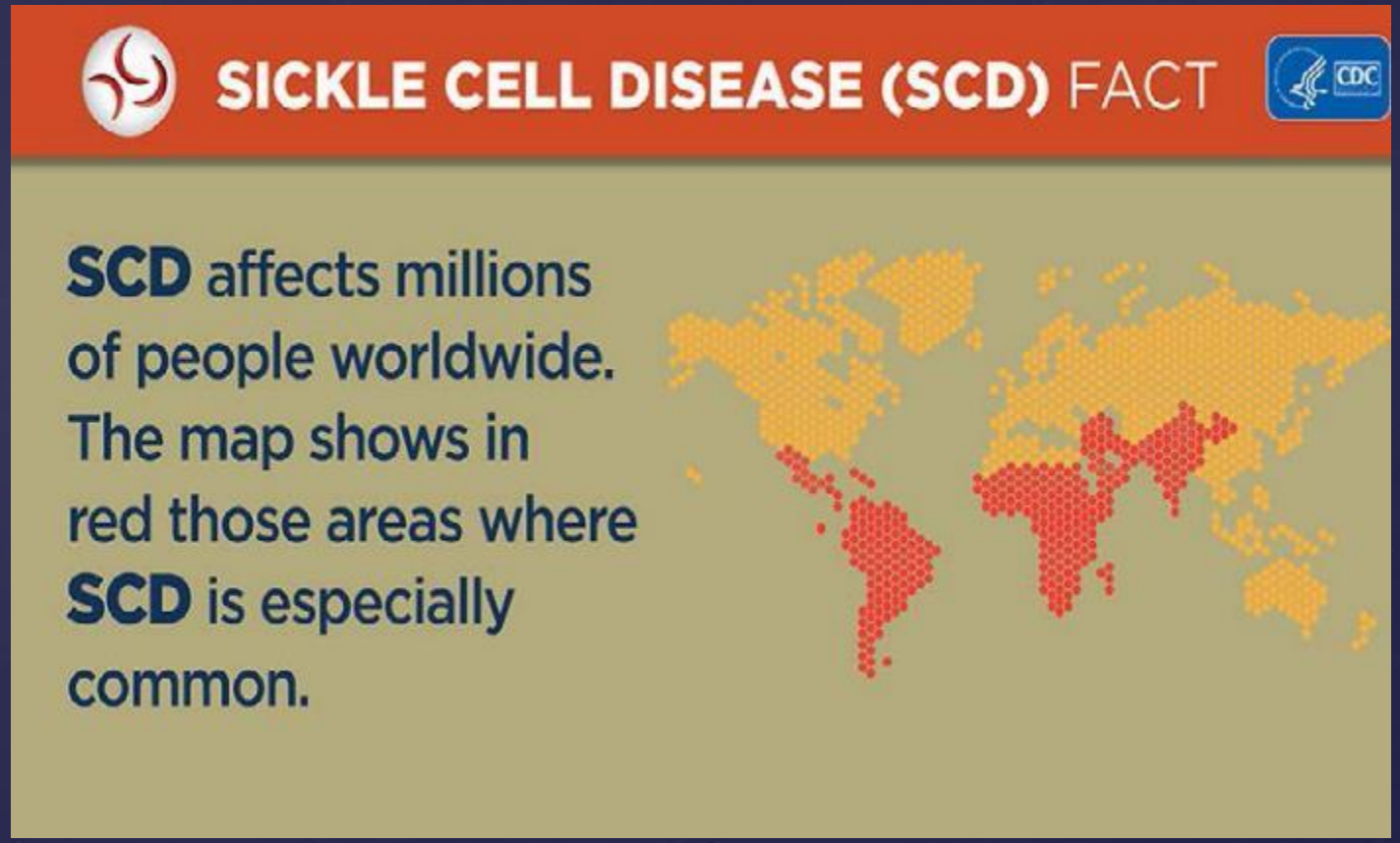
Epidemiology of Sickle Cell Disease

Sickle Cell Disease (SCD) affects millions of people throughout the world and is particularly common among those ancestors who come from sub-Saharan Africa, Spanish-speaking Western Hemisphere regions (South America, the Caribbean, and Central America); Saudi Arabia, India, and Mediterranean countries such as Turkey, Greece, and Italy.

- SCD affects approximately 100,000 Americans.
- SCD occurs among 1 out of every 365 Black or African-American births.
- SCD occurs among about 1 out of every 16,300 Hispanic-American births.
- 1 in 13 Black or African-American babies is born with Sickle Cell Trait (SCT).

CDC
CENTERS FOR DISEASE CONTROL AND PREVENTION

SCD Worldwide Distribution



Some Sickle Cell Disease TRIVIA

- Sickle Cell Disease occurs more often among people from parts of the world where malaria is common. It is believed the sickle cell trait has a protective effect against malaria.

- In 2004, there were about 113,000 hospitalizations for Sickle Cell related illnesses in the United States , 75% occurring in adults. The estimated annual cost of hospitalization that year was $488 million.

- Life Expectancy for male and female patients with SCD has been determined to be 42 and 48 years

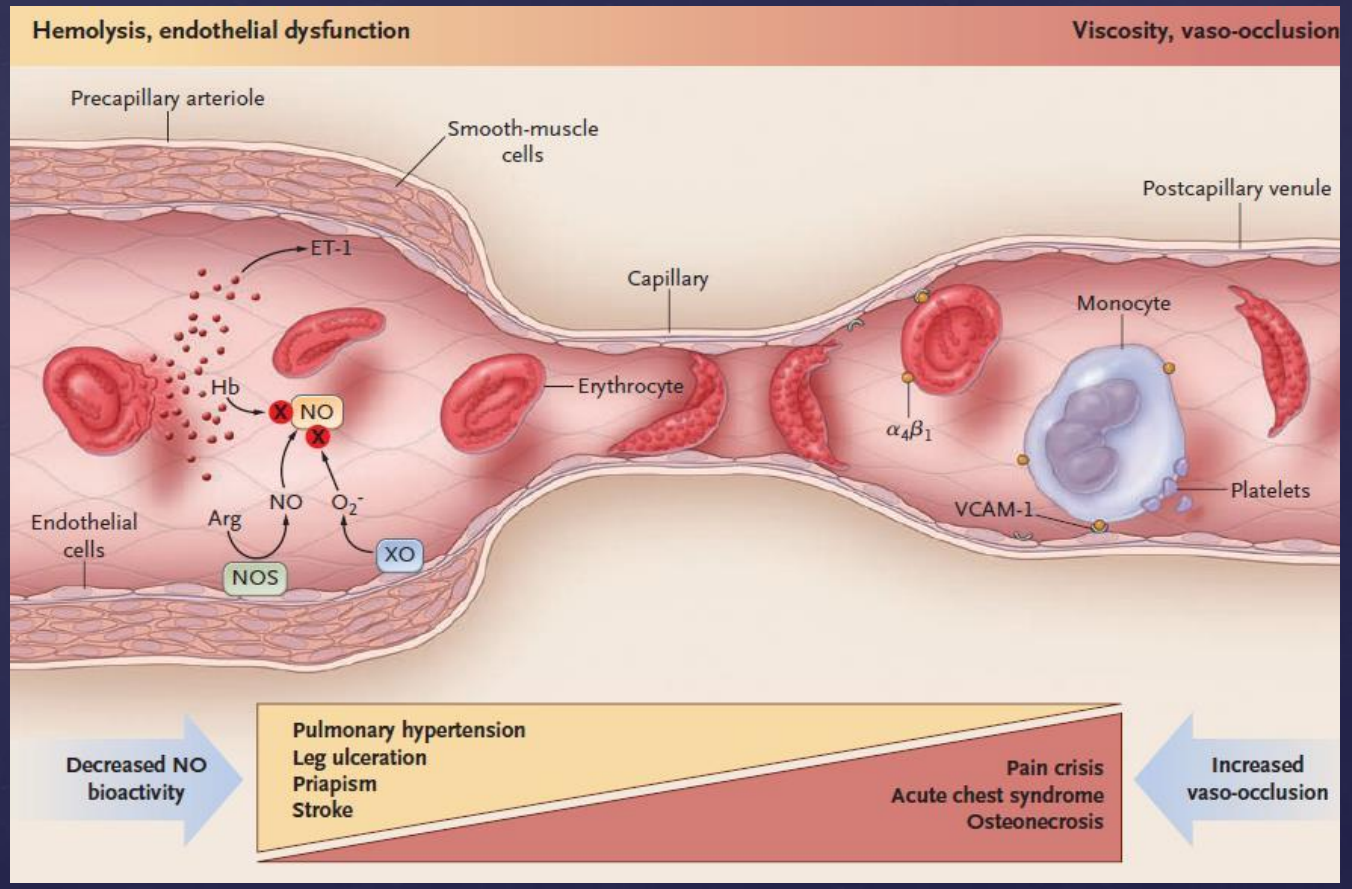
Sickling Mechanism

- Deoxygenation is probably the most important variable in determining the occurrence of sickling.
- Hb S that is not bound with oxygen forms aggregate of semisolid gel that become stacked within the erythrocyte, stretching it into an elongated crescent.
- Sickled erythrocytes are stiff and cannot change shape as easily as normal cells when they pass through the microcirculation.
- As a result, sickled erythrocytes tend to plug the blood vessels , causing vascular occlusion, pain and organ infarction.

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Clinical Manifestations

Major features are related to hemolytic anemia and vaso-occlusion, which can lead to acute and chronic pain and tissue ischemia or infarction.



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Acute Complications of SCD

- Splenic infarction leads to functional hyposplenism early in life, which in turn increases the risk of infection. SCD patients are on long term PCN-VK PPX.
- Severe Anemia
- Vaso-Occlusive Phenomena: Vaso-occlusive crisis begins with sickling in the microcirculation. As blood flow is obstructed by tangled masses of rigid sickled cells, vasospasm occurs and blood flow through the vessels is compromised. Thrombosis and infarction of tissue follow.





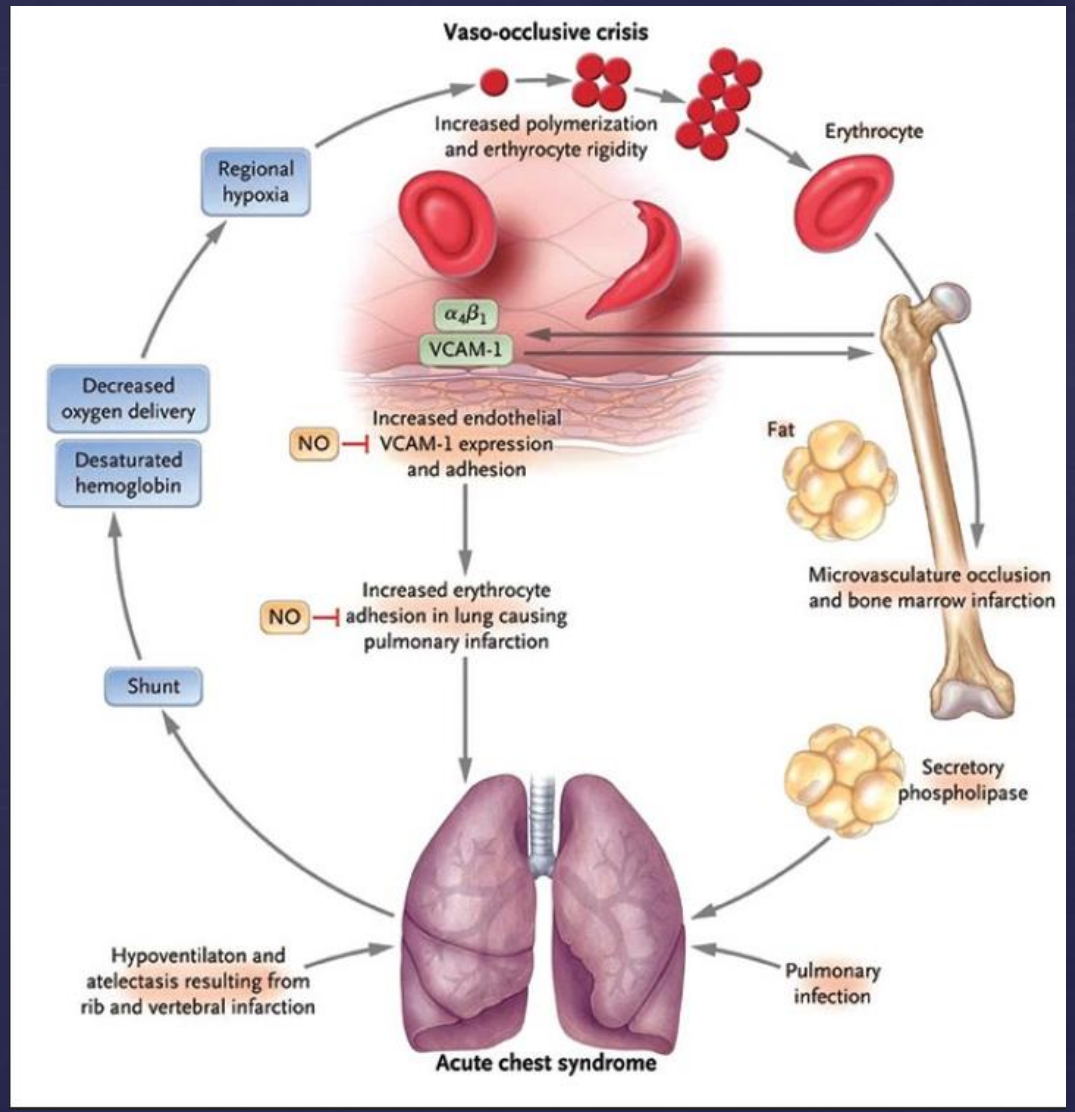
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Vaso-Occlusive Crisis leading to Acute Chest Syndrome

Presence of a new pulmonary infiltrate (involving at least one complete lung segment) with chest pain, a temperature of more than 38.5 C., increased respiratory rate, wheezing, or cough in an individual Sickle cell disease. An injured, under ventilated, and inflamed lung become “spleenlike” as sickle red cells attach to its, fails to be reoxygenated, and eventually undergoes more endothelium inflammation and lung infarction. Prognosis is poor, and infection is a leading cause of morbidity.

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The Vaso-Occlusive Crisis



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Chronic Complications of SCD

- Pain
- Anemia
- Neurologic deficits or seizure disorder
- Renal impairment & hypertension
- Osteoporosis & complications of bone infarction
- Pulmonary conditions
- Cardiomyopathy
- Hepatotoxicity
- Delayed puberty & reduced growth
- Chronic leg ulcers
- Proliferative retinopathy

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Current Therapies

- Supportive Care
  - Penicillin prophylaxis
  - Immunizations
  - Narcotics
- Prevention of complications
- Transfusion therapy
- Hydroxyurea

Allogeneic Hematopoietic Stem Cell Transplantation (AlloHSCT) remains the only established Curative Therapy.

Historical Review of HSCT

- In 1939 the first human "bone marrow" transfusion was given to a patient with aplastic anemia.
- The first Allogeneic HSCT was pioneered by E. Donnall Thomas and reported in the NEJM in 1957.
- In the late 1960s, methods to identify and type Human Leukocyte Antigens (HLA) in humans were developed and allowed for donor and recipient HLA matching.
- The first HLA-Matched Unrelated Donor (MUD) took place in 1979.
- The first HSCT for Sickle Cell Disease was in 1984 .

Basics of HSCT

Autologous HSCT

A procedure in which stem cells are removed, stored, and later infused to the patient.

Allogeneic HSCT

A procedure where a stem cell donor can be a matched related sibling, a haploidentical family relative or a HLA matched unrelated donor.

Human Leukocyte Antigen (HLA) typing is used to match patients and donors for bone marrow or cord blood transplants. HLA are proteins –or markers - found on most cells . The immune system uses theses markers to recognize which cells belong in your body and which do not.

Transplantation Indications

Autologous HSCT

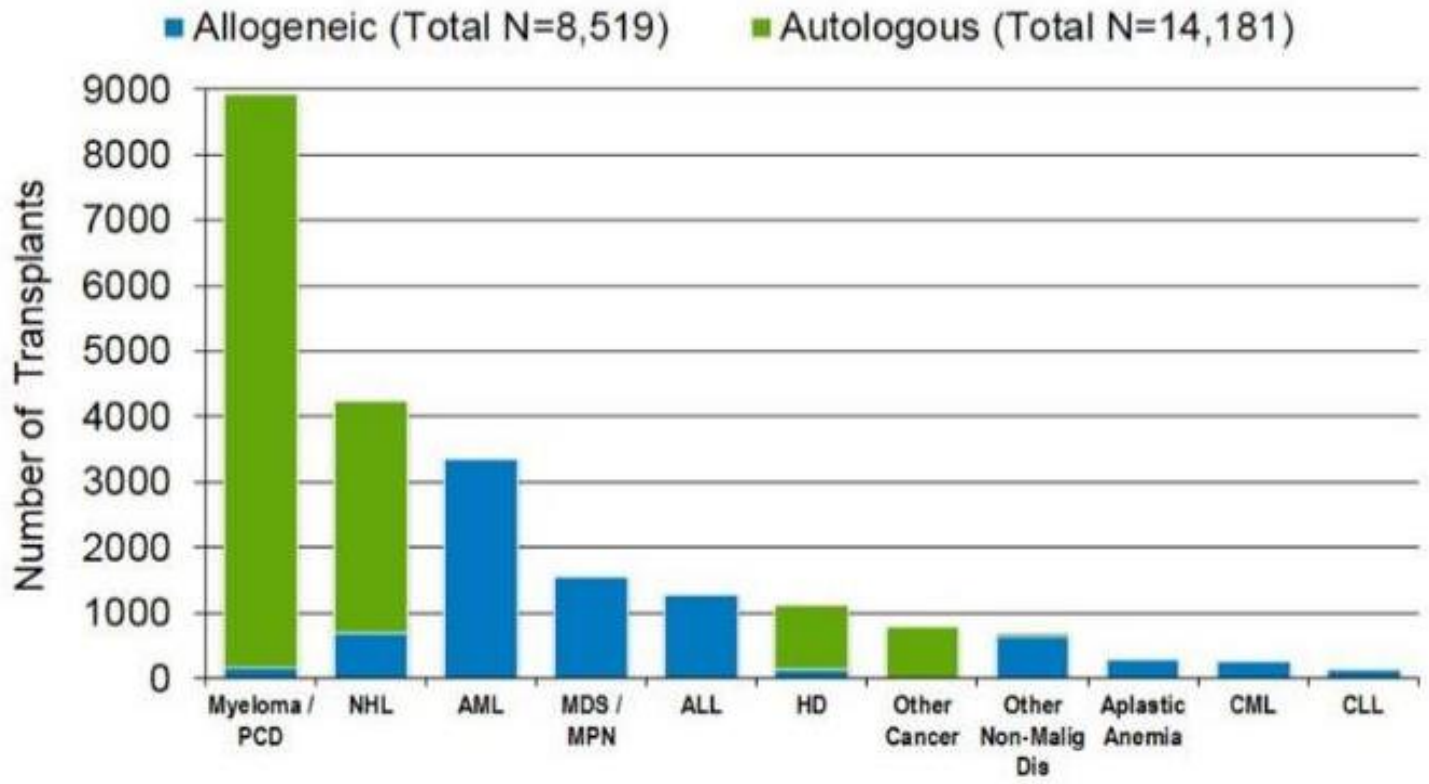
Multiple Myeloma
Non-Hodgin Lymphoma
Hodgkin Disease
Neuroblastoma
Ovarian Cancer
Autoimmune Disease
Amyloidosis

Allogeneic HSCT

Leukemia
Myelodysplastic Syndromes
Myeloproliferative Neoplasms
Lymphoma
Multiple Myeloma
Aplastic Anemia
Sickle Cell Anemia

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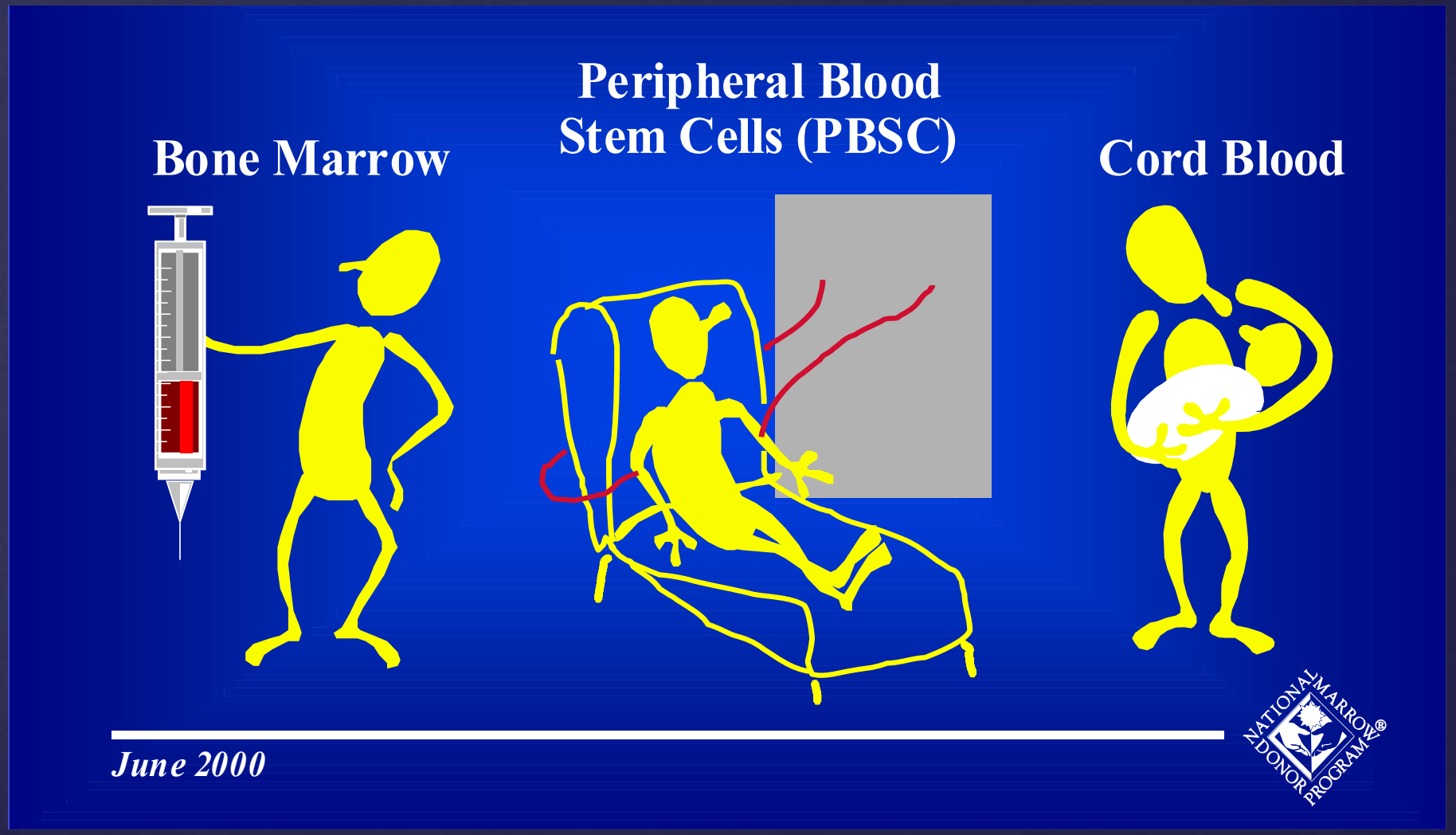
Indications for Hematopoietic Cell Transplant in the US, 2016



CIBMTR
CENTER FOR INTERNATIONAL BLOOD & MARROW TRANSPLANT RESEARCH

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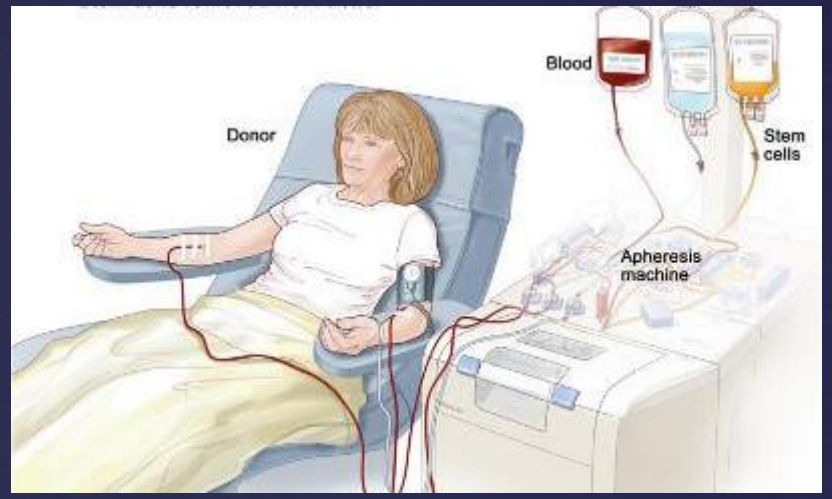
Sources of Stem Cells



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AlloHSCT Process

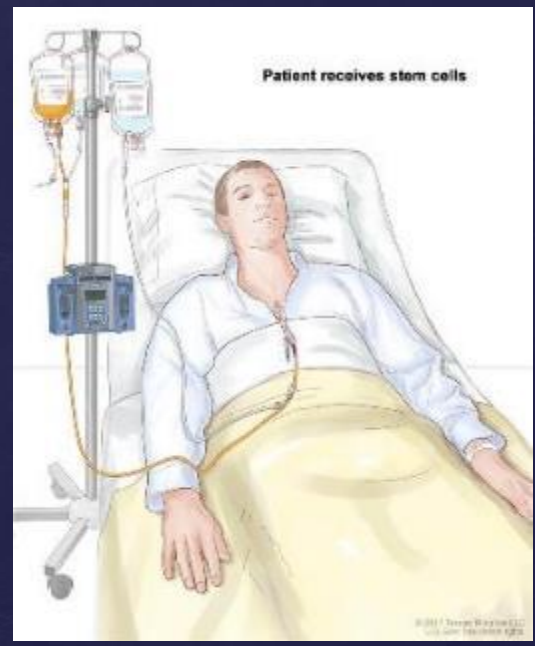
Stem Cell Collection →



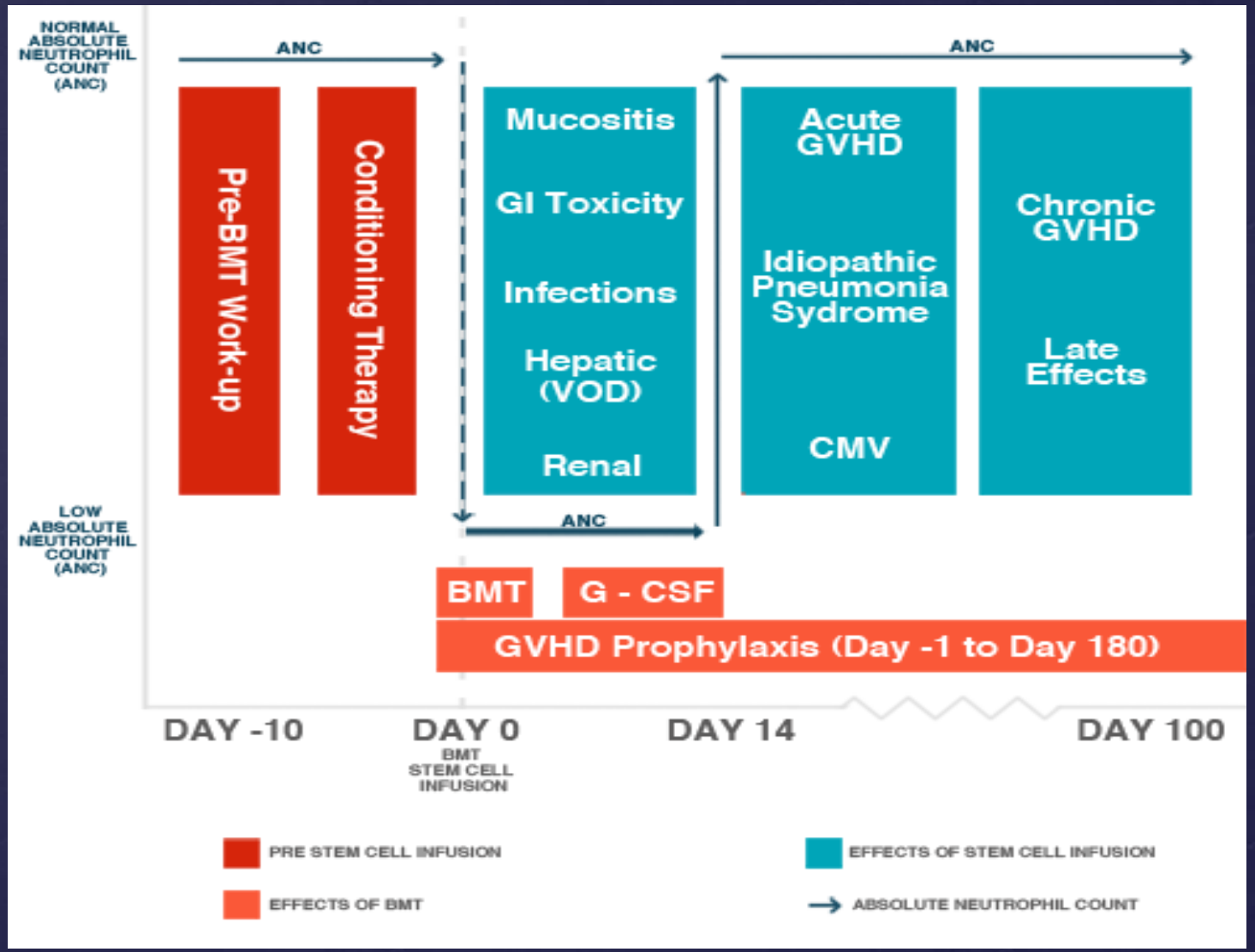


← Conditioning Chemotherapy

Stem Cell Infusion →

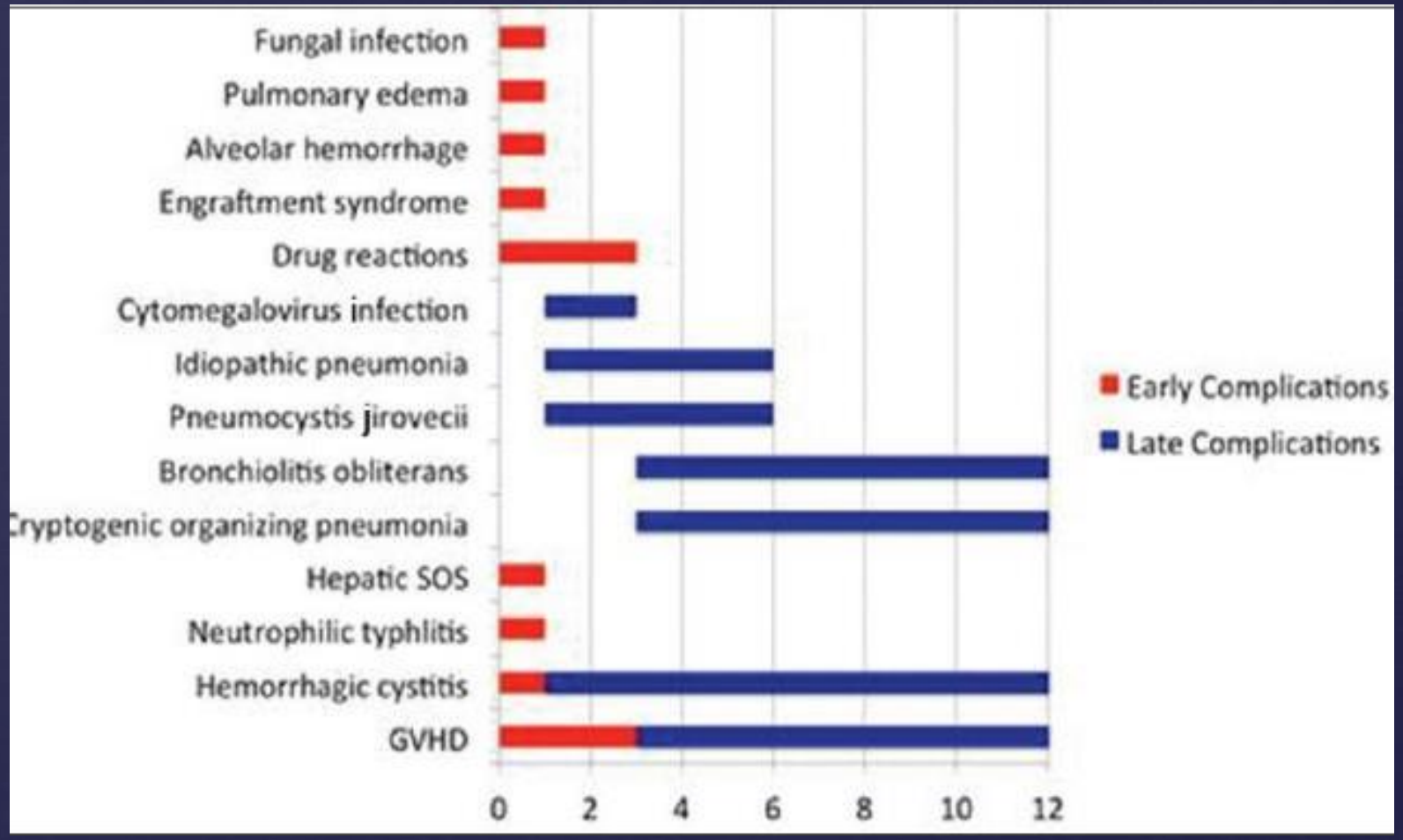


Toxicities/Complications the First 100 Days



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TOXICITIES/COMPLICATIONS THE FIRST YEAR



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What is the Role of Conditioning Regimens During the AlloHSCT ?

- Destruction of tumors cells resistant to conventional doses of chemotherapy without causing fatal non-hematologic organ toxicity.
- In SCD, the main goal of conditioning is to prevent rejection.
- Conditioning regimens must be sufficiently immunosuppressive to prevent the recipient from mounting an immune response capable of rejecting the graft.

Conditioning Regimen in AlloHSCT for SCD

Myeloablative Conditioning (MAC)

High dose chemotherapy kills cells in the bone marrow causing profound myelosuppression. MAC has produced the best HSCT outcomes from MRD in SCD. (Guilcher et. al., 2018)

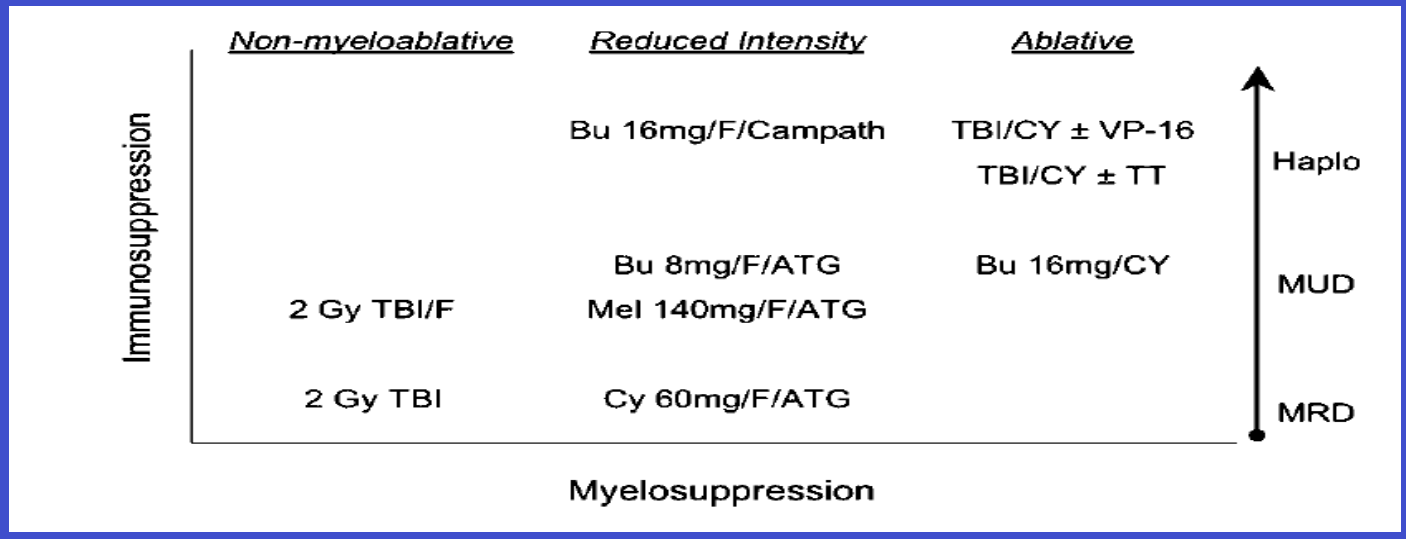
Reduced Intensity Conditioning (RIC)

Reduced dose of chemotherapy decreases the risk of Treatment related Toxicities.

Non Myeloablative Conditioning (NMAC)

Designed to allow Adults with severe SCD to undergo HSCT while avoiding toxicities of a myeloablative conditioning but graft rejection and Graft versus Host Disease (GVHD) remain significant. (Hsieh et. al., 2014)

Intensity of Conditioning Regimen



Abbreviations: TBI – Total Body Irradiation; F – Fludarabine; Bu – Busulfan; Mel – Melphalan; Cy – Cyclophosphamide; ATG – Anti-Thymocyte Globulin; VP-16 – Etoposide; TT- Thiotepa; Haplo – Haploidentical; MUD – Matched unrelated donor; MRD – matched related donor

Satwani et al, PBC 2008

Ablative regimens are more myelosuppressive. Haplo transplants require greater immunosuppression than MUD or MRD.

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Transplant Outcomes Based on Conditioning Choices

- Myeloablative transplant outcomes are best in the young (<16 years), especially with MRD transplants, likely due to the absence of comorbid conditions and organ decompensation. (Bernaudin *et al*. 2007)
- This age bar could be potentially be pushed higher into the second decade with a RIC approach that could be better tolerated in the presence of organ toxicity, however with an increased risk of graft failure.
- Early trials with NMAC to offset toxicities were met with high rates of graft failure and recurrence of disease symptoms, though they were tolerated well.

Patient Selection for HSCT in SCD

- Patient selection is based on the inclusion criteria from some of the early studies of SCD transplantation.
- Previous history of stroke and/or multiple episodes of ACS or VOC
- Patient with SCD with a MRD should be offered an AlloHSCT.
- AlloHSCT should be discussed early in the course of the relationship between hematologist and patient/family.

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Toward Expanding Donor Sources

- For over 2 decades, transplantation was offered only to patients with severe SCD and only if a matched sibling donor was available.
- In the absence of a MSD, additional donor options include a matched unrelated donor (MUD) , an umbilical cord blood (UCB) product or a hapla-identical donor from the family.
- All options are associated with complications innate to the graft source and transplant approach used and include Graft Rejection, GVHD, and delayed immune reconstitution.

Current Challenges of HSCT for SCD

Complications associated with the procedure beg for continued investigation.

Priority targets for improvement include HSCT-related organ toxicities, Graft *versus* host disease (GVHD), graft rejection (GR) rates and donor availability.

Fewer than 18% of patients have access to a MSD.

Bottom Line & Clinical Conundrums of AlloHSCT in SCD

MAC, RIC and NMAC produce normal donor erythropoiesis and is sufficient to provide a clinical cure. (Guilcher et. al. , 2018). Mixed Donor chimerism is acceptable.

BUT

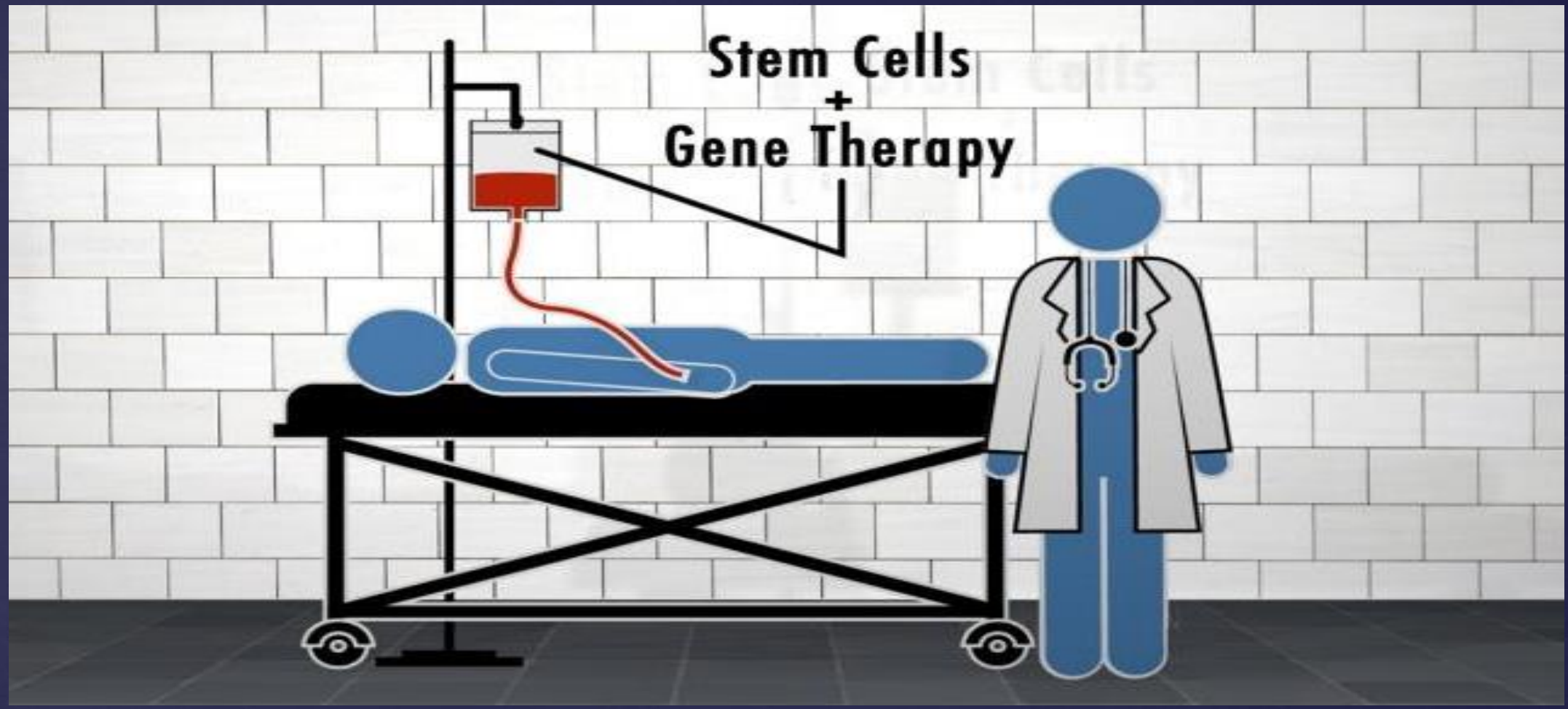
Debate has focused on the balance between disease severity and the risks of the procedure itself.

YET

There is no debate that the disease is invariably progressive causing irreversible damages despite the absence of overt symptoms and resulting in markedly reduced life expectancy. SCD is a progressive disease.

Can we do better ?





Oui, c'est possible !

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Gene Therapy in SCD

The NEW ENGLAND JOURNAL of MEDICINE

BRIEF REPORT

HGB-205

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.

HGB-205 “Bluebird Bio “ Case Report

- A child received a diagnosis of SCD at birth and was followed at Necker’s Hospital in Paris, France.
- Previous history of VOC’s, 2 episodes of ACS, and bilateral hip osteonecrosis .
- H/o cholecystectomy and splenectomy
- Initial screening showed a cerebral hypodensity without characteristics of cerebral vasculopathy was detected.

HGB-205 Gene Transfer Process

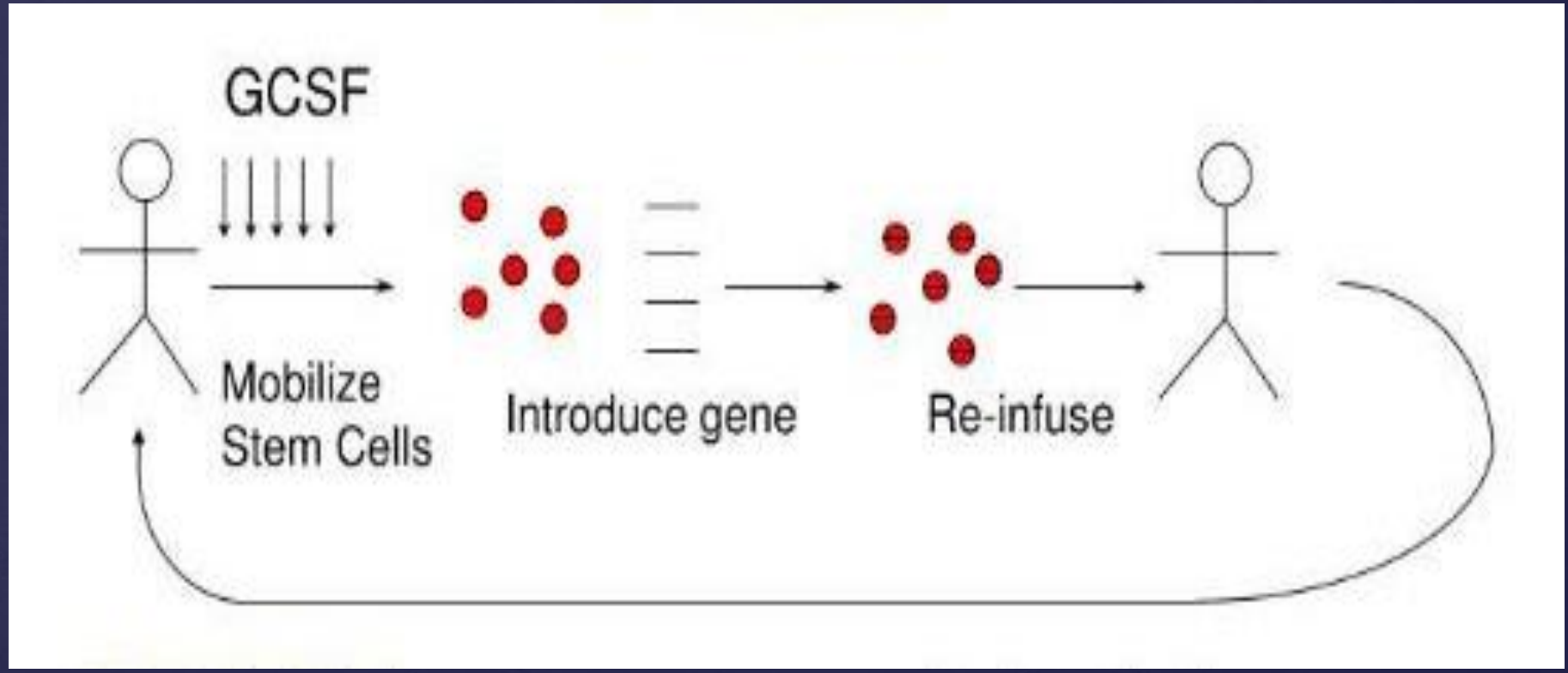
Bone Marrow was obtained from the patient to collect sufficient stem cells for gene transfer.

Bone Marrow enriched CD34+ cells were transduced with LentiGlobin BB305 vector.

Patient underwent MAC regimen with IV Busulfan.

After a 2 day washout period, transduced CD34 + cells were reinfused in to patient.

Gene Therapy for SCD

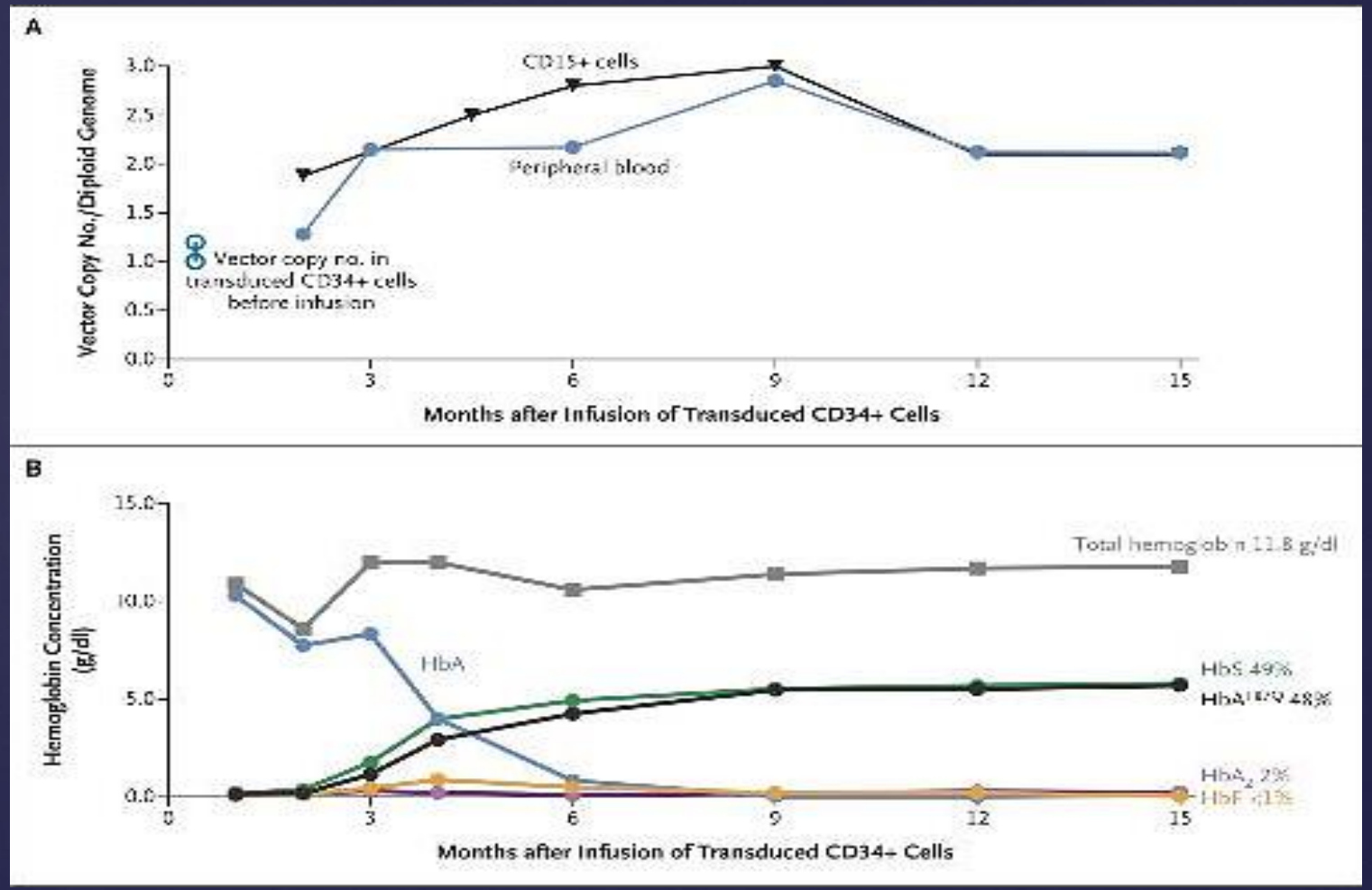


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HGB-205 … Findings & Results

- 15 months after treatment, the level of therapeutic antisickling β–globin remained at 50% without recurrence of sickle crises and with correction of the biologic hallmarks of the disease.
- No adverse events related to the LentiGlobin BB305-transduced stem cell were reported
- Patient was discharged home on day +50/Last prbc transfusion was on Day + 88.
- Patient reported full participation in normal academic and physical activities 15 months post cell therapy.

HGB-205 Engraftment & Gene Expression



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Why the optimism ?



Gene Therapy For SCD is a Paradigm Shift

A new option for curing SCD, a disease that still remains with only one FDA approved disease modyfing agent (hydroxurea).

Donor availability is no longer an obstacle for children and adults with SCD.

Limitations



Gene therapy will most likely be restricted to children rather than adults who may not tolerate a high dose of Busulfan.

Gene therapy is not an option for children with SCD living in low and middle income countries where approximately 90% of all children with this disease are born.

Looking Forward ….



Additional data on LentiGlobin treatment in CD is currently being collected in HGB-206, a multicenter, phase 1 clinical study in the USA….**NYP/CUMC.**

Preliminary reports in 7 patients enrolled in HGB-206 do not include any new safety findings. Gene transfer efficiency is expected to be lower than reported in the initial case report.





Thank You & Merci