Sindromi falcemiche: scambio eritrocitario, incognite e certezze

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SITE
SOCIETA' ITALIANA TALASSEMIE ED EMOGLOBINOPATIE

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If a man will begin with certainties, he shall end in doubts, but if he will content to begin with doubts, he shall end in certainties.

Se un uomo parte con delle certezze finirà con dei dubbi; ma se si accontenta di iniziare con qualche dubbio, arriverà alla fine a qualche certezza.

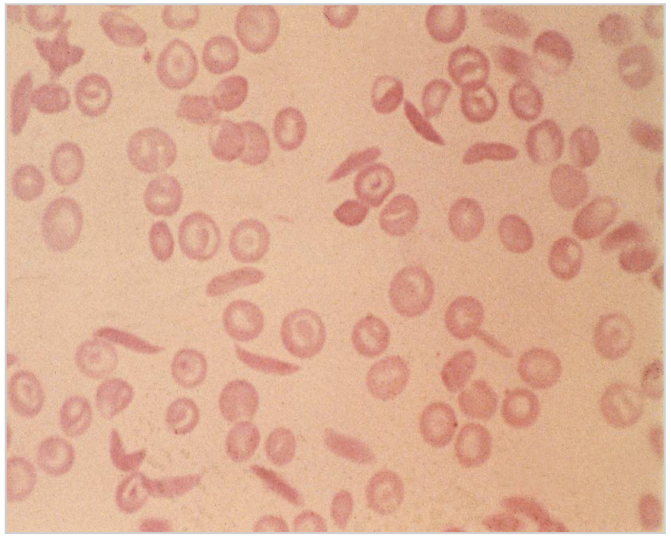
(Francis Bacon- scienzato, filosofo 1561-1626)

Eigentlich weiß man nur, wenn man wenig weiß, mit dem Wissen wächst der Zweifel.

In realtà si sa solo quando si sa poco; col sapere aumenta il dubbio.

(Johann Wolfgang von Goethe- poeta 1749-1832)

Red cells act as direct and indirect players in sickle cell related clinical manifestations

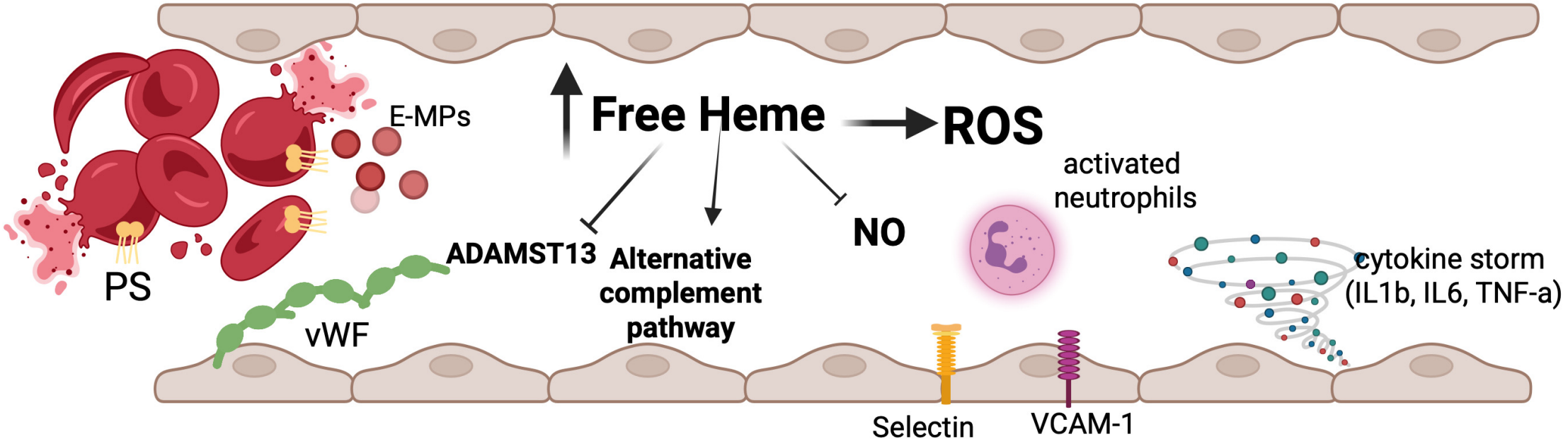


Dense RBCs

Erythroid microparticles

Free heme and free Hb

The biocomplexity of SCD involved vascular endothelial cells and the plasmatic compartment cross-talking with sickle RBCs



In SCD , Exchange Transfusion Strategies ->fast reduction in HbS and dense red cells (≤ 30% HbS)

Erytroexchange: *sostituzione (rimozione)* delle emazie patologiche circolanti contenenti HbS con emazie normali e riduzione nel numero di emazie HbS circolanti

Manuale (MEEX): unico accesso venoso, idratazione, salasso/i e trasfusione di eritrociti concentrati

Automatizzato (AEEX): scambio di 1 volume eritrocitario, corrispondente a circa 15-20 ml/Kg

Steen RG Am J Neuroradiol. 2003; Chou ST Blood Adv. 2020 Society of Hematology 2020 guidelines for sickle cell disease; Sickle Cell Society. Standard for Clinical Care of Adults with Sickle Cell Disease in the UK; Raccomandazione per le strategie trasfusionali nelle emoglobinopatie. Collana scientifica SITE volume n.3 2014

Indications for transfusion therapy in patients with SCD

Priapism unresponsive to medical treatments

Persistent leg ulcers despite the reduction in HU dosage (SCD related microangiopathy)

Table 1. **Summary of indications for transfusion therapy in patients with sickle cell disease.**

Indication	Transfusion method	Level of support
Transient aplastic crisis	Simple	Expert consensus
Acute multisystem organ failure	Simple or exchange*	Expert consensus
Acute hepatic sequestration	Simple or exchange	Expert consensus
Acute splenic sequestration	Simple via small volume aliquots of 3-5 mL/kg	Expert consensus
Acute splenic sequestration, recurrent	Simple as a bridge to splenectomy	Expert consensus
Acute ischemic stroke	Exchange > simple	Observational studies; expert consensus
Primary stroke prevention	Simple or exchange	Randomized clinical trial
Secondary stroke prevention	Simple or exchange	Randomized clinical trial
Moderate acute chest	Simple or exchange	Expert consensus
Severe acute chest	Exchange	Expert consensus
Acute chest, recurrent	Simple or exchange	Hydroxyurea preferable
Preoperative with > 1 hour with general anesthesia	Simple or exchange	Randomized clinical trial
Pregnancy with complications	Simple or exchange	Expert consensus
Pregnancy, uncomplicated	Simple or exchange	Under investigation
Prior to hematopoietic stem cell transplant	Simple or exchange	Under investigation
Uncomplicated vaso-occlusive episode	---	Transfusion not recommended
Priapism	---	Transfusion not recommended
Leg ulcers	---	Transfusion not recommended
Avascular necrosis	---	Transfusion not recommended

*The British Committee for Standards in Haematology recommend exchange transfusion for acute multisystem organ failure. Red cell exchange may be preferred for severe, acute multisystem organ failure.

Linder GE et al Haematologica 106: 1965, 2021

Automatized or Manual Erythro-Exchange *vs* Simple transfusion SCD

Advantages

- Rapid
- Little net iron gain
- Reduction of iron overload in some patients
- Better control of HbS while leaving hematocrit and whole blood viscosity unchanged

Disadvantages

- Increased red cell utilization
- Increased rate of donor exposure therefore increased risk of infection or alloimmunization
- Venous access can limit application
- Requires trained staff and specialized equipment for automated exchange
- In children, care is required to avoid removing or transfusing too much blood at one time

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Manual EEX and SCD

- Two equations for the calculation of HbS% and hemoglobin (Hb) after MEEX are proposed.

- The calculation is based on HbS% and Hb pre-MEEX, volumes exchanged and total blood volume of the patient.

- The equations were verified using the data of 228 MEEX procedures. Consecutive MEEX data were used to obtain the rate of variation between two exchanges.

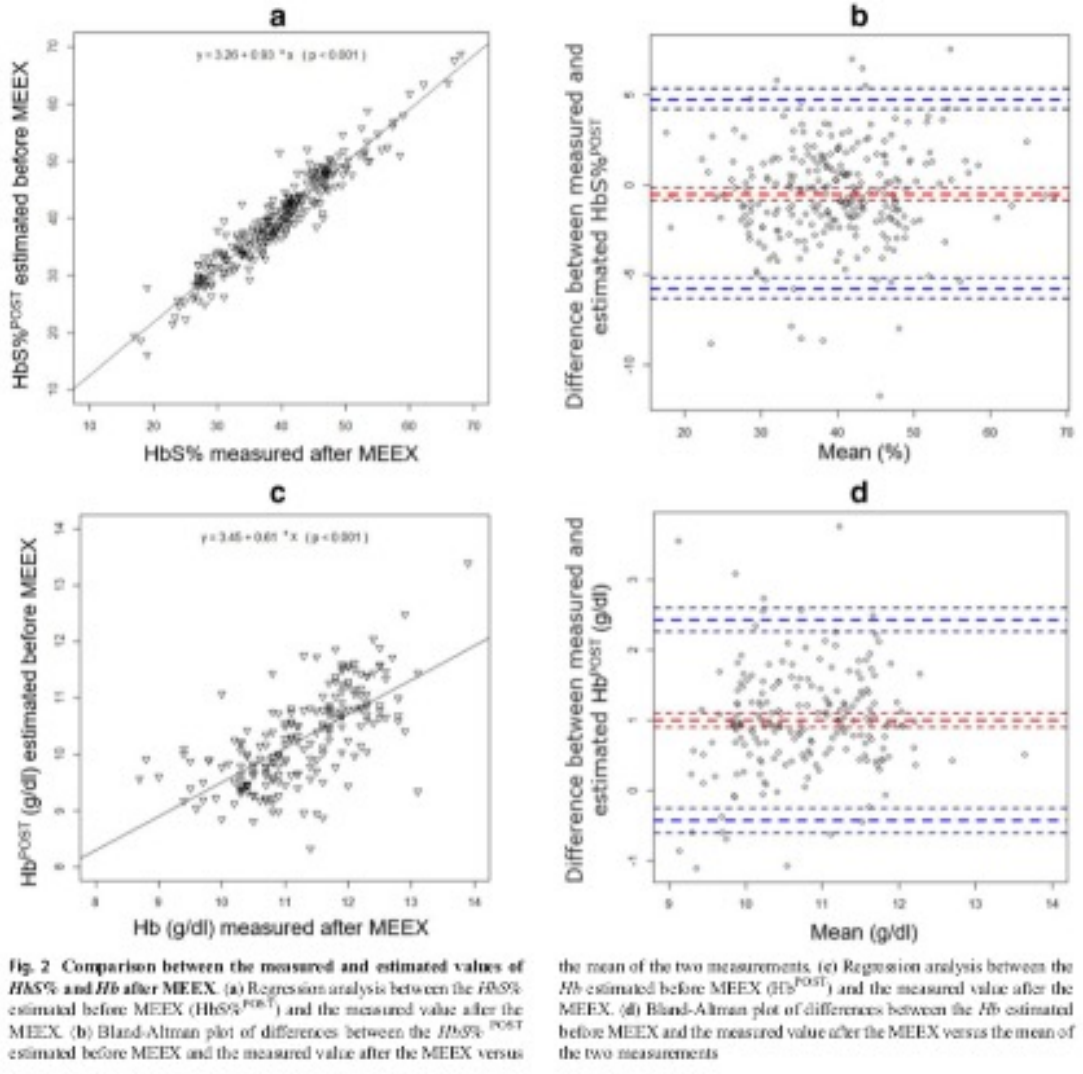

Fig. 2 Comparison between the measured and estimated values of *HbS%* and *Hb* after MEEX. (a) Regression analysis between the *HbS%* estimated before MEEX ($HbS\%^{POST}$) and the measured value after the MEEX. (b) Bland-Altman plot of differences between the *HbS%* ^{POST} estimated before MEEX and the measured value after the MEEX versus the mean of the two measurements. (c) Regression analysis between the *Hb* estimated before MEEX (Hb^{POST}) and the measured value after the MEEX. (d) Bland-Altman plot of differences between the *Hb* estimated before MEEX and the measured value after the MEEX versus the mean of the two measurements

Annals of Hematology
https://doi.org/10.1007/s00277-020-04188-y

ORIGINAL ARTICLE

Check for updates

Manual erythrocexchange in sickle cell disease: multicenter validation of a protocol predictive of volume to exchange and hemoglobin values

Barbara Stanesin[1] · Valeria Maria Pinto[1] · Maddalena Casale[2] · Paola Corti[3] · Carmela Falone[3] · Sabrina Quintino[1] · Vincenzo Voi[1] · Gian Luca Forni[1]

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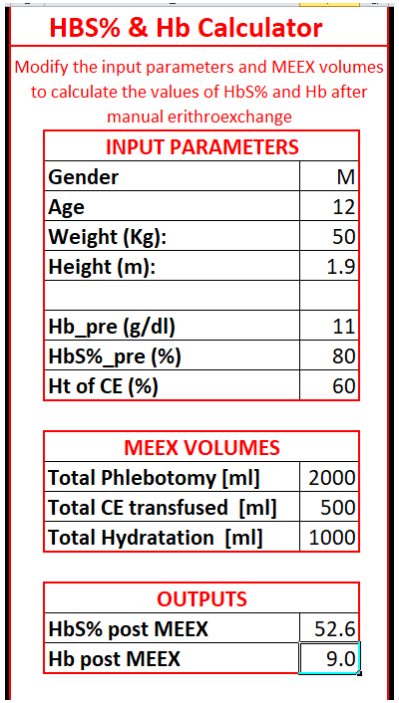
Development of a tool for the calculation of HbS% and Hb post-MEEX using Microsoft Excel

The analysis of 150 the couples of consecutive MEEX exchanges allowed us to estimate an increase of in time equal to 0.4/day (95% CI: 0.32-0.46); this rate of variation can be used to establish the most correct interval between two procedures



HBS% & Hb Calculator

Modify the input parameters and MEEX volumes to calculate the values of HbS% and Hb after manual erithroexchange

INPUT PARAMETERS	
Gender	M
Age	12
Weight (Kg):	50
Height (m):	1.9
Hb_pre (g/dl)	11
HbS%_pre (%)	80
Ht of CE (%)	60

MEEX VOLUMES	
Total Phlebotomy [ml]	2000
Total CE transfused [ml]	500
Total Hydratation [ml]	1000

OUTPUTS	
HbS% post MEEX	52.6
Hb post MEEX	9.0

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Manual *vs* automatized exchange in chronic treatments-I

- **Iron overload:** no significant differences in serum ferritin between the two procedures

- Iron overload might be favored by higher post-aEEX Hct starting by low pre-aEEX Hct:
  - **post-aEEX Hct of 34% :** appearance of iro-overload requiring iron chelation
  - **post-aEEX Hct of 30%:**no iron overload, appearance in a subgroup of patients of iron deficiency

- <u>Personalized post post-aEEX Hct might reduce the risk of iron overload</u>.

Mukherjee S et al 117: 989, 2022; Ross JM et al BJH 205: 1556, 2024; Uter S et al Blood Adv 5: 2586, 2021; Ross JM et al BJH 205: 1556, 2024

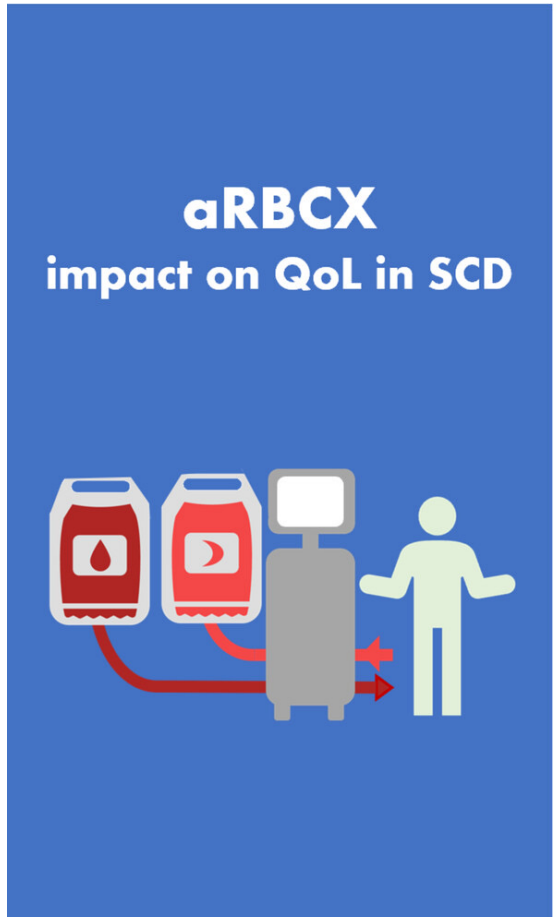
Manual *vs* automatized exchange in chronic treatments-II

- **Alloimmunization rate:** No differences between the 2 procedures or between the exchange and simple transfusion even in presence of larger exposition required by erythroexchange when compared to simple transfusion.

- **Risk of catheter thrombosis:** it is higher in automatizer exchange than in manual exchange- > related to the duration and the diameter of the intravenous catheter (large diameter= increased risk of thrombosis)

Naik R et al J Thromb Haemostasis 12: 2010, 2014; Evans RS et al Chest 143: 627, 3013; Woods D et al Ped Blood Cancer 64: e26635, 3017; Mukherjee S et al 117: 989, 2022

Chronic treatment: Automatized *vs* Manual Erythro-Exchange or simple transfusion in patients with SCD



QoL
— 3 months after procedure[10]
↑ vs. simple transfusion[20]

Hospital
↓ length of stay[18]

Complications
— overall vs. mRBCX[6, 13, 14]

Pain
↓ pain-related hospitalizations[18]

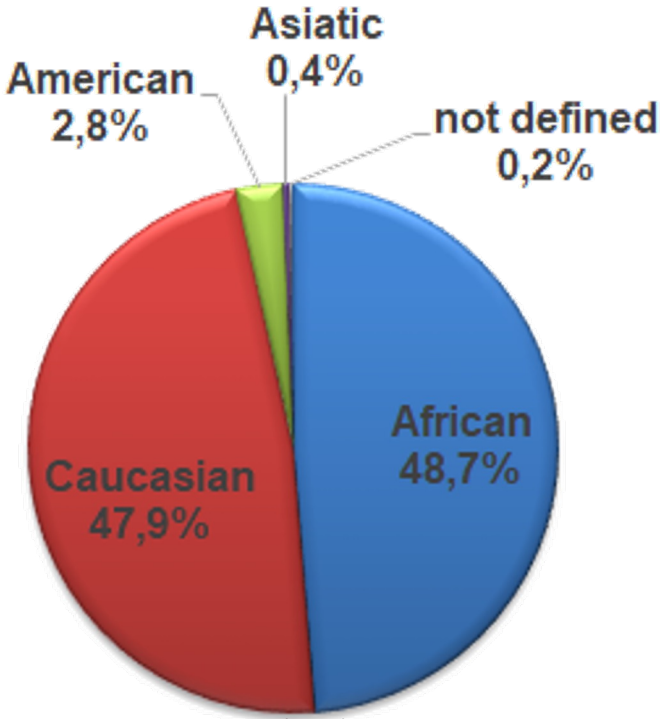
Time
↓ procedure time[6, 7]
↓ frequent procedures[7]

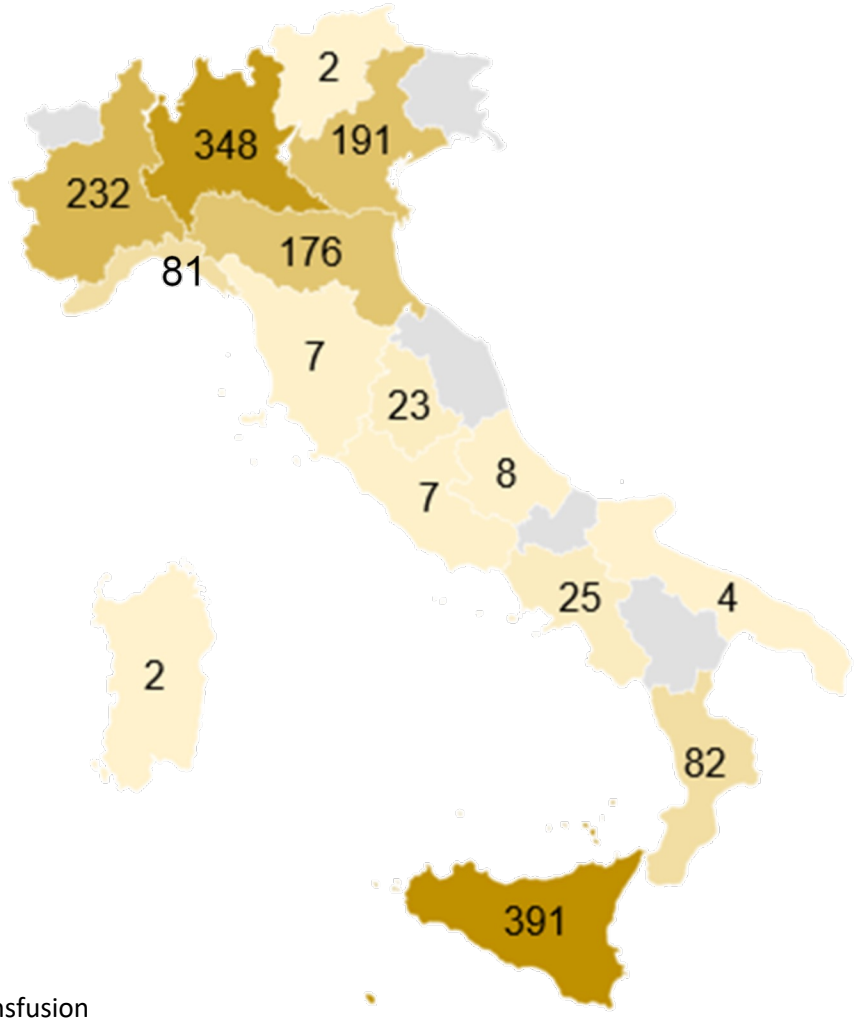
Vascular access
↑ more complex vs. mRBCX[7]

Dierick K et al Vox Sang 120: 4, 2025

Transfusional Approach in Multi-Ethnic Sickle Cell Patients Real-World Practice

- 34 Centers
- 15 Italian regions
- 1579 patients (802 male and 777 female)

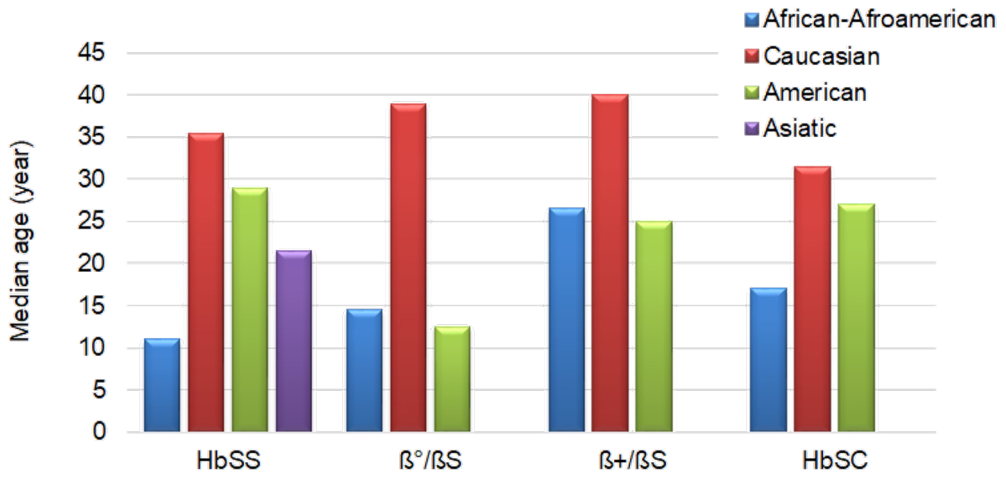




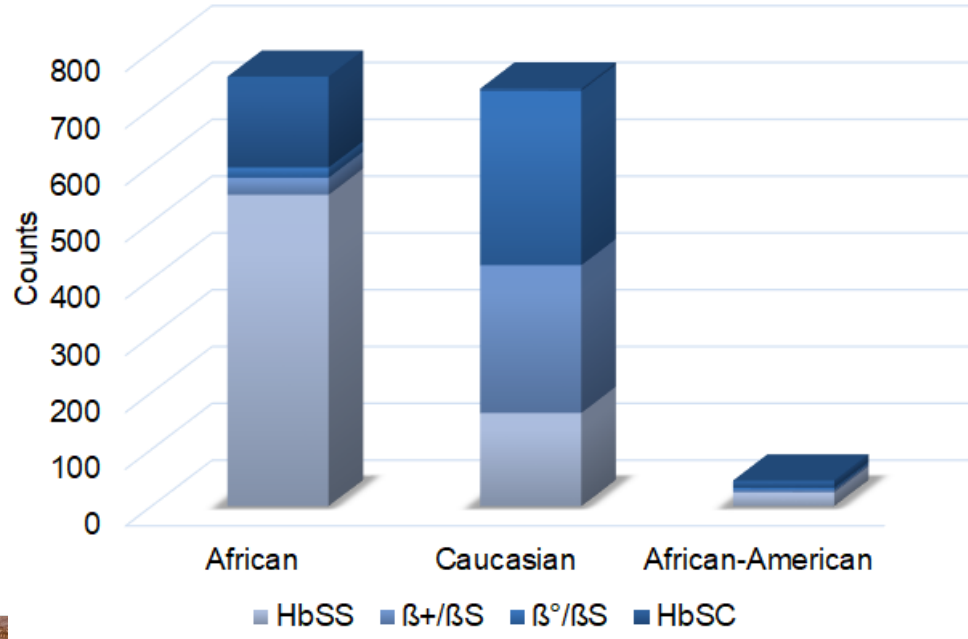
The Italian Society of Thalassemia and Hemoglobinopathies (**SITE**), in collaboration with the Society Italian Transfusion Medicine and Immunohematology (**SIMTI**) and the Italian Association of Hematology and Pediatric Oncology (**AIEOP**) conducted a **national survey** to collect information on transfusion approaches in clinical management of SCD

Graziadei G et al Front Med 9: 832154, 2022

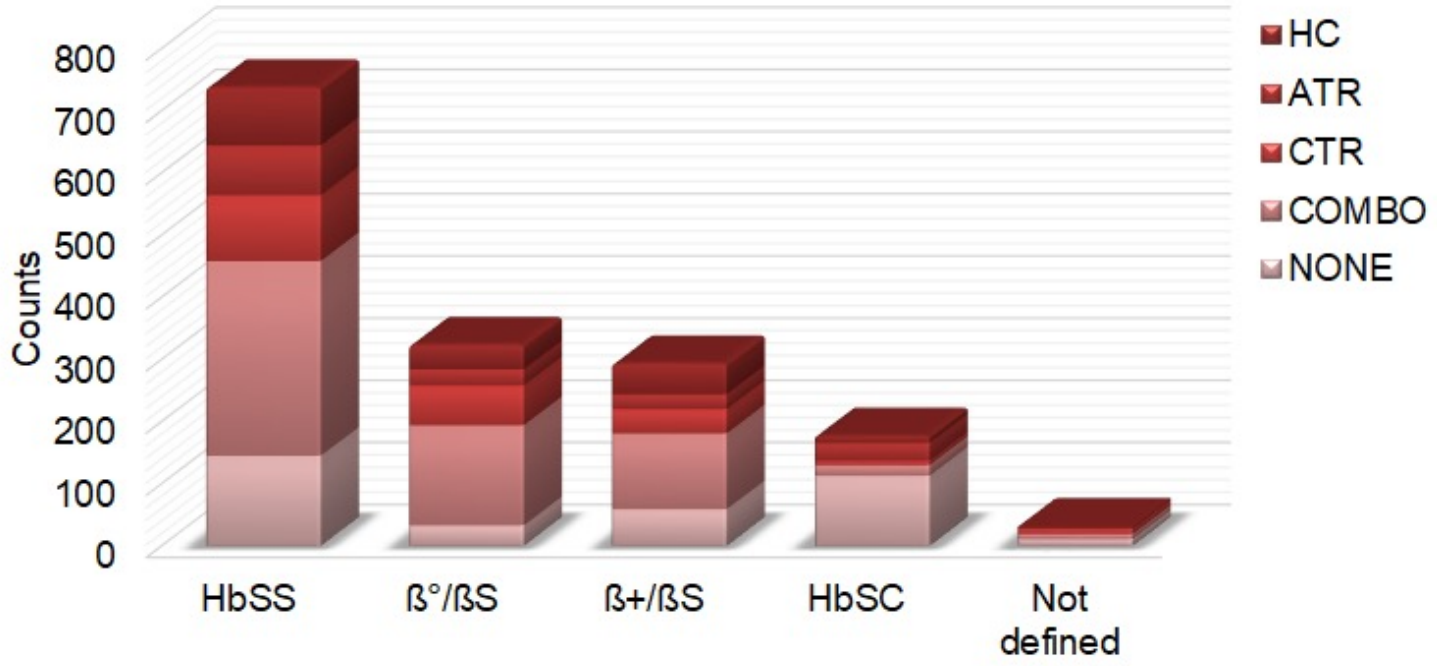
The median age of non-Caucasian patients was significantly lower than Caucasian ones (p<0.001)



Genotype vs Ethnicity:
SS genotype was the most represented



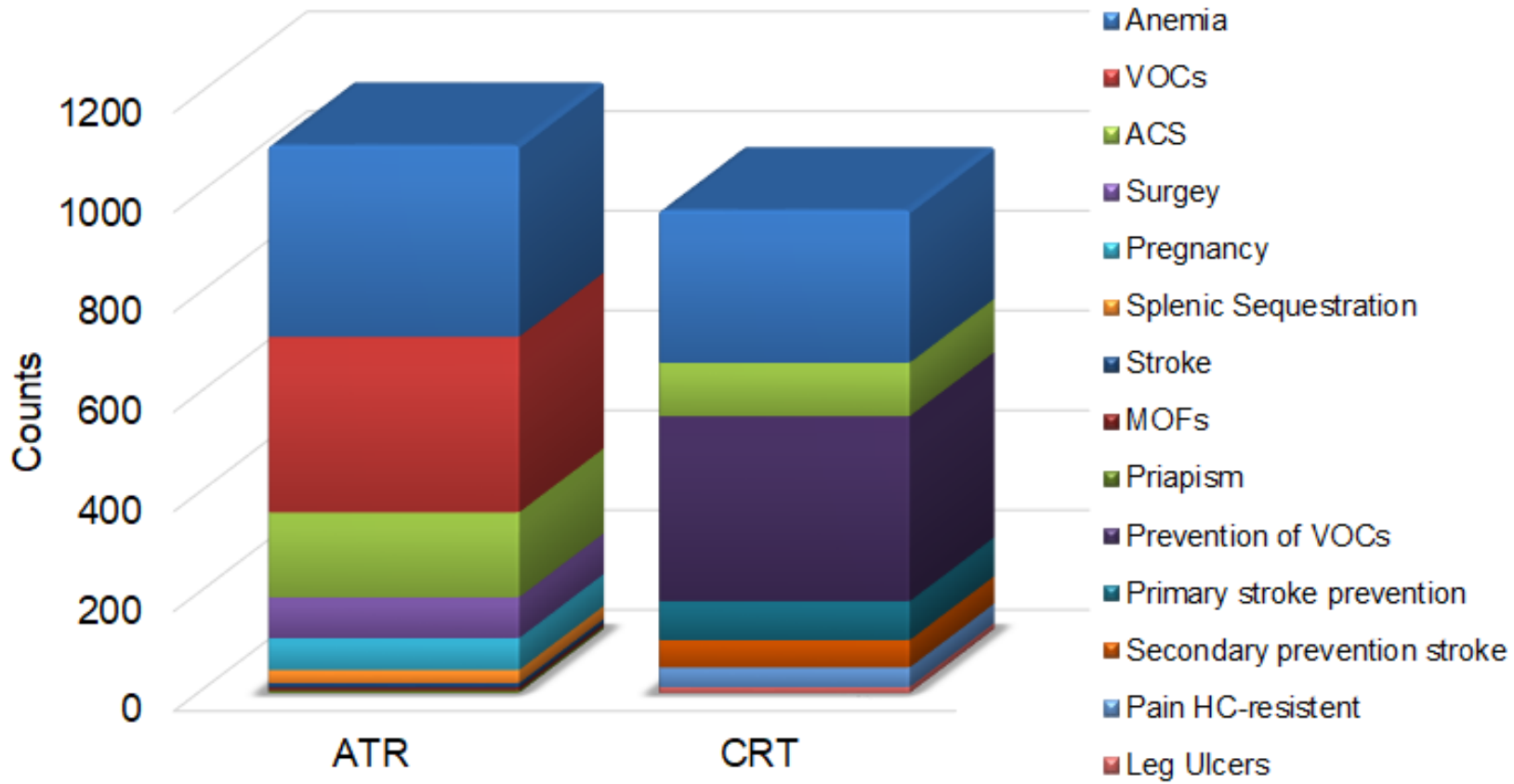
Graziadei G et al Front Med 9: 832154, 2022



Chronic transfusion regimen (CTR) and HC were found respectively in 226 (14%) and 197 (12.4%) patients. Noteworthy, we observed chronic transfusion regimen in combination with HC (CTR-HC) in 631 subjects (40%) (Fig. 4).

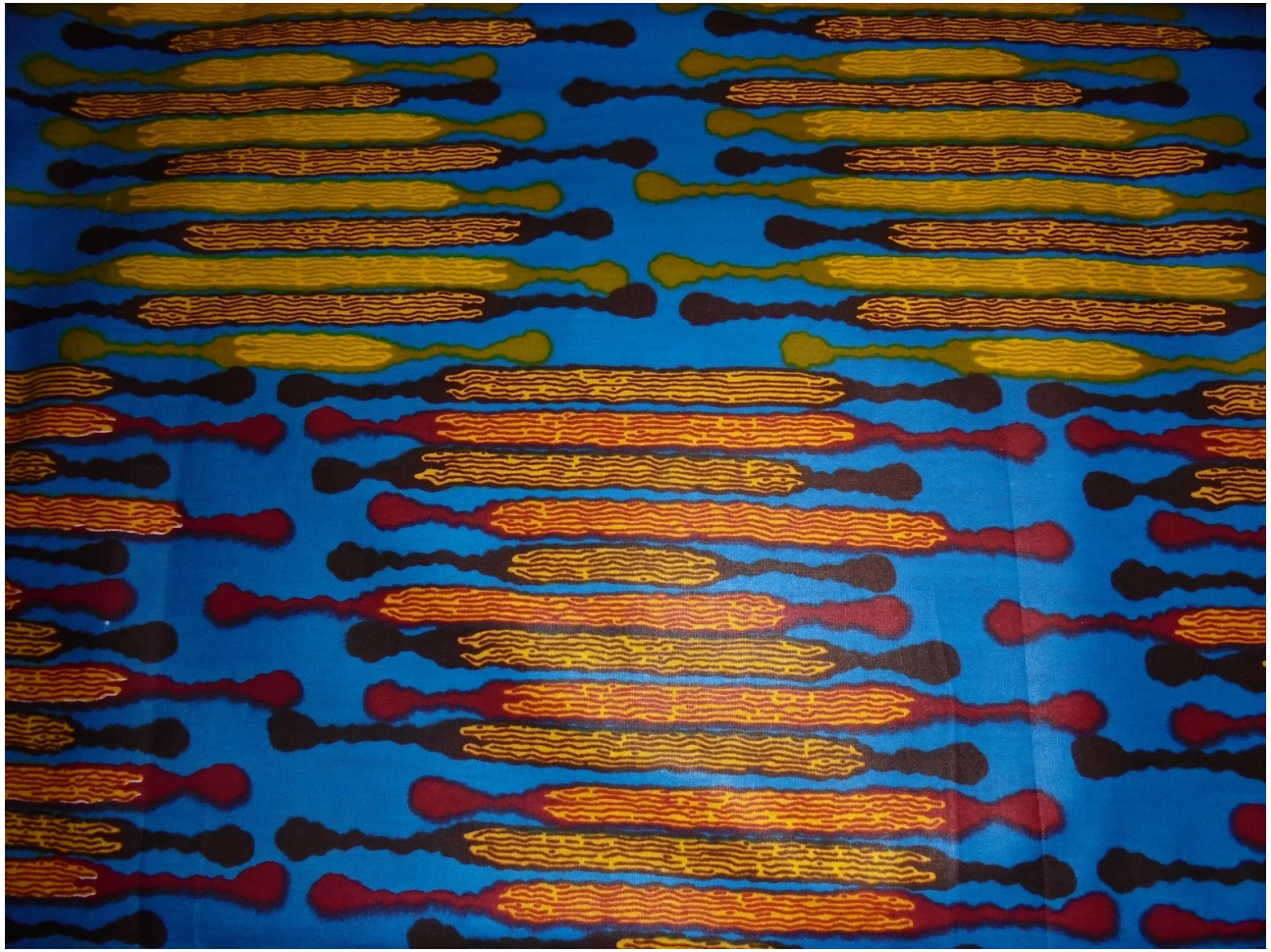
Graziadei G et al Front Med 9: 832154, 2022

Causes of acute (ATR) or chronic (CTR) transfusional approaches in Italian SCD population



Graziadei G et al Front Med 9: 832154, 2022

Pregnancy a special condition and role of aEEX or mEEX in women with SCD



ORIGINAL RESEARCH

Improvement of maternal and fetal outcomes in women with sickle cell disease treated with early prophylactic erythrocytapheresis

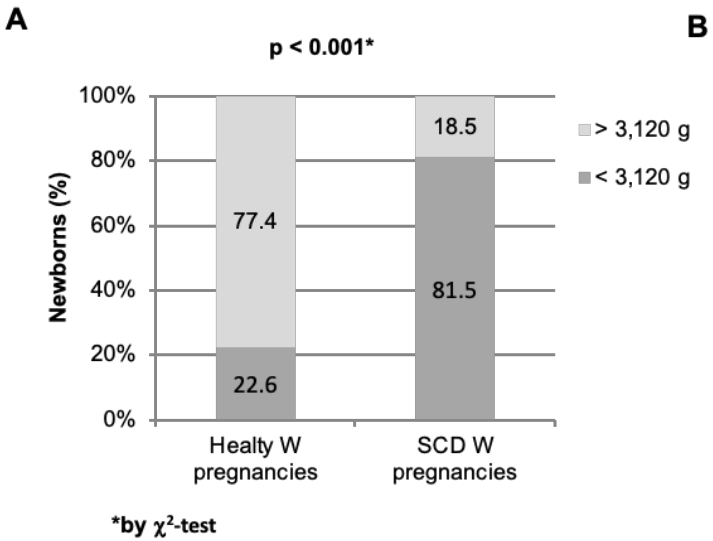
Alice Vianello,[1] Elisa Vencato,[1] Maurizio Cantini,[2] Giovanni Zanconato,[3] Erminia Manfrin,[4] Alberto Zamo,[4] Francesco Zorzi,[1] Filippo Mazzi,[1] Nicola Martinelli,[1] Elena Cavaliere,[3] Francesca Monari,[5] Donatella Venturelli,[6] Francesca Ferrara,[7] Oliviero Olivieri,[1] and Lucia De Franceschi[1]

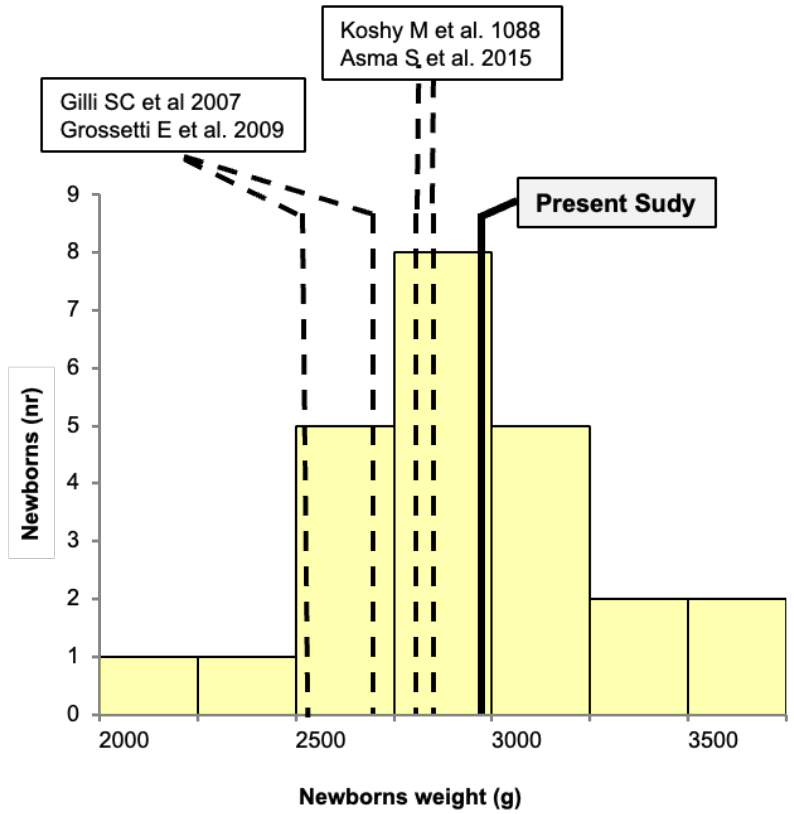
Double-center retrospective cross-sectional study on a total of 46 single pregnancies in SCD women from January 2008 to June 2017

A prophylactic ECP program was started at 10.7 +/- 5.2 weeks of gestation (n = 23), earlier than that reported in previous studies using either classic transfusion or ECP regimens. ECP was carried out every 3 o 4 weeks during pregnancy until delivery

Vianello A et al. Transfusion 2018 Sep;58(9):2192-2201

Early aEEX treatment improves maternal and fetal outcome in women with SCD





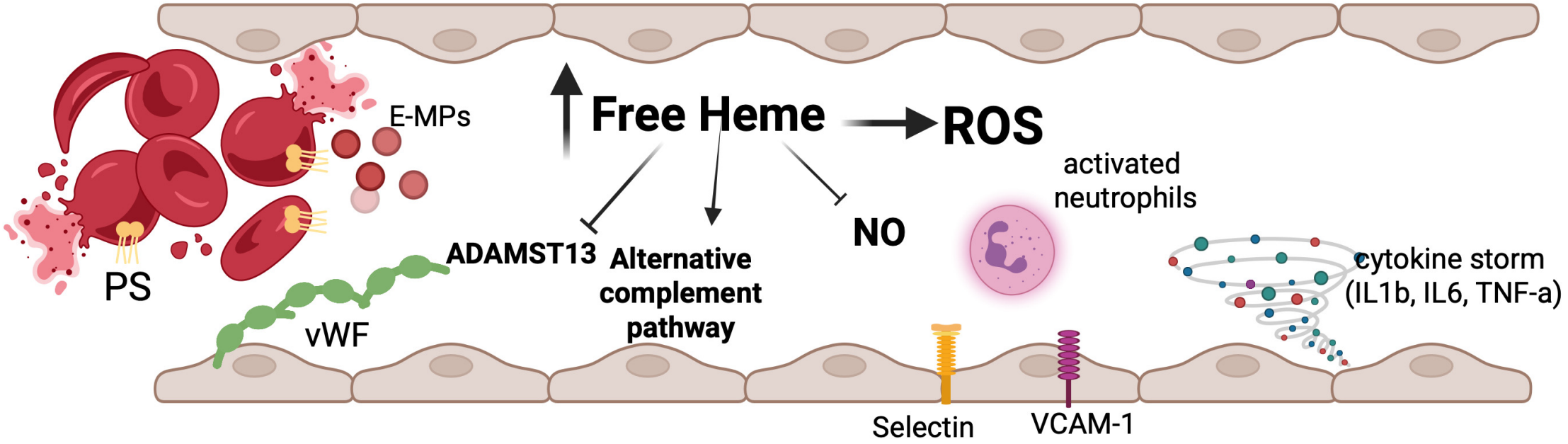
TAPS2-study:

Lower incidence of VOCs, preterm delivery, and improved birthweight was observed in the intervention group -> SCD women single pregnancy, starting EEX 6-18 weeks of gestation .

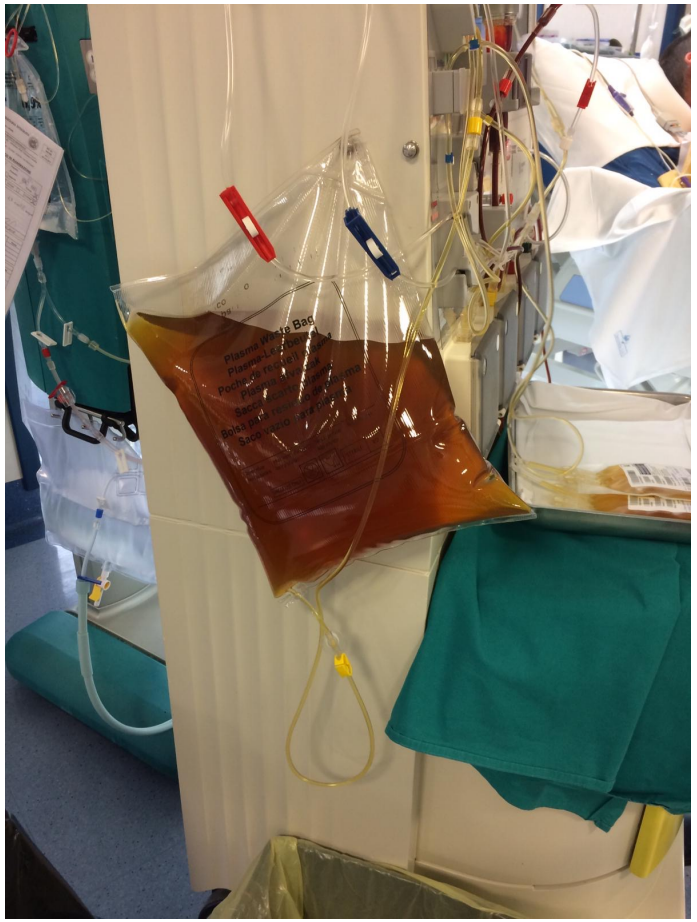
The newborn birth weight was positively related with maternal hemoglobin levels

Vianello A et al. Transfusion 2018 Sep;58(9):2192-2201; Oteng Nitim E et al Blood Adv 8: 4359, 2024

The biocomplexity of SCD involved vascular endothelial cells and the plasmatic compartment cross-talking with sickle RBCs



In acute severe VOCs: plasma is a crucial compartment to considered

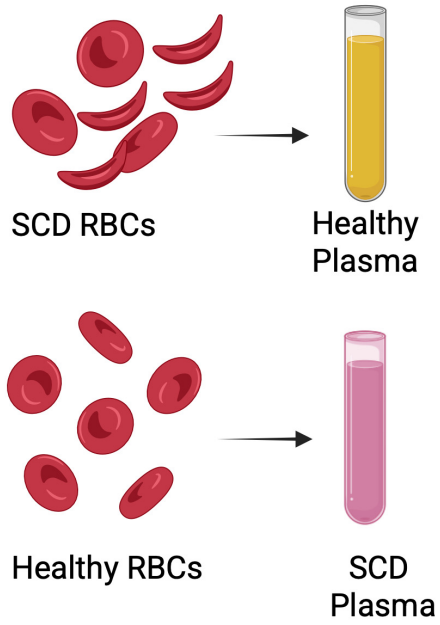


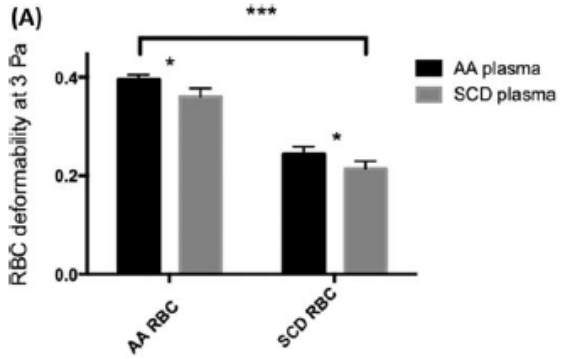
- **Pro-inflammatory and pro-oxidant molecules->** cytokines, free Hb, free heme

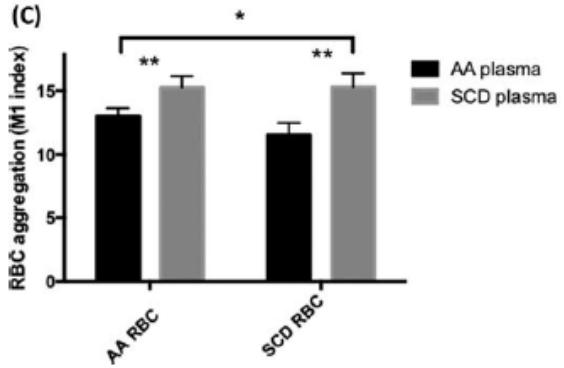
- **Components that increase blood viscosity->** ↑globulins (IgG), FBG, coagulation factors, relative reduction of ADAMST13a activity (↑ large vWF)

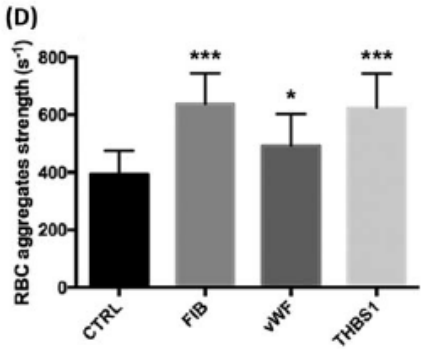
Ballas S et al Transfusion 57: 2277, 2017; Matte A et al Exp Opinion Invest Drug 29: 23, 2020; Matte A et al Mediterr J Hematol Infect Dis 11: e22019002, 2019; Schnog JJ et al. Am J Hematol 81: 492, 2006

Plasma from healthy donors ameliorates SS RBCs deformability and reduces SS RBCs aggregation









Incubation of SSRBCS with either Fibrinogen (FIB), Thrombospondin (THBS1) or vWF increases SSRBCs aggregation strenght compared to healthy RBCs

Clinical evidence of RCE combined with TPE in SCD patients with severe acute VOCs

- **Siddiqui RS et al.** (cases collection)
  - 2 pts with severe VOCs and MOFs refractory to RCE
  - ↓mortality when RCE was combined with 2-3 TPE

- **Zaidi GZ et al.:** (Retrospective case review, 4 years)
  - 7 pts with SCD severe VOCs and MOFs refractory to RCE
  - ↓mortality (6/7 survivors) when RCE was combined with 2-3 TPE-> ICU 5.6 days, hospital length 14 days.

Siddiqui RS et al J Clin Apheresis 36: 777, 2021; Zaidi GZ et al. J Intensive Care Med 35: 140, 2020

RCE combined with TPE (2-3 sessions): setting of severe sickle cell related clinical complications

- ACS resistant to RCE
- Severe VOCs with chest pain
- Priapism
- Sickle cell related acute hepatic crisis
- Fat embolism syndrome with neuro presentation
- Chronic leg ulcers

Therapeutic plasma exchange (TPE):

- **Plasma** (Hpt, Hpx, complement regulators)
- **Plasma/albumine**

Ballas S et al Transfusion 57: 2277, 2017; Tsitsikas DA et al Transfus Apher Sci 25: 103375, 2022; Tsitsikas DA et al. Trasfus Apher Sci 60: 103226, 2021; Ballas S et al Am Chem Lab Science 49: 836, 2019

Conclusions

- Erythroid exchange as either automatized or manual is a cornerstone in clinical management of acute and chronic SCD complication

- Manual Erythroid exchange should be available in all comprehensive centers for hemoglobinopathies with dedicated clinical pathways involving ED

- Growing evidence indicate that aEEX/TPE combination as separate or tandem procedures might be additional tools in clinical management of the severest sickle cell related acute complications.

Metodica trasfusionale	Vantaggi	Svantaggi
Trasfusione Semplice	Semplice Efficace Poco costosa Non necessita di personale dedicato	Diluzione di HbS (non sostituzione) Lenta riduzione di HbS Rischio di iperviscosità Sovraccarico di ferro Necessità di ferrochelazione
Scambio eritrocitario manuale (MEEX)	Semplice Efficace Poco costosa Rapida applicabilità in fase acuta ed in qualsiasi struttura Attuabile anche in contesti con scarse risorse Rapida diminuzione di HbS Ridotto rischio di iperviscosità Non necessita di personale specializzato Non richiede strumentazione specializzata Attuabile al letto del paziente Necessita di un solo accesso vascolare Facile esecuzione anche nei pazienti pediatrici Sufficienti 2-3 concentrati eritrocitari	Possibilità di sovraccarico di ferro Possibilità di ferrochelazione Nel regime cronico intervalli più brevi tra le procedure vs AEEX
Scambio eritrocitario con separatore cellulare o automatizzato (AEEX)	Efficace Maggiore rapidità di diminuzione HbS vs MEEX Maggiore efficacia nella riduzione di HbS vs MEEX Nel regime cronico intervalli maggiori tra le procedure vs MEEX Ridotto/assente rischio di iperviscosità Rimozione di parte del ferro Minor accumulo di ferro	Richiede valori più alti di Hb pre Non sempre di rapida applicabilità in fase acuta Necessita di struttura autorizzata in procedure aferetiche Necessita di personale esperto in procedure aferetiche Necessità di due accessi vascolari periferici o di un accesso vascolare centrale Non sempre attuabile nei pazienti pediatrici Costi (seppur bilancio costi/beneficio)