Aferesi terapeutica nelle emoglobinopatie con focus nei pazienti pediatrici

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XVII CORSO NAZIONALE DI AGGIORNAMENTO SIdEM
Palermo - Mondello 18 - 19 - 20 ottobre 2012

Sabato 20 Ottobre | Simposi Prima Parallela SIdEM - ESTM
per Medici / Biologi | Sala Cessati

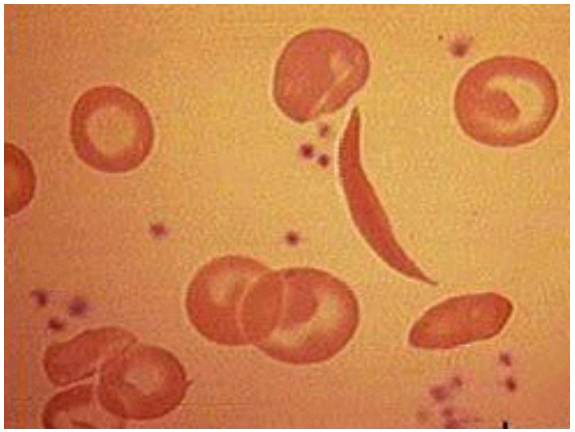
AGGIORNAMENTO SULLE EMOGLOBINOPATIE

MODERATORI: A. Iacone - U. Rossi

9.00	Origine e finalità della ESTM (European School of Transfusion Medicine) U. Rossi
9.30	La diagnosi delle emoglobinopatie R. Galanello
10.00	La terapia delle emoglobinopatie P. Cianciulli
10.30	L'alloimmunizzazione eritrocitaria A. Matteocci
11.00	*Coffee Break*
11.30	Aferesi terapeutica nelle emoglobinopatie con focus nei pazienti pediatrici G. Lodi
12.00	Il trapianto nelle emoglobinopatie P. Di Bartolomeo
12.30	Aggiornamento sulla terapia genica nelle Sindromi Talassemiche A. Maggio
13.00	Conclusioni A. Iacone
13.30	Chiusura Corso

Emoglobinopatie

- Disordini con ridotta sintesi emoglobinica (talassemie)
- Disordini con catena emoglobinica modificata (sindromi falcemiche)
- Disordini con difetto di *switch* delle catene globiniche (persistenza di emoglobina fetale)



Aferesi Terapeutica nelle Emoglobinopatie

- Disordini con ridotta sintesi emoglobinica (talassemie)
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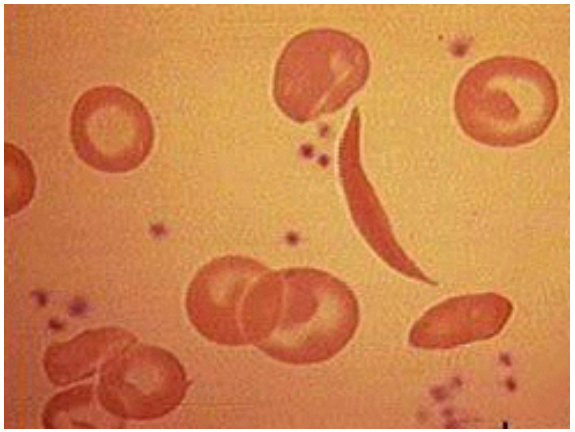
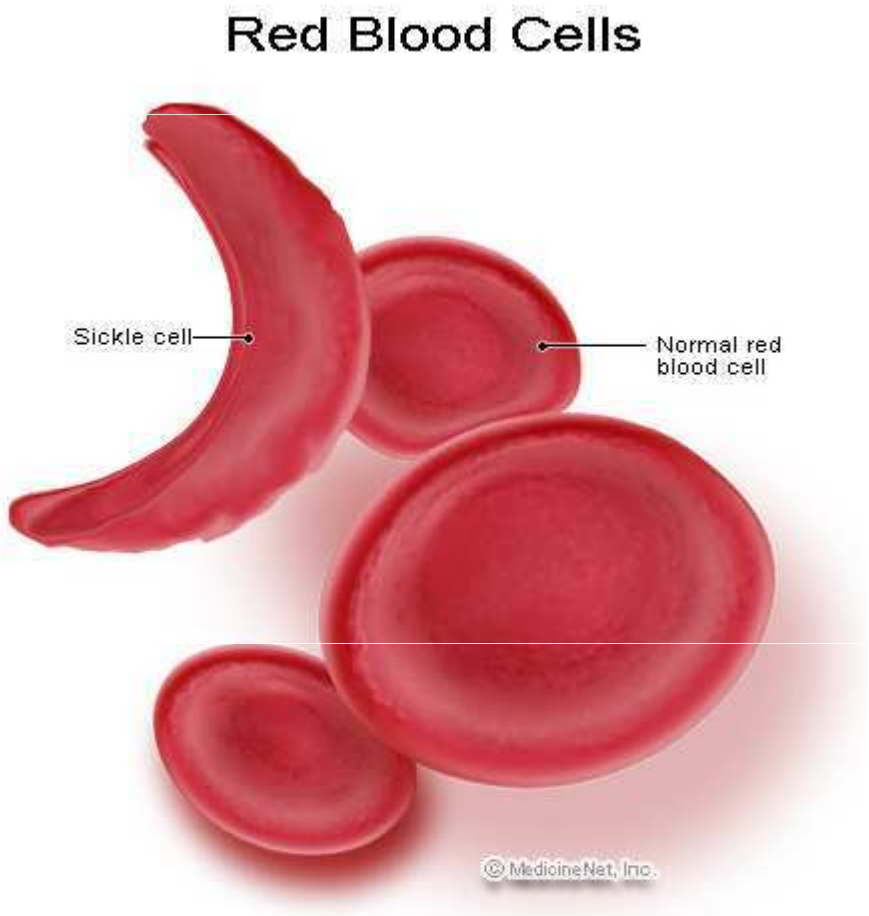


HbS


Red Blood Cells
Sickle cell
Normal red blood cell
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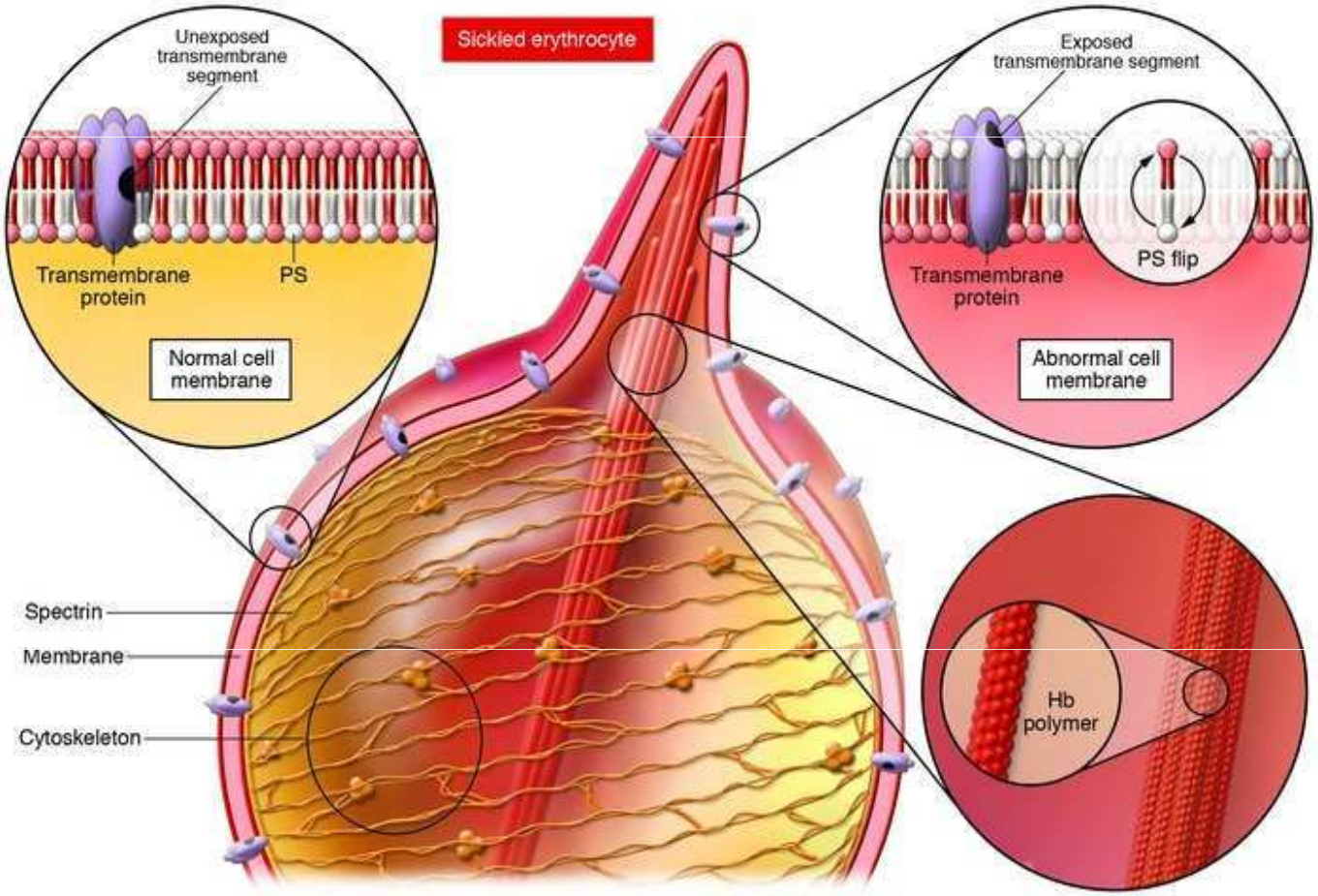
Sickle-cell disease

David C Rees, Thomas N Williams, Mark T Gladwin

Severe sickle-cell disease	
HbS/S (β6Glu>Val/β6Glu>Val); sickle-cell anaemia	The most common form of sickle-cell disease
HbS/β^0 thalassaemia	Most prevalent in the eastern Mediterranean region and India[34]
Severe HbS/β^+ thalassaemia	Most prevalent in the eastern Mediterranean region and India; 1–5% HbA present[34]
HbS/OArab (β6Glu>Val/β121Glu>Lys)	Reported in north Africa, the Middle East, and the Balkans; relatively rare[34]
HbS/D Punjab (β6Glu>Val/β121Glu>Gln)	Predominant in northern India but occurs worldwide[34]
HbS/C Harlem (β6Glu>Val/β6Glu>Val/β, β73Asp>Asn)	Electrophoretically resembles HbSC, but clinically severe; double mutation in β-globin gene; very rare[35]
HbC/S Antilles (β6Glu>Lys/β6Glu>Val, β23Val-Ile)	Double mutation in β-globin gene results in severe sickle-cell disease when co-inherited with HbC; very rare[35]
HbS/Quebec-CHORI (β6Glu>Val/β87Thr>Ile)	Two cases described; resembles sickle-cell trait with standard analytical techniques[37]
Moderate sickle-cell disease	
HbS/C (β6Glu>Val/β6Glu>Lys)	25–30% cases of sickle-cell disease in populations of African origin[33]
Moderate HbS/β^+ thalassaemia	Most cases in the eastern Mediterranean region; 6–15% HbA present[34]
HbA/S Oman (β^+/β6Glu>Val, β121Glu>Lys)	Dominant form of sickle-cell disease caused by double mutation in β-globin gene; very rare[39]
Mild sickle-cell disease	
Mild HbS/β^{++} thalassaemia	Mostly in populations of African origin; 16–30% HbA present[34]
HbS/E (β6Glu>Val/β26Glu>Lys)	HbE predominates in southeast Asia and so HbSE uncommon, although frequency is increasing with population migration[35]
HbA/Jamaica Plain (β^+/β6Glu>Val, β68Leu/Phe)	Dominant form of sickle-cell disease; double mutation results in Hb with low oxygen affinity; one case described[40]
Very mild sickle-cell disease	
HbS/HPFH	Group of disorders caused by large deletions of the β-globin gene complex; typically 30% fetal haemoglobin[34]
HbS/other Hb variants	HbS is co-inherited with many other Hb variants, and symptoms develop only in extreme hypoxia

Genotypes that have been reported to cause sickle-cell disease are listed. All include at least one copy of the β^S allele, in combination with one or more mutations in the β-globin gene. HbS=sickle haemoglobin. HbA=haemoglobin variant A. HbE=haemoglobin variant E. Hb=haemoglobin.

… in condizioni di **bassa tensione di O2**



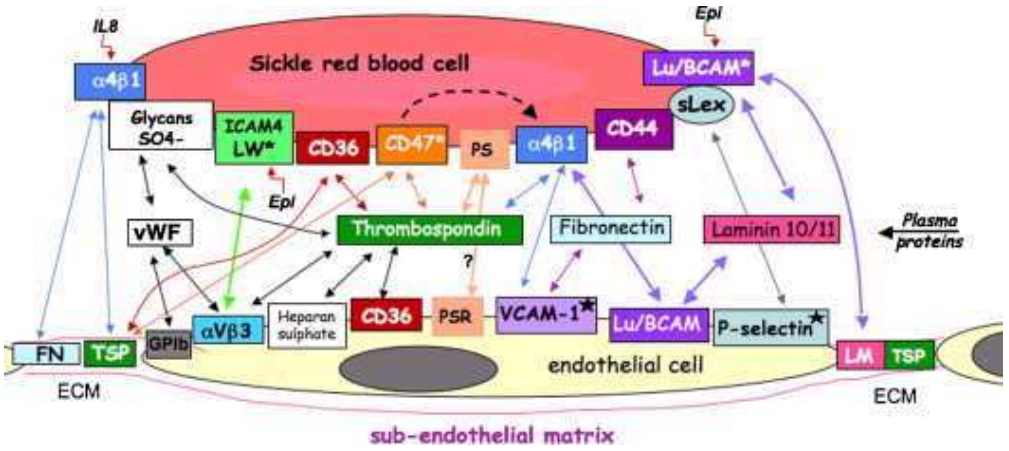
Blackwell Publishing (129)

… basse tensioni di O2 comportano un cambio di conformazione dell'HbS che porta alla formazione di polimeri di emoglobina

I polimeri di emoglobina danneggiano il citoscheletro e realizzano delle protrusioni nella membrana che conferiscono alla cellula la particolare forma

Il danno di membrana comporta perdita della deformabilità e rigidità … responsabili di un deciso incremento dell'adesività *vs* endotelio e cellule circolanti, con un netto rallentamento del flusso ematico

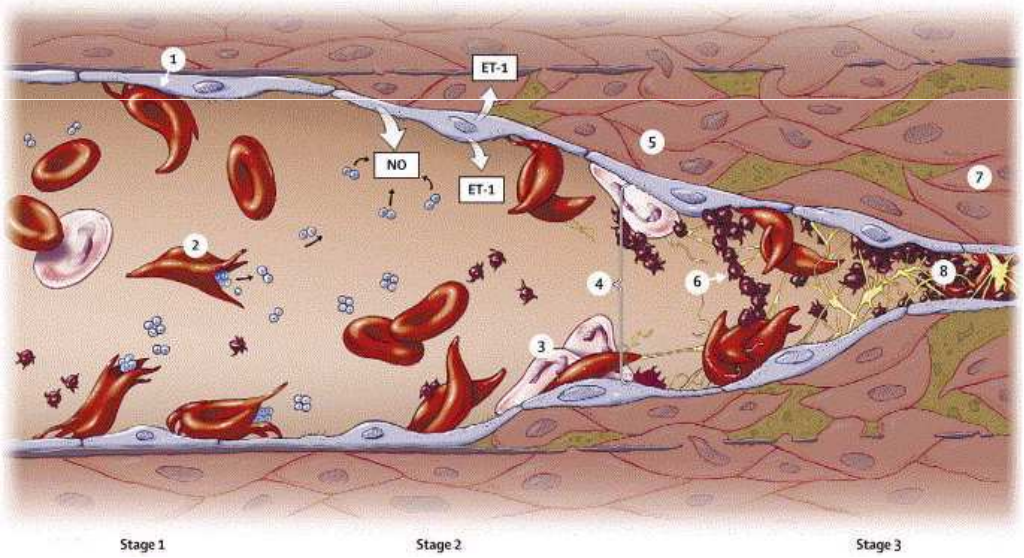
Il rallentamento del flusso è in grado di innescare fenomeni vaso-occlusivi, a loro volta responsabili di ulteriore calo della tensione di O2, che alimenta nuova formazione di polimeri di emoglobina



il danno di membrana causa …

1. **riduzione della vita media dei GR** (da 120 a 15 gg) … da **cronica anemia emolitica**
2. **crisi aplastiche** di solito conseguenti a infezioni virali (PV B19)
3. **fenomeni vaso-occlusivi** che si manifestano con:

- eventi dolorosi ossei distrettuali
- sequestro splenico ed epatico
- infarti cerebrali ricorrenti
- infarti polmonari, che possono dipendere anche da infezioni, sequestro e emboli grassosi
- perdita della capacità di concentrare le urine, da ostruzione vascolare nel circolo dell'ansa di Henle
- nefropatie glomerulari
- ulcere trofiche arti inferiori
- priapismo
- cecità

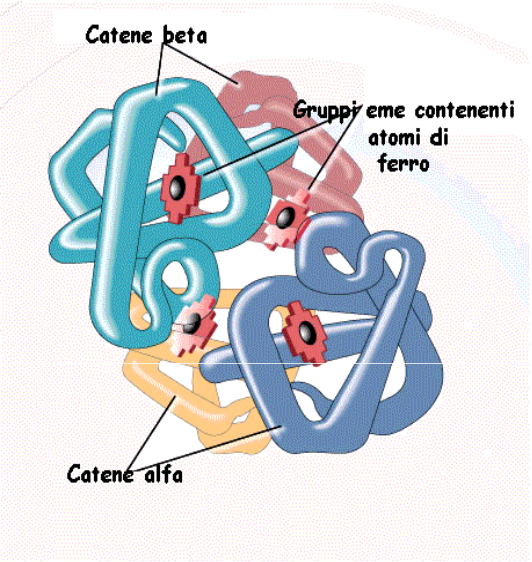


Intervento terapeutico

- Farmaci sintomatici e di supporto/cura delle complicazioni
- Antibiotici in via preventiva/causale
- Agenti in grado di
  - stimolare la produzione di Hb F
  - impedire l'adesività delle cellule tra loro e *vs* l'endotelio
- **Supporto trasfusionale**
  - ***simple***
  - ***exchange***

- Staminali midollari
- Terapia genica

Supporto trasfusionale
(simple / exchange)



risolve o previene

gli effetti di: anemia e crisi vaso-occlusive

<u>rendendo migliore la *cessione di O2* verso i tessuti</u>

… attraverso l'incremento dell'Hb totale

… e la riduzione della viscosità ematica in forza della riduzione della concentrazione di HbS

la cui produzione autologa viene inibita

Cessione di O2

è una funzione complessa che dipende da:

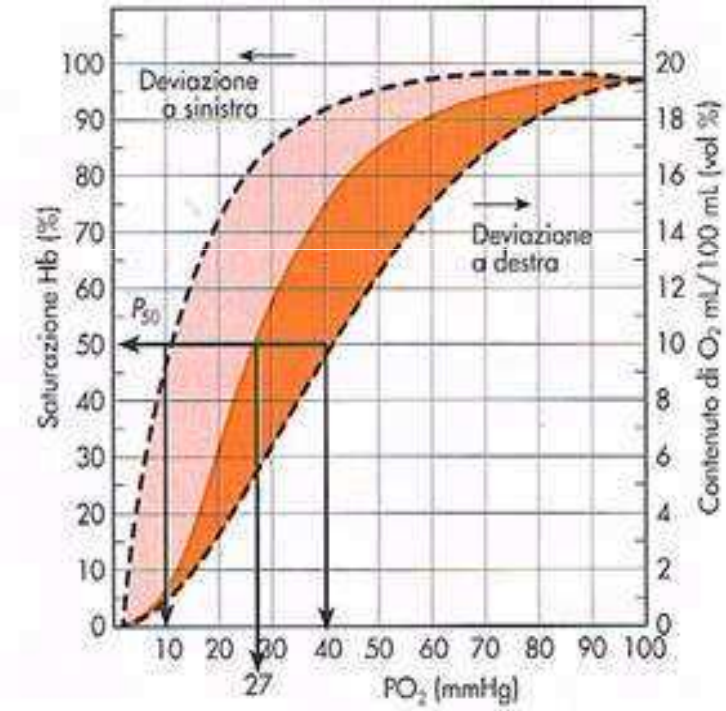
Hct, volume ematico, perfusione vascolare, affinità dell'Hb vs O2

... e dalla viscosità

... nelle sindromi falcemiche la viscosità incrementa in modo proporzionale con l'incremento della concentrazione di HbS

La *cessione di O2* migliora scambiando cellule falcemiche con cellule normali

... e l'effetto si rende ancor più evidente se viene mantenuto costante il valore Hct !!



(Schmalzer EA, Tranfusion 1987)

- *Viscosity of mixtures of sickle and normal red cells at varying hematocrit levels*
  - *Implications for transfusion*

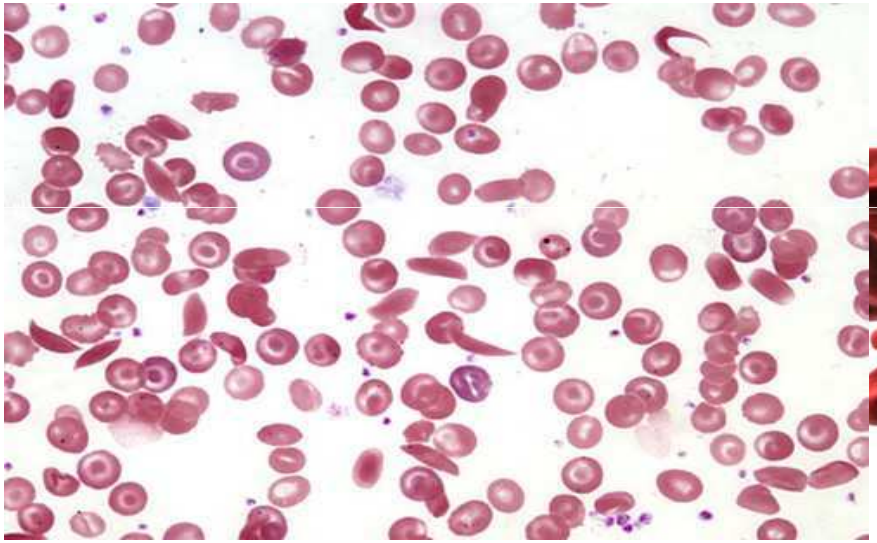
E. A. Schmalzer, J.O. Lee, A.K. Brown, S. Usami, S. Chien MD, PhD

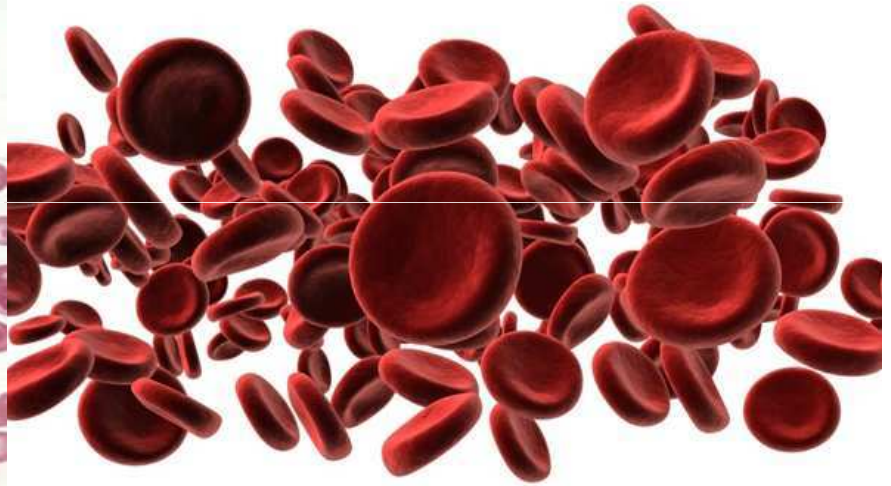
Article first published online: 5 MAR 2003

DOI: 10.1046/j.1537-2995.1987.27387235626.x

1987 AABB Issue & .Transfusion

Volume 27, Issue 3, pages 228–233, May-June 1987





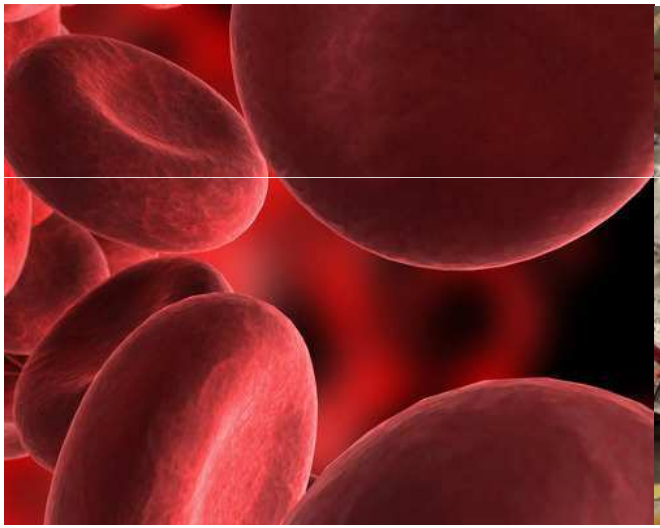
Supporto trasfusionale *(simple)*

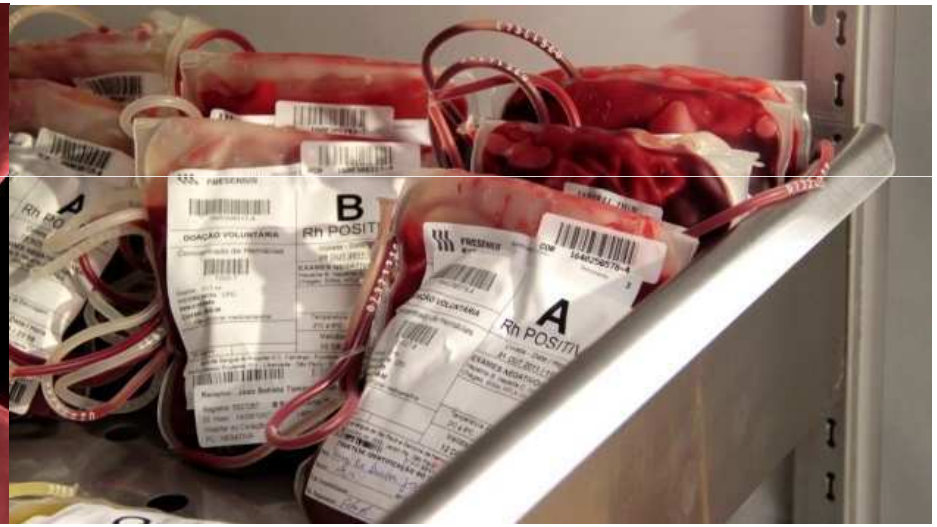
Permette di raggiungere rapidamente un livello di HbA del 60-70%
… diluendo e quindi abbassando la concentrazione di HbS

Ma induce inevitabilmente:

un incremento del valore Hct

un sovraccarico marziale e circolatorio





Supporto trasfusionale *(exchange)*

Permette di abbassare rapidamente la concentrazione di HbS … e di raggiungere valori ideali di Hb totale e di Hct, mantenendo valori di viscosità ematica ideali

Elimina le problematiche di sovraccarico marziale e circolatorio

Comporta tuttavia:

maggior utilizzo di emocomponenti

problematiche sugli accessi venosi

incremento dei costi (al momento)

Guidelines transfusion reccomending a uniform standard in SCD syndrome

Transfusion in the Patient With Sickle Cell Disease: A Critical Review of the Literature and Transfusion Guidelines

Cassandra D. Josephson, Leon L. Su, Krista L. Hillyer, and Christopher D. Hillyer

The clinical outcomes of sickle cell disease (SCD) have vastly improved over the years in great part as a result of advanced medical technologies, improved patient education, and multidisciplinary care. A key component in the successful management of patients with SCD is red blood cell transfusion therapy used in the treatment and prevention of sickle cell complications. However, although the successful application of transfusion therapy has significantly improved the morbidity and mortality of patients with SCD, the literature that addresses the appropriate selection and use of blood products continues to evolve with no clear universal standard of care. Our objectives were to provide an in-depth review of the current literature on transfusion therapy in SCD and to provide a set of guidelines for the transfusion management of patients with SCD.

Transfusion Medicine Reviews, Vol 21, No 2 (April), 2007: pp 118-133

Unica condizione da rispettare:

selezionare un metodo di trasfusione *(acute / chronic simple or exchange transfusion)* che non comprometta ulteriormente i meccanismi fisiopatologici della malattia

- non espandere il volume ematico nei cardiopatici
- non incrementare la viscosità quando ***HbS>50% … quando HbS<40% la simple transfusion causa minime variazioni di viscosità … ma quando HbS>60% è causa di gravi incrementi di viscosità!!***

(Schmalzer EA, Tr 1987)

viscosità vs sickling / delay time

Sickle Cell Anemia

Session Chair: Marilyn J. Telen, MD

Speakers: Paul S. Swerdlow, MD; Orah S. Platt, MD; and George F. Atweh, MD

Red Cell Exchange in Sickle Cell Disease

Paul S. Swerdlow

Red cell exchange transfusions remain an effective but possibly underutilized therapy in the acute and chronic treatment of sickle cell disease. In sickle cell disease, increased blood viscosity can cause complications when the hemoglobin exceeds 10 g/dL even if this is due to simple transfusion. Red cell exchange can provide needed oxygen carrying capacity while reducing the overall viscosity of blood. Acute red cell exchange is useful in acute infarctive stroke, in acute chest and the multi-organ failure syndromes, the right upper quadrant syndrome, and possibly priapism. Neither simple or exchange transfusions are likely to hasten resolution of an acute pain episode.

Hematology 2006

Nei distretti dove si presenta un calo della tensione di O2 …
le ***sickle cells*** non presentano immediatamente il fenomeno dello ***sickling*** …

… che si innesca dopo un certo tempo definito ***delay time***, che dipende in larga parte dalla ***concentrazione intracellulare di HbS***

Delay time vs flusso ematico

Con un normale flusso ematico …

- ✓ ***red cells …*** hanno il tempo di superare i territori critici (venule) e di raggiungere le vene di grosso calibro … fino ad arrivare nel piccolo circolo polmonare dove vengono nuovamente ossigenate

Con un flusso ematico rallentato (causa incremento della viscosità) …

- ✓ ***red cells …*** restano troppo a lungo nei territori critici e superano il ***delay time*** … per cui si crea l'innesco del fenomeno ***sickling …***
- ✓ ***red cells intraprendono le interazioni cellula-cellula che causano:***

  - ❖ ***adesione cellulare sull'endotelio***
  - ❖ ***attivazione della cascata coagulativa e altri processi dipendenti da tale interazione (complemento, ecc …)***
  - ❖ ***variazioni del tono vasomotorio***

Red cell exchange
(Swerdlow, 2006)

elimina le emazie patologiche, che alimentano i fenomeni vaso-occlusivi … anche se non risolve inneschi vaso-occlusivi ormai attivati!

riduce drasticamente l'emolisi (e le sue complicanze) … in particolare sul sistema renale provvede a migliorare la capacità di trasporto di O2, riducendo la **viscosità ematica**

trova indicazione per gli ***eventi acuti*** in quanto:

- riduce / elimina la sintomatologia delle complicanze ***(stroke, acs, mofs)***

… e nelle ***complicazioni a lungo termine*** in quanto:

- mantiene bassi livelli di HbS tanto da prevenire ***stroke I° / II°***e **ipertensione polmonare**

- non risolve (di solito) eventi dolorosi

Red cell exchange and SCD (I)

1. *Arch Inter Med 1963 – Anderson "Effect of normal cells on viscosity of sickle-cell blood" (5 pz trattati con successo con salasso di 500 ml di sangue intero seguito da trasfusione di 2 grc = scambio manuale del 30% dei grc in 90')*
2. *Arch Inter Med 1974 – Charache "The treatment of sickle cell anemia" (partial exchange transfusion can interrupt the vicious cycle of sickling … prima esperienza dello scambio in 3 fasi!!... manuale)*
3. *Transfusion '76 – White & White "Increasing whole blood oxygen affinity .." (1SS e 1SC > rapid eex with bc sep)*
4. *Transfusion '77 – Kernoff "Exchange transfusion in .." (case report pz > eex con separatore a flusso continuo)*
5. *Transfusion '80 – Klein "Automated partial exchange transfusion in SCD" (14 pz > eex sep a flusso discon)*
6. *Transfusion '81 – Kleinmann "Exchange red blood cell pheresis in .." (case report ped pz > eex small bowl)*
7. *J Clin Apher '84 – Kleinmann "Use of erythrocytapheresis in .." (9 pz ad/ped > eex … to determine guidelines)*
8. *J Clin Apher '90 – Talacki & Ballas "Modified method of .." (32 whole blood exchanges in 12 pz SCD)*
9. *Blood '94 – Kim & Dugan "Eex to riduced iron overload .." (14 vs 7 pz > eex vs simple transfusion)*
10. *Vox Sang '95 – Govoni & Lodi "Red cell exchange transfusion in .." (letter to the editor – case report ped)*
11. *BJH '97 – Janes & al "Automated red cell exchange in SCD" (20 procedure in 15 pz acuti e pre-operatori)*
12. *Blood Rev '97 – Davis & Roberts-Harewood "Blood transfusion in SCD" (good review!)*

Red cell exchange and SCD (II)

13. *NEJM '98 – Adams "Prevention of a first stroke by transfusion in .." (RCT for stroke, 3929 doppler on 1934 children) … Ped Blood Cancer **2011** – Kwiatkowski & Adams "Effect of transfusion therapy on transcranial doppler ultrasonography velocities in children with sickle cell disease (88 children with serial TCD data …)*

14. *AJH '98 – Hilliard "Eex limits iron accumulation in .." (11 SCD ped/ad .. stroke history converted .. simple to eex)*

15. *J Clin Apher '99 – Singer "Eex for chronically transfused children with SCD" (8 pz at risk for stroke & iron..)*

16. *Clin Lab Haem '99 – Lawson "Red cell exchange in SCD" (66 eex on 21 pz prophylactically or therapeutically)*

17. *Therap Apher 2002 – Danielson "The role of red blood cell exchange transfusion in the treatment and prevention of complication of SCD"*

Journal of Clinical Apheresis 3:1–2 (1986)

CHRONIC INFLAMMATORY DEMYELINATING POLYNEUROPATHY

On clinical grounds, autoimmune inflammatory demyelinating polyneuropathy (IDP) is divided into three types [1,2]: acute (single, acute episode; progressive over less than 30 days), relapsing (previous acute episode; recurrence in rapid or slow fashion) and chronic (progressive over more than 30 days; monophasic or stepwise) [3]. The diagnostic criteria for chronic IDP [3] are elevated CSF protein level, slowed nerve conduction velocities, symmetric weakness and evolution over several months.

Pathologically, peripheral nerves show discrete foci of inflammation and edema with segmental demyelination. There is evidence of myelin-binding antibodies in serum from patients with acute IDP (Guillain-Barré syndrome) [4] and deposits of IgM, IgG, and C^4 in chronic/relapsing IDP [5]. Serum from patients with acute IDP is capable of causing demyelination when applied to myelinated axons in vitro [4] and after intraneural injection in vivo [6], and of slowing nerve cor
An experimental model of acute IDP in animals, partially ameliorated by therapeutic plasmaphe autoantibody may be the primary pathogenic fact

In chronic IDP, the goal is to reduce the disability (25% confined to wheelchairs or bed with corticosteroid-refractory relapsing or chr improvement with TP [1,9-18].

In a randomized trial of TP in chronic IDI patients were treated. All patients had corti immunosuppressive agents were not administered received twice-weekly TP of one to 1.5 plasma for three weeks, and the control group (14 pat exchanges. The sham group subsequently receiv of the patients who received TP, the improvemer treatment was greater than the improvement seen Similarly, upon crossing over into the experim (sham) patients achieved a neurologic disabili receiving sham exchange. These results in a d demonstrate a clear benefit of TP in patients TP has not usually produced a sustained impact chronic disease without concomitant cytotoxic

In summary, numerous reports of the benef patients with chronic IDP have now been suppor benefit of TP. In view of the potential sever is recommended in any patient with chronic IDP (or who has more severe involvement) and in an whose disease cannot be adequately controlled fashion (two months of 1 to 1.5 mg/kg of body

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Journal of Clinical Apheresis 3:48–49 (1986)

IDIOPATHIC THROMBOCYTOPENIC PURPURA

Idiopathic thrombocytopenic purpura (ITP) is characterized by acutely or chronically low platelet counts with no apparent exogenous causative factors such as diseases known to be associated with secondary thrombocytopenia. The prevailing view is that ITP is an immune-mediated disorder with detectable platelet autoantibodies in circulating blood, on platelets or both [1]. Considering the autoimmune nature of ITP and the active use of therapeutic plasmapheresis (TP) in a wide variety of immunologic disorders, it is not unreasonable to attempt therapy with TP in patients with ITP. The therapy for ITP has consisted mainly of steroids as the initial modality, splenectomy for those considered unresponsive to steroids and immunosuppressive agents for patients severely affected or for chronic cases in which other treatments have failed. Of those patients who eventually undergo splenectomy about 5% to 10% do not achieve a wholly or partially successful outcome.

There are no published prospective, randomized controlled trials to evaluate the role of TP in ITP. The reported experience with TP for ITP includes data on 30 adult patients [2-7]. Of the 30 patients, 15 reportedly responded to TP with an increased platelet count of variable duration, 13 patients did not show a therapeutic response and two cases were equivocal. Three of the cases considered to show a good response seem questionable. Seven of 15 patients with acute ITP responded to TP plus steroids with complete remission after a variable follow-up period of up to one year. These results are better than those expected with prednisone alone.

A TP of one to 1.5 plasma volumes was used for the majority of the patients treated. A maximum of three TPs and a minimum of one TP was also a common feature. Replacement varied from group to group; it generally consisted of normal serum albumin, fresh frozen plasma or a mixture of both. The investigators who treated the largest number of patients believed that patients who received fresh frozen plasma fared better than those who received albumin. The data, however, were not sufficient to conclude that one replacement fluid was better than the other.

In summary, ITP in adults is an immunologic disorder generally responsive to steroids. In the absence of a controlled therapeutic trial of TP in ITP, no firm statements regarding use of TP can be made. On the basis of anecdotal evidence, TP appears to be of value in decreasing the number of patients with acute ITP who require splenectomy. Therapeutic plasmapheresis may be of particular value in patients with fulminant ITP and whenever splenectomy or immunosuppressive agents are contraindicated. Although chronic ITP is said to be less responsive than the acute form, occasionally patients may respond during bleeding episodes. Results of a controlled trial comparing TP treatment with albumin or fresh frozen plasma vs steroids alone may provide the evidence required to make firmer recommendations.

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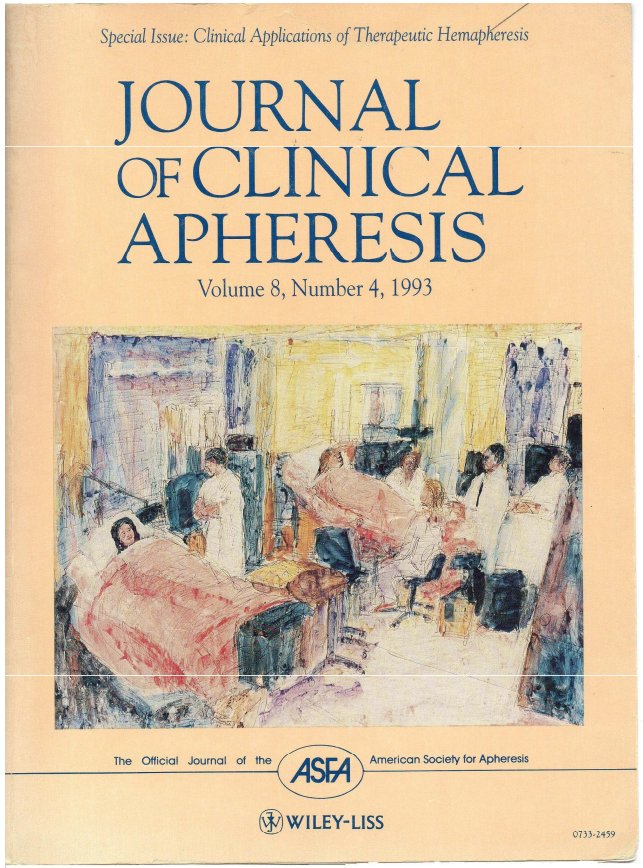

Journal of Clinical Apheresis 15:28–52 (2000)

TABLE I. Indication Categories for Therapeutic Apheresis in Hematological and Oncological Diseases

Hematological diseases	Procedure	Indication category
ABO Incompatible marrow transplant	Red cell removal (marrow)	I
	Plasma exchange (recipient)	II
Erythrocytosis/polycythemia vera	Phlebotomy	I
	Erythrocytapheresis	II
Leukocytosis and thrombocytosis	Cytapheresis	I
Thrombotic thrombocytopenia purpura	Plasma exchange	I
Post-transfusion purpura	Plasma exchange	I
☆ Sickle cell diseases	☆ Red cell exchange	☆ I
Myeloma/paraproteins/hyperviscosity	Plasma exchange	II
Myeloma/acute renal failure	Plasma exchange	II
Coagulation factor inhibitors	Plasma exchange	II
Aplastic anemia/pure red cell aplasia	Plasma exchange	III
Cutaneous T-cell lymphoma	Photopheresis	I
	Leukapheresis	III
Hemolytic disease of the newborn	Plasma exchange	III
Platelet alloimmunization and refractoriness	Plasma exchange	III
	Immunoadsorption	III
Malaria/babesiosis	Red cell exchange	III

Journal of Clinical Apheresis 22:106–175 (2007)

SICKLE CELL DISEASE ☆

Disease Group: Hematologic	**Procedure**	**Category**
Incidence: 289 per 100,000/year African–American population;	Erythrocytapheresis	I (life and organ threatening complications)
89.8 per 100,000/year Hispanics primarily from Caribbean islands	Erythrocytapheresis	II (primary and secondary stroke prophylaxis)
	Erythrocytapheresis	II (prevention of transfusion iron load)

# of reported patients*: >300

	RCT	CT	CS	CR	Strength of evidence
Sickle cell complications	0	1 (22)	28 (360)	34 (38)	Type II-1
Prevention of transfusion iron load	0	0	4 (42)	0	Type II- 2

Evidence level	Evidence quality
Type I	Obtained from at least one properly designed randomized controlled trial
Type II-1	Obtained from a well-designed controlled trials without randomization
Type II-2	Obtained from well-designed cohort or case-control analytic studies, preferably from more than one center or research group
Type II-3	Obtained from multiple time series with or without the intervention. Dramatic results in uncontrolled experiments could also be regarded as this type of evidence
Type III	Opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees

Sickle cell disease ☆	Acute stroke	RBC exchange	I	1C
	Acute chest syndrome	RBC exchange	II	1C
	Prophylaxis for primary or secondary stroke; prevention of transfusional iron overload	RBC exchange	II	1C
	Multi-organ failure	RBC exchange	III	2C

TABLE III. Grading Recommendations Adopted from Guyatt et al. [13]

Recommendation	Description	Methodological quality of supporting evidence	Implications
Grade 1A	Strong recommendation, high-quality evidence	RCTs without important limitations or overwhelming evidence from observational studies	Strong recommendation, can apply to most patients in most circumstances without reservation
Grade 1B	Strong recommendation, moderate quality evidence	RCTs with important limitations (inconsistent results, methodological flaws, indirect, or imprecise) or exceptionally strong evidence from observational studies	Strong recommendation, can apply to most patients in most circumstances without reservation
Grade 1C	Strong recommendation, low-quality or very low-quality evidence	Observational studies or case series	Strong recommendation but may change when higher quality evidence becomes available
Grade 2A	Weak recommendation, high quality evidence	RCTs without important limitations or overwhelming evidence from observational studies	Weak recommendation, best action may differ depending on circumstances or patients' or societal values
Grade 2B	Weak recommendation, moderate-quality evidence	RCTs with important limitations (inconsistent results, methodological flaws, indirect, or imprecise) or exceptionally strong evidence from observational studies	Weak recommendation, best action may differ depending on circumstances or patients' or societal values
Grade 2C	Weak recommendation, low-quality or very low-quality evidence	Observational studies or case series	Very weak recommendations; other alternatives may be equally reasonable

… nel rispetto di tali indicazioni

Presso il ns SIT … abbiamo reclutato **9** pazienti (5F / 4M) della Clinica / Divisione Pediatrica (AOU Arcispedale Sant'Anna) … tutti all'inizio del trattamento avevano un'età inferiore ai 18 anni

- 5 talasso-drepanocitosi
- 4 omozigosi S/S

Il principale motivo (4/9) della richiesta dell'***exchange*** è stato

il sovraccarico marziale da ***simple transfusion***,

in 2 casi … per sindrome toracica acuta,

in 2 casi … per presenza di segni patologici TCD,

in 1 caso … per crisi aplastica e sequestro splenico subentrante

Caratteristiche dell'aferesi

Dal marzo 1995 al luglio 2012 abbiamo eseguito

234 scambi eritrocitari (intervallo 64±22 gg)

con separatori cellulari a flusso continuo Fresenius AS 104/204 e Fresenius Kabi Com.Tec (progr. eritrociti / scambio – circuiti PL1)

Lo scambio veniva impostato secondo le indicazioni fornite dal *software* del separatore …

e quando le caratteristiche emodinamiche del paziente lo consentivano abbiamo impostato lo scambio in 3 fasi …

Scambio in 3 fasi

Prima fase

sola rimozione di rossi patologici, sostituiti con soluzione salina, albumina o *plasmaexpander*

Seconda fase

scambio di pari volume di emazie patologiche con emazie di donatore

Terza fase

somministrazione di emazie provenienti dal separatore più emazie di donatore fino al raggiungimento dell'Hct desiderato

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Terza fase

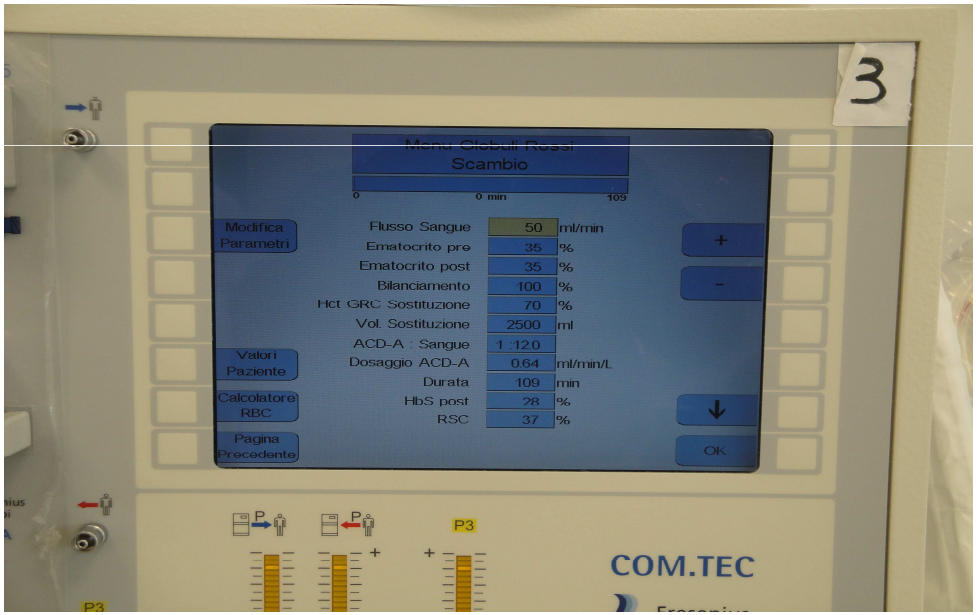
somministrazione di emazie provenienti dal separatore più emazie di donatore fino al raggiungimento dell'Hct desiderato

Volume processato

Ad ogni seduta abbiamo impostato lo scambio per arrivare alla sostituzione del volume eritrocitario teorico, calcolato in base ai dati antropometrici / ematologici ricavati immediatamente prima dell'aferesi

(Hb pre=9,7±1,0 ⇒ Hb post=10,5±1,3)

(HbS pre= 52±12% ⇒ HbS post=23±8%)



Accessi venosi

Ci siamo avvalsi della collaborazione dei colleghi della ***Terapia Intensiva Neonatale*** (per i casi più problematici) e della nostra personale esperienza per il posizionamento delle **agocannule periferiche.**

Con l'esclusione di qualche sporadico caso abbiamo sempre portato a termine lo scambio, senza dover ricorrere al posizionamento di **cateteri venosi centrali**

Emocomponenti utilizzati

Emazie leucodeplete *bedside* prelevate da non più di 10 giorni, compatibilizzate con *crossmatch*, rispettando – oltre all'ABO – il fenotipo Rh (salvo qualche isolata eccezione) e il sistema Kell

All'inizio del ciclo di aferesi abbiamo eseguito fenotipo eritrocitario esteso (nei pazienti non precedentemente trasfusi) … e *screening ac antieritrocitari* …

ripetuto in occasione di ogni aferesi

Reazioni indesiderate

In 1 caso comparsa di *ac* ***anti-C^{w}*** (alla V^{a} seduta)

In 2 casi – prima dell'inizio delle sedute di aferesi – erano presenti: *ac anti-M* in un caso e *anti-Lua* nell'altro caso

Nessuna reazione immediata o ritardata è comparsa nel corso del trattamento (se escludiamo qualche lieve reazione tipo brivido / pomfo) e non abbiamo avuto segnalazioni di ***sickle cell hemolytic transfusion reaction syndrome ...***

o altre temibili reazioni trasfusionali

Follow up …

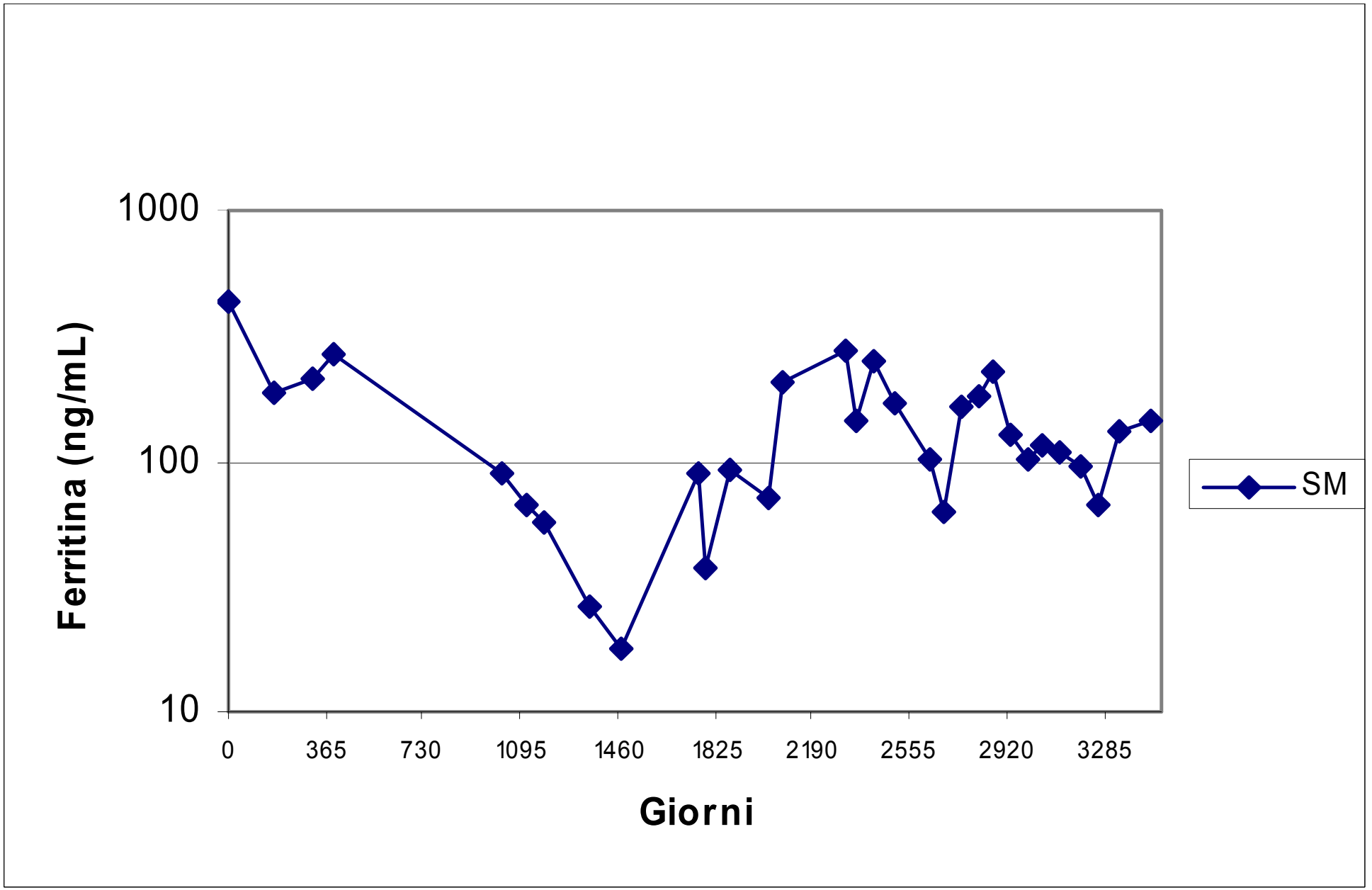
In 2 casi la terapia aferetica è stata abbandonata in quanto è stato effettuato *TMO*

In tutti gli altri casi la terapia aferetica è ancora programmata con l'esclusione di un caso per cambio di residenza

La sintomatologia all'esordio non si è più ripresentata se escludiamo:

- una recidiva di sindrome toracica acuta, subito rientrata con una seduta aferetica estemporanea
- … e un transitorio episodio di algie addominali, controllate con terapia farmacologica

Andamento paradigmatico dei valori di ferritinemia nel corso della programmazione delle sedute di scambio eritrocitario



Compliance

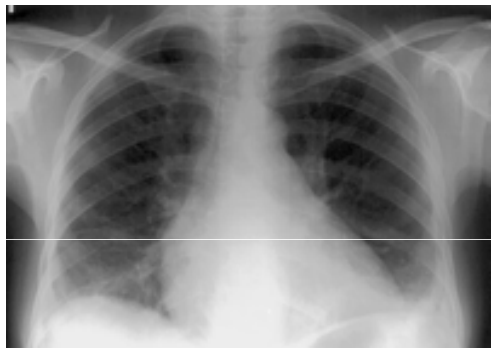
Assolutamente soddisfacente!!

La scomparsa della sintomatologia e l'abbandono della terapia ferro-chelante ha reso l'aferesi la terapia di scelta di questi selezionati casi … e la selezione resta la *conditio sine qua non* per affrontare questi difficili casi clinici, dove la collaborazione del gruppo di professionisti rappresenta il valore aggiunto nella gestione di una sindrome complessa e sempre più ricorrente …

Proposta

La nostra realtà vuole essere motivo di confronto con altre simili, per poter verificare su popolazioni più ampie di pazienti gli effetti dello scambio eritrocitario *vs* la semplice trasfusione rispetto alle complicazioni classiche nelle sindromi falcemiche quali

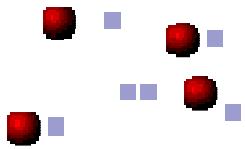
stroke, acute chest syndrome e *iron load*



Ringraziamento

Ai Colleghi del Servizio Trasfusionale, Clinica e Divisione Pediatrica, Terapia Intensiva Neonatale dell'AOU Sant'Anna - Ferrara

Gruppo Collaborativo SCD
Registro Nazionale delle procedure di Eritro-Exchange (EEX). Dati al 2009



EEX eseguite in pazienti pediatrici

Centro Microcitemie - Galliera **Genova** SIMT
Osp “S.Gerardo” **Monza**
SIT Osp. Policlinico **Verona**
SIMT Arcisp “S.Anna” **Ferrara**
SIT Osp. **Bergamo**
SIMT Osp “Pugliesi” **Catanzaro**
SIMT Osp. **Ravenna**
SIMT Az Osp. **Padova**
SIMT Az Osp. **Parma**
SIMT Osp “Gaslini” **Genova**
SIMT Osp. Policlinico **Modena**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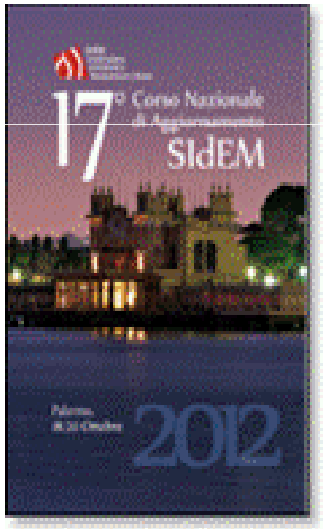
UN TEAM PRONTO A TUTTO



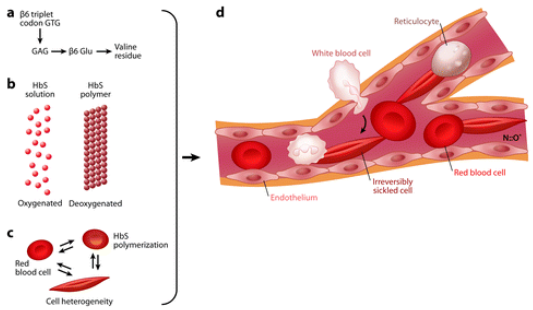
SIdEM

17° Corso Nazionale di Aggiornamento SIdEM

Programma Preliminare

Palermo
18/20 Ottobre
Mondello Palace Hotel

2012



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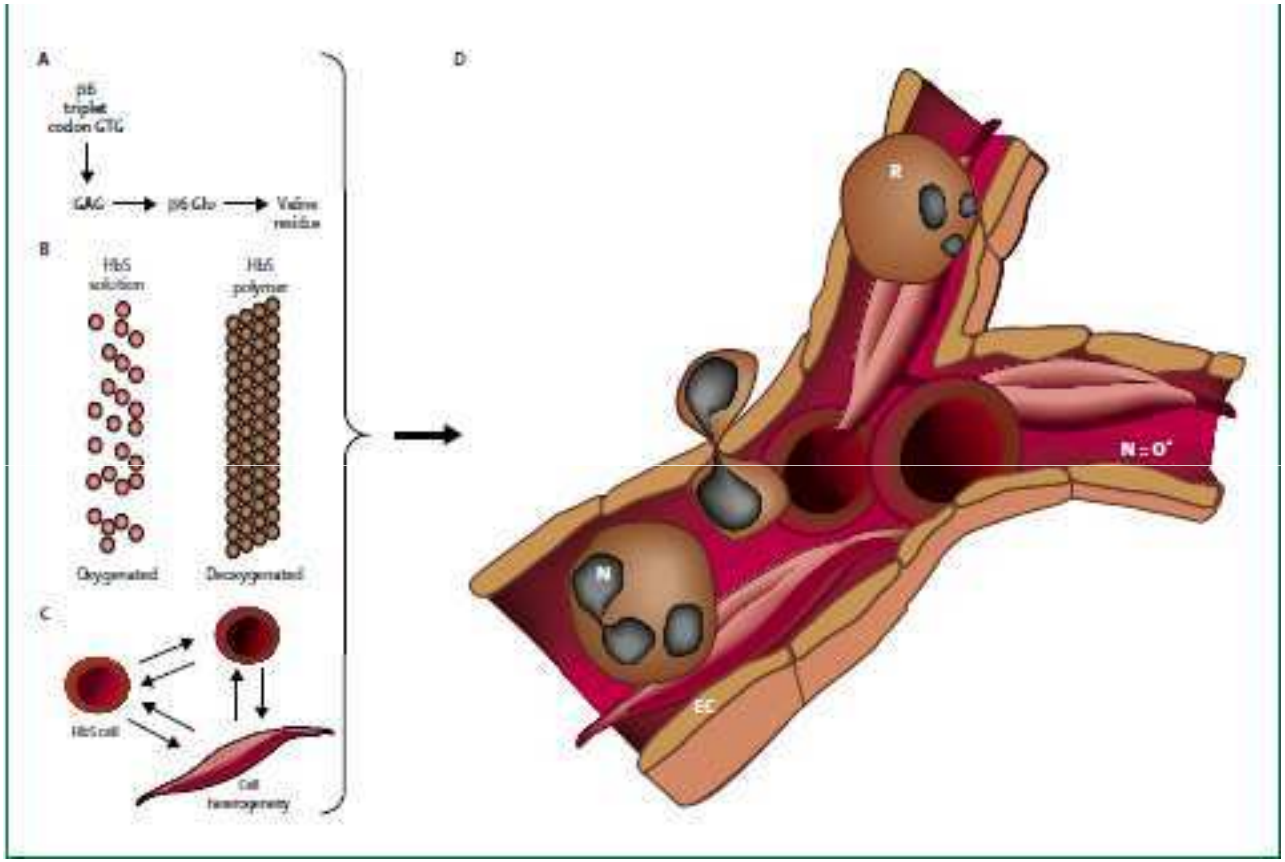

Figure 2: Pathophysiology of vaso-occlusion
(A) Single nucleotide substitution (GTG for GAG). (B) HbS polymerisation. (C) Cell shape changes of HbS-polymer-containing erythrocyte. (D) Cross-section of microvascular bifurcation. EC=endothelium. R=reticulocyte. ISC=irreversibly sickled cell. N=leucocyte. 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.

Panel 2: Basic pathophysiology of vaso-occlusion

1 **Prolongation of the erythrocyte microvascular transit time caused by:**
- Enhanced red cell adhesion to endothelium and heterocellular aggregate formation
- Abnormal cation homeostasis with cell dehydration, dense-cell formation, and irreversibly sickled cell formation
- Abnormal vasomotor tone favouring vasoconstriction (via NO, endothelin-1, and eicosanoid dysregulation)

2 **Reduction in delay time to HbS polymer formation caused by:**
- Red-cell deoxygenation
- Increase in intracellular HbS concentration
- Low concentrations of protective Hb types (eg, HbF, HbA_2)
- Fall in pH

3 **Miscellaneous potential modulators**
- Free-radical release and reperfusion injury
- Coagulation activation with proadhesive thrombin formation

Sickle-cell disease

Marie J Stuart, Ronald L Nagel

www.thelancet.com Vol 364 October 9, 2004

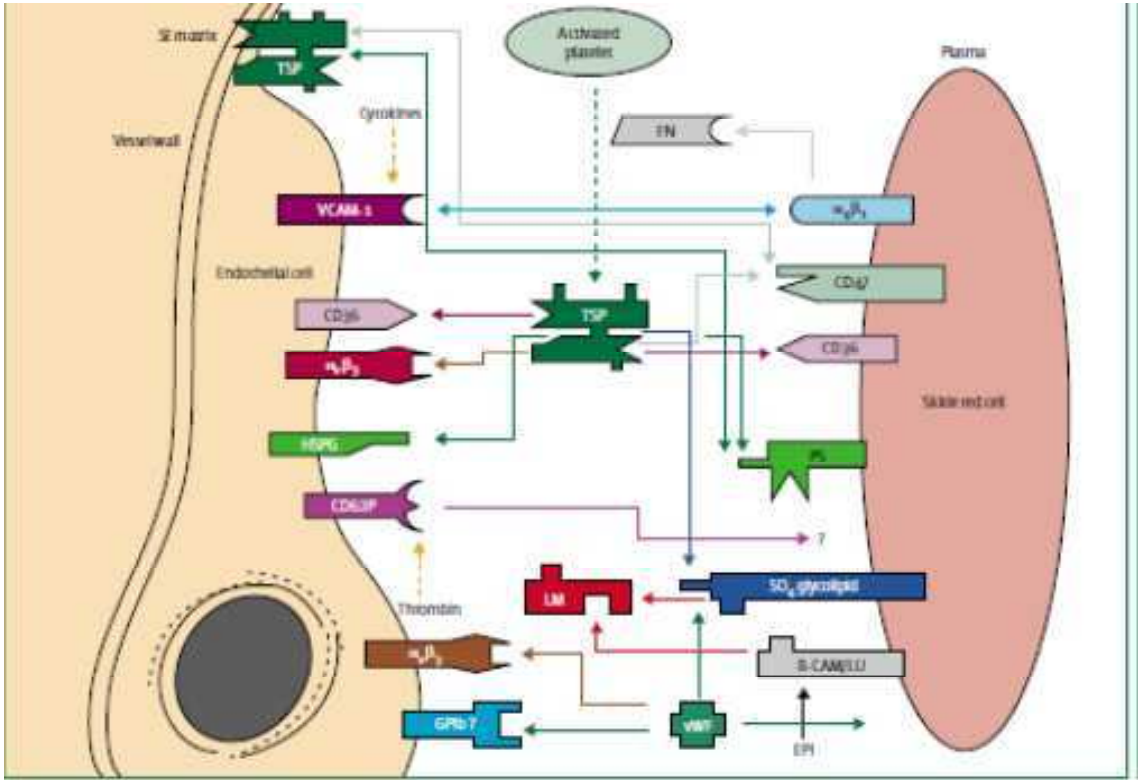

Figure 3: **Adhesive interactions between sickle erythrocytes and the endothelium, subendothelial matrix, and plasma ligands**
SO_4 glycolipid=sulphated glycolipids. PS=phosphatidylserine. TSP=thrombospondin. FN=fibronectin. LM=laminin. VWF=von Willebrand factor. SE matrix=subendothelial matrix. HSPG=heparan sulphate proteoglycans. EPI=epinephrine. CD62P=P-selectin. The red cell receptors associated with adhesion are either present in increased numbers on sickle reticulocytes ($\alpha_4\beta_1$ and CD36), on mature sickle cells, when compared with normal erythrocyte (B-CAM/LU) or exhibit abnormal structure-function activity in sickle red cells (B-CAM/LU and Integrin-associated protein). Phosphatidylserine levels are also raised on sickle when compared with control HbA A red cells. Figure adapted from reference 38, by permission of B N Y Serry.

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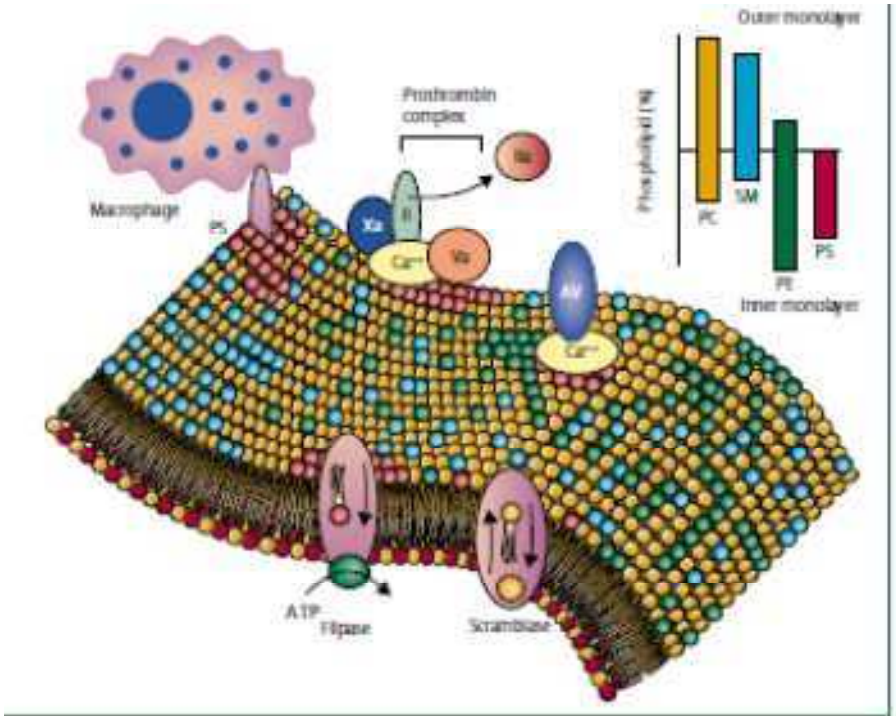

Figure 4: Perturbations in erythrocyte membrane lipids in sickle-cell disease
SM=sphingomyelin. PC=phosphatidylcholine. PE=phosphatidylethanolamine. PS=phosphatidylserine. AV=annexin V. Ca++=calcium ions. Phosphatidylserine exposed on the cell surface forms a docking site for haemostatic factors, such as the prothrombinase complex (factor Xa, Va, and II). Additionally, phosphatidylserine is recognised by macrophages and interacts with proteins such as annexin V, allowing its measurement by flow cytometry. Cell-surface phosphatidylserine also aids erythrocyte adhesion to the vascular endothelium and thrombospondin, an extracellular matrix component. Figure provided by F A Kuypers.

Sickle-cell disease

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QUALE PRODOTTO IMPIEGARE

(Vickinsky, 2001)

Pre-storage leuko-depletion … a Fe nemmeno per idea!! … per ridurre:

- reazioni febbrili
- immunizzazione HLA / refrattarietà piastrinica
- infezioni (in particolare da CMV)
- complicazioni citochine-indotte

- GRC filtrati e lavati solo per reazioni su base allergica
- GRC (o altro emocomponente) irradiato solo per candidati al TMO

(Vickinsky, 2001)

GRC prelevati entro 10 gg (nell'exchange entro 5 gg e nel pediatrico entro 3 gg)

Rispetto dell'assetto antigenico ABO, Rh, Kell, Kpa … e possibilmente Fy, Jk, Le (P, MNS …)

Screening Anticorpale allo start e (a Ferrara) ad ogni seduta trasfusionale

EFFICACIA DEL REGIME TRASFUSIONALE PERIODICO

Valutazione di:

Hb totale / Hct

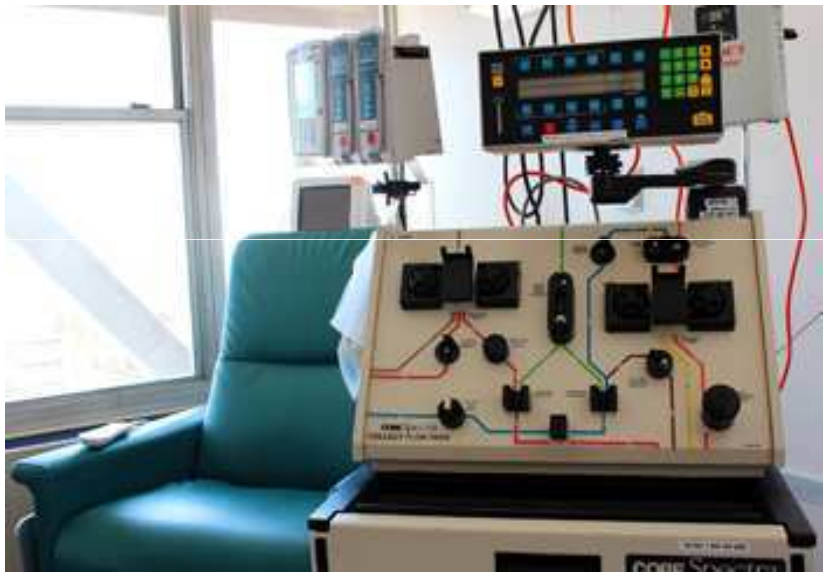
Percentuale HbS

Comparsa di allo* / auto anticorpi

*fattori che ne condizionano la formazione:

- Numero di trasfusioni (la > parte degli ac … anti Rh, Kell si sviluppano entro le prime 15 trasfusioni, mentre più avanti nel tempo si presentano ac contro ag a bassa frequenza … es Cw, Kpa)
- Età alla prima trasfusione (prima si trasfonde e meno si creano allo … per un meccanismo di tolleranza acquisita)
- Differenze antigeniche razziali (mm pz hanno origine africane = 93% ma la > parte dei donatori = 90% sono caucasici)

(Vickinsky, 2001)



Presso il ns SIT … abbiamo reclutato **9** pazienti (5F / 4M) della Clinica / Divisione Pediatrica AOU Arcispedale Sant'Anna … tutti all'inizio del trattamento avevano un'età inferiore ai 18 anni

5 talasso-drepanocitosi
4 omozigosi S/S

Il principale motivo (4/9) della richiesta dell'aferesi … sovraccarico marziale da regime trasfusionale periodico

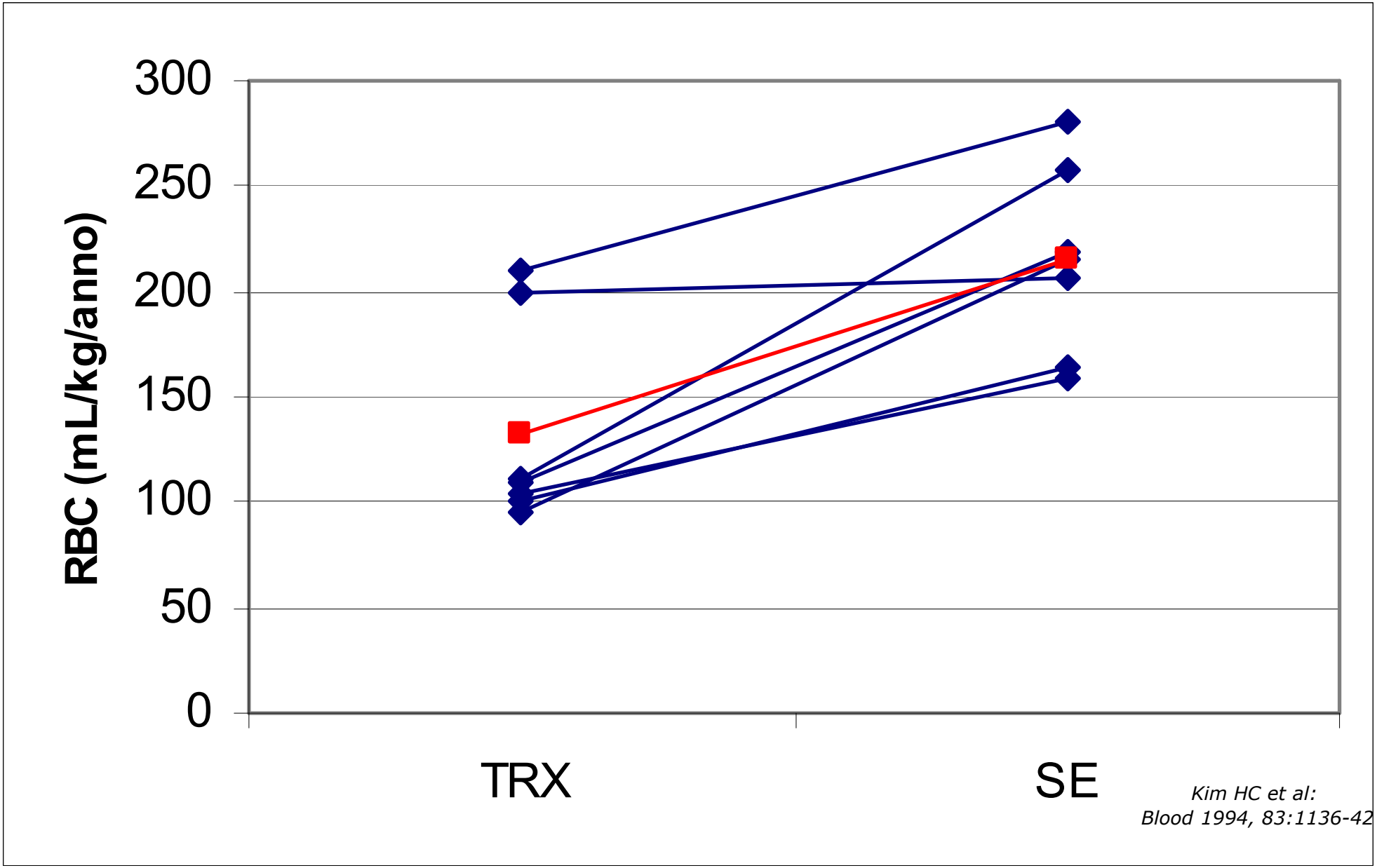
in 2 casi per sindrome toracica acuta

in 2 casi per presenza di segni patologici TCD

in 1 caso per crisi aplastica e sequestro splenico subentrante

LO SCAMBIO ERITROCITARIO NELLA DREPANOCITOSI

CONSUMO ANNUALE DI GLOBULI ROSSI



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