



XLIX
CONGRESSO
NAZIONALE
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CRISI EMOLITICHE E REAZIONI TRASFUSIONALI NELLA DREPANOCITOSI

Daniela Cuzzubbo

SOC Oncologia, Ematologia, TCSE

AOU Meyer IRCCS

Bologna, 2 ottobre 2024



La sottoscritta Daniela Cuzzubbo

ai sensi dell'art. 3.3 sul Conflitto di Interessi, pag. 17 del Reg. Applicativo dell'Accordo Stato-Regione del 5 novembre 2009,

dichiara

- ☐ *che negli ultimi due anni NON ha avuto rapporti diretti di finanziamento con soggetti portatori di interessi commerciali in campo sanitario*
- ☒ **X** *che negli ultimi due anni ha avuto rapporti diretti di finanziamento con i seguenti soggetti portatori di interessi commerciali in campo sanitario:*
 - Novartis (Advisory Board; Progetto Sickle Next)
 - Novo Nordisk (Advisory Board)
 - Vertex (Advisory Board)



TERAPIA TRASFUSIONALE NELLA SCD

- ✓ ruolo importante nel trattamento e nella prevenzione delle complicanze acute e croniche dei pazienti affetti da Sickle Cell Disease (SCD)
 - ✓ Specifiche raccomandazioni nazionali e internazionali
 - ✓ gli eventi avversi correlati alla terapia trasfusionale in questi pazienti sono frequenti e potenzialmente life-threatening:
- Alloimmunizzazione
 - Delayed Hemolytic Transfusion Reaction (DHTR)
 - sovraccarico di ferro





Tabella III. Indicazioni alla terapia trasfusionale acuta non EEX

Indicazioni riconosciute in letteratura

- ◆ **Stroke**, anche sospetto (Rees et al, 2003; Amrolia et al, 2006; Swerdlow et al, 2006, Gee, Guidelines) (vedi cap.8) **C**
- ◆ **ACS**. La terapia raccomandata in acuto è l'EEX, soprattutto per i casi con importante compromissione respiratoria. (Steinberg, 1999; Rees et al, 2003; Amrolia et al, 2006; Swerdlow et al, 2006, Gee, Guidelines) (vedi cap.9) **C**
- ◆ **Preparazione a intervento di chirurgia "maggiore" o oftalmica**. E' la terapia di elezione in assenza di anemia (Swerdlow et al, 2006, Gee, Guidelines). Se Hb < 9 g/dl, l'efficacia della trasfusione semplice di GRC finalizzata a portare Hb a 10 g/dl è analoga a quella della terapia manuale con PME (Steinberg, 1999; Amrolia et al, 2006; Chou et al, 2016) (vedi cap.20) **C**
- ◆ **Danno multiorgano acuto** (multiorgan failure) (Rees et al, 2003; Amrolia et al, 2006; Swerdlow et al, 2006)
- ◆ **Esami con mezzi di contrasto e.v. ad alte dosi** (Gee, Guidelines) es. TAC se HbS > 50% (vedi cap.20)

Indicazioni controverse

- ◆ **Grave crisi dolorosa** non responsiva a terapia reidratante e antidolorifica massimale (dopo 24 ore di osservazione) (Steinberg, 1999; Josephson et al, 2007; ,5, Amrolia et al, 2006; Chou et al, 2016) (vedi cap.6)
- ◆ **Priapismo**, da considerare se non detumescenza dopo 6-12 ore, dopo tentativo di irrigazione dei corpi cavernosi con adrenalina (Steinberg, 1999; Amrolia et al, 2006; Josephson et al, 2007; Chou et al, 2016) (vedi cap. 12)

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Tabella V. Indicazioni alla terapia trasfusionale **cronica**

Indicazioni riconosciute in letteratura

- ◆ **Prevenzione primaria di uno stroke** in bambini con TCD patologico (Adams et al, 1998) (*vedi cap. 8*) **A**
- ◆ **Prevenzione secondaria di stroke** **A**
- ◆ **Scompenso cardiaco cronico**, anche se non ci sono studi clinici che ne dimostrino l'efficacia nei bambini **C**

Indicazioni controverse

- ◆ **Insufficienza renale cronica** anche se non ci sono studi clinici che ne dimostrino l'efficacia nei bambini
- ◆ **Frequenti crisi dolorose**: la controversia è relativa al rapporto costo/beneficio delle trasfusioni, non rispetto all'efficacia che è riconosciuta, anche se non ci sono studi clinici che ne dimostrino l'efficacia nei bambini. Dall'introduzione dell'HU in età pediatrica, il regime trasfusionale cronico con trasfusioni periodiche per prevenire crisi dolorose appare una **seconda scelta** **C**
- ◆ **Acute chest syndrome ricorrente** in caso di mancata efficacia o controindicazioni alla terapia con HU, anche se non ci sono studi clinici che ne dimostrino l'efficacia nei bambini. (*vedi cap. 9*)
- ◆ **Ulcere malleolari** (*vedi cap. 17*)
- ◆ **Sequestro splenico ricorrente**, in bambini molto piccoli con controindicazione alla splenectomia, come terapia di seconda linea (*vedi cap. 11*)
- ◆ **Priapismo ricorrente** (*vedi cap. 12*)
- ◆ **Ipertensione polmonare** (Klings et al, 2014; Detterich et al, 2015)

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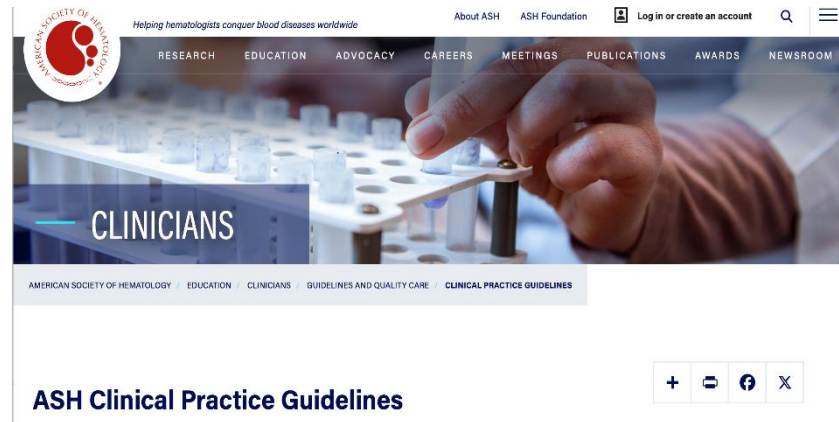
Indicazioni inappropriate o controindicazioni

- ◆ Anemia cronica stabile in paziente asintomatico
 - ◆ Crisi dolorose acute non complicate
 - ◆ Necrosi asettica della testa del femore della testa dell'omero, eccetto nei casi in cui si renda necessario un intervento chirurgico (vedi cap.10)
- ◆ Gravidanze singole non complicate (*vedi cap.19*)

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- L'incidenza di alloimmunizzazione è molto più alta nei pazienti SCD rispetto ad altri soggetti che ricevono emotrasfusione, malgrado l'utilizzo di protocolli di matching antigenico esteso
- 30% alloanticorpi negativi
- Spesso la DHTR è confusa con una VOC perché la presentazione clinica è simile e le VOC sono più frequenti
- Da considerare inoltre che i pazienti che hanno anche deficit di G6PD hanno crisi emolitiche più severe e sono quindi più a rischio di complicazioni trasfusionali, in particolare DHTR





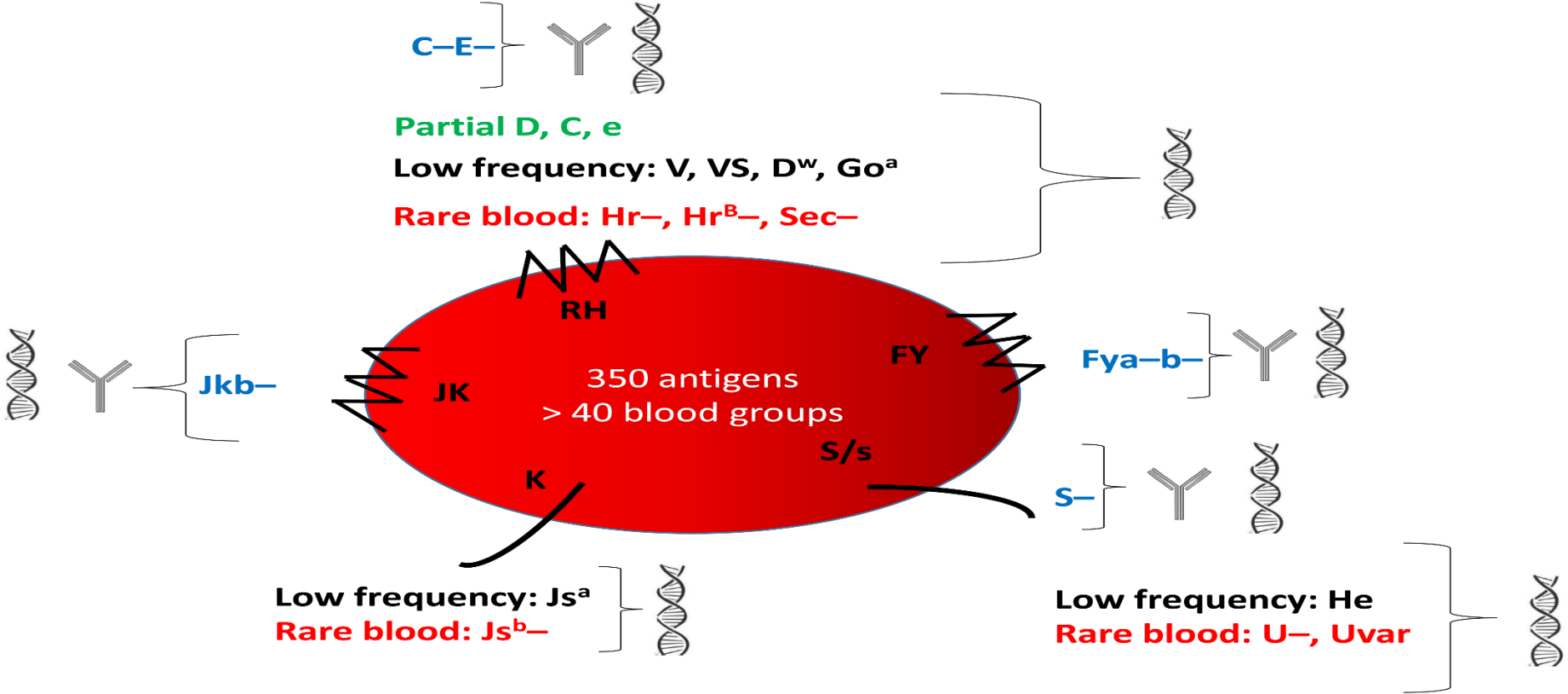
Why are patients with sickle cell disease at high risk of red blood cell alloimmunization?

- mismatch in RBC antigens expressed in the donor pool (primarily Northern European descent) and patients with SCD (mainly of African descent)
- remarkable *RH* allelic diversity in this population, with mismatch between serological Rh phenotype and *RHD* or *RHCE* genotype due to variant *RH* alleles in a large proportion of the individuals
- clinical context of RBC transfusion in SCD may also contribute to the higher rate of alloimmunization (inflammatory clinical state, occasional transfusion in acute situations)

S.L.Thein et al. Haematologica 2020



Aspetti unici e peculiari della SCD che espongono tali pazienti a rischio elevato di alloimmunizzazione in caso di terapia trasfusionale, malgrado l'utilizzo di protocolli di matching antigenico esteso



Characteristics of the main blood groups in SCD patients and their identification. This figure shows the 5 blood group systems most frequently involved in alloimmunization. The following are shown for each blood group: *blue*, the common antigens rarely expressed; *green*, the partial antigens; *black*, the low-frequency antigens most frequently expressed; *red*, the high-frequency antigens most frequently absent (rare blood groups). They can be identified by serology Y and genotyping DNA or genotyping alone.



Delayed Hemolytic Transfusion Reaction

L'incidenza di DHTR severa è del 11.5-16% in caso di matching antigenico solo per ABO e RhD e 4-7% in caso di match per Rh (D, C, E, c, e) and K

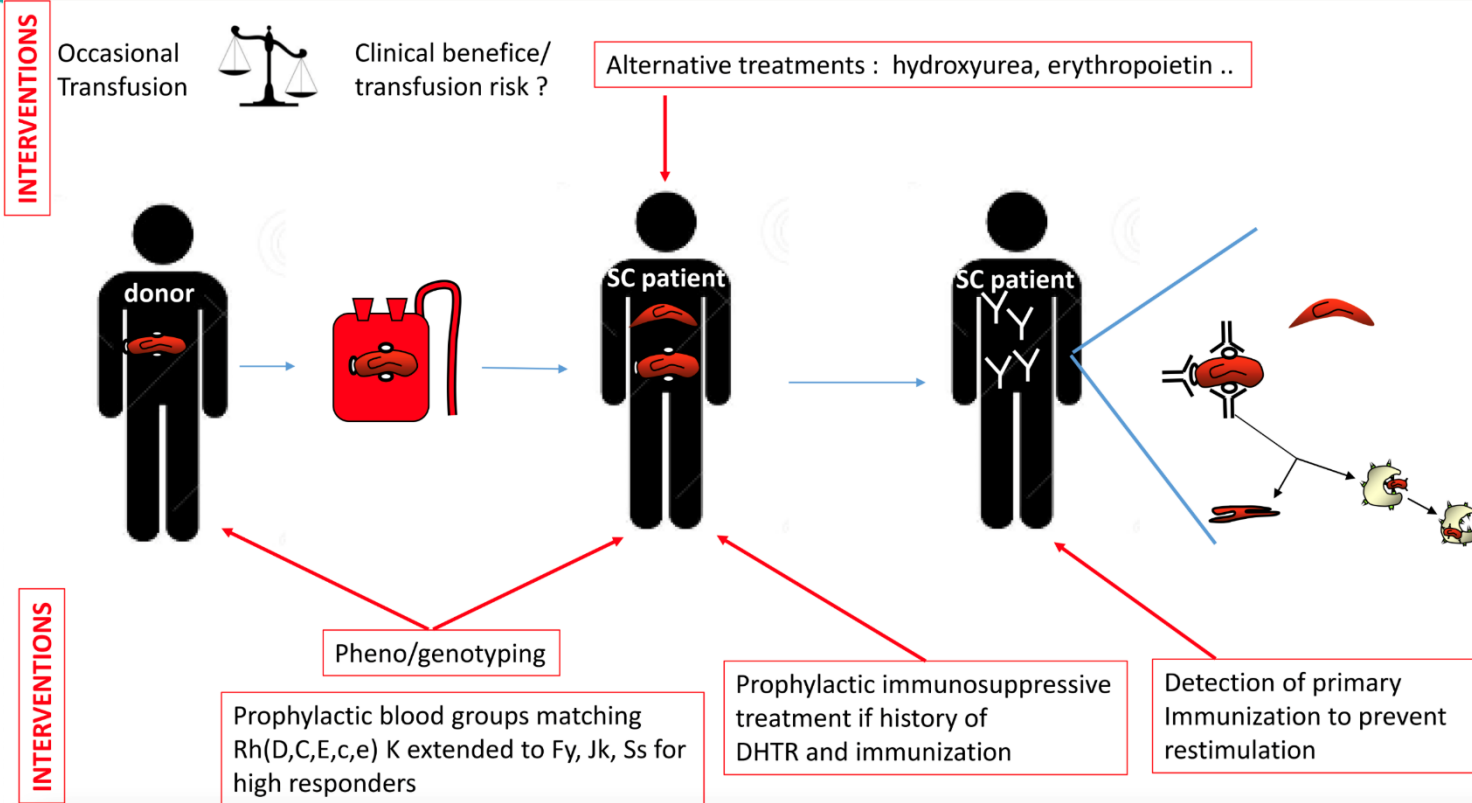
F. Pirenne and K. Yazdanbakhsh Blood. 2018 Jun 21; 131(25): 2773–2781

- La progressione da forma mild a severa, con evoluzione in MOF e possibile esito fatale, è imprevedibile, quindi **prevenzione, diagnosi e trattamento tempestivo** (compreso l'astenersi da ulteriori trasfusioni malgrado anemia severa) diventano cruciali

How to avoid the problem of erythrocyte alloimmunization in sickle cell disease

France Pirenne ✉, Aline Floch, Anoosha Habibi

Hematology Am Soc Hematol Educ Program (2021) 2021 (1): 689–695.



> Hematology Am Soc Hematol Educ Program. 2023 Dec 8;2023(1):653-659.
doi: 10.1182/hematology.2023000499.

Alloimmunization and hyperhemolysis in sickle cell disease

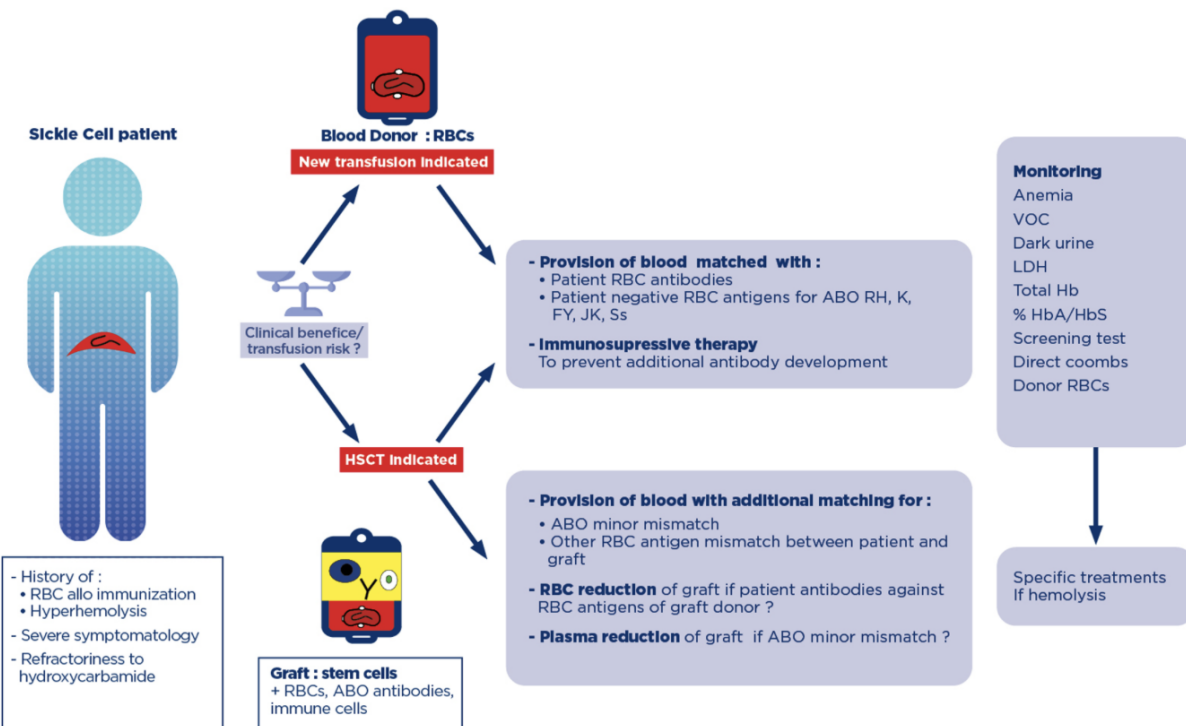
France Pirenne ^{1,2}, Corinne Pondarré ^{1,3}

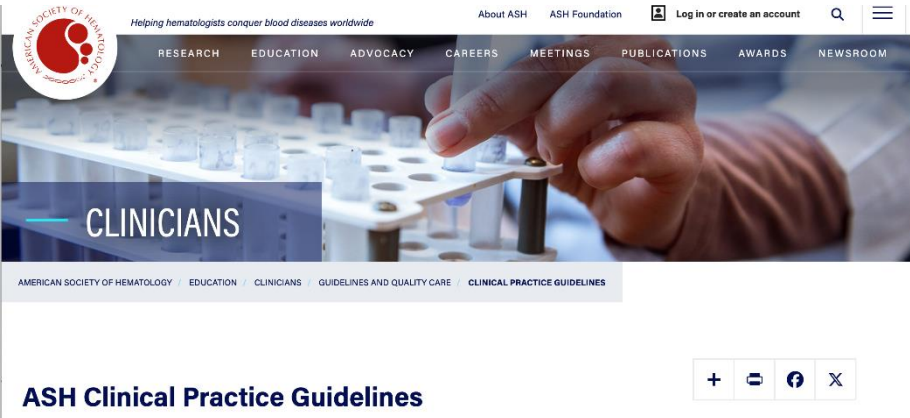
Affiliations + expand

PMID: 38066873 PMCID: PMC10727070 (available on 2024-12-08)

DOI: 10.1182/hematology.2023000499

- ✓ protocols combining the prevention of exposure to immunogenic antigens with immunosuppressive treatments must be implemented
- ✓ Close monitoring during post transfusion follow-up
- ✓ To diagnose hyperhemolysis as soon as possible
- ✓ To avoid retransfusion
- ✓ To administer specific treatments
- ✓ in patients with severe disease, HSCT may be indicated





- extent of red cell antigen typing and matching
- transfusion indications and mode of administration (simple vs red cell exchange [RCE] transfusion)
- prevention and management of alloimmunization and delayed hemolytic transfusion reactions (DHTRs)
- screening for iron overload.

American Society of Hematology 2020 guidelines for sickle cell disease: transfusion support

Stella T. Chou,¹ Mouaz Alsawas,² Ross M. Fasano,³ Joshua J. Field,⁴ Jeanne E. Hendrickson,^{5,6} Jo Howard,^{7,8} Michelle Kameka,⁹ Janet L. Kwiatkowski,¹ France Pirenne,¹⁰ Patricia A. Shi,¹¹ Sean R. Stowell,³ Swee Lay Thein,¹² Connie M. Westhoff,¹³ Trisha E. Wong,¹⁴ and Elie A. Akl¹⁵

Recommendation 1

The ASH guideline panel *suggests* obtaining an extended red cell antigen profile by genotype or serology over only ABO/RhD typing for all patients with SCD (all genotypes) at the earliest opportunity (optimally before first transfusion) (conditional recommendation based on very low certainty in the evidence about effects ⊕○○○).

Remarks:

- An extended red cell antigen profile includes C/c, E/e, K, Jk^a/Jk^b, Fy^a/Fy^b, M/N, S/s at a minimum.
- Red cell antigen profiles should be made available across hospital systems.
- A serologic phenotype may be inaccurate if the patient has been transfused in the past 3 months.
- Genotyping is preferred over serologic phenotyping, as it provides additional antigen information and provides increased accuracy for, among other things, C antigen determination and Fy^b antigen matching.

Recommendation 2

The ASH guideline panel *recommends* prophylactic red cell antigen matching for Rh (C, E or C/c, E/e) and K antigens over only ABO/RhD matching for patients with SCD (all genotypes) receiving transfusions (strong recommendation based on moderate certainty in the evidence about effects ⊕⊕⊕○).

Remarks:

- The extended red cell antigen profile may be determined by genotype or serology.
- Extended red cell antigen matching (Jk^a/Jk^b, Fy^a/Fy^b, S/s) may provide further protection from alloimmunization.
- Patients who have a GATA mutation in the *ACKR1* gene, which encodes Fy antigens, are not at risk for anti-Fy^b and do not require Fy^b-negative red cells.
- Patients identified by genotype with the hybrid *RHD*DIIa-CE (4-7)-D* or *RHCE*CeRN* alleles, which encode partial C antigen, may not require C antigen matching.

Recommendation 4

The ASH guideline panel *suggests* immunosuppressive therapy (IVIg, steroids, rituximab, and/or eculizumab) over no immunosuppressive therapy in patients with SCD (all genotypes) with a delayed hemolytic transfusion reaction and ongoing hyperhemolysis (conditional recommendation based on very low certainty in the evidence about effects ⊕○○○).

Recommendation 3

The ASH guideline panel *suggests* immunosuppressive therapy (IVIg, steroids, and/or rituximab) over no immunosuppressive therapy in patients with SCD (all genotypes) with an acute need for transfusion and at high risk for acute hemolytic transfusion reaction or with a history of multiple or life-threatening delayed hemolytic transfusion reactions (conditional recommendation based on very low certainty in the evidence about effects ⊕○○○).

Remarks:

- These are rare clinical situations in which patients are experiencing life-threatening anemia that require immediate red cell transfusion and either compatible blood cannot be found (ie, patients with alloantibodies for whom antigen-negative blood is unavailable) and/or the patients have a history of repeated episodes of severe hemolytic transfusion reactions with or without an antibody specificity identified (even when compatible blood is available).
- The hematologist and transfusion medicine specialist should have ongoing discussions to weigh the potential benefits and harms associated with transfusion vs the effect of ongoing life-threatening anemia and to consider the respective mechanisms of action for choice of therapy (IVIg, steroids, or rituximab).
- A shared decision-making process is critical.

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Recommendation 5

The ASH guideline panel *suggests* using automated RCE over simple transfusion or manual RCE in patients with SCD (all genotypes) receiving chronic transfusions (conditional recommendation based on very low certainty in the evidence about effects ⊕○○○).

Remarks:

- The decision-making process should consider the clinical indication, baseline and target total hemoglobin and HbS%, patient age, patient preferences (particularly if central venous access is needed), iron overload status and iron chelation compliance, feasibility, and availability of compatible red cells.

Compared with simple transfusion, automated RCE was associated with increased red cell unit requirement,^{88,89} but was not associated with increased alloimmunization or adverse transfusion reactions.^{85-88,90,93} Automated RCE was associated with lower levels of iron overload, with a mean difference between the 2 methods of ferritin change ranging from −106 (95% CI, −153 to −59) to −21.7 (95% CI, −27.8 to −15.6) ng/mL per month.^{87,91} The mean difference in liver iron stores was −7.0 (95% CI, −9.2 to −4.8) mg/g [dw] per year.^{87,99} Only 1 study assessed

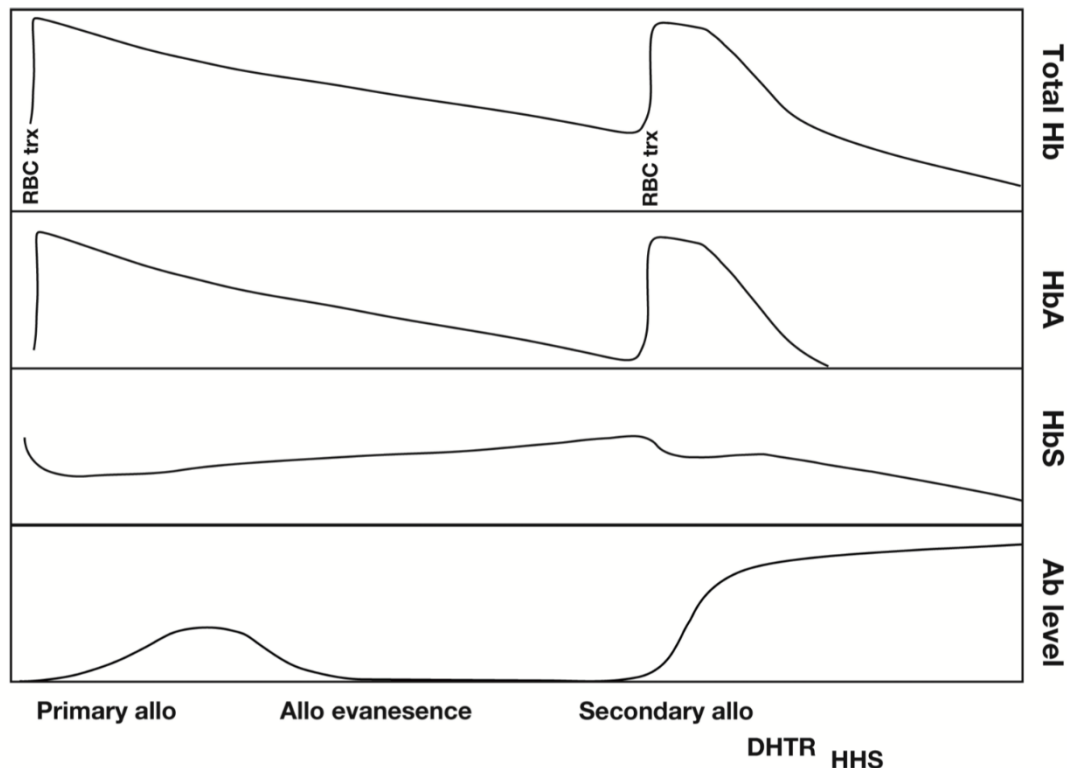
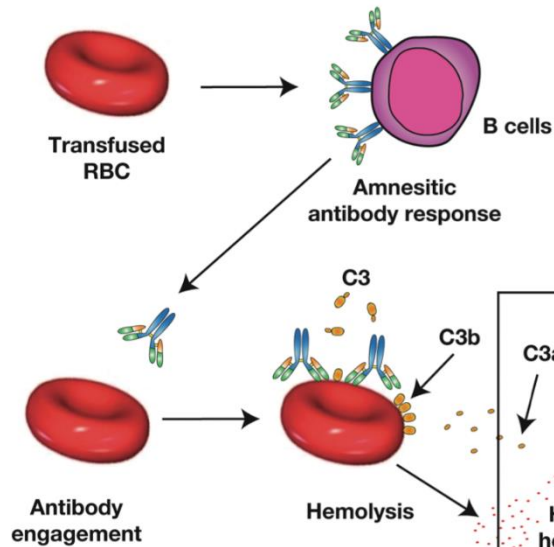
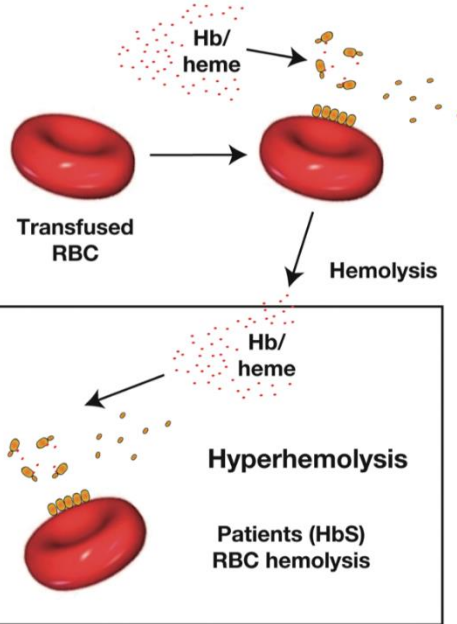


Figure 1. Delayed-type hemolytic transfusion reactions. (A) Exposure to a red blood cell (RBC) alloantigen through transfusion or pregnancy can result in the development of alloantibodies (allo) that quickly evanesce over time, possibly preventing their detection prior to a subsequent transfusion. Re-exposure to RBC expressing the same alloantigen can induce an amnestic alloantibody response, which can cause accelerated clearance of the transfused RBC, resulting in hemolysis and a delayed-type transfusion reaction (DHTR). Alloantibody-induced clearance of transfused RBC can occasionally result in hyperhemolysis, otherwise known as hyperhemolytic syndrome (HHS), which is signified by the accelerated clearance of the patient's own RBC and which can be particularly fatal. (B). Alloantibodies that

Alloantibody positive delayed-type transfusion reaction



Alloantibody negative delayed-type transfusion reaction



delayed-type transfusion reaction (DHTR). Alloantibody-induced clearance of transfused RBC can occasionally result in hyperhemolysis, otherwise known as hyperhemolytic syndrome (HHS), which is signified by the accelerated clearance of the patient's own RBC and which can be particularly fatal. (B). Alloantibodies that develop in response to exposure to alloantigens can lead to direct clearance of RBC through a variety of antibody effector mechanisms, including complement activation. Sometimes patients will experience a DHTR in the absence of a detectable alloantibody; an alloantibody may be present and simply be below the detection threshold of clinical assays or an alloantibody may be absent entirely, with the DHTR possibly reflecting heme-mediated complement activation and RBC hemolysis. Regardless of the mode of hemolysis experienced by transfused RBC in the setting of a DHTR, heme released may activate complement, thereby potentially contributing to the development of hyperhemolysis. Trx: transfusion; Hb: hemoglobin.

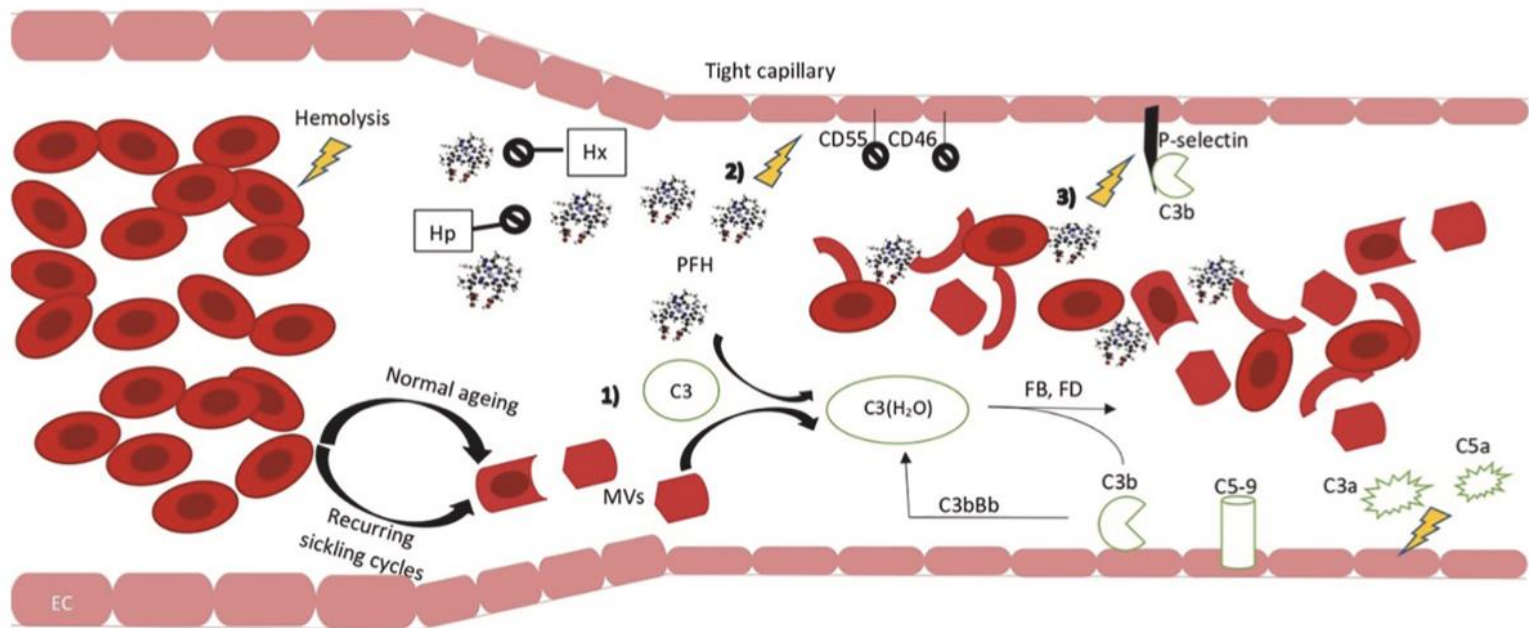


Fig. 3. Mechanisms of complement activation in sickle cell disease (SCD) due to plasma free heme (PFH) and heme-laden microvesicles (MV). SCD is characterized by chronic intravascular hemolysis. During hemolysis, plasma free heme is released and normally, heme scavenging mechanisms, such as haptoglobin (Hp) and hemopexin (Hx), suffice to remove the excess amount of heme load from circulation. However, this system gets saturated due to excess hemolysis in SCD. Therefore, extracellular heme accumulates with detrimental effects. Furthermore, heme-laden MVs, stemming from normal ageing or repeated sickling cycles, participate in heme-derived inflammation process. Heme mediates complement activation through different ways: 1) PFH and MVs promote activation of alternative pathway (AP) by directly inducing hydrolysis of C3; C3b derivative binds to endothelial cells (ECs) initiating a positive feedback cycle via formation of AP C3 convertases and generation of additional C3b and C5b-9; C3a and C5a provoke proinflammatory events. 2) PFH downregulates the expression of complement regulatory molecules such as CD55 and CD59 on ECs. 3) PFH augments expression of P-selectin on ECs, which in turn activates complement.



TONY , 24 aa, F

- SS in tp con HU
- Pregressa tp con crizanlizumab per VOC ricorrenti malgrado HU
- 1 episodio di ACS in anamnesi
- Hb di base intorno a 7,5-8 g/dl (sotto HU, dubbia osservanza)



- EEX fine dicembre 2023 per secondo episodio ACS
- Seconda metà gennaio 2024 accesso al PS di altro nosocomio per sospetto episodio infettivo (febbre, dolori) associato ad acutizzazione anemia (Hb 6 g/dl), trasfusa

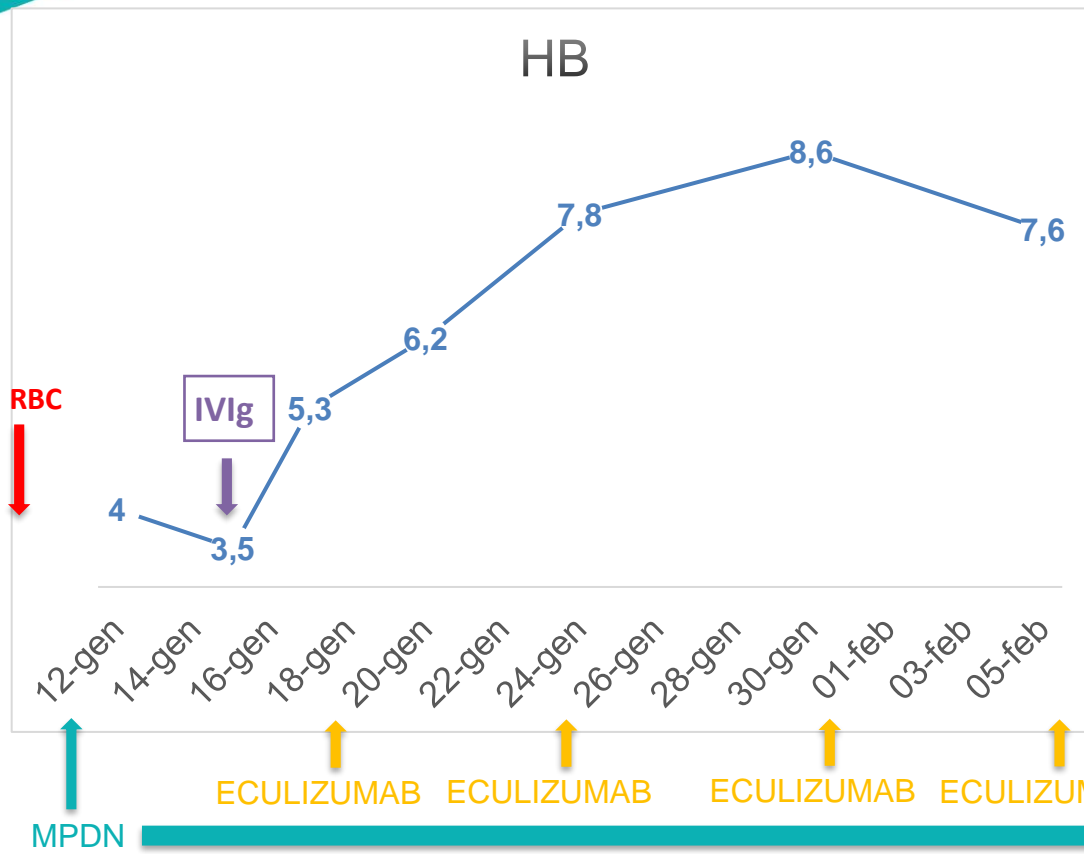


peggioramento clinico e dell'anemia (Hb 4 g/dl 24h post-ts)



Trasferita c/o il nostro Centro





*Successiva stabilizzazione
dell'Hb in linea con
baseline*



Take Home message (1)

- ❖ La DHTR è un'evenienza severa, può condurre a MOF con esito fatale
- ❖ Storia trasfusionale del paziente (numero trasfusioni occasionali e pregresso episodio di DHTR)
- ❖ I sintomi della DHTR mimano quelli delle VOC (febbre, dolori, malessere), con possibile ritardo nella diagnosi
- ❖ In circa 1/3 dei casi gli alloanticorpi non sono rilevabili
- ❖ Bassi livelli di HbA post-trasfusione e calo Hb $\geq 25\%$ rispetto al valore pre-trasfusione



PRINCIPALI TRATTAMENTI

- ❑ **IVIg**: attenzione a iperviscosità, ipercoagulabilità, nefrotossicità, e anche emolisi nei pazienti di gruppo non-O
- ❑ **Steroidi alte dosi**: attenzione rischio VOC
- ❑ **Combinazione IVIg e steroidi** alte dosi: azione sinergica sulla soppressione della risposta macrofagica
- ❑ **Eculizumab**:
 - Rapida risposta con diminuzione dei segni di iperemolisi dopo la prima dose e incremento con stabilizzazione dei valori di emoglobina dopo 2 dosi
 - Vaccinazioni germi capsulati e profilassi antibiotica
- ❑ **Rituximab** : anti-B cell
- ❑ **EPO** : utile nei pazienti con reticolocitopenia o in assenza di reticolocitosi
- ❑ **Ulteriori trasfusioni**: a volte inevitabili in caso di anemia grave, eventualmente previo Rituximab, anche se alloanticorpi non rilevati, favorendo matching antigenico sul genotipo se possibile



Take home messages (2)

- ❖ Attenersi alle indicazioni per la terapia trasfusionale nei pazienti SCD
- ❖ Strategie per ridurre al minimo il rischio di alloimmunizzazione (matching antigenico, fenotipo esteso/genotipo Rh, Kell, Fy, e MNS blood groups)
- ❖ Banca gruppo raro
- ❖ Profilassi secondaria (immunosoppressione) in caso di alloimmunizzazione/pregressi episodi di iperemolisi e soprattutto DHTR



GdL Patologie del Globulo Rosso



LIX CONGRESSO NAZIONALE AIEOP

BOLOGNA
30 settembre
2 ottobre

2024



GRAZIE!

Oncologia, Ematologia e TCSE
AOU Meyer IRCCS

