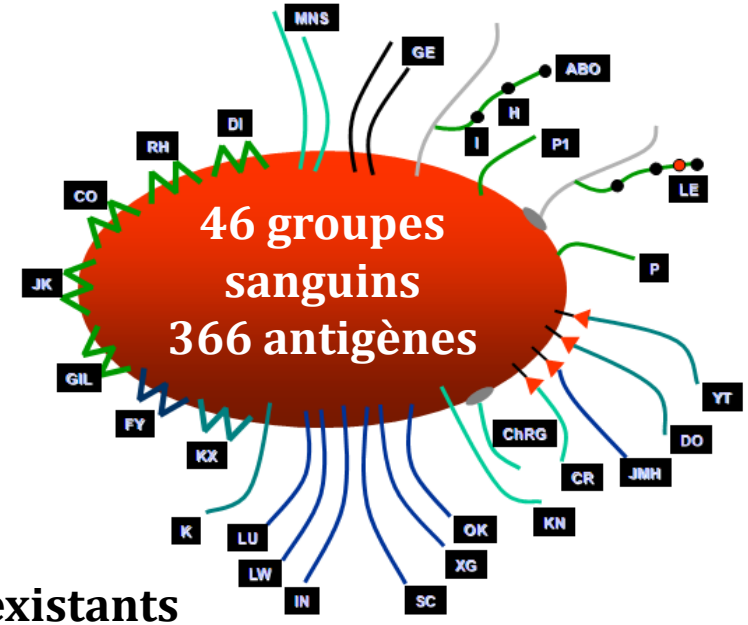
HÉMOLYSE POST-TRANSFUSIONNELLE RETARDÉE AU COURS DE LA DRÉPANOCYTOSE

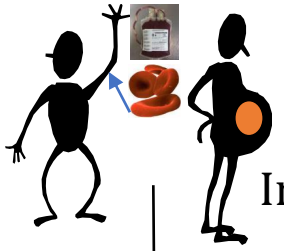
Pr France PIRENNE

Etablissement Français du Sang
Université Paris Est Créteil
INSERM U955 « Transfusion et maladies du globule rouge »

Rappel hémolyse post-transfusionnelle (HPTR)



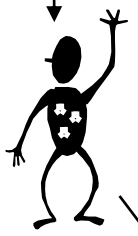
Autres groupes RH, KEL, FY, JK ..
Anticorps d'allo immunisation : exposition active



Immunisation primaire
Délai > 1 mois

ABO
Anticorps préexistants

persistance

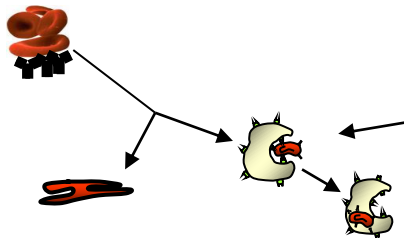


évanescence

RAI pré transfusionnelle négative
Pas de prise en compte
de l'immunisation primaire

Prévention du conflit
Par la RAI pré transfusionnelle

Restimulation
Délai 2-5 jours



Accident immédiat
Hémolyse intra <u>vasculaire</u> +++
Signes clinico-biologiques majeurs

Accident Retardé
Hémolyse intra <u>tissulaire</u> +++
Signes clinico-biologiques modérés

The sickle cell hemolytic transfusion reaction syndrome

L.D. Petz, L. Calhoun, I.A. Shulman, C. Johnson, and R.M. Herron

TRANSFUSION 1997;37:382–392.

TABLE 1. Components of the sickle cell HTR syndrome

1. Manifestations of an acute or delayed HTR.
2. Symptoms suggestive of a sickle cell pain crisis that develop or are intensified during the HTR.
3. Marked reticulocytopenia (a significant decrease from the patient's usual absolute reticulocyte level).
4. Development of a more severe anemia after transfusion than was present before. A rapid drop in Hb and Hct can occur when hemolysis of donor RBCs is accompanied by suppressed erythropoiesis, as sickle cell RBCs have an intrinsically short survival. In some patients, it is possible that hyperhemolysis of autologous RBCs (bystander immune hemolysis) may play a role in the decrease in Hb and Hct, although more definitive documentation of this phenomenon is necessary.
5. Subsequent transfusions may further exacerbate the anemia and it may become life-threatening or even fatal.[7,8]
6. Patients often have multiple RBC alloantibodies and may also have autoantibodies,[9-12] which makes it difficult or impossible to find compatible units of RBCs. However, in other patients, no alloantibodies are demonstrable,[13] or patients may have alloantibodies for which antigen-negative RBCs are readily obtainable.[14,15]
7. Serologic studies may not provide an explanation for the HTR.[8,13-15] Even RBCs that are phenotypically matched with multiple patient antigens may be hemolyzed.[14]
8. Recovery manifested by reticulocytosis and gradual improvement in Hb may occur only after the withholding of further transfusion. The administration of corticosteroids appears to be an important therapeutic measure in some patients.[10,11,13,15]
9. After a recovery period, similar symptoms may recur following subsequent transfusions, although other patients tolerate further transfusions without incident.[13]

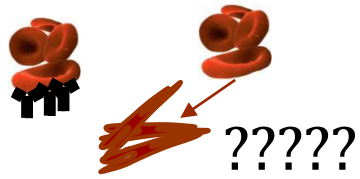
→ Symptômes vaso-occlusifs

→ Réticulocytopénie qui aggrave l'anémie

→ Hb post-T < Hb pré-T
Hémolyse GR transfusés + réticulocytopénie +
destruction des propres GR du patient
HYPERHEMOLYSE

→ Nouvelle transfusion : exacerbation

→ Ac Allo/auto, Ac non détectables



→ Amélioration sans ttt dans certains cas

→ Situation récurrente

UNE SITUATION SPÉCIFIQUE DE LA DRÉPANOCYTOSE ET DES THALASSÉMIES ?

Jacobs, 2023

TABLE 1 Underlying conditions in patients with hyperhaemolysis (HHS).

Condition	*N* (%), *n* = 51
Sickle cell disease (genotype not reported)	17 (33.3)
Sickle cell disease (HbSS)	10 (19.6)
Beta-thalassaemia	9 (17.6)
Haemoglobin H disease	2 (3.9)
Haemoglobin S/beta-thalassaemia	2 (3.9)
Haemoglobin SC disease	2 (3.9)
Alpha-1 anti-trypsin deficiency status-post liver transplant	1 (2.0)
Beta-thalassaemia, haemoglobin C trait, marginal zone lymphoma	1 (2.0)
Caroli disease	1 (2.0)
Chronic iron deficiency anaemia	1 (2.0)
Chronic lymphocytic leukaemia	1 (2.0)
Gastroesophageal varices and miscarriage	1 (2.0)
Hepatitis C virus and HIV infection	1 (2.0)
Mantle cell lymphoma	1 (2.0)
None	1 (2.0)

Dans le système d'hémovigilance en France

En 2024 , sur **30.000** patients drépanocytaires :

- **5000** ont été transfusés, ils ont reçu **70.000** CGR
- **45** cas d'HPTR ont été déclarés, dont la ½ ont nécessité une hospitalisation en réa
- **2 décès**

HPTR : 2nde cause de décès après l'OAP de surcharge

LES FACTEURS DE RISQUE CONNUS

Séries de cas rétrospectives et prospectives

Indication ponctuelle avec :

- ATCD d'allo immunisation et/ou RAI+
- ATCD d'HPTR
- Peu de CGR dans l'historique (<15-20)

Win, Transfusion, 2008
Montalembert, Haematologica, 2011
Vilder, Br J Haematol. 2015
Habibi, AJH, 2016
Narbey, AJH, 2017 (prospectif)
Rossi, Br J Haematol. 2023
Falguiere, Haematologica, 2023

Infection : risque indépendant de développer une HPTR *Merril, Transfusion, 2019*

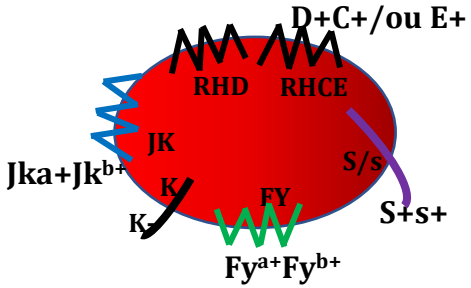
DÉCLENCHEUR

- Classiquement : re stimulation d'un anticorps évanescent méconnu dans l'historique
  - Allo immunisation anti-érythrocytaire

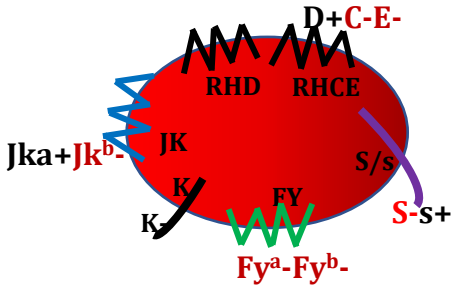
- Mais dans 30% des cas : pas d'anticorps détectables

ALLO IMMUNISATION ANTI-ÉRYTHROCYTAIRE : INCIDENCE ÉLEVÉE AU COURS DE LA DRÉPANOCYTOSE

- **Incidence** : sur 6500 patients connus en IDF , 27% sont immunisés *Floch, Blood Advances, 2023*
- **Polymorphisme des groupes sanguins entre receveurs et donneurs**
  - Receveurs Afro-Antillais/donneurs Caucasiens : dans >50% des cas



Combinaison fréquente d'Ag de GS **d'un donneur caucasien**



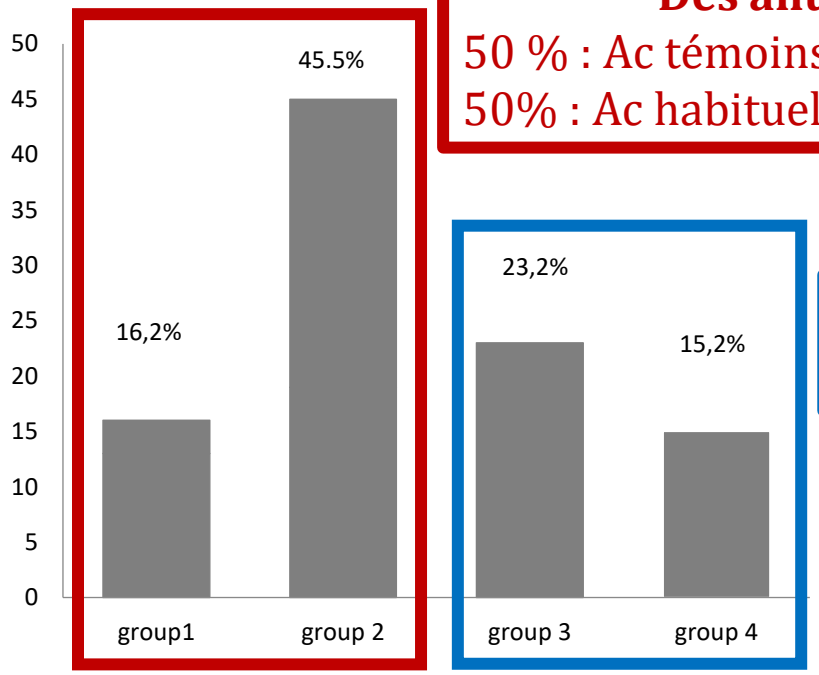
Combinaison fréquente d'Ag de GS **d'un patient Afro-antillais**
Combinaison < 1/1000 donneurs européens

Patients : fréquence d'anti-Jkb, anti-Fya, anti-S

- **Inflammation**
  - Modèles murins : *stimuli* inflammatoire nécessaire à l'allo immunisation *Hendrickson, 2006, 2007, Smith, 2011*
  - **Drépanocytose : maladie inflammatoire**

    Red blood cell alloimmunization is influenced by recipient inflammatory state at time of transfusion in patients with SCD . Fasano, BJH, 2015
    Proinflammatory state promotes red blood cell alloimmunization in pediatric patients with sickle cell disease. Zheng Y, Blood Advances. 2023

QUELS ANTICORPS DÉTECTÉS CHEZ LES PATIENTS AVEC HPTR



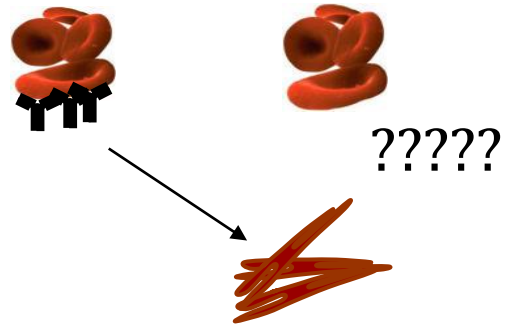
Des anticorps sont détectés dans 62% des cas

50 % : Ac témoins des différences de GS (anti-Jkb, Fya, U ..)

50% : Ac habituellement non dangereux (auto, Le, sans spécificité ..)

37% des cas, absence d'Ac détectables ou de nouvel Ac détectable

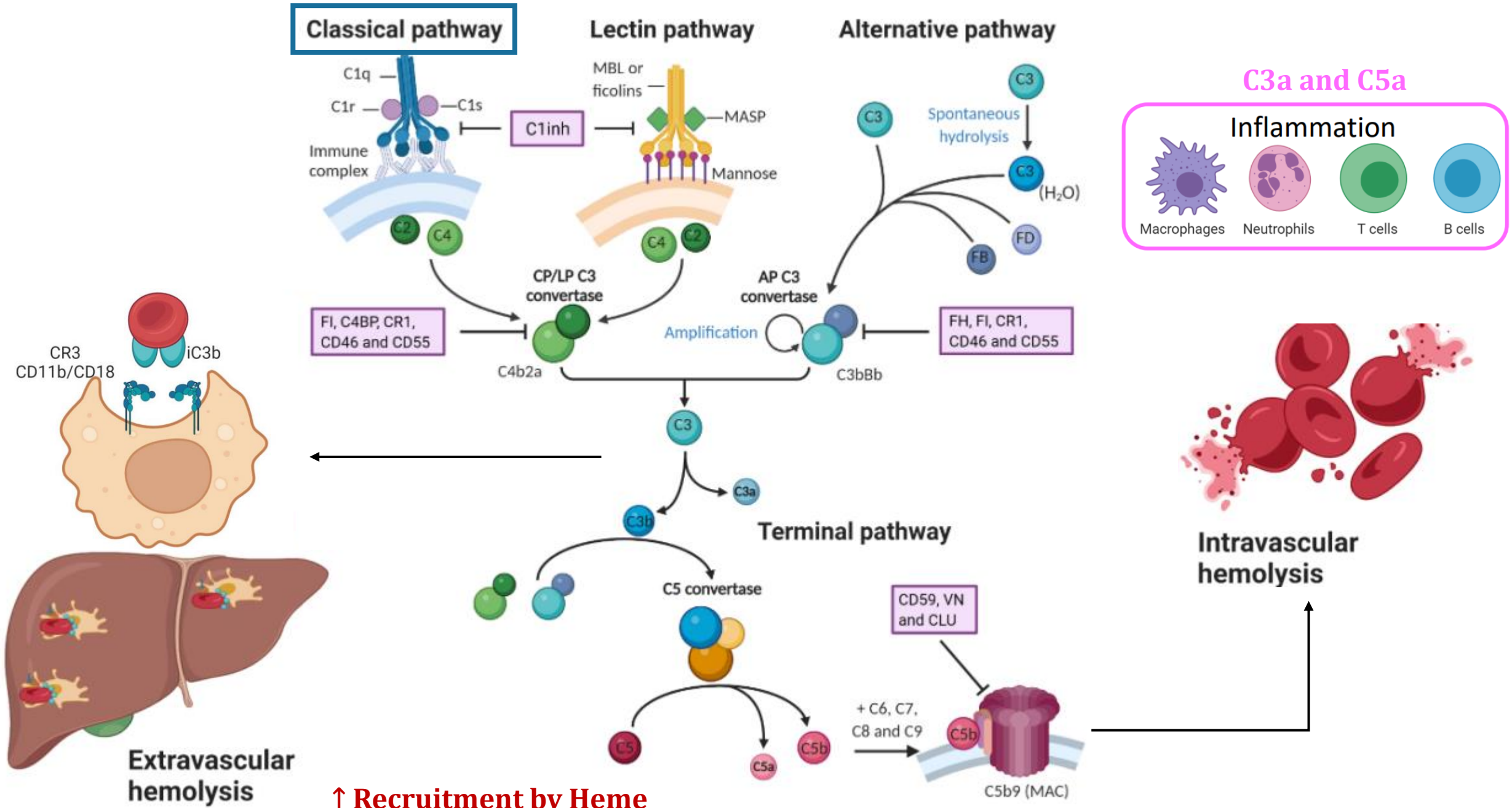
Sévérité non corrélée au profil immuno-hématologique



group 1**:** DHTR in non-immunized patients who developed antibodies
group 2: DHTR in previously immunized patients who developed newly formed antibodies
group 3: DHTR in non-previously immunized patients who did not developed antibodies,
group 4: DHTR in previously immunized patients who did not developed newly formed antibodies

Narbey, Am J Hematol, 2017

Mécanismes de destruction des globules rouges et facteurs potentialisateurs



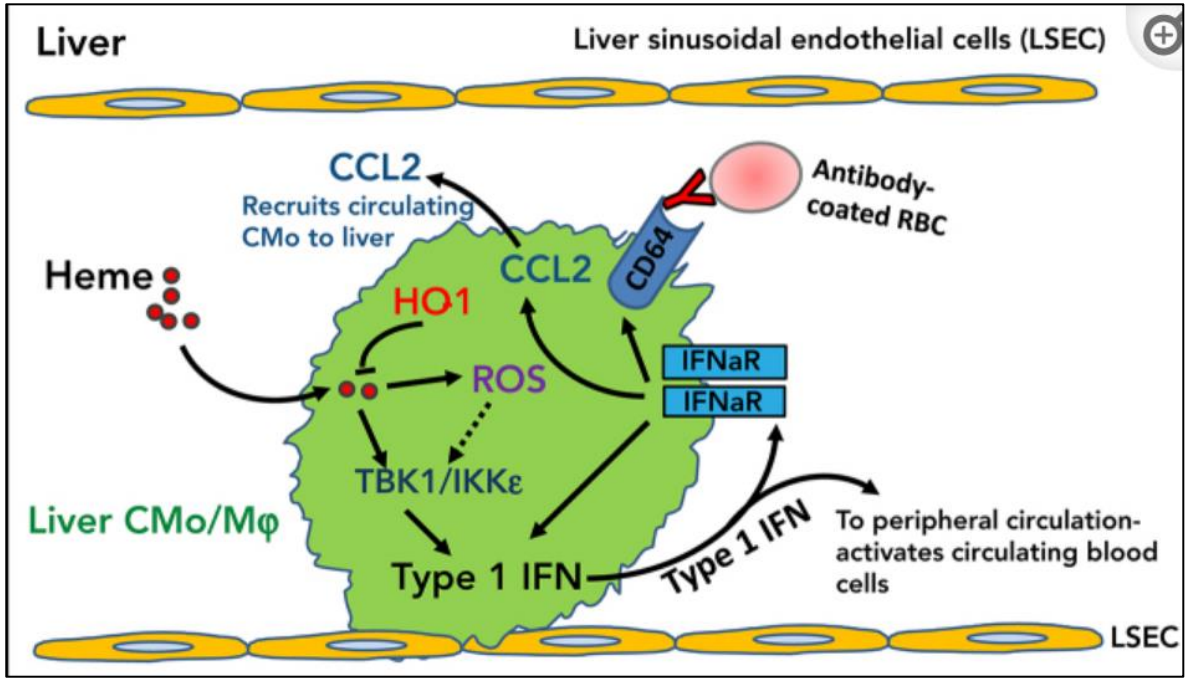
↑ Recruitment by Heme
↑ Inflammation by HbS

Adapted From Roumenina, ASH, 2023

Heme and HbS effects on macrophages

KEY POINTS

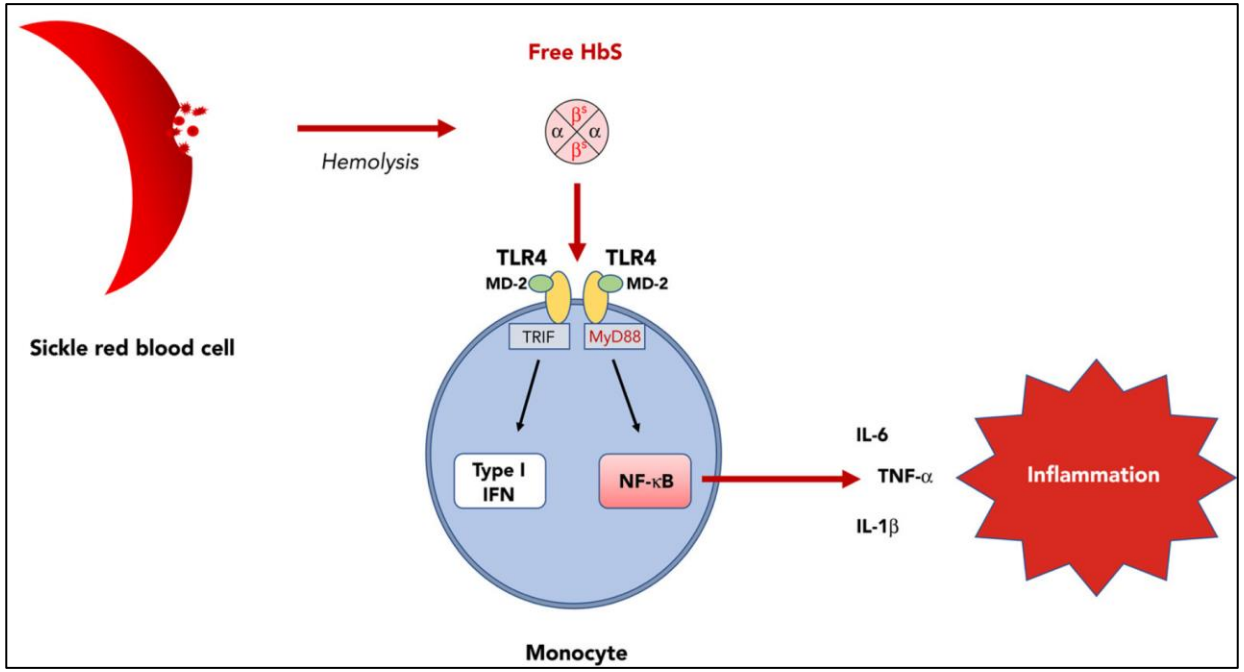
- Hemolysis induces IFN-I in liver monocyte/macrophages primarily through TBK1/IKKε, increasing plasma IFN-α levels in SCD.
- Heme-driven IFN-I promotes CMo recruitment and differentiation in SCD liver, enhancing antibody-mediated erythrophagocytosis.



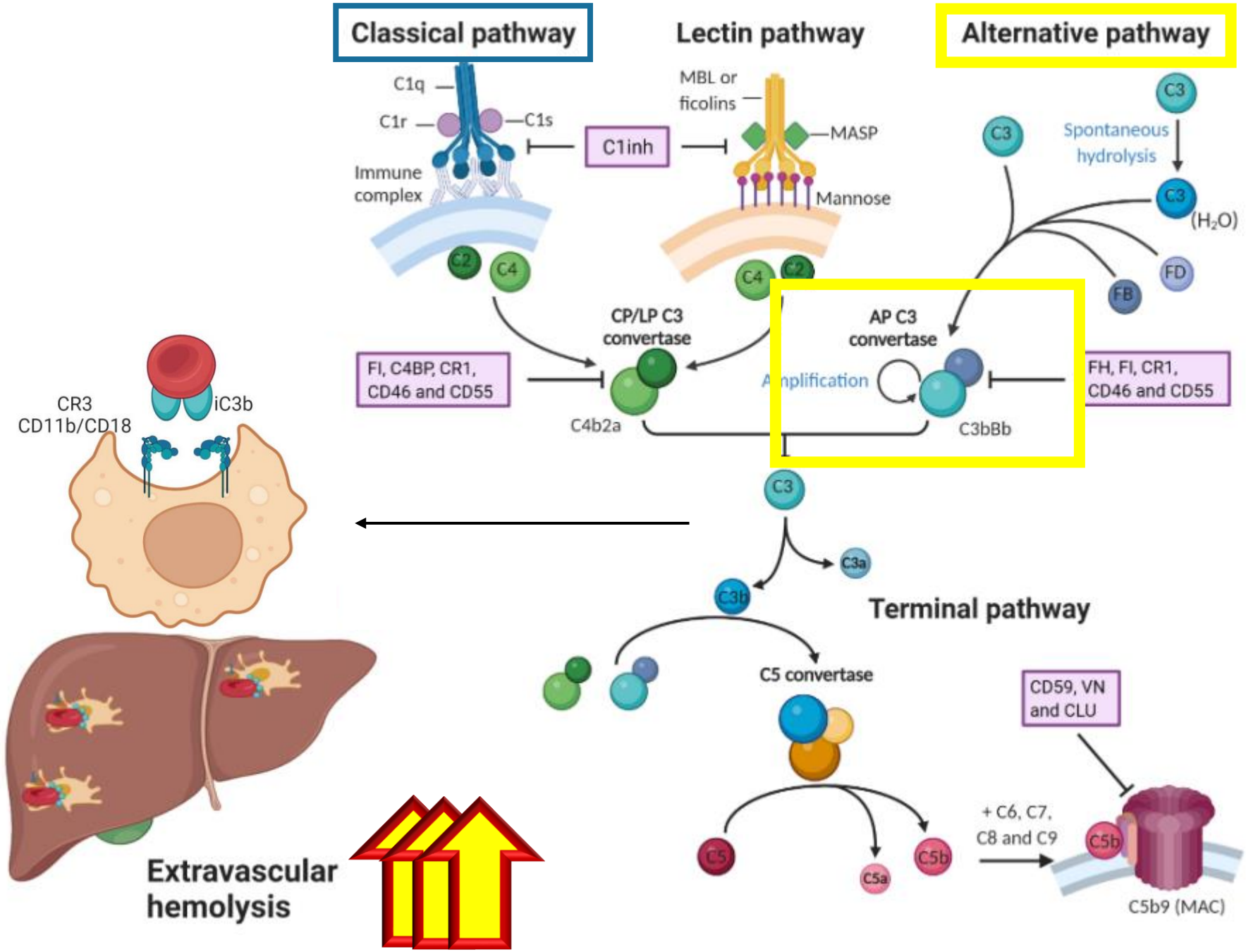
Liu, Blood, 2020

KEY POINTS

- Hemoglobin S, unlike hemoglobin A or heme, is responsible for TLR4-mediated monocyte activation.
- Interaction between hemoglobin S and the TLR4/MD-2 complex results in the activation of both the NF-κB and type I interferon pathways.



Allali, Blood, 2022



Heme Interferes with Complement Factor I-Dependent Regulation by Enhancing Alternative Pathway Activation
Gerogianni, Frontiers immunology, 2022

Intravascular hemolysis activates complement via cell-free heme and heme-loaded microvesicles
Merle, JCI insight, 2018

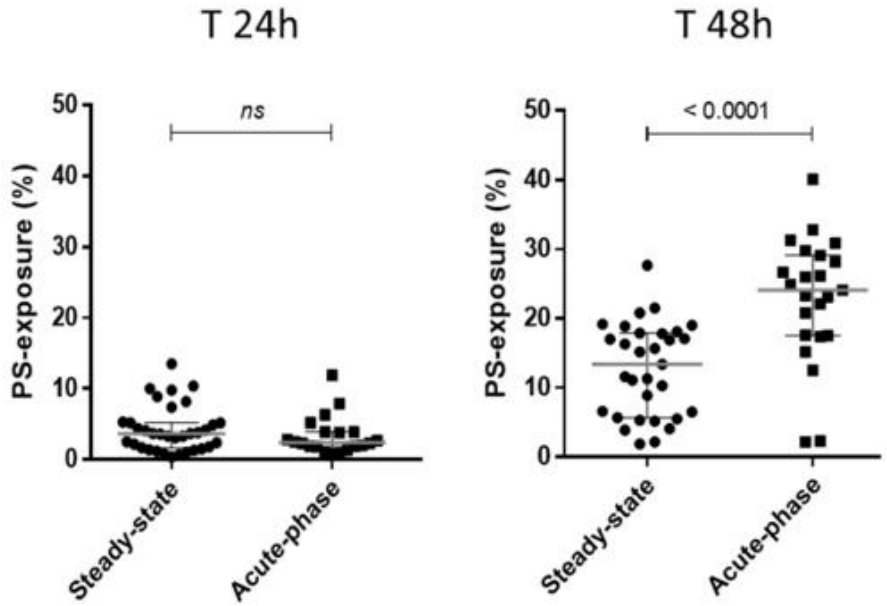
Adapted From Roumenina, ASH, 2023

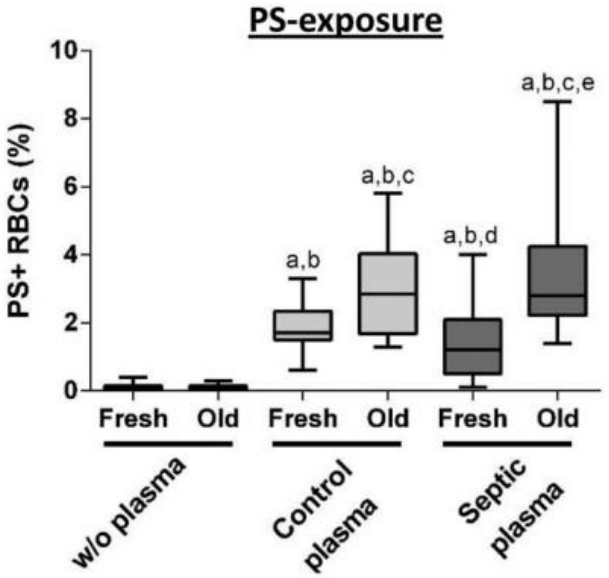
Table 1. Evaluation of complement pathway during DHTR episodes.

	DHTR #2 (Day 6)	DHTR #3 (Day 13) Pre 1st dose	DHTR #3 (Day 38) Pre 2nd dose	(Day 127) Clinic visit
C3a (25-88.2 ng/ml)	43.6	75.6	79.4	27.9
C5a (2.74-16.33 ng/ml)	26.8	25.1	23.2	17.3
Bb (0.49-1.42 mcg/mL)*	0.95	6.06*	1.53	0.96
SC5b-9 (≤ 244 ng/mL)	319	270	219	81
CH50 (101-300 units)	ND	335	320	352
C3 (71-150 mg/dL)	ND	135	ND	ND
C4 (15.7-47 mg/dL)	ND	21.4	ND	ND

Chonat, Haematologica, 2018

AUTRES MÉCANISMES POTENTIALISATEURS DE L'HÉMOLYSE : EFFET DU PLASMA DE DRÉPANOCYTAIRES EN PHASE AIGÜE SUR LES GR DE CGR





Effet non reproduit dans d'autres situations inflammatoires : sepsis , patients non drépanocytaires

Quel constituant du plasma est responsable de cet effet chez le drépanocytaire ?

Hème ?

Chadebech, Transfusion 2009, 2017
Biomolecules, 2021

AUTRES MÉCANISMES POTENTIALISATEURS ? CARACTÉRISTIQUES DES CGR AUTRES QUE L'EXPRESSION ANTIGÉNIQUE

- Déficit en G6PD : 13% des CGR issus de donneurs afro-antillais *Le Gallo, TCB, 2022*

G6PD	All RBCs n=98	Caucasian RBCs n=33	Afro-Caribbean RBCs n=65	
Mean level (U/gHb)	11.49	12.26	11.10	p=0.13
Normal activity (%)	88 (89.8)	33 (100)	56 (86.2)	p=0.03
Deficient activity (%)	9 (9.2)	0 (0)	**9 (13.8)**	p=0.03

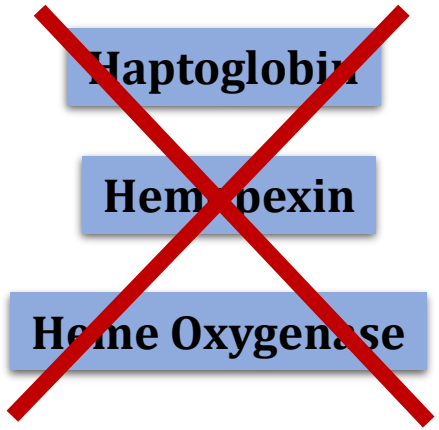
RESEARCH ARTICLE | Free Access

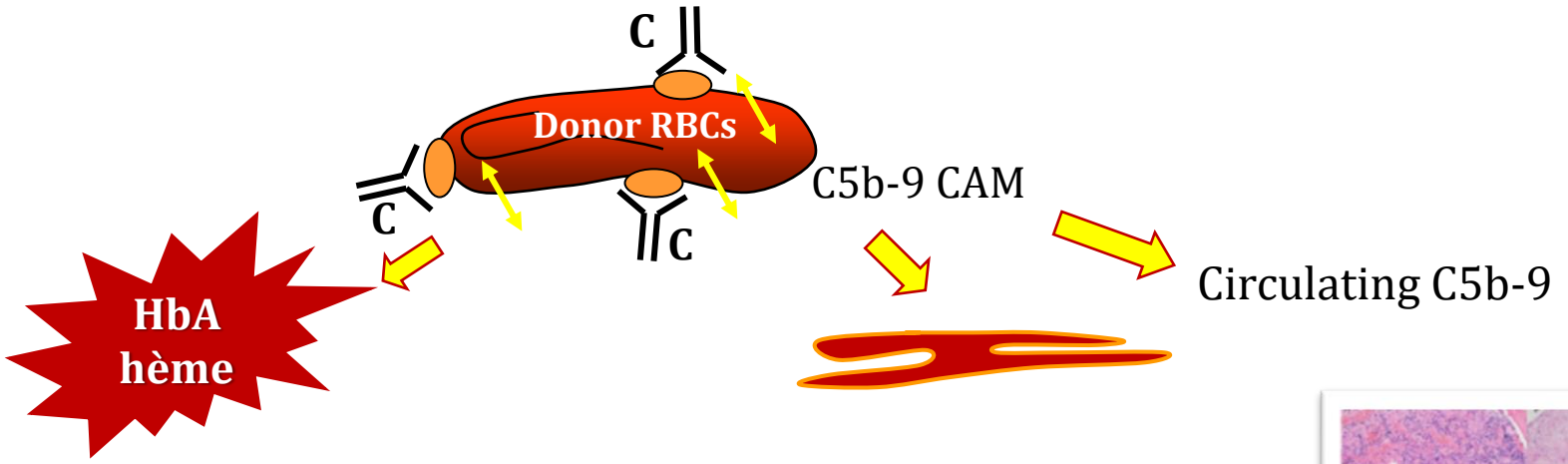
Glucose-6-phosphate-dehydrogenase deficient red blood cell units are associated with decreased posttransfusion red blood cell survival in children with sickle cell disease

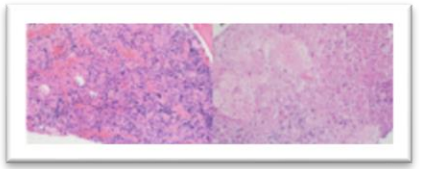
Eyal Sagiv, Ross M. Fasano, Naomi L. C. Luban, Cassandra D. Josephson, Sean R. Stowell, John D. Roback, Richard O. Francis, Marianne E. M. Yee

- Destruction des acides sialiques (*don't eat me signal*) sur les GR transfusés si infection et production de neuraminidase par certains germes

DESTRUCTION DES GR AUTOLOGUES : *BYSTANDER HEMOLYSIS*

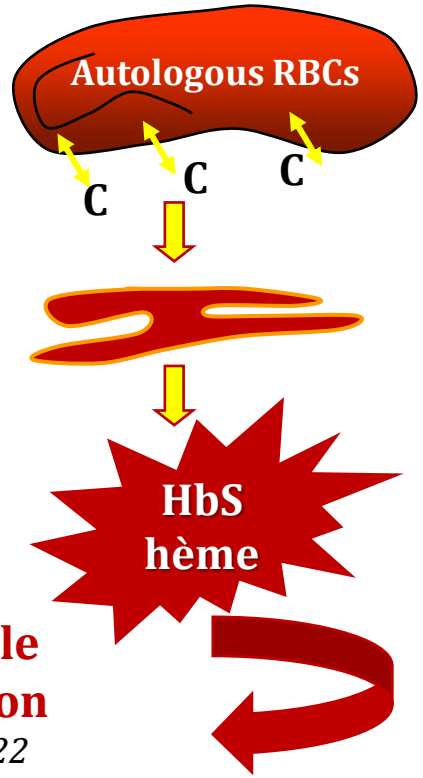






Complement and release of heme are involved

- CD35, CD55, and CD59 are reduced in dense RBCs in SCD (*Roumenina, AJH, 2020*)
- Terminal circulating C5b-9 can bind sickle RBC through PS exposure and induce hemolysis (Liu, Blood , 1999)
- Increased complement on RBCs during HHS episodes demonstrated that bystander hemolysis can occur in vitro (*Merill,Transfusion, 2019*)
- Heme increases alternate pathway destruction of non sensitized SCD RBCs



Vicious circle
Inflammation
Allali, Blood, 2022

Complement involved in profond reticulocytopenia

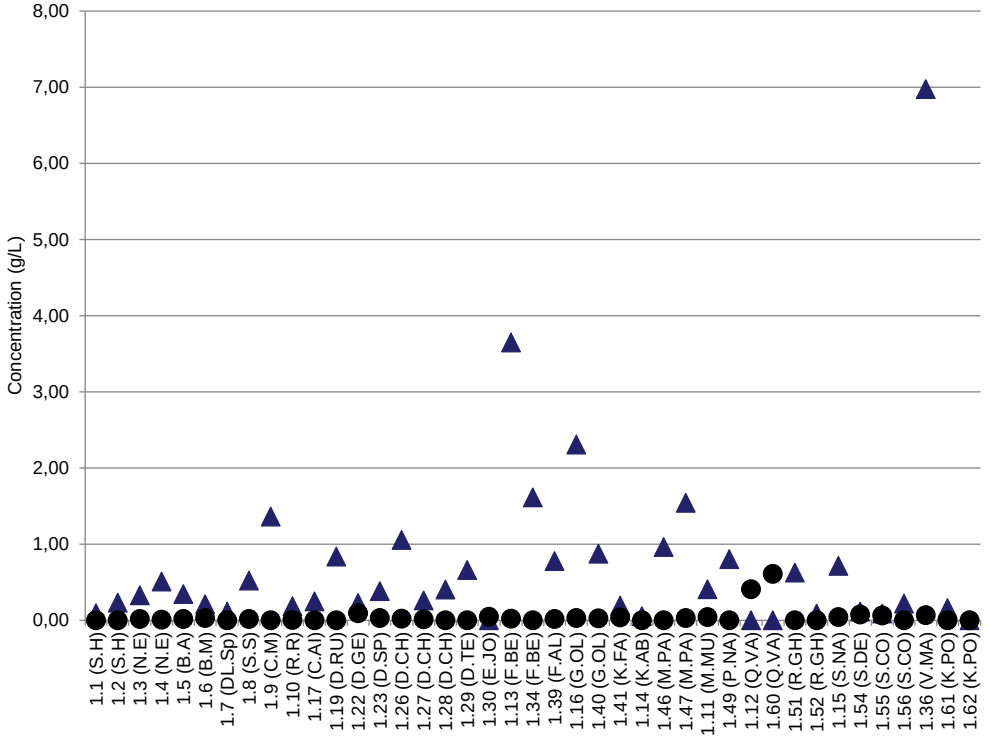
Evidence for complement-mediated bone marrow necrosis in a young adult with sickle cell disease
Azul, Blood Cell Mol Dis, 2021

Auto antibodies

- Classical feature in SCD poly transfused patients and allo immunized patients
  Garraty, Transfusion, 2007
- Cases with developement of AIHA
  Noizat-Pirenne, Haematologica, 2007
- Heme can induce antibodies polyspecificity

SÉVÉRITÉ : CAS SEVERES D'HPTR

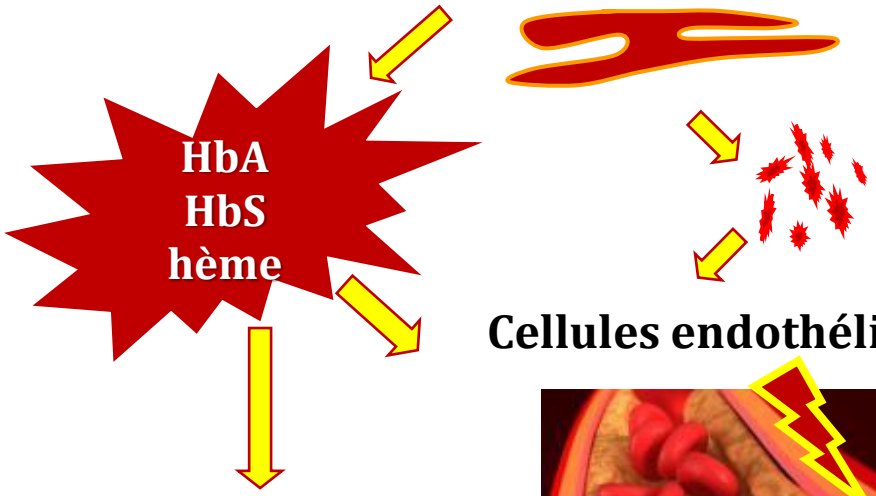
- Dans certains cas, l'évolution de l'HPTR est désastreuse :
  - En quelques heures : insuffisance multi organe
  - Associé à une hémolyse intra vasculaire



Kiger, non published data

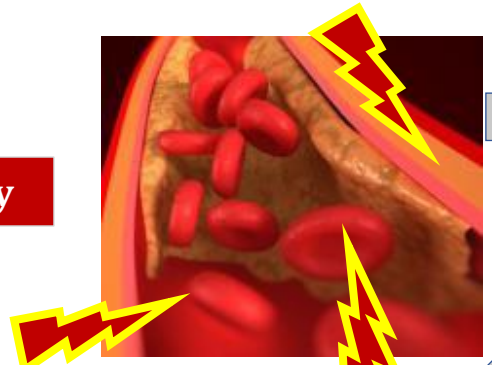
SÉVÉRITÉ : ATTEINTE D'ORGANE

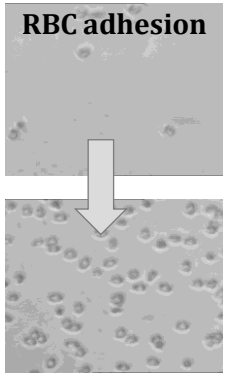
Autologous and
Transfused RBCs



↓ NO Biodisponibility

Cellules endothéliales

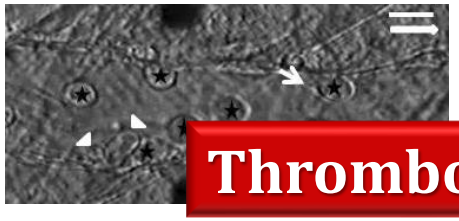




Inflammation

Complement deposition
on endothelial cell

Leucocytes adhesion



Thrombose

VASO OCCLUSIVE CRISIS
KIDNEY FAILURE
MULTI ORGAN DAMAGES

Nguyen, Blood, 2024

MÉCANISMES

- **Facteurs de risque**
  - Transfusion Ponctuelle
  - Allo immunisation
  - ATCD d'HPTR
  - Infection
  - Autres ?
- **Trigger**
  - Anticorps
  - Autres ?
- **Voies de destruction**
  - Complément Voie classique
  - Complément Voie alterne
  - Macrophage
  - Autres ?
- **Potentialisation de la destruction**
  - Hème
  - Activation préexistante du C
  - Infection and conséquences
  - Eryptose
  - Caractéristiques du donneur
  - Autres ?
- **Bystander hemolysis**
  - Déposition de complément
  - Stress oxydatif
  - Interaction C/Heme
  - Auto anticorps
  - Autres ?
- **Sévérité**
  - Toxicité hème, Hb libre(s), membranes des GR
  - Inflammation
  - Consommation du NO
  - Autres ?

COMMENT PRÉVENIR L'HPTR AVEC CE QUE L'ON SAIT ?

Patients transfusés ponctuellement

Historique d'allo immunisation

Historique d'HPTR
Avec ou sans allo immunisation

Historique souvent méconnu

COMMENT PRÉVENIR L'HPTR AVEC CE QUE L'ON SAIT ?

Patients transfusés ponctuellement

Historique d'allo immunisation

↓

CGR phénotypés RH/K
Compatibilité étendue aux cibles des Ac
+ phénocompatibilité FY/JK/MNS

Historique d'HPTR
Avec ou sans allo immunisation

Historique souvent méconnu

COMMENT PRÉVENIR L'HPTR AVEC CE QUE L'ON SAIT ?

Patients transfusés ponctuellement

Historique d'allo immunisation

Historique d'HPTR
Avec ou sans allo immunisation

CGR phénotypés RH/K
Compatibilité étendue aux cibles des Ac
+ phénocompatibilité FY/JK/MNS

Traitement immunosuppresseur
(Rituximab, autre)

Historique souvent méconnu

Objectifs des traitements	Traitements utilisés	TTT potentiellement efficaces
Traitement de support	Hydratation , Analgésiee, Oxygénation	
Stimulation de l'erythropoïèse	EPO, fer , folates, Vit B12	
Inhibition de la destruction des GR		
Macrophage/Ac -médié	IVIG	
Inhibition du Complément	Eculizumab	Autres anti-C ???
Elimination des toxiques	Plasmaphérèse	
Hème, hemoglobine, HbS		Hémopexine, Haptoglobine
Anticorps		Endopeptidase
Complément		
Action anti-inflammatoire	Corticoïdes (balance bénéfice/risques)	Tocilizumab
Transfusion additionnelle	Transfusion + rituximab	Transfusion + Daratumumab
Balance bénéfice/risque	Transfusion + eculizumab	Transfusion + Bortezomid
	Transfusion + corticoides	
Différents objectifs		Hémopure

CLINICAL GUIDELINES

blood advances

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

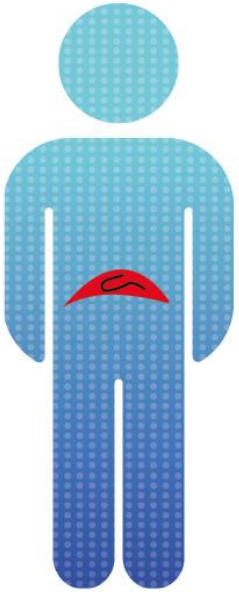
Stella T. Chou,[1] Mouaz Alsawas,[2] Ross M. Fasano,[3] Joshua J. Field,[4] Jeanne E. Hendrickson,[5,6] Jo Howard,[7,8] Michelle Kameka,[9] Janet L. Kwiatkowski,[1] France Pirenne,[10] Patricia A. Shi,[11] Sean R. Stowell,[3] Swee Lay Thein,[12] Connie M. Westhoff,[13] Trisha E. Wong,[14] and Elie A. Akl[15]

	Recommendations or suggestions of ASH	Grading of recommendations	Remarks
Questions 3 and 4: Use of immunosuppressive therapy[20]	**ASH SUGGESTS:** Immunosuppressive therapy over no immunosuppressive therapy **for high risk of acute hemolytic transfusion reaction or severe history of DHTR**	**Conditional recommendation** based on very low certainty in the evidence about effects	Share decision-making process is critical to weigh the potential benefits and harms associated with transfusion versus the effect of ongoing SC symptoms
	ASH SUGGESTS: Immunosupressive therapy over no immunosuppressive therapy **in patients with DHTR and ongoing hyperhemolysis**	**Conditional recommendation** based on very low certainty in the evidence about effects	Share decision-making process Immunotherapy should be initiated promptly if ongoing hyperhemolysis with: - First line: IVIG and high dose steroids - Second line: Eculizumab - Rituximab only to prevent additional antibodies Precipitation of VOC with steroids should be considered

RÉUNION DE CONCERTATION PLURIDISCIPLINAIRE

Indication of transfusion

Sickle Cell patient



History of hyperhemolysis

Multidisciplinary consulting meeting

- Benefice/risk of transfusion ?
- Alternative treatments ?

Transfusion indication maintained

Transfusion protocol ?

RH-K + extended matching :
- to the antibody targeted antigen
- for the negative donor antigens in FY, JK, Ss (MN discussed)

Immunosuppressive therapy ?

Rituximab

Close post-transfusion monitoring

Assessment of total Hb and HbA%
After transfusion (< 24H)

Clinical signs :
- VOC, anemia, dark urines

If signs develop :
- New assessment of total Hb and HbA%
- Bilirubin, LDH, hemoglobinemia, hemoglobinuria
- Immuno-hematological (IH) work up :
  - Screening test (sensitive techniques)
  - Direct antiglobulin test

Confirmation of new hyperhemolysis reaction

Rapid decrease of Hb and HbA% (+/- nomogram[25])
- HbA in the urine, increase of LDH and bilirubin
- IH work up positive or negative

Supportive care and specific treatments (table 2)

CONCLUSIONS

- L'HPTR au cours de la drépanocytose est un accident transfusionnel qui peut mettre en jeu le pronostic vital
- Ce syndrome n'est pas toujours reconnu car il présente des caractéristiques spécifiques
- L'allo-immunisation anti-érythrocytaire est le principal déclencheur , mais il existe près de 30% de formes sans Ac détectables
- L'activation du complément est le mécanisme majeur, potentialisée par le statut clinico-biologique du patient
- Les traitements sont adaptés aux mécanismes connus, ils doivent être développés en parallèle au développement des nouveaux traitements des maladies Ac et C-dépendantes