

Delayed hemolytic transfusion reaction in sickle cell disease patients - Créteil, France

# Immuno-hematological findings in Delayed Hemolytic Transfusion Reaction (DHTR)

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## Transfusion is still a key therapeutic tool in SCD patient management

### Features of blood transfusion in children with sickle cell disease

Marie-Hélène Odièvre<sup>1,2,3</sup>

*mt pédiatrie* 2017 ; 20(4) : 254-64 doi:10.1684/mtp.2018.0659

Thierry Peyrard<sup>1,2,4</sup>

- General population in 2016 => **0,78 %** (Annual report hemovigilance 2016 - ANSM)
- 150 SCD children (0,1-18 y/o) : **53 %** were transfused at least once
  
- Another cohort of 245 children : **71 %** were transfused at least once

*British Journal of Haematology*, 2017, **177**, 641-647

Chronic exposure to blood transfusion => 2 main complications :

- Iron overload
- Risk of allo-immunization

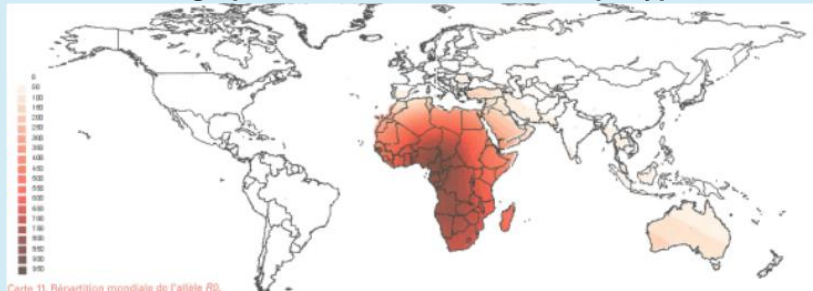
## Discrepancies between recipients and donors

Risk of allo-immunization => Phenotype **discrepancies** between recipients (African descendants) and donors (mostly europeans)

« Typical SCD recipient phenotype » :

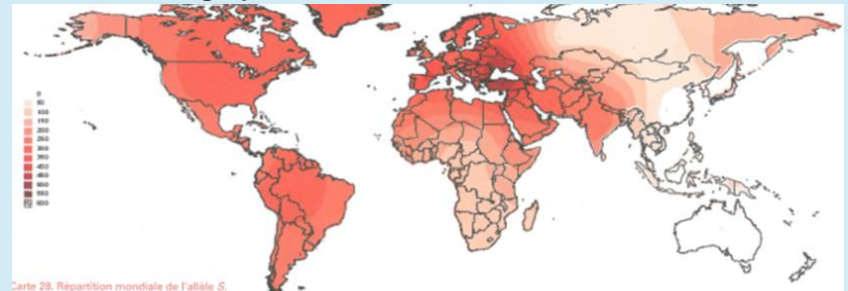
RH:1,-2,-3,4,5; KEL:-1; FY:-1,-2; JK:1,-2; MNS:-3,4

Geographic distribution of the R<sup>0</sup> haplotype

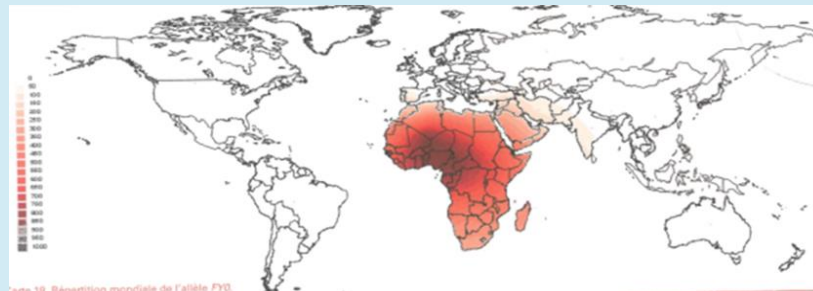


Carte 11. Répartition mondiale de l'allèle R<sup>0</sup>.

Geographic distribution of the GYPB\*03 allele

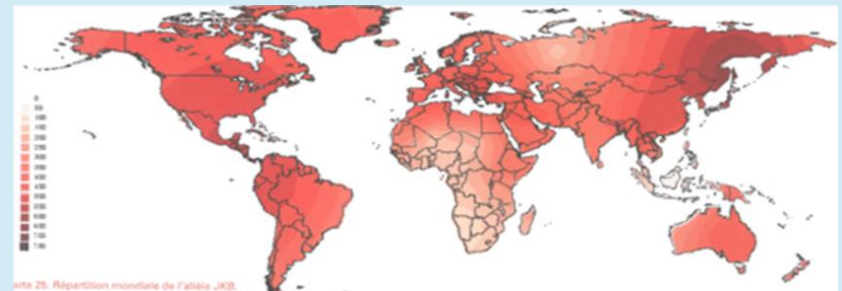


Carte 28. Répartition mondiale de l'allèle GYPB\*03.



Carte 19. Répartition mondiale de l'allèle FY\*02N.01.

Geographic distribution of the FY\*02N.01 allele



Carte 25. Répartition mondiale de l'allèle JK\*02.

Geographic distribution of the JK\*02 allele

## Discrepancies between recipients and donors

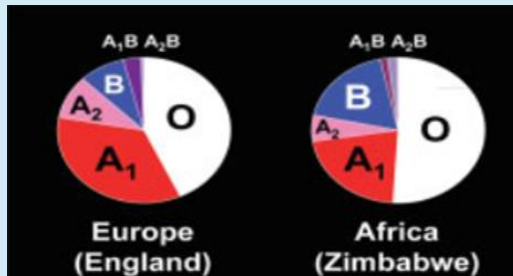
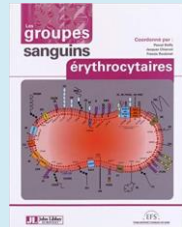
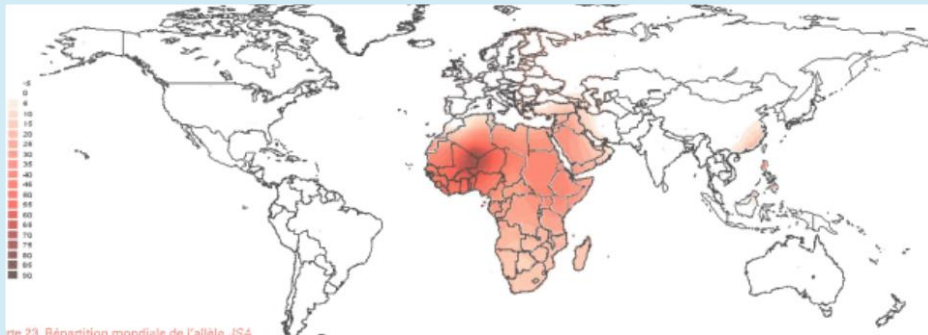


Diagram showing the distribution of ABO phenotypes in six selected populations

Human Blood Groups, Third Edition. Geoff Daniels. Page 31  
 © 2013 Geoff Daniels. Published 2013 by Blackwell Publishing Ltd.

### Group B

Geographic distribution of *KEL*\*02.06 (encoding Js<sup>a</sup> or KEL6)



Les groupes sanguins érythrocytaires,  
 Première édition. P. Bailly et al.  
 © 2015 John Libbey Eurotext, Paris. 2015

Prevalence => up to 20 % - Not really a low frequency antigen I

## Discrepancies between recipients and donors

### Red blood cell immunization in sickle cell disease: evidence of a large responder group and a low rate of anti-Rh linked to partial Rh phenotype

*Monique Silvy,<sup>1,2</sup> Christophe Tournamille,<sup>3,4</sup> Jérôme Babinet,<sup>3</sup> Sadař Pakdaman,<sup>3,4</sup> Sylvain Cohen,<sup>3</sup> Jacques Chiaroni,<sup>1,2</sup> Frédéric Galactéros,<sup>4,5</sup> Philippe Bierling,<sup>3,4</sup> Pascal Bailly,<sup>1,2</sup> and France Noizat-Pirenne<sup>3,4</sup>*

haematologica 2014; 99:e117

France - *RH* genotyping 403 patients

- ⇒ 34/403 with partial-D phenotype : 8,4 %
- ⇒ 21/101 with partial-C phenotype : 20,8 %
- ⇒ 14/400 with partial-e phenotype : 3,5 %

Allo Immunization rate 6/34: 17,6 %

Allo Immunization rate 3/21: 14,3 %

Allo Immunization rate 1/14: 7,1 %

Anti-e seems to be mostly autoantibody

### High prevalence of red blood cell alloimmunization in sickle cell disease despite transfusion from Rh-matched minority donors

Stella T. Chou,<sup>1</sup> Tannoa Jackson,<sup>1</sup> Sunitha Vege,<sup>2</sup> Kim Smith-Whitley,<sup>1</sup> David F. Friedman,<sup>1,3</sup> and Connie M. Westhoff<sup>2</sup>

BLOOD, 8 AUGUST 2013 • VOLUME 122, NUMBER 6

USA - *RH* genotyping 226 patients (Bead chip / BioArray and Sequencing)

⇒ *RHD* variant alleles in 36% of individuals

⇒ *RHCE\*ce* variant alleles in 72 % of individuals

Nb : these alleles may be compensated => number of individuals is lower

## Main features of the alloimmunization risk in SCD patients

- Much higher risk of immunization in SCD patients

3,9 % (general population)

7 % to 58 % (depending on unit selection policy)

23,4 % (pediatric cohort - 152 patients)

4 % to 16 % will experience a DTHR

haematologica 2014; 99:e116

BLOOD, 8 AUGUST 2013 • VOLUME 122, NUMBER 6

British Journal of Haematology, 2017, 177, 641-647

SOr2-2 Séances orales / Transfusion Clinique et Biologique 18 (2011) 328-337

blood® 2018 131: 2773-2781

- Once immunized 61% higher chance of developing a new Ab
- Presence of auto-Ab is risk factor for alloimmunization
- Evanescent Ab => up to 30 %
- Anti-RH2, anti-RH5, anti-RH1, anti-RH3, anti-FY1, anti-JK2, anti-MNS3 and anti-MNS1, anti-KEL3, anti-CO2 are the most common antibodies found

haematologica 2014; 99:e116

British Journal of Haematology, 2017, 177, 641-647

Transfusion Clinique et Biologique 15 (2008) 377-382

British Journal of Haematology, 2017, 177, 641-647

Transfusion Clinique et Biologique 15 (2008) 377-382

## Which specificities do we focus on ?

- Anti-H111
- Anti-RH1 (Anti-D) / anti-RH2 (Anti-C) / anti-RH5 (Anti-e)
- Anti-JK2 or Anti-JK1 (Anti-Jk<sup>b</sup> or Anti-Jk<sup>a</sup>)
- Anti-MNS3 (Anti-S)
- Anti-LFA => Anti-KEL6 (Anti-Js<sup>a</sup>) / Anti-RH10/20 (anti-V, anti-VS) / anti-RH23 (Anti-D<sup>w</sup>)
- Anti-HFA => Anti-MNS5 (Anti-U) / Anti-MNS30 / anti-FY3 (Anti-Fy<sub>3</sub>) / Anti-DO4 (Anti-Hy) / Anti-DO5 (Anti-Jo<sup>a</sup>) / anti-RH
- Ruling out every antibody of common specificity

RH1(D), RH2(C), RH3(E), RH4(c), RH5(e), RH8(Cw), KEL1(K), KEL2(k), KEL3(Kp<sup>a</sup>), KEL4(Kp<sup>b</sup>), FY1(Fy<sup>a</sup>), FY2(Fy<sup>b</sup>), JK1(Jk<sup>a</sup>), JK2(Jk<sup>b</sup>), MNS1(M), MNS2(N), MNS3(S), MNS4(s), LE1(Le<sup>a</sup>), LE2(Le<sup>b</sup>), P1PK1(P1), LU1(Lu<sup>a</sup>), LU2(Lu<sup>b</sup>), DO1(Do<sup>a</sup>), DO2(Do<sup>b</sup>), LU1(Lu<sup>a</sup>), LU2(Lu<sup>b</sup>), CO1(Co<sup>a</sup>), CO2(Co<sup>b</sup>), YT1(Yt<sup>a</sup>), YT2(Yt<sup>b</sup>), XG1(Xg<sup>a</sup>)

## What molecular workup do we perform ?

- Never conclude autoantibody in the RH system without performing molecular workup
  - If patient C+ (RH:2) => tested for (C)ce<sup>S</sup> and RN
  - If anti-D => genomics
  - If anti-e => testing for :
    - c.254C>G => *RHCE\*ceAG*
    - c.340C>T => *RHCE\*ceJAL*
    - c.667G>T => *RHCE\*ceMO*
    - c.712A>G => *RHCE\*ceAR* / *RHCE\*ceEK* / *RHCE\*ceBI* / *RHCE\*ceSM*
    - c.1006G>T => *RHCE\*ce<sup>S</sup>*
    - c.1025C>T => *RHCE\*ceTI*
- Perform an extended genotype to deduce the phenotype
  - DO1/DO2 (Do<sup>a</sup> / Do<sup>b</sup>)
  - RH10/RH20 (V/VS)
  - KEL6/KEL7 (Anti-Js<sup>a</sup> / Anti-Js<sup>b</sup>)



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# Different situations encountered when a DHTR was reported

## Case report n°1

- Patient O RH:-2,-3; KEL:-1; FY:-1,-2; JK:-2; MNS:-1,-3
- Immunized with Anti-RH2, Anti-MNS3, Autoantibodies
- In 2016 => Transfused accidentally with 1 unit MNS:3 unit (pre-T Ab screen negative)
- 10 days post-transfusion => DHTR diagnosis Hb = 3g/dL
- Ab identification (+11 days) => Anti-RH2 + anti-MNS3 + anti-MNS1 + anti-FY3
- 1 year after => Ab screen negative

## Case report n°1

- In 2018 hip surgery : Transfusion of 1 unit (fully matched) with premedication => DTHR 8 days after
- In the CNRGS Ab screen was confirmed to be negative
- New transfusion needed (Hb= 3g/dL) at day 10 (signs of cardiac failure) => made with eculizumab

## Case report n°2

- Patient B RH:-2,-3; KEL:-1,-3; FY:-1,-2; JK:-2; MNS:-3
- Immunized : Anti-RH5 (auto), Anti-KEL3, Anti-JK1 (auto), Anti-JK2 and Anti-MNS3, Anti-FY3
- Since 2012, the antibody screen was negative (about 5 transfusion episodes)
- Sept 2017 VOC => 2 units (09/09) / 2 units (14/09) and a new prescription of 2 units (21/09) => no fresh units available
- Local blood bank's demand => frozen units to treat resitant VOC
- Stop II => High suspicion of a DHTR Hb= 5,9 g/dL
- Ab screen showed an « autoantibody anti-HFA » and anti-RH10 / anti-RH20
- [Hb] nadir = 4,6 g/dL

## Case report n°2

- Investigation of the imputability of anti-RH10/RH20
  - Haemovigilance services called back the 4 donors of the 4 units transfused in September 2017
    - Phenotyped / genotyped
    - Cross match
- Anti-RH10 / anti-RH20
- Interestingly, in the local blood bank => Xmatches were positive for some units (auto ? or a new alloantibody ?)
  - Follow-up at 4 months : Autoantibody + anti-RH5 + anti-RH20 + anti-KEL3 + anti-MNS3
  - Follow-up at 6 months : same specificities / same intensities
  - New episode of DHTR 1 year after => Stand by of the bone marrow transplant

## Case report n°3

- Patient O RH:-3,P4; KEL:-1 (*RHCE\*ceBI* at heterozygous state)
- Genotyping => *FY\*O/FY\*O*; *JK\*1/JK\*2*; *MNS\*4/MNS\*4*; *DO\*2/DO\*2*; *MNS\*1/MNS\*2*; *KEL\*6/KEL\*7*
- Immunized : Anti-RH3, Anti-RH8, Anti-FY1, Anti-MNS3 and Anti-LE1
  
- 25-07 => Exchange transfusion (5 units)
  - RH:-3,-4; KEL:-1; *FY:-1*; JK:-2; MNS:-3.
- 03-08 => Cholecystectomy
- 04-08 => Suspicion of DHTR [Hb] nadir = 3,2 g/dL
- Ab screen in the local blood bank => pan agglutination

## Case report n°3

RH					KEL				FY		JK		LE		MNS					P	LU			DO	YT	CO	XG	GEL P	GEL G	GEL PAPG	GEL TRYG								
1	2	3	4	5	8	1	2	3	4	1	2	1	2	1	2	1	2	3	4	5	1	1	2	19	1	2	1	2	1	2	1	2	1	2	1	2			
-	-	-	-	-	-	-				-	+	+	+	-	+	+	+	-	+	+	-								++	+-	++	+							
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Auto :

+	+		+
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CNRGS identification of **anti-FY3**

Follow-up at 1 month : **anti-FY3**, **anti-DO1**, anti-KEL3, anti-RH3, anti-RH8 + « autoantibodies »

## Other situations

- Patient with a complex mixture of auto and alloantibodies :
- Anti-RH3, anti-RH4, anti-RH5, anti-FY1, anti-MNS1, anti-MNS3 and **anti-KEL6** (pre-transfusion Ab screen was negative)
- Anti-RH1 (auto), Anti-RH5(auto), Anti-RH7, Anti-KEL1, **Anti-KEL3, anti-FY1, anti-FY3, anti-JK1, anti-DO1, anti-MNS2 (Ab still detectable)**
  - GYPB sequencing to make sure that anti-MNS2 can be considered as an autoantobody => MNS:2 unit is safe to use.
- Sometimes what looks like an auto anti-U is an anti-MNS30 (alloantibody) => patient MNS:1,-2,-3,4 with a MNS\*4 variant allele



## Other situations

### **Anti-HI can cause a severe delayed hemolytic transfusion reaction with hyperhemolysis in sickle cell disease patients**

*Clara Ibanez,<sup>1</sup> Anoosha Habibi,<sup>2,3,4</sup> Armand Mekontso-Dessap,<sup>5</sup> Philippe Chadebech,<sup>1,2,4</sup> Btissam Chami,<sup>1</sup> Philippe Bierling,<sup>1,2</sup> Frédéric Galactéros,<sup>2,3,4</sup> Claire Rieux,<sup>6</sup> Joëlle Nataf,<sup>7</sup> Pablo Bartolucci,<sup>2,3,4</sup> Thierry Peyrard,<sup>4,7,8</sup> and France Pirenne<sup>1,2,4</sup>*

TRANSFUSION 2016;56:1828–1833

## Take-home messages

- DTNR Must be diagnosed as early as possible : Additional Transfusion worsens hemolysis => monitoring HbA is key
- Flag your patients with a history of DTNR
- Even a weak Ab / undetectable Ab can be dangerous
- Every specificity can be dangerous (including natural antibodies)
- Investigate partial antigen (mandatory for RH / should be considered for other systems)
- Think about « Low Frequency Antigens » => crossmatch every unit
- Not detecting antibodies does not rule out the diagnosis of DTNR (30%)
- Providing units with the matching phenotype is a must but is only one part of the solution
- Extended phenotype units : Implementing a phenotyping / genotyping policy / running a rare donor program
- Discuss a treatment of DTNR if transfusion is really needed (life-threatening situations)