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[1,2,3]
Thierry Peyrard[1,2,4]

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

- 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

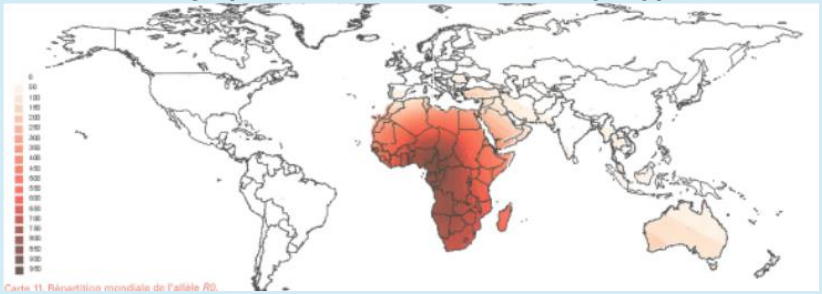
Discrepancies between recipients and donors

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

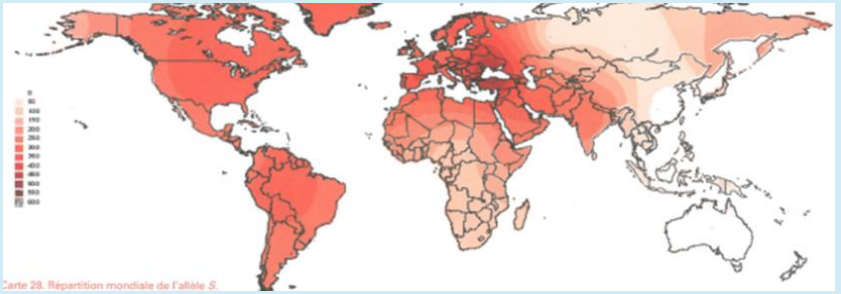
« Typical SCD recipient phenotype » :

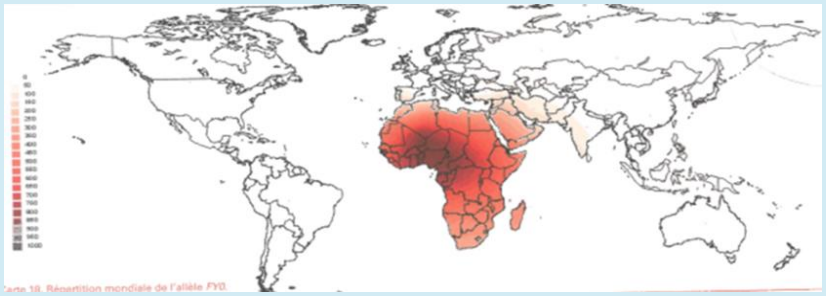
RH:1,-2,-3,4,5; KEL:-1; FY:-1,-2; JK:1,-2; MNS:-3,4

Geographic distribution of the R^0 haplotype

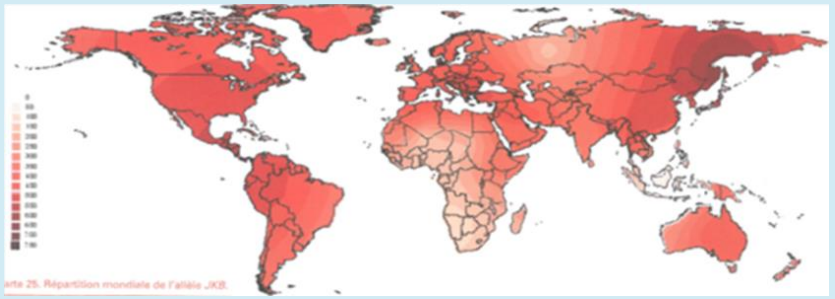


Geographic distribution of the *GYPB*03* allele





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



Geographic distribution of the *JK*02* allele

Discrepancies between recipients and donors

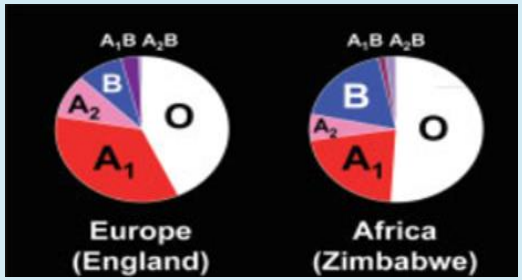
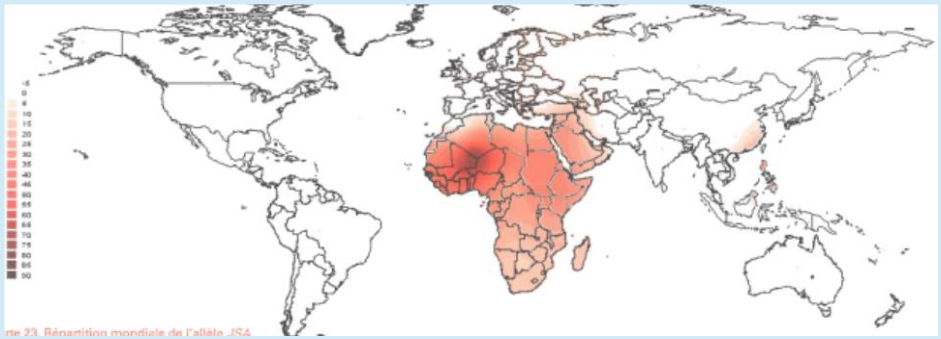


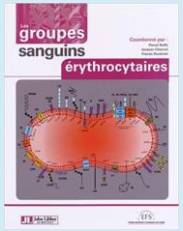
Diagram showing the distribution of ABO phenotypes in six selected populations

Human Blood Groups, Third Edition. Geoff Daniels. Page 31

Group B

Geographic distribution of *KEL*02.06* (encoding Js^a or KEL6)





les groupes sanguins érythrocytaires, Première édition. P.Bailly et al.

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

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,[1,2] Christophe Tournamille,[3,4] Jérôme Babinet,[3] Sadaf Pakdaman,[3,4] Sylvain Cohen,[3] Jacques Chiaroni,[1,2] Frédéric Galactéros,[4,5] Philippe Bierling,[3,4] Pascal Bailly,[1,2] and France Noizat-Pirenne[3,4]

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 Imminization rate 6/34: 17,6 %
Allo Imminization rate 3/21: 14,3 %
Allo Imminization 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,[1] Tannoa Jackson,[1] Sunitha Vege,[2] Kim Smith-Whitley,[1] David F. Friedman,[1,3] and Connie M. Westhoff[2]

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

haematologica 2014; 99:e116

- Presence of auto-Ab is risk factor for alloimmunization
- Evanesent Ab => up to 30 %

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

Transfusion Clinique et Biologique 15 (2008) 377–382

- 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

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^b or Anti-Jk^a)
- Anti-MNS3 (Anti-S)
- Anti-LFA => Anti-KEL6 (Anti-Js^a) / Anti-RH10/20 (anti-V, anti-VS) / anti-RH23 (Anti-D^w)
- Anti-HFA => Anti-MNS5 (Anti-U) / Anti-MNS30 / anti-FY3 (Anti-Fy3) / Anti-DO4 (Anti-Hy) / Anti-DO5 (Anti-Jo^a) / 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^a), KEL4(Kp^b), FY1(Fy^a), FY2(Fy^b), JK1(Jk^a), JK2(Jk^b), MNS1(M), MNS2(N), MNS3(S), MNS4(s), LE1(Le^a), LE2(Le^b), P1PK1(P1), LU1(Lu^a), LU2(Lu^b), DO1(Do^a), DO2(Do^b), LU1(Lu^a), LU2(Lu^b), CO1(Co^a), CO2(Co^b), YT1(Yt^a), YT2(Yt^b), XG1(Xg^a)

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^{S} 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^{S}*
    - c.1025C>T => *RHCE*ceTI*
- Perform an extended genotype to deduce the phenotype
  - DO1/DO2 (Do^{a} / Do^{b})
  - RH10/RH20 (V/VS)
  - KEL6/KEL7 (Anti-Js^{a} /Anti-Js^{b})

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

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,[1] Anoosha Habibi,[2,3,4] Armand Mekontso-Dessap,[5] Philippe Chadebech,[1,2,4] Btissam Chami,[1] Philippe Bierling,[1,2] Frédéric Galactéros,[2,3,4] Claire Rieux,[6] Joëlle Nataf,[7] Pablo Bartolucci,[2,3,4] Thierry Peyrard,[4,7,8] and France Pirenne[1,2,4]

TRANSFUSION 2016;56;1828–1833

Take-home messages

- DTHR Must be diagnosed as early as possible : Additional Transfusion worsens hemolysis => monitoring HbA is key
- Flag your patients with a history of DHTR
- 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 diganosis of DHTR (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
- Disscuss a treatment of DHTR if transfusion is really needed (life-threatening situations)