Red Cell Alloimmunisation in Sickle Cell Disease and Thalassemia

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Alloimmunisation to red cell antigens in SCD

Prevalence

- Prevalence 25% (8-35%) (Garratty et al 1997)
- Only 2.6% in a Jamaican cohort (Olujohungbe et al 2001)
- 6.1% in Uganda (Natakunda et al 2010)

Causes

- Antigenic differences between recipients and donors
- Exposure
- Predisposing factors
  - genetic
  - chronic inflammatory state (elevated IL1,IL6,IFN-γ)

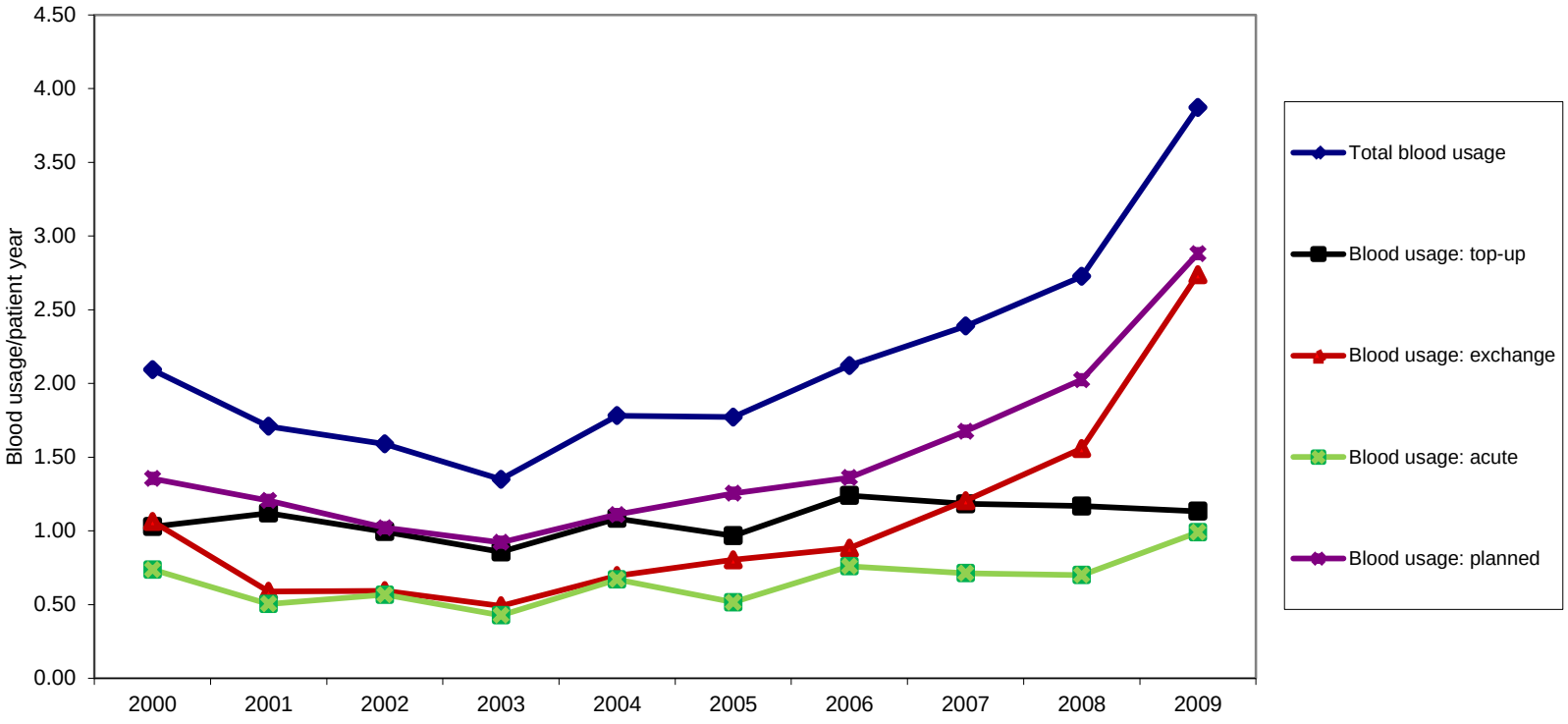
Blood group racial differences (modified from Yazdanbakhsh ,Ware & Noizat-Pirenne 2012)

Blood antigen	Caucasian donors (%)	Black recipients (%)
C	68	27
K	9	2
Fy(a)	66	10
Jk(b)	74	49
Partial antigens		
Partial D in D+	1	7
Partial C in C+	0	30
Low-incidence antigens		
VS (RH20)	0.01	26-40
Rare blood groups		
U negative	0	1
Hr^B negative	0	0.1

Alloimmunisation to red cell antigens - Individual susceptibility factors

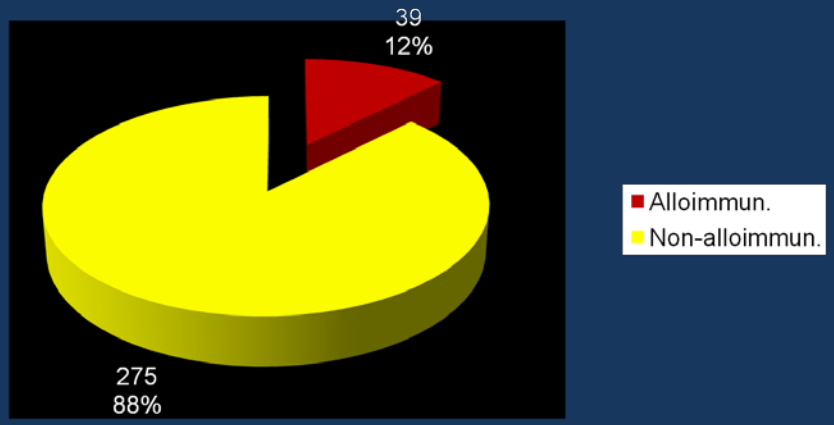
- HLA system: DRB1*04 and DRB1*15 linked with anti-Fy^a formation
- DRB1*07:01 increases risk of anti-Di^a formation (Baleotti W et al, *Transfusion* 2014)
- 2 SNPs in CD81 gene strongly associated with alloimmunisation (Tatari-Calderone Z et al, *Clin Dev Immunol* 2013)
- Weak T-reg (CD4+25+FoxP3+) cell activity – also implicated in high rates of *autoantibody* formation in alloimmunized patients.

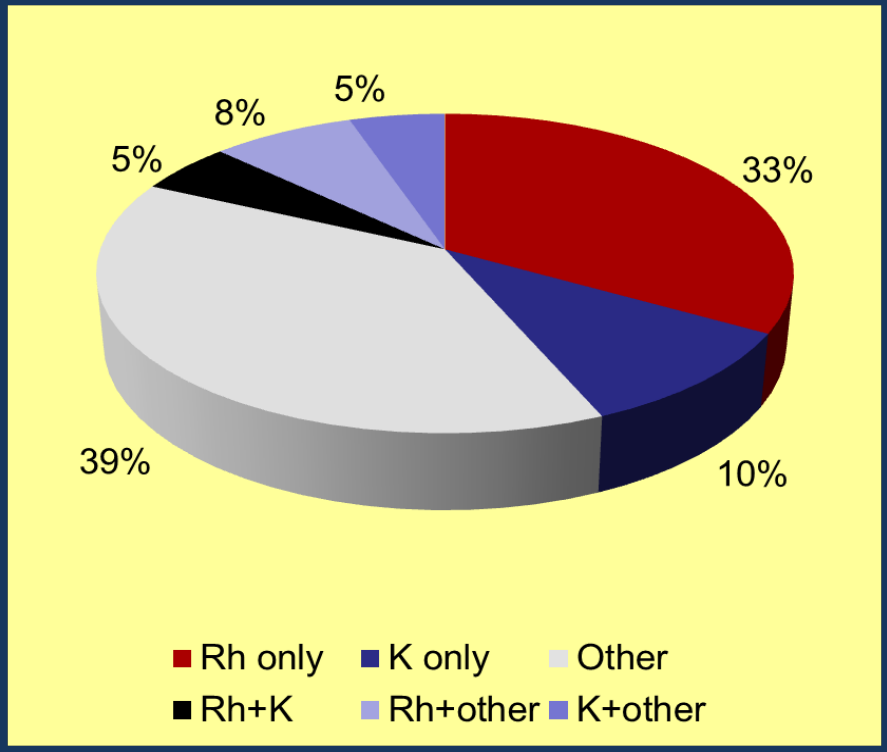
Blood usage for SCD patients at King's



Drasar E et al , BJHaem 2010

Alloimmunisation in SCD at King's



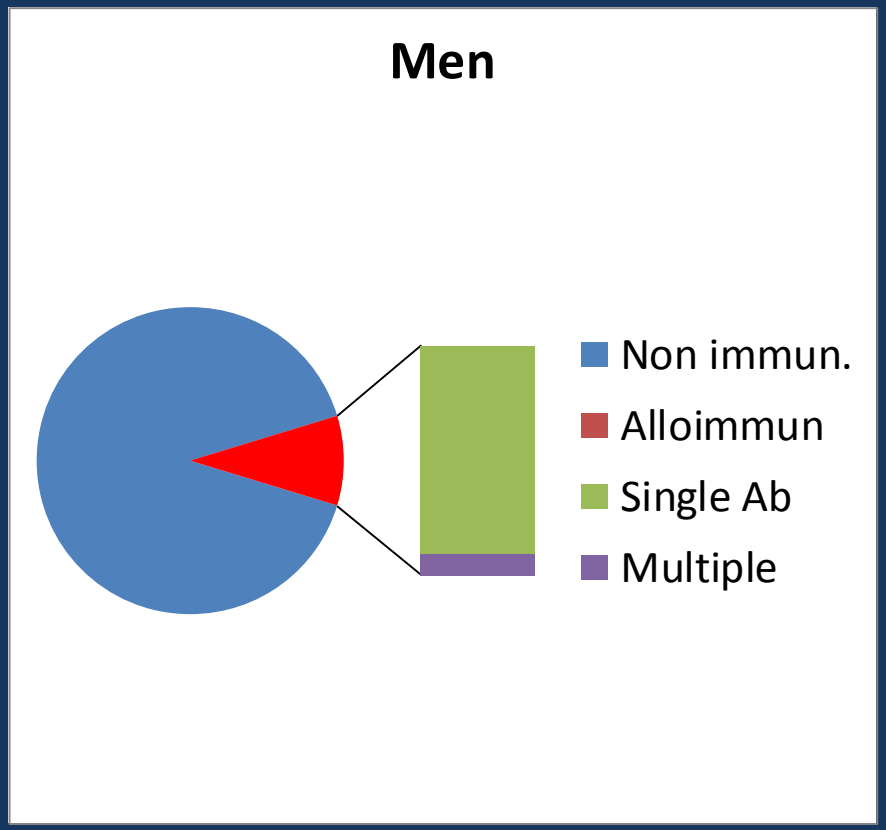


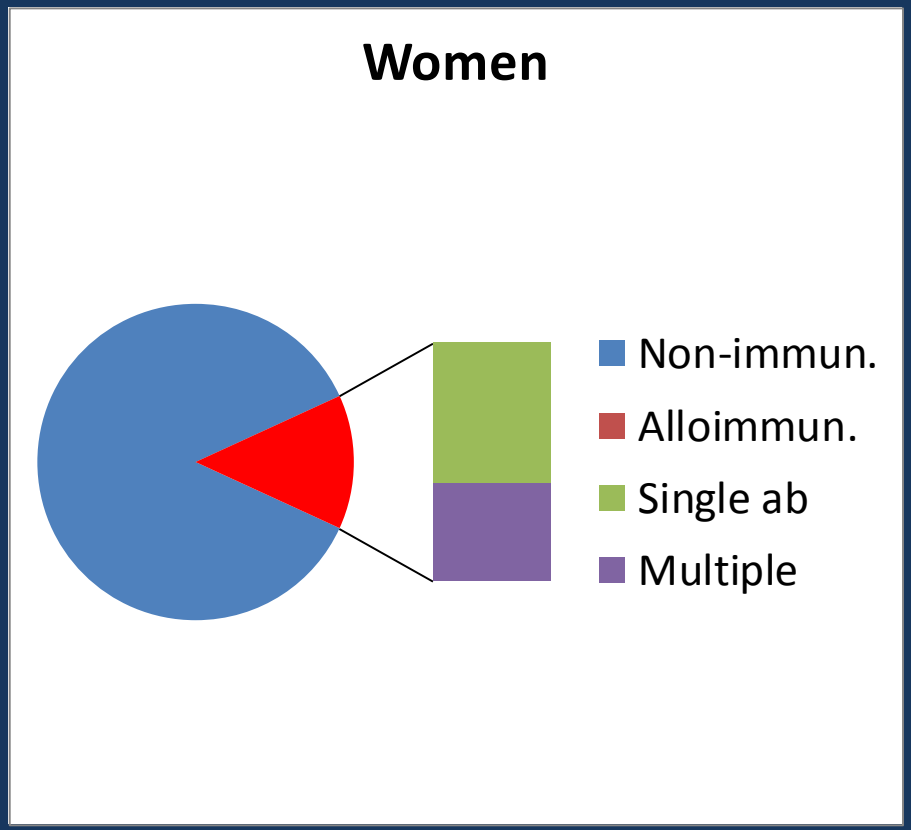
Mijovic,Perera,Thein
Transfusion 2013

Alloimmunisation in SCD

KCH,2011

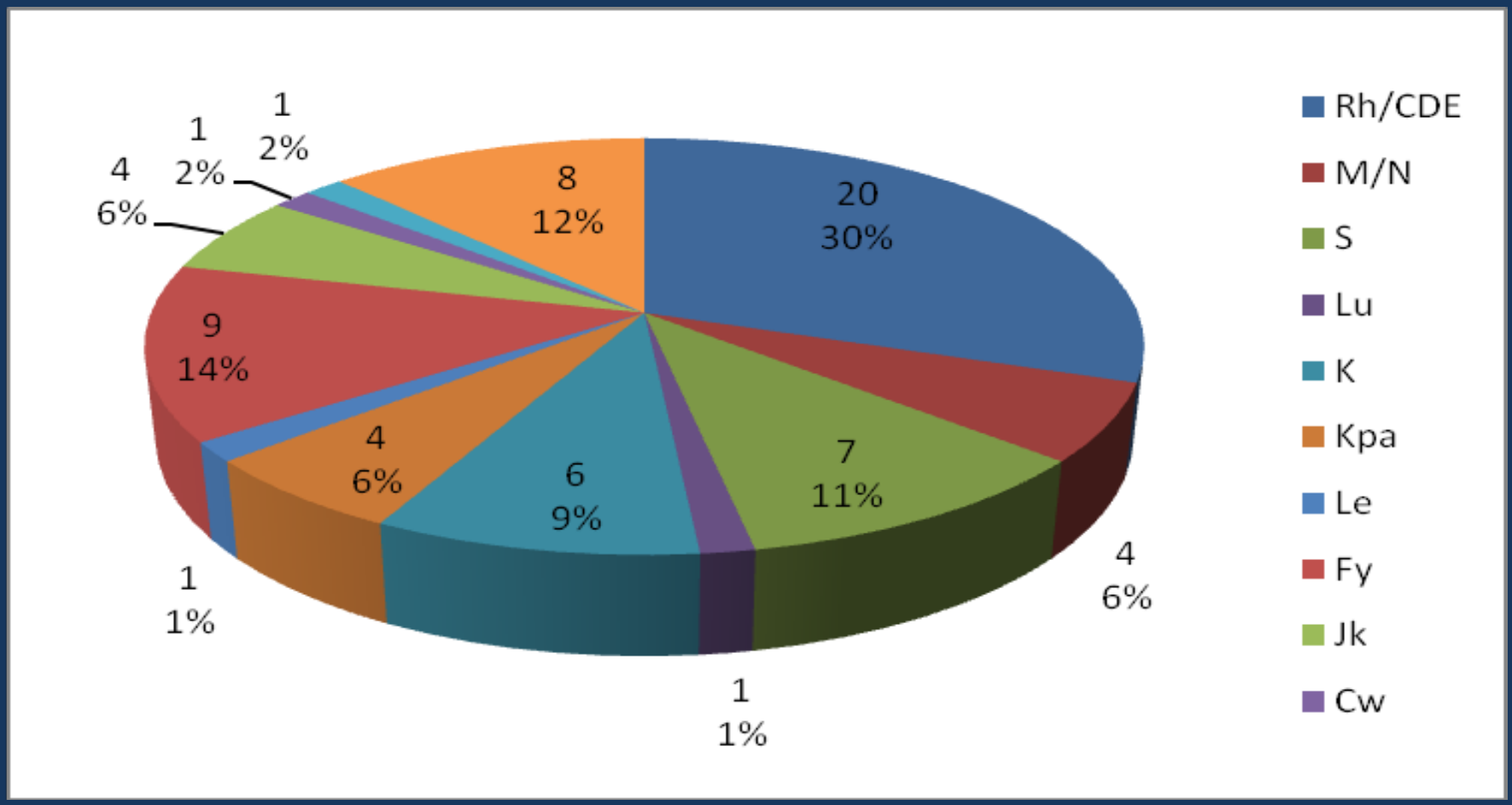
	Male	Female
Total	117	197
Alloimmunized	11(9.4%)	28 (14.2%)
Single Ab	10	17
Multiple Ab	1	11



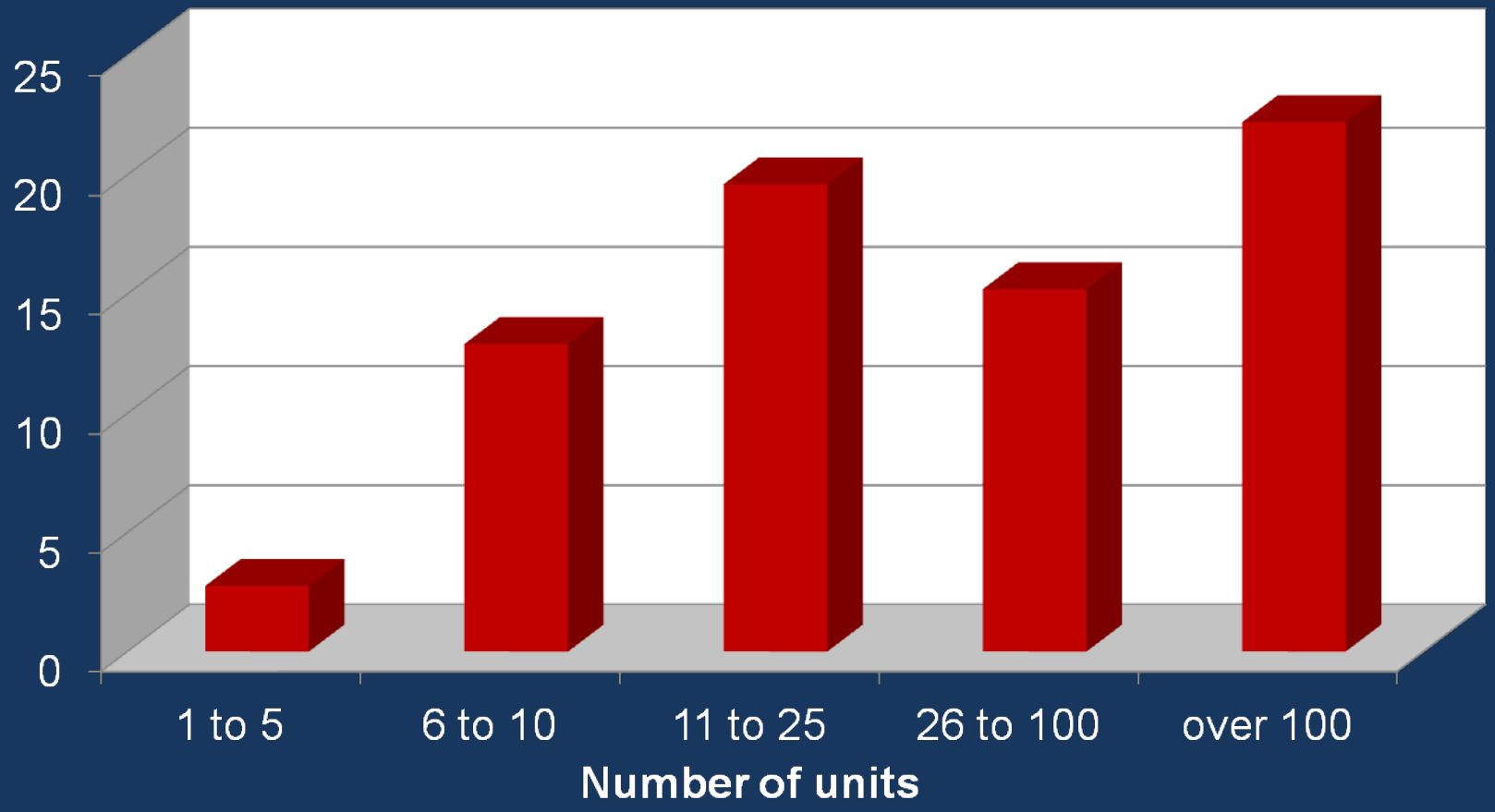


Distribution of red cell antibodies in SCD patients

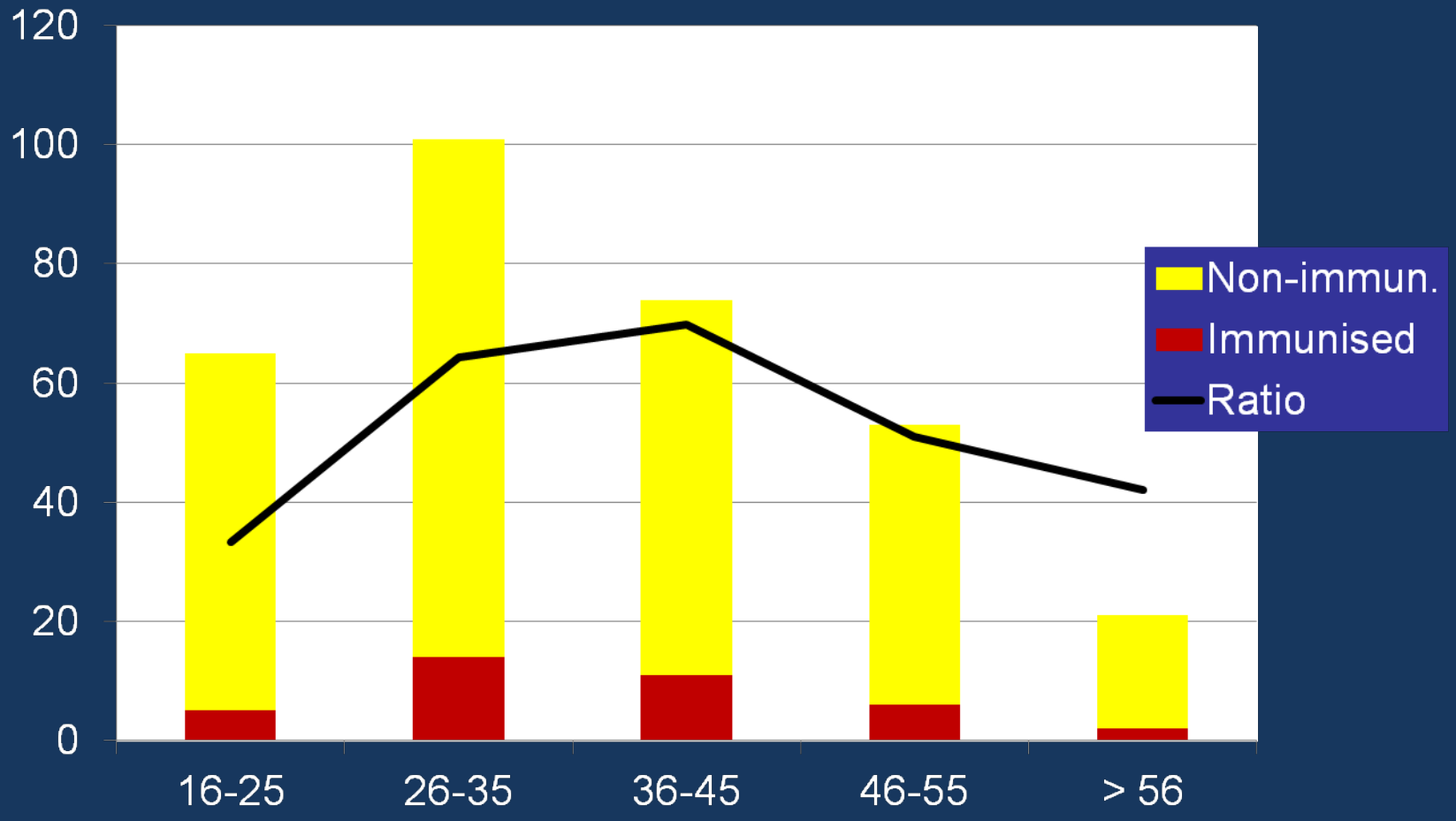
Rh	M/N	S	Lu	K	Kpa	Le	Fy	Jk	Cw	Js	Other
20	4	7	1	6	4	1	9	4	1	1	8



Alloimmunisation rate according to transfusion exposure



Proportion of alloimmunised patients by age group



“Untransfusable” patients

- Multiple alloantibodies, theoretical availability of blood < 1% (incl. only clinically significant antibodies)
- Antibodies against high frequency antigens
- Repeated DHTR

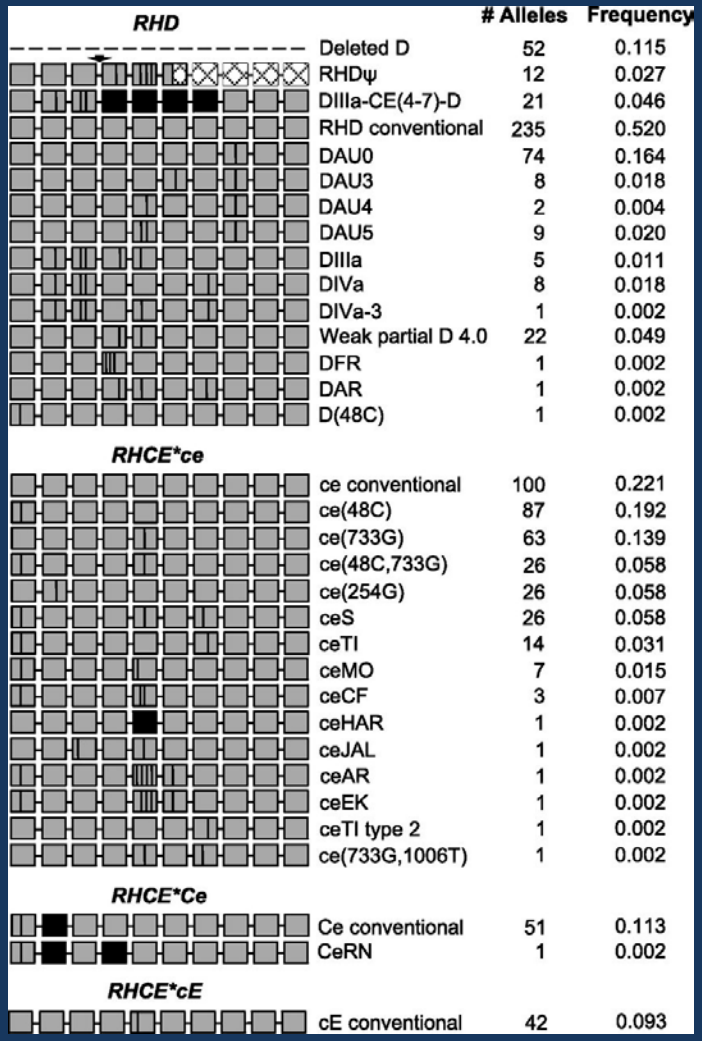
- Example: O, D+, anti-N, S,Fy^a ,Fy3,Lu^a ,Js^a ,V,Vs.
- Anti-U, anti-Hr^S , anti-Hr^B

= 4/39, i.e. 10% alloimmunised patients

Rh/K immunisation: still high despite antigen matching

- Some patients alloimmunised before routine Rh/Kell matching was introduced
- Less stringent matching in emergencies
- Errors in blood selection
- Transfusions received in other centres
- High frequency of variant Rh genes

RHD and RHCE diversity in 226 patients with SCD. RH alleles identified in patients with SCD. Each gray box represents 1 of 10 exons in the RH genes.

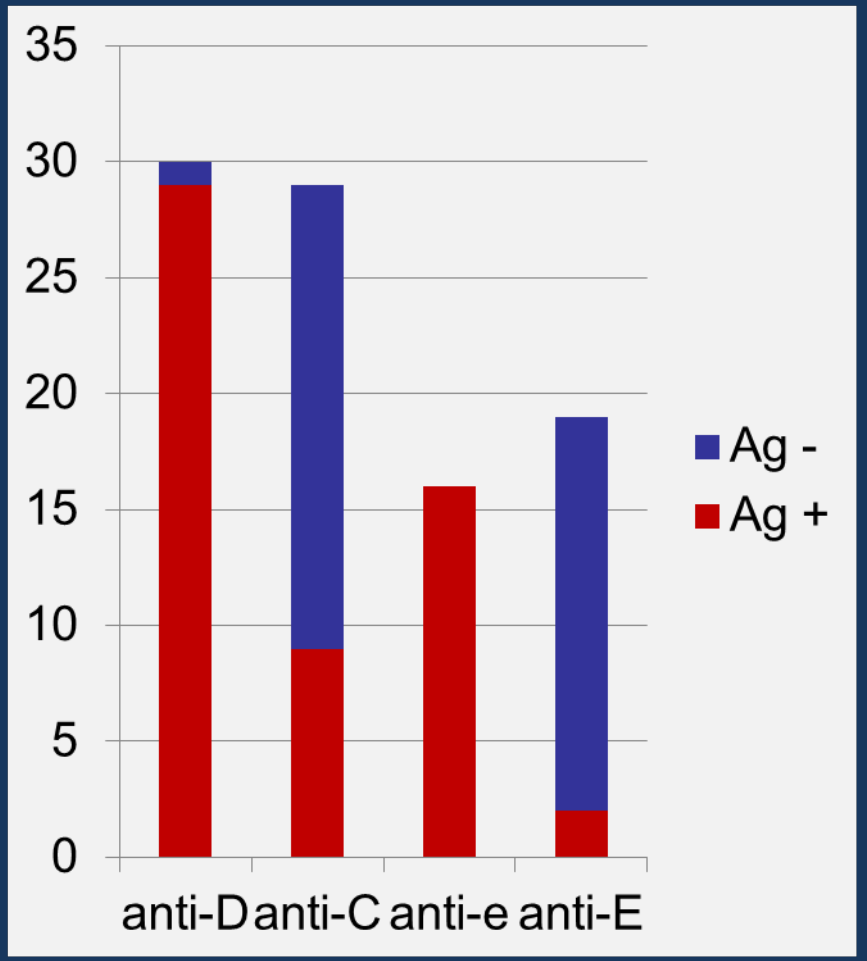


	# Alleles	Frequency
RHD		
Deleted D	52	0.115
RHDψ	12	0.027
DIIIa-CE(4-7)-D	21	0.046
RHD conventional	235	0.520
DAU0	74	0.164
DAU3	8	0.018
DAU4	2	0.004
DAU5	9	0.020
DIIIa	5	0.011
DIVa	8	0.018
DIVa-3	1	0.002
Weak partial D 4.0	22	0.049
DFR	1	0.002
DAR	1	0.002
D(48C)	1	0.002
RHCE*ce		
ce conventional	100	0.221
ce(48C)	87	0.192
ce(733G)	63	0.139
ce(48C,733G)	26	0.058
ce(254G)	26	0.058
ceS	26	0.058
ceTI	14	0.031
ceMO	7	0.015
ceCF	3	0.007
ceHAR	1	0.002
ceJAL	1	0.002
ceAR	1	0.002
ceEK	1	0.002
ceTI type 2	1	0.002
ce(733G,1006T)	1	0.002
RHCE*Ce		
Ce conventional	51	0.113
CeRN	1	0.002
RHCE*cE		
cE conventional	42	0.093

Chou S T et al. Blood 2013;122:1062-1071

RBC antibodies

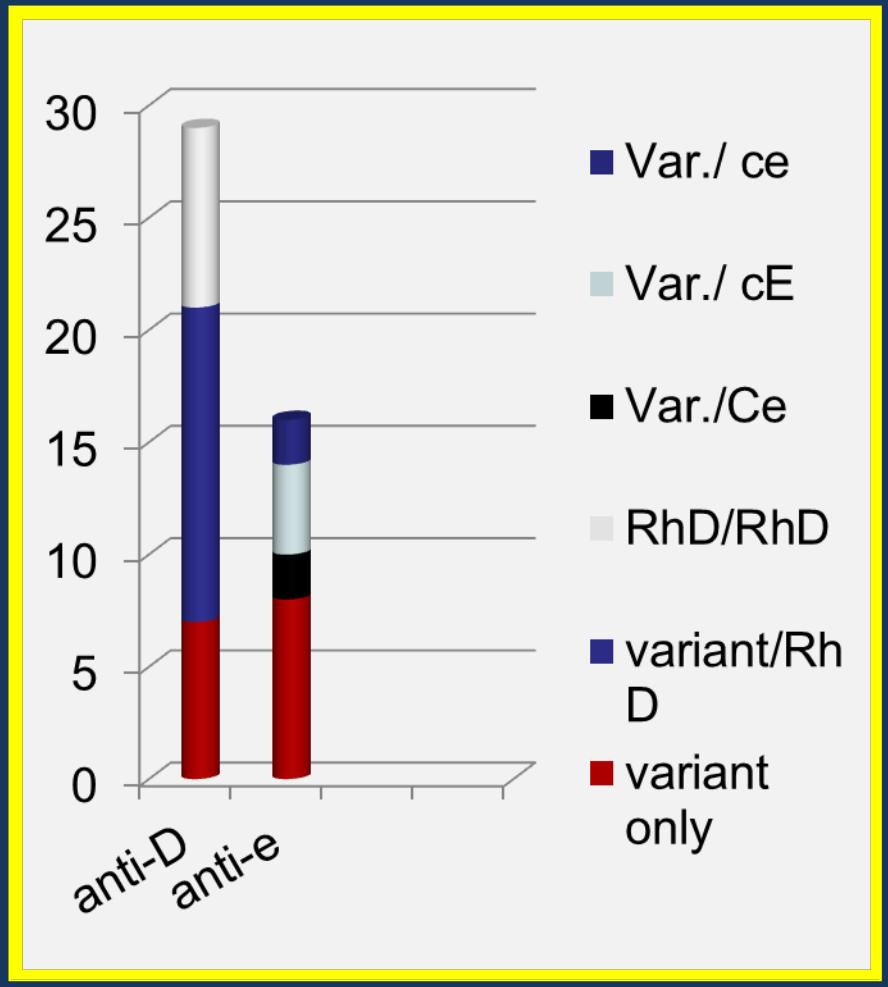
- 146 antibodies identified in 80 patients
- 94/146 (64.4%) Abs had specificity for D,C,E and e antibodies.
- 56 unexplained specificities in 45 pts who typed POS for corresponding antigen
- 35 unexplained spec. in 33 pts who typed NEG for corresponding antigen and received antigen-negative units



Chou S T et al. Blood 2013;122:1062-1071

Genetic diversity at RhD and RhCE loci
(Alloimmunised patients)

- 72% RhCE*ce alleles, and 41% RhD alleles, were variant (non-conventional).

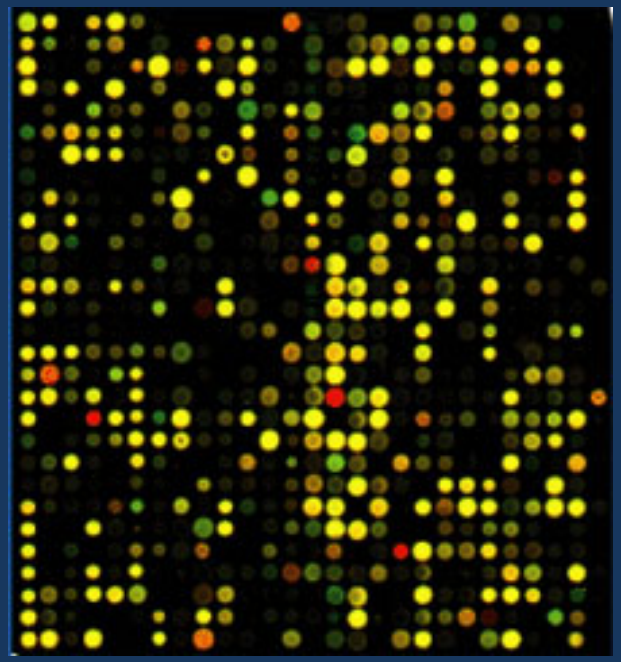


Extended phenotype matching

- Limited phenotype matching (ABO/D + C,c,E,e,K) prevents formation of 53% antibodies.
  - Availability 13.6%
- Extended matching (as above + S,Fy^a, Jk^b) prevents formation of 71% antibodies.
  - Availability 0.6%

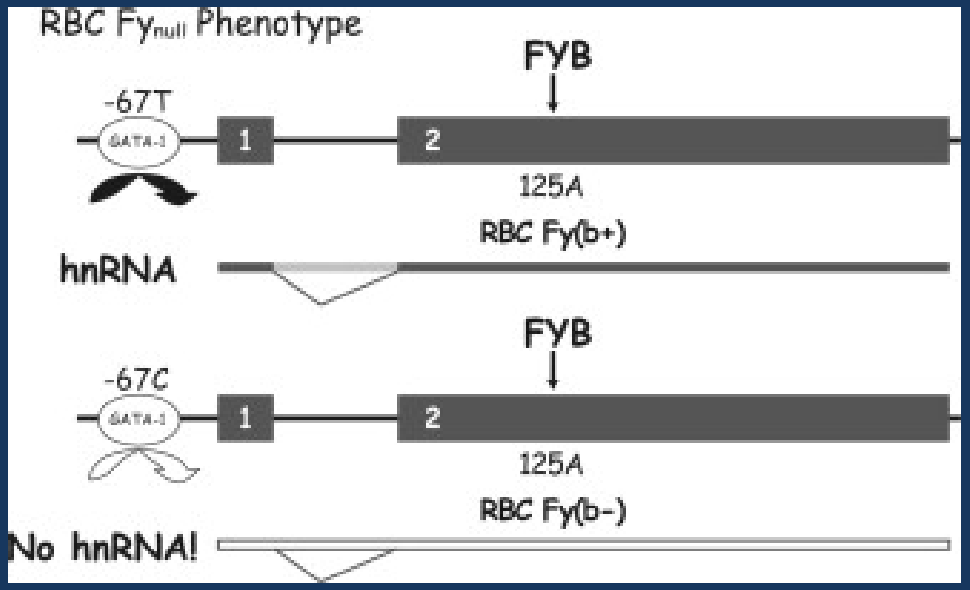
Castro O et al, 2002

Molecular genetic blood group analysis for all SCD patients ?



GATA binding site mutation

Single nucleotide mutation in the FY*B gene promoter prevents GATA-1 binding, with consequent lack of FyB expression in erythroid cells (but not in other tissues).



Extended phenotype matching : effect on blood availability

1. *Basic level match:*

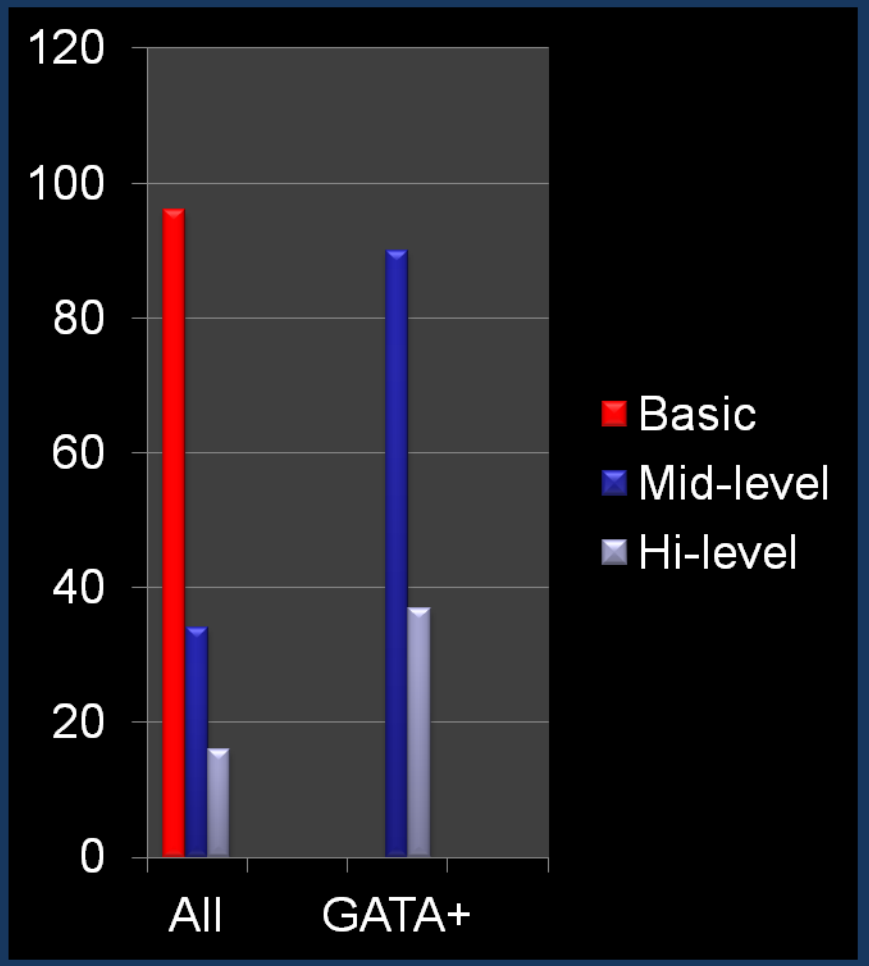
   ABO, DCcEe, K

2. *Mid-level match:*

   1 + Fya, Fyb

3. *High level match:*

   2 + Jka,Jkb,S,s



Wilkinson K et al 2012

ALLOIMMUNISATION IN THALASSEMIA

Alloimmunisation to Red Cells in Thalassemia Major

- 3-5% in Italy (*Sirchia et al 1985; Rebulla et al 1991*)
- 20.8% in Oriental Thal patients in USA (esp. anti-K) (*Singer et al 2000*)
- 16.5% in USA , 13.3% in Asians *vs* 21.2% in Caucasians (*Thompson et al 2011*) .
- Cheng CK et al (*2012*) found 20% alloimmunisation rate among regularly transfused Thal patients in Hong Kong

Ethnic differences in alloantibody frequency

Thompson et al 2011 (Asian 48%)

Antibody	Frequency (%)
Anti-E	19.0
Anti-K	18.1
Anti-C	9.5
Anti-Jk^a/Jk^b	7.8
Anti-c	6.0

Cheng et al 2012 (Asian 100%)

Antibody	Frequency (%)
Anti-E	39.3
Anti-Mi^a/Mur *	30.8
Anti-c	13.1
Anti-Jk^a	6.5
Anti-Fy^a, -S, _Di^a	1.9 each

* 15% Chinese Mi^a antigen +; 6-7% positive for Mur antigen.

Alloimmunisation to Red Cells in Thalassemia Major (II)

- Splenectomy imparted higher risk of alloimmunisation (OR 1.85, CI 1.12-3.05)
- But not confirmed by MvLR in study by Vichinsky et al (*Transfusion* 2014; 54:972)
- The only predictive factor identified :
- Duration of regular transfusions : 20+ years

Summary

- Alloimmunisation still common in SCD and Thal, occasionally insurmountable problem .
- Rate of alloimmunisation to Rh antigens remains high despite matching of blood.
- Partly explained by variant blood group genes
- Blood group genotyping of SCD/Thal patients, and also selected donors, may help alleviate the problem in future