AABB Annual Meeting Education Program 2014

October 25-28, 2014 | Pennsylvania Convention Center | Philadelphia, PA

Presentation Handouts

(9228-TC-HEM) How to Avoid Non-ABO Immune-Mediated Hemolysis and Red Cell Alloimmunization

October 26, 2014 ✧ 4:00 PM - 5:30 PM

Advancing Transfusion and Cellular Therapies Worldwide

Event Faculty List

Event Title: **(9228-TC-HEM)** How to Avoid Non-ABO Immune-Mediated Hemolysis and Red Cell Alloimmunization
Event Date: October 26, 2014
Event Time: 4:00 PM - 5:30 PM

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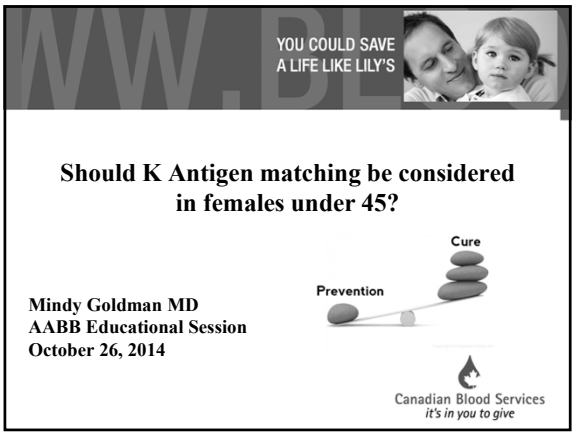
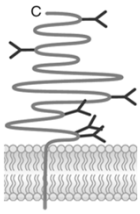


Kell Antigen System

- Transmembrane glycoprotein in the zinc endopeptidase family
- Well-developed at birth, found on fetal RBCs at 10-11 weeks gestation
- Expressed on mature RBCs and erythroid progenitor cells
- Encoded by a gene on chromosome 7



Essential Guide to Blood Groups, Daniels and Bromilow
Second Edition, Wiley-Blackwell

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Kell (K, K1, KEL1) Antigen

- K differs from k (KEL2, Cellano) by a single nucleotide change in exon 6
- This results in threonine in k and methionine in K at position 193
- K is found in 9% of Caucasians, <2% of other racial groups
- K is highly immunogenic
- Anti-K is the most common antibody outside of the ABO, Rh systems
- Usually IgG

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Canadian Blood Services (CBS)

- Acts as the blood supplier for all Canadian provinces and territories except Québec
- Performs prenatal testing for all western provinces
- Acts as the centralized transfusion medicine laboratory for the province of Manitoba

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4 Questions

1. How frequent is anti-K in prenatal patients?
2. How often is anti-K the result of transfusion?
3. What are the clinical consequences of anti-K in pregnancy?
4. What are we doing internationally?

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Frequency of anti-K in prenatal patients

- Ranges from 2.3 to 19 per 10,000 in European and US studies
- Much lower in studies from China, India
- From 2011-2013, 356,237 patients tested at CBS
- Rate of anti-K was 10.2 per 10,000 overall, ranged from 6.2 (BC) to 20.5 (Manitoba) per 10,000

E > K > D
19.1 10.2 7.9/10,000

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Anti-K and transfusion vs. previous pregnancy

- 9% of RBC units will be K+
- In Manitoba, female patients <45 received a median of 2 units and an average of 4 units per transfusion episode

- 9% of male partners will be K+, almost all heterozygous
- ~ 4.5% of fetuses will be K+

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Anti-K and transfusion

- History of transfusion in 50-83% of patients in case series
- In a Dutch case-control study of prenatal patients with and without alloantibodies, 83% of patients with anti-K had a history of transfusion (OR 96.4)
- Parity was not a significant risk factor for anti-K (OR 1.43, 95% CI 0.84-2.46)
- In Manitoba, 35% of perinatal patients with anti-K in 2011 and 2012 have a history of transfusion in Manitoba ≥ 2001

Koelewijn et al, BJOG 2009;116:655

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Clinical consequences of anti-K

24,390 patients transfused
0.41% alloimmunized

100 alloimmunized patients

90 partner K-

10 partner Kk

5 fetus kk

5 fetus Kk

2 severely affected

McKenna et al. Obstet & Gyn 1999;93,667
Bowman et al. Obstet & Gyn 1992;79:239

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HDFN anti-K vs. anti-D

	Anti-K (n=34)	Anti-D (n=157)	p value
IUT	**82%**	66%	0.07
Mean # of IUT	**3**	2	0.01
Hb at first IUT (g/L)	53	64	0.16
Hb at birth (g/L)	79	72	0.01
Bilirubin at birth (mg/dL)	3.1	**6.0**	<0.01
Phototherapy	91%	**98%**	0.07
days	2.4	**4.1**	<0.01
Exchange transfusions	6%	**62%**	<0.01

IUT = intrauterine transfusions
HDFN = hemolytic disease of the fetus and newborn

Rath et al. Vox Sang 2011;100,312

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HDFN due to anti-K

- May result in fetal death due to severe hydrops, although in general milder than HDFN due to anti-D
- Routine prenatal screening for antibodies and referral to high risk unit may decrease mortality
- More suppression of erythropoiesis and less hemolysis and hyperbilirubinemia compared to HDFN due to anti-D
- Titres do not correlate as well with severity, titre of at least 1:8 in affected cases and 1:32 in severe cases

Kamphuis et al. Transfusion 2008;48:953

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International policies for Kell matching, females ≤ 45

Country	National Standard	Practice	Reference/contact
Canada	No	Selected hospitals	Canadian Standards Association, Blood and blood components Draft standard Z902-15
US	No	No	AABB Standards for Blood Banks and Transfusion Services Naomi Luban, National Children's Hospital
Australia	No (under evaluation)	Selected hospitals	Joanne Pink, ARCBS
Denmark	No	Standard practice	Karin Magnussen, University of Copenhagen
Sweden	No	Done by some hospitals	Rut Norda, University of Uppsala
Israel	No	No	Vered Yahalom, Magen David Adam, Isreali National Blood Services

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International policies for Kell matching, females ≤ 45

Country	National Standard	Practice	Reference/contact
UK	Yes	K matched or K- Inconsistent age limit	British Committee for Standards in Haematology: Guidelines for pre-transfusion compatibility produces in blood transfusion laboratories Edwin Massey, NHSBT
France	Yes	Standard practice Also RhCE	Transfusion de globules rouges homologues, recommendations, 2002 Agence Francaise de Securité Sanitaire des produits de santé Olivier Garraud, Etablissement Francais du Sang
Netherlands	Yes	Females ≤ 45 c and E matched as well	Dutch Blood Transfusion Guideline, 2011 Kamphuis et al.
Belgium	Yes	Females ≤ 45 Also RhCE	Bonnes pratiques de transfusion à l'usage des hôpitaux 2010, Conseil Supérieur de la Santé Véronique Deneys, Croix-Rouge de Belgique
Germany	Yes	K matched or K- Also RhCE	Bundesanzeiger 57(209a):4-35, 2005 Willy Flegel, NIH

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RBC Phenotyping

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RBC Phenotyping at CBS

- Most hospitals prophylactically match for Rh C/c, E/e and K in sickle cell and thalassemia patients
- Phenotyping is done in 2 donor testing laboratories, using automated solid phase technology, results transferred to eProgesa
- Results print on RBC label if typing has been done on 2 different donations
- As of Sept/2014, 35% of active donors (donation in last 18 months) have been tested for K
- 92% of tested donors are K-

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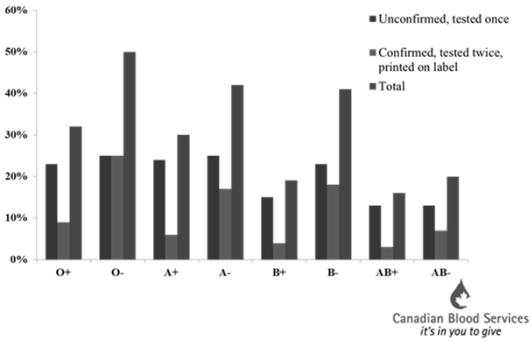
% of active donors in each ABO, RhD group known to be K-



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Summary – anti-K

- ~ 92% of the population are K- and at risk for alloimmunization
- 50-80% of anti-K is due to transfusion
- Anti-K is present in ~ 1 in 1,000 prenatal patients
- Anti-K can cause severe HDFN in ~ 1 in 50,000 prenatal patients (1 in 50 alloimmunized patients)
- ~ 12,500 matched transfusion episodes required to prevent 1 case of HDFN due to anti-K

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Summary – prophylactic matching

- In many European countries, K matched or K- RBCs are routinely used for females ≤ 45
- This is not currently done in the US, Canada, or Australia
- Blood centres are performing an increasing volume of phenotyping to provide antigen matching for other patient populations
- Phenotyping and labelling can be highly automated
- NYBC has started labelling all units for RhCE and K
- ~ 8% of RBC use occurs in females ≤ 45

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Pros – K matching, females < 45

- Anti-K may cause severe HDFN
- Should be feasible given low frequency of K+ donors, relatively small percentage of transfusions given to females < 45
- Standard in many European countries
- Automated mass phenotyping is already being performed to meet needs for phenotype matching of other patient groups

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Cons – K matching, females < 45

- Although rate of alloimmunization is relatively high, only 1 in 50 alloimmunized patients will have an affected baby
- ~ 12,500 matched transfusion episodes needed to prevent 1 case of HDFN
- If K typing is only indicated on a subset of RBC units, inventory management is more complex, and care must be taken not to divert phenotyped units from other patient groups

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Now What?

- A retrospective study by the BEST group on HDFN due to anti-K has started (Dr. Meghan Delaney, AMIGO study, Antigen Matching Influence on Gestational Outcomes)
- The Canadian Standards Association (CSA) is setting up a working group to further evaluate benefits, costs and feasibility
- CBS is assessing implementation of this policy in Manitoba

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Thank You!

- Robert Fallis
- Balkar Gill
- Ilona Resz

- International colleagues

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Non ABO hemolytic reactions in hemovigilance systems

Pierre Robillard MD
Medical director
Héma-Québec, Montréal, Canada

Plan of presentation

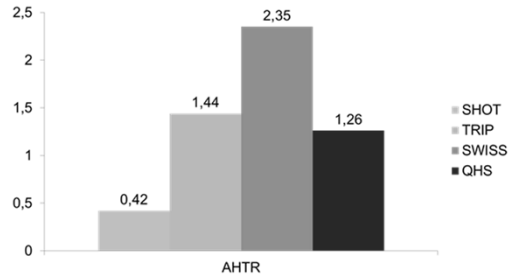
- Incidence of RBC-associated:
  - acute hemolytic transfusion reactions (AHTR)
  - delayed hemolytic transfusion reactions (DHTR)
  - Delayed serologic transfusion reactions (DSTR)
- Antibodies involved in hemolytic transfusion reactions
- Evaluation of a virtual transfusion registry in Québec

Source of data

- Published hemovigilance reports 2012
  - UK Serious Hazards if transfusion (SHOT)
  - Netherlands (TRIP)
  - Switzerland (Swissmedic)
  - French Hemovigilance System (FHS)
  - Québec Hemovigilance System (QHS)
- Evaluation study of a virtual transfusion registry in Québec

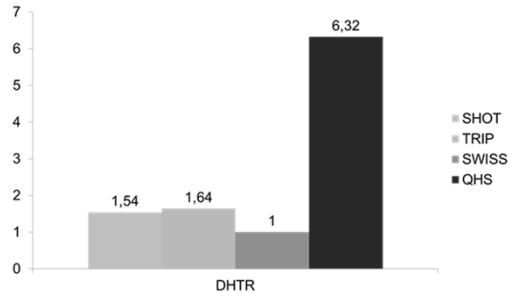
Incidence of AHTR 2012

per 100,000 RBC units

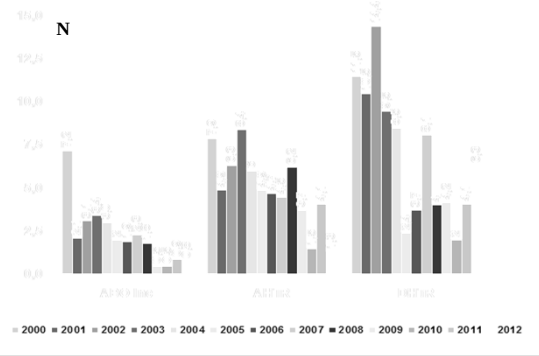


Incidence of DHTR 2012

per 100,000 RBC units

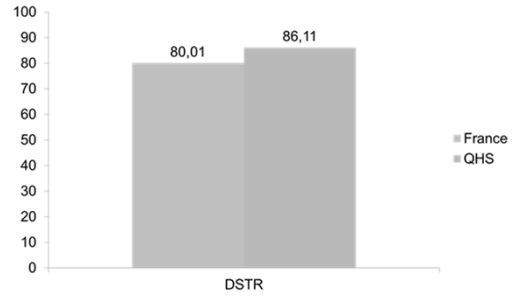


Incidence per100,000 RBC units transfused



Incidence of DSTR 2012

per 100,000 RBC units



Hemolytic reactions – SHOT 2012

DATA SUMMARY
Total number of cases: 42

Implicated components		Mortality/morbidity	
Red cells	42	Deaths due to transfusion	0
FFP	0	Deaths probably/likely due to transfusion	1
Platelets	0	Deaths possibly due to transfusion	0
Cryoprecipitate	0	Major morbidity	9
Granulocytes	0	Potential for major morbidity (Anti-D or K only)	0
Multiple components	0		
Unknown	0		

Gender		Age		Emergency vs. routine and core hours vs. out of core hours		Where transfusion took place	
Male	14	≥18 years	42	Emergency	3	Emergency department	1
Female	28	16 years to <18 years	0	Urgent	13	Theatre	3
Not known	0	1 year to <16 years	0	Routine	25	ITU/NNU/HDU/Recovery	5
		>28 days to <1 year	0	Not known	1	Wards	21
		Birth to ≤28 days	0			Delivery Ward	1
		Not known	0	In core hours	0	Postnatal	1
				Out of core hours	0	Medical Assessment Unit	6
				Not known/Not applicable	42	Community	0
						Outpatient/day unit	4
						Hospice	0
						Antenatal Clinic	0

AHTR – SHOT 2012 (n=9)

Antibody	Clinical signs	Indicators of haemolysis	Morbidity and imputability
Anti-Jk[a]	Hypotension, jaundice	bilirubin↑;Hb↓	ITU admission and death. Probably contributory
Anti-Wr[a]	Rigors, fever and hypertension	bilirubin↑;no Hb increment	Probable
Anti-E?	Chills, rigors; hypertension; low O2 sats	bilirubin↑;Hb↓; Hburia; slightly haemolysed plasma	Full recovery. Certain
None (hyperhaemolysis)	Tachycardia, fever, hypertension	bilirubin↑;Hb↓; haemolysed plasma; LDH↑; creatinine↑	Acute renal impairment with full recovery. Certain
Enzyme-only anti-E	Back pain, chest pain, pyrexia, jaundice	bilirubin↑;Hb↓; red urine; LDH↑	Full recovery. Probable
Autoantibody	Pyrexia, nausea, chest pain, rigors	bilirubin↑;Hb did not increment as expected	Full recovery. Probable
Anti-Wr[a]	Diarrhoea, vomiting, hypotension, jaundice	bilirubin↑;evidence of DIC	ITU admission with full recovery. Probable
Unspecified antibody to low frequency antigen	Back pain and vomiting	bilirubin↑;	Full recovery. Possible
?auto	Fever	No Hb increment	Full recovery

DHTR – SHOT 2012 (n=33)

Antibody specificity by blood group system and antigen		No. cases	No. cases where this was the sole new antibody
Kidd			
	Jk^a	15	8
	Jk^b	5	2
Rh			
	E	8	1
	c	4	1
	C	2	0
	C^w	1	0
	ce (f)	1	0
Duffy			
	Fy^a	4	1
	Fy^b	1	1
	FyG	1	1
Kell			
	K	4	2
MNS			
	M	1	0
	S	4	1
	U	1	0

There were 5 cases where the alloantibodies were not fully identifiable using standard IAT techniques:

AHTR – TRIP 2006-2012

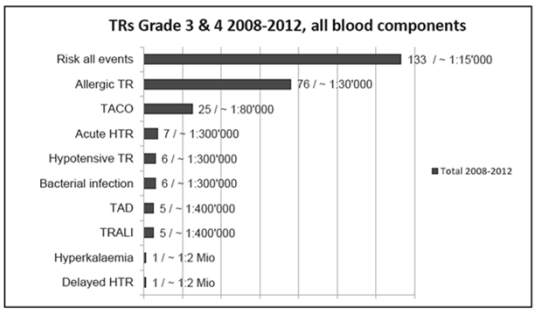
	AHTR total	Patient gender F	M	Reports with certain, probable or possible imputability	Severity grade 0	1	2	3	4
2006	19	10	9	18	1	11	5	1	
2007	11	7	4	10		8	2		
2008	18	14	4	17		10	7		
2009	18	13*	4*	17		11	4	1	1
2010	21	8	13	20		14	5	1	
2011	16	10	6	14		6	7		1
2012	7	5	2	7		4	2		1
Total	110	66*	43*	103		64	33	3	3

**1 x gender not stated*

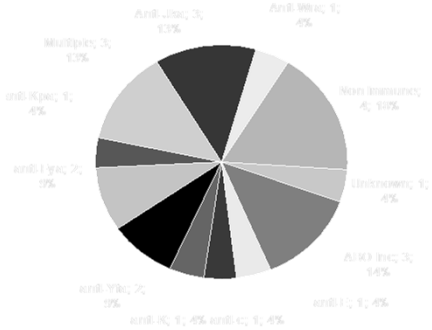
DHTR – TRIP 2006-2012

	Main category DHTR	Severity grade 2	1	0
2006	14	8	5	-
2007	11	4	4	1
2008	18	4	6	5
2009	8	3	5	-
2010	7	5	2	-
2011	9	1	8	-
2012	8	1	5	1
Total	75	26	35	7

AHTR DHTR – SWISS 2012 severity

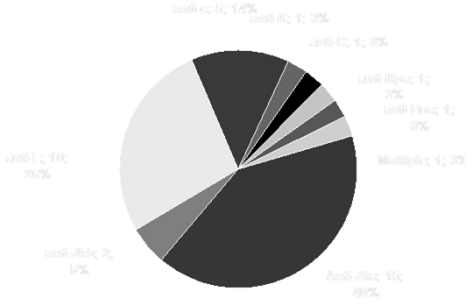


Causes of AHTR – QHS 2009-2012



N = 23

Causes of DHTR – QHS 2009-2012

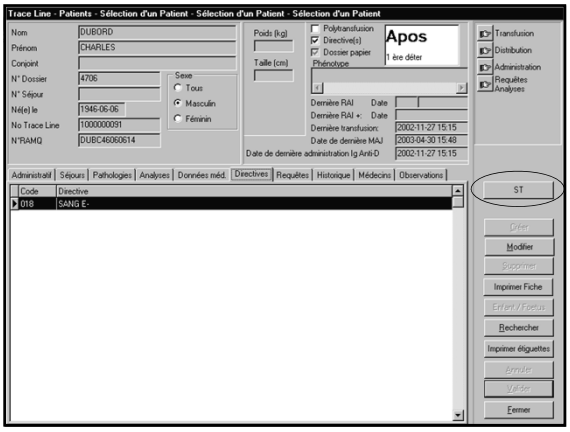


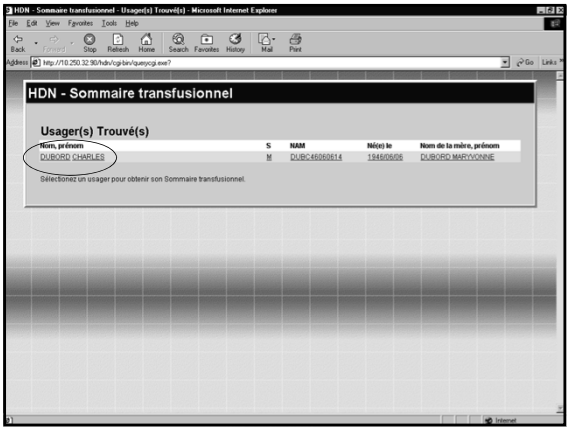
N = 37

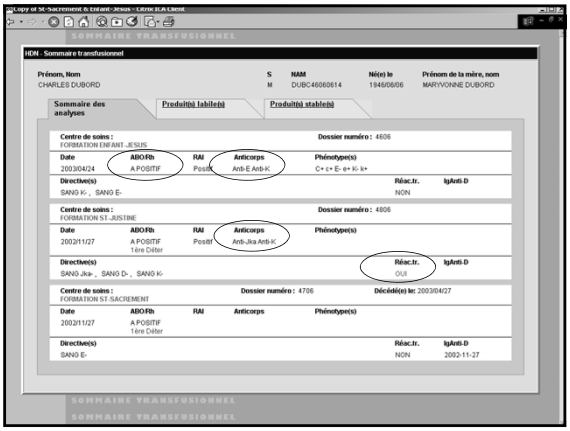
Evaluation of virtual transfusion registry in Québec

Online transfusion history

- In the period May 2003- Nov. 2005
  - All Québec hospitals were progressively computerized with the same blood bank software
- A query tool was added
  - Each hospital can query the BB database of all other hospitals to see if patient is present
  - If so information will appear on screen:
    - Blood group, irregular antibodies
    - Previous transfusions
    - Previous transfusion reactions, special requirements
  - This information can be compared with current info or test results on patients
  - Information cannot be saved and disappear from screen upon leaving the query tool.




HDN - Sommaire transfusionnel
Usager(s) Trouvé(s)
Nom, prénom
S
NAM
Né(e) le
Nom de la mère, prénom
DUBORD CHARLES
M
DUBC46060614
1946/06/06
DUBORD MARYVONNE
Sélectionez un usager pour obtenir son Sommaire transfusionnel.


HDN - Sommaire transfusionnel
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1946/06/06
Prénom de la mère, nom
MARYVONNE DUBORD
Sommaire des analyses
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Produit(s) stable(s)
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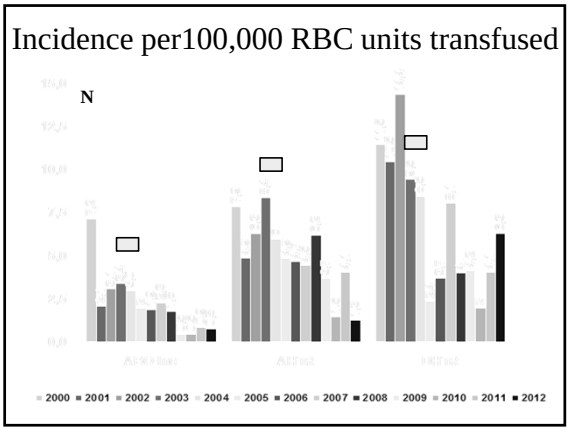

Incidence per100,000 RBC units transfused
N
2000 2001 2002 2003 2004 2005 2006 2007 2008 2009 2010 2011 2012

Methods

- **Data on reactions: AHTR, DHTR and ABO mistransfusions reported to the Quebec Hemovigilance System**
  - **Imputability possible, probable and definite**
  - **Red Blood Cells**
- **Data on actual number of RBC units transfused extracted from hospital monthly reports on utilization to the Health Ministry**

Methods

- **Each hospital contacted to collect:**
  - **Exact date when consultation of transfusion history started or**
  - **Month when started**
    - **15th of the month was used**
- **Pre and post consultation files created**
  - **Adverse reactions**
  - **RBC units transfused**

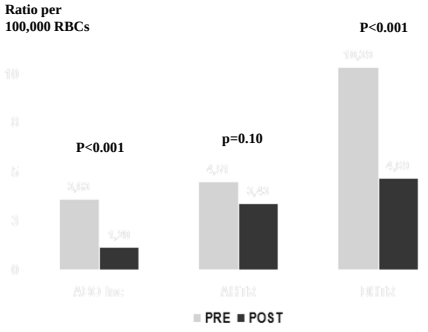
Methods

- **Analysis**
  - **Pre and post consultation incidence rates calculated**
  - **Fisher exact X^2 tests used for comparisons**

Effect of inter-hospital online transfusion history consultation

		ABO-INC	AHTR	DHTR	RBCs transfused
Pre	N	29	36	83	798,521
	ratio	1 : 27,535	1 : 22,181	1 : 9,621	
Post	N	21	60	82	1,747,447
	ratio	1 : 83,212	1 : 29,124	1 : 21,310	
RR		0.30 (0.17-0.53)	0.76 (0.50-1.15)	0.45 (0.33-0.61)	

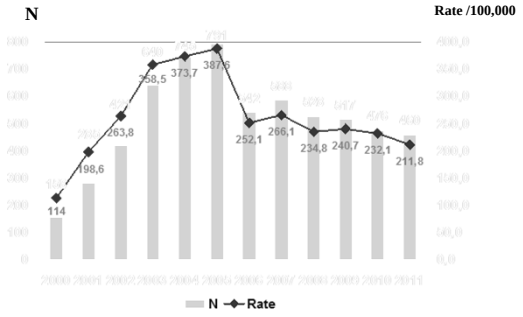
Effect of inter-hospital online transfusion history consultation



Alternate explanations

- **Reporting bias**
  - **unlikely**
- **Blood bank computerization alone**
  - **Impossible to isolate effect because implemented simultaneously with query tool**
  - **2/3 hospitals already computerized**
- **Education provided by TSOs**
  - **Not possible to control for**
    - **Results similar when excluding year 2000**
- **Implementation of stricter patient ID procedures**
  - **Impossible to control for with available info**
  - **No electronic patient ID implemented**

FNHTR - RBCs



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  - Impossible to control for with available info
  - No electronic patient ID implemented

Analysis excluding year 2000

Period 2001-2005

	ABO-INC	AHTR	DHTR
Pre	2.88	4.09	10.15
Post	1.20	3.43	4.69
p-value	<0.001	0.15	<0.001

Period 2000-2005

	ABO-INC	AHTR	DHTR
Pre	3.63	4.51	10.39
Post	1.20	3.43	4.69
p-value	<0.001	0.10	<0.001

Alternate explanations

- **Reporting bias**
  - **unlikely**
- **Blood bank computerization alone**
  - **Impossible to isolate effect because implemented simultaneously with query tool**
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    - **Results similar when excluding year 2000**
- **Implementation of stricter patient ID procedures**
  - **Impossible to control for with available info**
  - **No electronic patient ID implemented**

CONCLUSION

- AHTR and DHTR are not rare
- Majority of AHTR and almost all DHTR are due to irregular antibodies
- A significant proportion of AHTR and DHTR are severe with few occasional deaths
- DSTR incidence 10-20 fold that of DHTR
- A transfusion registry is an effective tool in preventing DHTR

HOW TO AVOID NON-ABO IMMUNE MEDIATED HEMOLYSIS AND RED CELL ALLOIMMUNIZATION (9228-TC)

RHD Genotyping for Pregnant Women and Transfusion Recipients With A Serological Weak D Phenotype

AABB Annual Meeting
October 26, 2014

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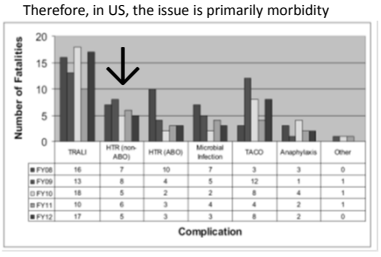
FDA: Transfusion Fatalities

In 2012, there were (only) 5 deaths reported due to non-ABO hemolytic transfusion reactions

Therefore, in US, the issue is primarily morbidity

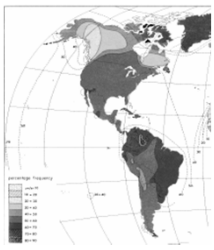


	TRALI	HTR (non-ABO)	HTR (ABO)	Microbial Infection	TACO	Anaphylaxis	Other
FY08	16	7	10	7	3	3	0
FY09	13	8	4	5	12	1	1
FY10	18	5	2	2	8	4	1
FY11	10	6	3	4	4	2	1
FY12	17	5	3	3	8	2	0

-- www.fda.gov

Distribution of the *d* Gene

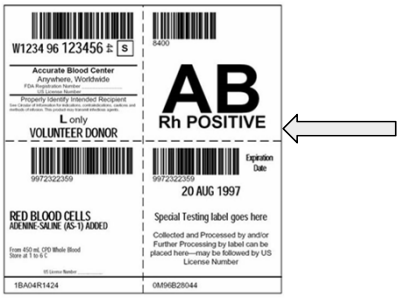
A.E Mourant. The Distribution of the Human Blood Groups, Oxford: 1976



Practices for Decreasing Rh Immune-Mediated Hemolysis and Red Cell Alloimmunization

- Avoid exposure of D- persons to D+ RBCs
- Rh Immunoprophylaxis
- AABB and ACOG guidance for serological weak D phenotypes
- Work Group: Genotype serological weak D phenotypes, when identified, and manage weak D types 1, 2 and 3 as Rh-positive
- Research: New immunosuppressive protocols for BMT and organ transplants prevent primary immune response to D+ RBCs

Blood Unit Labels Include RhD Blood Type



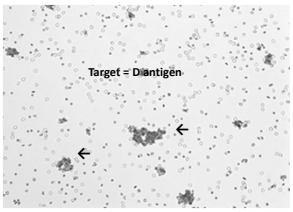
Postpartum Rh Immunoprophylaxis

4-Step Procedure

- Screen RhD-negative mother's blood for fetal RBCs
- Quantify D+ fetal RBCs in mother's blood
- Calculate volume of fetomaternal hemorrhage
- Estimate of number of vials of Rh immune globulin

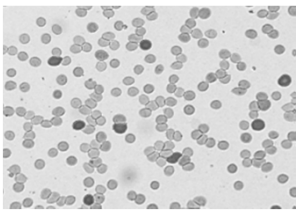
Qualitative (Rosette) Fetal RBC Screen

- Screen for RhD-positive fetal RBCs among RhD-negative mother's RBCs
- Will detect a 10 mL FMH



Quantitative Acid-Elution (K-B) Assay

Distinguishes HbF-containing fetal RBCs from HbA-containing adult RBCs



Policies for Decreasing Risk of Rh Alloimmunization

- 1992 ACOG: A woman with a weak D is Rh-positive and should not receive RhIG
- 2014 AABB *Standards* 29th edition: If the woman's test for D antigen is negative, a test for weak D is not required.

AABB-CAP Interorganizational Work Group on *RHD* Genotyping

Scientific Consultants

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Col. Clayton D. Simon, MD (ASBP)
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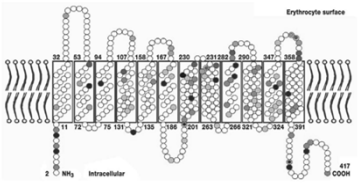
Serologically-Defined Weak D Phenotypes (Weak D, Partial D, DEL) Versus Molecularly-Defined Weak D Types (>200 reported)

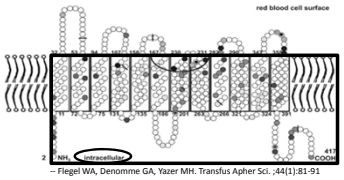


-- Flegel WA, Denomme GA, Yazer MH. Transfus Apher Sci. ;44(1):81-91.

Serological Weak D Phenotypes

- Definition: RBCs type as RhD-negative, inconclusive, or discordant by anti-D reagent, but RhD-positive by AHG (weak D) test
- Weak D types 1, 2 and 3 (95% of Caucasians) do not form anti-D [RhD-positive]
- Weak D types 4.2 (DAR), 11, 15, 21 and 57 can form anti-D [RhD-negative]
- Weak D types 4.0, 4.1 are inconclusive in US [Provisionally, RhD-negative]

Serological Weak D Phenotypes



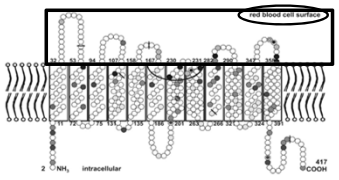
– Flegel WA, Denomme GA, Yazer MH. Transfus Apher Sci. ;44(1):81-91

Many serological weak D phenotypes are associated with one or more amino acid substitutions in the RhD protein within or below the RBC membrane causing decreased antigen expression on the red cell surface.

Partial D Phenotypes

- RBCs type as RhD-positive and, therefore, partial Ds are not identified by routine RhD typing
- Persons with a partial D may form anti-D after exposure to [normal, wild type] RhD-positive RBCs
- Monoclonal anti-D reagents type partial DVI, the most common partial D phenotype, as RhD-negative

Partial D Phenotypes



-- Flegel WA, Denomme GA, Yazer MH. Transfus Apher Sci. ;44(1):81-91.

Many partial D phenotypes are associated with one or more amino acid substitutions in the RhD protein above the RBC membrane causing lack D epitopes.

DEL Phenotypes

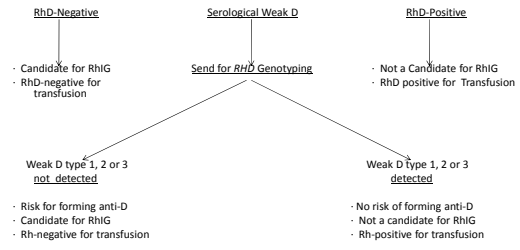
- Type as RhD-negative , but have complete repertoire of D epitopes
- Detected serologically only by adsorption and elution
- RhD-negative recipients unknowingly transfused with DEL-positive/RhD-negative RBCs have formed anti-D

Work Group Recommendation

RHD genotyping should be performed whenever a serological weak D phenotype is detected in a patient, including pregnant women.

Weak D types 1, 2 or 3 should be managed as RhD-positive with regard to administration of RhIG or for transfusion

Recommended Management of Routine RhD Typing Results in Patients



--Interorganizational Work Group on RHD Genotyping

It's time to phase in *RHD* genotyping for patients with a serological weak D phenotype

- Sandler SG, Flegel WA, Westhoff CM, Denomme GA, Delaney M, Keller MA, Johnson, ST, Katz L, Queenan JT, Vassallo RR, Simon, CD. It's time to phase in *RHD* genotyping for patients with a serological weak D phenotype (Commentary). Transfusion, 2014, in press (March, 2015).
- The Work Group will convene in November 2014 to draft a proposal for a Joint Statement "*RHD* Genotyping for Patients with a Serological Weak D Phenotype."

Seager A, Sandler SG. Immunosuppressive protocols for transplantation and certain hematological malignancies can prevent the primary humoral immune response to the D blood group antigen. Immunohematology 2013;29: 110-4.