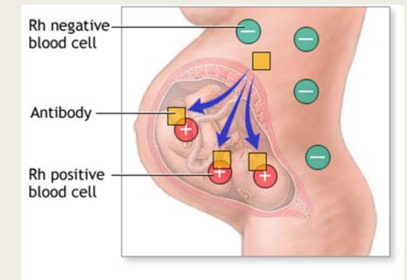
Antenatal case with an FMH where prophylaxis wasn't enough !

Austin Health

Helen Bardsley
Austin Health
NICE October 2016

1990's Administration of RhD-Ig



- **Post delivery**
- administration of RhD-Ig reduces the incidence of Rh isoimmunisation from ~ **13 % to 1 - 2%**

- Studies showed that if RhD-Ig is also given **antepartum at 28 weeks and 34 weeks gestation**
- Rh isoimmunisation can **be further reduced to <0.2%**

Australia commenced antenatal prophylaxis in November 2002

Short-term strategy (began November 2002) **Rh Neg Antenatal Primigravida**	Routine antenatal prophylaxis at 28 & 34 wks during their first pregnancy		625IU
	Post partum : imported product Canadian product WinRho SDF 600IU		600IU
Mid-term strategy All Rh Neg antenatal 1st January 2005	625IU Routine antenatal prophylaxis at 28 & 34 weeks for all Rh D neg women		625IU
	Post partum imported product Canadian product WinRho SDF 600IU		600IU
Long-term strategy Mid 2006	Routine antenatal prophylaxis at 28 and 34 weeks for all Rh D neg women Post partum Australia self-sufficient in Rh D immunoglobulin		625IU

March 2007

Australian & New Zealand Society of Blood Transfusion Ltd

The Royal Australian and New Zealand College of Obstetricians and Gynaecologists

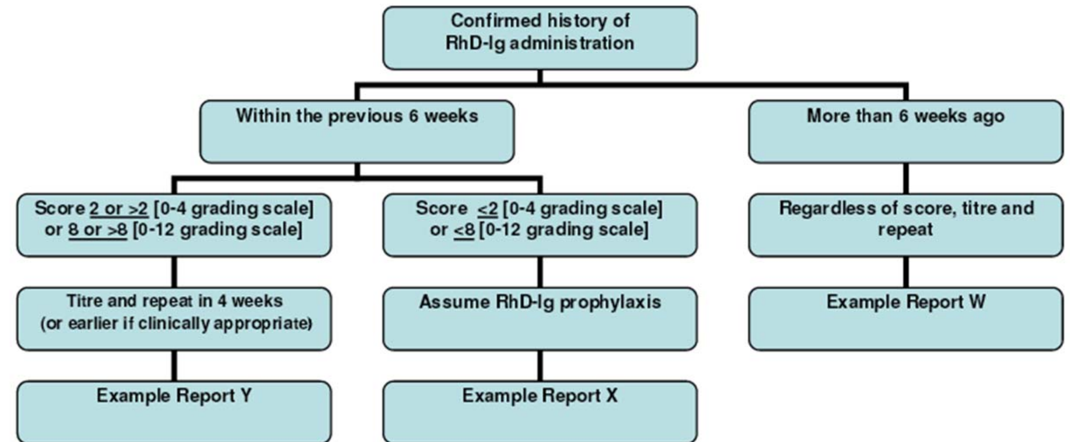
3rd Edition, March 2007

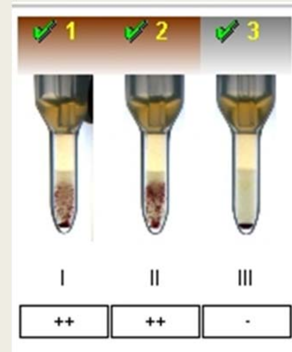
GUIDELINES
FOR
BLOOD GROUPING & ANTIBODY SCREENING
IN THE
ANTENATAL & PERINATAL SETTING

The Royal Australian and New Zealand College of Obstetricians and Gynaecologists

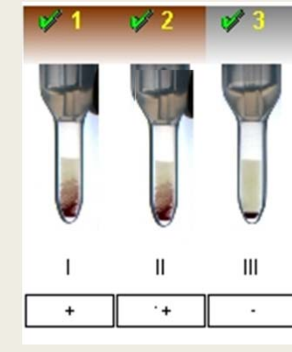
FLOW CHARTS

a] Confirmed RhD-Ig administration





RhDIg 2 weeks ago

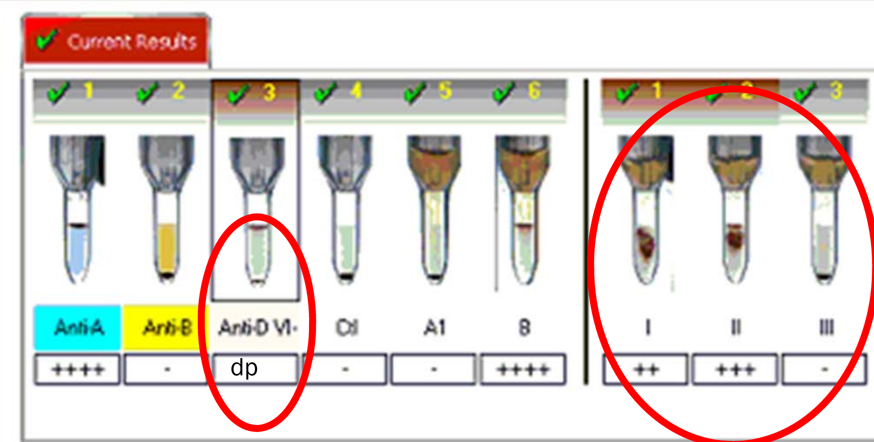


RhDIg 6 weeks ago

2016 -Current Rh D Ig dosing recommendations RhD negative pregnant women

Event	RhD Immunoglobulin Dose
1st trimester sensitising events	250IU
2nd and 3rd trimester sensitising events	625IU
Sensitising events in multiple pregnancies: all trimesters	625IU
Routine prophylaxis at 28-30 and 34-36 weeks	625IU
Postpartum (Birth of a Rh Positive baby)	625IU (dependant on Kleihauer)

- Antenatal case
- 12/02/2016
- Gestation 37+ weeks
- Presented to MHW ED
- 5 days decreased fetal movements



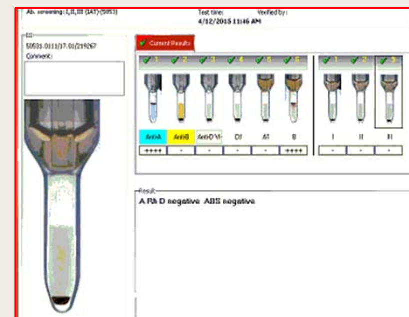
Antenatal blood tests

BB Warnings

List of Requests/Samples

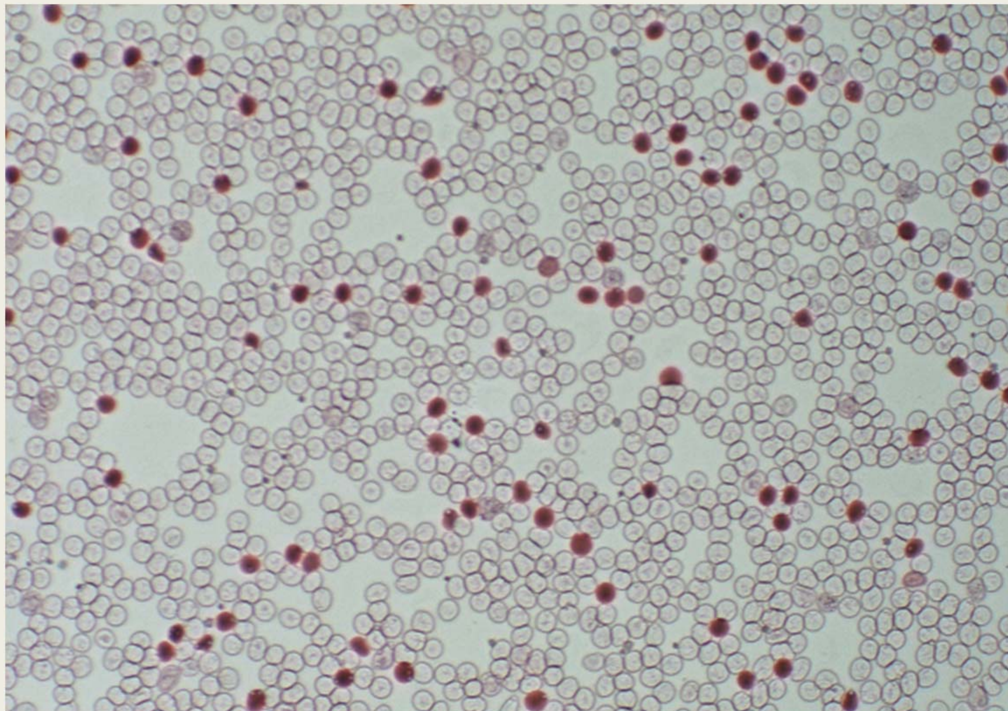
Request	Date	Time	Doctor	Tests Requested
	16/09/15	11:05	RASMI	U
	04/12/15	07:15	RASMI	FBE,GTTP,Ferr,VITD,VzG,RAN
	16/12/15	09:00	M	RHIG
	16/12/15	09:45	PERM02	LFT
	03/02/16	09:45	M	RHIG
	03/02/16	10:15	PERM02	LFT,FBE,TBA,GBSS
	12/02/16	12:09	M	FBE,Ue,LFT,UA,TBA,U,AST
	12/02/16	13:40	WALKS	KLEI,B2GP1,ACA,LAS,TSH,TA,INR,APTT,PARVO,

- 16/09/2015 19+ weeks Ultrasound Normal fetal development
- 04/12/2015 27+weeks Blood Group A RhD Negative
- Antibody screen Negative

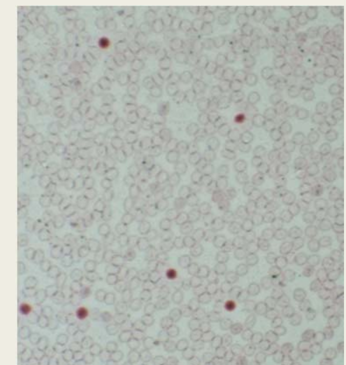


- 16/12/2015 29+ weeks RhD Ig given
- 03/02/2016 35+ weeks RhD Ig given

Kleihauer – fetal cells detected



Patient

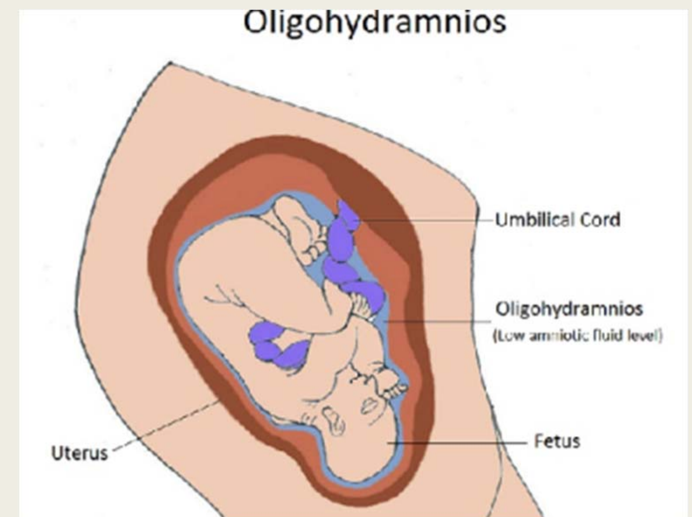


Positive Control

12/02/2016

- Friday evening shift @ 2200
- Abtectcell III 0.8% RhD Negative Screening Cells - Negative
- Mini titre = 16 (Diamed CAT method – quick)
- Kleihauer – Positive ++++
- Doctor notified
- Flow cytometry FMH will be performed on Monday

FDIU



- Ultrasound confirmed fetal death in utero (FDIU)
- Oligohydramnios (low amniotic fluid level)
- Fetal ascites
- Head and neck oedema
- Mother underwent induction of labour
- Delivered a stillborn baby girl at 0159 on 14/02/2016
- Weight 2647g

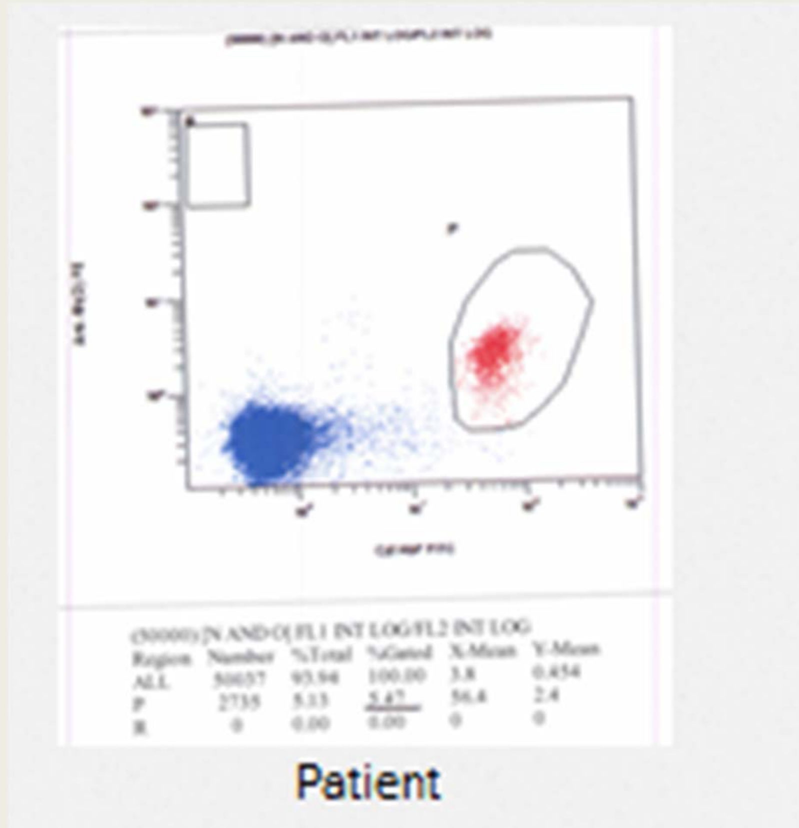
Cord blood unsuitable for testing due to marked haemolysis

Monday 15/02/2016

Flow cytometry FMH

Fetal cells = 5.47 %

FMH Volume = 136.8 ml



(50000) [N AND O] FL1 INT LOG/FL2 INT LOG

Region	Number	%Total	%Gated	X-Mean	Y-Mean
ALL	50037	93.94	100.00	3.8	0.454
P	2735	5.13	5.47	56.4	2.4
R	0	0.00	0.00	0	0

Patient

Monday 15/02/2016 : reviewed all results

- Primigravida
- No history of transfusion or previous pregnancy
- Shared care between Local GP / MHW
- FMH = 136.8 ml
- Antibody screen on 04/12/2015 @27+wks = Negative
- No further antibody screens performed until 12/02/2016
- Antibody screen now positive – stronger reactions than expected with RhDIg
- Titre = 16

- ? Passive Anti-D or alloimmune Anti-D

Currently if RhD-Ig is administered during pregnancy it is impossible to serologically distinguish between this passive immunity and low-level alloimmune anti-D otherwise stimulated by pregnancy or transfusion

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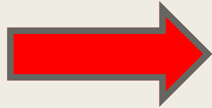
RANZCOG

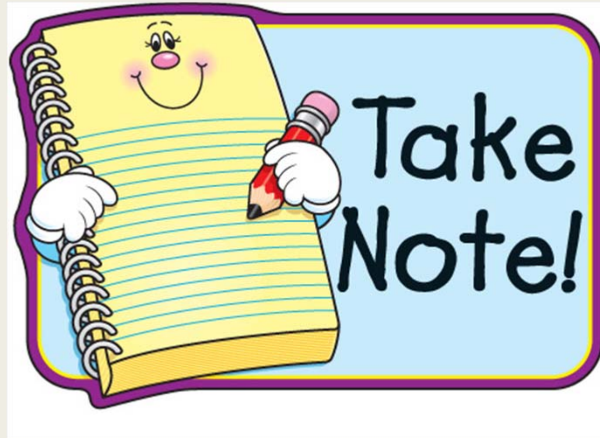
Guidelines for the use of Rh(D) Immunoglobulin (Anti-D) in obstetrics in Australia

Rh antibody testing and assessing magnitude of feto-maternal haemorrhage	
Recommendation 5	**Grade**
Blood should be taken for Rh antibody titre prior to administration of Anti-D, in order to detect those who have already become immunised.	Consensus-based recommendation
Recommendation 6	**Grade**
At 34 weeks gestation the test may be omitted if prophylactic Anti-D was given at 28 weeks.	Consensus-based recommendation
Recommendation 7	**Grade**
Rh (D) immunoglobulin should not be given to women with preformed Anti-D antibodies except where the preformed Anti-D is due to the antenatal administration of Rh (D) immunoglobulin.	Consensus-based recommendation
Recommendation 8	**Grade**
If it is unsure whether the Anti-D detected in the mother's blood is passive or preformed, the treating clinician should be consulted. If there is continuing doubt, Rh (D) immunoglobulin should be administered.	Consensus-based recommendation
Recommendation 9	**Grade**
All women who are given Anti-D in response to a potentially sensitizing event should have the magnitude of potential feto-maternal haemorrhage assessed and if necessary further Anti-D administered as appropriate. When more than four doses of anti-D are given and testing indicates that further anti-D will be required, consideration may be given to using the intravenous route for subsequent doses of anti-D. This will require anti-D specifically intended for intravenous usage (eg, Rhophylac).	Consensus-based recommendation



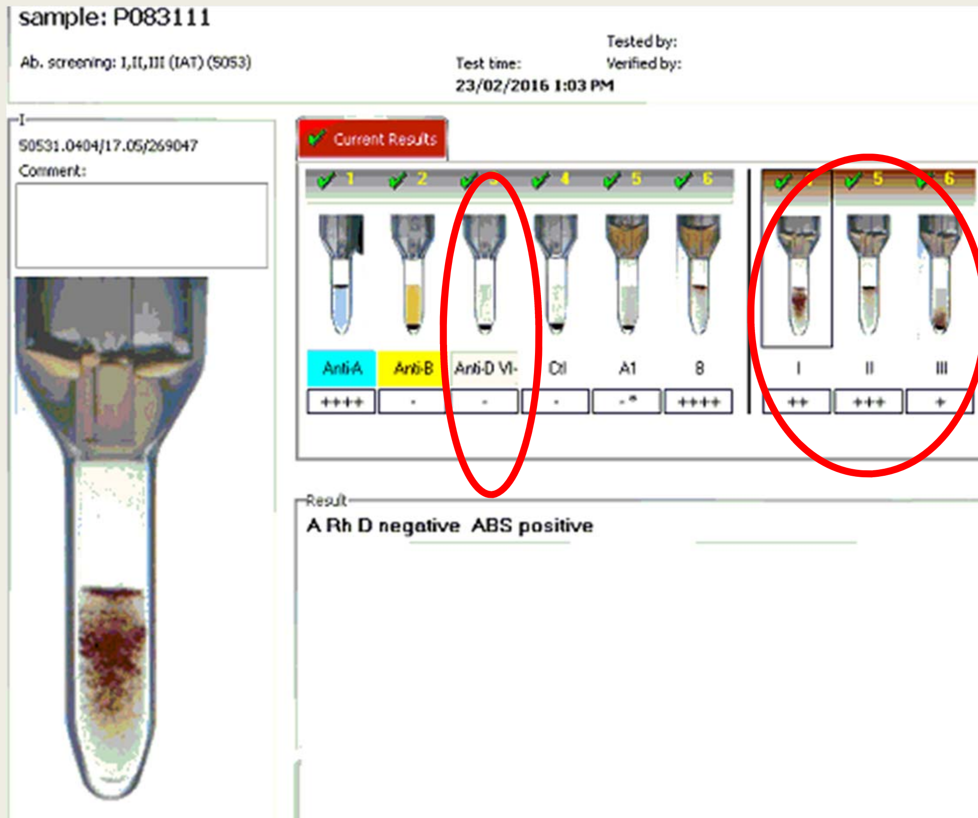
Do we issue prophylactic RhDIg to this patient ?

Professor – said NO !



- Added notes in computer to follow up patient at next visit in 4-6 weeks ?

23/02/2016 - Returned 11 days later



- No mixed field with Anti-D
- Antibody reactions stronger
- Also Weak reactions with
- Rh neg rr cells

23/02/2016

IAT Panel

Anti - D, C , & E

Reactions with rr

Anti-D titre : 16

Phenocell B 0.8% Antigen Composition Sheet — Batch No: 2653 148 — Expiry Date: 2

Cell No	Reference No	Rh Phen.	D	C	E	c	e	C^w	K	k	Kp^a	Fy^a	Fy^b	Jk^a	Jk^b	M	N	S	s	P1	Le^a	Le^b	Lu^a	Co^b	Additional Typings	Cell No	IAT	
			RH						KEL			FY		JK			MNS			P1PK	LE		LU	CO				
1	4104240	$R_1^wR_1$	+	+	0	0	+	+	0	+	0	+	0	0	+	+	+	+	+	+	0	+	0	0		1	8	
2	4124562	R_1R_1	+	+	0	0	+	0	+	+	0	0	+	0	+	+	0	+	0	+	0	+	0	0	Lu:14	2	10	
3	2165671	R_1R_1	+	+	0	0	+	0	0	+	0	0	+	+	0	0	+	0	+	0	+	0	0	0		3	[illegible]	
4	4125085	R_2R_2	+	0	+	+	0	0	0	+	0	+	0	+	0	+	0	+	0	$+^w$	0	0	0	0		4	12	
5	4398907	R_2R_2	+	0	+	+	0	0	0	+	0	0	+	0	+	0	+	0	+	$+^s$	0	+	+	0		5	12	
6	2094621	r'r	0	+	0	+	+	0	0	+	0	+	+	0	+	0	+	0	+	$+^w$	0	+	0	+		6	5	
7	2053543	r"r	0	0	+	+	+	0	0	+	0	0	+	+	0	+	0	+	0	+	0	+	0	0		7	8	
8	2054247	rr	0	0	0	+	+	0	+	+	0	+	0	+	+	0	+	0	+	$+^s$	0	+	0	0		8	0	+/-
9	2193428	rr	0	0	0	+	+	·0	0	+	0	0	+	0	+	+	0	0	+	0	0	0	0	0		9	+/-	
10	2056411	rr	0	0	0	+	+	0	0	+	0	+	0	0	+	+	+	+	+	0	+	0	0	+		10	0	
11	2055439	rr	0	0	0	+	+	0	0	+	0	0	+	+	+	0	+	+	0	+	0	+	0	0		11	0	+/-
Auto																										Auto	0	

Papain Panel

#	Rh-hr		Spender Donor Donneur Donatore Donante Dador	D	C	E	c	e	C^w	K	k	Kp^a	Kp^b	Js^a	Js^b	Fy^a	Fy^b	Jk^a	Jk^b	Le^a	Le^b	P_1	M	N	S	s	Lu^a	Lu^b	Xg^a	♀ ♂	Spez. Antigene Special types Antigènes part. Antigeni particolari Otros Antígenos Tipos especiais		Risultato / Resultad Resultado LISS / Coombs	Enzyme
				Rh-hr						Kell						Duffy		Kidd		Lewis		P	MNS				Luth.		Xg					
1	$CCC^WD.ee$	$R_1{}^WR_1$	096209	+	+	0	0	+	+	0	+	0	+	nt	nt	+	0	0	+	0	+	+	0	+	+	+	0	+	+			1		12
2	CCD.ee	R_1R_1	538206	+	+	0	0	+	0	+	+	0	+	nt	nt	0	+	+	0	0	+	+	0	+	0	+	±	+	+			2		12
3	ccD.EE	R_2R_2	240811	+	0	+	+	0	0	0	+	0	+	nt	nt	+	+	+	0	0	0	+	+	0	+	+	0	+	0			3		12
4	Ccddee	r′r	178782	0	+	0	+	+	0	0	+	0	+	nt	nt	0	+	+	0	0	0	+	+	+	+	+	0	+	+			4		12
5	ccddEe	r″r	113500	0	0	+	+	+	0	0	+	0	+	nt	nt	+	0	+	+	0	+	+	+	0	+	+	0	+	+			5		12
6	ccddee	rr	434747	0	0	0	+	+	0	+	+	0	+	nt	nt	+	+	0	+	0	+	+	+	0	+	0	0	+	+			6		10
7	ccddee	rr	110005	0	0	0	+	+	0	0	+	0	+	nt	nt	0	+	+	0	+	0	+	+	0	+	+	0	+	0			7		10
8	ccD.ee	R_0r	590768	+	0	0	+	+	0	0	+	0	+	0	nt	0	0	+	0	0	0	+	+	+	+	+	0	+	+		M1+*	8		12
9	ccddee	rr	026096	0	0	0	+	+	0	0	+	0	+	nt	nt	0	+	0	+	0	+	0	0	+	0	+	0	+	nt			9		10
10	ccddee	rr	267310	0	0	0	+	+	0	0	+	0	+	nt	nt	+	0	+	0	0	+	0	+	0	+	0	+	+	+			10		10
11	ccddee	rr	135145	0	0	0	+	+	0	0	+	+	+	nt	nt	+	+	+	+	0	+	0	0	+	0	+	0	+	+		Co(b+)*	11		10

ARCBS Report Summary
sample from 23/02/2016

- the sample contains anti-D, anti-C, anti-E
- an unidentified antibody reacting with a number of rr cells
- anti-D is more likely to be active rather than passively acquired

Clinical Notes: 3rd trimester miscarriage (hydrops) anti-D (?passive) possible further Rh antibodies/other antibodies.

GROUP: A Rh(D): Negative

PHENOTYPE: C-E-c+e+ (rr), K-Kp(a-), Fy(a+b-), Jk(a+b+), M-N+S-s+, Lu(a-b+), Co(b-), Ch+, Rg+,Yt(a+).

DAT: Negative by tube.
Very weakly positive by Bio-Rad DAT card due to IgG (score 3).

PLASMA: Anti-D weakly reactive by saline 22°C and strongly by PEG-IAT, BioRad LISS/Coombs card and papain technique.

Titre of the Anti-D by saline-IAT vs. R0r cells is 16.

Anti-C reactive by PEG-IAT, BioRad LISS/Coombs card and papain technique.

Anti-E reactive by PEG-IAT, BioRad LISS/Coombs card and papain technique.

In addition the plasma reacts with a number of rr cells weakly by saline 22°C and slightly stronger by PEG-IAT and BioRad LISS/Coombs card (score 3-5) but was negative by RAM-IAT.

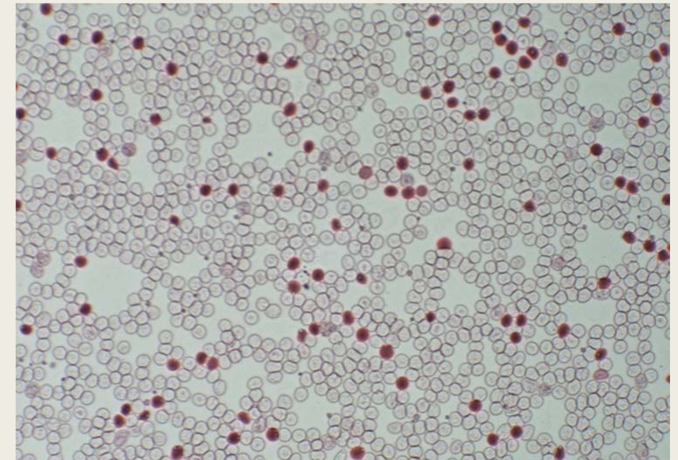
ELUATE: An acid-glycine eluate was negative when tested by tube IAT.

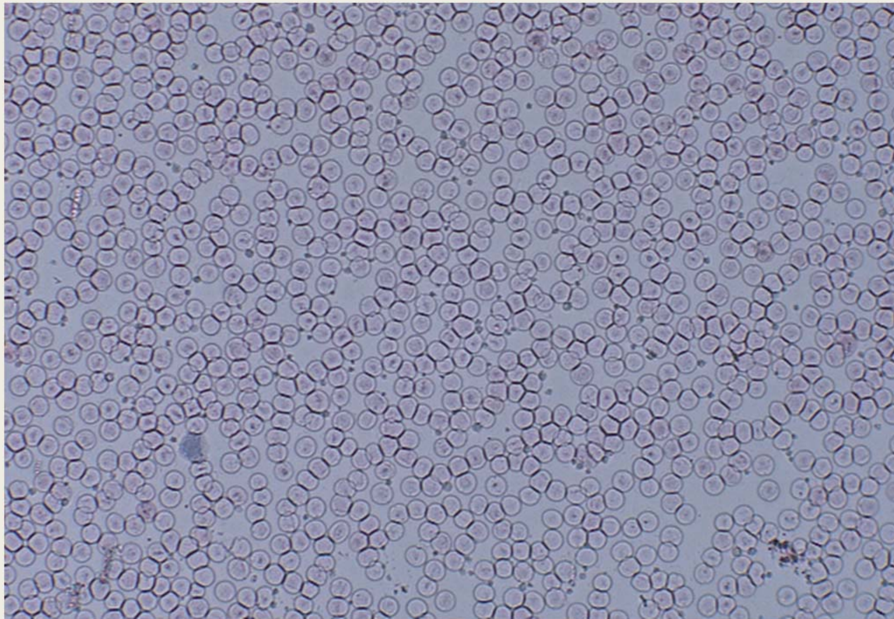
Comments:

The blood sample c contains anti-D, anti-C and anti-E and an unidentified antibody reacting with a number of rr cells. The anti-D is more likely to be active rather than passively acquired as it reacts by saline 22°C, reacts strongly by IAT and has a titre of 16.
We would recommend that a further blood sample be tested in approximately 3-6 months to determine if the anti-D is still present and therefore, an active anti-D, and if the reactions with the rr cells are still present.

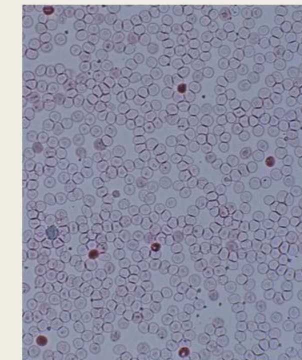
23/02/2016 Kleihauer

12/02/2016





Patient – No fetal cells



Positive Control

Antibody titre

Date	Anti-D	Anti-C	Anti-E
12th Feb	16		
23rd Feb	16 (ARCBS)		
24th March	2048		
19th May	512	32	128

Post mortem summary

- Cause of fetal death - erythroblastosis fetalis secondary to Rhesus alloimmunisation
- Autopsy findings of hydrops and nucleated erythrocytes in the placenta support this
- No report of abdoiminal pain or vaginal bleeding during pregnancy
- FMH occurred in late pregnancy

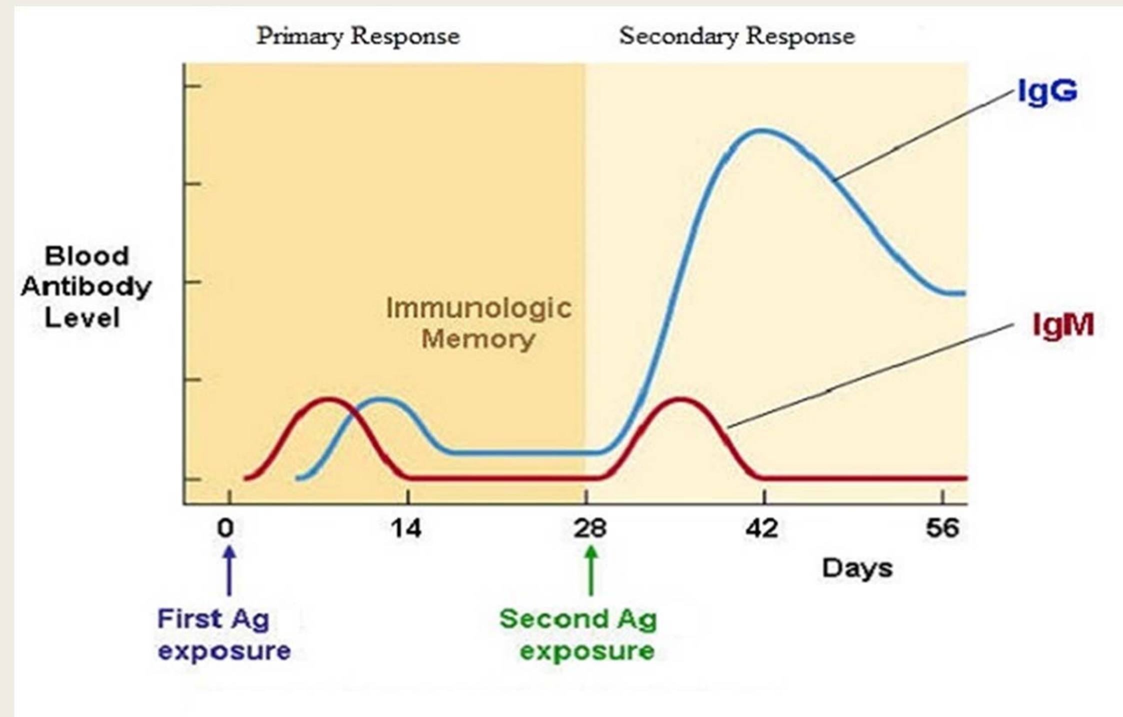
The cause of death in this infant appears to be erythroblastosis fetalis secondary to Rhesus alloimmunisation in a Rhesus D antigen negative mother. Autopsy findings of hydrops and nucleated erythrocytes in the placenta support this. In the setting of a negative history of previous pregnancy and blood tranfusion, no antenatal haemorrhage, negative maternal serum anti-D during pregnancy and a positive peri-partum Kleihauer test, it is likely that there was a sensitising occult fetomaternal haemorrhage during late pregnancy between the Rhesus D negative mother and assumed Rhesus D positive fetus. This theory is supported by the presence of maternal serum anti-D in the post-partum period, which had been negative approximately two months prior.

Summary of Antenatal case :

Fetal maternal haemorrhage : Acute on chronic bleed 137+ mls

Rh D immunised

Prophylaxis was not enough !



Primary and secondary immune antibody response

Acknowledgements : Masa Lasica - Haematology Registrar
Diana Kolar - Senior Scientist

References: NBA letter stage 1 2002
NBA letter stage 2 2004
NHMRC guidelines
ANZSBT guidelines
Use of RhDIg NBA and CSL 2014
RANZCOG 2015

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