Anti-D

The 2012 Annual SHOT Report, and more.....

Cambridge June 2014

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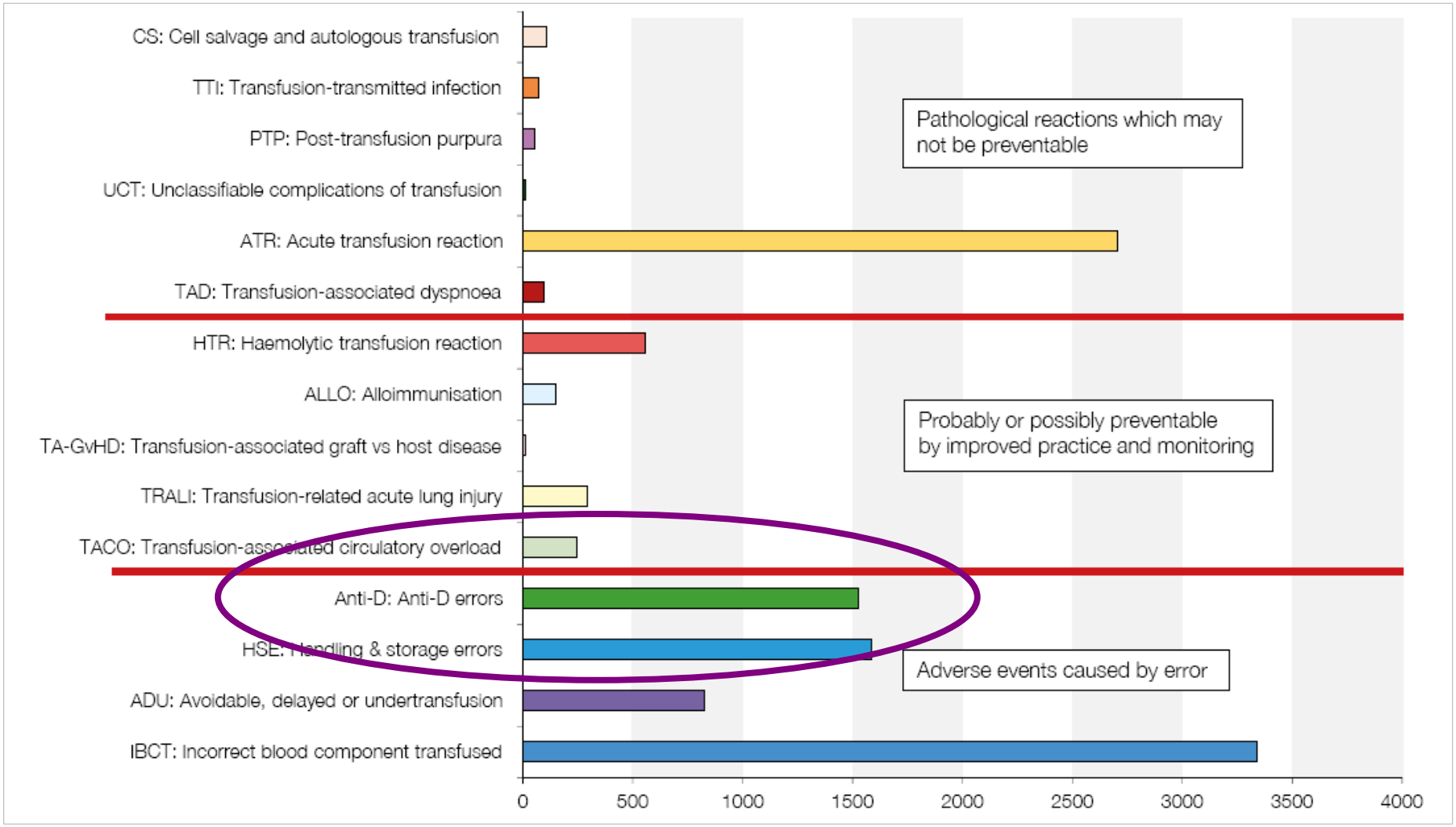
SHOT / NHSBT PBM Team

Why Anti-D Ig?

Although it is a medicinal blood product rather than a blood component, adverse events associated with anti-D immunoglobulin are included in the annual SHOT report as they provide a useful insight into process errors which may be applied to transfusion as a whole

SHOT cumulative data 1996-2012 (n=11,570)



Anti-D Ig Prophylaxis

- Post-delivery anti-D Ig prophylaxis for RhD negative women began in the UK in 1969
- The programme has been a huge success
- Deaths due to haemolytic disease:
  - **320 / 100,000** births in the 1940s
  - **46 / 100,000** births pre-1969
  - **18.4 / 100,000** births by 1977
  - **1.6 / 100,000** births by 1990

Liumbruno et al Review of antenatal prophylaxis Blood Transfusion 2010; 8: 8-16

- Risk of sensitisation if Baby RhD pos and ABO-compatible – 16%
- Risk of sensitisation if baby RhD pos and ABO-incompatible – 2% (so ABO antibodies are protective)
- 92% women develop immune anti-D AFTER 28 weeks gestation

Liumbruno et al Review of antenatal prophylaxis Blood Transfusion 2010; 8: 8-16

- Foetal red blood cells (typically <0.1mL) are found in;
  - 3% women in first trimester
  - 12% women in second trimester
  - 45% women in 3rd trimester
  - >50% women at delivery

Feto-Maternal Haemorrhages (FMH)

- **1st and 2nd Trimester:**
  - Miscarriage / Ectopic / TOP / CVS / Amnio
  - 0.05mL in 5% 0.5mL in 2%

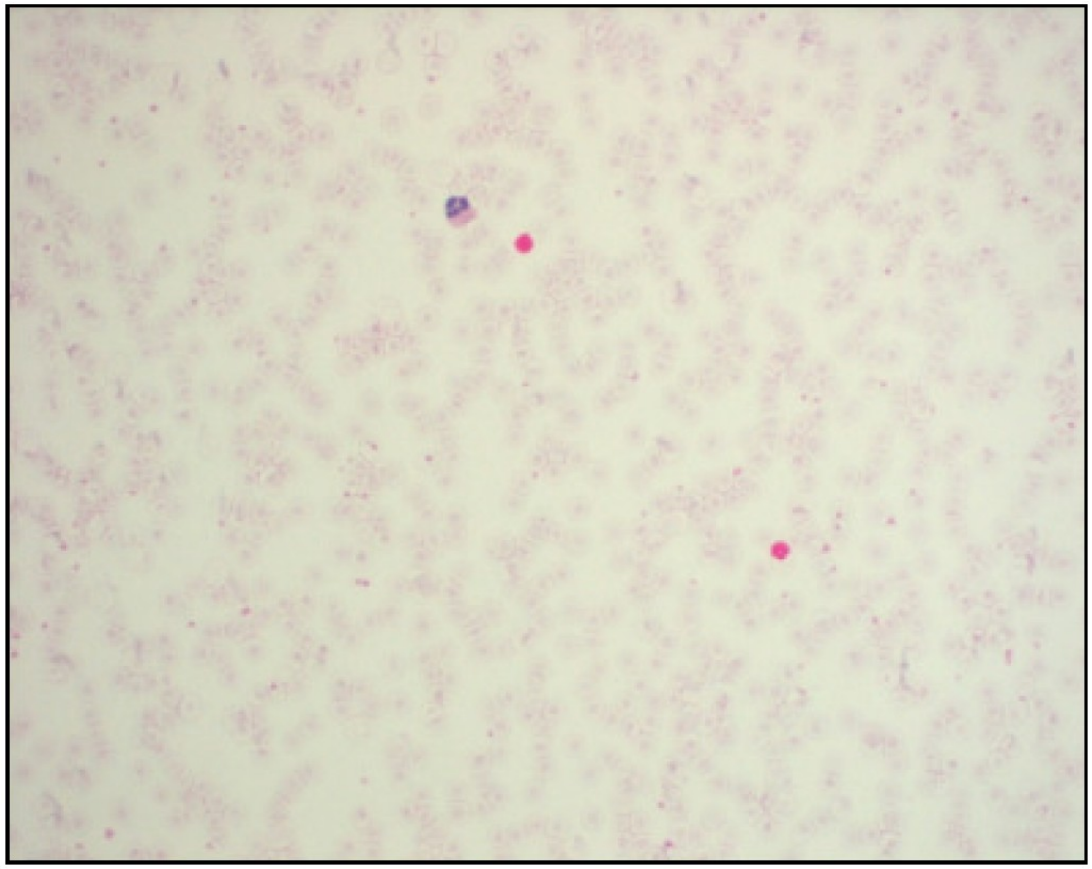
Feto-Maternal Haemorrhages (FMH)

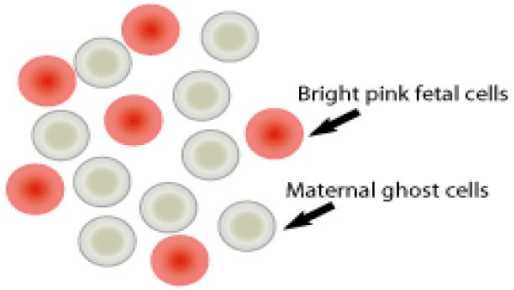
- **After 28 weeks:**
  - APH / Abruption / Trauma / Amnio / ECV
  - <2mL in 98% >30mL in 0.03%

Feto-Maternal Haemorrhages (FMH)

- **At Delivery:**
  - > 3mL in 1% >10mL in 0.03%
  - Increased by Caesarian Section, Cell Salvage or manual removal of placenta

The FMH (Kleihauer / Acid Elution) Test





What Guidelines are there ?

- **BCSH** Dec 2013
- **RCOG**
  - Green Top 22, 2011– Use of anti-D
  - Green Top 47, 2008/9 – Transfusion in Obstetrics
  - Green Top 38, 2010 – (molar pregnancies)
- **NICE**
  - Antenatal Care / Postnatal Care
  - Routine Antenatal Anti-D Prophylaxis
  - Early miscarriage & Ectopic pregnancy

What SHOULD we be doing.....

- **<12/13 weeks** gestation, give **at least 250iu** anti-D for surgical interventions (ectopic, molar, TOP) or persistent painful bleeding, within 72 hrs of the event

- **12/13 – 20 weeks**, give **at least 250iu** anti-D for PSEs such as bleeding, trauma etc

What SHOULD we be doing.....

- **>20 weeks** give **at least 500iu** anti-D for PSEs and perform Kleihauer test in case more is needed
- **28 – 34 weeks** Routine Antenatal Anti-D Prophylaxis RAADP,
  - **either** *at least* **500iu** at 28 and at 34 weeks
  - **OR 1 x 1500iu** at 28-30 weeks
- **At birth** (or stillbirth) If baby is RhD pos (or unknown) give **at least 500iu** anti-D and perform Kleihauer test in case more is needed

Cell Salvage in Obstetrics

An example of evolving practice, with increasing use of intra-operative cell salvage in the obstetric setting and the potential for relatively large volumes of foetal cells mixing with maternal circulation;

- Remember appropriate dosage of anti-D in RhD negative women – BCSH recommend *at least* 1500iu following cell salvage reinfusion, more if the Kleihauer indicates it

What Presentations of anti-D Ig are available ?

- **In the UK**:
  - CSL Behring: ‘Rhophylac’ 1500 IU pre-loaded syringe – IM/SC or IV
  - BPL: ‘D-Gam’
    - 250 IU – IM/SC only
    - 500 IU – IM/SC only
    - 1500 IU – IM/SC only
    - 2500 IU – IM/SC only
- **In Eire**;
  - Octapharma: ‘Rhesonativ’ 625 IU or 1250 IU vials
  - CSL Behring: ‘Rhophylac’ 1500 IU pre-loaded syringe

Should we give Rhophylac 1500IU IV in women with BMI >30 ?

- *Recent change in SmPC in Jan 2014 following concerns raised to the German licensing authority about POTENTIAL poor uptake following IM administration*
- *No clear evidence, no information about sites of injection etc etc*
- *Advise from BCSH, endorsed by RCOG members is to risk-assess process – very small risk of poor uptake balanced against training, calling women in to be cannulated, potential for error using BPL anti-D IV etc etc*

What Dose should we be using ?

- **Anti-D Ig given IV**
  - **100 IU** will clear 1 ml of foetal red cells
  - is instantly available
- **Anti-D Ig given IM**
  - **125 IU** will clear 1 ml of foetal red cells
  - will take hours to get into bloodstream via muscle, much longer (if at all) via fat and will lose some on the way

What levels does that produce in the maternal circulation ?

- Peak levels of prophylactic anti-D following administration of 500IU anti-D Ig administered **IM** will very rarely exceed **0.1 IU/mL**

- Peak levels of prophylactic anti-D following administration of 1500IU anti-D Ig will very rarely exceed:
  - **0.2 IU/mL** if administered **IM**
  - **0.4 IU/mL** if administered **IV**

NEQAS 2007 & 2010 - Post natal (PN) & Potentially Sensitising Events (PSE) (n=137)

Clinical scenario	Number (%) using anti-D Ig dose				
	250IU	500IU	1250IU	1500IU	Other
PSE <20 weeks	99 (72%)	11 (8%)	7 (5%)	19 (14%)	1 (1%)
PSE > 20 weeks	1 (1%)	104 (76%)	10 (7%)	22 (16%)	0 (0%)
Post-natal	0 (0%)	100 (73%)	10 (7%)	27 (20%)	0 (0%)

National Comparative Audit of anti-D

- Looking at a cohort of women who booked around September 2012, with expected delivery around May 2013
  - Were they RhD Negative ?
  - Did they receive RAADP (dose / timing) ?
  - Did they receive anti-D for PSE (dose / timing)?
  - Did they deliver a RhD positive baby ?
  - Did they receive post-natal anti-D (dose / timing)?
  - Did they receive further anti-D if indicated by FMH test (Kleihauer) ?

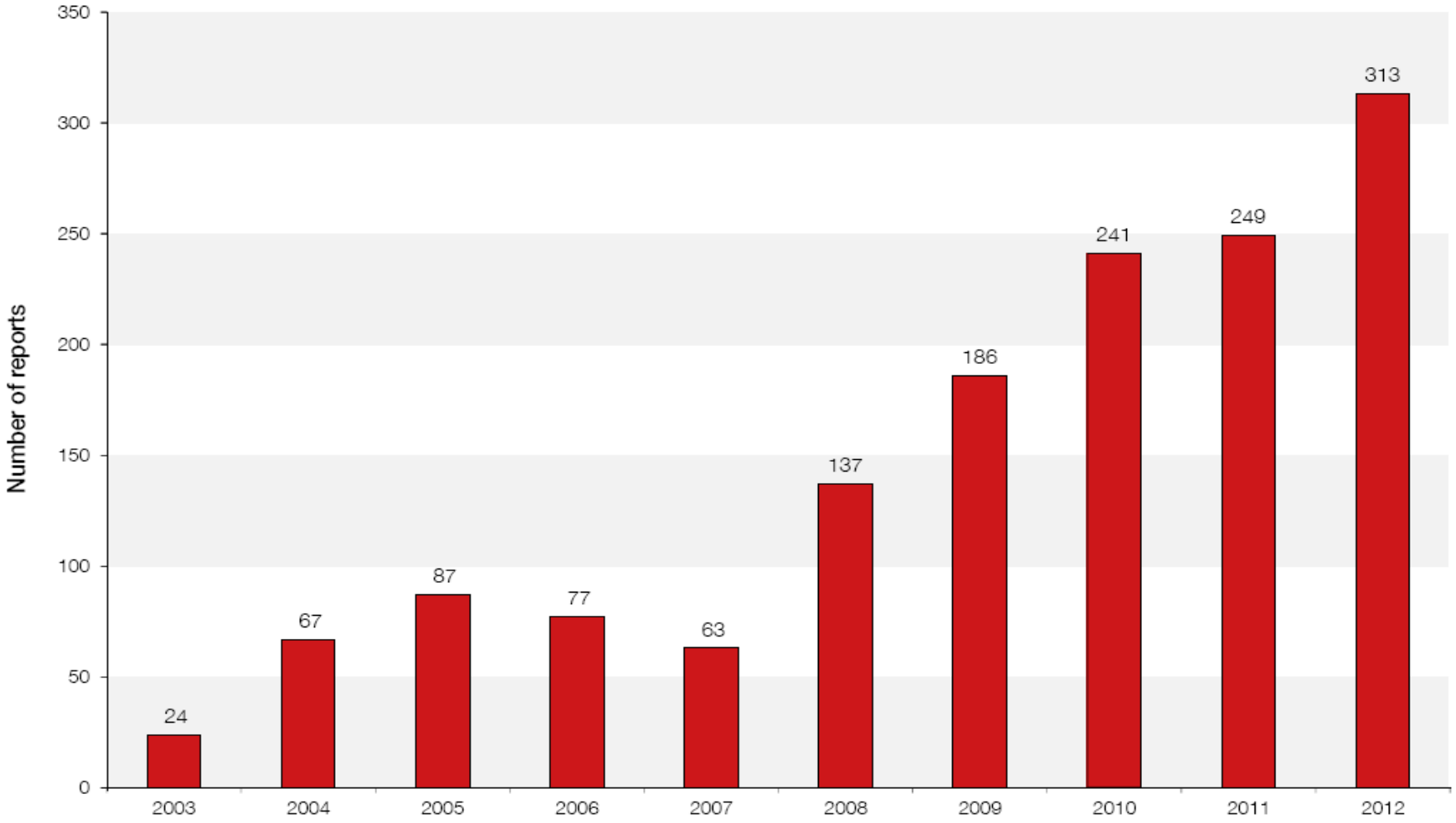
National Comparative Audit of anti-D

- 99 % women received their single dose RAADP and 89.9% received the right dose at the right time
- 98.7% received their two-dose RAADP and 58.6% received the right dose at the right time
- 98.5% received post-delivery anti-D and 91.6% received the right dose at the right time
- 95.7% women were given anti-D for PSEs, and 79% received the dose within 3 days, though 3.7% did not get the right dose
- 36% received patient information and 57% consented

Anti-D Ig Reporting Categories

- Omission or late administration of anti-D immunoglobulin
- Inappropriate administration of anti-D immunoglobulin to:
  - a RhD positive woman
  - a woman who already has immune anti-D
  - a mother of a RhD negative infant (erroneously)
  - a different woman from the woman it was issued for
- Incorrect dose of anti-D Ig given
- Handling and storage errors
  - administration of expired, or otherwise out of temperature control, anti-D immunoglobulin

Trend in Anti-D Ig reports



Anti-D Ig reports in 2012 (n = 313)

- **63** cases where anti-D Ig was inappropriately administered - *unnecessary exposure to a human medicinal blood product*
- **204** cases where anti-D Ig was delayed or omitted, putting patient at risk of sensitisation to the D antigen - *potential Major Morbidity*
- **20** cases where the wrong dose of anti-D Ig was administered (usually too little)
- **26** handling and storage errors

Student midwife relies on patient to confirm anti-D Ig administration

- *A student midwife asked a postnatal woman whether she had received her anti-D Ig and the woman confirmed that she had. The administration was confirmed on the electronic patient record and the woman was discharged*
- *The anti-D Ig labelled for the woman was found some days later in the maternity refrigerator, and it transpired that the woman had in fact received an injection of Syntometrine*
- *She was recalled and given her anti-D Ig a week late*

Poor decision by obstetric registrar when further administration of anti-D Ig was required

- *A woman presented with a bleed at 34 weeks gestation. She was discharged by the obstetric registrar who told her that no anti-D Ig was required as she had received routine antenatal anti-D Ig prophylaxis (RAADP) at 28 weeks*
- *The woman was concerned and contacted her midwife, who arranged administration of anti-D Ig 5 days post-event*

Lack of knowledge results in delay of administration of anti-D Ig

- *A woman presented with a PV bleed at 19 weeks of gestation, but was discharged by a doctor who informed her that anti-D Ig should only be given if a Kleihauer test is positive*
- *The woman was recalled and given anti-D Ig four days later*

Failure to issue anti-D Ig cover for RhD-incompatible platelets

- *A 4 year old female child with ALL whose group is A RhD negative was issued with RhD positive platelets*
- *The trainee biomedical scientist (BMS) did not issue anti-D Ig as cover, even though it was clearly stated in laboratory and clinical protocols, thus putting this child at risk of sensitisation to the D antigen and therefore compromising her future childbearing potential*

Group change following merger of patient records

- *Two patient records with identical names were merged in the laboratory computer, although one patient was O RhD negative, and the other was B RhD positive.*
- *The merged record showed the patient as having blood group O RhD negative, on which basis anti-D Ig was issued.*

Catalogue of errors leads to incorrect administration of anti-D Ig

- *A woman told her consultant that she was RhD negative, and anti-D Ig was requested on that basis*
- *The biomedical scientist (BMS) issued anti-D Ig even though the laboratory information management system (LIMS) record clearly showed the woman to be RhD positive*
- *The midwife administered the anti-D Ig, knowing the woman was RhD positive, because the consultant had prescribed it*

Failure to check historical laboratory records and lack of understanding by the midwife

- *A biomedical scientist (BMS) was 'busy' and failed to check computer records before issuing anti-D Ig for a woman known to have immune anti-D*
- *The midwife assumed that because the laboratory had issued it, it should be given, citing a lack of understanding of the 'science' of anti-D*
- *She also carried out a 'straw poll' of her midwifery colleagues that indicated every one of them would have administered the anti-D Ig because it had been issued by the laboratory*

Failure to take heed of laboratory reports

- *A woman with immune anti-D was being regularly monitored, and the notes contained laboratory reports showing a steadily rising level of anti-D antibody*
- *She presented with a bleed at 27/40 and was inappropriately administered anti-D Ig from stock held in the clinical area*

Overestimation of transplacental haemorrhage (TPH) due to high levels of haemoglobin F (HbF)

- *The laboratory reported a TPH of 37 mL fetal cells following a fetal death in utero (FDIU), and issued 6000 IU anti-D, which was administered*
- *Confirmation by flow cytometry indicated a bleed of 0 mL*
- *The woman was a beta thalassaemia carrier and had a raised level (5%) of HbF.*

Misunderstanding of principles of anti-D Ig

- *A woman attended her GP clinic early in pregnancy*
- *On taking her history, it transpired that there was an incidence of haemolytic disease of the newborn in one of her relations*
- *The GP ran round to the neighbouring practice, obtained a 1500IU dose of anti-D Ig and administered it to the woman 'to be sure'*
- *.....who was of course RhD positive.....*

Inappropriate administration of anti-D Ig to a male patient

- *An 84 year old O RhD negative male presented in the emergency department with a gastrointestinal bleed and was given a unit of O RhD positive red cells.*
- *The duty biomedical scientist (BMS) issued a dose of anti-D Ig; 'just in case the patient made immune anti-D'*

Expired anti-D Ig administered in the community

- *Anti-D Ig that had expired two months earlier was administered in the community antenatal setting*
- *On investigation, it transpired that the community clinic had 15 expired doses of anti-D Ig in stock still available for issue*

Poor advice from the laboratory results in incorrect route of administration of anti-D Ig

- *A BMS advised administering a 1500iu dose of anti-D Ig intravenously when the product issued (DGAM) is licensed only for intramuscular injection*

NHS Blood and Transplant

Anti-D
When and How Much?

This poster gives recommended dosages of anti-D immunoglobulin at different stages during pregnancy for women with an RhD negative blood type who do not already have immune anti-D antibodies.

At less than 12 weeks

- Anti-D is NOT usually indicated unless there has been therapeutic termination, molar or ectopic pregnancy, surgical intervention associated with miscarriage, or continued painful vaginal bleeding (request at least 250iu within 72 hours in these cases).

Between 12 and 20 weeks

- Administer at least 250iu anti-D Ig within 72 hours of a potentially sensitising event.

Between 20 weeks and delivery

- Administer at least 500iu anti-D Ig within 72 hours of a potentially sensitising event.
- Send a sample for a Kleihauer Test in case *additional* anti-D Ig is needed.
- *Anti-D Ig should be given for potentially sensitising events, even if RAADP has been given already.*

Routine Antenatal Anti-D Prophylaxis (RAADP) should be administered between 28 and 30 weeks

- Send a sample for blood group and antibody screen and then administer RAADP according to local policy, *even if anti-D Ig has been recently given for a sensitising event.*
- SINGLE DOSE: Administer 1,500iu anti-D Ig at 28-30 weeks.
- TWO-DOSE: Administer at least 500iu anti-D Ig at 28 and 34 weeks.

After delivery

- Send 'Mother & Cord' samples for testing.
- Where the baby is RhD positive, administer at least 500iu anti-D Ig within 72 hours of delivery.
- Administer further anti-D Ig on the advice of the laboratory if the Kleihauer shows a large fetomaternal haemorrhage.

For further information please refer to your local policy

British Committee for Standards in Haematology (BCSH) Guidelines for the use of prophylactic anti-D immunoglobulin 2006.

Royal College of Obstetricians and Gynaecologists (RCOG) Green Top Guideline No 22 The Use of Anti-D Immunoglobulin for Rhesus D Prophylaxis 2011.

BLC680.1 05/13

- If outside 72 hrs still give anti-D, as a dose up to 10 days may provide some protection
- Give RAADP **in addition** to prophylaxis for sensitising events, and *vice versa*

Anti-D Administration Flowchart for RhD Negative Pregnant Women

Wye Valley NHS Trust

Always confirm • the woman's identity • that the woman is RhD Negative using the latest laboratory report • that the woman does not have immune anti-D using the latest laboratory report • that informed consent for administration of anti-D Ig is recorded in notes	
Potentially Sensitising Events (PSEs) during pregnancy	
Gestation LESS than 12 weeks	
Vaginal bleeding associated with severe pain	Administer at least **250 IU** anti-D Ig within 72 hours of event. Confirm product / dose / expiry and patient ID pre administration
ERPC / Instrumentation of uterus	
Medical or surgical termination of pregnancy	
Ectopic / Molar Pregnancy	
Gestation 12 to 20 weeks	
For any Potentially Sensitising Event (PSE)	Administer at least **250 IU** anti-D Ig within 72 hours of event. Confirm product / dose / expiry and patient ID pre administration
Gestation 20 weeks to term	
For any Potentially Sensitising Event (PSE) (**Irrespective** of whether RAADP has been given)	Request a Kleihauer Test (FMH Test) and immediately administer at least **500 IU** anti-D Ig within 72 hours of event. Confirm product / dose / expiry and patient ID pre administration
Does the Kleihauer / FMH test indicate that further anti-D Ig is required ?	Administer more anti-D Ig following discussion with laboratory
For continuous vaginal bleeding at least **500 IU** anti-D Ig should be administered at a minimum of 6-weekly intervals, irrespective of the presence of detectable anti-D. A Kleihauer / FMH Test should be requested every two weeks in case more anti-D is needed. Cases where bleeding stops, then starts again should be treated as a new event.	
Routine Antenatal Anti-D Prophylaxis (RAADP)	
For Routine Antenatal Anti-D Prophylaxis (**Irrespective** of whether anti-D Ig already given for PSE)	Take a blood sample to confirm group & check antibody screen – do not wait for results before administering anti-D Ig
	Administer **1500 IU** anti-D Ig at **28 – 30** weeks
	Confirm product / dose / expiry and patient ID pre administration
At Delivery (or on diagnosis of Intra Uterine Death >20 weeks)	
Is the baby's group confirmed as RhD positive ? OR Are cord samples not available ?	Request a Kleihauer Test (FMH Test)
	Administer at least **500 IU** anti-D Ig within 72 hours of delivery Confirm product / dose / expiry and patient ID pre administration
Does the Kleihauer / FMH test indicate that further anti-D Ig is required ?	Administer more anti-D following discussion with laboratory

SHOT anti-D Ig Administration Flowchart v7 October 2012

Key Messages

- DO NOT wait for the result of a Kleihauer test before giving a standard dose of anti-D Ig
- If in doubt – GIVE IT !

Key Issues with Anti-D Ig

- Ignorance
- Failure to adhere to local protocol
- Failure to utilise IT systems properly / fully
- Late bookers
- Transfers of care
- Assumptions
- Failures of communication
- Failure to obtain valid consent for anti-D Ig

Anti-D Summary

- Effective anti-D prophylaxis is a *partnership* between the laboratory and the clinical area – *work together* to produce robust Trust guidelines
- Requests for anti-D should be driven by the clinicians, especially in early pregnancy
- the clinical area must be responsive to requests for follow-up from the laboratory, and the lab must not assume that action will be taken purely because they have issued a report

Thanks to;

- SHOT Team
- UK NEQAS
- Megan Rowley
- NCA Team
- **YOU** for listening