9 Adverse Events Related to Anti-D Immunoglobulin (Ig) n=400

Author: Courtney Spinks and Jennifer Davies

Definition:

An adverse event related to anti-D immunoglobulin (Ig) is defined as related to the prescription, requesting, administration or omission of anti-D Ig which has the potential to cause harm to the mother or fetus immediately or in the future. This category also includes events relating to the administration of anti-D Ig following transfusion of D-mismatched platelets.

Key SHOT messages

- Errors relating to cell-free fetal deoxyribonucleic acid (cffDNA) accounted for 47 cases, an increase from 2019. Continued reporting to SHOT helps promote learning from these events
- Review protocols and standard operating procedures (SOP) to reduce incorrect omission of routine antenatal anti-D Ig prophylaxis (RAADP) and anti-D Ig post potentially sensitising event (PSE)

Abbreviations used in this chapter

BSH	British Society for Haematology
cffDNA	Cell-free fetal deoxyribonucleic acid
G&S	Group and screen
HDFN	Haemolytic disease of the fetus and newborn
IBGRL	International blood group reference laboratory
IUD	Intrauterine death
Ig	Immunoglobulin
LIMS	Laboratory information management system
NICE	National Institute for Health and Care Excellence
NIPT	Non-invasive prenatal testing
NHSBT	National Health Service Blood and Transplant
PCR	Polymerase chain reaction
PSE	Potentially sensitising event
SOP	Standard operating procedure
RAADP	Routine antenatal anti-D Ig prophylaxis
UKAS	United Kingdom Accreditation Service
WBIT	Wrong blood in tube

Recommendations

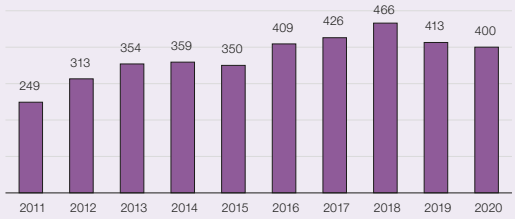
- Planned routine appointments must include processes to ensure that D-negative women receive routine antenatal anti-D Ig prophylaxis (RAADP) as appropriate
- Review processes to ensure that anti-D Ig post potentially sensitising event (PSE) is administered before patients are discharged from hospital
- Processes should be in place to ensure that cell-free fetal deoxyribonucleic acid (cffDNA) D type results are reviewed prior to order or administration of anti-D Ig or RAADP
- Laboratory processes should include appropriate actions to be taken when cffDNA D type is discrepant with cord D type

Action: Maternity services, laboratory management

Headline data 2020

Number of reports n=400
Deaths n=0
Major morbidity n=0

Anti-D reports by year



Demographic data

Male n=0
Female n=400
Adults n=395
Paediatric n=5

Potential for major morbidity n=275

Late/omitted RAADP n=136
Late/omitted anti-D following a PSE (including delivery) n=139

Introduction

In 2019 SHOT received 413 reports of errors relating to anti-D Ig, in this reporting year there was a nominal reduction with a total of 400 reported errors. Interestingly very few referenced the changes to practice that must have been introduced to manage patient and staff safety during the COVID-19 pandemic. Most errors (335/400, 83.8%) occurred in the clinical area. Omission or late administration of anti-D Ig accounted for 275/400 (68.8%) cases, there were 57/400 cases (14.3%) where anti-D Ig was administered to an individual with a D-negative infant, and 20/400 cases (5.0%) of administration to an individual with immune anti-D. Other cases included anti-D Ig administration to D-positive individuals (16/400, 4.0%), and incorrect dose (9/400, 2.3%). In 2 cases there were errors in administration of anti-D Ig post transfusion of a D-positive component to a D-negative individual; In 1 case anti-D Ig was not appropriate due to the age of the patient and in the other an incorrect dose was administered.

Deaths n=0

There were no deaths reported during 2020 related to anti-D Ig errors.

Major morbidity n=0

No cases resulting in major morbidity were reported in 2020. However, it should be noted that the impact of the errors reported in this category, in particular late or omitted anti-D Ig may not be fully realised at the time of reporting. All cases of immune anti-D identified in pregnancy and reported to SHOT are discussed in Chapter 25, Immune Anti-D in pregnancy. In 16 cases where immune anti-D was detected during pregnancy errors were noted in RAADP provision, in 15 cases no RAADP had been given and in 1 case RAADP was delayed.

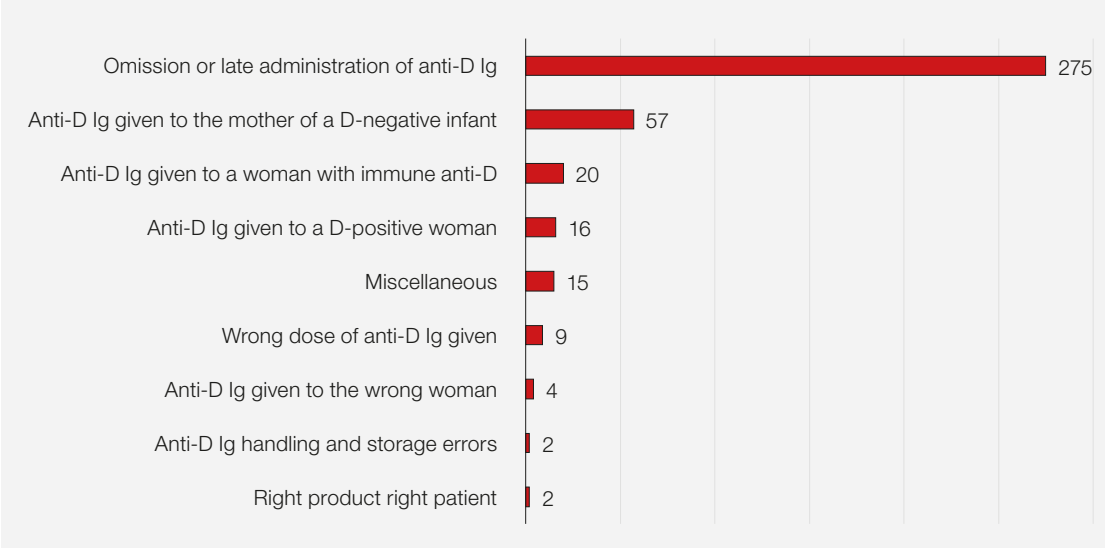
Overview of cases

There were 197/400 (49.3%) errors that occurred in either the community or outpatient settings. These largely involved late administration or omission of RAADP, 89/197 (45.2%), suggesting that the planning and processes for routine outpatient reviews could be improved. Errors occurring in the hospital ward setting accounted for 126/400 (31.5%) cases and 65/400 (16.3%) in the laboratory. Most errors in the ward setting related to failure to administer anti-D Ig (63/126, 50.0%), and 22 (17.5%) cases related to late administration of RAADP. Most laboratory errors related to failures in cffDNA processes (24/65, 36.9%), 16 (66.7%) of these resulted from apparent error in prediction of the fetal D-type by the testing laboratory.

There were 8/400 (2.0%) reported cases of transcription errors when documenting D status in the handheld

records, which were then used to inform treatment decisions. On each occasion the correct results were available electronically and if accessed, which should be policy, would have prevented the errors.

Figure 9.1: Distribution of anti-D Ig related error reports in 2020 (n=400)



Omission or late administration of anti-D Ig n=275

Omission or late administration continues to be the highest source of errors relating to the administration of anti-D Ig (275/400, 68.8%), with 136/275 (49.5%) relating to RAADP. In 139/275 cases (50.5%) there was failure to give anti-D Ig following a PSE (including post-delivery), mostly due to patients being discharged before administration (63/139, 45.3%) and 35/139 (25.2%) resulting from incorrect decisions in anti-D Ig administration. Last year's Annual SHOT Report made suggestions for how midwifery units could address omissions and delays in administration, specifically the provision of RAADP during pregnancy, administration post-delivery and administration after a PSE.

BSH guidelines for the use of anti-D immunoglobulin for the prevention of haemolytic disease of the fetus and newborn (BSH Qureshi et al. 2014) and NICE guidance (NG140 and NG126) should be reflected in local policies.

Case 9.1: Confusion caused by labelling of a cord blood sample

A midwife contacted the laboratory to enquire if a D-negative patient had received any anti-D Ig. According to the LIMS the named patient had not had a post-delivery sample, or request for a Kleihauer. There was also no record of the baby or that the cord blood sample had been received. On investigation by the laboratory, a sample for a baby with same date of birth and corresponding address to the mother was located, however the baby did not have the same surname and so had not been associated with the mother in question.

Case 9.2: Late administration of anti-D Ig post-delivery of twin infants

One infant tested D-positive to a D-negative mother. However only one cord sample was sent to the laboratory at the time of delivery, which tested D-negative. There was no indication of a twin delivery therefore anti-D Ig was not issued to the patient. Anti-D Ig was administered day 7 post-delivery.

Inappropriate administration of anti-D Ig

Case 9.3: Anti-D Ig given to woman who had pre-existing anti-D antibodies

A woman was referred to the fetal medicine institute for invasive sickle cell testing of fetus. The presence of alloimmune anti-D antibodies was not adequately identified by the referring hospital report. Although written in the blood transfusion report, it was embedded in a paragraph of text and difficult to identify. When the appointment was made the clerical team created a new record, although the woman had an existing record in the system (Failure to follow correct process of creating records by the administration team). A G&S sample was taken pre-administration of anti-D Ig, but

the midwives did not wait for the result to come back (usual practice) and issued anti-D Ig from the stock on the ward. The failsafe of a midwife checking the previous reports before issuing the anti-D Ig did not happen because the woman had two files and the report had been scanned into the wrong file. The research fellow did not identify that the patient had anti-D antibodies from the G&S report and prescribed anti D Ig. A second research fellow realised that the patient had alloimmune anti-D antibodies and alerted the consultant and fetal medicine midwives. A second failsafe, writing all procedures including blood group and virology, on a white board in the midwives' office had not happened because the member of staff responsible had been delayed due to a train strike.

Cell-free fetal deoxyribonucleic acid (cffDNA) n=47

High-throughput NIPT for fetal D genotype, also known as cffDNA for D testing uses a real-time quantitative PCR method for identifying fetal D genotype from fetal DNA in the plasma of D-negative women. The IBGRL at NHSBT offers a UKAS accredited fetal D screening service to all customers in the UK and Ireland. The test predicts fetal D status with high accuracy from a sample of maternal blood and will improve care for D-negative women by reducing the need to administer a blood product to healthy pregnant women.

IBGRL have optimised and automated the testing technology applied to pregnancies at risk of HDFN to enable high-throughput fetal D screening of all D-negative pregnant women, who have not formed immune anti-D or anti-G to guide antenatal anti-D Ig prophylaxis. The service aims to report 98% of samples within 10 business days of receiving the sample (further details in the link provided under references). High-throughput NIPT for fetal D genotype is recommended by the NICE as a cost-effective option to guide antenatal prophylaxis with anti-D Ig. Tools to put this NICE guidance into practice are available https://www.nice.org.uk/guidance/dg25.

The benefits of using high-throughput NIPT for fetal D genotype to guide antenatal prophylactic treatment with anti-D Ig as per the NICE guidance include:

- Preventing unnecessary administration of anti-D Ig and associated risk for D-negative mothers when the fetal D type is predicted as D-negative
- Reducing the number of antenatal anti-D Ig prophylactic clinic appointments needed, and the amount of anti-D Ig used
- Increasing the availability of anti-D Ig for use after PSE in pregnancy when the NIPT result for fetal D genotype is positive or unknown
- Reducing the anxiety associated with potentially sensitising events for D-negative women when the NIPT result for fetal D genotype is negative
- Providing information to allow D-negative women to make an informed decision about whether to have treatment with anti-D Ig

The test is highly accurate and can be performed from 11^{+2} weeks gestation. The assay has a false positive rate of up to 2%, where fetuses predicted to be D-positive will in fact be found to be D-negative at birth. The false D-negative predictive rate for fetal D screening is 0.1% according to the literature. At present IBGRL has a false negative prediction rate of 0.08%. It is also important to note that for NIPT, IBGRL requires only one sample and does not require or test a second sample from the patient at the same point in time. This is a routine test and samples are expected to be taken in a controlled environment by trained staff to avoid wrong blood in tube incidents.

A total of 47/400 (11.8%) cases were reported relating to cffDNA. In 16/47 (34.0%) staff acted on the cffDNA results and anti-D Ig was given or omitted because the cffDNA assay predicted an incorrect D type. In 8/16 (50.0%) of these cases the fetal D-type was predicted D-positive but cord sample tested was D-negative, and in 8/16 (50.0%) the fetal D-type was predicted negative but cord sample tested D-positive. All these cases were referred to IBGRL for investigation. In 22/47 (46.8%) cases anti-D Ig or RAADP was administered to a woman with a fetus predicted to be D-negative by cffDNA testing as a result of failure to check the fetal D screening results.

Other errors included:

- Failure to order anti-D Ig or RAADP when cffDNA results indicated a D-positive fetus (n=3)
- Delay in entering cffDNA results into the LIMS (n=1)
- Misinterpretation of cffDNA results (n=1)
- Incorrect advice (n=1)
- A cord sample WBIT (n=1)
- Patient insistence on receiving anti-D Ig despite cffDNA predicting a D-negative fetus (n=1)
- Manual transcription of results (n=1)

SHOT encourages further reporting of discrepant cffDNA results.

NHS Blood and Transplant FAQ's from September 2018 state: *'The fetal RHD screen has been set up to be highly sensitive for detection of fetal RHD, thus avoiding false negative results as in such cases anti-D Ig will not be given. The false negative rate in this case is 0.1% i.e. highly accurate. The false positive prediction is up to 2% although this is dependent on the ethnicity of the population.'*

False positive results may occur as a result of rare silent or variant Rh genes or weak D alleles, vanishing twin, or extraneous low-level DNA contamination of the sample. Where a fetal D-positive result has been reported but the cord blood tests D-negative, this should be reported to the testing laboratory and SHOT. Investigations at the local level could include WBIT (mother or cord) and weak D (cord sample), although this is not included in current guidelines. All cases of apparent false negative cffDNA results should be reported to the testing laboratory, along with blood samples from mother and baby. They should also be reported to SHOT. Local investigations should include WBIT (cord sample) and anti-D Ig prophylaxis should be given as appropriate.

Case 9.4: Apparent false positive cffDNA D-type due to vanishing twin syndrome

A cffDNA result issued by the NHSBT reference laboratory for a D-negative pregnant lady, predicted the fetus to be D-positive. Prophylactic anti-D Ig was given to the patient based on the cffDNA result. A cord sample taken at delivery grouped as D-negative. The laboratory confirmed the cord sample as fetal by performing an alkali denaturation test. It was not possible to obtain repeat samples for testing as mum and baby has been discharged. The NHSBT reference laboratory was notified. Further hospital investigation indicated that the incorrect predicted cffDNA result could possibly be due to the 'vanishing twin syndrome' as the patient had IUD of a twin on the first scan during the pregnancy at 16^{+5} weeks. It was unknown to be a twin pregnancy until the fetus had died. The cffDNA test was performed at 21 weeks.

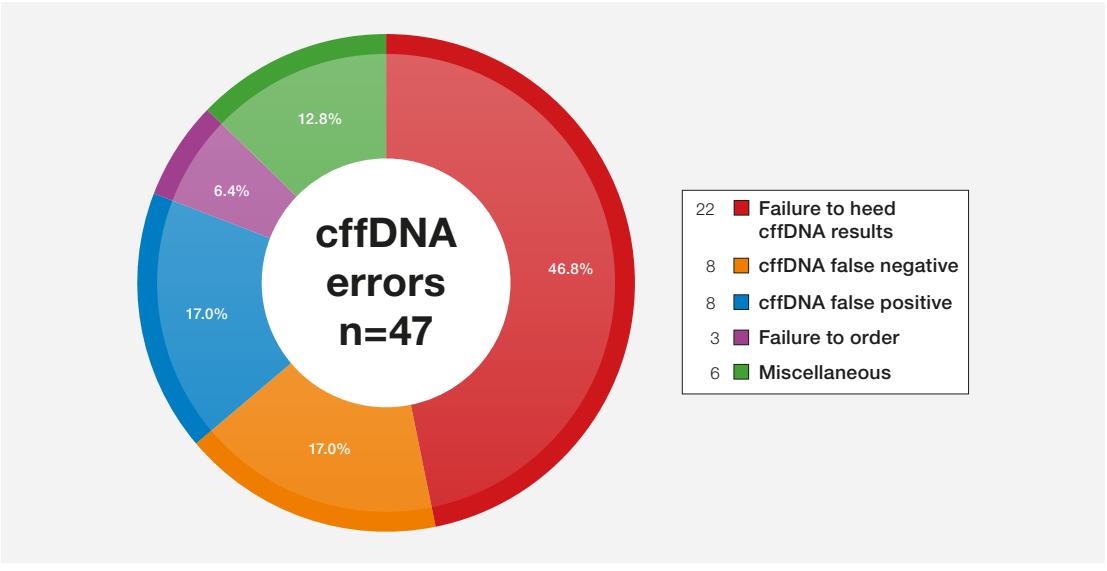


Figure 9.2: Errors relating to cffDNA in 2020 (n=47)

Near miss cases n=35

There were 35 near miss anti-D Ig errors in 2020. The largest sub-category of reports was those preventing late or omitted anti-D Ig,16/35 (45.7%). Most of the near misses were errors in the laboratory, 20/35 (57.1%), with 14 clinical errors, and 1 miscellaneous error.

Conclusion

Omission or late administration of anti-D Ig accounts for most errors in this category. Administration of RAADP at the recommended gestation period is critical in reducing risk of immunisation to the D antigen (see Chapter 25, Immune Anti-D in Pregnancy).

SHOT recommend that gynaecology, early pregnancy units and maternity units review their procedures to ensure that care pathways reflect the environment that care is being delivered in and subsequently avoid omissions or late administration of anti-D Ig and RAADP. As the uptake of NIPT for fetal D increases laboratories and maternity units need to ensure that processes are in place for checking the cffDNA result prior to issue and administration of anti-D Ig or RAADP. There also needs to be awareness of the sensitivity and specificity of the assay and the actions to be taken in the event of discrepant results when cord blood samples are tested.

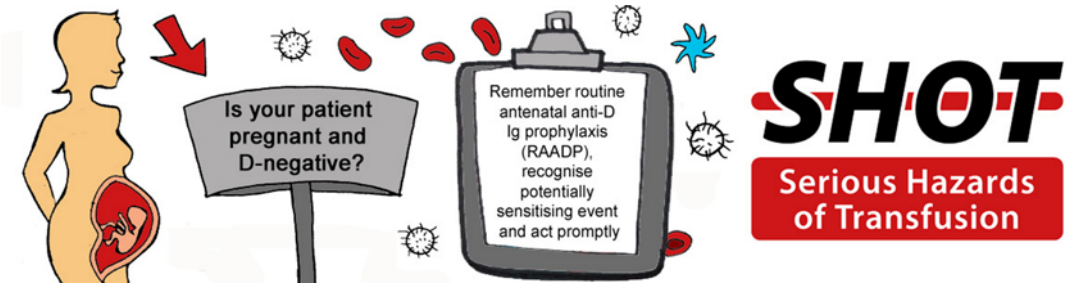
Recommended resources

Anti-D Immunoglobulin (Ig) Administration to avoid sensitisation in pregnancy - an aide memoire SHOT 2020
https://www.shotuk.org/resources/current-resources/

SHOT Bite No 2: Anti-D Ig Administration
https://www.shotuk.org/resources/current-resources/shot-bites/

Blood assist App to cover anti-D following transfusion
Apple (https://apps.apple.com/gb/app/blood-assist/id1550911130)
Google play (https://play.google.com/store/apps/details?id=uk.nhsbt.bloodassist)
Web based (www.bloodassist.co.uk)

NHSBT FAQ document
https://nhsbtdbe.blob.core.windows.net/umbraco-assets-corp/12552/fetal-rhd-screen-questions-answers.pdf



References

BSH Qureshi H, Massey E, Kirwan D, et al. BCSH guideline for the use of anti-D immunoglobulin for the prevention of haemolytic disease of the fetus and newborn. Transfus Med 2014;**24(1)**:8-20. https://doi.org/10.1111/tme.12091 [accessed 28 April 2021].

NHSBT FAQ's (September 2018) https://nhsbtdbe.blob.core.windows.net/umbraco-assets-corp/12552/fetal-rhd-screen-questions-answers.pdf [accessed 10/06/2021].

NICE Guidance: Routine antenatal anti-D prophylaxis for women who are rhesus D negative 2008 WBIT https://www.nice.org.uk/guidance/ta156/chapter/1-Guidance [accessed 10/06/2021].

NICE Guidance: High-throughput non-invasive prenatal testing for fetal RHD genotype 2016 https://www.nice.org.uk/guidance/dg25 [accessed 10/06/2021].