8 Adverse Events Related to Anti-D Immunoglobulin (Ig) n=341

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Definition:

Events relating to the requesting and administration of anti-D immunoglobulin (Ig) to women of childbearing potential and events relating to the administration of anti-D Ig following transfusion of D-mismatched red cells or platelets.

Abbreviations used in this chapter

BSH	British Society for Haematology
cffDNA	Cell-free fetal deoxyribonucleic acid
CI	Confidence interval
EPR	Electronic patient records
FMH	Fetomaternal haemorrhage
HFIT	Human factors investigation toolkit
IBGRL	International Blood Group Reference Laboratory
Ig	Immunoglobulin
IT	Information technology
LIMS	Laboratory information management system
NHSBT	National Health Service Blood and Transplant
NICE	National Institute for Health and Care Excellence
NPEx	National Pathology Exchange
PSE	Potentially sensitising event
PV	Per vaginal
RAADP	Routine antenatal anti-D Ig prophylaxis

Key SHOT messages

- Non-invasive prenatal testing for fetal D-type should be made available to all D-negative women in the UK during pregnancy. The service is available from organisations in the UK, including the IBGRL at the NHSBT in England and the Exeter Genomics Laboratory
- Anti-D Ig should be administered prior to patient discharge to avoid delays and omissions of anti-D Ig
- Formal incident investigation should take place where errors in the management of anti-D Ig and RAADP have been identified. These should be discussed at relevant governance meetings

Recommendations

- IT systems, including LIMS, EPR systems, integration systems (such as NPEx) and electronic blood-tracking systems should be used to their full potential to support safe and appropriate management of anti-D Ig and RAADP. System providers should work with subject matter experts and IT departments within organisations to develop and implement functionality designed to support good practice

Action: Suppliers of all hospital IT systems, subject matter experts, IT departments

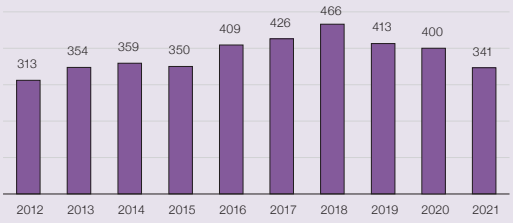
- Where IT systems are not yet available, or do not include decision support for good practice, checklists, such as the SHOT anti-D aide memoire, should be readily accessible in transfusion laboratories and clinical areas. These should also be embedded in processes relating to the management of pregnancy in D-negative individuals

Action: Maternity services, gynaecology services, laboratory management

Headline data 2021

Number of reports n=341
Deaths n=0
Major morbidity n=0

Anti-D Ig reports by year



Demographic data

Male n=0
Female n=341
Adults n=338
Paediatric n=3

Potential for major morbidity n=228

Late/omitted RAADP n=55
Late/omitted anti-D Ig following a PSE (including delivery) n=172
Unknown n=1

Introduction

Appropriate and timely administration of anti-D Ig post sensitising events and RAADP reduces the risk of development of immune anti-D resulting from pregnancy (BSH Qureshi et al. 2014; NICE TA156 2008; NICE NG140 2019; NICE NG126 2019). BSH guidelines and NICE guidance should be reflected in local policies. Anti-D Ig is also important in reducing the risk of developing immune anti-D in D-negative patients with childbearing potential (including paediatric patients) following transfusion of D-positive blood components. In this chapter 341 cases have been analysed, 338/341 (99.1%) related to pregnancy and 3/341 (0.9%) involved the transfusion of D-positive platelets.

SHOT data over the years demonstrate that errors in anti-D Ig and RAADP management occur in both the clinical and laboratory setting. The management of anti-D Ig and RAADP is complex, involving healthcare professionals in primary care and secondary care. It involves consideration of many aspects of the clinical picture, including patient D-type, fetal D-type predicted by cffDNA screening, immune anti-D status, gestation period, and requires coordination between several staff groups. Errors can occur at any stage of the process, from identification of the requirement for anti-D Ig or RAADP, ordering, prescription, laboratory release, storage and administration of anti-D Ig.

Deaths n=0

There were no deaths reported in the cases analysed for 2021 related to anti-D Ig errors.

Major morbidity n=0

No cases related to major morbidity were noted as a direct result of anti-D Ig errors. However, delays, omissions, under-dosing and failures to perform follow up testing after a FMH of more than 4mL have the potential to result in development of immune anti-D and haemolytic disease of the fetus and newborn in future pregnancies. More information regarding the clinical outcomes resulting from failures in anti-D Ig and RAADP management can be seen in Chapter 25, Immune Anti-D in Pregnancy. The impact of anti-D Ig and RAADP errors should not be underestimated.

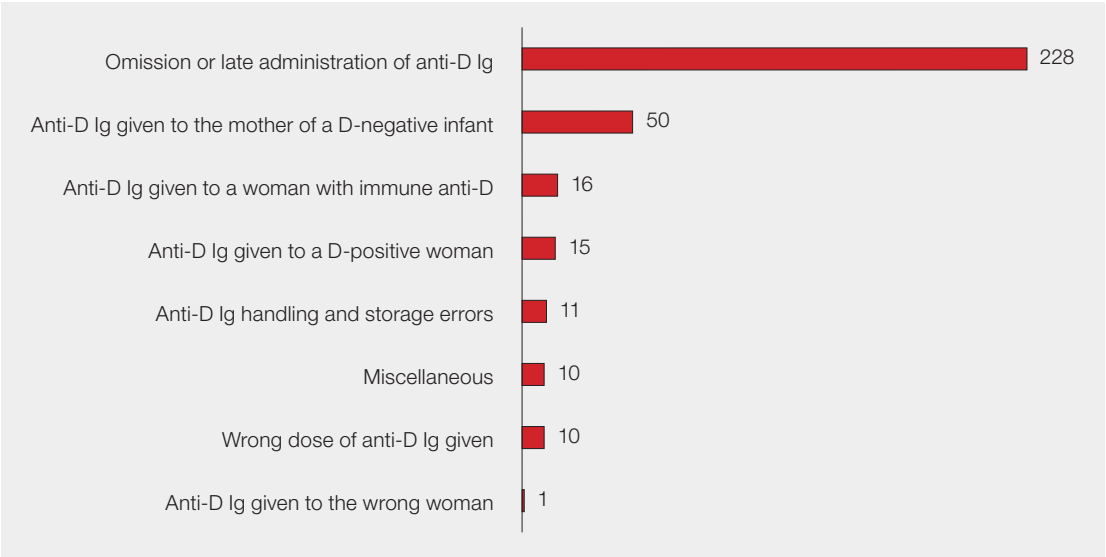
Overview of cases n=341

Omission or late administration of anti-D Ig or RAADP accounted for the majority of cases analysed 228/341 (66.9%), 98/228 cases (43.0%) were related to PSE, 74/228 (32.5%) to post-delivery, 55/228 (24.1%) involved RAADP, and in 1/228 (0.4%) case the reason for anti-D Ig was not recorded. Patient discharge prior to administration of anti-D Ig was implicated in 63/228 (27.6%) of these cases and

49/228 (21.5%) were a result of flawed decision making.

The distribution of the remaining anti-D Ig errors can be found in Figure 8.1.

Figure 8.1: Distribution of anti-D Ig related error reports in 2021 (n=341)



Note: Miscellaneous cases included 4 failures to complete follow up post FMH greater than 4mL, and 6 failures in sample taking or testing processes

Errors in the clinical setting accounted for 271/341 (79.5%) of cases and laboratory errors accounted for 70/341 (20.5%) cases. In 301 cases the stage of the process that the error originated was recorded, 254/301 (84.4%) of these noted the error at a single point and 47/301 (15.6%) noted errors at multiple points in the process.

Table 8.1: Location of clinical anti-D Ig errors n=271

Location	Number of reports	% of clinical reports
Delivery suite	70	25.8%
Community setting	33	12.2%
Out-patient department	25	9.2%
Antenatal clinic	23	8.5%
Maternity ward	21	7.8%
Emergency department	15	5.5%
Gynaecology ward	11	4.1%
Other	35	12.9%
Unknown	38	14.0%
Total	**271**	**100%**

A root cause analysis, or other equivalent formal investigation had been completed in 187/341 (54.8%) of cases, with 110/341 (32.3%) of reporters stating no investigation had been completed. This information was not available for 44 cases. Where information was provided regarding incident review by maternity governance, 141/341 (41.3%) reported that the cases were discussed, with 153/341 (44.9%) stating no discussion had taken place. Lack of formal investigations and no discussion of these cases at a governance level indicate missed opportunities for identification of the causes of errors and implementation of effective corrective and preventative actions.

The COVID-19 pandemic was implicated in 20 cases, 16 of these related to omission or late administration of anti-D Ig or RAADP. The impact of the pandemic on errors was varied and included mothers being unable to attend clinics because they had COVID-19 or were self-isolating, clinics being cancelled to reduce attendances, changes to patient mixes in wards, misunderstanding of changes to policies related to the use of anti-D Ig, cancellation of training and educational activities, staff re-deployment and early discharge of patients to reduce potential risk of exposure.

Case 8.1: Patient discharged before being given anti-D Ig

The patient had a PV bleed at 38+6 weeks gestation. She attended maternity triage the same evening and a sample was taken for a Kleihauer test. A standard dose of anti-D Ig was issued by the laboratory. Kleihauer tests are not routinely completed overnight at this hospital, a standard dose should be given with a follow up once Kleihauer result is available, if more anti-D Ig is required. However, the patient was sent home without the standard dose being given because the doctor was waiting for the Kleihauer result before giving any anti-D Ig. The midwife was asked to write the patients details in the follow up diary to be contacted the next day, which she did. Unfortunately, the midwife on duty the following day overlooked this in the diary. The patient was therefore not contacted. The anti-D Ig was found in the blood refrigerator during subsequent checks. The patient had not been given a date or time to attend for anti-D Ig administration by the discharging doctor, neither had she been contacted by the midwives. The anti-D Ig was administered but beyond the required 72-hour period.

A standard minimum dose of anti-D Ig should be administered before the patient is discharged from the hospital to ensure that it is given within the recommended 72-hours. FMH requiring additional doses, as indicated by laboratory testing, such as Kleihauer tests, is uncommon, and administration of anti-D Ig should not be delayed whilst waiting for test results.

Human factors

A review of the HFIT responses can be found in the supplementary information on the SHOT website (https://www.shotuk.org/shot-reports/report-summary-and-supplement-2021/).

Cell salvage and anti-D Ig n=2

There were 2 cases where incorrect doses of anti-D Ig were administered following the use of cell salvage, both resulting in under-dosing. In 1 case, the incorrect dose was selected by the biomedical scientist. In the 2nd case, the use of cell salvage was not communicated to the transfusion laboratory and a standard dose of 500IU was given.

Case 8.2: Failure to inform the transfusion laboratory of cell salvage reinfusion

A D-negative mother delivered by emergency caesarean section, and cell salvage was used during the procedure. The transfusion laboratory was not informed that cell salvage had been used for this patient. The patient received 515mL of salvaged blood and baby was D-positive so she should have been given 1500IU anti-D Ig. However, because the transfusion laboratory staff were unaware that cell salvage had been used only 500IU anti-D Ig was issued to the patient. This was discovered retrospectively by the transfusion practitioner after receiving the cell salvage data collection form.

Non-invasive prenatal testing n=52

Fetal D-typing using cffDNA screening is a highly accurate non-invasive method supporting the appropriate use of anti-D Ig and RAADP, reducing exposure to blood products for D-negative women carrying D-negative fetuses (NICE 2016). However, the assay has limitations, with sensitivity of 99.3% (95% CI 0.982-0.997) and specificity of 98.4% (95% CI 0.964-0.993) (Mackie et al. 2017), leading to a small risk of false positive or false negative results. Anti-D Ig should be given when results are inconclusive.

Fetal cffDNA screening for D should now be now considered standard practice. The service is provided by specialist laboratories in the UK, including the IBGRL and the Exeter Genomics Laboratory. Maternity services currently not offering cffDNA screening for D routinely should be actively working towards implementation.

It is important to investigate, and report results that are discrepant with cord D-type to the referral laboratory and to SHOT. NHSBT report that the false negative rate has remained below 0.1%. Between September 2019 to April 2021, the false predicted D-negative rate has remained at 0.06%. The reasons for incorrect results could be varied and have been covered in the NHSBT information sheet (NHSBT 2022). Fetal DNA in maternal plasma represents a very small fraction of the total DNA in plasma and

this increases during pregnancy. In some cases, the amount of fetal DNA may be too low to detect, especially in early pregnancy which can cause a false negative result. Errors in testing and wrong blood in tube could also lead to false negative results. False positive results may, on rare occasions, be caused by presence of genes which are not expressed on red cell surface (i.e., the phenotype does not reflect genotype). Some blood group genes are inactivated by mutations distinct from the blood group gene itself. Other causes of false positive results may be due to either extraneous contamination of the blood sample or extraneous contamination of testing reagents (despite existing precautions taken to prevent this), testing errors, WBIT or due to vanishing twin (Vanishing twin syndrome is the name given to a type of miscarriage that usually happens in early pregnancy with twins or triplets, when one embryo miscarries and the pregnancy continues. Vanishing twin is the term given to the baby that doesn't fully develop). 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). Anti-D Ig prophylaxis should be given as appropriate. 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. Reporting to the referral laboratory ensures that accurate data on the sensitivity and specificity of the screening assay is available and can be used in the informed consent process during antenatal care.

Errors related to cffDNA screening were identified in 52 cases (Table 8.2), 29/52 (55.8%) occurred in the laboratory and 23/52 (44.2%) in the clinical setting. In 37/52 (71.2%) anti-D Ig was administered unnecessarily to women carrying fetuses predicted to be D-negative.

Table 8.2: Errors in cffDNA screening n=52

SHOT reporting category	Cause of error	Number of cases	% of cffDNA errors
Anti-D Ig given to the mother of a D-negative infant	False positive cffDNA result	13	25.0%
	Failure to check the cffDNA result	20	38.5%
	Misinterpretation of cffDNA report	4	7.8%
Omission or late administration	False negative cffDNA result	5	9.6%
	Misinterpretation of cffDNA result	6	11.5%
	Failure to check the cffDNA result	2	3.8%
	cffDNA result from previous pregnancy used	2	3.8%
Total		**52**	**100%**

Case 8.3: Failure to review cffDNA results leads to unnecessary administration of anti-D Ig

The patient was admitted to the labour ward assessment unit following a PSE. The patient was D-negative and the fetus was predicted to be D-negative. An FMH test was carried out by the transfusion laboratory and no further anti-D Ig was recommended for the PSE. The cffDNA results were available to view on the electronic patient record but were not viewed the day of the event and 500IU anti-D Ig was given to the patient unnecessarily.

Near miss anti-D Ig cases n=15

There were 15 near miss cases analysed in 2021, errors were mainly prevented by robust pre-administration checks by clinical staff and infants fortuitously being D-negative.

Digital solutions to ensure patient safety

Previous Annual SHOT Reports have recommended review of procedures and processes as a means to improve practice. Whilst these recommendations are still applicable, compliance is inherently reliant on the knowledge, skills, experience and understanding of the individuals involved. Systems should be designed with consideration of human factors, including barriers to prevent unsafe practice based on the principles of the intervention hierarchy to truly improve practice. The advancement of digitalisation in healthcare has accelerated, particularly during the COVID-19 pandemic and in line with government strategies (DHSC 2018; Scottish Government 2018; Welsh Government 2021; Government of Ireland

2020), presenting opportunities to improve the management of anti-D Ig and RAADP by building functionality into clinical and laboratory IT systems that support good practice. IT has been proven to reduce risk of error and support good practice relating to the management of blood component transfusion (Murphy et al. 2019; Staples et al. 2020; Goodnough and Hollenhorst 2019), it is incumbent on IT providers to now develop their systems to support similar functionality for anti-D Ig and RAADP.

The SHOT SCRIPT user survey identified improved management of anti-D Ig as one of the top ten functions that laboratory users would like to see in the LIMS that it does not currently support. A follow up survey with LIMS suppliers noted a paucity of functionality within LIMS to support safe practice. SCRIPT have recommended that suppliers explore improvements in functionality in their LIMS to support safe release of anti-D Ig dependent on test results within the patient record. Transfusion service managers should work with the LIMS supplier to ensure that current functionality is utilised to its full potential. The SCRIPT survey results can be accessed on the SHOT website (https://www.shotuk.org/resources/current-resources/script/).

Electronic transmission of cffDNA results to hospital LIMS, using integration systems such as the NPEx would streamline this process, reducing risk of transcription errors and increasing visibility of results. The SCRIPT supplier survey identified that the majority of LIMS already supported interfacing via NPEx, with the remainder engaged in pursuing interoperability. This functionality should be explored and expedited by transfusion laboratory and referral laboratory service managers.

EPR systems provide opportunities for electronic clinical decision support, for the management of anti-D Ig and RAADP, using algorithms based on information within the patient record relating to pregnancy, D-status and cffDNA screening results. EPR providers should review the functionality within their systems that could be harnessed to support safe practice, working with subject matter experts to ensure this is used to its full potential. EPR and electronic blood-tracking systems should provide functionality that can be harnessed to support safe administration and traceability of anti-D Ig and RAADP.

Conclusions

Current IT systems may not have the functionality to provide robust electronic decision support, organisations should continue to ensure that systems, educational activities, processes and procedures support good practice in anti-D Ig management. When developing IT systems to support the management of anti-D Ig, human factors must be considered to reduce risk of workarounds and technology complacency. However, the age of digitalised healthcare has arrived and we must embrace the opportunities that this has provided for us to truly improve the future management of anti-D Ig and RAADP.

Recommended resources

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

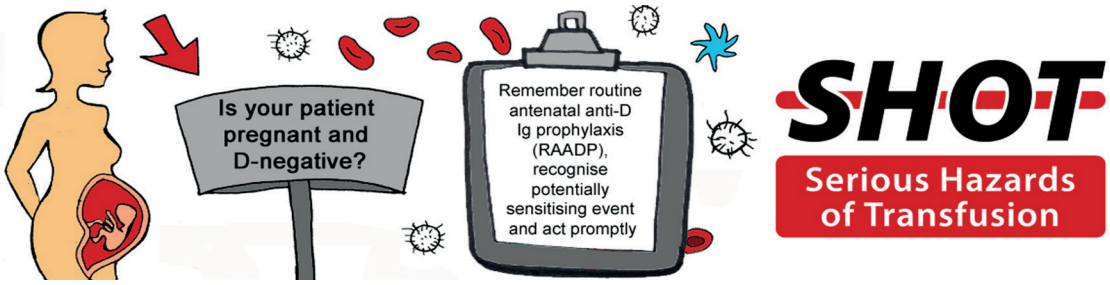
SHOT Bite No 2: Anti-D Ig Administration
https://www.shotuk.org/resources/current-resources/shot-bites/

SHOT Video: Anti-D Ig and Immune anti-D (part 1 and part 2)
https://www.shotuk.org/resources/current-resources/videos/

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 (https://www.bloodassist.co.uk/)

cffDNA testing centres
Exeter Genomics Laboratory (https://www.exeterlaboratory.com/genetics/non-invasive-cell-free-fetal-rhesus-d-rhd-genotyping/)

IBGRL (NHSBT)
https://ibgrl.blood.co.uk/services/molecular-diagnostics/fetal-rhd-screen/



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