Adverse Events Related to Anti-D Immunoglobulin (Ig) n=345

8

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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 platelets.

Abbreviations used in this chapter

BSH	British Society for Haematology	**LIMS**	Laboratory information management system
cffDNA	Cell-free fetal deoxyribonucleic acid	**NICE**	National Institute for Health and Care Excellence
FMH	Fetomaternal haemorrhage	**PCR**	Polymerase chain reaction
HFIT	Human factors investigation toolkit	**PSE**	Potentially sensitising event
Ig	Immunoglobulin	**RAADP**	Routine antenatal anti-D Ig prophylaxis
IT	Information technology	**RPRP**	Right product right patient

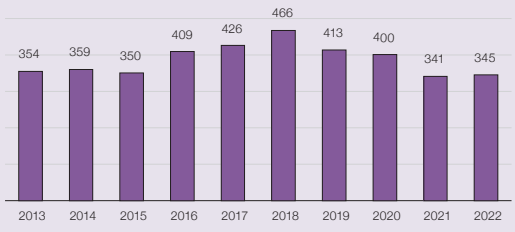
Key SHOT messages

- Omission or late administration of anti-D Ig or RAADP accounted for most cases analysed, 232/345 (67.2%)
- Errors in the clinical setting, 273/345 (79.1%) accounted for most cases
- Use of non-invasive cffDNA screening reduces unnecessary exposure to mothers carrying D-negative fetuses and protects supplies of the product. Staff need to be aware of false-positive and false-negative results that impact on patient care, and these should be investigated appropriately

Headline data 2022

Number of reports n=345
Deaths n=0
Major morbidity n=0

Anti-D Ig reports by year



Demographic data

Male n=0
Female n=345
Adults n=335
Paediatric n=2
Unknown n=8

Potential for major morbidity n=232

Late/omitted RAADP n=75
Late/omitted anti-D Ig following a PSE (including delivery) n=156
Unknown n=1

Recommendations

- Where the D-type of the mother is equivocal and not confirmed this must be clearly reported through the LIMS
- Cases where the cord D-type is discrepant with the D-type predicted by cffDNA should be investigated in a timely manner to ensure appropriate administration of anti-D Ig
- Laboratories should have processes for follow up of anti-D Ig that has not been collected from blood refrigerators to support administration within the 72-hour window

Action: Laboratory management

- Confirmation that anti-D Ig has been administered prior to discharge must be included in the discharge pathway to prevent delays and omissions
- Where mothers have been unable to attend appointments for RAADP, there should be processes to pursue alternative dates and clear communication of the risks with delays and omissions

Action: Maternity and gynaecology services

- Development of IT, including interoperability between laboratory and clinical IT systems, to support appropriate management of D-negative pregnancies must be considered a priority and supported with adequate resourcing to prevent transcription errors

Action: Trust/Health Board IT services, laboratory management

Introduction

Guidelines for safe and appropriate administration of anti-D Ig post sensitising events and RAADP have now been in place for many years (BSH Qureshi et al. 2014; NICE TA156; NICE NG140; NICE NG126). It is essential that these guidelines are reflected in local policies and systems are in place that support compliance in all healthcare settings. 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 345 cases have been analysed, all related to anti-D Ig management during pregnancy.

Deaths related to anti-D Ig n=0

There were no deaths reported in the cases analysed for 2022 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. It is important to recognise that delays, omissions, under-dosing and failures to perform follow up testing after an 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 past failures in anti-D Ig and RAADP management can be seen in Chapter 26, Immune Anti-D in Pregnancy. The impact of anti-D Ig and RAADP errors should not be underestimated.

Overview of cases n=345

Errors in the clinical setting, 273/345 (79.1%) accounted for most cases, and 72/345 (20.9%) errors occurred in the laboratory setting.

Where information regarding the reason for anti-D Ig was available, errors occurred post-delivery, 127/345 (36.8%), RAADP, 113/345 (32.8%) and PSE, 103/345 (29.9%).

Errors in the clinical setting were seen in a variety of settings including delivery suites, 84/273 (30.8%), community, 40/273 (14.7%), antenatal clinic, 37/273 (13.6%), maternity wards, 11/273 (4.0%) emergency

departments, 5/273 (1.8%) and gynaecology wards, 3/273 (1.1%), however, in 38 cases the location was not recorded. Anti-D Ig was given unnecessarily in 87/345 (25.2%) of cases.

Good practice was noted in 4 cases, where routine laboratory practice included a review of uncollected anti-D Ig in blood refrigerators, facilitating communication with the clinical team. Unfortunately, in each of these cases it was still not possible to administer the product within the time frame, but it is suggestive that this practice does have the ability to prevent omissions and delays and should be adopted widely.

Figure 8.1 shows the distribution of anti-D Ig related error reports in 2022 (n=345).

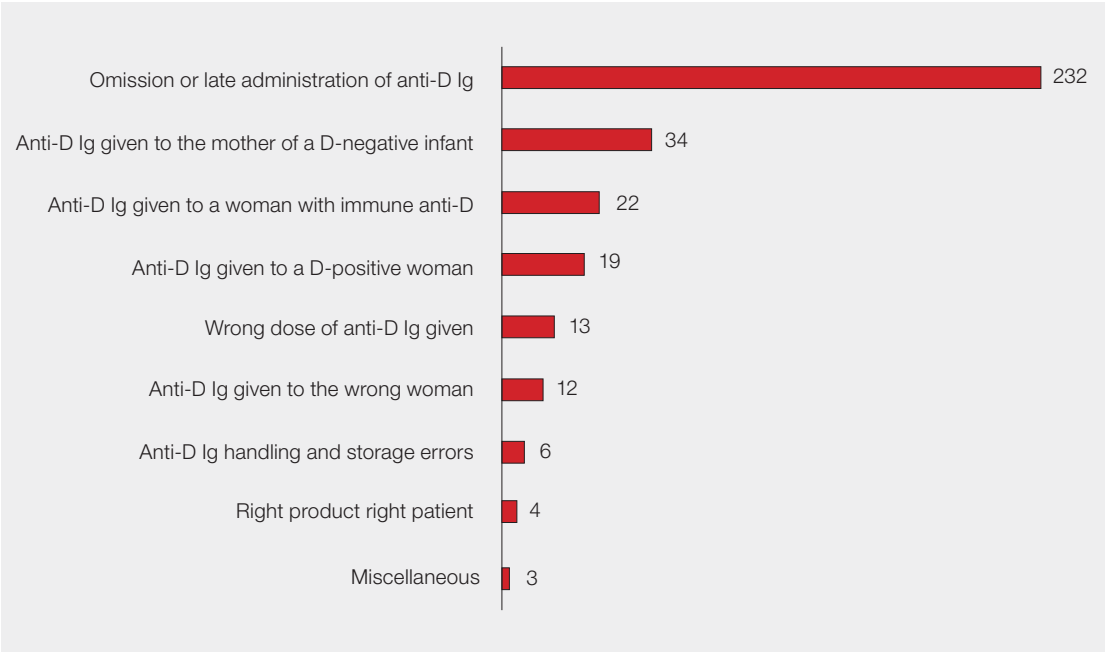


Figure 8.1: Distribution of anti-D Ig related error reports in 2022 (n=345)

Omission or late administration of anti-D Ig errors n=232

Omission or late administration of anti-D Ig or RAADP accounted for most cases analysed 232/345, (67.2%); 51/232 (22.0%) related to patient discharge prior to administration and 26/232 (11.2%) related to flawed decision-making.

Case 8.1: Failure to attend appointment and no follow up

A D-negative mother did not receive RAADP at 28 weeks in the community setting. The mother did not attend the clinic appointment at 28 weeks, and this was not followed up by the clinical team. The omission was noticed later in the pregnancy by the laboratory team.

The incident was reviewed, and improvement actions identified. It was agreed that the community clinic would be included in the hospital patient booking system so that non-compliance could be managed electronically by sending reminders to both mother and clinic staff.

Failure to attend appointments is a challenge across the whole of healthcare. Omission or delay resulting from patient non-compliance is not SHOT-reportable, however, it was unclear in this case whether the mother made a conscious and informed decision not to attend for anti-D Ig administration but there was no evidence of follow up by the clinical team. It is encouraging to see in this case that the improvement action has included using IT systems to provide an effective process for follow up where appointments have been missed.

Learning point

- Systems should be in place to ensure that, where mothers have not attended an appointment, there is a follow up and effective communication of the risks of not having anti-D Ig administered

Case 8.2: Discharge prior to administration leading to delay

A D-negative patient had a termination of pregnancy at 12+1 weeks. Anti-D Ig was issued but not administered before the patient was discharged. The ward staff realised the patient required the anti-D Ig and arranged for it to be administered 2 days after the procedure. The patient then informed the clinical team that they a positive lateral flow COVID-19 test and so were unable to attend for the appointment. Confirmatory COVID-19 PCR testing was negative 2 days later and the patient attended for the anti-D Ig injection, 4 days post procedure.

Discharge prior to administration of anti-D Ig is a common reason for delays and omissions. This case demonstrates good communication between the clinical team and the patient, with every effort being made to attempt to administer the anti-D Ig within 72-hours. The delay could have been prevented by ensuring that anti-D Ig is always administered prior to discharge. Other cases reported highlight the challenges with administration of anti-D Ig post-discharge; cost of living pressure impacting on travel to appointments, conflicting advice on requirement for anti-D Ig, lack of understanding of the potential risks of delay or omission.

Due to the retrospective nature of anti-D Ig submissions, COVID-19 pandemic themes continue to resonate in the 2022 reports (Almozain et al. 2022). Contributory factors to omissions and delays included changes in policies for anti-D Ig administration to reduce hospital appointments, staff re-deployment, mothers moved to COVID-19 wards where staff were unfamiliar with anti-D Ig, inability to attend appointments due to self-isolation. Whilst these reasons may diminish as the world learns to 'live with COVID-19', there are important messages within these themes that will remain. Unfamiliarity with the use of anti-D Ig is a recurrent theme in SHOT reports, particularly where mothers are seen outside of the maternity or gynaecology setting.

Learning points

- It is essential that anti-D Ig is administered prior to discharge, this should be supported by effective processes in maternity and gynaecology service, with confirmation of administration included within the discharge checklist and summary
- It is important that all staff have a basic understanding of management of D-negative pregnancies, this should be included in the regular transfusion training programs. SHOT provide educational videos that can be incorporated into local training packages

Other anti-D Ig errors n=113

Administration to a mother carrying a D-negative infant accounted for 34/345 (9.9%) of cases, 9/34 due to failure to check cffDNA or cord blood D-types and 11/34 due to false positive D-types predicted by cffDNA screening.

Anti-D Ig was administered to mothers with immune anti-D in 22/345 (6.4%) cases, 8/22 resulted from failures to check records.

D-positive mothers received anti-D Ig inappropriately in 19/345 (5.5%) cases, 7/19 of these were weak D-types, other errors included failure to check results and transcription errors.

There were 13/345 (3.8%) cases that involved administration of incorrect doses, 5/13 related to failure to perform Kleihauer testing, cases of under-dosing related to cell salvage and miscalculation of FMH, over-dosing resulting from miscalculation of FMH and challenges around appropriate administration following frequent PSE. Failures in FMH estimation should be investigated. Whilst under-dosing has a real risk for development of immune anti-D, there are no patient safety risks associated with perceived over-dosing.

Anti-D Ig was administered to the wrong woman in 12/345 (3.5%) cases, all resulted from failures in positive patient identification.

Errors in the handling and storage of anti-D Ig accounted for 6/345 (1.7%) of cases, 2/6 cases of administration of expired products, 2/6 storage errors and 2/6 administered without prescription. Finally, 3 cases were classified as miscellaneous, and 4 RPRP cases related to errors in labelling of anti-D Ig.

From the information available related to incident investigations, it is encouraging to see the increase in cases being formally investigated and reviewed and less emphasis placed on individual staff members. A human factors and systems-based approach supports identification of true causes of error and implementation of effective interventions to reduce risk of recurrence.

Involvement of information technology

IT was noted as being involved in errors in 54/345 (15.7%) of cases, the majority of these related to omission or delay (28/54) and anti-D Ig administered to a mother with a D-negative infant (14/54). The involvement of IT was varied but the main theme was transcription errors due to lack of interoperability of laboratory and clinical systems. It is interesting to note that IT is being seen as involved in only a small number of cases and mainly associated with lack of interoperability. IT systems are now prevalent in healthcare, these should be developed and configured to support safe and appropriate practice across the whole of anti-D Ig management, not just transfer of laboratory results.

Non-invasive prenatal testing n=23

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). 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.

A total of 23 cases were reported relating to cffDNA screening. Of these, 11/23 were false positive and 8/23 were false negative screening results, these are described in the laboratory errors chapter. The remainder comprised of failures to check cffDNA results prior to order, release or administration of anti-D Ig and a laboratory failure to report the results which led to them not being visible to the clinical team.

The limitations of the screening assay include a low risk that predicted D-types may be discrepant with cord D-types (Narayan et al. 2022). The false negative rate (where women would not be offered anti-D-Ig and so be at risk of sensitisation) is very low at 0.34% (95% CI 0.15 to 0.76) and the false positive rate 1.26% (95% CI 0.87 to 1.83) (Yang et al. 2019). It is important that discrepant results are followed up to ensure that anti-D Ig is provided appropriately. A checklist for investigation of discrepant results is now available on the SHOT website that can be used for local investigations (see ‘Recommended resources’).

Near miss anti-D Ig cases n=37

There were 37 near miss cases analysed in 2022, which is an increase from 15 in 2021. Errors were detected by laboratory staff in 22/37 (59.5%) of cases, and by a registered nurse or midwife in 15/37 (40.5%).

Conclusion

SHOT data continue to demonstrate that errors in anti-D Ig and RAADP management occur in both clinical and laboratory settings. The management of anti-D Ig and RAADP is multifaceted, errors occur at all stages of the process, from the identification of the requirement, ordering, prescription, laboratory release,

storage and administration. The implementation of non-invasive cffDNA screening has undoubtedly improved practice by targeting administration of this blood product to those who need it, both reducing unnecessary exposure to mothers carrying D-negative fetuses and protecting supplies of the product. Access to the screening program should now be an accepted standard in all maternity services.

In the 2021 Annual SHOT Report (Narayan et al. 2022), this chapter stressed the importance of harnessing the power of IT to support the safe and appropriate management of anti-D Ig. This message is becoming more vital as the healthcare service struggles with current challenges of staffing, workload and post-pandemic backlogs. IT provides an opportunity for clinical decision support, checklists, fail-safes and user alerts within patient records in both the clinical and laboratory settings. IT is not dependent on staff knowledge, memory or familiarity with tasks. IT can pull different aspects of the clinical record, including pregnancy status, D-type, cffDNA result, together to support flags and alerts for anti-D Ig administration, and reminders for appointments. It is incumbent on IT providers, clinical users and patient groups to work together to configure and design IT systems that support good practice. SHOT resources are available to guide how IT systems can support good practice in the management of anti-D Ig. The SHOT anti-D aide-memoire provides a checklist that can be used in the absence of IT support, but also as resource for designing IT systems to support safe practice.

SHOT provide a variety of resources that can be used as training aides for healthcare staff and are open access for patients and carers. Mothers are often well informed on their pregnancies and should be included in discussions relating to requirement for anti-D Ig, the importance of timings for administration and the risk of delays and omissions in administration. Healthcare services are now promoting patient-centred care, where patients are not only involved in decisions about their own treatment, but encouraged to become involved in incident investigation, suggesting improvements in care and system design. The management of anti-D Ig should be integral in this initiative. It is only by working together, with buy in from all stakeholders, that we can truly improve practice and reduce risk of error.

Recommended resources

Anti-D Immunoglobulin (Ig) Administration to avoid sensitisation in pregnancy - an aide memoire SHOT 2020
IT supports anti-D Ig management
Template for investigation of discrepant cffDNA results in hospitals
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/

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/

References

Almozain N, Davis J, Narayan S. COVID-19 pandemic impact on management of anti-D Ig in pregnancy: Insights from SHOT. *Vox Sang* 2022;**117(1)**:49-50.

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 2023].

Mackie FL, Hemming K, Allen S, et al. The accuracy of cell-free fetal DNA-based non-invasive prenatal testing in singleton pregnancies: a systematic review and bivariate meta-analysis. *BJOG*. 2017;**124**(1):32-46. doi: 10.1111/1471-0528.14050. https://pubmed.ncbi.nlm.nih.gov/27245374/ [accessed 30 April 2023].

Narayan S (Ed), Poles D, et al. on behalf of the Serious Hazards of Transfusion (SHOT) Steering Group. The 2021 Annual SHOT Report (2022). https://www.shotuk.org/shot-reports/ [accessed 27 April 2023].

NICE (TA156). Technology appraisal guidance TA156: Routine antenatal anti-D prophylaxis for women who are rhesus D negative (2008). https://www.nice.org.uk/guidance/ta156/chapter/1-Guidance [accessed 28 April 2023].

NICE (DG25). High-throughput non-invasive prenatal testing for fetal RHD genotype (2016). https://www.nice.org.uk/guidance/dg25 [accessed 28 April 2023].

NICE (NG126). Ectopic pregnancy and miscarriage: diagnosis and initial management (2019). https://www.nice.org.uk/guidance/ng126/chapter/Recommendations#anti-d-rhesus-prophylaxis [accessed 28 April 2023].

NICE (NG140). Abortion care (2019) https://www.nice.org.uk/guidance/ng140/chapter/Recommendations#anti-d-prophylaxis [accessed 28 April 2023].

Yang H, Llewellyn A, Walker R, et al. High-throughput, non-invasive prenatal testing for fetal rhesus D status in RhD-negative women: a systematic review and meta-analysis. *BMC Med.* 2019;**17**:37. https://doi.org/10.1186/s12916-019-1254-4 [accessed 28 April 2023].