Red blood cell transfusion in sickle cell disease

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Chapter 6

Extended Phenotyping Does Not Preclude the Occurrence of Delayed Haemolytic Transfusion Reactions in Sickle Cell Disease

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ABSTRACT

Delayed haemolytic transfusion reaction (DHTR) is a potentially life-threatening complication of red blood cell (RBC) transfusions in sickle cell disease (SCD) and is classically induced by reactivation of previously formed antibodies. Improved antigenic matching has reduced alloimmunization and may reduce DHTR risk. We conducted a retrospective cohort study to investigate the incidence rate of DHTR in SCD patients receiving extended matched units (ABO/RhDCcEe/K/Fy^{a}/Jk^{b}/S). Occasional transfusion episodes (OTE) between 2011 and 2020 were reviewed for occurrence of DHTR symptoms using four screening criteria: decreased Hb, increased lactate dehydrogenase (LDH), pain, and dark urine. We included 205 patients who received a cumulative number of 580 transfusion episodes of 1866 RBC units. During follow-up, 10 DHTR events were observed. The incidence rate of DHTR was 13.8/1000 OTEs (95% confidence interval (CI): (7.37-22.2)), with a cumulative incidence of 15.2% ((95% CI: (8.4%-24.0%)) after having received 25 RBC units. One DHTR event was fatal (10%). Symptoms were misdiagnosed in four DHTR events (40%) as other acute SCD complications. In spite of a lower incidence rate compared to most other studies, the incidence rate of DHTR in SCD remains high, despite extended matching of donor RBCs. Increased awareness of DHTR is of utmost importance to facilitate early diagnosis, and consequently improve outcome.

INTRODUCTION

Red blood cell (RBC) transfusions remain a key treatment for patients with sickle cell disease (SCD).[1] While the introduction of leukoreduction and extended matching over the past decades has significantly increased the safety of RBC transfusions, patients with SCD are still prone to transfusion-related complications.[2] RBC alloimmunization incidence in SCD patients is much higher than in other disease populations receiving donor RBCs, despite extended matching protocols.[3, 4] Main risk factors include the antigen mismatch between predominantly Caucasian donors and African recipients, chronic inflammation and genetic predisposition.[5-8] Because of the alloantibodies, patients are at risk for severe transfusion reactions.[9]

A delayed haemolytic transfusion reaction (DHTR) is the most severe and potentially life-threatening transfusion reaction in SCD. A DHTR is classically induced by reactivation of previously formed alloantibodies, which leads to intra- and extravascular hemolysis of the transfused RBCs.[9-11] In the most severe cases, haemolysis of autologous RBCs may be involved, resulting in haemoglobin (Hb) levels below the pre-transfusion level, so-called hyperhaemolysis. Although the exact mechanism remains unclear, activation of the alternative complement pathway via cell-free haeme may be involved.[11, 12] This propagates a cascade of immune activation that accelerates the ongoing haemolysis. Interestingly, antibody activation is not always evident during DHTR episodes. The pathophysiology of these episodes is not yet completely understood.[13, 14]

Diagnosis of DHTR in SCD is challenging, as the clinical presentation may mimic a vaso-occlusive crisis (VOC). This is problematic, as a DHTR is potentially lethal and requires aggressive treatment with immunosuppressant therapy and support of erythropoiesis.[14] Importantly, during a DHTR new RBC transfusions should be withheld if possible, as this might aggravate haemolysis.[9, 14]

Recent evidence suggests that SCD patients are at particularly high risk of DHTR when receiving an occasional RBC transfusion for acute or preoperative indications, while DHTRs are rarely reported in patients on chronic transfusion schemes.[13, 15, 16] It is hypothesized that the inflammatory condition in which occasional transfusions are administered puts patients at increased risk of post-transfusion complications due to increased consumption and enhanced presentation of transfused RBCs.[6, 17]

In the literature, reported incidence rates of alloimmunization have decreased over the last decades, which has been attributed to the introduction of extended matching for ABO/RhDCcEe and K in SCD. However, DHTR still occurs frequently with a reported incidence rate of 41.7/1000 occasional transfusions.[13] Moreover, DHTR has been reported to be

fatal in 11.5% of the events and to account for 4.2% of all-cause mortality in SCD.[13, 18] Further extension of the antigen matching protocol and nationwide registration of previously formed antibodies, which is common practice in the Netherlands since 2007 (Transfusion Register of Irregular Antibodies and Cross-match Problems (TRIX) registry[19]), may reduce the incidence of DHTR. In this study, we aimed to describe the incidence and to examine the determinants of DHTR in an extended matched population (ABO/RhDCcEe/K/Fy^a/ Jk^b/S).

MATERIAL AND METHODS

Subjects and study design

A retrospective cohort study for the period between 1 January 2011 and 30 April 2020 was performed in the Amsterdam University Medical Centre in the Netherlands. The institutional review board approved the study, which was conducted in accordance with the Declaration of Helsinki. All records of the source population of 664 SCD patients (both adults and children) under treatment were assessed.

Patients of all ages and all SCD genotypes were eligible for inclusion if (i) they had received ≥1 RBC unit during the observation period and (ii) the transfused unit was part of an occasional transfusion episode (OTE). Both top-up transfusions and RBC exchange transfusions were included in the analysis. Chronic transfusions and transfusions administered prior to stem-cell transplantation with concurrent immunosuppressive therapy were excluded, as the risk for DHTR in this group is considered low. Patients received RBC transfusions matched by serology for ABO/RhDCcEe/K/Fy^a/ Jk^b/S, and for previously detected antibodies registered in TRIX,[19] a database that registers all antibodies ever encountered in a patient. Even if the antibody was evanescent, RBC units were still selected to be compatible.

Data collection

Data were collected from the electronic patient files using an electronic case-report form.[20] Collected data included the following baseline characteristics: year of birth, gender, SCD genotype, history of pregnancy, geographic origin, and the number of historical RBC units. Furthermore, alloimmunization status and history of DHTR prior to the study period were documented.

For the identification of potential DHTR events, data were collected from between 3 and 25 days after each OTE.[9] All units that had been administered within 1 week of the index transfusion were analysed as one OTE, whereas units administered more than 1 week after the index transfusion were considered a new OTE.

Definition of DHTR

For our retrospective assessment, four screening criteria, based on literature guidelines, were used to identify a potential DHTR: (i) a drop in Hb of <1.5 g/dL compared to post-transfusion Hb, or Hb below the pre-transfusion level, (ii) dark urine, (iii) increased LDH (>1.5x baseline), and (iv) appearance or recurrence of VOC-like pain.[9] If any of the above-mentioned criteria were present, further laboratory and clinical data were evaluated. Laboratory data included HbA%, bilirubin, direct antiglobulin test (DAT), and antibody screen. Clinical data included information on diagnosis of post-transfusion complications, treatment, and outcomes of the DHTR. Potential events were classified as (i) DHTR diagnosed, (ii) DHTR suspected, but not diagnosed, (iii) alternative diagnosis, no DHTR. All suspected and diagnosed events were discussed with an expert panel consisting of treating (paediatric) haematologists and were classified as either 'DHTR confirmed' or 'alternative diagnosis more likely'.

Statistical analysis

SPSS statistical software version 26 (IBM Corp., Armonk, NY, USA) and Graphpad Prism version 8 (Graphpad Software, San Diego, CA, USA) were used for analysis. Continuous variables were expressed as mean with standard deviation (SD) or median with interquartile range (IQR) as appropriate. Categorical variables were expressed as proportion (percentage). Cumulative incidence and incidence rates per 1000 OTEs and per 1000 RBC units were calculated. When calculating the incidence rate, only the first DHTR event of each patient was considered, as a previous DHTR increases the risk of a subsequent DHTR, also patients with a diagnosis of DHTR before the start of the observation period were excluded from the incidence calculation.

For comparison of the incidence rate with current published literature, a concise review of studies specifically mentioning the incidence rate in patients receiving OTEs was established. For this purpose, data from other studies were recalculated to incidence rates per 1000 OTEs or 1000 RBC units.

To adjust for the cumulative number of exposures to RBC units we calculated Kaplan-Meier cumulative DHTR incidences with DHTR as the event and the cumulative number of RBC units as the time variable. Only patients with complete documentation of their transfusion history were included for this analysis. A maximum of five untraceable units (data not easily accessible due to transfusion abroad) was allowed to minimize confounding while retaining a sufficient sample size. For cumulative incidence calculation of DHTR, historical units that were transfused as part of a chronic transfusion scheme were also included. DHTRs diagnosed before the observation period were included as outcomes in cumulative incidence calculation.

For identification of risk factors for DHTR, Cox proportional hazard models with the number of RBC units as time variable should be used. But because of the relatively small sample size,

this analysis was not possible. Hence, we constructed a table to compare characteristics between patients who developed a DHTR and patients who did not develop a DHTR. For the time-dependent variables (age, history of alloimmunization, historical number of OTEs, historical number of RBC units) data were collected at last transfusion in patients who did not experience a DHTR, or at triggering transfusion in patients who experienced a first DHTR.

RESULTS

Patient characteristics

During the observation period of 9 years and 4 months, 205 (31%) of the 664 patients received at least one OTE and were included in this study. Baseline characteristics of the group are described in **Table 1.** The genotype distribution was 166 (81%) HbSS/HbSβ^0 and 39 (19%) HBSC/HbSβ$^+$. The median age at start of the observation period was 19 years (IQR 8-28), and 101 patients (49%) were male. Patients underwent 580 separate transfusion episodes with a median of two OTEs (range 1-24) per patient. In total 1878 RBC units had been transfused with a median of five units (range 1-78) per patient. Of the 205 included patients, 115 (56%) had received at least one RBC transfusion before 2011 and one patient was diagnosed with a DHTR before 2011.

Table 1. Baseline characteristics.

Baseline characteristics	N=205
Gender (male) *N* (%)	101 (49.3)
Age, median (IQR)	19 (8-28)
Hb Genotype *N* (%)	
HbSS/HbSβ0	166 (81)
HbSC/HbSβ+	39 (19)
Ethnicity* *N* (%)	
Africa	73 (39.5)
Latin-America/Carribean/Surinam	98 (53)
Asia/Pakistan/India	1 (0.5)
Arabic/Middle-East	6 (3.2)
Mediterranean	3 (1.6)
Other	4 (2.2)
Total number of units transfused	1866
Total number of OTEs	580
No. of OTE per patient, median (range)	2 (1-17)
No. of units per patient, median (range)	5 (1-78)

*IQR= interquartile range, OTE = occasional transfusion episode, *= unknown in 20 patients*

DHTR incidence

At least one of the four criteria for DHTR was fulfilled in 68 (12%) OTEs in 56 patients. In 46 episodes, there was a clear alternative diagnosis. In the remaining 22 episodes, a DHTR was diagnosed in six, while in 16 episodes DHTR was not diagnosed, yet in hindsight suspected. These 16 episodes were discussed with the expert panel, which concluded that in four episodes DHTR was the most likely diagnosis in retrospect, and in 12 episodes an alternative diagnosis was more likely **(Fig 1).**

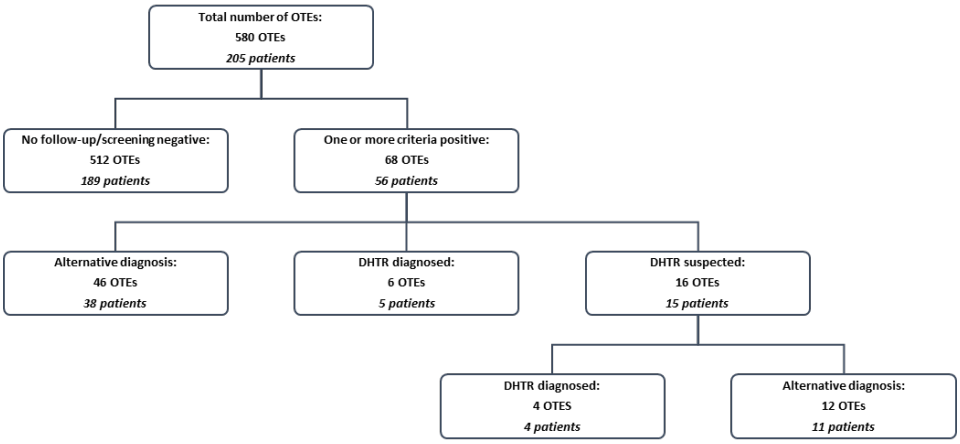

Figure 1. Flowchart incidence delayed hemolytic transfusion reactions.
OTE = occasional transfusion episode. DHTR = Delayed hemolytic transfusion reaction. NB number of patients is not equal in each tier, since a number of patients is represented in more than one category.

Two DHTR events were excluded from the incidence calculation. For one DHTR event, the patient had experienced a DHTR before the start of the observation period, and for the other event a patient experienced a DHTR twice during the observation period. This resulted in 8 out of 204 (3.9%) patients being diagnosed with a first DHTR during the observation period of this study. The incidence rate of DHTR was 13.8/1000 OTEs (95% confidence interval (CI) 7.37/1000 – 22.2/1000), and 4.3/1000 RBC units (95%CI 1.2/1,000 – 9.4/1000). **Table 2** shows a summary of the incidence rates compared to the current literature. Three studies mentioned the incidence rate of DHTR in patients receiving OTEs and demonstrated an incidence rate between 2.6/1000 OTEs and 41.7/1000 OTEs.[13, 15, 16]

The cumulative DHTR risk in our cohort increased from 0.8% (CI 0.01-3.6) after five RBC units, to 6.0% (CI 2.1-11.9) after 15 RBC units, up to 15.2% (CI 8.4-24.0) after 25 RBC units (**Fig 2**).

Table 2. Overview of incidence rates of DHTR in patients receiving occasional transfusions.

Author/year	Matching policy	Number of DHTR	Total number of patients	Follow-up period (years)	Number of transfused RBC units	DHTR incidence rate /1000 RBC units	Number of OTEs	DHTR incidence rate / 1000 OTEs
This study	AB0/RhDCcEe/K/ Fya/Jkb/S	8	205	9.3	1866	4.3/1000	580	13.8/1000
Michot/2015[17]	AB0/RhDCcEe/K	4	139	6	2674	1.5/1000	1519	2.6/1000
Vidler/2015[16]	AB0/RhDCcEe/K	20	NA	5.4	NA	NA	591	33.8/1000
Narbey/2017[13]	AB0/RhDCcEe/K	15	221	2.5	NA	16.4/1000	360	41.7/1000

OTEs = occasional transfusion episodes, NA= Not available

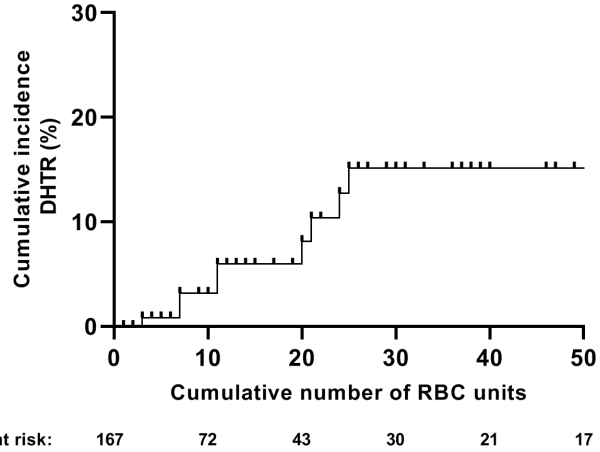

Figure 2. Kaplan Meier curve of cumulative incidence of delayed hemolytic transfusion reactions with the cumulative number of RBC units as time unit.

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Clinical details DHTR

Transfusion history and clinical presentation DHTR

The details of the individual DHTR episodes are summarized in **Table 3**. The median age at DHTR was 26 years (range 4-32), and in half of the events, the patients were female. The cumulative number of RBC units transfused before the DHTR ranged from zero in two patients to 29 units in one. In four of the 10 DHTRs, no previous antibodies were detected. Indications for transfusion were acute SCD related complications (e.g. acute chest syndrome (ACS) or VOC) in six events, a preoperative transfusion in three patients and cerebral infarction in one patient.

Patients experienced the first symptoms of the DHTR after a median of 9 days following RBC transfusion (range 3-21). At initial presentation, the most common reported clinical symptoms were pain and fever occurring in 60% and 50% of the DHTR events, respectively.

In four events, a DHTR had not been diagnosed at the time but was identified during the evaluation of this study, despite newly detected antibodies in two events. In these events, alternative diagnosis at the time was ACS with severe haemolysis in three patients, and autoimmune haemolytic anaemia in one.

Laboratory results

In almost all DHTR events (90%), an increased LDH at initial presentation was found, whereas a drop in Hb of >1.5g/dL was initially only observed in seven of the 10 events.
During follow-up, all patients developed varying degrees of anaemia (median nadir Hb 3.7 g/dL (IQR 2.7-4.4)), all well below the immediate post-transfusion levels (median 9.0 g/dL (IQR 8.1-10.0)). Median peak LDH was 2552 U/L (IQR 1376-3971). HbA% was assessed both directly after transfusion and during follow-up in only one patient (1 day after transfusion: Hb 7.7 g/dL and %HbA 76, +14 days: Hb 4.8 g/dL and %HbA 18%), demonstrating a high risk for DHTR based on the previously published nomogram.[21] A DAT was positive in the majority of events (n=8; 89%) when tested. Five DHTR events resulted in newly detected clinically significant alloantibodies within 9-17 days after transfusion. As these antibodies were all detected within approximately 2 weeks after transfusion, this most likely resulted from boosting of pre-existing antibodies that were never detected because of waning titres. In four events, at least one of the newly detected antibodies was directed against antigens included in the matching protocol.

Treatment and outcome

The treatment of DHTR varied between patients. Prednisone (1-2mg/kg/day) was the main treatment in most (66%) diagnosed events. Three DHTR events presented with concomitant reticulocytopenia and were all treated with erythropoietin. Four severe events had additionally been treated with rituximab (375mg/m^2, 3-4x), and two with the addition of immunoglobulins (IVIG). In most DHTR events (80%), subsequent transfusions were administered, generally with the addition of rituximab or C1-esterase inhibitor to abrogate further antibody-induced haemolysis. One patient died the day after the start of symptoms due to hyperhaemolysis with a haemodynamic shock after unsuccessful resuscitation. The outcome of the other DHTR events was favourable.

Risk factors for DHTR

An overview of the characteristics of patients who experienced a DHTR compared to those who never experienced a DHTR is provided in **Table 4.** Patients who experienced a DHTR more often had a history of alloimmunization (56% vs 10%) and had received a higher number of OTEs (median 4 (IQR 2-11) vs. 2 (IQR 1-7)) and RBC units (median 11 (IQR 7-23) vs. 7 (IQR 2-21)) than patients who never experienced a DHTR.

Table 3. Clinical characteristics of the 10 DHTR episodes.

Case ID	Age (gender)	Hb genotype	No. of past units	DHTR in history	Historical antibodies	Indication for transfusion	No. units transfused	Post TF Hb (g/dL)	Time until start symptoms
1	16 (F)	SS	2 (2 OTEs)	N	-	Pre-op	2 (TU)	10.4	11 days
2	18 (F)	SS	17 (12 OTEs)	N	-	ACS	6 (RCE)	9.0	8 days
3	26 (F)	SS	12 (6 OTEs)	Y	Jkb, Cw, S	ACS	5 (RCE)	10.1	9 days
4a	26 (M)	SS	17 (7 OTEs)	N	Lua, Lea, auto-e	ACS	8 (RCE)	8.3	7 days
4b	29 (M)	SS	29 (11 OTEs)	N	Fya, N, S, Lua, Lea, auto-e	ACS	6 (RCE)	9.9	14 days
5	32 (M)	SS	19 (12 OTEs)	N	S, NS-WAU	Pre-op	2 (TU)	ND	21 days
6	4 (F)	SS	2 (2 OTEs)	N	-	Start CTS	1 (TU)	9.4	9 days
7	22 (M)	SS	10 (4 OTEs)	N	Jkb, NS-WAU	VOC	1 (TU)	7.4	6 days
8	26 (M)	SC	0 (0 OTEs)	N	-	ACS	10 (RCE)	8.5	3 days
9	31 (F)	SC	0 (0 OTEs)	N	S	Pre-op	3 (TU)	7.8	14 days

F= female, M= male, OTE = occasional transfusion episode, N= No, Y= Yes, TU = top-up transfusion, RCE = Red blood cell exchange transfusion, pre-op = pre-operative, ACS= Acute chest syndrome, CTS= Chronic transfusion scheme, VOC = Vaso-occlusive crisis, DAT = direct antiglobulin test, NS-WAU = Nonspecific warm autoantibodies, NS-CAU = Nonspecific cold autoantibodies, WHEM = Warm haemolysins, EPO = erythropoietin, IVIG = intravenous immunoglobulins C1-Inh = C1-esterase inhibitor, RBC TF= red blood cell transfusion

Table 4. Overview of characteristics of patients with vs. without DHTR.

	DHTR + n= 9	DHTR - n = 196
Gender (male)	4 (44)	97 (49)
Age, median (IQR)	22 (17-26)	21 (10-31)
Hb Genotype		
HbSS/HbSβ0	7 (78)	159 (81)
HbSC/HbSβ+	2 (22)	37 (19)
History of alloimmunization, *N* (%)	5 (56)	19 (10)
No. of OTEs per patient, median (range)	4 (2-11)	2 (1-7)
No. of units per patient, median (range)	11 (7-23)	7 (2-21)

Time dependent variables were measured at end of follow-up or at time of first DHTR. OTE = occasional transfusion episode

Symptoms	DHTR diagnosed?	Time to diagnosis in days	Hb nadir (g/dL)	peak LDH (U/L)	DAT	New Ab formation	Treatment	Outcome
Hb ↓, LDH ↑, pain	Y	5	3.0	5063	+	Anti-Lea, Anti-Leb	RBC TF, EPO, IVIG, prednisone, rituximab	Alive
Hb ↓, LDH ↑	Y	23	2.7	3948	+++	NS-WAU	prednisone, RBC TF, rituximab, IVIG	Alive
Hb ↓, LDH ↑, dark urine, fever	Y	0	2.6	2172	+	Anti-K, Anti-N	EPO	Alive
Hb ↓, LDH ↑	Y	0	4.3	1227	+++	Anti-Fya, Anti-N, Anti-S	RBC TF, prednisone, rituximab	Alive
Hb ↓, LDH ↑, pain, dark urine, fever	Y	0	3.5	2932	++	-	RBC TF, C1-Inh	Alive
Pain	Y	30	4.2	1592	+++	-	EPO, rituximab, prednisone	Alive
Hb ↓, LDH ↑, pain, fever	N		4.6	1426	+++	Anti-I, anti-C, anti-Lua, WHEM, Auto-e, NS-CAU, NS-WAU	Prednisone, RBC TF	Alive
Hb ↓, LDH ↑, pain	N		2.6	4042	-	-	RBC TF, thrombolysis	Deceased
LDH ↑, dark urine, fever	N		6.1	3268	ND	-	RBC TF	Alive
LDH ↑, pain, fever	N		3.8	1063	+	Anti-Fya, NS-CAU, NS-WAU	RBC TF	Alive

DISCUSSION

DHTR is a potentially lethal complication of transfusion therapy in SCD and remains incompletely understood. In our study, we have shown that despite the extended matching protocols and the national antibody registry that was used for all our patients, DHTR still occurred relatively frequently.

Compared to the current literature, we found a lower incidence rate of DHTR in patients receiving OTEs (13.8/1000 OTEs) than previous observations by Vidler et al. (33.8/1000 OTEs) and Narbey et al. (41.7/1000 OTEs), although our incidence rate was higher than reported by Michot et al (2.6/1000 OTEs).[13, 15, 16] Comparison of the incidence rate with other studies was hampered, because in those studies no distinction was made between occasional and chronic transfusions.[22, 23] This is likely to have suppressed the DHTR incidence rate in those studies, as patients on chronic transfusions receive the majority of the RBC units while being at a particularly low risk of DHTR.

The lower incidence rate in our study could be attributed to the positive effect of our extended matching protocol, as all RBC units were matched for the significant antigens ABO/RhDCcEe/K/Fy^a/ Jk^b/S while matching in the other studies was limited to ABO/RhDCcEe/K. In addition, the unique Dutch national antibody registry possibly prevented mismatch transfusions caused by false-negative antibody screens due to waning antibody titres.[19] Vidler et al.[15] included recurrent DHTRs in the same patients in incidence calculations. As the risk of DHTR is increased after the first DHTR, this will have increased the reported incidence rates compared to our study. Alternatively, patients in our study were exposed to a lower number of RBC units compared to the other studies, which potentially resulted in a lower incidence rate of DHTR.[13, 15] Michot et al. reported a lower incidence rate of DHTR in patients receiving occasional transfusions.[16] However, in this retrospective study, only previously registered DHTRs were included, most likely leading to an underestimation of the incidence. Perhaps, too, there was some underestimation of the true incidence of DHTR in our study as well. Forty per cent (4/10) of the events in our study were not identified at the time of the event and had been misdiagnosed as ACS, and mild cases were possibly never registered. It should be noted that anaemia was not always apparent at initial presentation, because of an initial compensatory reticulocyte response, though severe haemolysis eventually overwhelms the compensatory reticulocytosis.[14] This underlines the challenging clinical presentation of DHTR and may have reduced our incidence rate when compared to a prospective study that diagnosed DHTRs more appropriately on a nomogram that measured changes in HbA compared to the early post-transfusion level.[13, 24] Unfortunately, as %HbA was rarely measured, we were unable to validate this promising nomogram that may facilitate early diagnosis.

Patients with previously formed antibodies seem to be at highest risk of DHTR, as demonstrated in our study. This highlights the importance of prevention of alloimmunization in SCD patients, as alloimmunization rates remain high.[2, 3, 25, 26] Half of the DHTR events resulted in newly detected alloantibodies that were previously not recorded in the national antibody registry. This was likely to be the result of the boosting of evanescent antibodies caused by historic transfusions. Antibody evanescence frequently occurs in SCD, consequently leading to false-negative antibody screens prior to subsequent transfusions.[27-29] Strikingly, four patients with DHTR had newly detected antibodies against antigens that were included in the matching protocol. Even though in these patients RBC units were correctly matched for antigen phenotype (data not shown), potential antigenic variants of the donor, predominantly in RH and MNS system, or weak Fy^a expression, could have been missed.[30-33] In one case, the antibody formation was potentially induced by pregnancy.[34] However, the occurrence of these antibodies is surprising and warrants further investigation. These results substantiate the need for prospective genotyping of both patients and donors to identify antigenic variants, thereby preventing potential mismatches based on phenotype matching alone.[4, 33]

Some limitations to this study should be acknowledged due to the retrospective design. First, the incidence rate of DHTR is most likely underestimated, as clinical and laboratory data were not always complete, patients were lost to follow-up, or mild symptoms were mistakenly attributed to an uncomplicated VOC. Second, the small number of events and incomplete patient data meant that assessment of risk factors for DHTR was limited.

In conclusion, we have shown a lower incidence rate of DHTR compared to most previous studies, which may be attributed to a protective effect of extended matching and the use of a national antibody registry. Timely diagnosis of DHTR remains challenging because of the non-specific symptoms at presentation. Therefore, DHTR should always be considered as a diagnosis in SCD patients who present with acute pain, and have recently been transfused. Routine HbA% testing could be a valuable addition for distinction of DHTR from other SCD related events. There is an urgent need for prospective studies that focus on risk assessment and treatment of this potentially life-threatening complication, and for increased awareness of DHTR among healthcare providers and patients.

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