Delayed haemolytic and serologic transfusion reactions: pathophysiology, treatment and prevention

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Purpose of review
The aim of this study was to summarize the basic epidemiology, pathophysiology and management of delayed serologic and delayed haemolytic transfusion reactions (DHTRs), as well as recent developments in our understanding of these adverse events.

Recent findings
Several studies have identified risk factors for DHTRs, including high alloantibody evanescence rates among both general patient groups and those with sickle cell disease (SCD). Antibody detection is also hampered by the phenomenon of transfusion record fragmentation. There have also been enhancements in understanding of what may contribute to the more severe, hyperhaemolytic nature of DHTRs in SCD, including data regarding 'suicidal red blood cell death' and immune dysregulation amongst transfusion recipients with SCD. With growing recognition and study of hyperhaemolytic DHTRs, there have been improvements in management strategies for this entity, including a multitude of reports on using novel immunosuppressive agents for preventing or treating such reactions.

Summary
Delayed serologic and haemolytic reactions remain important and highly relevant transfusion-associated adverse events. Future directions include further unravelling the basic mechanisms, which underlie DHTRs and developing evidence-based approaches for treating these reactions. Implementing practical preventive strategies is also a priority.

Keywords
anamnestic responses, antibody evanescence, bystander haemolysis, delayed haemolytic transfusion reactions, delayed serologic transfusion reactions, hyperhaemolysis, hyperhaemolytic delayed transfusion reactions

INTRODUCTION

Alloimmunization to blood group antigens remains among the most common and significant adverse effects of transfusion and pregnancy. For patients undergoing transfusion, a history of blood group antibodies creates numerous risks. One danger of subsequent red blood cell (RBC) exposure for an alloimmunized patient is the possibility of a haemolytic transfusion reaction. Notably, for the majority of alloimmunized patients, the risk for haemolysis after forming a non-ABO antibody is *not* experienced acutely at the time of RBC infusion, but rather is separated in time relative to transfusion. Delayed haemolytic transfusion reactions (DHTRs) therefore constitute an important hazard of blood component therapy. However, DHTRs are complex entities with significant pathobiological, clinical and laboratory nuances [1]. Therefore, our aim is to provide an up-to-date review of relevant clinical aspects of delayed transfusion reactions.

EPIDEMIOLOGY

An older investigation suggested that DHTRs occurred in 1 : 6700 RBC transfusions in the USA

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KEY POINTS

- DHTRs are a leading cause of transfusion-associated morbidity and mortality
- A subset of these reactions, referred to as hyperhaemolytic DHTRs, can be particularly severe and devastating in patients with haemoglobinopathies, such as SCD.
- The pathophysiology of DHTRs depends upon the evanescence of previously induced alloantibodies, re-exposure to the cognate antigen and a rapid anamnestic response 3–14 days after transfusion; multiply transfused patients with evanescent antibodies and those who seek care at more than one facility are at the highest risk.
- Most DHTRs are mild, requiring only supportive care and subsequent transfusion with antigen-negative, crossmatch-compatible RBC units.
- For severe DHTRs with hyperhaemolysis, current treatment strategies include avoidance of additional RBC exposure as long as tolerated, immunosuppression and close monitoring of end organ function.
- Preventive strategies include avoiding primary/secondary alloimmune responses to RBC antigens, enhancing detectability of developing antibodies and increasing portability of alloimmunization records. Immunosuppression prior to subsequent transfusions may potentially be beneficial for patients at a very high risk of life-threatening DHTRs.

[2]. Subsequently, a Canadian study concluded that DHTR risk was about 10–11 per 100 000 transfused RBC units [3]. Hemovigilance databases also provide insights into morbidity/mortality associated with DHTRs. Data collected by the US FDA indicate that HTRs attributable to non-ABO antibodies are a leading cause of transfusion-associated fatalities [4]. Moreover, reports from the UK's Serious Hazards of Transfusion (SHOT) database show that nearly 10% of DHTRs are associated with major morbidity, while nearly 60% with mild-to-moderate morbidity [5].

PATHOPHYSIOLOGY

Overview of events leading to a delayed haemolytic transfusion reaction

For a DHTR to occur, several antecedent events must take place, including

(1) A patient is exposed to blood group antigens and develops at least one alloantibody (*primary* alloimmunization).
(2) The alloantibody (ies) diminish in titre and can no longer be detected by blood bank serological techniques.
(3) The patient is re-exposed to the antigen(s) to which they have been immunized.
(4) An anamnestic (*secondary*) antibody response takes place following RBC re-exposure, usually 3–14 days after transfusion.
(5) Antibodies are reinduced at titres high enough to potentially result in accelerated clearance of recently transfused RBCs.

Primary alloimmunization, evanescence and anamnestic responses

Recent studies have enhanced our understanding of blood group antibody development. Polymorphisms within blood group antigens or a recipient's class II HLA [6,7], degree of recipient inflammation at the time of infusion [8,9], disease state [10,11] and the immune response generated at the time of RBC exposure [12–14] have all been linked to primary alloimmunization. Although a discussion of these is beyond the scope of this review, other articles provide extensive information [15,16].

As noted earlier, most DHTRs are ultimately attributable to the fact that antibodies associated with a primary alloimmunization event become undetectable over time. This phenomenon, referred to as 'antibody evanescence', is the primary risk factor for DHTRs. Analyses performed in general patient populations [17–21], as well as those in SCD [22,23▪], have provided insight into the antibody specificities that are most likely to become evanescent (Table 1). A more recent study suggests that antibodies against the MUT and Mur antigens are also associated with high evanescence rates [24▪].

Although evanescence has been well described epidemiologically, there are few studies evaluating *why* alloantibody titres wane over time, and we cannot predict *who* may be at risk for this loss of detectability. Nonetheless, some data shed light on practical issues influencing antibody detection. In several investigations, the testing platform employed for screening influenced detectability, with unmodified tube methods appearing the least sensitive and gel/solid phase methods the most sensitive [25,26]. In another study, the essentially random nature with which screening is performed posttransfusion, when combined with antibody disappearance trends, indicates that only about one-third of transfusion-induced antibodies are ultimately detected [27▪].

There are limited data on biological factors in alloimmunized individuals, which may influence the duration of antibody detectability, or the risk

Table 1. Alloantibody evanescence rates by antibody specificity and patient population, listed highest to lowest, and limited to antibodies reported five or more times when combined across all studies[a]

Evanescence rate in general patients[19-21]	Evanescence rate in SCD patients[22,23]
Lu[a] (65%; 11/17)[b]	Js[a] (80%; 12/15)[b]
C[w] (61%; 19/31)[b]	Fy[b] (78%, 7/9)
Jk[b] (54%; 7/13)	S (66%, 14/22)
Le[b] (52%; 13/25)	Jk[b] (58%; 11/19)
P_1 (50%; 9/18)	Le[a] (54%; 14/26)
Jk[a] (49%; 30/61)	Fy[a] (51%; 18/35)
Le[a] (47.5%; 19/40)	C (47%; 27/57)
E (38%; 134/353)	Go[a] (43%; 3/7)[b]
K (32%; 117/366)	E (41%; 37/90)
M (30%; 12/40)	K (41%; 23/56)
S (30%; 8/27)	Le[b] (40%; 4/10)
c (27%; 23/84)	V (39%; 7/18)[b]
C (19%; 21/109)	M (38%; 3/8)
Fy[a] (17%; 16/94)	D (36%; 10/28)
D (12%; 32/262)	c (0%; 0/5)

SCD, sickle cell disease.
[a]Data were extracted from previous studies [19–22,23▪], with evanescent antibodies of each specificity summed and divided by the sum of total antibodies of that specificity detected across all studies.
[b]Reported evanescence rates for antibodies with these specificities should be interpreted with caution, as these antigens may not always be represented on standard screening cells.

for DHTR development. Polymorphisms in low affinity FcR gamma receptors were examined in alloimmunized patients with SCD with no correlation found between these polymorphisms and risks for DHTR development [28▪▪]. Two groups of investigators also examined patients with multiple alloimmunization. Both found that, for alloimmunized patients with more than one antibody, antibodies typically shared the same 'fate', that is the multiple antibodies were either persistently detectable or evanescent [29,30]. Therefore, multiple alloimmunization events do not appear to impact the duration of the humoral response [21,29,30].

Red blood cell clearance

Once a patient undergoes an anamnestic response, reinduced antibodies clear the transfused, incompatible RBCs [31]. Haemolysis is largely extravascular, although occasional reactions have an intravascular component. Although there have been few major discoveries regarding RBC clearance in the past several years, one animal model study showed that CXCL1 generated as a result of haemolysis contributed to vaso-occlusion in the setting of SCD [32].

CLINICAL MANIFESTATIONS

When considering how DHTRs manifest, there are three overarching types of presentation:

(1) A newly detectable antibody but no increased RBC clearance, or
(2) An anamnestic antibody associated with increased RBC clearance, but typically without major morbidity or mortality, or
(3) An anamnestic response clearing not only incompatible RBCs, but with severe hemolysis of endogenous, nontransfused RBCs.

The clinical/laboratory manifestations of these possible outcomes are summarized in Table 2 and reviewed as follows.

Delayed serologic transfusion reactions

Delayed serologic transfusion reactions (DSTRs) occur in patients who have experienced an anamnestic antibody response, but in whom no clinical or laboratory evidence of haemolysis is evident [33]. DSTRs almost always come to light as a result of repeated antibody screening via the blood bank. As part of a standardization effort, the Centers for Disease Control (CDC) codified definitions for transfusion-associated adverse events. According to the CDC, DSTRs are defined as [34]

(1) absence of clinical signs of haemolysis and
(2) demonstration of a new, specific RBC alloantibody 24 h to 28 days after transfusion by either
  (a) a newly positive DAT, or
  (b) a newly positive antibody screen with a specific antibody.

Some speculated causes regarding the absence of haemolysis include [31]

(1) very low titre antibody response incapable of substantial RBC clearance;
(2) generation of a low-avidity alloantibody;
(3) nonimmune clearance of incompatible RBCs before a high-titre antibody response is attained or
(4) underlying recipient immunosuppression.

Delayed haemolytic transfusion reactions without hyperhaemolysis (i.e. without significant bystander haemolysis)

The second possible outcome of an anamnestic response is accelerated RBC clearance with clinical/laboratory evidence of haemolysis. The CDC

Table 2. Clinical and laboratory manifestations of delayed serologic and haemolytic transfusion reactions, as well as brief treatment strategies for each of these entities

Reaction category	Common clinical symptoms	Common laboratory findings	Treatment strategies[a]
DSTR	(1) None	(1) Newly positive DAT (2) Newly positive alloantibody screen (3) No significant changes in haemolysis markers (e.g. LDH, total/indirect bilirubin, haptoglobin) (4) No reticulocytosis (5) No abnormal findings on urinalysis	(1) No specific therapy required for this reaction (2) Antigen-matched, cross-match compatible RBCs for future transfusions
DHTR *without* hyperhaemolysis	(1) Low-grade fever (2) Mild tachycardia (3) Mild evidence of renal insufficiency (4) Mild jaundice	(1) Newly positive DAT (2) Newly positive alloantibody screen (3) ↑ LDH, total/indirect bilirubin, creatinine (4) ↑ reticulocytes (5) ↑ microspherocytes on peripheral smear (6) ↑ urobilinogen on urinalysis	(1) Primarily supportive care and treating mild symptoms (2) Close monitoring of renal function with hydration if required (3) Antigen-matched, cross-match compatible RBCs for future transfusions
DHTR *with* hyperhaemolysis	(1) Fever and chills (2) Tachycardia and tachypnoea (3) Evidence of renal insufficiency with or without other end-organ damage (4) Significant jaundice (5) Vaso-occlusive crises in patients with hemoglobinopathies (e.g. acute chest syndrome) (6) Clinical evidence of consumptive coagulopathy	(1) Newly positive DAT (2) Newly positive alloantibody screen (3) ↑↑↑LDH, total/indirect bilirubin, creatinine (4) ↓↓ reticulocytes (5) ↑↑↑ microspherocytes on peripheral smear (6) ↑↑↑ urobilinogen on urinalysis; occasionally ↑↑↑ free hgb	(1) Avoidance of additional RBC transfusions for as long as clinically tolerated (2) Close monitoring of renal function and for end-organ damage or vaso-occlusive crises (particularly for patients with hemoglobinopathies) (3) Consideration of immunosuppressive, rEPO and iron therapies

DAT, direct antiglobulin test; DHTR, delayed haemolytic transfusion reaction; DSTR, delayed serologic transfusion reaction; hgb, haemoglobin; LDH, lactate dehydrogenase; RBC, red blood cell; rEPO, recombinant erythropoietin.
[a]For a more detailed discussion of treatment strategies, particularly for DHTRs with and without hyperhaemolysis, please see the corresponding 'Treatment and management' section of this manuscript.

has established diagnostic criteria for DHTRs to include [34]

(1) a positive DAT 24 h-28 days after RBC transfusion and either
   (a) a positive RBC elution study with specific alloantibody detected, or
   (b) a newly detected antibody in the recipient's serum or plasma
(2) Manifestation of either
   (a) a blunted response to a recent transfusion with or without a fall in haemoglobin levels to pretransfusion levels, or
   (b) increased microspherocytes without any other clinical explanation.

In these circumstances, RBC clearance is not typically life-threatening, usually including mild tachycardia, shortness of breath, low grade fevers, mild jaundice and/or evidence of mild renal insufficiency [31,35]. Laboratory studies typically reveal serologic evidence of a new antibody by the blood bank, in addition to a blunted response to transfusion (or lower haemoglobin/haematocrit than pretransfusion), as well as mild increases in bilirubin, lactate dehydrogenase (LDH) and/or creatinine [31,34,35].

Delayed haemolytic transfusion reactions with hyperhaemolysis (i.e. with significant bystander haemolysis)

Among patients manifesting an anamnestic response to RBC transfusion, a small subset will demonstrate severe reactions, typically involving not only destruction of the transfused, incompatible RBCs but also with accelerated clearance of their own RBCs. This phenomenon, also referred to as hyperhaemolysis, is particularly prevalent amongst patients with hemoglobinopathies such as SCD [36], although it has been (rarely) noted in the absence of congenital RBC disorders [37].

Although the CDC does not have diagnostic laboratory criteria for this form of reaction, DHTRs can be scaled according to their severity [34]. Typically, DHTRs with hyperhaemolysis fall into CDC categories of 'Severe' or 'Life-threatening'. Clinically, patients demonstrate a shock-like picture (fever, tachypnoea, tachycardia and blood pressure fluctuation) with renal impairment and/or evidence of other end organ damage [36,38▪▪]. These reactions can also trigger vaso-occlusive crises and pulmonary hypertension in SCD patients [38▪▪].

One of the largest case series of severe DHTRs in patients with SCD provides unique insight into the clinical and biological properties of such reactions [38▪▪]. From a laboratory standpoint, this study and other experiences highlight unique features of hyperhaemolytic DHTRs, including [36,38▪▪,39]

(1) reticulocytopenia
    (a) The reticulocytopenia is paradoxical for the degree of RBC destruction and is not seen in most other forms of immune-mediated haemolysis.
(2) marked increases in LDH, total/indirect bilirubin and urobilinogen;
(3) decreased haptoglobin.

The recently published work of Mekontso Dessap *et al*. [40▪] offers a promising laboratory-based nomogram allowing for DHTR probability stratification based primarily on changes of haemoglobin A concentration relative to the time since the patient's most recent haemoglobin analysis.

Importantly, a subset of cases of hyperhaemolysis may be encountered without a newly detectable alloantibody [38▪▪]. In these settings, patients may develop positive DATs with associated autoantibodies, or may have nonspecific antibodies in their plasma. Some patients may have completely negative antibody screen tests, with no evidence of an alloantibody or autoantibody. However, the remaining features of such cases will closely mimic those of hyperhaemolytic reactions described above and, given the close-in-time proximity to RBC transfusion, these patients are often treated as if they were experiencing an antibody-associated DHTR.

One possibility in 'alloantibody negative' severe DHTR cases is that alloantibodies *are* being developed as part of an anamnestic response, but they may be directed against low incidence antigens, or antigens not routinely identified on screening cells. For example, there have been several reports of HTRs attributable to antibodies against Dombrock antigens, which are not routinely identified on screening cells [41–43]. In one case series, haemolytic transfusion reactions in several SCD patients were mistakenly attributed to nonspecific or autoantibodies detected in plasma until Dombrock antibodies were ultimately identified; haemolysis abated once Dombrock-negative RBCs were provided [42].

There are few concrete explanations as to why patients with disorders such as SCD may manifest such severe haemolysis, nor a clear understanding as to why endogenous RBCs are cleared. One study examined phosphatidylserine expression on recipient RBCs during DHTRs. Operating under the hypothesis that immune activation and oxidative damage could increase phosphatidylserine exposure resulting in 'suicidal RBC death', the authors reported marked increases in phosphatidylserine expression on endogenous RBCs amongst SCD patients experiencing severe DHTRs [44]. This finding was confirmed in another study [45].

In addition, others speculated that autologous RBC clearance is akin to immune dysregulation disorders resulting in an attack against self-RBCs, with the DHTR acting as a trigger. Indeed, one DHTR case report was associated with a marked increase in ferritin (to $>10\,000\,\mu g/l$) and a clinical picture similar to macrophage activation syndrome or hemophagocytic lymphohistiocytosis [46]. Another group examined 12 SCD patients with a history of hyperhaemolytic DHTRs [47]. Utilizing whole exome sequencing, the investigators found function-impacting variants in immune-related genes such as *MBL2* and *KLRC3* amongst study patients. These investigations lend credence to the notion that immune dysregulation may help explain why endogenous, nontransfused RBCs are targeted as part of a hyperhaemolytic reaction.

Although the described studies suggest possible pathways leading to the severe nature of hyperhaemolytic DHTRs, cohorts for these investigations have been small. More work is required to broaden our understanding of the complex mechanisms at play in these reactions. To overcome obstacles associated with studying a rare disorder such as hyperhaemolytic DHTRs, some have proposed establishing a hyperhaemolysis database/registry to allow for larger scale studies [48].

TREATMENT AND MANAGEMENT

Delayed serologic transfusion reaction treatment and management

As DSTRs do not have clinical sequelae, they do not require specific therapy [35,49]. However, blood banks and transfusion services must accurately identify the reinduced antibody (ies) and provide compatible, antigen-negative units for subsequent

transfusions. Closely monitoring apparent DSTRs to ensure that they do not evolve into DHTRs over time is also warranted [35].

Delayed haemolytic transfusion reactions without hyperhaemolysis

There have been no randomized trials to assess various treatment regimens for mild-moderate DHTRs; hence, there are no rigorous, evidence-based strategies. However, anecdotal data suggest supportive measures, including crossmatch-compatible, antigen-negative RBC transfusions, treatment of mild symptoms and close monitoring of renal function [35,49]. Should renal insufficiency be encountered, vigorous hydration has been recommended [35,49].

In selected DHTR scenarios, more aggressive interventions may be warranted. For example, there are case reports on using automated RBC exchange for individuals exposed to very large amounts of incompatible RBC who may be at risk for massive haemolysis from anamnestic responses [50,51]. Plasma exchange, to reduce circulating RBC antibody titres, has also been occasionally used for mitigating haemolytic reactions [52]. Although such prophylactic apheresis procedures would not be indicated for most DHTRs, they could be considered in cases wherein a patient has been exposed to a large volume of circulating incompatible RBCs, or where reinduced antibodies are known to be more strongly associated with complement-mediated intravascular haemolysis.

Delayed haemolytic transfusion reactions with hyperhaemolysis

DHTRs with hyperhaemolysis must be recognized as soon as possible, given their severity and potential adverse sequelae. The tenets for treating hyperhaemolytic DHTRs revolve around

(1) avoiding additional RBC transfusions unless absolutely needed;
(2) considering recombinant erythropoietin (EPO) and/or iron therapy;
(3) close monitoring of renal and other end-organ functions;
(4) considering immunosuppression.

Numerous anecdotal reports suggest that providing additional, exogenous RBCs (including crossmatch-compatible, antigen-matched units) 'fuels the fire' of hyperhaemolysis. As such, most facilities avoid additional RBC transfusion unless absolutely clinically needed [36,39]. In at least one severe DHTR case, wherein RBC transfusion was deemed life-saving due to severe congestive heart failure, a plasma-to-RBC exchange (i.e. where plasma exchange was performed but the replacement fluid was RBCs) was performed, with cessation of haemolysis and a postexchange increase in haemoglobin levels [53].

As an alternative to RBC transfusion, some have recommended providing recombinant EPO. Reported high-dose approaches (150–300 μg of darbepoeitin-alpha or 10–60 000 IU of epoetin-alpha) continued for 1–3 weeks during, and immediately after, severe DHTRs have successfully reconstituted erythropoiesis [36,39,54]. Some have also advised providing iron for transferrin saturations under 20% [54].

Because of the immune-activation observed in severe DHTRs, attempts at immunosuppression may be warranted. Published experiences are as follows:

(1) Corticosteroids:
   (a) Hydrocortisone, prednisolone (2 mg/kg/day over days to weeks in children) and methylprednisolone (0.5 g/day over 5 days in adults) have been used in case reports/series involving severe DHTRs [54,55].
   (b) The risk/benefit ratio of using corticosteroids in patients with SCD must be carefully considered, given their potential impact on vaso-occlusive pain [55].
(2) Intravenous immune globulin (IVIG)
   (a) Although often reported in combination with corticosteroids, there is no evidence-based dose recommendation for IVIG [55]; some experience-based guidance documents [54] suggest doses of 1 g/kg/day for a short trial over a few days (potentially applicable to both children and adults)
   (b) The risk/benefit ratio of using IVIG in patients with SCD must be considered, given potential adverse renal sequelae, as well as the impact IVIG may have on serological testing.
(3) Rituximab
   (a) There have been two primary uses of rituximab in severe DHTRs: to treat active alloantibody-mediated haemolysis [54–56], and to provide prophylaxis for preventing DHTRs in patients with a history of this reaction, but who require subsequent transfusion [56,57].
   (b) From a preventive standpoint, one of the largest case series used this strategy and, amongst patients treated, regimens varied from 375 mg/m^2 x 2 doses in the weeks preceding transfusion ($n = 1$) to doses of

Table 3. Practical strategies to reduce the occurrence of delayed haemolytic transfusion reactions

Avoid primary and/or secondary alloimmunization events	(1) Judicious use of RBC transfusions to limit foreign antigen exposures (2) Provide phenotype or genotype-matched RBCs for chronically transfused patients (3) Potentially consider immunosuppressive medications or regimens pretransfusion, particularly for patients who have experienced life-threatening DHTRs
Blood group antibodies	(1) Perform follow-up antibody screen studies in the 4 to 12-week window following transfusion (or postpartum) (2) Utilize the most sensitive laboratory techniques available for antibody screening and identification
Enhance portability of blood group antibody history for evanesced alloantibodies	(1) Assess a patient's transfusion or pregnancy history, including previous facilities wherein they received care and where evanesced antibodies may be documented (2) Distribute wallet cards or medical bracelets with a patient's alloantibody history (3) Develop, and participate in, blood group alloantibody registries

DHTR, delayed haemolytic transfusion reaction; RBC, red blood cell.

1000 mg x 1 about 1 month to 10 days before transfusion ($n = 7$) [57].
   (c) The risk/benefit ratio of using Rituximab in patients with SCD must be considered.
(4) Eculizumab
   ○ Because of the potential role played by complement activation in hyperhaemolysis, recent reports explored using eculizumab for treating these reactions.
      (a) One study used a dose of 1200 mg (weekly x4 weeks, followed by maintenance therapy) combined with subsequent rituximab therapy after haemoglobin stabilization for a patient with a severe DHTR [58].
      (b) Its use as a salvage therapy for SCD patients was reported in a case series of three patients with hyperhaemolytic DHTRs; each patient received two fixed doses of 900 mg, 1 week apart [59].
      (c) In contrast, another study found no benefit from a single dose of 600 mg, given one time to a non-SCD patient with a severe DHTR [37].
         (i) The risk/benefit ratio of using eculizumab in patients with SCD must be considered, given the increased risk of meningococcal infection after treatment. Vaccination pretreatment is warranted, if not already up-to-date.
(5) Other immunosuppressants
   (a) There are a few reports on the use of immunosuppressants, such as cyclosporine, azathioprine, cyclophosphamide and busulfan, for severe DHTRs; there is also little consensus on dosing [55].

All the above strategies are based on anecdotal experiences or small case series, and there is no standard-of-care in managing hyperhaemolysis. A typical approach usually involves recognizing the reaction and, as initial steps, limiting additional RBC transfusions with supportive care provided in parallel. Immunosuppressive therapies may be introduced in critical situations, with case series/reports describing an approach of corticosteroids and/or IVIG, rituximab or eculizumab [54,55].

PREVENTION

Although DHTRs are a pervasive problem in transfusion medicine, steps can be taken to mitigate their harmful effects (Table 3):

(1) Avoiding primary and/or secondary alloimmunization;
(2) Improving detection of newly-developed alloantibodies;
(3) Enhancing the portability of alloimmunization history.

Increasing evidence suggests that prophylactic antigen matching (i.e. providing RBCs matched for antigens that a recipient lacks) is highly impactful in lowering alloimmunization rates amongst chronically transfused patients, thereby decreasing risks for DHTRs. For example, the US National Institutes of Health recommends minimally matching for K/E/e/C/c antigens for transfusions to patients with SCD [15]. Although serological-based phenotypic matching is beneficial [60], at least one study showed that polymorphisms in RBC antigens (especially within the Rh family) may necessitate molecular/genetic matching for patients with SCD [6]. Other means for preventing alloimmunization include judicial use of RBCs and consideration of immunosuppressive medications such as rituximab for patients with a

history of severe DHTRs with hyperhaemolysis, should future transfusions be required [57].

Few tools are available to enhance alloantibody detection. Although solid phase and gel technology have increased sensitivity [25,26], even these approaches fail to identify very low titre alloantibodies. As such, some have argued that screening for alloimmunization should be performed in the weeks after RBC exposure, even if a future RBC transfusion is not imminent. As discussed earlier, a recent study has shown that potentially large swaths of alloantibodies may go undetected because of the essentially random nature of follow-up antibody screening, combined with antibody evanescence [27▪]. On the basis of these data, one approach of follow-up antibody testing on a regimented basis 1–4 months after RBC transfusion to screen for new alloantibodies (not unlike the setting of tissue transplantation) was proposed [61].

It is important to note that even if antibody detection methods are significantly enhanced, antibodies still have a high likelihood of disappearing from detection over time [21,23▪]. This becomes even more problematic when patients seek transfusion-related care at multiple hospitals. Several studies explored the issue of transfusion record fragmentation, that is evanesced antibodies not documented at all facilities wherein a patient receives care. Alarmingly, one study [62] found discrepant antibody records for nearly two-thirds of patients shared between two nearby hospitals. In addition, SCD patients with evanesced alloantibodies visited a median of three hospitals over the course of their care [63]. Thus, transfusion record fragmentation potentially contributes to DHTRs.

Wallet cards and alert bracelets are two simple means by which a history of alloimmunization can be communicated to patients and providers [60]. However, such systems are difficult to keep current and may fail because they rely almost exclusively on patient recall [60]. Therefore, there are increasing appeals for developing regional or national alloantibody registries [23▪,64]. Although such registries are relatively rare in the USA, at least one study involving a regional database documented prevention of DHTRs [65].

CONCLUSION

DHTRs remain important transfusion-associated adverse events. Because of the myriad ways such reactions manifest, and their potentially life-threatening nature, it is vital that blood bank specialists and haematologists have a detailed understanding of their signs, symptoms, pathophysiology, treatment and prevention. Future challenges include enhanced understanding of the basic mechanisms underlying severe DHTRs, developing rigorous, evidence-based approaches for treating these reactions, and implementing achievable strategies for their prevention.

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Papers of particular interest, published within the annual period of review, have been highlighted as:

- ▪ of special interest
- ▪▪ of outstanding interest

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